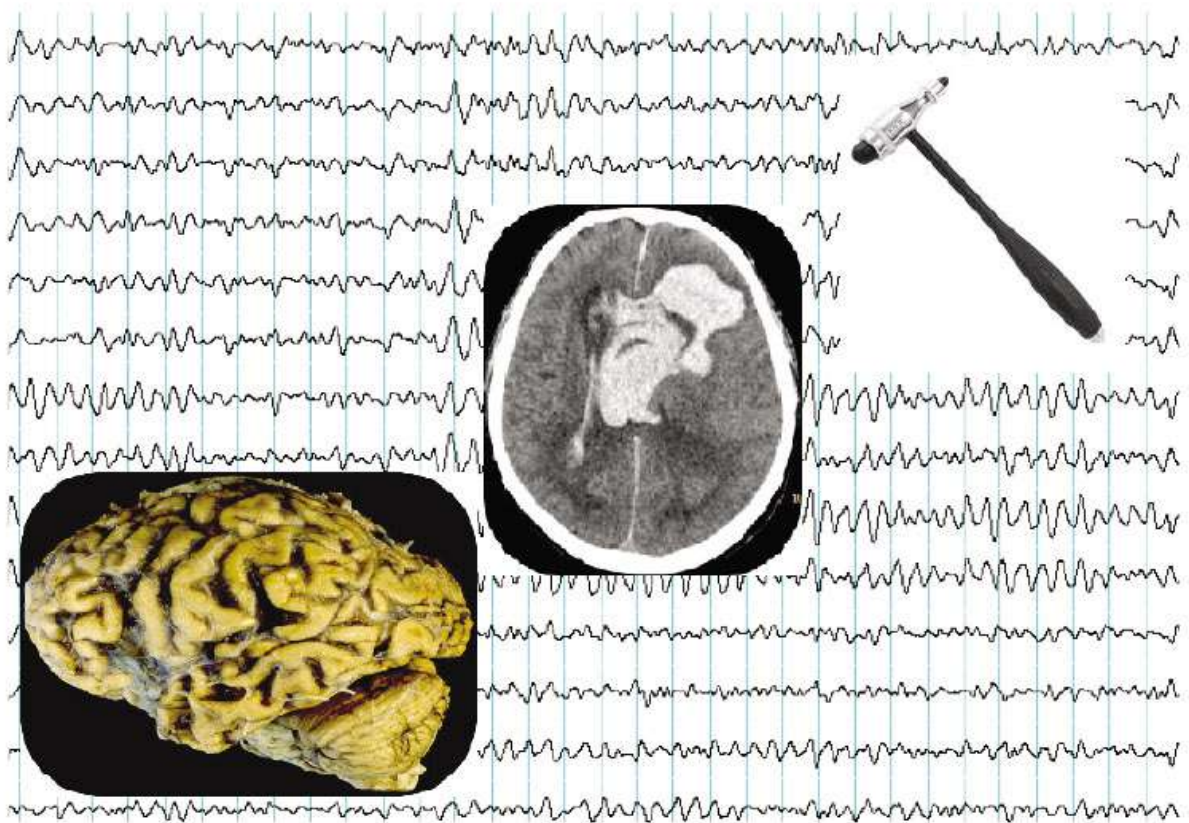


UNIVERSITY OF DEBRECEN
FACULTY OF MEDICINE
DEPARTMENT OF NEUROLOGY

SELECTED TOPICS IN NEUROLOGY



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DUPress

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SELECTED TOPICS IN NEUROLOGY

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Neurological examination

BERTALAN VÁMOSI MD.

Taking neurological history

History is one of the most important parts of neurological evaluation. It provides information, which helps the tentative diagnosis. This initial diagnosis can be verified or refuted later by examination and diagnostic testing. However, obtaining a good history is not easy because it requires the knowledge of the basic principles of the various neurological processes.

On the occasion of taking neurological history, two opposite requirements should be reconciled: partly the patient should be allowed to explain his/her complaints freely and without any suggestion, partly it is inevitable to ask questions which construct the talking and supplement the lacking data. It is – however - rather art than science.

In addition to the *autoanamnesis* (i.e., information obtained from the patient), it is always useful and sometimes inevitable to obtain information also from other persons knowing the patient (*heteroanamnesis*) as family, colleague or an accidental eyewitness as well. There is no substitution for the heteroanamnesis in cases of seizures and other states accompanied by disturbed consciousness, oligophrenia, dementia, personality disorder, psychoses, etc.

The **introductory part** of the neurological history is similar to that of the internal one:

- Age, sex and occupation of the patient;
- Hereditary diseases in the family;
- Disturbances in the intrauterine life; birth; early development;
- Diseases of childhood;
- Past medical history;
- Craniovertebral injury (with or without loss of consciousness?);
- Alcohol and drug history;
- Handedness (Right or left handed? Left or right hemispheric dominance can be rendered probable?);
- Social history.

The **history of the present illness** should include the following information:

- Character of the symptom onset (acute, subacute, chronic, insidious?);
- Duration and course of the illness (regressive, static, progressive, relapsing or remitting?);
- Associated symptoms (weakness, dizziness, pain, headache, nausea, vomiting, seizures, etc.) in chronological order.
- Pain should be further defined according to the followings:
 - location (ask the patient to point with one finger, if possible);
 - radiation (dermatomal?);

- quality (dull, burning, throbbing, stabbing, lightninglike, etc.);
- severity (estimate functional limitation);
- diurnal or seasonal variation;
- precipitating and relieving factors (stress, periods, allergens, sleep deprivation, etc.);
- Dizziness should be further characterized, too, as
 - systematic (vertigo or leaning sensation to a steady direction) or
 - diffuse (unsteadiness without a consistent direction, lightheadedness); or
 - atypical dizziness: unsteadiness with rapid onset accompanied by dyspnoea, hyperventilation, palpitation, sweating and very intense anxiety; no adequate neurologic symptom (nystagmus, Romberg sign, etc.) but often elicitable by 3 min voluntary hyperventilation.
- Miscellaneous: previous diagnosis and therapy; the patient's ideas regarding his/her illness.

The doctor is justly expected to take care first of all for the problems which mostly trouble the patient. Therefore it is quite right if the taking of history starts with the „Present illness” and not - for example - with the „Hereditary diseases in the family”.

Physical examination

Mental status

Here the main points of view of the normal mental state will only be described. Normally, the patient **cooperates** adequately, and has orderly **appearance**.

The **consciousness** state is normal: he/she is alert, awake and **oriented** in place, time and person.

His/her **behavior** is appropriate. Anxiety, depression, personality disturbance, hallucination or delusion is not suspected.

Both remote and recent **memories**, as well as the ability to store new information seem to work normally.

The use of **language** is adequate: the comprehension is undisturbed, the motor expression is fluent and grammatically correct, the ability to repeat words and sentences is retained. The reading, writing and counting abilities are undisturbed, too. Aphasia, apraxia or agnosia is not suspected.

Some **screening tests** could be very useful for the rapid assesment of patients with suspected psychiatric disorders. For example, the Mini Mental State Examination (MMSE) is a useful test, it screens elderly patients for mental decline. The Abbreviated Mental Test Score (AMTS) can be used to assess elderly patients

for the possibility of dementia and the younger patients for confusion and other cognitive disturbances rapidly.

Meningeal signs

Signs of meningeal irritation indicate serious diseases with urgency: meningitis, meningo-encephalitis, subarachnoid hemorrhage, intracranial tumors (first of all those in the posterior fossa), cerebral edema, cerebrospinal fluid hyper- or hypotension, etc.

The most important meningeal signs are the followings:

Nuchal rigidity or neck stiffness is tested by placing the examiner's hand under the patient's head and gently trying to flex the neck. Normally, the patient's chin reaches his/her chest easily. Inappropriate resistance suggests the irritation of the cervical nerve roots from meningeal origin, but neck stiffness can be induced by several other causes, too.

Brudzinski's sign is the flexion of the knees while nuchal rigidity is being tested. This sign indicates the diffuse meningeal irritation of the spinal nerve roots.

Kernig's sign is elicited by flexing the hip and knee on one side, while the patient is in supine position, then extending the knee with the hip still being flexed. Hamstring spasm results in pain in the posterior thigh muscles and inhibits knee extension. In case of severe meningeal irritation, also the opposite knee may flex during the test.

Normally: no sign of meningeal irritation can be detected; the head can be moved freely (no cervical rigidity), Kernig's or Brudzinski's signs can not be elicited.

Cranial nerves (CNs)

Some cranial nerve **symptoms** can be noticed even **before starting of exam**, e.g.:

- ptosis (dropping of the upper eyelid - CN III or sympathetic deficit);
- lagophthalmus (inability to close the eyelids - CN VII);
- uni- or bilaterally slow or missing blinking (CN VII, parkinsonism);
- abnormal or asymmetrical pupils (CN II, III, symp.);
- abnormal eye position (CN III, IV, VI);
- atrophy in chewing muscles (CN V);
- facial droop or asymmetry, twitchings (tic or spasm) in face (CN VII);
- scarcely audible and/or hoarse voice (CN X);
- articulational disturbances of words (CN V, VII, IX-X, XII);
- swallowing disturbance, sialorrhoea (CN IX-X);
- torticollis (wryneck), atrophy in sternocleidomastoid and trapezius muscles (CN XI), etc.

CN I. Olfactory nerve

Olfactory testing: the patient with his/her eyes closed, sniffs a familiar aromatic odor (e.g. coffee, vanilla, tobacco, soap, etc.) from a small vial. The nostrils should be alternately occluded to test each side separately. Substances such as acetic acid and ammonia should be avoided for testing, because they cause strong trigeminal stimulation and can be sensed in case of anosmia, too.

Normally, the patient identifies correctly the odors in each side and considers the odor intensities to be bilaterally equal. He/she refers no subjective smell disturbances.

Pathologically, the smelling can be depressed (**hyposmia**) or lost (**anosmia**), or on the contrary, the patient may be hypersensitive to odors (**hyperosmia** - frequently in gravidity), or he/she may be unable to identify any odor but considers all the odors unpleasant (**parosmia**, **cacosmia**), finally, in certain cases (complex partial epilepsy, migraine, etc.) **olfactory hallucinations** may appear.

Damages affecting the olfactory trigone or the more peripheral parts of the olfactory pathway (the olfactory tract, bulb, nerve filaments or olfactory mucosa) result in **neurogenic unilateral hyp- or anosmia**.

If the destructions lie at or more centrally from the partial crossing of olfactory pathways through the anterior commissure, bilateral lesions can depress (**bilaterally**) the olfactory function only.

Potentially *irritative lesions* (tumors, post-traumatic or ischemic scarrings, arteriovenous abnormalities, etc.) in the olfactory cortical regions may be the source of *epileptic activity* and could cause **olfactory hallucinations**, which are usually unpleasant or even disgusting, and could not be lateralized by the patient.

Some causes of smell disturbances:

- Smell disturbances frequently have *local, non-neural causes* such as common cold or other forms of rhinitis, deviated nasal septum, nasal polyp,ozena, etc.;
- Hyposmia (and more rarely parosmia) may be associated with *metabolic disorders* caused by deficiency on Vitamin A, Vitamin B₁₂, Zinc, as well as hepatic failure and some cases of diabetic neuropathy, multiple sclerosis and herpes simplex encephalitis (localization!);
- *Occipital head trauma* (with shearing effect on fila olfactoria);
- *Frontal trauma* (it usually associates with nasal liquorrhoea, if the fracture line crosses the cribriform plate);
- *Basofrontal tumors* – are mostly meningiomas in the olfactory groove or on the sphenoid ridge. The latter may press both the olfactory and the optic nerve, and cause ipsilateral anosmia and optic atrophy, as well as contralateral papilledema (due to the increased intracranial pressure): Foster-Kennedy syndrome.

CN II. Optic nerve

The neurologist regularly tests

- 1.) visual acuity,
- 2.) visual fields, and performs
- 3.) funduscopy.

1.) Testing visual acuity

Allow the patient to use his/her glasses or contact lenses if available. Position the patient 5 m from the Kettesy's eye chart or 20 feet from the Snellen's eye chart. Cover the patient's eye which is not being tested. Ask the patient to read the progressively smaller letters (or other symbols) until he/she stops. Record the smallest line the patient could have read successfully and repeat the examination on the other side.

If the patient is unable to read the top line, ask him/her to count your fingers. Designating: CF (count fingers) 5 → 0,1 m.

If a patient can not count fingers, ask him/her to determine whether the examiner's hand is moving or not: HM (hand motion perception): yes or no.

If a patient is unable to perceive hand motion, see if he/she is able perceive light: LP (light perception): yes or no.

2.) Testing visual fields

At the bedside, the *confrontation* is the most commonly applied screening method of the kinetic perimetry for estimating the boundaries of the visual fields. „Confrontation” means that the front of the examiner and that of the patient are parallel to each other, therefore the examiner's fields (considered to be normal) serve as a measure to compare the patient's fields. However, we will see that this statement is a rough approaching only, and not directly valid.

Technique: The patient covers his/her eye on one side, and is asked to fix the examiner's forehead at a distance of approximately 30-40 cm. Then the patient is asked to indicate with a quick „yes!” when he/she sees any moving thing. The examiner's hand enters in the patient's field with wriggling fingers. It is very important to consider where the testing hand starts from and what course it will run through. It should be considered that 1.) the human binocular visual field in the horizontal plane is about 180-190 degree, and 2.) the basic rule of the kinetic perimetry is that the test object must always start from an area, which the patient cannot sense, i.e., temporally, from behind the frontal plane (Figure 1B). Consequently, the principle of „the examiner's field is the measure for testing the patient's field” would require the coincidence of the examiner's and patient's frontal plane, which can scarcely be put into the practice. So it is also inaccurate when the testing hand starts and moves in a plane halfway between the patient and the examiner (Figure 1A). Correctly, the testing should always start from a certainly blind area (Figure 1B) and its further course runs along a quarter of circle until it is stopped by the patient's „yes” or reaches the centre of the field (in case of a hemianopsy). To assess the boundaries of one eye's field, the above described procedure should be repeated at least 8 times with 45 degree-steps. Additionally, it

is critical to observe whether the patient fixates on the central object steadily (i.e., examiner's forehead) during the examination.

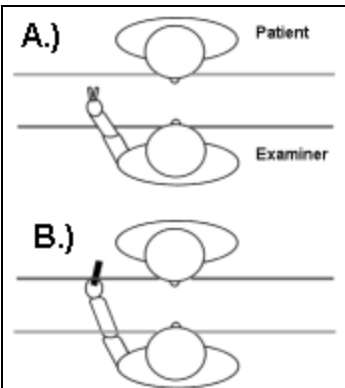


Figure 1
Testing of visual field by confrontation.
A.) The testing begins inside the visual field, therefore the borders of the visual field can not be correctly determined.
B.) Testing should always be started from a certainly blind area, i.e. temporally from behind the patient's frontal plane.

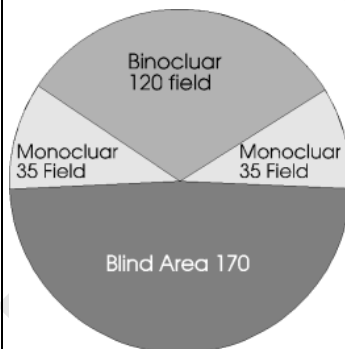


Figure 2
The visual field's view from above. The blind area is about 170 degree (as it was recognized by Leonardo da Vinci already in 1510).

Confrontation as a screening method can detect hemi- and quadrant anopsies, and other coarse deficiencies of the visual fields. More detailed results can be obtained by the various diagnostic perimetries, e.g. by Goldmann's perimetry.

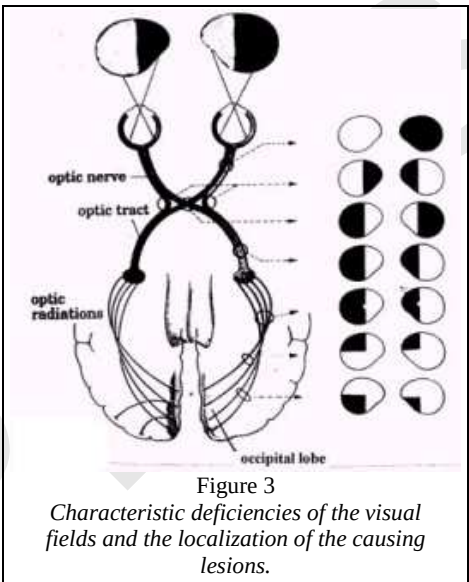


Figure 3
Characteristic deficiencies of the visual fields and the localization of the causing lesions.

Some basic rules:

- Monocular defects are caused by unilateral lesions of the retina or the optic nerve.
- Chiasmatic and retrochiasmatic lesions result in bilateral field defects:
 - heteronym defects are caused by (peri)chiasmatic lesions,
 - the homonym hemi- and quadrant anopsies are caused by retrochiasmatic (optic tract, optic radiation or occipital cortex) lesions.

3.) Funduscopy is not discussed here.

Normally, the visual acuity (*visus*) - with the correction of refraction failures, if available - is bilaterally 1,0 (Kettesy's eye chart) or 20/20 (Snellen's eye chart). The visual field tested with confrontation is full and the optic fundus is normal on each side.

CNs III - IV- VI. Oculomotor, Abducens and Trochlear nerve

Regularly, the followings are examined:

- 1.) extraocular movements and
- 2.) pupillary reactions.

1.) Extraocular movements

Technique of examination:

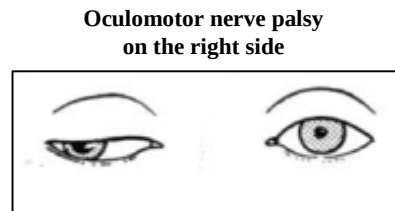
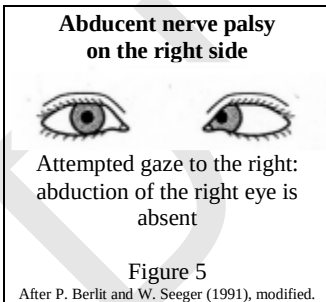
- Observe for *ptosis*.
- Test A.) *smooth pursuit eye movements* and B.) *saccadic eye movements*.

A.) *Smooth pursuit eye movements*: stand about 2 to 3 feet in front of the patient and ask him/her to follow your finger (the visual target) with his/her eyes without moving the head. Check gaze tested in the 9 cardinal directions (Figure 4) and check convergence, too, by moving your finger toward the bridge of the patient's nose. Pause during lateral and upward gazes in order to check nystagmus and ask the patient if he or she senses any occasional double vision.



Figure 4
Gaze in the 9 cardinal directions

Main symptoms of the peripheral palsy of the 3 ocular motor nerves (Figure 5-7):



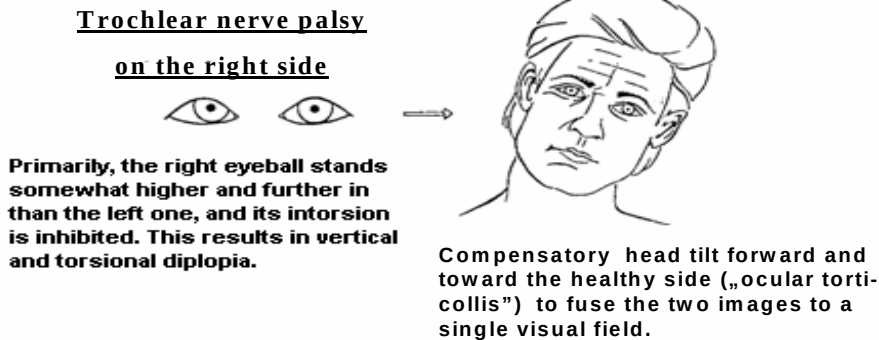


Figure 7

After P. Berlitz and W. Seeger (1991), modified.

B.) Saccadic eye movement:

B1.) *Commanded eye movements:* the patient is asked to look quickly „right!”, „left!”, „up!”, „down!”, etc. (without any visual target).

B2.) *Searching eye movements:* the patient is asked to find „a lamp, a window, a water tap”, etc. (i.e., search for a well-defined visual object).

Note, whether all these eye movements are smooth, conjugated, accurate, run their courses freely and with normal velocity. You may find abnormalities requiring further testing to explain esophoria, esotropia, dysconjugate movements, overshoot or undershoot during saccadic movements, nystagmus, diplopia, etc.

Normal oculomotor state: both smooth pursuit and saccadic eye movements are free, precise and conjugated. No ptosis, double vision, or nystagmus is observed.

2.) Examination of the pupils

A.) *Introductory observations at rest:* note the patient’s pupil size (in mm), equality (isocoria) or inequality (anisocoria), shape (round or irregular), position (central or excentric) and the state of the pupillary margin (regular, intact or irregular, extracted, etc.).

B.) *Test the followings:*

- *direct and consensual light reaction,*
- *swinging-flashlight test,*
- *accommodation and (forced) convergence reactions.*

Technique: examination of the pupillary light reactions should be performed in a semidarkened room by using a strong penlight. The patient should fixate a distant object in order to prevent both the accommodative and convergence reactions.

Direct light reaction: shine the light with short breaks repeatedly in the eye on one side, while the other eye is covered, and notice the narrowing and widening of the illuminated pupil. Repeat the procedure on the other eye, too.

When **anisocoria** occurs and the examiner is unsure whether **the abnormal pupil** is the constricted or dilated one, the pupils should be reassessed in varying illumination. If the dimming of light does not cause the smaller pupil to dilate, or alternatively, the increased light does not cause the larger pupil to constrict, the not reacting or more sluggish pupil is the abnormal one.

Consensual light reaction: use your stretched hand as a screen: fit it over the patient's nose and forehead parallel with the centre line of the face. Shine the light into the eye on one side, while observing the other, non-illuminated eye. Normally, the reactions of the non-illuminated eye should be completely identical with that of the illuminated eye. Note the symmetry of the responses!

„*Swinging-flashlight test*“: compared to the previous examinations it tests the afferent limb of the pupillary light reflex. The examiner directly moves the light from one eye to the other one for several times. If the light is swunged from the right eye to the left and the left pupil dilates, then the afferent input from the left optic nerve is less than the right one. In this case the patient has an „**afferent pupillary defect**“ (APD), also called a „**Marcus-Gunn pupil**“. If the optic media is clear, it suggests defect of the optic nerve (e.g., retrobulbar neuritis in multiple sclerosis).

Accommodation pupillary reaction: have the patient focused to a distant target then immediately to a near one (but the latter should not be nearer than the near point of the patient). The normal response is for the pupils to narrow slightly.

(Forced) convergence pupillary reaction: firstly consider: accommodation and convergence are conjugate functions tested between the optical infinite and the near point, and the pupillary narrowing induced by them cannot be separated. Now ask the patient to focus on a target lying within the distance of the patient's near point, e.g., the tip of his/her nose („Fly on the nose test“). In comparison to the preceeding test, in this case the accommodation cannot increase further, but the convergence - and the pupillary narrowing induced by them - can do it! Therefore the resulting constriction will be more abundant than that of associated with the accommodation + not forced convergence reaction.

Anisocoria

The pupils are not of equal size. It is often a benign, idiopathic condition („habitual anisocoria“), which can be seen on old photos of the patient, too. An acute anisocoria may be caused by drugs with mydriatic or miotic effect getting into one of the eyes, and the lesion of the parasympathetic or sympathetic pathways influencing the pupillomotoric activity. Anisocoria in patients suffering from decreased or disturbed mental state, severe headache, hemiparesis, etc., can be a sign of intracranial bleeding, tumor or other pathologic processes, which compress some critical structures including the oculomotor nerve. Wide and fixed pupil indicates neurosurgical emergency possibly requiring surgery („surgical pupil“).

Near/far reflex triade

- 1.) Dioptric accommodation of the lens resulting in increased/decreased refracting power,
- 2.) Convergence/divergence to prevent double vision, and
- 3.) Constriction/dilation of the pupils serving as diaphragm.

Light-near dissociation: a condition where the light reflex is absent or abnormal but the near response is intact.

Argyll Robertson pupil (ARP)

Hallmark of neurosyphilis. Light-near dissociation: no reaction to light but brisk response to near. Both pupils are usually involved. The pupils are small and frequently irregular in shape, dilate poorly after the instillation of mydriatics.

Adie's (tonic) pupil

The etiology is unknown. The causing lesion lies in the ciliary ganglion which leads to denervation of the postganglionic nerve supply to the sphincter pupillae and ciliary muscle. The pathology is unilateral in about 80% of cases resulting in anisocoria. The rate of women:men is 3:1, and the typical manifestation's time is the 3rd to 4th decade of life.

On the affected side there is an internal ophthalmoplegia with loss of sphincter function and accommodation. There is no response to either direct or consensual light reflex, and the accommodation is very sluggish. The affected pupil is relatively dilated in bright light and relatively constricted in dim, so its functioning is expressively slow, i.e., tonic.

0.125% pilocarpine 1 gtt placed in both eyes will cause the Adie's pupil to constrict because of denervation hypersensitivity, whereas the normal pupil will not be affected by such a low concentration of pilocarpine (the normal eye drops are of 2% and 1%, respectively).

The patellar and ankle reflexes are often hypoactive in these patients, which - with the peculiar pupillary light reflexes together - could give rise to an unjustified suspicion of neurosyphilis. Adie's pupil is in fact a benign condition; with time the accommodative response improves while the tonicity of the light response gets worse. There is no treatment.

Horner's syndrome

The classical symptom triad of the (negative*) Horner's syndrome:

1. ptosis (a moderate one, caused by the paralysis of Müller's muscle in the upper eyelid),
2. miosis (*conditio sine qua non!*); although the pupil's light reflex is maintained, anisocoria is more marked in dim illumination.
3. enophthalmus (the affected eye appears to be sunken)

The above triad may be accompanied by anhidrosis (lack of sweat secretion) and flushing on the ipsilateral side of the face, as well as by injected conjunctiva. In children, Horner's syndrome sometimes leads to heterochromia: a difference in eye color between the two eyes (melanocyte dysfunction).

*Rarely one can see also a positive Horner's syndrome with lagophthalmus, mydriasis and exophthalmus as expression of a circumscribed, temporary sympathetic excitement.

Do not forget the rule of thumb:

ptosis + miosis combination mostly refers to Horner's syndrome (sympathetic lesion), and

ptosis + mydriasis together hints at (partial) Oculomotor nerve lesion (parasympathetic damage).

The Horner's causative lesion (mostly compression) damaging the sympathetic centres and/or pathways can be

- *preganglionic* (located in the posterior hypothalamus, brainstem, spinal cord, neck or chest), and
- *postganglionic* (damaging the paravertebral ganglionic trunk and/or the postganglionic sympathetic fibres).

The differential diagnosis could be made by 1% hydroxyamphetamine instilled in both eyes. This drug will dilate both the normal and the preganglionic lesion pupils, but not the postganglionic lesion pupil. The prognosis is generally much better if the causative lesion is postganglionic than preganglionic. The most common causes acquired in adult age are - unfortunately - the malignant tumors of the upper lobes of the lung (Pancoast's tumor), which press the cervical sympathetic trunks.

As for the normal state of pupils, there is a common abbreviation in the English speaking countries: PERRLA, that stands for „Pupils Equal, Round, Reactive to Light and Accommodation“. However, in Central Europe it is customary to test additionally the consensual light reaction and the forced convergence reaction, too.

CN V. Trigeminal nerve

Trigeminus is the motor nerve of the chewing muscles and the sensory nerve of the face.

Its entry zone is at the mid pons with the motor nucleus and the main sensory nucleus (*nucleus sensorius principalis nervi trigemini*), which conveys discriminatory touch and other sensations of deep sensibility. The axons serving for the superficial sensibility (pain and temperature) descend to the level of CV-VI segments and synapse with the *nucleus tractus spinalis descendens nervi trigemini*. Second order neurons of both sensory nucleus cross over, join to the medial lemniscus or spinothalamic tract, and ascend to the ventral posteromedial nucleus of the thalamus. The mesencephalic „nucleus“ of trigeminal nerve is in fact a sensory ganglion formed from pseudounipolar cytes, which in course of ontogeny get into the substance of the mesencephalon. It conveys deep sensations from the periodontal membranes (pressure) and the masticatory muscles (tension), synapses with the trigeminal motor nucleus forming a monosynaptic reflex arc, which continuously regulates the chewing's power. This reflex arc is the neural substrate of the so-called masseter reflex, too.

Now we look up the supranuclear innervation of the trigeminal motor nucleus with that of the other cranial motor nerves together. As a main rule, *the motor*

cranial nerves have bilateral supranuclear innervation, i.e., they receive both contralateral crossed fibres and ipsilateral non-crossed fibres, too, from the higher motor centres. For this reason, unilateral supranuclear lesions mostly do not cause serious symptoms, while the remaining ipsilateral control works also one's own satisfactorily. There are - however - *three interesting exceptions* from below the main rule, which concern some parts of the *motor nucleus of the Vth, VIIth and XIIth* cranial nerves. These nuclear sections innervating certain muscles *receive exclusively crossed supranuclear fibres from the contralateral side*. In such cases, the supranuclear lesions cause symptoms on the contralesional side, while the nuclear and/or peripheral lesions do it on the ipsilesional side (Table 1).

Technique of examination:

Motor part of CN V: after the temporal and masseter muscles have been inspected at rest (atrophy?), the patient is asked to open his/her mouth (jaw deviation?), move the jaw to right and to left, to backwards and to forwards, then clench the teeth; and while he/she is doing this, the examiner palpates the chewing muscles (strength? tone?).

Sensory part of CN V: test the three divisions of the trigeminal nerve on both sides

- for sensation of light touch using a whisp of cotton,
- for sensation of pain using a freshly disinfected safety pin or other suitable sharp object,
- for sensations of temperature using tubes containing hot and cold water or a tuning fork heated and cooled with flowing tapwater, and
- for recognition of the discriminative sensations (see below!) using figures and other symbols written on the skin of the face with a blunt device (graphaesthesia or dermolexia).

Remember: in addition to the peripheral sensory divisions there are nuclear or segmental divisions of the trigeminal nerve, too, which show an „onion-like“ concentric structure (Figure 8). Sensory disturbances distributed according to this type often occur in vertebrobasilar TIAs and strokes.

Corneal (trigemino-facial) reflex: ask the patient to look up and away. From the other side, touch the limbus of the cornea lightly with a gently twisted wisp of cotton. The normal reaction is a bilaterally (!) brisk blinking response evoked from either side. Repeat on the other side.

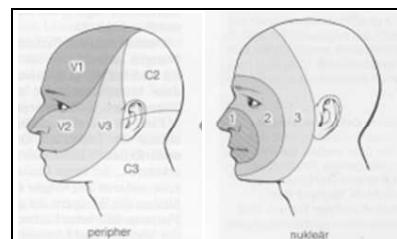


Figure 8
The well-known peripheral (links) and the nuclear or segmental (rights) divisions of the CN V
After Masuhr KF, and Neumann M (1992), modified.

Table 1
Some peculiarities of lesions of the Vth, VIIth and XIIth motor cranial nerves

	Supranuclear or central (upper motor neuron) lesion		Nuclear and/or peripheral (lower motor neuron) lesion	
	Involved muscles	Symptoms	Involved muscles	Symptoms
CN V th	External pterygoideal muscle on the contralesional side.	By opening of mouth jaw deviation to the contralesional side.	All of the ipsilesional masticatory muscles.	Visible and palpable atrophy of temporal and masseter muscles; by opening of mouth jaw deviation to the ipsilesional side.
CN VII th	The mimic muscles around the mouth on the contralesional side of the face.	The forehead and periorbital muscles of both sides function well, but the nasolabial sulcus get smooth, the angle of mouth stands lower and at teeth showing lags behind on the contralesional side	All of the muscles of facial expression on the ipsilesional side of the face (<i>prosopoplegia</i>).	<i>Lagophthalmus</i> ; the wrinkles of forehead and the nasolabial sulcus get smooth, eye closure and teeth showing weakened.
CN XII th	Genioglossus muscle on the contralesional side (acting with its counter-part together, protrudes the tongue).	Neither atrophy, nor fasciculation; the tip of the protruded tongue deviates to the contralesional side.	All of the muscles of the ipsilesional half of the tongue.	The ipsilesional half of the tongue shows atrophy and fasciculation. When attempted to put it out, the tip of tongue deviates to the ipsilesional side.

Normally: Mass and strength of the chewing muscles are preserved. No atrophy of temporal and masseter muscles is observed; no jaw deviation is seen, when the patient is opening his/her mouth. The patient reports bilaterally equal sensations in all the three (peripheral and segmental) divisions of the trigeminal nerve evoked by light touch (deep sensibility), pinprick or thermic stimuli (superficial sensibility). He/she recognizes figures and other symbols written on the skin of the face (discriminative sensibility - dermolexia) correctly. The corneal reflex evoked from either side is bilateral brisk blinking reaction.

CN VII. Facial nerve

The VIIth cranial nerve consists of two parts:

- A.) the genuine facial nerve and
- B.) the intermedius nerve.

A.) **The genuine facial nerve** arises from the *nucleus motorius nervi facialis* in the caudal pons, and contains pure motor fibres for the muscles of facial expression and also function as the efferent limb of the corneal reflex and the acoustic (stapedius) reflex. The fibres of the genuine facial nerve loop around the abducens nucleus forming the *genu internum* of the facial nerve. Thereafter they accompany by the fibres of intermedius nerve coming from three different sources (see below) and they step out together from the brainstem into the subarachnoidal space of the cerebellopontine angle, then into the internal auditory meatus. Here they are in the company of the cochlear and vestibular nerve as well as the internal auditory artery. From here the facial nerve steps over into its own canal (facial or Fallopian canal).

B.) **The intermedius nerve** (Wrisberg's nerve) is composed from 3 substituents and subserves the following functions:

- taste perception from the anterior two-thirds of the tongue (→ *chorda tympani* → *ganglion geniculi* → *nucleus tractus solitarii*→);
- somatosensory perception from some parts of the external auditory canal and eardrum, from over part of the pinna and from certain mastoid region (→ *ganglion geniculi* → *nucleus sensorius principalis nervi trigemini*(!) or *nucleus tractus spinalis descendens nervi trigemini*(!)→);
- parasympathetic secretomotor innervation (*nucleus salivatorius superior* →) of the
 - lacrimal gland (→ *n. petrosus superficialis maior* → *ganglion sphenopalatinum* → *n. lacrimalis*) and the
 - submandibular and sublingual salivary glands (→ *chorda tympani*→ *n. mandibularis* → *ganglion submandibulare* and *ganglion sublinguale*).

The Fallopian canal is Z-shaped, and up to its exit point (i.e. the mastoidal foramen) it is approximately 3 cms long osseous passage in the temporal bone, which can be divided into labyrinthine, tympanic, and mastoidal segments. Inside

the canal, three branches arise from the nerve trunk: the petrosal major nerve, the stapedian nerve and the chorda tympani. Extracranially, the facial nerve has five major branches: these are the temporal, zygomatic, buccal, marginal mandibular and cervical branches.

Supranuclear innervation for the facial movements arises from two sources. Corticobulbar (pyramidal) projections from the motor cortex (precentral gyrus) through the genu of the internal capsule are the major pathway for the *voluntary* facial movements. The facial expression is, however, also controlled by the limbic system and some subcortical structures, too, which structures play a role in expressing strong emotions on the face *involuntarily*. The voluntary and involuntary pathways can be also separately damaged. It occurs, that despite the severe weakness around the mouth with supranuclear facial palsy, the mouth may actually move better than normally for emotional triggers (hypermimia). In case of the bilateral damage of the voluntary motor pathways the face may be markedly over-expressive and may not reflect the patient's consciously perceived emotions (pseudobulbar affect).

Technique of examination:

First we observe *at rest*, if the face is symmetrical? Are the forehead wrinkles and nasolabial sulci of the same depths, the palpebral apertures equally wide and is the blinking synchronous on both sides? Is the symmetry preserved during speaking, smiling and frowning, too? - However, subtle asymmetry is common, and its normality can usually be established by looking at a previous photo of the patient.

At testing, have the patient look up (elevating the eyebrows and creasing the forehead - frontalis muscle), have forcibly close the eyes and resist the examiner's attempt to open them (orbicularis oculi), show his/her teeth (buccinator muscle), and purse lips or fill his/her cheeks with air with the lips tightly closed (orbicularis oris muscle).

Gustatory exam: the examiner can use a cotton tip applicator dipped in a solution that is sweet, salty, sour, bitter or tasteless. Apply the test solution to one side then the other side of the protruded tongue. Take care not to make it spread to the other side. The patient should tell his/her decision on the taste speechless, before he/she pulls back his/her tongue: he/she can show the answer on a suitably prepared table. Between the tests the patient should rinse out the mouth thoroughly. The taste sensation can be normal, diminished (*hypogeusia*) or absent (*ageusia*).

Normally: At rest, the face is symmetrical: forehead wrinkles and nasolabial sulci are of the same depths, palpebral apertures are equally wide and blinking is synchronous on both sides.

At testing, furrowing brows, closing eyelids (also against resistance) and showing teeth is performed symmetrically and with a good muscle strength. Mimicking movements of face (smiling, frowning, etc.) are symmetric, too.

Gustatory exam: the patient reports that the basic tastes (sweet, acid, bitter, salty, tasteless) cause sensations of the same intensity on the two half of anterior 2/3 of the tongue.

Pathologically:

A.) *The upper motor neuron lesion* of the facial nerve (i.e. *central type facial lesion*) is one of the most frequent and most important clinical signs, which is often present in many kinds of CNS diseases. The part of the facial motor nucleus which innervates the perioral muscles, has an exclusive unilateral, contralateral supranuclear innervation. Therefore in case of an unilateral supranuclear lesion, only the lower half of the face will be paralysed on the contralesional side (Table 1). The periorbital and forehead muscles function well, but the nasolabial sulcus gets smooth, the angle of mouth stands lower and lags behind while teeth showing (Figure 9A).

B.) The clinical picture of a *lower motor neuron lesion* (i.e. *peripheral type facial lesion*) can be caused either

B.1.) by damage of the motor nucleus, or

B.2.) by damage of the peripheral part of the nerve.

Ad B.1: An isolated **nuclear lesion of the facial nerve** is rather uncommon due to the proximity of many sensory and motor pathways running through the brainstem. Other signs of neurological damage (hemiparesis, hemihypesthesia, gaze palsy, etc.) are also present, when the facial nerve is affected at this level.

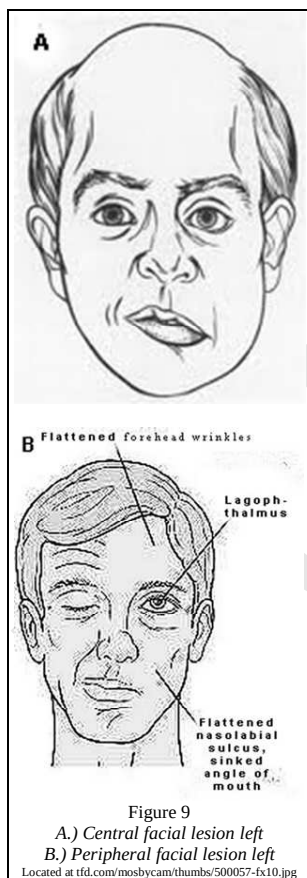
Ad B.2: The complete **peripheral facial lesion** involves all of the muscles of facial expression on the ipsilesional side of the face (*prosopoplegia*). Because of the weakened eye closure the palpebral aperture is wider than that of on the normal side (*lagophthalmus*), the wrinkles of forehead and the nasolabial sulcus are smooth, and the teeth showing and lips pursing are weakened (Figure 9B). These motor symptoms could associate with further sensorial and secretorial disturbances, too.

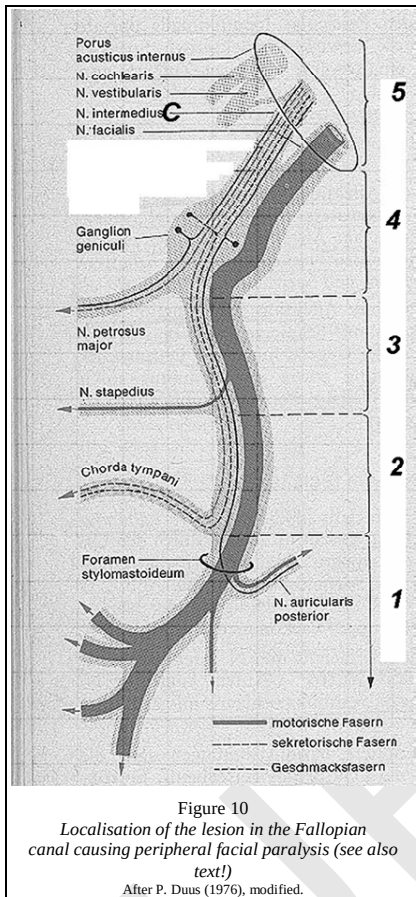
Analysis of the above mentioned symptoms provides a more precise *topical localisation of the causative noxa* (see Figure 10):

1.) If the lesion is located at or near to the level of the stylomastoid foramen, then occurs prosopoplegia alone.

2.) If the lesion includes the arising of the Chorda tympani: prosopoplegia + hypo- or ageusia.

3.) If the lesion includes the origin of the stapedius nerve: all of the foregoing symptoms + hyperacusis (perception of sound as excessively loud and irritating on the side of damage, because of failure of the acoustic reflex).





4.) If the lesion contains the arising of the greater superficial petrosal nerve: all of the previous symptoms + *xerophthalmia* (dry eye because the failure of tear secretion).

5.) If the lesion is located in the internal auditory canal: all of the foregoing symptoms + tinnitus, hearing defect, vertigo, nystagmus, etc.

The most common form of the peripheral facial lesion is **Bell's palsy**. It is an idiopathic condition that may be resulted by viral infection, induced inflammatory swelling of the facial nerve in the Fallopian canal. The swelling can press the nerve, resulting in damage by direct effects and by impairing the blood circulation in the *vasa nervorum*. The paralysis of the mimicking muscles usually becomes complete within a few hours. The patient may complain about moderate pain in the external auditory canal and over the mastoid region, due to the irritation of the somatic nerve fibres. Most cases of the uncomplicated Bell's palsy recover quite well. In its most severe form, the infarction of the nerve may occur followed by a prolonged and often incomplete process of regeneration. This is more common when a longer course of the nerve is affected.

In some cases, facial palsy is produced by a very clear infection of the geniculate ganglion with Herpes zoster (**Herpes zoster oticus** or **Ramsay Hunt syndrome**). It associates with ear pain and vesicles on the tympanic membrane and the outer auditory canal. The facial weakness or paralysis is caused by swelling. **Lyme's disease** also could cause facial palsy, which is sometimes bilateral.

CN VIII. Cochleo-Vestibular or Stato-Acoustic nerve

The VIIIth cranial nerve consists of two parts:

- A. Cochlear or Acoustic nerve, and
- B. Vestibular or Static nerve.

A.) As for the **Cochlear nerve**, mostly two questions are asked in the neurological examination:

- 1.) Is the hearing impaired?
- 2.) If yes, is the impairment of sensory-neural or conductive nature?

To answer these questions, the following **screening tests** can be applied:

Ad 1.) Understanding and **repeating** well-known, **whispered words** of 2-3 syllables can be performed without difficulty

- normally from a distance of 6 m,
- pathologically only from a distance of 5 m → ½m or directly in ear (*hypacusis*) or not at all (*anacusis or surditas*).

The examiner should ask the patient to close his/her eyes during the test in order to prevent lip reading.

Ad 2.) The **tuning fork tests** (Weber's, Rinne's and Schwabach's) make it possible to differentiate between the conductive deafness (caused by the diseases of the external or middle ear) and perceptive or sensory-neural deafness (caused by the diseases of the inner ear or the nerves).

Weber's test: compares the bone conductions of both ears of the patient. The test result is termed in normal case „infinite“ („∞,“) because sound of vibrating tuning fork placed on the vertex should be heard equally in both ears as if it would come from the infinite. (Pathologically, sound is „lateralized“: with unilateral sensory-neural damage it is heard better in the ear with normal acuity, and in case of conducted deafness it is lateralized to the side of the diseased ear (!); the latter phenomenon is the so-called „*tuning fork paradox*“).

Rinne's test compares the air conduction and the bone conduction of the same ear. The vibrating tuning fork first is held in front of external auditory meatus (air conduction), then placed firmly on mastoid process (bone conduction). Then, the intensities perceived by the patient at the two places are to be compared. Air conduction is more intense - *defined „positive“* - in normal persons and patients suffering from sensory-neural deafness. Bone conduction is more intense - *defined „negative“* - in patients with conduction deafness (middle or outer ear disease).

Schwabach's test makes a comparison between bone conduction of the patient and the examiner (supposing that the examiner has a normal hearing). The vibrating tuning fork is placed alternately on the mastoid process of the patient and of the examiner. If the patient can no longer hear the sound even though the examiner can hear it, the test's result is termed „*shortened*“ and it is indicative of a sensoryneural loss. If the examiner stops hearing while the patient can still hear it, the test's result is termed „*lengthened*“ and suggests a conductive hearing loss. If neither shortening, nor lengthening can be stated, the result of the test is „*normal*“.

In bilateral and mixed cases of sensoryneural and conductive hearing loss the tuning fork tests can give inconclusive results.

B.) Signs referring to **vestibular state** see under „Coordination“!

CN IX-X. Glossopharyngeal and Vagal nerves

These nerves are connected to each another by many structures, such as the same brain stem nuclei (nucleus ambiguus, dorsal motor nucleus of the vagus, nucleus solitarius, sensorius principalis and spinal nucleus of the trigeminal nerve), the side-to-side exit from the brainstem, the common further course through the jugular foramen in the periphery, and - last but not least - the common or

overlapping functions. Their damage also occurs often together. Clinically, these two nerves are lumped together. Despite their fairly complex anatomy and functions, they provide rather a few opportunities to be explored by simple physical examination. These are the motor innervation of the pharyngeal and laryngeal muscles, the sensations of the pharynx and the tasting on the posterior one-third of the tongue.

Technique of examination:

- First listen to the patient's voice, if it is clear and adequately loud? Is his/her speech well articulated?
- Ask the patient to swallow a mouthful of water. Is the swallowing undisturbed?
- Ask him/her to open the mouth and say „Aaah!“. Watch the position and movements of the soft palate and the pharynx: are the arches of the soft palate symmetrical? Is the uvula in the midline? Does the patient rise the softpalate equally on both side at vocalisation?
- The gustatory examination can be performed together with the similar test of the facial nerve (see above!).
- Test the soft palatal reflex and the pharyngeal gag reflex, which reflexes involve both the sensory and motor components of the glossopharyngeal and vagal nerve.
 - The **soft palatal reflex** is obtained by touching the basal part of the anterior pharyngeal arch with the tongue depressor, which results in the elevation of the soft palate and ipsilateral deviation of the uvula.
 - The **pharyngeal gag reflex** occurs in response to touching the posterior wall of the pharynx, and results in tongue retraction as well as elevation and constriction of the pharyngeal musculature.

Each stimulus may cause nausea, or possibly vomiting, too.

Normally: The patient's voice is clear and powerful, his/her speech is well articulated, the swallowing is undisturbed. The uvula is in midline, the arches of soft palate are symmetrical, the palate rises at vocalization vively. Both the soft palatal reflex and the pharyngeal gag reflex are brisk on each side.

Pathologically:

Lesions of CN IX. and CN X. may play a central role in disturbances of phonation (*dysphonia*, *aphonia*), articulation (*dysarthria*, *anarthria*) and swallowing (*dysphagia*, *aphagia*).

Lesions affecting the glossopharyngeal nerve result in loss of taste in the posterior third of the tongue and loss of pain and touch sensations in the same area and in the soft palate and the pharyngeal walls.

In unilateral paralysis of CN IX. and/or CN X., the arch of the soft palate stands lower on the ipsilesional side, and the uvula deviates toward the normal side (!), because that side is pulled up higher. With bilateral lesion, the soft palate hangs down, elevates weakly at vocalisation or stimulation or it does not elevate at all, and there will be marked nasal air escape.

Unilateral paralysis of the recurrent laryngeal branch of vagus nerve results in hoarseness of voice. Bilateral paralysis results in stridor and requires immediate attention to prevent aspiration and its attendant complications.

The acute (!) bilateral lesion of the vagus is incompatible with life.

CN XI. Accessory nerve

The pure motor CN XI has two components:

1.) The smaller **cranial part (*Accessorius vagi*)** arises from the cells of the lowest portion of the nucleus ambiguus. Immediately after leaving the brain stem, it connects with the spinal part for a short distance, then branches off and connects with the vagus nerve. Axons deriving from this central portion of CN XI. innervate the intrinsic laryngeal muscles.

2.) The greater **spinal part (*Accessorius spinalis*)** arises in the first 5 to 6 cervical spinal segments from the lateral portion of the ventral horn. The spinal roots ascend laterally, at the back of denticulate ligament and enter the skull through the foramen magnum. Here - after the short linkage with the central portion - the spinal part turns laterally to pass through the jugular foramen along with CN IX. and CN X. The spinal accessory nerve provides the motor innervation of the sternocleidomastoid muscle (SCM) and the upper half of the trapezius muscle.

Recent studies suggest that in the majority of cases, the cranial component does not make any distinct connection to the spinal component. Therefore the cranial part might be considered as belonging rather to the vagus nerve than to the spinal part.

Technique of examination:

- First, the bulk and outline of the muscles should be observed: atrophy or asymmetry of the SCM muscle can be detected by looking at the patient from the front, and those of the trapezius muscle by looking at him/her from behind.
- Now ask the patient to shrug shoulders against resistance.
- Ask him/her to turn his/her head against resistance. Watch and palpate the SCM muscle on the opposite side (remember, that the SCM tilts and bends the head to the own side, but it turns the head to the opposite side!).

Normally: Sternomastoid and trapezius muscles are bilaterally symmetrical and free from any atrophy. Shoulder shrugging and head turning are carried out well and powerfully also against resistance on each side.

Pathologically:

Atrophy is common after the damage of the nerve and fasciculations may be seen especially in motor neuron diseases. An **isolated damage** of the accessory nerve is rare; if yet, it is mainly caused by surgery.

A common injury of the CN IX, CN X. and CN XI. occurs in the **jugular foramen syndrome** (Vernet). Its symptoms are aspiration, difficulty in phonation,

ipsilateral motor paralysis of the vocal cord, soft palate, superior pharyngeal constrictor, sternocleidomastoid, and trapezius muscles. The most frequent causes are trauma (basilar skull fracture) or tumor growth.

The tone of the SCM muscle is often affected by **spasmodic torticollis**. In this condition, there is an excessive activity of unknown etiology in one (rarely both) of the SCMs. This results in an obvious deviation of head position: the subject's head is spasmodically turned away from the involved muscle which usually shows hypertrophy.

By bending the head forward, the two SCM muscles act together symmetrically. **Bilateral weakness** of SCMs may prevent the patient from lifting his/her head off a pillow and the head may be inclined posteriorly due to the lack of flexor tone. Bilateral weakness suggests muscle or neuromuscular disease. If the head is fixed in a reclined position, the powerful contraction of the SCM muscles will elevate the chest and - e.g., in the state of a serious dyspnoea - the SCMs work as *accessory respiratory muscles*.

CN XII. Hypoglossal nerve

The nucleus of the CN XII. is in the lower medulla, in the most medial and superficial position from all of the nuclei of the CNs. The nerve leaves the cranial cavity through its own, hypoglossal canal. The pure motor hypoglossal nerve supplies motor innervation for all the extrinsic and intrinsic muscles of the tongue. The nucleus has bilateral supranuclear innervation except the portion innervating the genioglossus muscle which receives only contralateral supranuclear fibres. The genioglossus muscle - acting with its counterpart together - protrudes the tongue.

Technique of examination:

- Listen to the articulation of the patient's speech: is there any dysarthria?
- Observe the tongue as it lies in the mouth: is there any atrophy and/or fasciculation? (Fasciculations of the tongue are fine, random, multifocal twitches of muscle. They are evaluated by observing the tongue while it is at rest in the floor of the mouth. Protrusion frequently causes undulant movements or a fine tremor in the normal tongue, which can obscure or mimic fasciculations).
- Ask the patient to:
 - protrude the tongue (is there a deviation to any side?), then
 - move the tongue from side to side (can it be freely moved in all direction?).

Normally: The speech of patient is well articulated. No atrophy or fasciculation is to be seen on the tongue lying in the mouth. The tip of the protruded tongue shows in the middle, it can be freely moved in all direction.

Pathologically:

In case of a **central (supranuclear) lesion** of the hypoglossal nerve, the tip of the protruded tongue deviates to the contralesional side, but neither atrophy, nor

fasciculation is to be seen (Table 1). Eliciting factor may be any noxa damaging the corticobulbar tract.

In case of a **peripheral paralysis** of the CN XII., the ipsilesional half of the tongue shows atrophy and fasciculation; when attempted to protrude it, the tip of the tongue deviates to the ipsilesional side. These symptoms can be caused by both the lesion of the nerve itself (e.g., hypoglossal neurilemmoma, nasopharyngeal tumor along the base of the skull, basal skull fracture, etc.) and by the damage of the nucleus in the brain stem (e.g., medullary stroke, motor neuron disease, bulbar poliomyelitis, etc.).

As for the **articulation**, weakness of the tongue manifests itself as a slurring of speech. The patient complains that his/her tongue feels „thick”, „heavy”, or „clumsy”. Lingual sounds (i.e., l’s, t’s, d’s, n’s, r’s, etc.) are slurred. A repetitive or complex lingual sound (e.g., „la la la la” or „methodist artillery”) often shows impediment when any part of the vocal apparatus is affected (e.g., Broca’s region, motor cortex, basal ganglia, cerebellum, brain stem, hypoglossal nucleus or nerve).

Motor system

The examination of the motor system includes:

- A.) Inspection (Involuntary movements? Mass and volume of muscles?)
- B.) Muscle tone
- C.) Muscle strength

A.) Inspection

Pathological involuntary movements are normally not present. Mass, volume and consistence of musculature are normal, its symmetry is preserved. No fasciculation. No muscular atrophy (with particular attention to the hands, shoulders, pelvic girdle muscles and thighs). No pseudohypertrophy (with special regard to the sural muscles).

B.) Muscle tone

The muscle tone is **normal**, when the repeated flexion and extension of wrist, elbow, ankle and knee evoke a small, continuous resistance to passive movement. The examiner uses his/her own „proprioceptive” sense to assess whether muscular tone of the patient is normal, hypo- or hypertensive.

Pathologically, the muscle tone may be decreased (*flaccide*) or increased (*spastic or rigid*).

Muscular hypotension or flaccidity is mostly caused by peripheral nerve lesion or cerebellar disease and often associates with decreased or missing deep reflexes, paresis, atrophy, possibly fasciculation.

Muscular hypertension is of two sorts: spasticity and rigidity.

Spasticity is an increase in muscle tone due to a velocity-dependent hyperexcitability of the stretch reflex. The resistance of a spastic limb reminds of that of a rubber cord or of a steel spring. Spasticity is indicative of the upper motor

neuron damage. It is usually accompanied by pyramidal signs, hyperreflexia, clonus and the clasp-knife phenomenon (if a spastic muscle - either in extension or flexion - continues to be stretched, at a certain degree ensues a sudden relaxation like to that of a closing or opening clasp knife, which has initial resistance and then closes or opens more easily).

Rigidity is a state of hypertonia where muscle resistance occurs throughout the entire range of motion independently of direction and velocity. Rigidity frequently occurs in lesions of the basal ganglia, clinically in parkinsonism. In the majority of cases, the patients have „smooth rigidity”, also termed „leadpipe rigidity” (when the examiner bends the patient’s limb feels a resistance similar to that as if he/she would bend a leadpipe). Another form of rigidity is the so-called *cogwheel phenomenon*. This is a circular jerking rigidity occurring in both flexion and extension, in a background of tremor. The feeling in the examiner’s fingers placed on the contracting or relaxing biceps muscle of patient is resembling to that which arises at the movement of badly fitting cogwheels.

C.) Muscle strength

Screening

Normally, the handgrip is bilaterally powerful. The Barré and Mingazzini tests are well performed.

Barré’s test: the patient is asked to stand for 20-30 seconds with both arms straight forward, palms up, and eyes closed. Then he/she will be instructed to keep the arms still while the examiner presses them briskly downward. After this fatiguing exercise, a patient with pyramidal tract lesion will not be able to maintain contralesionally extension and supination but falls and „drifts to pronation”. Nowadays the test is often carried out with patient lying in supine position with arms raised straight in a 45° angle.

Mingazzini’s manoeuvre: the patient lies with closed eyes in supine position with both legs raised straight in a 45° angle from the bed. Ankles are dorsiflexed at 90°. The position is held for as long as possible to a maximum of 30 seconds. The test is abnormal if the leg begins to fall.

More detailed examination

If it is necessary, the strength of several muscle groups can be separately tested (Table 2). In this way, one can obtain important contribution to solve the question, whether the muscle weakness is caused by a central or radicular or peripheral nerve lesion. The strength of the following movements is often tested (in parentheses: the innervating radix, and the peripheral nerve and/or the innervated muscle).

Table 2 <i>British Medical Research Council (MRC) scale for Grading Muscle Strength</i>	
Grade	Description
0/5	No muscle movement
1/5	Visible muscle movement, but no movement at the joint
2/5	Movement at the joint, but not against gravity
3/5	Movement against gravity, but not against added resistance
4/5	Movement against resistance, but less than normal
5/5	Normal strength

Upper extremity

Flexion at the elbow (C5, C6, biceps);
Extension at the elbow (C6, C7, C8, triceps);
Extension at the wrist (C6, C7, C8, radial nerve);
Squeeze two of your fingers as hard as possible („grip,” C7, C8, T1);
Finger abduction (C8, T1, ulnar nerve);
Opposition of the thumb (C8, T1, median nerve).

Lower extremity

Flexion at the hip (L2, L3, L4, iliopsoas);
Adduction at the hips (L2, L3, L4, adductors);
Abduction at the hips (L4, L5, S1, gluteus medius and minimus);
Extension at the hips (S1, gluteus maximus);
Extension at the knee (L2, L3, L4, quadriceps);
Flexion at the knee (L4, L5, S1, S2, hamstrings);
Dorsiflexion at the ankle (L4, L5);
Dorsiflexion of hallux (L5, extensor hallucis longus);
Plantar flexion (S1).

Sensory system

One part (the greater one) of sensorial impulses *becomes conscious*, while the other part (first of all those traveling in the spinocerebellar tracts to the cerebellum) *remains unconscious*.

The *conscious sensory modalities* are transported by 2 major ascending pathways:

- 1.) the **spinothalamic tracts (ST)** which are components of the spinal anterolateral system, and
- 2.) the **dorsal column (or Goll-Burdach) - medial lemniscus (DCML)** system.

Both pathways comprise 3 neurons with 2 connections and 1 crossing of the 2nd order neurons.

The **sensory modalities for the ST** system are pain and temperature (lateral ST), and the rough touch - pressure sense (anterior ST). The latter is of little importance in humans. The modalities for ST are termed **superficial** or **vital** or **protopathic** senses.

The **sensory modalities for DCML** system are the light touch, vibration and position sense, as well as the discriminatory or integrative sensations as tactile direction, two-point discrimination, graphesthesia, stereognosis and double simultaneous stimulation. For apperception of the discriminatory sense, not only the DCML system but also the parietal cortex must be intact. The modalities bounded to DCML are termed **deep** or **gnostic** or **epicritic** sense.

Warning: the sensory exam mostly provides very useful informations for the localization diagnosis. On the other hand, it is the most subjective part of the entire neurological exam, and the patient's responses may occasionally be difficult to interpret.

General proposals:

- 1.) The patient's eyes should be closed during the testing.
- 2.) Compare:
 - a.) symmetrical areas on the two sides of the body (hemi-syndrome?!);
 - b.) distal and proximal areas of each extremity (polyneuropathy?!);
 - c.) if necessary, neighbouring or near dermatomes (radicular syndrome?!);
 - d.) as a base for comparison could serve a presumably intact area of the body, e.g. the forehead of patient.

The innervation by the peripheral nerves (Figure 11) and that by the spinal roots (Figure 12) see more precisely in the anatomical atlases!

Some „guide-post” radicular dermatomes: Shoulders (C4); Inner and outer aspects of the forearms (C6 and T1); Thumbs and little fingers (C6 and C8); Mamillae (T4); Umbilicus (T10); Inguinal furrows (T12-L1 boundary line); Front of both thighs (L2-3); Medial and lateral aspects of both calves (L4 and L5); Big toes (L5); Little toes (S1); Riding-breeches (more correctly: riding-path) sensory area (S3→coccyg.).

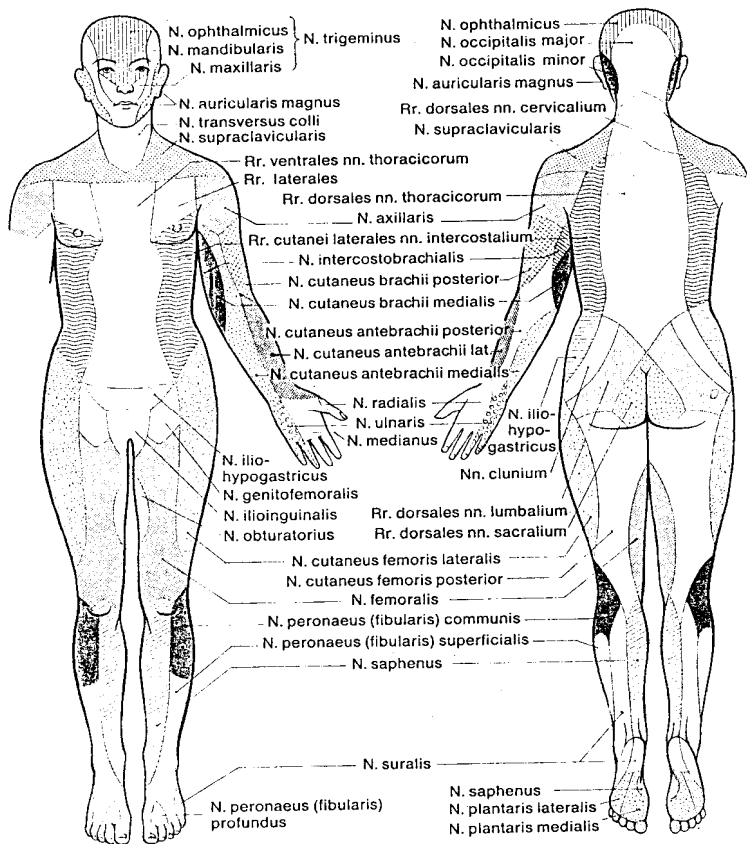


Figure 11
Peripheral innervation

After P. Duus (1976), modified.

Exam Tests

1.) The **ST is examined** by testing pain and temperature.

Pain is tested by using a sharp object such as a freshly disinfected safety pin or a freshly broken wooden stick which is disposable. Terminology: *hyp- and analgesia*: they don't need explaining; *hyperpathia*: an upgraded or increased pain sensation; *allodynia*: pain due to a stimulus which does not normally provoke pain; *anesthesia dolorosa*: pain in an area or region which is anesthetic.

Temperature can be tested by means of tubes containing hot and cold water or by a tuning fork heated and cooled with flowing tapwater. The temperature testing is often omitted if the test of pain sensation is normal. Terminology: *thermohyp- and thermoanesthesia*; *thermoperversion*: the patient is feeling some kind of thermal sensation but is not able to distinguish heat and cold stimuli from each other.

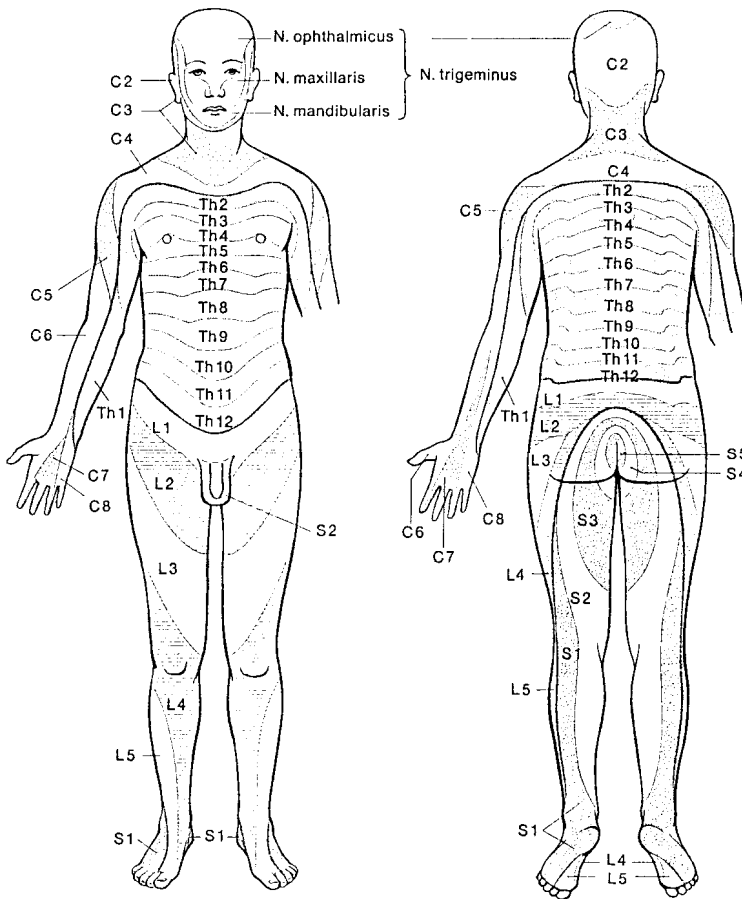


Figure 12
 Radicular dermatomal innervation

After P. Duus (1976), modified.

2.) The DCML examination

Light touch is tested by touching the skin with a wisp of cotton. Note, that many authors in the English-speaking countries count light touch both among ST and DCML systems. Terminology: *tactile hyp- or anesthesia*; *hyperesthesia*: increased sensitivity to stimulation including both diminished threshold to any stimulus and an increased response to stimuli that are normally recognized; *paresthesia*: an abnormal but not unpleasant sensation, whether spontaneous or evoked; *dysesthesia*: also an abnormal sensation that is - however - always considered to be unpleasant.

Vibration sense (*pallesthesia*) is tested by using a 128 Hz tuning fork placing the stem (!) of the the vibrating (!) instrument over a bone or bony prominence. It

is advisable to begin with, e.g., the distal interphalangeal joint of the big toes and that of the index fingers. The examiner can detect in pallesthesia any deficits by varying the force of vibration and comparing the patient to him/herself. If vibration sense is impaired distally, proceed proximally: medial malleoli, tibiae, anterior superior iliac spines, costae, clavicles, wrists, elbows, spinous processes. Terminology: *pallhypesthesia*, *pallanesthesia*.

Position sense (*proprioception*) is tested by holding a big toe away from the other toes to avoid friction. Now show the watching patient „up” and „down” bending, then perform the test with the eyes closed: move the toe slightly up or down by chance, and ask about the direction of the movement. The patient should be able to detect 2-3° of movement of a toe and 1° of that of a finger. If he/she can't accurately detect the distal movements, then progressively test a more proximal joint. Both conscious and unconscious proprioception manifest themselves in performances of the coordination of the movement.

Discriminative sensations require for their apperception the functional integrity of both the DCML system and the parietal cortex. Therefore, if the vibration sense and the position sense - as signalling qualities for DCML - are normal, then discriminative testing is well suited to explore the parietal cortex; such a testing is, however, meaningless, if the above mentioned DCML qualities are disturbed. The most important discriminatory senses are the following:

a.) *The tactile movement* tests the patient's ability to detect the direction of a 2-3 cm line-like cutaneous stimulus. The patient with closed eyes should recognize 4 directions: „up”, „down”, „right” and „left”. A significant insufficiency indicates a lesion in the contralateral primary somatosensory cortex. In case of repeated exams, the comparison of the error ratios makes a quantitative, longitudinal analysis possible.

b.) *Two-point discrimination* is preferentially applied in situations where more quantitative data is needed, such as following the progression of a cortical lesion. Use an opened paper clip to touch the patient's skin in one place or alternatively, in two places simultaneously. Alternate by chance and ask the patient to identify „one” or „two”. Find the minimal distance at which the patient can discriminate. Normally, this distance is 1-3 mm on a fingertip or on the lip and 5-6 cm on the back. Disturbance of the 2-point discrimination indicates a lesion in the contralateral primary somatosensory cortex.

c.) *Graphesthesia* (or *dermolexia*) is the ability of a person to identify with eyes closed characters that are written on his/her skin using a dull device, e.g., the blunt end of a pen or pencil. The examiner draws a large number in the patient's either palm or on the front of either thigh, and asks the patient to identify the number. Then the test is repeated on the other side of the body. The failure of this test is called *agraphesthesia* and indicates a lesion of the contralateral parietal cortex.

d.) *Stereognosis* is the ability to identify familiar objects (coin, paper clip, pencil, etc.) that are placed both in the right and left hand when the eyes are closed. Then the patient is asked to identify the objects without looking at them. The inability to do this called *astereognosis* and indicates parietal lobe dysfunction. Stereognosis is an alternative to graphesthesia.

e.) *Double simultaneous stimulation*: normally, the patient should be able to attend to and identify a tactile stimulus that is applied to both sides of his/her body at the same time with the eyes closed. Pathologically, when the patient is touched on the right or left he/she correctly identifies the side touched, but when both sides are touched simultaneously, he/she neglects the stimulus on the side which is contralaterally to a posterior parietal lobe lesion. This phenomenon is called *extinction* or *simultanagnosia*.

Main types of sensory disturbances:

The knowledge of the location, size and shape of area involved by some kind of sensory disturbance often make possible inferences regarding the localization and sometimes the nature of causing factor, too.

A.) The main types of the **peripheral nerve lesions** are the following:

- 1.) A sensory deficit from a *single peripheral nerve* lesion will be in the distribution of that peripheral nerve (in „anatomical atlas-position” - See Figure 11!).
- 2.) A sensory deficit from a *polyneuropathy* will have a distal and symmetrical „knee-socks and ball-glove” distribution, because the longest axons are the most vulnerable.
- 3.) A sensory deficit from a *spinal root or spinal nerve* lesion will be in a dermatomal distribution (Figure 12).

B.) Sensory deficits from **spinal cord lesions** have 3 main subtypes:

- 1.) „Transverse lesion” from *complete transection* of the cord: under the transverse level bilateral, total anesthesia and total spastic para- or tetraplegia.
- 2.) Brown-Séquard syndrome from *hemisection*: ipsilateral spastic mono- or hemiplegia and loss of DCML sense with contralateral loss of ST sense.
- 3.) Syringomyelia-type sensory disturbance from *lesion around the central canal* of the cord: bilateral segmental ST loss, i.e., analgesia and thermoanesthesia with preserved DCML qualities, in accordance with the size of the lesion damaging the anterior white commissure. (A historical case: Gaius Mucius Scaevola B.C. 508).

Spinal cord diseases go characteristically with a sensory level which has a great value in determining the segmental localization of the pathogenic process. Don't forget, that the vertebrae and the spinal cord segments having the identical serial number don't coincide: the latter lie higher, because the spinal cord is considerably shorter than the spinal canal, so the terminal cone of the cord is in the altitude of vertebra L II.

C.) A **brainstem lesion** can result in *crossed or alternating sensory deficit* (affecting one side of the face and the opposite side of the body). Lower brainstem and spinal cord lesions might cause *sensory dissociation*, too, which means one sensory system (e.g. ST) is affected without the other one (without DCML).

D.) The lesion of a **brain hemisphere** and - in the majority of cases - that of the brainstem, too, results in a *hemi-syndrome*, i.e., sensory deficit on the same side of face and body.

Reflexes

Reflexes are the most objective part of the neurologic examination. They require minimal cooperation on the part of the patient and produce a response that can be objectively evaluated by the examiner.

Reflexes involving the cranial nerves (e.g., pupillary, corneal, jaw-jerk, soft palate and gag reflex, etc.) were mentioned previously. In this chapter, the evaluation of *commonly tested reflexes of the spinal cord* will be discussed.

From clinical point of view, the **reflexes can be divided** into the following groups:

- 1.) Deep (or tendon or own) reflexes: the receptors and the effectors are included in the same muscle; these reflexes are monosynaptic.
- 2.) Superficial (or skin and mucosal or strange) reflexes: the receptors and effectors lie separated in the skin and/or mucosa, and in the muscle, respectively; these reflexes are polysynaptic.
- 3.) Pyramidal signs/reflexes.
- 4.) Primitive reflexes or liberation signs.

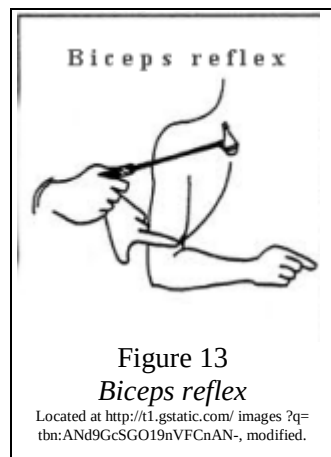
1.) Deep (or tendon or own) reflexes

The patient should be informed, relaxed and properly positioned before starting. Recumbency is the most advisable position for examining deep reflexes. Note: the spinal segment which plays the key role is indicated with bold and underlined characters in each reflex.

Biceps reflex: have the patient rest the forearm on the abdomen and place your thumb or index finger over the biceps tendon applying slight pressure (Figure 13). Now strike your finger with the reflex hammer and observe the arm movement. Then repeat on the opposite arm and compare the two. This reflex tests the **C5** and **C6** nerve roots.

(Brachio-)Radialis reflex: have the patient's forearm in unchanged position and strike the styloid process of radius about 2-3 cm above the wrist. Watch the flexion and supination of the forearm. This tests the **C5** and **C6** nerve roots.

Ulnar reflex (pronator reflex): the position of the upper limb is identical with that by biceps and radial reflex. When the styloid process of the ulna is struck, there is extension and ulnar abduction of the wrist. This tests the **C8** and **T1** nerve roots.



Triceps reflex: hold the arm with elbow flexed at 90° and just below the level of the shoulder, close to the chest of the patient. Find the triceps tendon insertion on the olecranon and strike the tendon 1-2 cm above its insertion. Observe the movement of the forearm and repeat it on the other side. This tests the C6 and **C7** nerve roots.

Patellar reflex: have the patient lie with the knee flexed. Locate the quadriceps tendon (*Ligamentum patellae*) below the kneecap and place one hand above the knee on the patient's thigh and strike the patellar tendon firmly. Watch the moving of the lower leg and feel the contraction in the thigh muscles. Repeat and observe it with the other leg and compare them. This tests the L3 and **L4** nerve roots.

Achilles or ankle reflex: grasp the patient's foot, dorsiflex it up to 90° at the ankle and strike the Achilles tendon. Watch and feel for plantar flexion at the ankle. This tests the **S1** and S2 nerve roots.

Clonus: the clonus is a rhythmic, permanent jerking; if the reflexes are hyperactive, test for ankle and patella clonus!

Ankle clonus: support the knee in a partly flexed position. With the patient relaxed, quickly dorsiflex the foot and keep the pull until a few seconds. Observe for rhythmic jerks.

Patella clonus is less common than ankle clonus. The

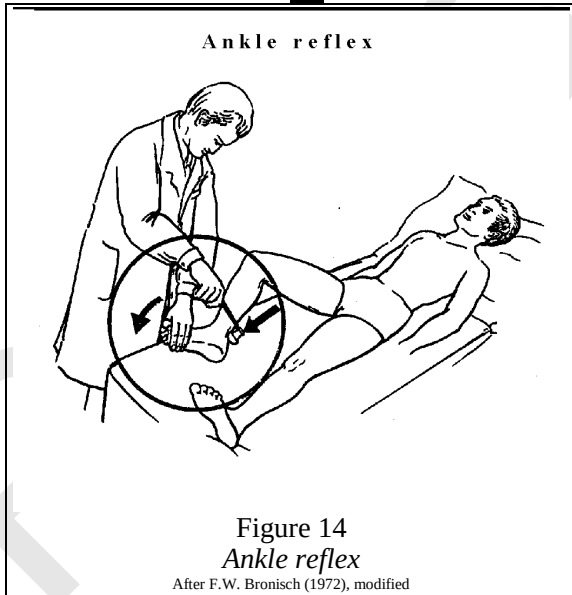
examiner holds the patient's patella between thumb and index finger and sharply pulls down patella. If clonus is present then there is a sustained rhythmical contraction of the quadriceps as long as the examiner maintains downward pressure on the patella. The clonus is usually abnormal although a few beats of non-sustained transient clonus may occasionally be seen.

The deep reflexes can be graded on a 0 - 4+ scale (Table 3).

Normally, the reflexes should be *symmetrical*.

Lesions that **damage** either sensory or motor limb of a spinal segmental **reflex arc** at any level, will *diminish or abolish* that reflex.

Most of the descending pathways have a tonic inhibitory effect on spinal reflexes. For this reason, the net result of lesions that **damage the descending tracts** is facilitation, i.e., the spinal reflexes become *hyper-active* (possibly after a short period of diaschisis associated with hypoactivity).



Some individuals especially young anxious people may have brisk reflexes which are not necessarily pathological. There should be, however, no asymmetry!

Before concluding that reflexes are absent, reinforce it by performing an isometric contraction of other muscles: e.g. clench teeth or oppose limb for upper extremity reflexes or pull hooked fingers apart for lower extremity reflexes (Jendrassik manoeuvre - see Figure 15!).

Table 3
Deep Reflex Grading Scale

Grade	Description
0	Absent
1+ or +	Hypoactive
2+ or ++	„Normal”
3+ or +++	Hyperactive without clonus
4+ or ++++	Hyperactive with clonus

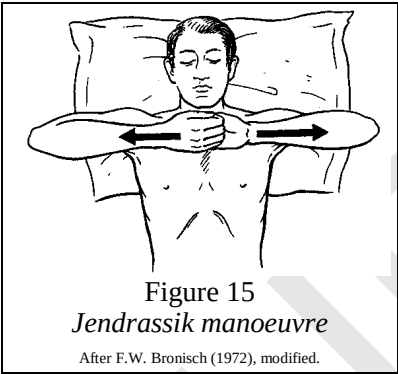


Figure 15
Jendrassik manoeuvre

After F.W. Bronisch (1972), modified.

After acute lesions, spinal reflexes often pass through an initial stage of hypoactivity. This stage has been called „spinal shock” or „diaschisis” and is more severe in proportion to the degree of damage.

When the above listed monosynaptic spinal segmental reflexes are intact, integrity of the following functions is confirmed: proprioceptive innervation, motor supply, and cortical input to the corresponding spinal segme

2.) *Superficial (or skin and mucosal or strange) reflexes*

Superficial reflexes are motor responses to scraping of the skin. These are polysynaptic segmental reflex responses that - similarly as the deep reflexes - indicate the integrity of cutaneous innervation and the corresponding motor outflow, i.e., the integrity of the spinal part of the reflex-arc. However, in superficial reflexes - in contrast to deep ones - *the sensory signal* has to not only reach the spinal cord, but also *must ascend the cord to reach the brain*. The motor limb then has to descend the spinal cord to reach the motor neurons. This polysynaptic reflex *can thus be abolished at several levels*, among others also by lesions that interrupt the pathways between the brain and spinal cord. In such conditions, while the superficial reflexes are diminished or abolished, the deep reflexes become exaggerated and pyramidal signs arise.

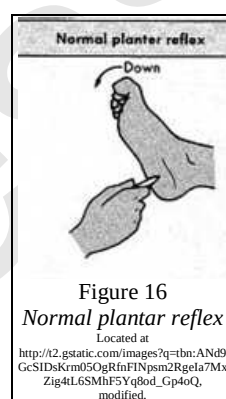
The superficial reflexes are **graded** simply as *present* or *absent*, although markedly asymmetrical responses should be considered abnormal as well.

Abdominal (skin) reflexes (T7-12) mean the contractions of the abdominal muscles on stimulation of the abdominal skin. It is stimulated by tangential scratching the skin toward the umbilicus, drawing lines according to the diagonals of the upper (T7-8), middle (T9-10) and lower (T11-12) sextants of the abdominal surface. Because the umbilicus and the scraping pin move in opposite directions, a mechanical effect can be excluded. Always the reflexes of identical segments should be compared. Absence of abdominal reflexes is an inconclusive finding in multiparas, in patients with obesity, lax abdominal musculature, cicatrized abdomen after repeated surgical procedures, etc.

Cremasteric reflex (S1): this is elicited by scratching the skin of the medial thigh, which should produce a brisk and brief elevation of the testis on that side. Because of the less favourable venous drainage, the left testis is somewhat greater and heavier than the right one. For this reason, the reflex elevation of the left testis is physiologically a bit slower than that of the right one.

Plantar reflex (S1-2) can be elicited by scratching the sole of the foot from the heel along the lateral aspect of the sole and then across the ball of the foot to the base of the great toe. This normally results in flexion of the great toe and all of the toes. The evaluation of the plantar response can be complicated by voluntary withdrawal responses to plantar stimulation (defensive withdrawal).

Anal „wink” (S4-5): this is a contraction of the external anal sphincter when the skin near the anal opening is scratched. This is often abolished in spinal cord damage (along with other superficial reflexes).



3.) Pyramidal signs/reflexes

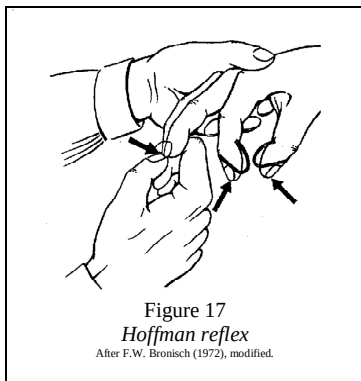
The diagnostic importance of the pyramidal signs is well-known, scarcely needs an explanation.

Mayer's reflex (basal joint reflex): when firm passive flexion of the 3rd, 4th or 5th finger is made at the metacarpophalangeal joint, normally it elicits an opposition and adduction of the thumb with flexion at the metacarpophalangeal and extension at the interphalangeal joint. The reflex is present normally but is diminished or absent in pyramidal lesion.

Léri's sign: in passive flexion of fingers and forcible wrist flexion there is a reflex flexion of the elbow joint. This reflex flexion is diminished or absent in pyramidal lesion.

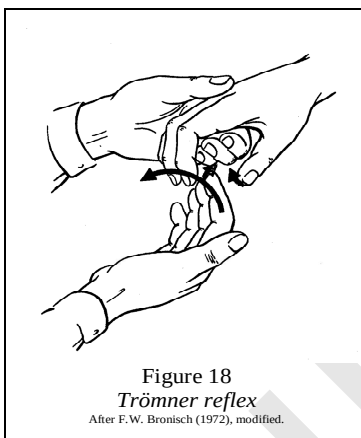
Both Mayer's and Léri's reflexes are to be considered pyramidal signs if they are diminished or absent unilaterally; the diagnostic value of the bilaterally absent reflexes is uncertain.

Hoffmann's response (Figure 17): grasp the patient's middle finger between your thumb and index finger, and tell him/her to relax. Press downward into the patient's fingernail with the tip of your thumbnail and drag it outward until it

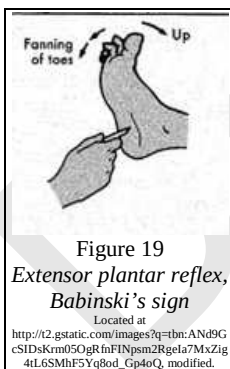


„clicks” over the end of the patient’s nail. If the other fingers flex when you do this, it’s called a positive Hoffman’s response. Perform the test on both hands.

Trömner’s reflex (Figure 18): with the fingers of the patient partially flexed, the tapping of the volar aspect of the tip of the middle or index finger causes flexion of all four fingers and thumb on the affected side. This phenomenon is associated with pyramidal tract lesions.



Babinski sign: if the plantar reflex results in dorsiflexion of the great toe, then Babinski sign is present which strongly suggests an upper motor neuron lesion. Dorsiflexion of the big toe (*Babinski I.*) also may be associated with fanning out of the other toes (*Babinski II.*). Most neurologists consider this phenomenon to be a not essential accompaniment of a very important abnormal response. At eliciting the Babinski sign, flexion of the knee and hip (with the ankle dorsi-flexion together: *triflexion*) may occur in the paretic leg associated with urinary and fecal incontinence (*en-mass reflex*). Babinski is a normal reflex in infants which is suppressed by supraspinal activity sometime before 6 months of age.



Chaddock’s reflex: stimulation below the external malleolus (i.e.,stroking with the stem of the reflex-hammer along the outer edge of the foot) causes extension of the great toe, in lesions of the pyramidal tract.

Oppenheim reflex: stroking downward along the medial side of the tibia causes dorsiflexion of the big toe in pyramidal tract disease.

Rossolimo’s reflex: an exaggerated plantar flexion of the toes can be elicited on tapping their plantar surface on the side affected by pyramidal lesion.

4.) Primitive reflexes or „frontal release signs”

As a rule, these signs are generally absent in adults. When present in the adult, they sign **diffuse cerebral damage**, particularly but not solely that of the frontal

lobes (hence the term „frontal lobe release signs”). For this reason, primitive reflexes are primarily tested in patients with suspected brain injury.

These reflexes and signs can be divided in the following groups:

- a.) Sucking reflex group
- b.) Grasping reflex group
- c.) Mesial line reflexes
- d.) Forced crying and laughing, echo phenomena, paratonia

a.) Sucking reflex group:

Sucking reflex: sucking movements of the lips elicited by touching the lips or the skin near the mouth.

Rooting reflex: the patient turns his/her head toward anything that strokes his/her cheek or mouth, searching for the object (for the breast) by moving his head in steadily decreasing arcs until the object is found.

Bulldog reflex: when a tongue-depressor is placed between the patient’s teeth, he/she clamps his/her jaws upon it and will not let it go.

b.) Grasp reflex group:

Grasp reflex: flexion or clenching of the fingers or toes on stimulation of the palm or sole. It usually affects both hands, even when the lesion is unilateral.

Forced grasping is an exaggerated form of the grasp reflex in which the patient is unable to release the caught object, e.g., the examiner’s hand. In such a way, the patient could be dragged from his/her bed out as well.

Visually elicited grasp reflex: a direct tactile stimulation isn’t necessary; the patient shows involuntary, repeated grasping of visible objects within reach of his/her hands, despite being commanded not to grab.

c.) Mesial line reflexes

Glabellar reflex is a deep reflex of the orbicular oculi muscles. It can be elicited by repetitive tapping on the forehead. Normally, subjects blink in response to the first taps. If the blinking persists, this is abnormal.

Jaw reflex (jaw jerk reflex; masseter reflex) is a deep reflex of the masticatory muscles (Figure 20). It appears as a closure of the mouth caused by a downward blow on the passively hanging chin. This reflex is normal in healthy persons, but it is hyperactive in diffuse corticospinal tract lesions.

Mediopubic (mediopubic) reflex can be elicited by percussion on the examiner’s index finger placed on the symphysis of the patient. The normal response is abdominal muscle contraction and adduction of the knees. In diffuse pyramidal lesion, this reflex is exaggerated and becomes wider with a bilateral hip flexion.

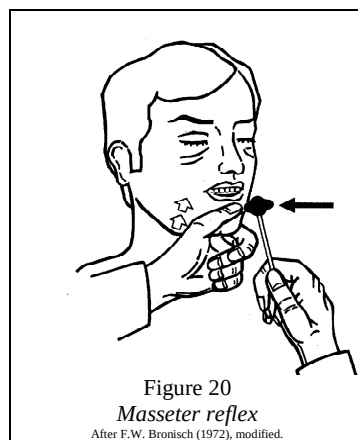


Figure 20
Masseter reflex

After F.W. Bronisch (1972), modified.

d.) Forced (compulsive) crying and laughing, echo phenomena, paratonia

Forced crying and laughing: with bilateral damage to the motor cortex (particularly when the cortico-bulbar system is heavily affected), inhibitory control of the complex emotional expression reflexes becomes defective. These patients cry or laugh with minimal emotional provocation without feeling a true distress or happiness. They consider these emotional symptoms strange from him/herselves and do not understand why they are crying or laughing. These complex emotional reflexes are subserved by the limbic system and are normally under inhibitory modulation by the neocortex.

Echo phenomena: patients with diffuse cortical lesion could show *perseveration*, inappropriately repeating the just heard words and sentences (*echolalia*) or - rarely - repeating the movements seen in the environment (*echopraxia*). These are caused by the inability to inhibit ongoing activity.

Paratonia (Frontal resistance; Gegenhalten) is a peculiar form of perseveration. It manifests itself when the examiner attempts to passively move a part of the patient's body. In such a case the patient is unable to relax, still it could appear as if he/she would willfully resist the passive movement.

Coordination, Balance and Gait

The most important area of the brain from the point of view of coordination is the **cerebellum**.

It has 3 functional subdivisions:

1.) The vestibulocerebellum consists of the connection between the vestibular system and the flocculonodular lobe. Its dysfunction results in nystagmus, truncal instability (titubation), and truncal ataxia.

2.) The spinocerebellum consists of the connections between the proprioceptive and cutaneous information coming from the spinal cord to the vermis and paravermis regions with corrective feedback to the muscles of truncal stability and gait. Its dysfunction causes gait and truncal ataxia.

Clinically, the ataxic syndromes caused by vestibulocerebellar and spinocerebellar disease are lumped together and are called **midline or equilibratory (gait) ataxias**. The hallmarks of these midline ataxic syndromes are truncal instability manifested by titubation (tremor of the trunk in an antero-posterior plane at 3-4 Hz) and gait ataxia (wide based, irregular steps).

3.) The cerebrocerebellum consists of connections from the cerebral (predominantly motor) cortex to the cerebellar hemispheres then back to the cerebral cortex. It is important in motor planning. Dysfunction of the cerebellar hemispheres results in ataxia of speech (scanning dysarthria) and ataxia of the extremities (ipsilateral to the dysfunctional cerebellar hemisphere!). The findings are muscular hypotonia, decomposition of movement, dysmetria, and difficulty with rapid alternating movements (dysdiadochokinesia).

One might from the first minute **observe the spontaneous movements** of the patient.

Normally, his/her gait, the start and stop of walking, turning, sitting down and raising from sitting position are easy-flowing, well-balanced, harmonious and carried out with a normal speed.

For **screening the disorders of coordination** the following tests are used:

A.) Exam to sensory, vestibulocerebellar and spinocerebellar ataxias:

A1. Romberg's test: the patient stands stable with feet together („attention!") with eyes open, then with eyes closed for 5-10 seconds.

Normally, the patient performs the test without any difficulties.

Pathologically: a patient with significant proprioceptive loss or some degree of vestibular dysfunction could be able to stand still with eyes open because vision will compensate for the imbalance. Therefore if he/she becomes unstable or falls after closing his/her eyes, it indicates proprioceptive or vestibular disorder and the test is said to be „positive". If the instability is before and after eye-closure alike, it points to cerebellar disease.

A2. Bárány pointing test: the examiner and the patient stand facing each other. The patient extends his/her arms and points with the index fingers to the examiner's index fingers (the latter remain fixed during the test). The patient is now asked to close the eyes and locate the position of examiner's fingers by sense of touch, too. After that he/she is asked to lower the hands and arms to vertically hanging position, then advance the arms again and bring his/her index fingers into contact with those of the examiner.

Normally, this task can be performed exactly or near to exactly.

Pathologically: in the presence of vestibular or cerebellar lesion, the patient's fingers deviate to the side of lesion.

A3. Blind walking: the patient can keep the straight direction by walking with closed eyes and even by „heel-to-toe walking", too.

Normally: a younger patient should well perform walking on his/her toes and heels in a straight line (and even jumping in place on each foot, and doing a shallow knee bend standing without support on either foot).

In pathological case, the patient deviates from the straight line to the right or to the left.

B.) Exam to cerebrotocerebellar ataxia:

B1. Rapid alternating movements

B1.1. Fine finger movements. The patient taps his thumb with the index finger of the same hand several times in a row.

Normally: the movement has a large amplitude with little variability and has a speed of about 2 taps/sec.

Pathologically: a cerebellar lesion produces irregular, imprecise movements ipsilesionally, while a pyramidal lesion causes slowing and decrease in amplitude of the repetitive movement contralesionally, but the movement remains regular.

B1.2. Forearm roll: The patient rapidly rolls each forearm around the other for 5 to 10 seconds in each direction.

Normally, the arms rotate around one another symmetrically.

Pathologically: when the response is abnormal, the healthy arm orbits around the abnormal one like a satellite.

B2. Point-to-point movements

B2.1. Finger-to-nose: the patient moves his/her index finger from his/her nose to the examiner's finger as the examiner moves his finger to new positions and tests accuracy at the furthest position of the arm.

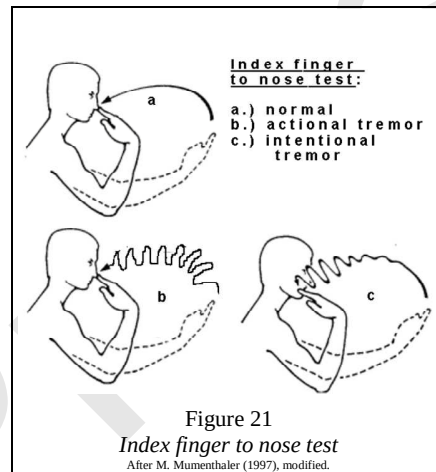
B2.2. Heel-to-knee: the patient places his/her heel on the opposite knee then runs the heel down the shin to the ankle.

B2.3. Toe-to-finger: the patient touches his/her toe to the examiner's finger repetitively as the examiner moves his/her finger to new positions.

Normally, all these tasks are performed with exact pointing and in a smooth coordinated fashion.

Pathologically, the pointings are wrong, the movements incoordinated and dysmetrical, and intention tremor* can occur.

(*The intention tremor is triggered by aiming for a target. It starts at the beginning of a purposeful voluntary movement, its amplitude steadily increases in course of the movement and reaches a maximum just before the target (Figure 21). The aim of the movement is often prevented by this disorder.)



B3. Rebound phenomenon

The patient is asked to move a limb against resistance. When the resistance is suddenly removed, the limb *normally* moves a short distance in the desired direction and then *rebounds* (jerks back in the opposite direction); the limb of a patient with *cerebellar dysfunction* flies, however, uncontrolled in this situation and the patient can strike him/herself because the rebound is insufficient or absent. Contrary to some prevalent belief, already Gordon **Holmes** (1917) pointed out that **the rebound phenomenon is**

- (1) present in normal limbs,
- (2) exaggerated in spastic limbs, and
- (3) absent in limbs affected by cerebellar disease.

C.) Other causes of coordination disorders

Although incoordination is primarily a symptom of cerebellar disease, there are also other causes such as the followings:

C1. Sensory dysfunction: loss of large myelinated sensory axons serving proprioception. This causes a *sensory ataxia*. To differential diagnosis: loss of position sense on the sensory exam and a positive Romberg.

C2. Peripheral vestibular dysfunction: To differential diagnosis: vertigo; intense vegetative symptoms; the falling tendency in Romberg, the dispointing in Bárány, the deviation by blind walking and the slow component of nystagmus equally have the same direction.

C3. Corticospinal tract disease: can cause incoordination of the distal extremities. To differential diagnosis: pyramidal signs.

Vegetative functions

Here we rely on historical data and information gathered from our problem-oriented observations.

Vital signs can reflect abnormalities in the nervous system, too.

Respiration: Evaluation of the respiratory rate and pattern is particularly important in the evaluation of patients with disturbed consciousness. Namely, each level of bilateral damage to the brainstem - from the diencephalon through the mesencephalon and pons to the medulla - causes a characteristic pathological pattern of breathing (see in capitel of coma!).

Pulse: Increased intracranial pressure as a rule slows (*bradycardia*) but rarely accelerates (*tachycardia*) the pulse. Arrhythmias, particularly sinus arrhythmias, and nonspecific ST-T wave changes are frequently seen on electrocardiograms of persons with subarachnoid hemorrhage or stroke. Atrial fibrillation is one of the most important risk factors of systemic embolization.

Blood pressure: Increased *intracranial pressure* and *recent stroke* are usually associated with increased systemic blood pressure. In stroke the blood pressure will revert to baseline level over hours to days after the stroke without need of therapeutic intervention. Attempts to lower the blood pressure, unless it is at an extreme high level ($\geq 220/110$ mm Hg), can be counter-productive by producing hypotension that results in further ischemia. — Medullary or upper spinal cord lesions often drop blood pressure to very low levels.

Orthostatic hypotension: Sympathetic nerves increase the vasomotor tone in the lower portion of the body when going from lying to sitting or standing position. If this does not happen, hypotension ensues. The symptoms: dizziness, blurred vision possibly to momentary blindness (*obscuration*), distortions in hearing possibly tinnitus, generalized numbness and collapse. — The assessment of orthostatic hypotension (*Schellong's test*) requires measuring blood pressure and pulse rate in every minute at least for 5-5 minutes both in the recumbent and upright position. We are looking for a drop of at least 20 mmHg of systolic pressure, or a decrease of at least 10 mmHg of the diastolic pressure within three minutes of standing. Symptoms of lightheadedness, faintness and even syncope could associate to the orthostasis. The increase in pulse rate is normally not more than 10-20/min. A higher value points to (relative) hypovolemia. — As for the diagnosis of orthostasis, the Schellong's test can be considered as a screening procedure, but the up-to-date method is the tilt-table testing.

Dermographism can be observed in about 4-5 percent of the general population within very few minutes after scratching or pressing the person's skin. This situation is given, e.g., after eliciting of the abdominal skin reflexes. The symptom is a red (*dermographia rubra*) or rarely white (*dermographia alba*), urticaria-like swelling on the place of the former scratching. The causing factor is histamine released by mast cells having particularly weak cell membrane in these patients. This weak membrane easily and rapidly breaks down under physical pressure causing an allergic-like reaction.

About the **urinary and anal sphincter control and sexual functions** of the patient we gather information from the history. A rectal examination might be indicated in patients with tendency to incontinence. In case of further problems, consultation with an adequate specialists (urologist, gynecologist, sexologist, surgeon, etc.) is inevitable.

About the **trophic state of skin, mucous membranes and nails** we obtain direct impressions during the physical examination. Dystrophic changes occasionally worsening to ulceration can mostly be found in generalized neuropathies (diabetes, alcoholism, malnutrition, etc.). Inadequate, exaggerated or absent **vaso-, sudo- and pilomotor reactions** indicate functional disturbances of the vegetative nervous system.

Normally, the respiratory rate and pattern, pulse rate and blood pressure are between physiological limits. There isn't pathologic orthostatic hypotension. There isn't urticaria-like dermographism. According to the patient's history, the urinary and anal sphincter controls are preserved and the sexual functions are intact. The trophic state of common integument and the vaso-, sudo- and pilomotor reactions are normal.

The normal neurologic status (Collected from the previous segments)

Mental state

The patient has an orderly **appearance** and **cooperates** adequately.

The **consciousness state** is normal: he/she is alert, awake and **oriented** with respect to place, time and person.

His/her **behavior** is appropriate. No suspicion of anxiety, depression, hallucination or delusion.

Meningeal signs

No sign of meningeal irritation can be detected: the head can be freely moved (no cervical rigidity), Kernig's or Brudzinski's signs can not be elicited.

Cranial nerves

CN I. Olfactory nerve

The patient refers no subjective smell disturbance.

He/she identifies correctly the odors on each side and considers the odor intensities to be bilaterally equal.

CN II. Optic nerve

The *visual acuity (visus)* - with correction of refraction failures if necessary - is bilaterally 1.0 (Kettesy eye chart) or 20/20 (Snellen eye chart), respectively;

The *visual field* - tested with confrontation - is full and the *optic fundus* is normal on each side.

CNs III - IV- VI. Oculomotor, Abducens and Trochlear nerve

Both smooth pursuit and saccadic eye movements are free, precise and conjugate. No ptosis, no double vision, no nystagmus.

The pupils are equal, round, reactive to light both directly and consensually, as well as to accommodation and (forced) convergence.

CN V. Trigeminal nerve

Mass and strength of chewing muscles are preserved: no atrophy of temporal and masseter muscles; no jaw deviation when opening mouth.

The patient reports bilaterally equal sensations in all the three (peripheral and segmental) divisions of the trigeminal nerve evoked by light touch (deep sensibility), pinprick or thermic stimuli (superficial sensibility). He/she correctly recognizes figures and other symbols written on the skin of the face (discriminative sensibility - dermolexia).

The corneal reflex evoked from either side consists of an always bilateral brisk blinking reaction.

CN VII. Facial nerve

At rest, the face is symmetrical: forehead wrinkles and nasolabial sulci bilaterally are of the same depths, palpebral apertures are equally wide and blinking is synchronous on both sides.

At testing, furrowing brows, closing eyelids (also against resistance) and showing teeth is performed symmetrically and with a good muscle strength. Mimicking movements of face (smiling, frowning, etc.) are symmetric, too.

Gustatory exam: the patient recognizes the basic tastes (sweet, acid, bitter, salty, tasteless) correctly and reports that they cause sensations of the same intensity on the two halves of the tongue.

CN VIII. Cochleo-Vestibular or Stato-Acoustic nerve

The patient can understand and repeat well-known, 2-3-syllables *whispered words* from a distance of 6 m without difficulty.

Tuning fork tests: Weber: infinite; Rinné: positive; Schwabach: normal.

Signs referring to vestibular state see under "Coordination"!

CN IX-X. Glossopharyngeal and Vagal nerve

The patient's voice is clear and powerful, his/her speech is well articulated, the swallowing undisturbed.

The uvula is in midline, arches of soft palate are symmetrical, the palate rises at vocalization vividly.

Both the soft palatal reflex and the pharyngeal gag reflex are brisk on each side.

CN XI. Accessory nerve

Sternomastoid and trapezius muscles are bilaterally symmetrical and free from any atrophy.

Shoulder shrugging and head turning are carried out well and powerfully also against resistance on each side.

CN XII. Hypoglossal nerve

The speech of patient is well articulated.

On the tongue lying in the mouth no atrophy or fasciculation is to be seen.

The tip of the protruded tongue shows in the middle, it can be freely moved in all directions.

Motor system

At inspection:

Pathological involuntary movements are not present, mass and volume of musculature are normal.

No fasciculation.

No muscular atrophy (with particular attention to the hands, shoulders, pelvic girdle muscles and thighs).

No pseudohypertrophy (with special regard to the sural muscles).

Muscle tone is normal (when the repeated flexion and extension of wrist, elbow, ankle and knee evoke a small, continuous resistance to passive movement). Neither muscular hypotonia nor muscular hypertonia (spasticity or rigidity) can be found.

Muscle strength screening:

The handgrip is bilaterally powerful,

Barré's and Mingazzini's tests are well performed.

Sensory system

The patient reports no subjective sensory disturbance (pain, dysesthesia, paresthesia, etc.).

He/she signals and identifies correctly sensations evoked by pinprick, thermic stimuli (ST system) or light touch and vibration; his/her position sense is undisturbed, too (DCML system). He/she correctly recognizes figures and other symbols written on his/her skin (discriminative sensibility). The patient considers the intensity of sensations to be equal in the symmetrical areas on the two sides of the body and in the distal and proximal areas of each extremity.

Reflexes

The biceps, radialis, triceps and ulnar reflexes, as well as the the patellar and Achilles reflexes (deep reflexes) are normoactive and symmetrical. No clonus.

The abdominal skin -, cremasteric - and plantar reflexes (superficial reflexes) are surely elicitable and bilaterally symmetrical.

Mayer's and Léri's reflexes can be well elicited and are equally normoactive on both sides.

No pyramidal signs, no primitive reflexes.

Coordination, Balance and Gait

At inspection: the patient's gait, the start and stop of walking, turning, sitting down and raising from sitting position are easy-flowing, well-balanced, harmonious and carried out with a normal speed.

At screening to vestibulocerebellar, spinocerebellar and sensory ataxias:

The patient stands still in *Romberg position* with eyes closed, points exactly (or nearly exactly) to the examiner's index fingers in *Bárány's test*, and

can keep the straight direction at *blind walking* even by "heel-to-toe walking", too.

At screening to cerebrocerebellar ataxia:

The *rapid alternating movement* (fine finger movements, forearm roll, etc.) are quick, symmetrical and have a large amplitude with little variability.

The *point - to - point movements* (finger - to - nose, heel - to - knee, etc.) are performed with exact pointing and in a smooth coordinated fashion.

The *rebound phenomenon* works efficiently.

Other possible causes of coordination disorders (sensory disturbances, peripheral vestibular dysfunction, corticospinal tract disease, etc.) were also not detected.

Vegetative functions

The **vital signs**, i.e., the respiratory rate and pattern, blood pressure and pulse rate are between physiological limits.

No pathologic **orthostatic hypotension**.

No urticaria-like **dermographism**.

According to the patient's history, the urinary and fecal **sphincter controls** are preserved and the **sexual functions** are in order.

The **trophic state** of common integument and the **vaso-, sudo- and pilomotor reactions** are normal.

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The brief neurological examination of cooperating patient

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History

Family members

In case of neurological disorders data obtained from family members are very important. 80 % of the neurological disorders can be diagnosed by carefully elicited clinical history. As for some of these illnesses can be accompanied by the disturbances of consciousness (e.g. in case of epilepsy or head trauma), heteroanamnesis can help to diagnosis.

Family members may know such information, that the patient can not or do not want to tell us (problems in the family or at the workplace, urinary or sexual disorders). Besides the information obtained from family members, we should inform about the patient's life (e.g. birth, development, educational level, accidents) and collect facts related to disease progression (e.g. family problems or difficulties at work). Avoid taking heteroanamnesis in the presence of the patient.

The patient

Collect information about the patient's life, family, social situation and work, and gather facts about his/her condition before and after the illness is developed. Besides routine questioning (e.g. if he/she had any relevant disease in the past) ask if he/she had any surgical intervention, accident, head trauma, or if she/he experienced loss of consciousness at any time. Inform about endemic diseases: hypertension, diabetes and hyperlipidemia. Collect data about habits affecting the illness: smoking, coffee and alcohol consumption, medications and allergies. When questioning about the symptoms, try to put them in chronologic order (what was the first/second/third/... symptom and when did the patient experience it?). Medicines: Recording medicines taken by the patient is very important.

PQRST: you can use this acronym to assess diseases accompanied by pain

Provokes: factors triggering or alleviating the disease

Quality: the quality of the complaints (e.g. pulsating, sharp or pressing pain)

Region: the localization of the symptoms (head, face, trunk, extremities).

Severity: endurable, intolerable, increasing or continuous intensity, can the patient work while having the symptoms

Time course: continuous or temporary, when does the patient experience it or how long does it take, other symptoms (appetite, weight loss, menstrual cycle, urinary habits and defecation)

Inspection

While performing the physical examination, the patient should be undressed to the underwear. Take a look at his/her position while being rest and sitting, and observe his/her walk, too. Inspection can provide much information to the neurologists, e.g. the patient can have herpetic eruptions, cirrhosis, ascites, striae or neurofibromas. Examine the patient systematically from head to toe, by observing carefully the head, chest, abdomen and extremities. Pay attention to certain conditions, such as atrophy or fasciculation, which can be benign, but in most cases it is the symptom of motoneuron disease. Record every abnormality including internal symptoms too (e.g. edema of the lower extremities, cyanosis or anemia).

Physical examination

Neurological examination starts with the general medical examination. Internal diseases can be accompanied by neurological symptoms, and neurological diseases also can have internal complications, which can not be emphasized enough. On neurology wards there are no patients treated only with neurological disorders, but patients who have neurological symptoms dominating among the others. That is why neurological examination also includes body temperature measuring, chest auscultation, abdominal palpation, blood pressure and pulse measuring, the auscultation of cardiac and vascular murmurs, and the examination of the renal areas and the extremities (e.g. edema, pulse).

The examination can not be simplified to the algorithm listed below, but it can help to examine every patient carefully (and observe at least three parameters in every area):

Head: signs of trauma, neck stiffness and apertures (eyes, oral cavity, nose, ears).

Chest: body temperature (measured at least by palpation), blood pressure and pulse.

Abdomen: defense, parenchymal organs (liver and kidney), normal or overfilled bladder.

Extremities: position (outward rotation?), symmetry of movements (both spontaneous or pain-provoked), pathologic reflexes.

Brief neurological examination

The short examination of neurological patients involves the assessments of cranial nerves, mental state, reflexes, and sensory and motor systems.

During the examination of patients being able to walk follow this cranio-caudal sequence: cranial nerves, reflexes, sensory and motor functions. If you can not examine the patient in laying position, the reflexes can be evoked while the patient is sitting, too, but make sure that he/she is barefooted and undressed to underwear.

Cranial nerves: Can the patient sense odors bilaterally?

Vision: Ask the patient to cover one of his/her eyes while reading the newspaper held in his/her hands, or ask to count your fingers from the distance of one or two meters. The preliminary examination of the visual fields is based on the optico-palpebral reflex: move your hand suddenly from one side to the other and watch if the patient reacts with immediate eye-closure. Blindness may be hidden if affecting only one side and developed suddenly, and can be revealed by covering the other eye. Generally, unilateral blindness is caused by neurological or ophthalmological diseases, while bilateral blindness is typically caused by systemic illnesses, metabolic diseases or intoxication (except bilateral cortical blindness of vascular origin).

Cranial nerves III-IV-VI: Minimal anisocoria can be observed in healthy persons, too, but newly developed anisocoria should be investigated (ask for photos taken previously to decide whether it is a new symptom or not). Unilateral or bilateral ptosis is also an important sign, which can be noticed on the old photos, if it is developed earlier. Even the minimal dysfunction of the III-IV-VI cranial nerves can cause double vision, which is recognized by the patient immediately. If diplopia develops only when looking to lateral, mostly, the abducent nerve is damaged. If nystagmus is the only symptom, metabolic or pharmacological effect is suspected. Nystagmus is often caused by brainstem diseases and associated with other symptoms (e.g. truncal ataxia, deviation to one side, paresis, ataxic extremities with or without dizziness).

Cranial nerve V: It can be assessed by palpation of muscle. The investigation of the corneal reflex can be performed also on patients with disturbance of consciousness.

Cranial nerve VII: Face asymmetry is commonly seen in healthy people too (old photos). It is important to decide whether it is caused by the peripheral or the central palsy of the facial nerve. The peripheral type of facial palsy affects not only the ipsilateral forehead but also the periorbital and perioral muscles. The central type of lesion will result in asymmetry only by the ipsilateral mouth region (at rest and during innervations). The central type of facial nerve lesion is frequently accompanied with ipsilateral hemiparesis.

Cranial nerve VIII: Test sound perception by snapping your fingers simultaneously on both sides.

Cranial nerves IX-X: Dysarthria can be noticed immediately when taking the patient's medical history. This type of speech disorders reminds for "drunken" speech (brain stem, inferior cranial nerves). Always inform about swallowing liquids and solid foods.

Cranial nerve XII: The atrophy of the tongue (bilateral or unilateral) is always caused by organic disorders, and must be investigated carefully.

The tendon/proprioceptive reflexes: It can also be assessed in sitting position, when the side difference can be diagnosed too. We consider unilateral Mayer's, Léri's, Hoffmann's and Trömmner's reflexes as the result of pyramidal tract damage.

Sensory system: Side difference can be detected by touching the body with a piece of cotton. If the patient does not report major side differences, and the quality of sensation is approximately the same on both sides (face, hands and feet), sensory disturbances are not suspected.

Motor system: It can be assessed safely in GP's office too. Flexed walking posture, shambling, loss or decreased mimics suggest the diagnosis of parkinsonism. The so-called Wernicke-Mann posture (unilateral flexion in the upper and extension in the lower extremity) refers to previous vascular disease. Paresis can be assessed quickly by using the following method: the patient raises his/her arms towards with fingers stretched and **palms up**. If the patient can keep this position symmetrically for a certain period of time without pronation, and the handgrip is also powerful bilaterally, he/she is not likely to have proximal or distal paresis in the upper extremities. If the patient can squat and stand up with hands on the hip, or he/she can stand on his/her heels and toes without any side difference, paresis of the proximal and distal muscles can be excluded in the lower extremities, either.

Mental state

The orientation can be assessed with questioning the patient's orientation in time and place. Ask the patient to add two numbers, and before leaving the hospital room ask him/her again what the question was. Generally, patients with dementia do not realize the loss of cognitive functions, while patients with neurosis or pseudo-dementia are complaining about the progressive memory loss. Patients with dementia are usually uninterested, "colorless". Motor or sensory aphasia can be tested by observing the spontaneous speech, give simple commands and check if the patient can name his/her fingers.

Summary

In case of neurological diseases (especially if combined with temporary unconsciousness) information obtained from family members and witnesses is very important.

The patient should be undressed for examination, because it can reveal important clues for the diagnosis (e.g. traumas, rashes, signs of alcoholism).

In case of trauma the localization and extent of wounds should be recorded too, because it may have legal consequences. Always give the exact time of examination (record the minutes too). If possible, document the case by camera.

During neurological examination collect information about visual abilities (double vision, visual field lesions, impaired visual acuity), sensory functions (numbness, spontaneous pain), and motor functions (mono-, hemi- or paraparesis, involuntary movements).

Aphasia and dysarthria must be distinguished. If pain is the major symptom, use PQRST to establish the diagnosis.

Always perform the general medical examination before neurological testing and follow the cranio-caudal direction.

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The examination of non-cooperating patients

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History

When information can not be obtained from the patient directly due to unconsciousness or communication disturbances, the importance of reliable data on medical history and risk factors can not be emphasized enough.

Information should be collected not just about the previous diseases, such as hypertension, diabetes, cardiovascular or hematological disorders, infective or immunological conditions, but the medications too. Check, if the patient took abnormal amount of tablets than recommended (sleeping pills, sedatives, anticoagulants). Life habits are very important, because alcohol consumption or certain hepatic diseases alter the effects of medications, and smoking or obesity disposes to vascular disorders, too.

It should be investigated if the family members experienced any change in the patient's behavior, difficulty in his/her verbal communication. Did the patient complain about numbness, visual problems or double vision?

Inquire about epileptic seizures possibly happened in the past (epileptic seizures are often followed by Todd-paresis, which could be easily misdiagnosed as stroke!), migraine (atypical case with transient paresis!), head injuries (subdural hematoma can also be the cause of hemiparesis!), abnormal weight loss or symptoms referring to gastrointestinal disorders (recurrent diarrhea and obstipation), and suspicion for tumors (coughing, hemoptysis, blood-stained stool, urinary problems). Encephalitis might begin with fever, aphasia and consciousness disturbances. Brain metastasis can cause epileptic seizures and disorientation or disturbances of consciousness even if the patient was previously asymptomatic.

A detailed physical examination of non-cooperative patients *(Listed in craniocaudal sequence)*

Nuchal rigidity or neck stiffness can be caused not just by meningitis (vomitus, fever, headache, drowsiness), subarachnoidal hemorrhage (sudden, severe headache and photophobia, mostly following physical effort), but dehydration, spondylosis and parkinsonism, too.

The scalp should be investigated for head injuries, and the apertures (nostrils, ears) should be examined too (blood or cerebrospinal fluid?).

Is there any anisocoria (often seen after cataract's surgery!), xanthelasma palpebrarum (hypercholesterolemia), concentric gray area on the iris (hyperuricemia) or any sign of anemia (suspicion for tumors)?

Facial asymmetry can be assessed at rest and after activation. Does the patient have dentures, and if yes, does it cause any difficulty in breathing? (Usually, dentures should be removed.)

Can opticopalpebral reflex be evoked (eyelid closure after sudden exposure to subjects)?

If the patient is awake but does not cooperate adequately, provoke pain in the inner corners of both eyes, and look for the asymmetry of the facial movements and the movement of the upper and lower extremities. While touching the eye corners, observe the pulsation of the ophthalmic arteries. More intense pulsation on one side can be the result of internal carotid artery occlusion.

The yellowish discoloration of the sclera refers to hepatic disorders or alcoholism.

The conjugated deviation of eyeballs and the neglect of events happening only in one visual field refer to supratentorial stroke, while anisocoria, the divergence of eyeballs (the so called “postman-eye”: one eye is watching the house-address, while the other is focusing the letter), the pinpoint pupils (pons) and the nystagmus suggest the diagnosis of cerebrovascular insufficiency in the brainstem.

The examination of optic fundus requires skill. Retinal infarcts and cholesterol embolism are indirect signs of carotid stenosis or ulcerated plaques. *The ceasing venous pulsation is the early symptom of the increased intracranial pressure.* Papilla edema may refer to brain tumors, brain edema, subdural hematoma or cerebral venous sinus thrombosis. Vitreous or peripapillary hemorrhage (Terson syndrome) may suggest subarachnoidal hemorrhage.

Unilateral mydriasis is usually evoked by the damage of the oculomotor nerve on the affected side caused by the increased intracranial pressure. Slight pupillary reactions refer to midbrain lesion (e.g. in case of downward herniation of the midbrain into the foramen magnum). Pinpoint pupils are the signs of pontomedullary lesion.

Brainstem or internuclear tract damages can be investigated by injecting cold water to the ears. During the caloric reflex test, the patient’s head should be elevated with 30 degree. Inject at least 50 ml cold (icy) water slowly (approximately for 30 sec) into the patient’s ear. Wait 1 minute. If the brainstem is intact, after one minute the eyeballs deviate slowly to the side of the injection. Chloroethyl solution is also used for vestibular caloric stimulation.

The glabellar reflex is elicited by repeated tapping on the forehead. Normally, in healthy individuals the reflex habituates and blinking is stopped after the first several taps. Persisting blinking is seen in patients with Parkinsonism or diseases affecting the frontal area.

The cyanosis of lips, tachypnea and dyspnea are the signs of respiratory insufficiency. Heavy smokers have brownish skin, yellowish moustache and fingers.

Sucking reflex can be evoked by touching the lips and palmomental reflex is elicited by stroking the palmar side of the thumb (results in twitch of the chin muscle).

Sudden onset of bilateral perioral paresthesia might refer to vertebrobasilar insufficiency.

The examination of tongue may reveal anemia, chronic gastritis or dehydration. To assess dysphagia the examination of pharyngeal and palatal reflexes and swallowing is very important.

Perform carotid auscultation at three areas: above the clavicles, besides the thyroid cartilage, and near the mandibular angles. This method can help you to differentiate from transferring of cardiac murmurs. Document the presence of murmurs thoroughly, and always perform heart and lung auscultation, too. Listen the subclavian arteries in the supraclavicular regions. Abnormal sounds can be provoked often by elevating the patient's arm.

Measure blood pressure on both sides in sitting and standing position. If there is difference of at least 20-30 mmHg between the recorded values, subclavian stenosis or subclavian steal syndrome is suspected.

In case of new onset of hemiparesis the fingers are in slightly flexed position, spontaneous movements are absent. As for the lack of the fine movements cornification develops on the affected fingers, which is noticeable if compared to the other, not affected side.

In case of bed-ridden, non-communicating patients, the abdominal palpation is very important and can reveal dehydration ("crackling" sound). By thorough palpation of the abdomen the early sign of obstipation can be detected, which often develops in prolonged bed rest. The absence of chest hairs refers for alcoholism, especially, if accompanied by gynecomastia, ascites or dilated superficial abdominal veins. In case of aphasia, or when historical data can not be obtained from family members, scars can suggest previous surgeries, such as bypass operation or sympathectomy. Always palpate the urinary bladder, as for urinary retention can explain the patient's agitation (e.g. if accompanied by confusion and aphasia). In patients with urinary catheter the tube could be clogged or broken, so urinary retention can develop. Poor skin turgor and dark urine refer to insufficient hydration. In paretic patients who are not able to communicate, the fluid and electrolyte disturbance develops inevitably, especially at summer. Perform auscultation above the abdominal aorta and femoral arteries near the Poupart's ligaments (murmurs?).

Examine the gluteal region, where decubitus ulcers often evolve (even in hours!).

Subclinical thrombosis can be diagnosed by comparative palpation of the femoral muscles. The affected extremity is swallowed, with smooth skin. The cadaveric position of lower extremity (outwardly rotated foot) suggests which side is paretic, but can refer to a common stroke related injury, the femoral fracture too.

Check the pulses of the feet and measure the blood pressure both on the ankles and upper arms (by using ultrasound or oscillometry). If the ankle-brachial pressure index is less than 0.9, the patient is more likely to have arteriosclerosis.

Subclinical paresis can be revealed by the following test: the patient lying with closed eyes stretches his/her arms upwards, and elevates his/her flexed leg to horizontal position. On the affected (weaker) side the patient pronates his/her palm and lowers it together with his/her leg. The damage of the corticospinal tract is tested by performing fine movements. (Ask the patient to tap his/her thumb and forefinger quickly, and observe the rapid alternating movements of the hands.)

If possible, observe the patient's walking. Severe symptoms can be hidden in lying position, e.g. the patient might be unable to walk because of gait ataxia. Subclinical paresis can be revealed by walking on the heels or on the outer edges of

the feet (“indian-walking”). In case of subclinical paresis the patient flexes his/her arm on the affected side while walking, and the paretic upper extremity fails to move normally.

The examination of sensory functions is difficult on confused, elderly patients. If the corneal reflex can not be elicited on one side, it may refer to unilateral sensory damage. Severe sensory disturbance can be excluded by touching the right and left part of body with a wad of cotton, pin or the cold handle of the reflex hammer. Always ask the patient if he/she senses any side difference. If needed, ask the patient if he/she is able to recognize the touch of your finger on both sides.

Other aspects

Patients treated in hospitals are generally elderly people. Senile patients can easily get confused and anxious when leaving their accustomed environment, and can produce the symptoms of tachycardia and hyperventilation, which makes the circulation and oxygenisation insufficient. Inhalation of oxygen can be useful in these cases. Our behavior and gestures should be friendly and calming. Avoid complete dark at nights and tying the restraint to the bed in order to prevent moving, use bed-frame instead. Alcoholic patients can suffer from delirium if admitted to hospital.

In obese patients circulation and oxygenisation are more effective in the 30-40 degree head-up position (abdominal organs and intestines do not press the diaphragm up, so the aorta and the great vessels are not compressed too). This position also decreases the hypoxia and dyspnea related anxiety and fear. If the patient becomes anxious or confused and his/her heart rate accelerates, beside the measurement of blood pressure, pulses, and body temperature always examine the patient for urinary retention, and check his/her blood glucose level and the blood gases, too. These symptoms can be caused by temporary arrhythmias (especially in case of strokes affecting the right hemisphere and the insula), myocardial infarction or pulmonary embolism (angina, enzymes?). The administration of sedatives is rarely recommended and can be used only if organic causes are excluded. If needed, use short-term sedation (the risk of thrombosis and pneumonia is increased in elderly patients, and it can alter the sleep-wake circadian rhythm, too).

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The examination of the cerebrospinal fluid

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Cerebrospinal fluid (brain and spinal cord fluid) is spread between the two layers of the leptomeninges (arachnoid and pia mater) covering the brain, the spinal cord and the inner surface of the cerebral ventricles. The two symmetrical, lateral ventricles are in connection with the third ventricle. The aqueductus Sylvii leads from the third ventricle through the mesencephalon to the fourth ventricle. The fourth ventricle communicates with the subarachnoid space via the foramina. The ependyma covering the inner surface of the ventricles, the parenchyma and the vascular system of the pia take part in the production of the cerebrospinal fluid. The CSF passes through the choroid plexus to the ventricular system.

The composition of the cerebrospinal fluid differs from that of the serum. Not every component of the serum can get into the liquor or into the brain tissue. The blood-liquor and blood-brain barriers separate the blood-liquor and blood-brain tissues, respectively. The function of the brain-liquor barrier ensures that not every substance can pass from the brain tissue to the cerebrospinal fluid.

In healthy adults the cerebrospinal space contains approximately 150-200 ml fluid. The flow of the liquor is permanent and slow. If the flow of the cerebrospinal fluid is disturbed by pathological space-occupying processes, the intracranial pressure increases. Due to the increased intracranial pressure the ventricles become enlarged and compress the brain tissue. The increase of the intracranial pressure occurs more frequently than its reduction. These conditions have the same symptoms: nausea, vomiting, headache and dizziness. The pressure of the cerebrospinal fluid may decrease after lumbar puncture.

The pressure of the cerebrospinal fluid as measured by lumbar puncture is 120-180 mmH₂O in lying position and 300-600 mmH₂O in sitting position. The cerebello-medullar cistern has the pressure of 0 mmH₂O. The cranium and the spinal canal should be considered as a hermetically closed cavity system with an inflexible wall, containing the brain, spinal cord, blood and cerebrospinal fluid. If any of them increases in volume, the elevated intracranial pressure will transpose to the spinal canal, the labyrinth and the liquor situated in the optic nerve sheath.

The amount of the cerebrospinal fluid increases if its production is larger than its absorption (e.g. in case of meningitis), or its absorption is disturbed, or the liquor pathways are obstructed. It causes hydrocephalus in every case.

In the majority of the organic diseases of the central nervous system, the flow and the compounds of the cerebrospinal fluid is changed, therefore, the examination of liquor is very important. Liquor for testing purpose is gained by lumbar, cisternal or ventricle puncture. Before performing lumbar or cisternal puncture, it is essential to exclude if the intracranial pressure is increased by ophthalmoscopic examination of the fundus. Performing the puncture without the examination of the optic discs is a medical malpractice.

Lumbar puncture should be performed at the level of the third or fourth lumbar vertebra, or even more caudally. The hiatus, which is located between the spinous

processes of the third and fourth lumbar vertebrae can be found easily with the help of an imaginary line connecting the highest points of the two hip plates. The lumbar needle should be inserted in the middle of this line, between the spinous processes of the LIV-V., or LV-SI. vertebrae. Due to the pressure of the cerebrospinal fluid, it drops through the needle. Do not use syringe for taking cerebrospinal fluid. During the examination, the pressure of the cerebrospinal fluid is also measured with manometer.

Cisternal puncture should be performed between the external occipital protuberance and the spike of the atlas. During the insertion of the needle we can feel the elastic resistance of the dura. After the withdrawal of the mandrine of the needle, the emptying of the liquor is not necessarily spontaneous, because the pressure in the cistern is zero. In this case liquor is drawn by a syringe.

After lumbar puncture patients should stay in horizontal position for 24 hours. If the patient stands up after the puncture, the symptoms of headache, nausea, vomiting and nuchal rigidity may appear. These symptoms and complaints are caused by the decreased cerebrospinal pressure.

The normal liquor is colorless and clear. In case of certain diseases blood could get into the cerebrospinal fluid (e.g. in case of aneurysm rupture or traumatic injury). Blood may get into the liquor artificially too, if the needle damages the veins during the puncture. Liquor containing blood homogeneously could be resulted by diseases, while the strip-like bloody liquor with streaks of blood is a sign of artificial bleeding (traumatic puncture). In case of traumatic puncture the supernatant of the centrifugated liquor is clear, because the red blood cells are sedimented to the bottom of the vial. The supernatant becomes yellowish (xanthochrom) in pathological bleeding.

Normally, there are only 3-4/ μ l cells in the liquor taken with lumbar puncture (these cells are lymphocytes). Normally, maximum 1-2/ μ l cells can be found in the cisternal part of the liquor. In case of elevated cell count, qualitative examination is required.

The examination of the chemical contents includes the detection of protein and glucose levels. Normally, 0.2-0.4 g/l protein is found in the lumbar liquor and < 0.2 g/l in the cisternal part. The normal glucose concentration of the cerebrospinal fluid is about 2/3 that of the serum.

In case of autoimmune diseases immunological test should be performed. Isoelectric focusing is used for analyzing the protein composition of the cerebrospinal fluid. The concentration of the gamma globulins and immunoglobulins is increased in the liquor and can be separated by isoelectric focusing. During isoelectric focusing the immunoglobulins separate in form of bands, called as oligoclonal bands or oligoclonal gammopathy). Protein tests should be performed simultaneously on blood and cerebrospinal fluid samples. If inflammation is suspected, bacterial tests are recommended.

Indications of lumbar puncture

-diagnostic (Table 1.): suspicion of inflammation, malignancy, atypical subarachnoid bleeding and degenerative diseases of the nervous system.

-therapeutic: spinal anesthesia, intrathecal treatment (antibiotic or cytostatic), increased cerebrospinal pressure.

Lumbar puncture is essential for the diagnosis of meningitis and encephalitis, but useless in the diagnosis of abscess or empyema. The test is sensitive and specific for most organisms.

Table 1
Diagnostic indications of the liquor examinations

Diagnostic indication	Liquor tests
<i>Infectious diseases</i> Bacterial, viral, fungal meningitis Encephalitis, myelitis Polyneuropathies	cell count, cytology, total protein, glucose, oligoclonal gammopathy, lactate, bacteriology, serology, PCR
<i>Autoimmune inflammatory diseases</i> Multiple sclerosis Primer cerebral vasculitis Syndrome of Guillain-Barré Autoimmune neuropathies Systemic autoimmune diseases with neurological complication	cell count, cytology, total protein, oligoclonal gammopathy, albumin, immunoglobulins (IgG, IgA, IgM index), myelin basic protein, myelin-associated-glycoprotein
<i>Hematologic, oncologic diseases</i> Leptomeningeal metastasis Paraneoplastic syndromes	cell count, cytology, flow cell-measure, total protein, glucose, oligoclonal gammopathy paraneoplastic antibodies
<i>Metabolic encephalopathies</i>	cell count, total protein, glucose, pyruvate, lactate
<i>Atypical subarachnoid bleeding</i>	cell count, total protein
<i>Degenerative diseases</i>	cell count, total protein, glucose, pyruvate, lactate
Creutzfeldt-Jakob disease	14-3-3 protein
Dementias	tau, phospho-tau, and amyloid-beta 1–42 protein

Table 2
The specific signs of meningitis with different causes

	Bacterial	Viral	Fungal	Tuberculous
<i>Appearance</i>	yellowish, turbid	clear	yellowish, viscous	yellowish, viscous
<i>Opening pressure</i>	normal or high	normal	normal or high	usually high
<i>WBC (cell/mm³)</i>	1,000-10,000	< 300	20-500	50-500
<i>PMN (%)</i>	>80	<20	<50	~20
<i>Mononuclear cells</i>		lymphocytes		
<i>RBC (cell/mm³)</i>	slightly increased	normal	normal	normal
<i>Protein (mg/100 ml)</i>	markedly increased (100-500)	slightly increased or normal	increased	increased
<i>Glucose (mg/100 ml)</i>	decreased (< 40)	normal	usually decreased (< 40)	decreased (< 40)
<i>Gram staining</i>	60-90 % positive	negative	negative	AFB stain positive in 40-80%
<i>Culture (% positive)</i>	70-85	25	25-50	50-80

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Electroneurography

FERENC MECHLER MD.

Electroneurography (ENG) is the functional investigation of the peripheral motor and sensory nerve fibers. The electrical stimulation of the nerve evokes an impulse passing along the nerve fibers and the response can be recorded by special equipments.

The procedure is simple, reliable, safe and well standardized. The duration of the impulse is usually 0.1 – 0.2 msec, the intensity is supramaximal for motor, and suprathereshold for sensory nerve fibers.

Surface electrodes are used both for stimulation and registration. Two different amplification systems are needed for the recording of motor and sensory nerve responses, because the motor responses have a range of millivolt, while the sensory potentials have a range of microvolt. The recording of sensory potentials usually needs an averaging procedure, too.

Practically, the motor, sensory and mixed nerve conduction velocities represent the maximal conduction velocities of the fastest conducting motor, sensory and mixed nerve fibers, respectively.

The investigation of motor nerve fibers

The response is recorded from the muscle innervated by the nerve investigated. The recording electrode is placed over the belly of the muscle, the reference electrode on an inactive site.

The parameters to be determined:

1. **distal or terminal latency:** the time required for the response with distal stimulation. The distance between the stimulating and recording points should be standardized;
2. **motor conduction velocity:** the nerve is stimulated at two points along the course of the peripheral nerve. The difference between the two latency time is the conduction time. The distance between the 2 stimulated points should be measured. Conduction velocity is determined by dividing this distance by the conduction time. The EMG apparatus usually accounts these data automatically;
3. **amplitude:** the maximal (peak to peak) amplitude of the motor response;
4. **potential duration,**
5. **potential dispersion.**

The investigation of sensory nerve fibers

This can be performed either orthodromically or antidromically. With orthodromic method the sensory nerve fibers are stimulated distally and recording proximally. With antidromic method the stimulating and recording electrodes are switched.

The parameters to be determined:

1. **latency:** the time from the stimulation to the appearance of the response;
2. **sensory nerve conduction velocity (SNCV),**
3. **potential duration,**
4. **potential dispersion.**

The usefulness of ENG investigations

They *are essential* in the diagnosis of any damage of peripheral nerves, thus to diagnose polyneuropathy, to localise the exact place of local compression or injury of nerves, and they can help in the diagnosis of radicular damages.

The ENG investigation may answer the following questions:

1. the function of peripheral nerve is normal or not,
2. what is the pathophysiological basis of the symptoms: the damage of the axons or myelin sheaths or their combinations,
3. the peripheral nerve lesion is focal, multifocal or diffuse,
4. what is the exact localisation of the lesion,
5. how severe is the nerve damage,
6. what are the dynamics and prognosis of the peripheral nerve lesions.

The ENG investigation is indicated:

1. *in cases of distal sensory symptoms,*
2. *in cases of distal sensory-motor symptoms and signs,*
3. *in cases of mononeuropathy, tunnel syndromes, traumatic nerve lesions.*

The ENG investigation is able to give information about the pathological bases of nerve damage.

Electromyography

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Electromyography (EMG) is the extracellular registration of bioelectrical potentials by concentric needle electrodes during the activity of striated muscle fibers. The basis of the clinical EMG is the functional unit of neuromuscular system, the motor unit which includes the neuron cell, its axon and the muscle fibers innervated by this single axon. The **muscle unit action potentials** are recorded during the EMG investigation.

The EMG procedure includes 3 steps:

1. We observe and record the spontaneous activity in muscle **at rest**.
2. We ask the patient for a **weak contraction** of the muscle and we record motor unit action potentials and analyse their main parameters: duration, amplitude, shape, phases, stability. The modern EMG equipments measure these parameters automatically.
3. Finally we ask for a **maximal contraction** and analyse the activity pattern: **unit, mixed or interference patterns**.

As you can see, the EMG investigation requires the cooperation of the patient. According to the request and problems, usually several (2–6) muscles should be investigated.

Indications

The EMG investigation plays an essential role in the diagnosis of disorders affecting the lower motor neuron. Its most important diagnostic value is the differentiation between the myogenic and neurogenic muscle diseases.

The EMG may help to clear up:

1. is it any muscle disease at all,
2. if yes, it is myogenic or neurogenic,
3. localisation of the disease process,
4. predicting the prognosis.

Contraindications

1. hemophilia,
2. high INR value.

*The following **spontaneous potentials** can be recorded in disorders affecting the neuromuscular system:*

1. **denervation potentials** (fibrillation potentials, positive sharp waves),
2. **fasciculation potentials**,
3. **myotonic salve** (high frequency repetitive discharges).

EMG characteristics in myogenic muscle diseases:

1. decrease of duration of the motor unit action potentials,
2. decrease of the potential amplitude,
3. increase of polyphasic potentials with short duration,
4. interference pattern with low amplitude.

EMG characteristics in neurogenic muscle diseases:

1. increase of duration of the motor unit action potentials,
2. increase of the potential amplitude,
3. increase of polyphasic potentials with increased duration,
4. reduced pattern (unit or mixed).

Messages

EMG is indicated:

1. *in cases of muscle atrophy,*
2. *progressive muscle weakness with normal nerve conduction velocity,*
3. *the myogenic or neurogenic origin of muscle weakness is not known.*

The indication of EMG study is a specialist's task. The EMG investigation itself does not give clinical diagnosis!

Electroencephalography

KLÁRA FEKETE MD.

Definition, introduction

Electroencephalography (EEG) is an important part of the electrophysiological examinations. Simply, it maps and records the electrical function of the brain for further analysis (i.e. it is a functional examination). Berger developed the first electroencephalograph and established the first EEG-laboratory between 1924 and 1938. The EEG-signal is a sum of postsynaptic potentials (both excitatory and inhibitory), and the extracellular longitudinal current compensates the cell membranes local potential differences. Both neuron cells and glia cells play a role in the formation of the electrical signal. The development of the EEG-signal is a complex biophysical, biochemical and neurophysiological procedure, which is not the task of this brief issue.

Technique

In everyday practice, scalp registration is widespread, which means the detection of low amplitude (μV) 0.5-40 c/s frequency electrical activity on the scalp. In preoperative evaluations, of course, supplemental electrodes are needed, such as subdural strip, semi-invasive sphenoidal electrodes or intracerebral electrodes.

In the clinical practice the use of 19 electrodes (with 1-2 reference electrodes) are used routinely. To eliminate the bias from the variability of individual head shapes, the so-called 10-20 system is used (Figure 1). The registration may be monopolar or bipolar. Monopolar registration means that the active electrodes are correlated to one average point, and as a result, the difference between them is detected. In case of bipolar technique the difference between the two active electrodes is measured.

The registration can be analogue (with paper registration), or – what is more common nowadays – digital (computer) (Figure 2). Digital technique makes post processing much easier, and the frequency and voltage mapping possible, which may help to localize the focus better.

The examination must be performed in a quiet, calm, dark (or semi-dark) room, if possible, the patient should be in lying position with eyes closed, and at least 20 to 40 minutes registration is recommended. After EEG is performed at rest **provocation** is used.

1. **Hyperventilation for 3 minutes:** it is used to provoke a moderate intracellular pH shift. *Contraindicated in intracranial bleeding, acute stroke, and severe heart failure!*
2. **Fotostimulation:** 1, 3, 10, 20, 30, 60 Hz are recommended – but it can differ in individual laboratories.

3. **Eye opening and closing:** with closed eyes alpha waves are seen normally, eye opening causes alpha blockade (desynchronisation can be seen), after eye closing the alpha waves seen previously can be detected again.
4. **Stimuli**, which may provoke the seizures, must be tested too (e.g. **pain, noise, music, smell**).
5. **Sleep-deprivation:** it can provoke ictal and interictal phenomenon. In adults it means a 24-hour sleep deprivation. In children the duration of sleep deprivation may differ by age, so always contact the EEG-laboratory. No stimulants are allowed (coffee, black or green tea, caffeine-containing soft-drinks). If sleep deprivation EEG is followed by a sleep-time EEG, more information can be gained.

Video-monitoring during EEG-registration is essential in order to see the proper course of the seizure, or to decide between psychogenic, involuntary extrapyramidal movements and real epileptic attacks.

Evaluation of the EEG result

Basic waveforms, background activity

Those, who are not electrophysiologists, should be familiar with the basic waveforms: **delta: 0.5-4 c/s, theta: 4-7 c/s, alpha: 8-12 c/s, beta >12 c/s**. Each brain area is characterized by different wave pattern. Alpha waves are usually seen in the parieto-temporo-occipital region, while beta activity is mainly detected over the anterior central and posterior central gyri.

Reactivity

As mentioned above, in resting position with closed eyes alpha activity is seen, which changes for eye-opening, or attention i.e. desynchronisation /alpha-block (low amplitude, fast activity due to asynchronous function) is seen. Fist clenching blocking the beta activity over the anterior and posterior central gyri is also the part of the routine examination.

Pathological graphoelements

The localization, asymmetry, and reaction to provocation techniques must be documented. They can be focal or generalized: (e.g.) slowing, spike, spike and wave complexes, periodic patterns, triphasic waves.

Artifacts

Artifacts can disturb the evaluation or even mask the pathological elements. The common causes of artifacts are faulty electrodes, muscle movements, blinking and sweating.

It is always important to keep in mind, that the neurological examination involves EEG too, and must be evaluated together with the history and symptoms (e.g. one can be a “spike-carrier” without having seizures – no treatment is needed in this case).

Indications of EEG

Since EEG abnormalities can be similar in different entities, the referral letter must contain the patient’s history, examinations and findings, list of the medication, and the correct clinical question (what we are investigating about). Correct result can be given only to correct referral letters. EEG is a functional examination, thus it does not replace the modern imaging techniques, but supplements them.

Main indications

A. EEG is indicated in epilepsy for localizing the focus and finding the typical ictal or interictal elements. Two or three EEG examinations may be needed; one should be performed right after the sleep deprivation test. EEG control is necessary during treatment if: the seizure frequency increases, the type of the seizures changes, the medication is discontinued, and in case when the symptoms are characteristic for toxicity. *Continuous* EEG monitoring is required in case of *status epilepticus* if for instance phenobarbiturate or propofol is given, or artificial ventilation is needed. In case of impaired consciousness, if *non-convulsive status epilepticus* is suspected, EEG must be done.

B. Inflammation of the central nervous system (encephalitis): diffuse slow activity can be seen, which can indicate the prognosis. Special patterns are detected in *herpes encephalitis* (fronto-temporal dominant slow activity with typical periodic spikes in the temporal records), subacute sclerosing panencephalitis -SSPE (periodic high voltage slow waves, which are synchronous with the myoclonus followed by a relatively flat pattern).

C. Metabolic encephalopathies. In case of prolonged hypoglycemia diffuse slow activity may remain for a while, even if the blood glucose level was normalized. In renal encephalopathy, besides triphasic waves, spikes can occur. Hepatic encephalopathy and chronic cerebral hypoxia cause slow background activity and triphasic waves.

D. Intoxication is suspected: diazepam-like sedatives cause diffuse monotonic beta activity, and the use of major tranquillants provokes diffuse slow activity.

E. Dementia: in classical Creutzfeldt-Jakob disease periodic triphasic waves are seen, but in the new variant they are not characteristic. In dementia the slowing of the background activity may predict the prognosis and the severity.

With EEG the electrical activity of the brain is examined. The result must be evaluated together with other clinical findings.

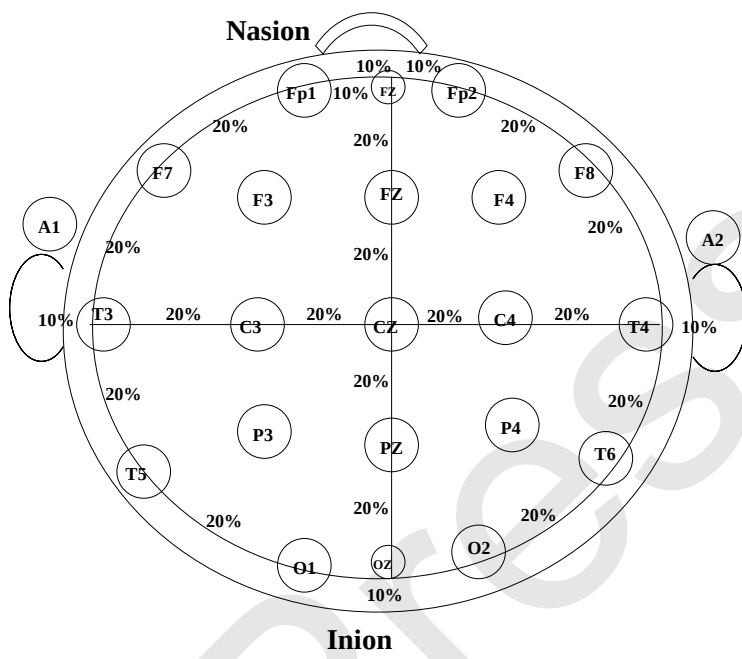


Figure 1
The proper localization of electrodes according to the international 10-20 system. Even numbers indicate right side, uneven numbers refer to the left side.

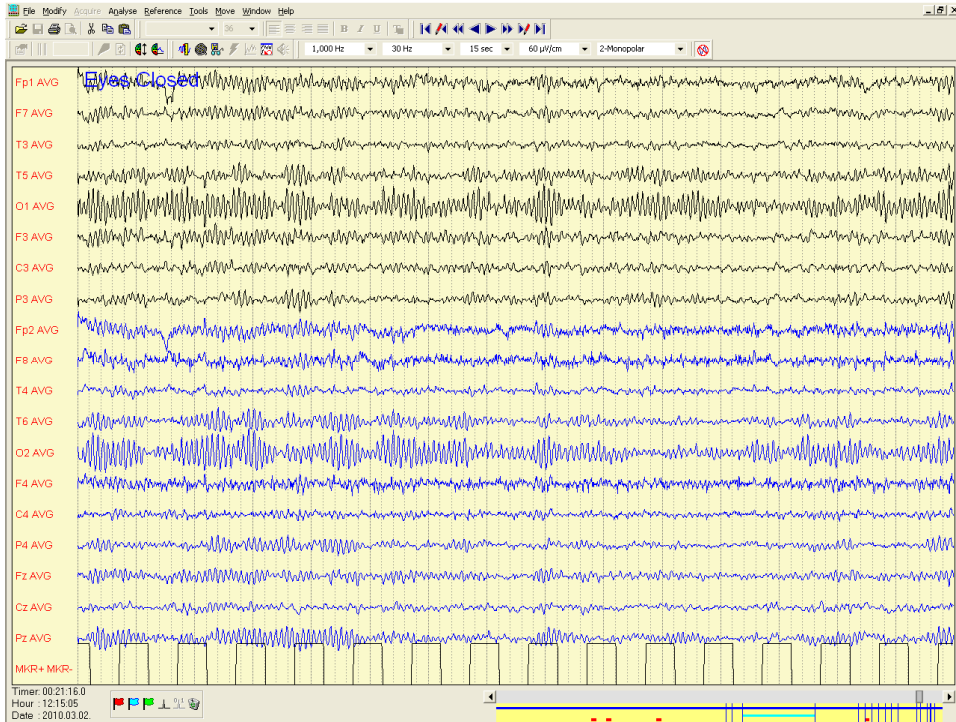


Figure 2
Normal alert digital registered EEG with closed eyes (monopolar technique).

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Evoked potentials

JUDIT BOCZÁN MD.

Definition

Evoked potentials (EP) are functional electrophysiologic examination methods with the capacity of testing certain central nervous system pathways. Their advantage is that they are capable of detecting microscopic damages of the nervous system which are undetectable by imaging techniques.

Evoked potential examinations are used mainly in the following indications:

- confirming multiplicity in multiple sclerosis,
- differentiating between central and peripheral vertigo,
- detecting myelopathy.

The averaging of curves is necessary for visualizing the evoked potentials because their small size makes impossible to differentiate them from the EEG curves.

Main points of the evaluation of the evoked waves are their

- latency,
- shape,
- reproducibility,
- differences between the hemispheres.

Evoked potential examinations are performed by special assistance, and they are analyzed by neurologists trained in electrophysiology. The duration of an examination is about 20 minutes.

Visual Evoked Potentials (VEP)

The visual pathway is stimulated by a flash or by a chessboard seen on a screen. The eyes are stimulated separately. The evoked potential is registered by a surface electrode positioned on the occipital scalp. P100 is the first positive (downwards running) wave detected after the stimulus with a delay of an approximately 100 ms (Figure 1).

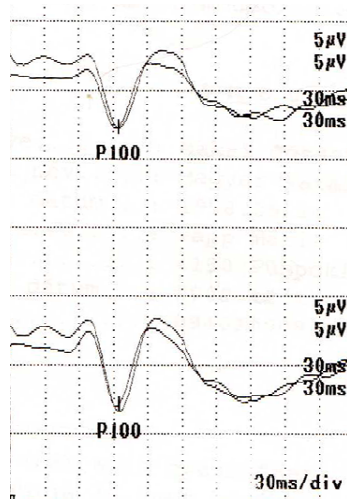


Figure 1
Normal VEP

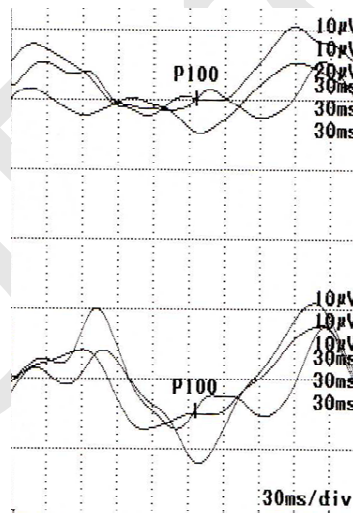


Figure 2
Abnormal VEP

Increased latency of the P100 wave is often seen in

- retrobulbar neuritis,
- optic neuropathy caused by chronic ethanol consumption, ischaemia or lues,
- rarely in glaucoma, or
- in other neurodegenerative diseases.

In severe cases the wave is undetectable (Figure 2). Postchiasmal damage of the visual pathway results in asymmetry between the two hemispheres or in significant difference of the amplitudes of the potentials detected over the two hemispheres.

Brainstem Auditory Evoked Potentials (BAEP)

BAEP examinations are performed in silent environment. The auditory nerves are stimulated separately by a short knocking sound above the patients auditory threshold. Evoked potentials are registered by a surface electrode on the mastoid process. Different evoked waves are generated by different structures playing role in the auditory pathway (wave I – cochlear nerve, wave II – cochlear nucleus, wave III – superior olive, wave IV – lateral lemniscus, wave V – inferior colliculus, wave VI – medial geniculate body, Figure 3).

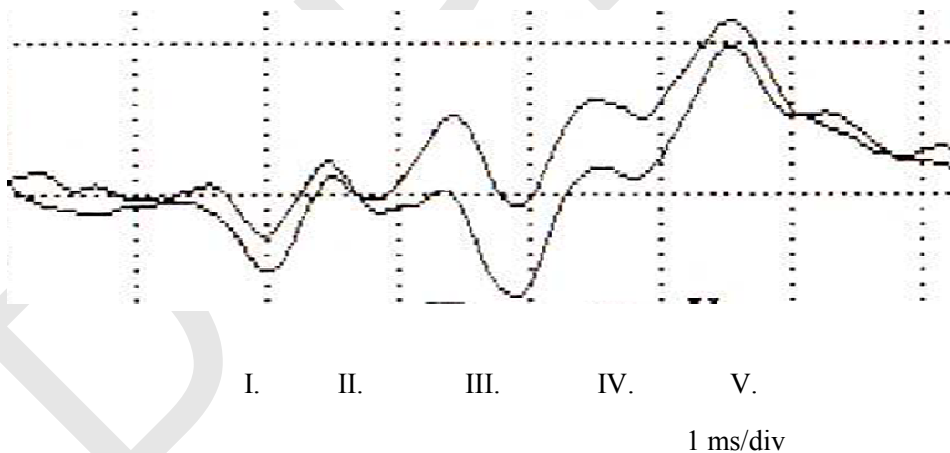


Figure 3
Normal BAEP

Localization of the lesion is possible if the following findings are present:

- a wave is absent,
- interpeak latencies are increased.

Latency and reproducibility of waves I-V are checked in the everyday routine. The damage of an anatomic structure results in delay or amplitude reduction of the corresponding wave.

Evaluation:

- Absence of wave I with normal III-V interpeak latencies refers to a severe damage of the peripheral auditory nerve.
- Increased I-III interpeak latencies refer to a damage of the acoustic nerve between the terminal nerve endings in the cochlea and the synapses in the pons.
- Increased III-V interpeak latencies refer to a lesion in the pons.
- Reduced amplitude of waves IV and V are characteristic for a lesion of the lateral lemniscus.

BAEP is pathologic in 50 to 70 percent of multiple sclerosis cases even in the absence of clinical symptoms of brainstem damage. In early phases of acoustic neurinoma (vestibular schwannoma) BAEP shows acoustic nerve damage before the positivity of CT or auditory examination methods. The use of this technique during the operation of the tumor may help in protecting the nerve. Central or peripheral etiology of vertigo can be differentiated in cases with mild clinical symptoms, negative MR and Doppler. BAEP can also be used for detecting brainstem damage in patients with coma, or even in the diagnosis of brain death.

Somatosensory Evoked Potentials (SSEP)

Somatosensory evoked potentials provide information about the sensory pathway, particularly the dorsal column (deep sensation). Intact function of the peripheral nerves is necessary to evaluate SSEP. Median, tibial or peroneal nerves are stimulated by an approximately 5 Hz stimulus. In case of upper limb SSEP examinations, the registering electrodes are placed above the clavicle (Erb's point), 2nd cervical vertebra, and the scalp above the contralateral somatosensory cortex. The name of the potential detected above the Erb's point is EP. The wave registered above the cervical point is named N13/P13 because it can be detected after the stimulus with a delay of an approximately 13 ms. N19/P22 wave can be detected above the cortex (Figure 4A). In case of lower limb SSEPs, the registering electrodes are placed above the lumbar root and the scalp above the contralateral somatosensory cortex, where P37 wave can be detected (Figure 4B).

EVOKED POTENTIALS

Dysfunction of the somatosensory pathway results in increased interpeak latencies. This method is used mainly in the diagnosis of multiple sclerosis and myelopathies.

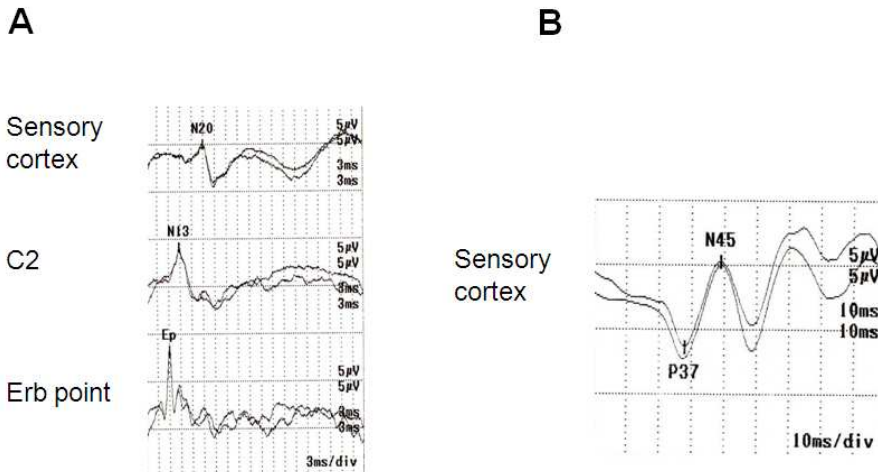


Figure 4
A. Normal upper limb SSEP
B. Normal lower limb SSEP

Transcranial Magnetic Stimulation (TMS) or Motor Evoked Potentials (MEP)

Transcranial magnetic stimulation is a method for testing the reactivity of the motor cortex and the corticospinal pathway. When 1.5-4 Tesla magnetic field is applied above the primary motor cortex, it induces electric current in the tissue, which results in an action potential of the neurons. The activated pyramidal tract stimulates the alpha motoneurons in the ventral horn of the spinal cord resulting in the contraction of the corresponding skeletal muscle fibers. The summated action potential of the muscle fibers is detected by a surface electrode. In case of upper limb TMS, the contralateral motor cortex and ipsilateral cervical roots are stimulated by the magnetic field and the evoked answer is detected by a surface electrode placed above the 1st dorsal interosseous muscle of the hand. In case of lower limb TMS, the contralateral motor cortex and ipsilateral lumbar roots are stimulated and the evoked motor answer is registered above the extensor digitorum brevis muscle of the leg.

Central motor conduction time (CMCT) is calculated by the subtraction of the latency of MEP by cervical or lumbar magnetic stimulation from the latency of

MEP by cortical magnetic stimulation. Increased CMCT is the sign of pyramidal tract lesion.

Magnetic stimulation has almost no side effects, and it can be tolerated well. Since there is a theoretical risk for provoking epileptic seizure in epileptic patients, epilepsy is a relative contraindication for this technique.

Magnetic stimulation cannot be used in patients with

- pacemaker,
- clipped intracranial aneurysms,
- intracranial metal implants,
- metal implants used for stabilization of the spine.

TMS is a useful technique for detecting subclinical pyramidal tract lesions with no pyramidal signs. It is also informative when imaging techniques are negative or when the damage of the peripheral nervous system makes pyramidal tract lesion clinically undetectable. On the other hand, TMS does not give any additional information when pyramidal signs can already be detected or imaging techniques are positive. TMS is mainly used in the diagnosis of amyotrophic lateral sclerosis, different myelopathies (compression myelopathy by cervical spondylosis, combined degeneration of the spinal cord caused by vitamin B₁₂ deficiency) or in some cases of multiple sclerosis.

Electronystagmography

In electronystagmography eye movements are detected by electrodes placed around the eyes or by the help of video cameras, and the collected data are analyzed by a computer. Registered curves provide information about the amplitude, direction, frequency, and the angular velocity of the slow and fast component of the nystagmus, showing the connection of the vestibular and oculomotor system.

The examination has three phases:

- evaluation of the oculomotor system (the patient has to focus on a light spot then he has to follow a red light moving along a line),
- position examination (eye movements are detected in different body positions),
- caloric stimulation of the vestibular system.

Electronystagmography is a useful technique in the differentiation of central and peripheral vertigo. The side of the lesion is defined by the caloric testing and position examination.

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Conventional X-ray, CT, MR, PET, isotope-diagnostic methods and angiography

ANDRÁS LENGYEL MD

Conventional X-rays

The role of conventional X-ray examination has decreased in the neurological practice. In case of many abnormal neurological conditions, it provides only poor information compared to the results of the current imaging techniques (CT, MRI). There are situations, however, when X-ray imaging is the primary method of diagnostics, mainly because of its low expense.

The examination of the skull

Generally, conventional X-ray uses the following projections: lateral (both sides), Towne, posteroanterior (PA) and basic (submentovertical) projections.

Imaging of paranasal sinuses differs from the standard imaging techniques listed above, because it is primarily used to assess the frontal air-filled spaces of the skull. The test can be performed in both sitting and standing position, and in case of sinusoidal fluid niveau (a border between the fluid and air) can be detected.

Calcification seen in conventional X-rays may have several causes, such as the calcification of the meninges, pineal corpus, parenchyma or tumor. Falx calcification located medially is a common finding. Large and calcified craniopharyngeomas or aneurysms are also detected by conventional X-ray techniques. If the localization of calcification is unsure, two perpendicular images can help the diagnosis.

Many genetic and ethnical features may have influences on what is considered to be normal on human skulls. There are many normal variations being described in literature.

Abnormal conditions

There are just a few conditions, which can be detected more effectively by using conventional X-ray, rather than CT or MRI. These conditions are generally related to the shape or size of the skull.

Platybasia, basilar impression, basilar invagination

By using special lines and radiation angles, such developmental bone anomalies can be detected, which can be accompanied by brainstem defects and symptoms of the inferior cranial nerves, too.

In case of platybasia the basis of the skull is abnormally flat. The term basilar impression refers to another skull base malformation with the congenital bulging

upwards of the floor of the posterior cranial fossa. This condition is usually associated with the occipitalisation of the atlas (the fusion of the C1 vertebra and the occipital bone) and the upward dislocation of the dens adjacent to the foramen magnum. Basilar impression (congenital type) or basilar invagination (acquired type) develops if more than half of the odontoid process is located above the Chamberlain's line. The examination of the cranio-cervical zone developed significantly by the spreading of the MRI imaging.

Congenital abnormalities

There are several cranial malformations affecting the development of the brain, but most of them can be evaluated more effectively by using MRI or CT imaging.

In case of craniosynostosis, the sutures of calvaria fuse prematurely.

Dolicocephaly means having a long or narrow head due to the premature fusion of the sagittal suture. The condition when relatively broad head is developed called brachycephaly and is caused by the early fusion of the coronal suture.

These cranial abnormalities are not accompanied by clinical symptoms, as long as they are not parts or consequences of clinical syndromes or metabolic diseases, respectively.

Trauma

The fractures of cranial bones might be accompanied by subdural hematomas or parenchymal damage, but they can be solitary findings, too. Head injuries can have intracranial complications without bone fracture that is why CT scan is the primary examination if severe injury is suspected. As for the whole basis of the skull can be evaluated by conventional X-ray technique, cranial X-rays are useful in the assessment of linear fractures. Despite of the bone window of CT imaging, linear fractures, if not accompanied by impression, sometime can be visualized only by X-ray.

In many non-traumatic cases (e.g. headache) X-ray is performed to ensure the diagnosis, although, it does not have therapeutic consequences.

Fractures are classified into the following categories: linear, diastatic, fragmented and impression fractures. Fragmented and impression fractures should be taken with care because they are often accompanied by parenchymal and vascular damages (e.g. middle meningeal artery), and require neurosurgical intervention. In these situations CT imaging is always justified. Their late complications might be empyema and brain abscess. In case of the damage of superior orbital fissure, the optic nerve can be affected too. In case of pyramidal bone fracture, deafness or hearing loss can develop due to the discontinuation of the bone-chain participating in the sound transfer. Fractures affecting the skull base might be accompanied by the damage of the venous system and inner ear.

Tumors

Conventional X-ray imaging is not capable of diagnosing tumors, but sometimes, it can suggest their presence. Multiple myeloma developed mainly in elderly people is the most common malignancy, and often involves the cranial bones and vertebral column. Plasma cells induce the osteolysis of bones by

infiltrating the bone marrow. The disease usually generates multiple bone lesions, but it may appear as a solitary lesion, too (called plasmocytoma). Myeloma activity can be detected on the X-ray as several well-defined lytic lesions having well visible sclerotic margins. In myeloma the erythrocyte sedimentation rate (We) is significantly elevated.

Clouded, sporadic calcification refers for chordomas. Those variations, which involve the skull, always evolve from the clivus and may spread to the anterior fossa.

Metastases of the cranial bones

Metastases often appear in cranial bones, but have less significance compared to brain or vertebral metastases. Every tumor can produce metastases in the cranial bones, but metastases are usually the consequences of primary breast, lung, prostate and kidney tumors. Lymphoma, leukemia or neuroblastoma can metastasize the skull. Hematogenous spreading is the most common way of dissemination, but certain tumors can spread directly too (e.g. nasopharyngeal tumors). Bones can react to metastases with either bone resorption (lytic lesions) or bone formation (blastic lesions) or with both of them at the same time. *In case of bone metastases scintigraphy is essential.*

Infections

In case of the acute bacterial infections of the paranasal sinuses, conventional X-ray can confirm the diagnosis. X-ray technique visualizes the fluid-gas border (niveau) or the filled sinuses. In case of complications, chronic infections or planned surgery, coronal CT scan of the facial bones is preferred.

Cranial abnormalities caused by metabolic or systemic diseases (e.g. Paget's disease or hyperparathyreosis) are detailed in the relevant literature.

The examination of the spinal column

The whole series of X-rays performed for the assessment of the vertebral column consists of lateral, antero-posterior (AP), special "open mouth", right oblique and left oblique projections. The routine examination of the thoracic spine is performed in AP and lateral projections, while the lumbosacral spine examination requires AP, lateral, right oblique and left oblique projections.

In neurology the most common indication of spinal X-ray is the pain, which can occur in every part of the spinal column. It usually affects the cervical and lumbar regions, but can radiate into the extremities as well (irradiating pain and/or numbness).

The most common painful *congenital abnormality* is the cervical rib arising from the CVII vertebra. Its presence is usually asymptomatic. The sacral spina bifida is also a benign condition if not accompanied by skin symptoms or vegetative complications.

The most common *degenerative disorders* are:

- spondylosis,
- osteophytosis,
- spondylolysthesis,
- and spondylolysis.

If not accompanied by nerve compression they require rheumatic treatment. In severe cases surgical intervention could be necessary.

Instability developed due to pathological fractures caused by osteoporosis or osteolysis also indicates neurosurgical procedures. Vertebroplasty may help to reduce the pain.

Tumor or metastasis provoked pain does not ease at rest, increases at nights and can be accompanied by local tenderness, weight loss and anemia.

In case of spine related symptoms the CT and MRI imaging took over the role of conventional X-rays. However, do not forget to perform X-ray examination if malignancy is suspected, because it can reveal the lytic lesions earlier!

Myelography

Nowadays, myelography is performed rarely due to the wide availability of MRI. However, if MRI is contraindicated, myelography can be useful in the diagnosis of spinal abnormalities.

During the process of myelography, cerebrospinal fluid is obtained from the patient by a procedure called lumbar puncture. This is similar to that of we use for conventional cerebrospinal fluid testing. When the cerebrospinal fluid is removed, the patient lays on his/her side (and does not sit!). After this, iodinated media is injected to the subarachnoid space to replace the removed liquor. The contrast media is located by altering the patient's position. Next, X-rays are made in AP, lateral and oblique projections. The contrast media fills the subarachnoid space, and shows its inverse picture. The area of examination depends on the amount of the injected media (thoracic or lumbar part, or the entire spinal region). In case of spinal assessment CT scan is recommended to complete the information (CT-myelography).

Computed tomography (CT)

The use of CT revolutionized the diagnostics and treatment of neurological disorders. Nowadays, MRI is often prioritized, but CT imaging is faster, less expensive, and more available compared to MRI. That is why CT is the primary choice in many cases. The use of the new diagnostic approach, the CT-angiography, is spreading too.

The use of contrast materials is important in the diagnosis of tumors, inflammations and infections. CT imaging with the application of contrast media provides further information than native examinations. It may have complications such as allergy and renal insufficiency and should not be indicated routinely. Contrast materials are contraindicated in patients with iodine allergy and should be applied with utmost care in dehydrated patients with diabetes to prevent the development of renal insufficiency.

Nomenclature

During CT imaging the density of the examined structure is compared to the density of the normal parenchyma. If the density of the examined structure is similar, it is called as isodense. Structures appearing brighter or darker are called as hyperdense or hypodense, respectively. Mass effect is a nonspecific, but widely used term referring to all pathologic conditions, including hemorrhage or tumors, which distort the normal intracranial situation.

Abnormal conditions

Cerebrovascular diseases

The aim of CT imaging used in stroke cases is to differentiate hemorrhage and ischemia. Virtually, acute hemorrhage has increased density on CT scans while ischemic lesions might be visualized as isodense or hypodense areas. These findings are very important, because hemorrhage and ischemia cannot be differentiated only by their clinical symptoms. Nowadays, CT imaging is essential before starting specific stroke therapy or secondary stroke profilaxys (anticoagulant or antiplatelet therapy).

Ischemic CT findings

In case of acute ischemia, abnormalities do not appear on the CT scan right after the development of the event. During this so called “window period”, which can last for 48 hours, ischemic lesions can not be identified. The length of the window period depends on the extent of the infarction, the quality of the CT scanner and the skill of the examiner. At first, the signs of edema can be detected in the affected area.

The early ischemic signs are the followings:

- the fissures disappear, the gyri become smooth,
- the basal ganglia are blurred,
- the insular cortex disappears,
- the differentiability of the gray and white matters decreases.
- According to the localization of the fresh thrombus or embolus, hyperdense arterial sign can be detected in the vessel supplying the affected area (its presence depends on the pathomechanism). This is not a direct early ischemic sign, but usually evaluated as an evidence of arterial occlusion.

In order to assess the criteria listed above, CT scans should be taken symmetrically!

Hours after the ischemic event, the density of the affected area decreases gradually, and days later it becomes permanently hypodense. From that point, when the infarct is demarcated from the normal parenchyma, there won't be more changes. Sometimes, in case of excessive colliquative necrosis, cavities appear and become filled up with liquor-dense fluid in the infarcted area.

In most of the cases, the pathologic process can be identified by the assessment of hypodensity:

– *Territorial infarcts*

If the occlusion is located in one of the arteries of circle of Willis, hypodensity is detected in the area supplied by the affected artery. Occlusion might be caused by either local thrombus formation or embolism.

– *Watershed infarcts*

Watershed (= borderzone) infarcts are characterized by hypodensity located between the areas supplied by two main arteries (middle cerebral artery and anterior cerebral artery, or middle cerebral artery and posterior cerebral artery). Watershed infarctions are mainly caused by cardiac arrest related hypoperfusion or carotid stenosis provoked hypotension.

– *Lacunar infarcts*

In radiological point of view hypodensity is considered as lacunar infarct, if its area is smaller than 1.5 cm. In these cases the etiology is uncertain. Hypodensity affecting the basal ganglia is usually resulted by lypohyalinosis related occlusion, but near the convexity, lacunar hypodensities are probably caused by embolism.

Evolution of the infarcts

After the acute ischemic insult, follow-up CT (performed 5-8 days after the acute period) often reveals irregular, patchy hyperdensity in the affected hypodense area. This is a so-called hemorrhagic transformation which is caused by the spontaneous, but too late recanalisation. Hemorrhagic transformation can occur spontaneously without any specific treatment, mainly in cortical infarcts or when the origin is embolic. In these cases the affected area can be either patchy or confluent hyperdense. The incidence of these complications is still unknown, it may reach up to 10-15% of the ischemic cases.

As the time goes, later, focal atrophy develops in the affected area and its surround, and the parenchymal loss causes dilatation of the ventricle (ex vacuo hydrocephalus) if located near the ventricular system.

Parenchymal hemorrhage

If the bleeding strikes into the parenchyma and is larger than 1-2 mm, the hemorrhage can be *detected immediately on CT scans in form of hyperdensity*. Right after the event CT shows only the increased density of the affected area. A few hours later, spreading hypodense area appears at the margin of the hyperdensity, referring for edema. While the hyperdensity remains constant in the first two weeks, the edema (and hypodensity) increases gradually, especially in the

first 4-5 days. Next, the hemorrhage degrades and starts to be absorbed, and the hyperdensity decreases too. The edema decreases gradually, and after a few weeks it disappears. If the patient survives the event, weeks or months later only a hypodense area is seen in the place of the hemorrhage. At this point hemorrhage and ischemia can not be differentiated by each other only with using CT imaging itself. Certain MR sequences (gradient echo) can identify the anamnestic hemorrhage, too.

The most common areas of parenchymal hemorrhage are (listed in the order of decreasing prevalence):

- basal ganglia,
- thalamus,
- pons,
- cerebellum,
- and lobar hemorrhage.

Lobar hemorrhage has a different origin. While the others are caused by vascular ruptures due to diseases affecting the microvasculature, in lobar hemorrhage - located on the border of the gray and white matters – the etiology depends on the patient's age. In senile patients (over the age of 70-80) hemorrhage is mainly resulted by amyloid angiopathy. Younger patients must be treated with utmost care, because arteriovenous malformation (AVM), aneurysm rupture or tumor can be in the background.

Neurosurgical intervention of parenchymal hemorrhage is indicated, if:

- the extent of cerebellar hemorrhage is larger than 3 cm, and the patient's condition declines,
- the patient's neurological status is continuously worsening,
- the bleeding strikes into the ventricles, or causes stop in the circulation of the cerebrospinal fluid .

Subarachnoid hemorrhage

Unlike parenchymal hemorrhage, the successful detection of subarachnoid hemorrhage highly depends on the localization and amount of bleeding, the CT scanner, and the examiner. In some cases, acute hemorrhage does not appear on cranial CT scans, so negative result does not exclude the presence of bleeding. If the CT scan is considered to be normal, and the typical symptoms of SAH are present, the certain diagnosis can be obtained by the analysis of the cerebrospinal fluid therefore spinal tap is obligatory.

In case of subarachnoid hemorrhage, the blood appears in the fissures, ventricles and basal cisterns. The parenchyma is often slightly blurred on CT scans due to the generalized edema. Larger amount of blood can be found near the source of bleeding. After the verification of the subarachnoid hemorrhage by CT scan or lumbar puncture, the next diagnostic step is to identify the source of bleeding (e.g.

aneurysm, arteriovenous malformation, dura fistula). As for hemorrhage is often revealed by native CT, and the patient already lays on the CT table, the most appropriate method for further investigation is the CT angiography. However, the gold standard of the diagnosis is the digital subtraction angiography (DSA), which is indicated if the source of bleeding cannot be revealed by CT angiography. In some cases the source cannot be identified in the acute period due to injury related smooth muscle contraction or vasospasm. After 3-4 weeks, the angiography should be repeated, because cryptogenic SAH can be diagnosed only by repeated and negative DSAs. The source of bleeding remains hidden in 10% of the SAH cases, however aneurysms are often multiple findings on CT scans.

Intracranial sinuses and venous occlusion

CT imaging is not sensitive enough for the identification of intracranial sinus thrombosis and venous occlusion. In case of the occlusion of large sinuses (mainly superior sagittal sinus, transverse sinus, sigmoid sinus, and the confluence of the sinuses) the so-called “empty delta” sign might be present. On the transversal section the sinus (delta) is empty or filled partly with contrast material due to the presence of the acute thrombus. Empty delta is not a reliable sign for diagnosing sinus thrombosis, and it can be identified retrospectively. Venous infarctions and the consequent irregular, atypical bleedings may be resulted by venous congestion. They suggest the problem of venous system, especially if presented in the puerperal period or in sepsis. The presence of clinical symptoms (headache, papillary edema, abducent nerve lesion, epileptic seizure) also helps the diagnosis. If sinus thrombosis is suspected, CT venography may be useful, but MRI and MR venography provide more reliable data and became the primary diagnostic methods.

CT findings in the inflammations of the central nervous system

CT imaging is not specific enough for the diagnosis of inflammatory disorders affecting the central nervous system. The viral meningitis is asymptomatic on CT scans, but bacterial meningitis may cause enhancement of the contrast media due to the inflamed meninges. In encephalitis the typical finding is diffuse, irregular hypodensity combined with slight contrast enhancement in the affected area. In herpes encephalitis the frontobasal, temporal or subinsular hemorrhage can help the diagnosis. In some cases, contrast media enhancement is visualize on the edge of major abscesses, but metastases, cystic tumors or former hemorrhages may also have the same CT findings. Overall, the CT is not sensitive enough for diagnosing the inflammatory disorders of the central nervous system, therefore, MRI should be the primary imaging method of the assessment. Of course the diagnosis is based on the analysis of cerebrospinal fluid.

Tumors

Intracranial tumors, if being larger than 2-4 cm, are detected by CT imaging. Though, this method is non-specific for tumors, CT findings may contribute to the diagnosis. The sensitivity to tumors can be increased by the use of contrast materials, and if not contraindicated, always perform the *CT scan with contrast*.

Tumors are often surrounded by hypodensity due to edema. This type of edema differs from that of developed in stroke cases. In stroke cases cytotoxic edema develops, while in tumors or parenchymal inflammations (encephalitis) vasogenic edema is observed. Cytotoxic edema affects both the gray and white material, while vasogenic edema does not involve the cortex. This type of edema appears on the CT scan as “fingers of glove” following the fissures and gyri, and not affects the cortical area (Dawson’s fingers). The differentiation of edemas has therapeutic consequences too. Cytotoxic edema is mainly treated with mannitol and glycerin, while in vasogenic edema steroids are useful.

Hydrocephalus

Though, both the CT and MRI are sensitive for the detection of hydrocephalus, MRI is more efficient in revealing its pathologic background.

Degenerative disorders

In the degenerative disorders of the central nervous system (e.g. Alzheimer’s disease) no CT findings can be detected in early stages. In case of some conditions (e.g. amyotrophic lateral sclerosis or ALS) CT is negative even if the disease has progressed. In dementia the fissures become wider and the ventricles are enlarged due to parenchymal atrophy. The extent of atrophy rarely correlates with the clinical symptoms, and some atrophy is usually observed in healthy people too due to the age-related involution of the brain. Cognitive functions cannot be assessed by CT results, that is why the frightening diagnosis of mild atrophy is unnecessary.

Trauma

Computed tomography is useful in identifying the consequences of traumas involving the central nervous system. CT can reveal fractures, epidural or subdural hematomas, contusion, subarachnoid hemorrhage and cerebral edema with their mass effect. In traumatic patients the cranial cavities should be assessed carefully, because fractures of the skull base may result in bleeding from these holes, characterized by hyperdensity on CT. In case of head injury CTs should be performed with bone window to detect fractures. On CT scans epidural hematomas usually appear convex in shape, while subdural hematomas are classically crescent-shaped hyperdensities contributing to the increase of intracranial pressure. 80% of subdural hematomas (both unilateral and bilateral) are detected by cranial CT scans. The detection of subacute or chronic cases is more difficult, but the use of MRI can help the diagnosis. In case of contusion the fissures are filled with blood (traumatic subarachnoid hemorrhage) and superficial hyperdensity is detected.

Spinal CT

If the primary aim is the assessment of the spinal nerves or discs, CT imaging can be useful, but MRI shows these structures more precisely. The CT is less expensive, and able to detect the major abnormalities. For the assessment of the spinal cord the CT method is inappropriate. Usually, CT scans are performed to

show only three vertebrae in order to decrease the effect of radiation. The major part of the patients suffers from chronic diseases, and many scans are performed on them over the years. Thus, if possible, the examination should involve only three segments. If the localization is unsure and the examination is not urgent, MRI is the preferred method to reveal the diagnosis.

CT angiography

During CT angiography the scans are performed when the contrast material is injected to the vessel. This method allows the examination of the aortic arch, the carotid, the major intracranial arteries (mainly the primary arteries of the circle of Willis) and the major veins. After the reconstruction of the CT slides (source images) and the computerized data assessment the arterial system can be precisely visualized, which allows the detection of stenosis, occlusions, aneurysms, and arteriovenous malformations. In case of repeated examinations the risk of the relatively high exposure to radiation should be taken into consideration.

Ischemia and hemorrhage cannot be differentiated only by their clinical symptoms. Nowadays, CT imaging is essential before starting any specific stroke treatment.

In some cases, acute subarachnoidal hemorrhage is not shown on cranial CT scans, so negative result does not exclude the presence of SAH.

In stroke cases cytotoxic edema develops, while in tumors or parenchymal inflammations (encephalitis, abscess) vasogenic edema is observed. Cytotoxic edema affects both the gray and white matter, while vasogenic edema relatively spares the cortex

When the patient is suspect for tumors or inflammation of the central nervous system, if not contraindicated, always perform the CT scan with contrast media.

CT imaging is inappropriate for the assessment of the spinal cord.

In case of head injury CTs should be performed with bone window to detect fractures.

Cerebral angiography, digital subtraction angiography (DSA)

In case of the less invasive diagnostic methods are contraindicated or not effective, cerebral angiography (DSA= digital subtraction angiography) is used for the detection of the diseases of intra- and extracranial vessels (e.g. the assessment of carotid arteries, arteriovenous malformations, aneurysms or the identification of the source of bleeding). Nowadays, the use of CTA or MRA makes the DSA unnecessary, but DSA is still the gold standard of vascular assessment, and more specific for the diagnosis of certain cases such as the identification of small intracranial aneurysms or cerebral vasculitis. DSA is previously used only as a

diagnostic method, though it has therapeutic values too (e.g. intracranial aneurysm coiling, intraarterial thrombolysis, mechanical thrombectomy in acute occlusions, or AVM sclerotherapy).

The complications of DSA are the allergic reaction to iodinated contrast materials, thrombosis or hemorrhage in the area of the catheter insertion, arrhythmias, epileptic seizures or even the development of stroke. In case of its diagnostic use the risks and advantages should be considered thoroughly, because CTA and MRA have far less complications.

Magnetic resonance imaging (MRI)

The spread of MRI has a great influence on the neurological patient care. As for this diagnostic method is more available, it is necessary to know its diagnostic possibilities. The physical and mathematical background of MRI is difficult, and might be frightening too, but average users do not have to be familiar with these details, such as car drivers do not have to know the technical details of the cars to be able to drive. As for MRI provides a lot of data, doctors should ask directly for the information they really need. They should be able to orientate well on the MRI scans, and know the diagnostic values of basic sequences.

Most frequently used MRI sequences

T1

- The cerebrospinal fluid is hypointense (black), and the gray material is hypointense compared to the white material.
- This scan is used for the assessment of anatomical features.

T2

- The cerebrospinal fluid is hyperintense (bright/white).
- This scan is used for the detection of white matter edemas (inflammation, tumor) and demyelination.

FLAIR (fluid attenuation inversion recovery)

- The cerebrospinal fluid is darker (hypointense), and the gray matter is brighter (hyperintense) compared to the white matter.
- A variety of T2 sequences, used for the detection of abnormalities seen in T2 scans. During the image reconstruction, the visible contrast between the tissues is inversed, which makes the cerebrospinal fluid hypointense instead of hyperintense. This method can visualize more effectively the abnormalities in the white matter, near the ventricles and the convexity. FLAIR is less sensitive than T2 sequences in the scala posterior.

Proton weighted MRI

- a kind of T2 technique with the same application area, but considerably high signal-to-noise ratio.

T1 weighted MRI with contrast material

- used for the identification of the blood-brain barrier damage (inflammations!) and tumor localization.

Specialized sequences

STIR (short tau inversion recovery)

- fat-suppression technique, used for the assessment of areas where fatty tissues may cover the abnormal condition (e.g. orbit - retrobulbar optic neuritis, spine surrounding diseases)

DWI (diffusion-weighted MRI)

- DWI is sensitive for the early detection of cytotoxic edema (within minutes). Previously, it was used only for the diagnosis of acute stroke cases, but it provides many diagnostic possibilities in neurometabolic and degenerative diseases. Combined with PWI (perfusion weighted sequence) technique, which can visualize the perfusion of certain areas after injecting contrast materials, DWI is able to show the area of the ischemic penumbra helping the patient selection for thrombolysis.

Gradient echo (T2*)

- is useful in the detection of hemoglobin degradation (hemorrhage!) and conditions accompanied by metal-containing depositions.

There are many non-conventional MRI techniques, which are not reviewed in this chapter (e.g. magnetization transfer MRI, tractography, diffusion tensor MRI, or magnetic resonance spectroscopy). Doctors interested in MRI should be familiar with these techniques too, because MRI is continuously developing. Techniques considered as curiosities today will become routine examinations soon, contributing to the development of clinical differential diagnostics.

In case of the diseases listed below MRI is the primary diagnostic method:

- lesions in the scala posterior (e.g. brainstem abnormalities, cerebellar lesions, Arnold-Chiari's malformation)
- conditions affecting the sella (i.e. sella tumors)
- diseases of the inner ear (acoustic neurinoma) and
- diseases of the white matter, which are accompanied by inflammation (encephalitis), demyelination (SM), or myelination abnormalities,
- diseases affecting the spinal cord,
- patient selection for thrombolysis,
- the detection of cortical abnormalities and minor cerebral defects in case of therapy resistant epilepsy.

The MRI examination lasts for 10-60 minutes depending on the type of the examination and the machine. During this time the patient should lay motionless. Both pulsating magnetic field and static high intensity field are used. The patient realizes the pulsating magnetic field in form of loud pulsating sound effects ("clacking").

MRI is contraindicated in the following conditions:

- patients with *pacemakers*,
- *clipped intracranial aneurysms*,
- *foreign particles* in the brain and eyes, which can be magnetized,
- intracranial insertion of *metal particles*, or
- *artificial heart valves*.

The possible risk of MRI should be considered for each patient individually. In some cases MRI is contraindicated, so always check these conditions before indicating it.

In case of tumors or inflammation, the use of contrast materials (gadolinium is a iodine-free contrast material) may increase the diagnostic value of MRI. Though, the application of contrasts rarely has complications, after using gadolinium, fatal dermatopathy may develop in patients suffering from renal insufficiency (nephrogenic fibrotizing dermatopathy).

MRI is preferred method in the examination of cranial parts having many osseous artefacts on CT scans, such as the region of the brainstem and spinal cord.

The use of MRI is limited in those cases when the patient does not cooperate and is difficult to be immobilized, or the primary aim is to locate the bleeding (subarachnoid hemorrhage). In the future the development of the software and alternating pulse sequences may resolve this problem.

The MRI examinations of the central nervous system

Epileptic seizures

MRI should be indicated for those patients, who had their first epileptic seizures and did not experience head injury before the attack. By using 3 different planes, MRI is more specific in the detection and localization of seizure-provoking abnormalities than CT. Coronal MRI is sensitive for the assessment of temporal lobe defects. By using MR imaging, arteriovenous malformation, tumors, cortical dysgenesis and the disorders of gray matter migration can be also detected in the background of epileptic seizures.

Headaches

MRI should be indicated in those cases, when CT is unable to reveal the background of the newly developed or progressive headache, because MRI can detect smaller tumors, arteriovenous malformation, cerebral venous thrombosis, small subdural hematomas, aneurysm, intracranial hypotension syndrome and hydrocephalus, too.

Stroke

In case of acute stroke, cerebral CT should be indicated primarily to exclude hemorrhage.

Conventional MRI is more sensitive than CT in the detection of

- subacute bleeding or hemorrhagic transformation,
- small infarctions within 48 hours after the onset of the symptoms,
- infarctions located in the scala posterior,
- pathologic disorders imitating stroke (e.g. tumors),
- sinus thrombosis,
- new MRI techniques (DWI - diffusion-weighted MRI) can indicate the localization of the lesion even a few minutes after the ischemic event.

Head injuries

In the primary care of head injuries CT is recommended to assess extraaxial bleeding (sub- or epidural hemorrhages), acute brain damage or acute cranial fractures (bone-window). MRI is commonly used in the subacute period for the detection of smaller contusions or shearing injuries of the brain.

Dementia

MRI is useful for the examination of patients with dementia, because it is more sensitive for those conditions that may cause dementia (such as tumors, multiple infarctions, microbleeds, thiamin and B₁₂ vitamin deficiencies, white matter disorders, infections and Creutzfeldt-Jacob's disease) than CT. In case of primary dementia, MRI is able to measure the extent of cerebral atrophy quantitatively, by using new techniques.

Multiple sclerosis

In SM patients MRI is useful in the detection of those demyelisation lesions, which are invisible on CT scans. Specific periventricular MRI findings may be identified in the brain, even if the cerebral symptoms are missing (e.g. retrobulbar neuritis or spinal cord symptoms), and they can help to assess the onset and localization of the disease. By using contrast material, small inflammations can be identified too, which may have therapeutic consequences.

Spine and spinal cord

MRI is recommended for the assessment of diseases involving the spine and spinal cord. MRI is sensitive for the detection of intraspinal tumors, metastases, meningeal carcinomatosis, syringomyelia, hematomyelia, inflammations, and disc-related disorders.

Congenital anomalies

MRI is a valuable method for the detection of congenital anomalies, such as Dandy-Walker's cyst, Arnold-Chiari's malformation, or the agenesis of the corpus callosum. It is able to show the fine details of brain dysmorphia (myelisation disorders, gray matter disorders).

Magnetic resonance angiography (MRA)

MRA technique is able to visualize the vessels non-invasively. The reconstruction of flow signals detected in the vessels allows the assessment of intra- and extracranial vessels.

MRA has two major techniques: TOF (time of light) and PC (phase-contrast) MRA. TOF-MRI detects the differences of the signal amplitudes of moveless and moving tissues, while PC-MRA evaluates their phase-difference.

The use of MRA is limited, because movement-generated artefacts and turbulent flows may disturb the imaging. However, it is a useful supplementary method for the assessment of stenosis, aneurysms, AVMs, intracranial sinuses and veins.

SPECT

Single-photon emission computed tomography (SPECT) is a nuclear medicine tomographic imaging technique using gamma rays. It is very similar to conventional nuclear medicine planar imaging using a gamma camera, however, it is able to provide true 3D information but with relatively low resolution. Soluble gamma emitting isotopes are injected into the patient, such as gallium isotopes, which accumulate in the relevant organs and tissues. In many cases isotopes are linked to special ligands specifically binding the target organs or tissues, which allow further indications. The accumulated gamma emitting isotopes are detected by gamma cameras, and the amount of emission can be given quantitatively. After the intravenous injection, the isotopes distribute in the brain according to the perfusion. On those area, where the perfusion is low, hypoactivity is detected, while in case of hyperperfusion the activity is increased. This is an unspecific signs not referring to the etiology!

The most common indications of SPECT:

- *Cerebrovascular diseases* (the use of SPECT is limited in acute conditions, but it can help the assessment of perfusion before stenosis related operations, and by using acetazolamide it helps to select the patients for surgeries, too.)
- In *epilepsy* the detection of the perfusion may help the identification of the epileptic center (during the seizure, the activity is significantly increased).
- Some type of *dementia* can be characterized by the pattern of hypoperfusion (SPECT has a limited differential diagnostic value!).
- In case of *intracranial tumors*, SPECT may help to differentiate the active and necrotic areas, and allows the selection of the appropriate area for biopsy.
- Gallium SPECT is useful in the identification of *intracranial inflammations affecting the bones* (osteomyelitis).

PET

In case of PET (positron emission tomography), short-lived carbon, nitrogen, oxygen or fluorine isotopes are injected to the patient's vessel. The isotope is linked to a biologically active molecule, and these two are called together as tracer. After a certain time period, the active molecules are accumulated in the relevant tissues (for the FDG it takes an hour). After the patient is laid into the scanner, the actual imaging starts, and the PET camera detects the photons emitted during the process of annihilation (the interaction of positrons and electrons).

The resolution of PET images is significantly less than CT's, but besides the static imaging, it provides information on the tissue function, too. PET scans can be combined with CT and MRI images giving both anatomical and functional information. That is why CT scanners are integrated in the modern PET machines (co-registration), which allows performing CT and PET scans at the same time, without the need of changing the patient's position.

The use of PET in the clinical practice:

- searching for tumors,
- the assessment of tumor response for therapy,
- tumor staging, searching for metastases - tracer: fluorodeoxyglucose (FDG),
- the identification of tumors of the central nervous system (malignancies or not, tumor tissue or radiation necrosis) – tracer: methionine-PET, FDG-PET.
- The PET is more reliable in the diagnosis of *dementias* than the SPECT.

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Extracranial and intracranial ultrasonography

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Introduction

Pierre Curie and his brother, Jacques Curie discovered direct piezoelectric and converse piezoelectric effects in 1880, which allowed the generation and detection of ultrasounds. Ultrasonography was used as a therapeutic and diagnostic tool for the first time in the late 1940s in medical sciences. Since the 1950s, scientific articles have been continuously reporting the results of ultrasonic examinations applied by different specialties.

Diagnostic ultrasonography operates in the frequency range of 2 to 10 MHz. The tissues absorb the ultrasound waves depending on their frequency. Ultrasounds with higher frequencies provide better resolution, but less penetration. Higher frequencies are used to assess superficial structures, such as carotid artery. For the detection of deep structures the frequency is reduced.

Applications detecting the blood flow use the Doppler phenomenon. Doppler devices have two main types: continuous wave (CW) and pulsed-wave (PW) devices. The size and depth of sample taking can be identified by using pulsed-wave technique. Doppler curves represent the differences between the frequencies of particles moving toward and away from the detector. The Doppler sign is positive if the particles are moving towards from the detector, and negative if the particles are moving away from that.

The following conditions can modify the Doppler curves without the presence of vascular abnormality:

- older age,
- conditions influencing the heart frequency: fever, anemia, hyperthyreosis, hypothyreosis,
- cardiac arrhythmias,
- aortic stenosis and insufficiency,
- arterio-venous malformation,
- cerebral vasospasm,
- dilatation of cranial vessel due to elevated CO₂ concentration.

The ultrasonography of the extracranial vessels

Nowadays, Doppler ultrasonography is the most commonly used diagnostic imaging technique for the examination of the carotid arterial system (common carotid artery, internal and external carotid arteries) and the vertebral arteries. By using the Doppler effect, ultrasonography shows not just surroundings of these arteries, but it visualizes the blood flow too (color Duplex). It can even make the flow audible (Doppler spectrum). The assessment of large arteries requires high

quality scanners and linear array transducers operating in the frequency range of 5-10 MHz.

The indications of ultrasonography

- cerebrovascular diseases,
- headaches,
- vertigo with central origin,
- unilateral visual impairment (amaurosis fugax, ischemic ophthalmopathy),
- murmurs above the supra-aortic arteries,
- blood pressure differences between arms (over 20 mmHg),
- the primary prevention of vascular disorders, if risk factors are present (diabetes, hypertension, hypercholesterolemia, smoking, positive family history),
- secondary prevention of stroke,
- before certain surgeries (e.g. coronary bypass or heart valve surgeries),
- follow-up examinations for patients with carotid stenosis or unstable plaques or after vascular surgeries.

The examination of the carotid system

The operator sits behind the patient or at the patient's side. The patient can be either in half-sitting or lying position.

A. B-mode (gray scale, real-time) **examination:** We follow the artery from the proximal part of carotid arteries and vertebral arteries to the distal part, both on cross-sectional and longitudinal view.

The external and internal carotid arteries can be differentiated by the followings:

- the external artery is usually more gracile,
- the external artery has many collateral branches, and the superior thyroid artery can be visualized well (internal carotid artery has no branches!),
- the spectrum of external carotid artery has pulsatility pattern of high peripheral resistance with the color decreasing at the end of diastole,
- by the repeated compression of the superficial temporal artery (the terminal branch of external carotid artery) oscillations can be evoked on the Doppler spectrum of the external carotid artery.

This technique visualizes the morphological variations of the vessels:

- kinking: a tight curl or bend of the artery,
- coiling: the twirling of the artery usually without flow disorders.

The lumen and caliber of vessel can also be detected:

- wide: anatomic variations (diffuse), aneurysm (local),
- narrow: hypoplasia (diffuse), distal from the occlusion.

The intima-media thickness is measured on the distal wall of common carotid artery from 1-3 cm to the carotid bifurcation. The intima-media thickness refers for the thickness of the echogenic layer of intima and the echolucent layer of media, together. Normally, it is between 0,4-0,8 mm. The value of IMT is continuously rising with the patient's age.

During *plaque-analysis*, the localization, shape, maximal thickness, surface, echogenicity and heterogeneity of the detected plaques are identified. The presence of ulcerated plaques with uneven surface increases the risk of stroke. Echolucent plaques with blood-like density referring to fatty, edematous, hemorrhagic plaques or acute thrombus are also associated with the higher risk of stroke.

B. Color duplex sonographic examination can visualize echolucent plaques, which cannot be identified on B-mode images, turbulent flows (e.g. on the surface of an excavated plaque) and other flow disorders associated to stenosis. Color duplex sonography allows angle-corrected measurement (the applied ultrasound and the blood flow should make a 60-degree angle) and color adjustment. The flow moving towards or away from the transducer is marked as red or blue, respectively.

The use of color duplex ultrasonography is necessary to measure the extent of stenosis. *There are 3 widely accepted methods:*

1. *diameter stenosis*: the residual lumen is related to the original diameter of the vessel (ECST method), or to the diameter of the intact lumen located distally to the stenosis (NASCET method).

2. *area stenosis* (used rarely): a cross-sectional examination, comparing the residual area of the maximal stenosis to the intact area of the vessel's lumen.

3. *residual lumen diameter*: the width of color sign detected at the maximal stenosis.

In case of occlusion flow cannot be detected in the affected vessel, and the color might change in the occluded part due to the adverse flow.

C. The velocity in the vessels can be documented by the application of spectral Doppler, which, besides duplex scanning, helps to detect the stenosis size.

During the examination the size of stenosis can be established by measuring the peak systolic velocity, end-diastolic velocity, and the internal carotid artery/common carotid artery velocity ratio. The upper limit of normal peak systolic velocity is 120 cm/s. Values above 120 cm/s refer to carotid stenosis of 50%. In case of young age, hyperkinetic circulation, anatomic variations (e.g. coiling) or internal carotid artery occlusion of the contralateral side higher velocity values can be measured without stenosis.

D. Compression tests

If the total or subtotal occlusion of carotid artery is suspected, the measurement of the ophthalmic artery flow is recommended. If the occlusion or significant stenosis of the carotid artery is located below the ophthalmic artery, the flow in periorbital vessels (supratrochlear and supraorbital arteries) is ceased/stopped, or even adverse flow may be detected. The carotid compression test investigates the

collateral pathways. During the test the collaterals of the external carotid artery (facial artery, superficial temporal artery) are compressed on both sides.

The examination of the vertebral arteries

The examination of vertebral arteries aims to assess the stenosis (occlusion) and flow direction. The examination of the cervical part of the vertebral artery is less reliable than that of the carotid arteries, due to the presence of veins and small vessels. The diameter of vessel varies in healthy people too, and the examination of the distal V3 segment is also limited.

The most common location of vertebral occlusions is the area where the vertebral artery originates from the subclavian artery. In case of **stenosis** the velocity is increased, and values above 100 cm/s refer to severe strictures. The occlusion or stenosis of distal vertebral artery cannot be differentiated well from the hypoplasia (the vessel diameter is less than 2,5 mm), aplasia and vertebral dissection. Well-visualized vertebral artery without flow refers to occlusion. Ultrasonography can detect proximal stenosis of more than 70% with the specificity of 99% and sensitivity of 71%.

The dissection of vertebral artery is commonly located in the V3 segment, where the artery penetrates the dura mater. The assessment of this area is limited with extracranial duplex methods, but the use of transcranial color-coded duplex sonography (TCCD) through the occipital foramen may help the diagnosis.

In case of **subclavian steal syndrome** the flow is totally or partially reversed in the vertebral arteries. Incomplete subclavian steal syndrome is developed due to the stenosis of 70-80% of the subclavian artery. Usually spectral Doppler detects bidirectional flow in the vertebral artery, and arm exercises on the affected side can provoke a flow pattern of complete subclavian steal syndrome.

The advantages of ultrasonography

- Ultrasonography is a non-invasive, inexpensive, fast and bedside diagnostic tool.
- It provides real time data about the morphology and function of the vessels in both longitudinal and transversal sections.
- It detects carotid stenosis with high specificity and sensitivity (90-99%).
- New methods are available (B-flow imaging, 3/4D imaging).

The disadvantages of ultrasonography

- operator-dependent method,
- anatomic variations,
- acoustic shadows by calcified plaques may have an influence on the results,
- the overestimation of stenosis,
- the lack of standardized criteria,

- it is less sensitive in the diagnosis of diseases affecting the vertebral arteries,
- technical difficulties: short and thick neck, high carotid bifurcation, cranky vessels, acoustic shadows, tracheostomy, non-cooperative patients, limited laying position.

Intracranial ultrasonography

Introduction

Table 1
Common arterial findings with transcranial Doppler

Vessel	Acoustic window	Depth (mm)	Velocity (cm/s)	Flow
<i>Middle cerebral artery (MCA)</i>	transtemporal	40-60	70-90	positive (towards the detector)
<i>Anterior cerebral artery (ACA)</i>	transtemporal	60-70	70-90	negative (away from the detector)
<i>Posterior cerebral artery (PCA)</i>	transtemporal	60-70	30-50	P1-positive P2-negative
<i>Basilar artery (BA)</i>	suboccipital	60-120	30-70	negative

The indications of transcranial Doppler

- if the findings of duplex sonography do not explain the symptoms of acute stroke,
- subarachnoid hemorrhage, vasospasm monitoring,
- vertebrobasilar insufficiency,
- increased intracranial pressure,
- coma diagnosis,
- paradoxical embolism (patent foramen ovale - PFO),
- embolism detection,
- intraoperative monitoring,
- arteriovenous malformation,
- to increase the efficacy of thrombolytic treatment.

Subarachnoid hemorrhage, vasospasm

After subarachnoid hemorrhage, vasospasm of the Willis' circle develops in 30-70% of the patients. It can be detected for the first time on the third day after the hemorrhage, and lasts for two weeks. The risk of vasospasm is low, if it cannot be detected by TCD even on the fifth day.

In case of vasospasm the blood flow velocity of medial cerebral artery increases. Velocity over 120 cm/s refers for diameter reduction of 50%. In case of values between 120-200 cm/s the stenosis is likely to be moderate, but values over 200 cm/s refer to severe stenosis with at least a diameter reduction of 70%. If the blood flow velocity increases to 140 cm/s, neurological symptoms develop and the risk of ischemic stroke becomes high.

Functional TCD

Functional transcranial Doppler sonography (functional TCD) is a neuroimaging tool for measuring cerebral blood flow velocity changes due to neural activation.

The most commonly used methods are acetazolamide test, apnoe test, hyperventilation, orthostatic reaction, visual stimulation and embolism detection (referring for microembolism).

Functional TCD helps to detect the cerebral blood flow velocity changes (the cerebrovascular reactivity and reserve capacity) induced by neural activation in the resistance vessels (precapillary arterioles) maintaining the persistent blood circulation of the brain.

Cerebral vasoreactivity:

$$CVR=100 \times (MCAv_{\text{test}} - MCAv_{\text{resting}}) / MCAv_{\text{resting}}$$

$MCAv_{\text{test}}$: the blood flow velocity of the medial cerebral artery measured after vasoreactive activation.

$MCAv_{\text{resting}}$: the blood flow velocity of the medial cerebral artery during rest.

Functional TCD is indicated in internal carotid artery occlusion, hemodynamic stroke, and before performing carotid endarterectomy or cardiac surgery, because patients with decreased reserve capacity are likely to have an increased risk of stroke.

We used to apply acetazolamide activation to detect the changes of blood flow velocity, but nowadays the non-invasive breath-holding method is preferred. We get the cerebral blood flow velocity changes in percentage, if the percentage of main velocity increase measured during breath-holding is divided by the time as long the patient is able to hold his/her breath. In healthy people the cerebral blood flow increases with 25-62%. If the blood flow velocity changes of the medial cerebral artery do not exceed the 15% of the resting value, the reserve capacity is seriously impaired.

Embolism detection

The 50% of ischemic stroke cases is caused by embolism. Usually, the embolus derives from the heart or the carotid arteries. TCD can monitor asymptomatic microembolism. The passing of microemboli temporarily increases the performance of the ultrasound, and causes high intensity signs on the Doppler spectrum (HITS). The intensity of the sign depends on the composition of the embolus (gaseous or solid).

Indications:

- stroke in early ages,
- severe carotid stenosis (over 50%),
- cardiac diseases: artificial cardiac valve, atrial fibrillation, patent foramen ovale (PFO),
- endovascular intervention (angiography),
- intraoperative monitoring (carotid or heart surgeries).

Transcranial Doppler is used not just for detecting embolism, but monitoring the efficacy of treatment too.

Transcranial color-coded duplex sonography (TCCD)

Intracranial vessels

The use of transcranial color-coded duplex sonography (TCCD) is spreading for the assessment of intracranial vessels. With the help of modern, high quality scanners and appropriate transducers (1,75-3,5 MHz), the transcranial color-coded duplex sonographic technique is even able to visualize the vessels of the Willis' circle and cerebral parenchyma comparing to the TCD. The blood flow and the localization of stenosis are detected more precisely by using vessel visualization and angle correction.

The 20% of examined patients has poor bone window, thus in these cases the Doppler sign can be enhanced by intravenous contrast material. The safe contrast material has high stability and contains microbubbles of less than 10 μm . These microbubbles enhance the Doppler sign and make more vascular segments and longer parts of lumens visible while passing through the heart and the microcapillary system. The successful detection of clinically significant vessels is increasing from 70% to over 90% by using contrast enhanced TCCD. The sensitivity of TCCD for the detection of middle cerebral arterial occlusion verified by angiography is approximately 90%, and if combined with contrast material, TCCD has the same reliability as MRA in the detection of intracranial occlusion.

Brain hemorrhage

If the hematoma is larger than 1 cm, transcranial color-coded duplex sonography can diagnose the supratentorial intracerebral hemorrhage with a specificity of 96% and sensitivity of 88%. Intracerebral hematomas are visualized as echogenic areas with sharp margin.

It is difficult to differentiate the subcortical hemorrhage (less than 1 cm), hemorrhagic transformations and cerebral tumors.

Transcranial color-coded duplex sonography can be used for visualizing subarachnoid and ventricular hemorrhage, but CT imaging is still prioritized for the diagnosis of intracerebral hemorrhage.

Parenchyma

Transcranial color-coded duplex sonography can visualize the midbrain structures and basal ganglia. In case of parkinsonism the echogenicity of the substantia nigra increases, while echolucent raphe nuclei may prognosticate depression. Connection is found between the echogenic caudal nucleus and drug-induced psychosis, while the dilatation of the horns of the cerebral ventricles, exceeding 20 mm, may refer to dementia.

TCCD is able to detect the position and diameter of cerebral ventricles, allowing the visualization of dilated or dislocated ventricles.

Thrombolytic treatment

Transcranial Doppler operating with the frequency of 2 MHz is able to enhance the activity of tPA applied for thrombolysis. The results of the CLOTBUST clinical trial showed, that thrombolysis combined with ultrasonography resulted in complete recanalization in 25% of the patients within 2 hours after the thrombolytic treatment, compared to the 8% of the patients receiving only tPA. Combined therapy also resulted in better outcome 3 months after the stroke event (the difference between the two group was 13%). Both TCD and TCCD are used for monitoring the recanalization of the occluded vessels.

In the future the use of microbubbles may enhance the thrombolytic treatment combined with ultrasonography due to the mechanical grinding of thrombi, or the transportation of drugs eliciting thrombolysis.

The use of contrast materials increases the rate of recanalization from 38% to 55%, if it is administered 2 hours after the ultrasound-combined thrombolytic treatment.

Contrast-enhanced sonographic techniques are widely used for the monitoring of oncotherapeutic treatment with angiogenesis inhibitors. Angiogenesis inhibitors do not decrease the tumor size in the early stages, but they cause necrosis and microvascular changes, which can be detected by contrast-enhanced sonography.

The developing ultrasound modalities are necessary in the diagnostics, monitoring or treatment of cerebrovascular diseases. They provide fast and safe bedside assessment in acute cases, and may replace other imaging techniques too.

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Muscle, nerve and brain biopsies

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Muscle biopsies

Proximally dominant muscle weakness, cramps, fatigue, pain can be caused by myositis, myopathy or muscular dystrophy (on the other hand in case of fluctuating muscle weakness myasthenia gravis should also be considered). Age of the patient, positive or negative family history, the pattern of weak, atrophic or painful muscles help to further differentiate these conditions. Neurogen or myogen etiology of muscle disease can be well distinguished by electromyography. It is also necessary to check serum levels of CK, LDH, AST (GOT), ALT (GPT). Changes in serum electrolytes, lactate, pyruvate, ammonia, thyroid gland function might result in myopathies, elevated red blood cell sedimentation rate, CRP, and anti-Jo positivity in some cases refers to myositis. To confirm the pathology in the background of the muscle disease biopsy should be taken.

Muscle biopsy is taken by a surgeon as a one-day-surgery procedure within approximately 20-30 minutes. After applying local anaesthetics to the skin and subcutaneous tissues, a 1 cm³ muscle tissue has to be removed. Since local anaesthetics cause artefacts during the histopathological processes, anaesthetics are not allowed in the muscle itself, making the removal step unpleasant. Removal of the muscle block does not affect muscle function.

Selection of the muscle to biopsy:

- chronic disease: muscle with moderate weakness,
- acute disease: muscle with severe or moderate weakness,
- best specific muscles: deltoid, biceps, quadriceps, tibial anterior.
- MRI can be used to select pathological muscle site in difficult cases.
- Avoid muscles that were site of EMG within 6 weeks, or those with injections, or trauma!

Handling of sample:

- Muscle tissue can be kept at room temperature in a sterilized gauze for a few minutes. Fixation should be performed as soon as possible in isopentane cooled in liquid nitrogen (-160 °C). Frozen blocks can be kept at -80 °C for years. One piece of the tissue is also fixed in 4% glutaraldehyde and embedded in plastic for ultrastructural analysis and electronmicroscopy.

Muscle biopsy stains:

- **Histochemical reactions: hematoxylin and eosin staining** is used for description of general morphology, other methods give detailed information about different subcellular structures (Gömöri trichrom – sarcoplasmic reticulum and mitochondria, Oil red O – fat, PAS – glycogen, acid phosphatase - lysosomes).
- **Histochemical reactions:** ATPase staining – differentiation of fibre types (1, 2A and 2B), NADH-TR – mitochondria, succinate dehydrogenase (SDH) – mitochondria, cytochrome oxidase (COX) – mitochondria, phosphorylase – sarcoplasmic reticulum.
- **Immunohistochemistry:** in order to differentiate between different forms of muscular dystrophies special proteins are stained with antibodies (eg. dystrophin, sarcoglycans, desmin, dysferlin, caveolin, utrophin, emerin).
- **Thin sections:** 1 μm thick, analyzed with light microscopy, gives information about capillaries, intermyofibrillar and cytoplasmic bodies.
- **Electronmicroscopy:** rarely used, gives detailed information about mitochondria, sarcomeres.

Important things to consider upon analysis:

- diameter and variability of diameter of muscle fibres,
- shape: rounded or angular,
- fibre types: grouping, fibre type predominance,
- fibre necrosis,
- myofibrillar anomalies (eg. vacuoles, abnormal distribution of nuclei, inclusion bodies, storage material – glycogen, lipids, mitochondria),
- inflammatory cells, cell types,
- amount of connective tissue.

Based on the above mentioned conditions neuropathologists can differentiate between neurogen or myogen muscle damage, inflammation (myositis), necrosis (muscular dystrophies, severe cases of myositis, severe metabolic myopathies), muscular dystrophies and myopathies. Muscle disease caused by motoneuron, radicular or peripheral nerve pathology can also be differentiated.

Nerve biopsies

After confirming polyneuropathy by electroneurography (ENG) detailed laboratory tests help to uncover the etiology of the disease. In case of asymmetric symptoms, when ENG reveals mononeuropathy multiplex, and laboratory tests do not give exact diagnosis nerve biopsy should be considered.

Biopsy is taken from the sural nerve in most cases, because injury of this pure sensory nerve will not result in paresis. On the other hand, long lasting paresthesia and numbness on the skin innervated by the sural nerve can be a late consequence. An approximately 1 cm long, half cylinder piece of the nerve is removed by a neurosurgeon. The nerve sections are then viewed by a neuropathologist. Ultrastructural analysis is also available by electronmicroscopy. In extremely rare cases, when exclusively motor fibres are affected, biopsy can be taken from the radial superficial nerve or the innervating motor fibres of the extensor digitorum brevis muscle of the lower extremity.

Sural biopsy is most informative in mononeuritis multiplex caused by vasculitis, in these cases infiltration of vasa nervorum by mononuclear cells can be observed. In addition, biopsy is also helpful in the diagnosis of polyneuropathy caused by amyloidosis, sarcoidosis, different storage diseases (Fabry, Krabbe, metachromatic leukodystrophy), or leprosy.

Formerly, sural nerve biopsy was used for the diagnosis of several hereditary neuropathies (eg. hereditary neuropathy with liability for pressure palsies, HNPP) or in chronic inflammatory demyelinating polyneuropathy (CIDP). Today these diseases can be diagnosed by genetic or special laboratory tests without performing a nerve biopsy.

Brain biopsies

In cases of intracranial undetermined diseases with uninformative imaging data brain biopsy should be performed for exact diagnosis. This method is also very helpful when the pathology involves eloquent areas of the brain.

Appearance of glioma, primary intracerebral lymphoma, brain abscess, and inflammation caused by opportunistic pathogens can be very similar on CT or MRI scans. Differentiation of these conditions is also possible by biopsy. Headache, focal neurological signs can be caused by primary intracerebral vasculitis, which can be diagnosed by the biopsy of the temporal lobe of the subdominant hemisphere and leptomeningeal vessels. Immunohistochemical staining of prion proteins in brain biopsies is diagnostic for Creutzfeldt-Jakob disease which results in progressive dementia, myoclonus, and ataxia. In cases of patients with cognitive dysfunction, personality change, dementia and focal neurological signs, progressive multifocal leukoencephalopathy should be considered. Inclusion bodies in oligodendrocytes confirms diagnosis in these cases.

Laboratory investigations in neurology

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Measurement of serum drug levels

The maintenance treatment of several neurologic diseases requires the continuous monitoring of the therapeutic drug levels. The therapeutic drug concentration is the concentration that ensures adequate efficacy under usual circumstances without any toxic symptoms.

An important aspect of the investigation is the timing of blood sampling. In case of evaluating the blood level of a newly administered drug, the investigation should be done after the evolution of the steady state. In case of insufficient drug effect the timing of blood sampling should be when the lowest serum/plasma concentration is anticipated (e.g. immediately before taking the first morning dose). If toxic side effects emerge the investigation should be done when the peak concentration of the drug is expected (after administration of the drug, taking the method of administration, the formulation and the pharmacokinetic peculiarities of the medication into consideration).

Indications of the examination:

1. *Absolute indication:* signs and symptoms of drug toxicity, suspicion of drug interaction, biological change requiring dose correction (age, body weight, pregnancy).
2. *Relative indication:* establishment of the steady state concentration, clarification of insufficient drug effect, monitoring the change of dose or medication, monitoring compliance.

One of the treatments where therapeutic drug monitoring is very frequently used is the antiepileptic therapy. Determination of carbamazepine and valproic acid is possible under routine laboratory conditions, examination is done using native blood. The therapeutic dose range for carbamazepine and valproic acid is 4-10 mg/L and 40-100 mg/L, respectively.

Monitoring the therapeutic efficacy is very important for oral anticoagulants (e.g. warfarin, acenocoumarol). The aim is to maintain the INR value in the range recommended by specific treatment guidelines (for example in case of artificial heart valve the target INR is between 2.5 and 3.5, for biological heart valves and chronic atrial fibrillation it is between 2 and 3). Oral anticoagulant therapy requires individual INR evaluation and titration.

Generally speaking an INR below 2 indicates therapeutic insufficiency, whereas values above 4 mean increased risk of bleeding. The patient's attention should be called to take precautions to avoid any mechanical trauma.

It should be noted that numerous medications may increase or decrease the effect of oral anticoagulants:

Increases: amiodaron, anabolic steroids, aspirin (salicylates), azapropazon, cimetidine, danazol, dextran, erythromycin, ethacrynic acid, vitamin E, phenacetin, phenylbutazone, fluconazole, glucagon, indomethacin, itraconazole, ketoconazole, quinidine, quinine, kloroquin, chlorpromazine, clofibrate, colchicine, metronidazole, miconazole, nalidixic acid, naproxen, penicillin, paracetamol, piroxicam, sulfapyrazone, sulfonamides, tamoxifen, tetracycline, thyroid hormones.

Decreases: barbiturates, phenytoin, oral contraceptives, ginseng, glutethimide, haloperidol, carbamazepine, cholestyramine, corticosteroids, vitamin K, metformin, estrogens, rifampin, spironolactone, thiazide diuretics.

Additionally several foods *decrease* the effect of oral anticoagulants: apple, avocado, broccoli, strawberry, cooking oil, mushrooms, cabbage, cauliflower, liver, raspberry, orange, pepper, tomato, carrot, lettuce, asparagus, spinach, egg, butter, green beans and green tea.

Determination of hormone levels

The hypothalamo-hypophyseal axis is an endocrine system that has the most explicit influence on the central nervous system. Any malfunctioning, or hormonally active tumors of the endocrine organs belonging to this system may be detected by determining the blood levels of the hormones produced. Therapeutic efficacy for these conditions may also be monitored. The large number of hormones and releasing factors justify the involvement of an endocrinologist.

Assessment of thyroid hormones (T_3 , T_4) is also fundamental in neurology as these hormones have an important role in the normal development and functioning of the central nervous system. In view of this it is not surprising that both hypo- and hyperthyroidism manifest in neurologic symptoms as well.

Hypothyreosis

Hypothyreosis is one of the most common hormonal abnormalities. It can be easily diagnosed by using laboratory examinations. Its presence must be ruled out in cases of infertility of women of childbearing age, and elderly people with slowed psychomotor function, or depressive disorder. The most prevalent acquired form is the (advanced stage) autoimmune Hashimoto's thyroiditis. The adult onset form starts insidiously, fatigue, lethargy, uncertain muscle cramps, hypothermia, cold intolerance and decreased relaxation time of deep tendon reflexes may be present years before the diagnosis. In the full blown form of the disease every known psychotic symptom may be present although (reversible) dementia and depressive disorder can be seen most often.

Due to the age-dependent decrease in the functioning of the thyroid gland elderly people often suffer from hypothyreosis. Since these patients are more

susceptible to the resultant decrease in thyroid hormones the probability of developing manifest symptoms is higher. The prevalence of both hypothyreosis and depression increases with age, and since the two diseases may interact, depression recalcitrant of antidepressant medication may respond well to L-thyroxine.

Susceptibility to cerebrovascular diseases

Accelerated atherosclerosis due to low thyroid hormone levels may stand behind the neurologic symptoms seen in hypothyreosis. Hypothyreosis predisposes to hyperlipidemia and hypercoagulability, and endothelial dysfunction may evolve. These changes may be prevented and (with the exception of manifest atherosclerosis) may be reversed by hormone replacement therapy.

Cerebellar signs

Since thyroid hormones have an important role in the development and functioning of cerebellar neurons (they modulate the specific growth factor and the transcription of other genes) an underactive thyroid gland should be suspected, if cerebellar signs (especially ataxia) emerge.

Peripheral symptoms

A common symptom of hypothyreosis is paresthesia caused by distal, symmetrical sensory polyneuropathy (with histologically proven axonal degeneration). The polyneuropathy however is rarely severe. Presence of carpal tunnel syndrome due to compression caused by the myxedematous tissues is also common. Hormone replacement usually improves these symptoms within three months, so surgical intervention should be delayed.

The most frequent symptom involving the muscles is myalgia presenting with muscle cramps and weakness with a proximal predisposition involving mainly the shoulder and the pelvic gird. Very rarely rhabdomyolysis may occur.

Hyperthyreosis

The cause of this disease is the elevation of thyroid hormones. Most often this is due to the autoimmune Graves-Basedow's disease (in 65–75% of the cases) where the TSH receptor specific autoantibodies overstimulate the thyroid gland.

Almost every hyperthyreoid patient manifests mild-moderate neurologic symptoms and psychiatric changes. Increased irritability, excitability, hypervigilance, hand tremor, restless leg syndrome, susceptibility for anxiety, emotional lability, sleep disorder, fatigue and perhaps decreased ability to concentrate and deterioration of cognitive function may be seen.

Apathic thyrotoxicosis

Rare disease, the clinical picture resembles that of hypothyreosis. Most often it manifests in elderly women, and usually the patient hasn't been diagnosed with hyperthyreosis. Symptoms include slowed psychomotor function, lethargy, apathy, depressive disorder. Other symptoms may include extensive weakness of the

proximal muscles (shoulder and pelvic gird). Weight loss is frequent, however the typical symptoms of thyrotoxicosis are not present. The patient may gradually fall into coma without any antecedent alarming symptoms.

Hyperthyroid dementia

Dementia may be seen in the presence of an overfunctioning thyroid as well, however this is less frequently diagnosed than the dementia of hypothyroidism. The significance of precise diagnosis is that unlike the clinically closely resembling Alzheimer's disease, this form of dementia responds well to therapy (although the objective cognitive dysfunction may remain even after therapy).

Other central nervous system symptoms

A quickly progressing form of hyperthyroidism may manifest with confusion, and the development of focal and/or generalized epileptic seizures. If hyperthyroidism co-exists with epileptic seizure the frequency of seizures may increase and status epilepticus may develop. Spasticity, pyramidal signs, brisk reflexes may be present as isolated symptoms, that improve upon therapy.

Myopathy

In case of the myopathy of a middle aged patient (especially man) the possibility of an overactive thyroid gland must be investigated. Progressive weakening and atrophy of the skeletal muscles in the pelvic gird is the most common symptom, urine creatinine may be a little elevated, however it shows no correlation with the severity of muscle weakness. Isoenzymes are not elevated in the blood, in fact they may decrease (as opposed to the myopathy of hypothyroidism, where CK is elevated). EMG is normal. Biopsy of the swollen muscles shows many degenerated fibers with lymphocytic, monocytic and adipocytic infiltration. The swelling of the external ocular muscles may cause weakness, and space-occupying lesions at the tip of the orbit may lead to the ischemic lesion of the optic nerve.

Myasthenia gravis

Both hyperthyroidism and hypothyroidism may be complicated with this typical autoimmune disease. Five percent of myasthenic patients are known to have hyperthyroidism as well, and myasthenia gravis is 20-30 times more prevalent among hyperthyroid patients, compared to the whole population.

Polyneuropathy

The thyroid must be investigated for overfunctioning in case of demyelinating, lower extremity dominant polyneuropathy involving the motor fibers, since hyperthyroidism may be the cause. Very rarely acutely evolved lower extremity weakness can be the manifestation of thyrotoxicosis (Basedow's paraplegia).

Determination of biomarkers

For many years the paradigm of „one therapy fits all” was sufficient, but nowadays trends seem to be shifting to the „right medication at the right time, for the right patient” approach, leading to personalized medicine. Biomarkers (objectively quantifiable biochemical parameters that provide information about the presence, severity or increased risk of a disease or state, and possibly about the probability of the success of a therapy) are anticipated to assume a significant role in personalized medicine. The combination of information derived from different biomarker sources is becoming more and more important. Use of biomarkers enables the identification of patients who will probably respond to a specified medication, or who are likely to develop an untoward side effect. This is made possible by the fact that different populations have different response to the same medication due to genetic reasons. Using biomarker diagnostics both untoward side effects and poor response to therapy can be screened. Identification of novel biomarkers and elucidation of disease mechanisms all mandate the establishment of biobanks and relating epidemiologic databases. In 2007 the Hungarian Clinical Neurogenetic Society established a biobank called NEPSYBANK with the participation of all four Hungarian medical universities. They collect the samples of patients with neurologic and psychiatric diseases.

S-100 protein

S-100 proteins (named after the fact that they dissolve 100% in ammonium-sulphate solution used to denaturize proteins) are Ca^{2+} -binding proteins with a regulatory role, similar to calmodulin. They are only present in certain cell types e.g. cells derived from the neural crest. Different isotypes may be found in different cell types, and their intracellular concentration depends of the environmental factors influencing the cell. The blood level of some isotypes is elevated in certain malignancies (e.g. malignant melanoma, malignant schwannoma, paraganglioma, clear cell sarcoma), therefore they are used as tumor markers. This use however is not widespread (Nonaka et al, 2008; Lab Tests Online).

The neurological significance of S-100 protein is that the S-100B isotype is elevated in case of brain trauma, following ischemic or haemorrhagic stroke and in conditions where the blood-brain barrier is damaged. It has a prognostic value, a higher S-100B value generally indicates shorter survival. In case of the brain damage of a fetus S-100B level is elevated in the amniotic fluid as well as in the umbilical cord blood (Bánfalvi et al, 2004).

Neuron-specific enolase

The neuron-specific enolase is a glycolytic enzyme present in the plasma of neurons and neuroendocrine cells. As a tumor marker it may be used to monitor the therapeutic efficacy in neuroblastoma and small cell carcinoma of the lung but its blood and liquor value is an indicator of the severity of stroke (Lab Tests Online; Skopál, 2002).

Molecular genetic examinations

In some neurological diseases the precise diagnosis mandates the identification of a certain genetic abnormality. These include spinocerebellar ataxia (primary ataxia, showing autosomal dominant trait) as the 17 subtypes cannot be differentiated purely on basis of the clinical syndrome. Spinocerebellar ataxias are caused by trinucleotide repeats. All subtypes have a specific gene with a specific trinucleotide repeating sequence (e.g. CAG or CTG). The trinucleotide repeat may be identified with great precision using appropriate DNA tests, therefore the clinically similar ataxia types may be identified (Klívényi et al, 2004).

The assessment of onconeural markers

The so called onconeural antigens are physiological macromolecules that show cross reaction with tumor specific antigen effectors (antibodies, cytotoxic cells, etc) of the immune system. Due to the cross reaction paraneoplastic syndromes may evolve (PNS) and as autoimmune neurodegenerative disease they have various forms: polyneuropathy, motoneuron disease, dementia, ataxia, epilepsy. Although these diseases may have numerous other causes (genetic, metabolic, inflammatory or toxic) the autoimmune origin may be proved by detecting the antibodies in the blood that cross react with the onconeural oncogenes. These so called onconeural markers play an important role in the early identification and typing of the underlying malignancy and even in assessing prognosis. Identification of paraneoplasia and detection of onconeural markers provides an opportunity to offer personalized therapy for a malignancy before other symptoms emerge.

Approximately 14 autoantibodies were identified in neurological diseases (Table 1.; Darnell and Posner, 2006; Kovács and Voigtlander, 2004). The so-called “well defined antibodies” were identified in large laboratories, assessing a large number of patients. The “partially defined antibodies” include those antibodies that were described in only one laboratory or in a few patients. Antibodies belonging to the third group may be seen in both the presence and absence of malignancies.

Numerous neurological diseases may have a paraneoplastic etiology including paraneoplastic limbic encephalitis (PLE), paraneoplastic cerebellar degeneration (PCD), opsoclonus-myoclonus-ataxia syndrome and paraneoplastic encephalomyelitis (PEM). In addition to this several malignancies may manifest as neurologic diseases, different neuropathies, stiff person syndrome, motoneuron disease, and chorea. The most prevalent paraneoplastic disease of the peripheral nerves is called peripheral sensory neuropathy syndrome (PSN), but additional to this several (acute and chronic) neuropathies, plexus lesions may suggest a paraneoplastic pathology.

The two characteristic paraneoplastic diseases of the neuromuscular junction are the Eaton-Lambert syndrome linked to the small cell carcinoma of the lung, and thymoma seen with myasthenia gravis. Of the diseases of the skeletal muscle paraneoplastic origin must be ruled out in case of dermatomyositis, polymyositis and necrotizing myopathy.

Table 1

Paraneoplastic antibodies, related malignancies and related symptoms
 (PEM: paraneoplastic encephalomyelitis, PSN: paraneoplastic sensory neuropathy,
 PCD: paraneoplastic cerebellar degeneration)

Antibody	Cloned genes	Malignancy	Symptoms
Well defined antibodies			
<i>Anti-Hu</i>	HuD, HuC, HuB	small cell lung cancer, neuroblastoma	PEM, PSN, autonomic dysfunction
<i>Anti-Yo</i>	CDR34, CDR62	ovary, breast, lung	PCD
<i>Anti-Ri</i>	Nova	breast, gynecologic, lung, bladder	
<i>Anti-CRMP5</i>	CRMP5	small cell lung cancer, thymoma	PEM, PCD, PSN
<i>Anti-amphiphysin</i>	Amphiphysin	small cell lung cancer, breast	stiff-person syndrome
<i>Anti-Ma2</i>	Ma2	testis	PEM, brainstem encephalitis
<i>Anti-recoverin</i>	Recoverin	small cell lung cancer	carcinoma associated retinopathy
<i>Anti-titin</i>	Titin	thymoma	myasthenia
Partially defined antibodies			
<i>Anti-Zic4</i>	Zic4	small cell lung cancer	PCD
<i>Anti-mGluR1</i>	Glutamate receptor	Hodgkin disease	PCD
<i>Anti-Ma1</i>	Ma1	lung, other	PCD, brainstem encephalitis
<i>Anti-PCA-2</i>	?	small cell lung cancer	PEM, paraneoplastic myasthenic syndrome
<i>Anti-gephyrin</i>	Gephyrin	unknown	stiff-person syndrome
<i>Anti-Tr</i>	?	Hodgkin disease	PCD
<i>Anti-ANNA3</i>	?	lung	PEM, PSN
<i>Anti-bipolaris retina cell</i>	?	melanoma	melanoma associated retinopathy
Antibodies presenting with or without malignancies			
<i>Anti-VGCC</i>	P/Q type VGCC	small cell lung cancer	Eaton-Lambert syndrome
<i>Anti-nAChR</i>	Nicotinic AChR	small cell lung cancer	subacute autonomous neuropathy

*Diagnosis of paraneoplastic diseases***Serologic diagnosis**

In many cases paraneoplastic processes if linked to malignancies of high immunogenicity cause symptoms, before detection of the tumor would be possible using routine diagnostic methods. If a paraneoplastic disease is highly suspected it is possible to search for autoantibodies specific for onconeural antigens in the patient's blood or cerebrospinal fluid. As an initial screening, the patient's serum should undergo immune-histochemical assessment using either rat or human brain slices. Afterwards if the possibility of paraneoplasia is still open Western blot examination of the patient's serum is recommended using rat or human brain homogenate. In addition to this specific screening for onconeural autoantibodies may also be performed by immune-blotting cloned and purified onconeural proteins. High specificity of these examinations is indicated by the fact that in the event of positivity for a single autoantibody's there is a near 100% chance for a paraneoplastic syndrome. In case of positive results the malignancy should be identified as soon as possible.

Positron-emission tomography (PET)

If the routine diagnostic work-up is unsuccessful but there is a strong suspicion for paraneoplasia, whole body FDG-PET (fluoro-dezoxi-glucose positron emission tomography) may be done to detect the tumor.

Laboratory investigation in dementia

Although the diagnosis of dementia is based on clinical examination, differential diagnosis mandates the following laboratory investigations: blood glucose, qualitative and quantitative blood count, T_3 , T_4 and TSH (thyroid stimulating hormone), B_{12} (serum cobalamine), serum carbamide, AST and ALT (aspartate transaminase and alanine transaminase), LDH (lactate dehydrogenase), and γ -GT (γ -glutamyl transpeptidase).

Treponema, Borellia and HIV serology is indicated if such infection is suspected based on the case history.

Laboratory assessment of cerebrospinal fluid is only needed if nuchal rigidity is present or if pathogens, malignant cells or indicators of Creutzfeldt-Jakob disease are anticipated in the liquor based on the clinical symptoms. Presence of β -amiloid and (phospho)tau protein in the cerebrospinal fluid indicates Alzheimer type pathology, but these investigations are not recommended routinely either.

Genotyping is a tool for early diagnosis in Huntington's chorea. Genetic investigation may be contemplated if other forms of familial dementia are suspected, but this isn't performed routinely either (EÜM; Tariska et al, 2002).

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Ischemic cerebral stroke

LÁSZLÓ CSIBA MD.

Stroke (brain attack)

Stroke is a rapidly developing neurological syndrome caused by cerebrovascular circulatory insufficiency. Strokes can be classified into two major categories: ischemic and hemorrhagic strokes. About 80-85% of stroke cases are caused by ischemia, and the remainder by hemorrhage. The main types of hemorrhagic stroke are the spontaneous intraparenchymal hemorrhage and the non-traumatic subarachnoidal hemorrhage. The abnormality of intracranial vessels and sinuses can also produce various symptoms, including the symptoms of strokes.

Stroke is the third leading cause of death in the world, and the major cause of permanent disability. Approximately 50,000 stroke cases occur in Hungary each year, and less than 20% of nonfatal hemorrhagic stroke survivors will be independent. The prognosis of ischaemic stroke is better, one third of the patients would regain their independency, one third would be fatal, and one third would need more or less assistance in the future. In Hungary, strokes mainly develop in the average age of 68 for men and 74 for women but 8% of the patients are younger than fifty years.

Symptoms

As it is discussed in a chapter about the emergency cases, hemorrhagic and ischemic strokes can not be differentiated from each other only with the help of neurological investigations. They have similar risk factors:

- hypertension,
- diabetes,
- dyslipidemia
- morphological and functional abnormality of the heart (arrhythmias, valve defects etc.),
- coagulopathies,
- atherosclerosis, inflammation or degeneration of the vessels (eg. dissection).

If the patient has several risk factors, the symptoms developing in the morning, and the patient is conscious, then ischemia might be in the background. In these cases, usually, the blood pressure is elevated but not very high. Bruit might be detected above the carotids.

Hemorrhage usually develops during daily activity, accompanied by serious symptoms of severe hemiparesis, rapidly impairing consciousness, livid face, forced breath and high blood pressure.

In case of embolism the symptoms develop suddenly without any warning sign, however, the patient often has cardiac disorders in the medical history. In most of

the cases damage of the cortex is typical (such as aphasia or visual field abnormalities), which may improve later.

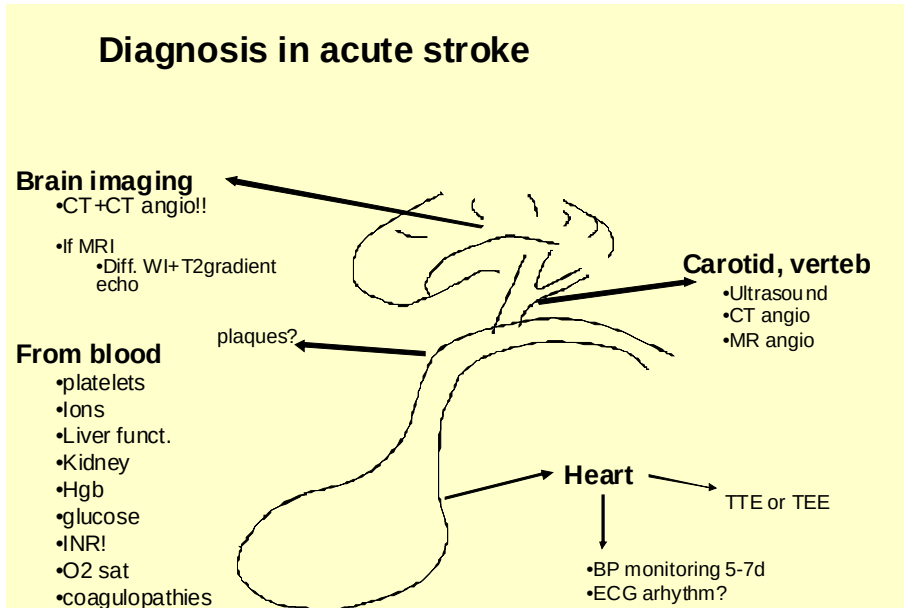


Figure 1
summarizes the most important diagnostic examinations in stroke.

We would like to highlight four of them:

- computer tomography (with angiography if possible),
- cervical and transcranial ultrasound,
- ECG and echocardiography,
- laboratory examinations.

The main symptom of the subarachnoidal hemorrhage is thunderclap headache often accompanied by nausea and vomitus, which usually develops when the patient defecates or performs physical effort (e.g. lifting weight). **The bleeding affects the subarachnoidal space (not always intrudes into the parenchyma)**, that is why hemiparesis rarely develops in the early stages. However, it may also happen that the bleeding (provoked e.g. aneurysm rupture) intrudes into the parenchyma. Hemiparesis can also develop 5 or 7 days later, due to the appearance of a serious consequence, the vasospasm.

Both hemorrhagic and ischemic strokes can affect the hemispheres (carotid or supratentorial stroke) or the brain stem (infratentorial or vertebrobasilar stroke) or they can combine.

Symptoms of carotid artery disease and stroke

Supratentorial circulatory insufficiency, developed in 80% of stroke cases, is characterized by unilateral symptoms. If the middle cerebral artery is affected, paresis is more severe in the upper extremity less severe in the lower extremity. The paresis of the lower extremities develops more rarely, and refers to the ischemia or hemorrhage of the area supplied by the anterior cerebral artery. If both upper and lower extremities are equally affected, internal carotid occlusion can be the pathological background. If the ischemia involves the cortical region of the dominant hemisphere, aphasia might be present. Difficulties of the orientation in space suggest the damage of the right hemisphere.

Vertebrobasilar insufficiency

The 20% of stroke cases is caused by vertebrobasilar insufficiency, which can be characterized by dominating brain stem symptoms, such as suddenly developed double vision, dizziness, dysarthria or dysphagia, gait and limb ataxia. Paresis can be unilateral, but it may affect an arm and a leg on the opposite sides (crossed paresis), or all the four extremities (tetraparesis). If the reticular formation is affected, somnolence, stupor or coma can develop.

The following diseases can imitate a hemiparetic stroke event: epileptic seizures followed by hemiparesis (Todd's paresis), hypoglycemia, subdural hematoma, encephalitis in early stage, tumor, atypical migraine, multiple sclerosis.

**The most important task of general practitioners
in the management of acute stroke**

The most important: the exact time of the onset of symptom(s).

As part of the primary care, the first person noticing the stroke event should record the patient's medication and medical history (with particular attention to vascular disorders, surgeries or malignancies).

Document carefully the results of examinations and the applied medication, and record the exact time of the examination, too.

Document any changes in the patient's condition during the observation (unconsciousness, paresis in the upper or lower extremities, aphasia, vomitus, pupils, eye bulbs?). Did the patient have urinary or defecation problems, or epileptic seizure?

Measure the blood pressure on both side. If the ambulance is delayed, measure it in every 15 minutes.

Test blood glucose level. Avoid giving glucose infusion, unless the patient has severe hypoglycemia (1-2 mmol/l). Do not reduce the blood pressure till 220/110 mmHg. Above this value or if cardiac failure develops during the observation and the blood pressure is abnormal, captopril, urapidil and/or diuretics should be administered.

The patient should lay in half-sitting position. Take care for the prevention of aspiration, and urinary retention. If the patient is unable to urinate, catheter is indicated.

The most important task is to transfer the patient with acute stroke to an institute, where urgent CT examination (and if needed, thrombolysis) is available.

Hemorrhage and ischemia can not be differentiated from each other clinically, because they might have the same symptoms.

Optimally, stroke patients having compensated cardiorespiratory condition and normal conscious state, should be delivered directly to imaging laboratories, where the neurological evaluation and CT or MRI can be performed immediately.

The treatment of TIA (transient ischemic attack)

Symptoms of TIAs usually last for less than an hour. In case of TIA, the risk of stroke is increasing with the patient's age, the duration of symptoms (especially aphasia), and associated diabetes. TIA clinics, being organized widely, prevent stroke cases efficiently by the diagnosis and treatment of intermittent or permanent arrhythmias, carotid stenosis, inherited or aquired disorders of hemostasis and cardiac disorders.

Thrombolysis in acute ischemic stroke

Venous thrombolysis should be performed within 3 hours after the first symptoms. If the patient is younger than 80, does not suffer from diabetes, had no stroke in his/her medical history does not take any oral anticoagulant, and the area of hypodensity is less then 1/3 of the MCA area, thrombolysis time window can be extended till 4,5 hours. **Before starting the treatment, CT scan must be performed!** CT angiography is also advisable, because the physician will immediately have information if extra-or intracranial, large or small vessels are occluded.

The optimal candidates for thrombolysis:

- intact consciousness,
- do not suffer from malignant diseases,
- are in good general condition,
- have normal platelet count, hemoglobin,
- not anticoagulated if yes, INR value is below 1,7
- have normal hepatic and renal functions,
- did not have any surgical operation right before the stroke event.

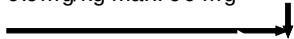
The usual dose is 0,9 ml/kg (max. 90 mg). After intravenous bolus of 10%, the rest of the usual dose should be administered within an hour. The treatment improves the condition of 32 patients among 100, and does harm for only 3 patients. The sooner we start the treatment the better chances we have. If

thrombolysis can be started within an hour, or within 90 to 180 minutes, we have to treat two or nine patients to make one patient improving or asymptomatic, respectively.

The venous thrombolysis improves not just the mortality rate but their functional outcome too, so we have to do everything

- to diagnose stroke cases as soon as possible,
- to transfer the patient to a stroke-center,
- to have the imaging performed immediately,
- to start the treatment as soon as possible, and
- to monitor the patient continuously after the thrombolytic treatment.
- Rehabilitation should start in the acute period, too.

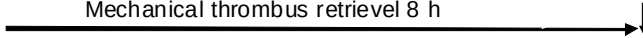
Iv. thrombolysis within
3 (some cases 4.5 h) t-PA
0.9mg/kg max. 90 mg



Intraarterial lysis in MCA occlusion within 6 hours



Mechanical thrombus retrieval 8 h



ia. or iv. thrombolysis within **12 hours**, if worsening of sympt. of basilar artery occlusion



Figure 2
Thrombolysis under different pathological conditions.

The patient should avoid antiplatelet medication or heparin for 24 hours after the venous thrombolysis. **A second CT scan should be performed** to detect hemorrhagic complications. Thrombolytic treatment has the risks of allergic reactions, systemic or intracranial hemorrhage. Intracranial hemorrhage is the most dangerous complication of thrombolytic treatment.

Other methods for recanalisation in ischemic stroke

The efficacy of venous thrombolysis (performed within 3 or in some cases 4,5 hours after the first symptoms) is verified by studies having appropriate criteria and involving a large number of patients. Unfortunately, less than 10-20% of the stroke patients is admitted to hospital within 3 hours, therefore, new methods are developed to extend this time period.

According to less convincing observations in case of the occlusion of the middle cerebral artery, arterial thrombolysis is also an efficient treatment if started within 6 hours after the first symptoms. Usually, for intraarterial thrombolysis 20-30 mg tPA is administered. As for the arterial lysis is an invasive technique, it requires specialists in the field of intervention and well equipped technical background. Arterial thrombolysis has also a considerable risk of hemorrhage. According to the European guidelines in case of middle cerebral artery occlusion, always start the treatment with venous thrombolysis (and depending on the individual characteristics of the patient continue with arterial lysis).

Special attention should be paid to the treatment of basilar artery occlusion accompanied with vertebrobasilar insufficiency (tri-tetraplegia, disturbances of consciousness, double vision, dysarthria). According to the European guidelines, some observations suggest that the window period of venous or arterial thrombolysis in basilar artery occlusion can be extended up till 12 hours.

The efficacy of lysis might be improved with the following experimental procedures in the future:

- the venous treatment combined or continued with arterial thrombolysis,
- the administration of fibrinolytics is combined with antiplatelet therapy,
- the efficacy of venous or arterial lysis is enhanced with external ultrasound with 2MHz frequency,
- the co-administration of neuroprotective agents (although no proven neuroprotective drug has been developed).
- use of intraarterial mechanical devices (e.g. MERCI, Penumbra, Solitaire etc.) has already been authorized in some countries. They can be applied if the thrombus does not react for the thrombolytic treatment or the intravenous lysis is contraindicated. The time window may be extended for 8 hours. These devices work as a corkscrew or use aspiration technique, or stent-like use, but they can apply also ultrasound or laser to improve their desobliterative effect, too.

There are several experimental or still unproven methods for treating stroke, and continuous efforts are made to improve their efficacy (e.g. hypothermia). The central nervous system is sensitive to hypoxia and ischemic events, that is why the early diagnosis of stroke and the development of medical transport and new diagnostic methods will be still prioritized in the future.

The optimal type of treatment of stroke cases will be individual, and the consideration of all facts will be needed to chose the appropriate method among the intravenous, intraarterial and mechanical methods, or their combination.

Non-specific treatment of patients with acute ischemia

In 2011, 50 000 patients suffered from stroke, and approximately 1100 cases of thrombolysis were performed in Hungary.

If a patient is not suitable for thrombolysis, the main aspects of the treatment are the following:

- Even without performing CT scan, aspirin (160-320 mg) could be administered in the first 2 days of acute stroke.
- The blood pressure might become normal within a few days even without treatment. Therefore, caution is the best strategy. Avoid the use of antihypertensive drugs, if the blood pressure is below syst 220 mmHg. The optimal value for blood pressure is still controversial, but syst 160 mmHg is likely to be the optimal for the central nervous system with impaired autoregulation.
- Saturation of oxygen should be kept over 90%.
- In acute ischemic stroke routinous anticoagulation is not recommended.
- The advantage of steroids has not been proved. If brain edema detected by CT imaging is accompanied by progredient hypoxic type of disturbance of consciousness or worsening paresis, the administration of glycerin, mannitol or diuretics is indicated.
- The ceasing of the venous pulsation of the fundus is the early sign of the increased intracranial pressure. The monitoring of cardiorespiratory status of stroke patients is very important in the first 72 hours (12-lead ECG, blood pressure, oxygenation).
- In case of young patients, echocardiography should be performed (even in case of elderly patients, if having cardiac diseases in their medical history) and the laboratory values should be regularly checked.
- Both hypoglycemia and hyperglycemia (over 11 mmol/l) should be avoided.
- Avoid the routine use of antibiotics, but in case of fever, antibiotics and antipyretics should be administered.
- In case of repeated seizures, the use of antiepileptics is recommended.
- Even in case of hemorrhage LMWH or low dose (e.g. 5000 IU) unfractionated heparin sodium can be administered to prevent deep venous thrombosis.
- If the patient has dysphagia (not improving after 3-4 weeks use of nasogastric tube), percutaneous endoscopic gastrostomy should be applied to prevent aspiration pneumonia.
- Rehabilitation and speech therapy should be started in the acute phase in the hospital.
- The temporary removal of cranial bone (hemicraniectomy) reduces the edema and improves the prognosis, if the patient is younger than 60 years and suffers from the occlusion of the middle cerebral artery, and develops malignant edema (midline-shift, worsening of consciousness, anisocoria, conjugated deviation of the eyes etc).

The prognosis of ischemic events

The patient's condition might worsen any time even if it improved previously. Pulmonary embolism, pulmonary edema or cardiac infarction may happen any time. Significantly more patients die from pneumonia or cardiac infarction than from complications affecting the central nervous system. Pulmonary embolism can be prevented by using elastic socks, passive and active moving and LMWH treatment. The following statements refer for non-complicated cases:

In the first year after the ischemic stroke event the risk of death is 25%, but later it becomes 7%. In 10-15% of the patients the ischemic stroke event occurs again within one year, later, the risk of new stroke decreases to 4-5%. In case of hemorrhage the mortality rate is 40% in the first month, later it becomes 8%. If the patient is unable to rise (from the bed) his/her arm one week after the stroke event, he/she will not be able to use it properly either in the future. If the patient is unable to elevate his/her leg one week after the stroke event, he/she will not be able to walk independently.

Rehabilitation of stroke patients

Rehabilitation should be performed according to the followings in every type of stroke:

- rehabilitation should start in the hospital,
- it should be multidisciplinary,
- and it should continue even after the patient is discharged from the hospital.

Before making a rehabilitation plan, rehabilitation specialists assess the functional ability of the patients by examinations and tests. Daily active and passive moving performed under the physiotherapist's guidance is essential not just for regaining the strength of muscles but for the prevention of contractures. Generally, in stroke related spastic paresis electrotherapy should be avoided. The treatment of speech disorders is conducted by speech therapists. Patients with aphasia have to perform tests, writing and articulation exercises and repetition (pictures, sounds, objects, reading-writing). The treatment of aphasia may last for 1 or 2 years.

In case of subacute or chronic stroke, the cognitive rehabilitation is the important part of the treatment (according to the neuropsychiatric symptoms: writing, reading, counting, gnostic disorders, memory defects, dementias, behaviour disorders etc.) The environment of stroke patients should be re-built (handrails, ramps, doorstep removing, alarm bell, slip-resistant floor). Many other aids might be necessary, which help the independent eating, cleaning and clothing.

The complications of post-stroke cases, their prevention and treatment

Pneumonia caused by aspiration is one of the most important complication in stroke patients. Aspiration often occurs in patient with dysphagia. Oral feeding should be suspended until we make sure that the patient is able to swallow water, or solid food.

Pneumonia developed due to aspiration can be prevented by using nasogastric tube or percutaneous endoscopic gastrostomy.

The risk of pulmonary embolism and deep venous thrombosis can be reduced by early mobilization and the wearing of stockings. In case of patients having the risk of pulmonary embolism or deep venous thrombosis (e.g. obesity, immobilization, diabetes, or stroke in the medical history), the profilactic treatment of low dose heparin (5 000 IU bid.) or LMWH is recommended.

The prevention of decubit ulcers involves the frequent moving, the optimal alimentation and skin care. In case of incontinence the patient's skin should be kept dry. Mattress filled with gas or fluid is recommended for patients with extremely high risk.

In the early stage of ischemic stroke and later, epileptic seizures (both partial or generalized seizures) may develop. According to the medical guidance of epilepsy treatment, antiepileptics should be administered either intravenously or orally.

Agitation or desorientation may occur in every phases of stroke, but it may be associated to complications, such as fever, dehydration, or infections. The administration of sedatives or antipsychotics should be anticipated by the treatment of possible causes. If needed, agitation can be treated with haloperidol (2-4 mg) or temporary clozapine (10-50 mg), which is tolerated well by elderly patients, too. Meprobamat can be cumulated, but 4-6 tablets (4-6x200mg) can be administered to the patient occasionally. In case of sleep disorders, cinolazepam, zopiclon, zolpidem or nitrazepam should be administered.

Falls are common problems after the stroke events. Moving, calcium supplementation and bisphosphonate taking improve the strength of the bones and reduce the rate of fractures. During hospitalization hip protectors may reduce the number of fractures.

Patients commonly experience shoulder pain (PSSP) after stroke, especially if the arm function is affected, too. It can be prevented by the passive movements of the paretic extremity. The administration of lamotrigin and gabapentin should be taken into consideration in case of neuropathy-associated pain. Spasticity developed in chronic stages may have negative influence on life quality. The use of oral medicines (e.g. baclofen, tolperison) is limited due to their side effects. In case of central pain, the tricyclic antidepressants clomipramin (Anafranil) or SSRIs might be administered. SSRIs have less side effect, thus they could be combined with antiepileptics.

The post-stroke depression is one of the most common consequences of cerebral vascular disorders, which can be treated well. It has many etiological factors. Without treatment half or two-third of the cases become chronic. SSRIs

have an important therapeutic role in the treatment of post-stroke depression, but tricyclic antidepressants should be avoided.

Vascular dementia might be treated with piracetam, which is tolerated well by patients with vertigo or cognitive dysfunctions. The dose of piracetam can be increased carefully (from 1200 mg TID to 3600 mg TID). According to studies vinpocetin has favourable hemorrheologic effect, which improves the cerebral microcirculation. The extract of *Gingko biloba* (also called as maidenhair tree) is reclassified as antidementia treatment in the ATC classification system, and is indicated mainly in cognitive disorders. Nicergolin also has many favourable effects including its antiapoptotic effects. Selegiline or memantine might be useful, especially for the treatment of mixed type dementia (vascular and Alzheimer's type), in serious cases donepezil or rivastigmin may be suggested.

Aftercare

Patients leaving the hospital should be visited by the family doctor in every month, and stroke patients should participate in cerebrovascular follow up in every 3-6 months, too.

The pillars of the aftercare:

- Hypertension should be treated with ACE inhibitors (with or without diuretics). The combination of perindopril and indapamide is useful even for normotensive patients too. In case of diabetic patients, ARBs are preferred, and the target value is less than 130/80 mmHg.
- Every ischemic patient should receive antiplatelet therapy. Aspirin combined with dipyridamol (2x25mg + 200mg ER-dipyridamol) is more effective than the aspirin monotherapy (100 mg). Aspirin can be replaced by 75 mg clopidogrel daily.
- Statins should be administered for post-stroke patients to reach the target of LDL-C (1.8 mmol/l).
- In case of cardiogen stroke (e.g. atrial fibrillation), the patient should receive anticoagulants with coumarin derivatives (INR 2-3). If the anticoagulant treatment can not be monitored (lack of compliance, frequent falls) antiplatelet therapy is recommended. The new anticoagulants (rivaroxaban, dabigatran, etc.) do not need regular blood control (e.g. INR) but we have not yet enough experience about their interactions with thrombolytics (e.g. t-plasminogen activator). At present, patients on dabigatran, rivaroxaban, apixaban can not be treated with i.v. tPA thrombolysis.
- Carotid reconstruction is recommended within 2 weeks after TIAs or minor strokes if the patient has symptomatic carotid stenosis of 70-99%. Specialist should decide about the surgery or stent implantation. In majority of cases carotid endarterectomy is preferred.

For the family physician the following recommendations could be summarized for the primary vascular prevention (2011):

1. *Family history to identify high risk patients.*
2. *Target < 140/90 mmHg blood pressure and < 130/80 mmHg in diabetic or nephropathic patients*
3. *Other:*
 - a) *statins in diabetics, coronary heart disease or high risk profile patients*
 - b) *anticoagulation in atrial fibrillation patients at high risk*
 - c) *physical activity*
 - d) *reduce alcohol intake*
 - e) *weight loss in obese patients*

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Parenchymal cerebral hemorrhage

ISTVÁN FEKETE MD.

Epidemiology

Intracerebral hemorrhage is the most devastating form of stroke. 70% of non-traumatic intracerebral hemorrhage is parenchymal cerebral hemorrhage, 20% is caused by aneurysm rupture, and the last 10% is resulted by other conditions such as tumors, hematological dyscrasia, anticoagulants, etc. Parenchymal cerebral hemorrhage is developed in 10-15% of stroke cases, and has an age-related incidence (below the age of 40 the incidence is 2 cases/100000 yearly, but over the age of 80 it becomes 350 cases/100000 yearly).

Parenchymal cerebral hemorrhage has the mortality of 35-50%! The 30-days and one-year mortality rate is 44% and 47%, respectively. Severe neurological symptoms and coma often develop. Survivors may experience the following complications: cognitive and emotional disorders, depression and impaired quality of life.

The risk factors and causes of intracerebral haemorrhages

Hypertension is the major risk factor of intracerebral hemorrhage, especially if being untreated. Besides hypertension, the most important risk factors are diabetes mellitus, smoking and excessive alcohol consumption. Lipohyalinosis in cases of chronic hypertension and deposition of amyloid in cerebral vessels in cerebral amyloid angiopathy leads to reduced elasticity of the arteries making them susceptible to rupture in response to acute elevations in intravascular pressure.

Intracerebral hemorrhage not accompanied by hypertension is called as *spontaneous cerebral hemorrhage*. Nowadays, definite relationship is found among cholesterol level, hypertension and spontaneous cerebral hemorrhage.

Other causes:

- vascular abnormalities: saccular aneurysm, angioma, arteriovenous malformation,
- cerebral amyloid angiopathy, vasculitis,
- coagulopathy: anticoagulants, fibrinolytics, diseases with discoagulation,
- head injuries (parenchymal hemorrhage may develop due to contusion),
- hemorrhage of preexisting cerebral lesions: tumors, granulomas, meningencephalitis, hemorrhagic conversion of ischemic stroke,
- drugs: cocaine, pseudoephedrine, amphetamine.

The location and symptoms of intracerebral hemorrhage

In most of the cases the first symptom is a suddenly developed headache, which becomes permanent. Cerebral hemorrhage develops mainly in the daytime (morning or afternoon) during working or contraction of the abdominal muscles. Intracerebral hemorrhage occurs most frequently before cold fronts.

Depending on the location of bleeding, symptoms may appear immediately. Usually, the patient has red face and hypertension, but feeling of sickness, vomiting and epileptic seizures may also develop. Symptoms may progrediate depending on the size and progression of hemorrhage. Disturbances of consciousness or even coma can develop if the bleeding is accompanied by increased intracranial pressure and mass effect. Suddenly developed unconsciousness refers to large parenchymal hemorrhage or brain stem hemorrhage.

The **location** of bleeding is important, because it defines the symptoms (we do not discuss the indirect symptoms here). The 85% of cerebral hemorrhage is **supratentorial**.

The bleeding can be:

- large, excessive hemispheric,
- basal ganglia,
- thalamic,
- or lobar hemorrhage (frontal, parietal, temporal, occipital).

Usually, the neurological **symptoms of brain hemorrhage** are more serious than the symptoms of ischemia. In the damage of the pyramidal tracts flaccid hemiparesis might develop, which becomes spastic after a few weeks. If the bleeding involves the prefrontal cortex, conjugated eye deviation is observed to the contralateral side of hemorrhage (the patient looks the paretic extremities). If the affected area is seriously damaged, the contralateral side takes over its function. The eyes are deviated to the side of the bleeding.

Depending on the location, **hemorrhage affecting the dominant hemisphere** may cause speech disturbance (aphasias), gnostic and cognitive dysfunction, or anosognosia (in case of the bleeding of the subdominant hemisphere).

Thalamic hemorrhage is characterized by contralateral hemiparesis (if involving internal capsule) and hemisensory symptoms, hemiataxia, gait ataxia, forced downgaze, thalamic pupils.

Infratentorial hemorrhage includes brain stem hemorrhage and cerebellar hemorrhage. The most familiar type of brain stem hemorrhage is the pontine hemorrhage, but the bleeding may affect the mesencephalon and medulla oblongata too.

Cerebellar hemorrhage is characterized by limb ataxia, gait ataxia, dysarthria, hypotonic extremities, impaired deep tendon reflexes and nystagmus. In case of large bleedings or progression, brain stem compression and consequent deepening unconsciousness can develop. Symptoms referring to brain stem lesions are

present, and the risk of brain herniation is extremely high. Therefore, the close monitoring and radiological follow-up (CT imaging) are very important.

Primary brain stem hemorrhage is characterized by pupillary and gaze abnormalities, ocular palsies, other cranial nerve palsies, crossed hemiparesis or quadriparesis, hemisensory impairment, stupor or coma and insufficiency of the respiration. It has unfavourable prognosis and fatal outcome.

The major part of spontaneous or hypertension related brain hemorrhage is characterized by progression. The bleeding may be two- or multiphased, which may contribute to its progression. The decrease of blood pressure is important, as the risk of bleeding is high in the first hours.

The diagnosis of brain hemorrhage

Cerebral hemorrhage can be detected immediately on cranial CT scan. In case of aneurysm, angioma and arteriovenous malformation the application of contrast media is recommended (CT angiography) followed by cerebral angiography *pro re nata*. Coagulopathies (chronic anticoagulant treatment, hepatic disorders) should be excluded by laboratory examinations. Hematology test can reveal leukemia or the consequences of cytostatic treatment.

Prognostic factors

In case of large, destructive hemispheric hemorrhage, mass effect and herniation (cingular, uncus, tonsillar) may develop, which are associated with poor prognosis. Cerebral hemorrhage may cause acute hydrocephalus, if the bleeding is located to the brainstem, provokes compression or secondary brainstem hemorrhage, or intraventricular hemorrhage complicates the intracerebral hemorrhage. The prognosis is worse if the patient is older (above the age of 70) and has severe concomitant diseases.

The risk of early repeated hemorrhage is increased within the first 24 hours (usually, bleedings reoccur within 3-6 hours), and associated with the progression of the symptoms. The risk of late repeated hemorrhage is 2.3% per patient yearly.

Lobar hemorrhage has an increased risk of repeated bleedings, especially, if the patient is treated with anticoagulants.

In the treatment of brain hemorrhage the following aspects are important:

General practitioner, ambulance:

- immediate transport to hospital,
- the assessment of vital functions, the prevention of aspiration,
- the treatment of hypertensive crisis,
- the treatment of epileptic seizures.

Hospital:

- antihypertensive treatment to reach the mean arterial pressure of 130mmHg (referring for a tension of 180/11 mmHg in patients suffering from hypertension),
- the treatment of coagulopathy,
- the assessment of cardiac function and oxygen saturation,
- the treatment of electrolyte imbalance,
- the treatment of cerebral edema and increased intracranial pressure,
- the maintenance of normoglycemia and normothermia,
- the treatment of fever and hyperglycemia,
- the treatment of epileptic seizures,
- the treatment of inflammations,
- the prevention of gastrointestinal bleeding,
- in case of progression cranial CT and neurosurgical consultation is indicated (cerebellar hemorrhage and ventricular drainage),
- treatment according to the operative guidelines and protocols.

Brain hemorrhage is a severe and fatal disease. The incidence of cerebral hemorrhage can be reduced by the prevention and treatment of hypertension. The immediate action to transfer the patient with cerebral hemorrhage to hospital and the adequate treatment improve the prognosis significantly.

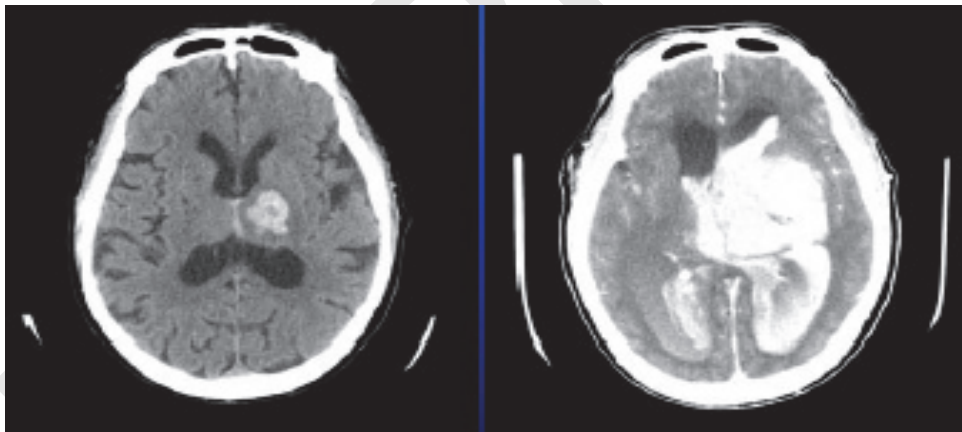


Figure 1
Cranial CT scan

*On the left side: thalamic hemorrhage without significant mass effect.
On the right side: a large cerebral hemorrhage with significant mass effect strikes into the ventricles obstructs the liquor pathways and causes midline dislocation. It is accompanied by multiple small bleedings in both hemispheres and subarachnoid hemorrhage, and developed 10 hours after the first symptoms.*

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Subarachnoid hemorrhage, sinus thrombosis and venous diseases

ISTVÁN FEKETE MD.

Subarachnoid hemorrhage (SAH)

The etiology and epidemiology of SAH

Subarachnoid hemorrhage is the extravasation of blood into the subarachnoid space due to the rupture of blood vessels. Usually, SAH occurs from a ruptured saccular aneurysm or arteriovenous malformation, but rarely it can be caused by cranial injuries, vascular disorders due to amphetamine or cocaine abuse, amyloid angiopathy, hypertension-evoked vascular ruptures, cerebral venous sinus thrombosis or hemorrhagic diathesis, too.

The prevalence of SAH is 15/100000. This rate may have seasonal variability, as the prevalence may be higher in spring and autumn. The mortality rate is high (33%), but due to neurosurgical procedures the number of survivals has doubled.

Subarachnoid hemorrhage usually occurs on the proximal part of the vessels arising from the Willis' circle. The narrowed wall of aneurysms ruptures and in mild cases blood leakage develops ("tearing aneurysm"). 85% of the aneurysms develop in the anterior circulation, and 25% in the posterior area. The 15-20% of the aneurysms is multiple. During SAH thromboxane, free radicals, and serotonin are released in the blood and induce vasospasm, which causes secondary ischemic damage with neurological symptoms. It has the prevalence of 15-45%.

Symptoms of subarachnoid hemorrhage

In the medical history significant physical effort or sexual intercourse can be found. The symptoms of SAH involve sudden and severe headache having high intensity on the forehead. In severe cases consciousness disturbances may develop. Light sensitivity might be present (the patient keeps his/her eyes closed to avoid light). Physical examination may reveal nuchal rigidity, meningeal signs, vegetative dysregulation (arrhythmias, ECG abnormalities), hypertension (rarely hypotension) and fever. Focal neurological signs develop, if the bleeding strikes into the parenchyma (e.g. in case of aneurysm rupture on the middle cerebral artery). The symptoms appearing a few days later are caused by vasospasm. Epileptic seizures may occur. Hematomas involving the subarachnoid space may cause hydrocephalus or cerebral herniation (uncal, tonsillar). Late symptoms are caused by repeated ruptures, vasospasm and consequent infarction, or late hydrocephalus.

Table 1

The severity and prognosis of SAH are classified by using the Hunt and Hess scale.

Severity	I	II	III	IV	V
<i>Progression</i>	5%	20%	25%	50%	80%
<i>Repeated hemorrhage</i>	10-15%	10-15%	10-20%	20-25%	25-30%
<i>Fatal outcome</i>	3-5%	6-10%	10-15%	40-50%	50-70%

Grade I: minimal headache

Grade II: severe headache with nuchal rigidity,

Grade III: somnolence, confusion, minor neurological symptoms

Grade IV: disturbance of consciousness, hemiparesis, vegetative symptoms

Grade V: coma, decerebrate rigidity

Subarachnoid hemorrhage is a life-threatening condition. Right after the symptoms have developed the patient has to be transferred to hospital, where neuroradiological and neurosurgical services are available.

Until the transfer the patient should be laid down to rest. The monitoring and correction of vital parameters might be necessary depending on the severity of the symptoms.

Diagnosis

Cranial CT is the primary examination to detect hemorrhage. In the 2-5% of the cases the native CT scan might be negative, but it has the specificity of 92% in the acute period. In certain cases CT results may refer to the localization of bleeding, but it depends on the time of onset. If the patient has relevant history and the symptoms of SAH, lumbar puncture is needed (minor hemorrhage might not be detected by cranial CT). Computed tomography angiography (CTA) usually reveals aneurysms larger than 5 mm, and suggests further examinations. The gold standard of the detection of ruptured aneurysms, the digital subtraction angiography (DSA), should be performed immediately. If the first examination does not provide information, it should be repeated 3-4 weeks later. The development of vasospasm can be monitored by TCD: if the flow velocity in the middle cerebral artery exceeds 120 mm/s, vasospasm has been evolved. The extent of the infarction can be assessed by using CT or MR imaging.

The treatment of subarachnoid hemorrhage

The urgent localization and treatment of aneurysms are necessary, because untreated aneurysms have the risk of repeated hemorrhage. The timing of the

intervention depends on the patient's condition, thus it should be decided by a neurosurgeon or specialist (the need of neurosurgical clipping or endovascular coiling).

If surgical procedure is not necessary, the following conservative treatments are used to prevent complications:

- bed-rest is recommended to reduce the risk of repeated hemorrhage, and antihypertensive therapy might be needed.
- antipyretic treatment (acetaminophen, ibuprofen, cooling and central venous heat exchange catheter). The prevalence of fever is 50-70% in the first 72 hours, but it reaches up to over 90% in patients treated for more than 14 days.
- arrhythmia and neurogenic pulmonary edema require ECG and intensive monitoring or, if needed, inotrope treatment.
- the daily administration of 40-60 mg oral nimodipine may prevent the development of vasospasm and cerebral ischemia.
- the treatment of late cerebral ischemia involves hypertension, hypervolemia and hemodilution ("3H").
- the monitoring of fluid and electrolyte abnormalities and the use of crystalline solutions are necessary.
- routine anti-edemic treatment is not recommended (mannitol, glycerol).
- analgesic, antiemetic treatment, sedatives or anxiolytics should be used to ease the symptoms of SAH.

The diseases of cerebral sinuses and veins

The occlusion of cerebral sinuses and veins is caused by thrombosis, thrombophlebitis or tumor. It has the prevalence of 1% among other stroke cases, and develops more often in women between 20 and 40 years.

Predisposing factors

Postoperative period, contraceptive agents, hypercoagulability, pregnancy, puerperal period, systemic infections, DIC, inflammations (head or sinuses after trauma), tumors (paraneoplastic syndrome).

General symptoms

- headache,
- epileptiform attacks,
- increased intracranial pressure,
- neurological symptoms, meningeal signs,
- hemorrhage,
- enlarged veins.

*The most common syndromes***A/ Sagittal sinus thrombosis**

Septic fever, disturbance of consciousness, forehead and scalp edema, enlarged veins (presenting as caput medusae), empty delta sign on CT scan, MRI: the thrombus visualized as a bundle. Focal neurological signs might be present.

B/ Transversal sinus thrombosis

Otogenic, characterized by the presence of Gradenigo's syndrome.

C/ Cavernous sinus thrombosis

The involvement of the III-IV-VI-V/1 cranial nerves, sudden onset, septic fever, periorbital edema, chemosis, retrobulbar pain and papilledema.

Diagnosis

If sinus thrombosis is suspected, CT and MRI (CT venography or MR venography) should be performed.

Treatment

Firstly, the causes of thrombosis should be treated (inflammation, trauma, hypercoagulability, etc.). Heparin should be administered intravenously: 5000 IU in bolus followed by infusion with iv. pump. APTT is used to monitor the level of heparin, the APTT ratio should be between 1.5-2. Heparin inhibits the enlargement of the thrombus, decreases the venous congestion and creates favourable conditions for recanalization. CT venography or MR venography might be needed (assessment of therapeutic effect, prognosis or progression). The administration of heparin should be continued till the definite improvement, even if hemorrhage develops near the sinuses. Chronic anticoagulant treatment is needed for 6 months, followed by the administration of antiaggregants. Instead of heparin LMWH treatment can be suggested. In case of cavernous sinus thrombosis, the use of steroid reduces the pain.

Arteriovenous malformations, angiomas

Angiomas and arteriovenous malformations with congenital origin are mainly located on the surface of the brain, but rarely, they can involve the brainstem and cerebellum too. They may have various sizes, or even occupy an entire hemisphere.

Clinical symptoms

Symptoms usually develop between 10 to 30 years, but they can be asymptomatic, too.

- subarachnoid hemorrhage (50%)
- headache (50%)
- epileptiform seizures (40%)
- neurological symptoms

Diagnosis

Above the skull murmur can be detected by auscultation (25%). Cranial X-ray shows calcification according to the malformation. CT and MRI reveal the diagnosis, but DSA may visualize these malformations completely.

Therapy

In case of seizures the use of antiepileptics are recommended (mostly lamotrigine, or carbamazepine). Stereotaxic surgery or embolization might be needed. Arteriovenous malformations involving the hemispheres are inoperable.

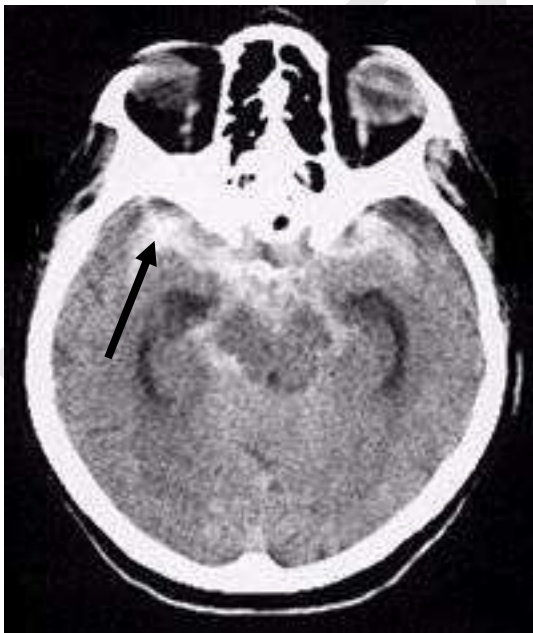


Figure 1
Subarachnoid hemorrhage caused by aneurysm rupture on the anterior communicating artery (the arrow points the blood mass in the subarachnoid area).

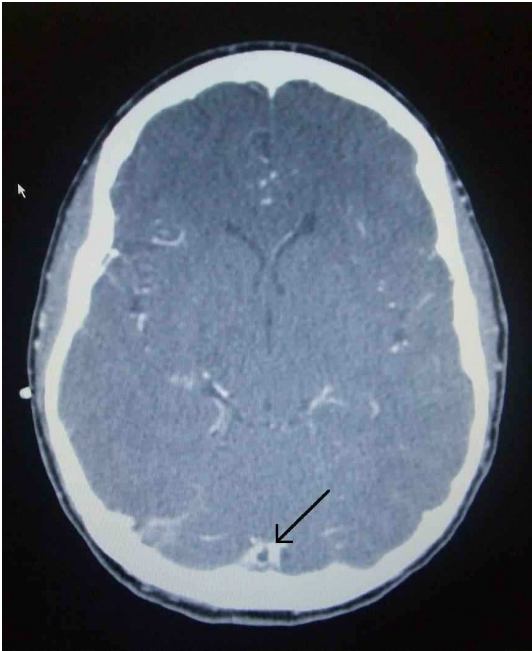


Figure 2
*Superior sagittal sinus thrombosis
(the arrow indicates the absent of
contrast media).*

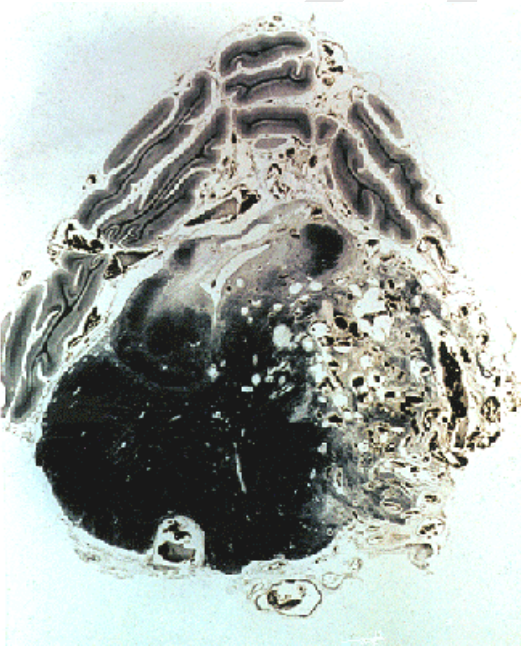


Figure 3
Brainstem hemangioma

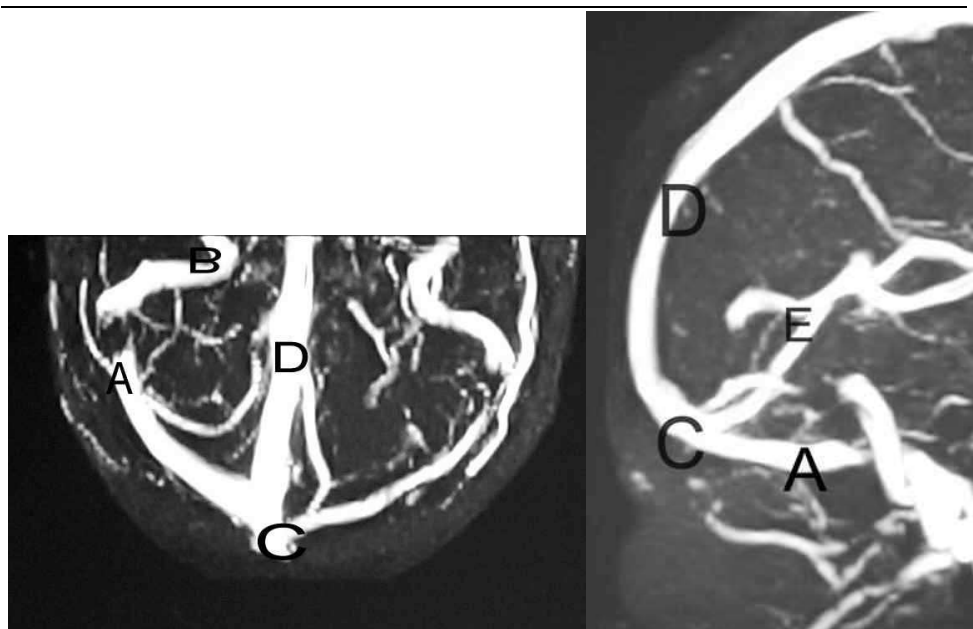


Figure 4
MR venous phase (left: axial, right: sagittal)
A= transversal sinus
B= sigmoid sinus
C= confluence of sinuses
D= superior sagittal sinus
E= rectal sinus

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Headaches and facial pain

LÁSZLÓ OLÁH MD.

Classification

One of the most common complaints in physicians' office is headache or facial pain. An imaginary line connecting the orbits and the tragi divides the territories of headaches and facial pains. For convenience, facial pains are discussed here together with headaches.

Headaches can be classified into two major groups: symptomatic (secondary) or idiopathic (primary) headaches. While symptomatic headaches are the symptoms of other underlying diseases, idiopathic headaches are the diseases themselves. The most common idiopathic headaches involve migraine, tension and cluster headaches, however, many rare types are classified as idiopathic, too. Symptomatic headaches are discussed in the second part of this chapter.

Medical history and the aim of the examination

In case of patients with headache, carefully elicited medical history is important. Since the primary headaches are usually symptom-free from the neurological point of view, the following questions may help the diagnosis:

When did the headache start? How often does it develop? Where does the patient feel the pain? What is the quality of the pain? How long does it take? How severe are the symptoms? What symptoms is the headache accompanied by? Does physical activity aggravate the headaches? Are the headaches so intense that they prevent the patient from participating in normal activity? Does it react to analgesics?

These obligatory questions can be memorized easily by using the following mnemonic initialism, the **PQRST of pain**:

P: provocation and palliation. What makes the pain better or worse?

Q: quality of the pain (sharp, dull, pressing, tightening, crushing, burning, tearing).

R: region. Where the pain is located (retrobulbar, unilateral, nuchal, diffuse, band-like)?

S: severity. Pain should be scored on a scale from 0 to 10. In time, pain can be decreasing, increasing or constant.

T: time course. How long the pain has been going on and how it has changed since onset (frequent, rare, intermittent)?

The aim of the examination of the patient and the medical history taking is the decision between idiopathic (primary) and symptomatic (secondary) headaches. In case of symptomatic headache, its cause should be treated; this probably relieves or stops the headache too. In case of idiopathic disease the type of analgesic treatment

should be decided. Rarely presenting pain can be treated with painkillers occasionally, i.e. only when the headache presents. However, if the symptoms are frequent, initiation of prophylactic treatment should be considered in order to reduce the frequency of the attacks and to decrease the dose of painkillers.

The other question that has to be answered is whether alarming signs or symptoms indicating urgent examination are present.

The alarming signs and symptoms are the followings:

- *headache starting in elderly ages,*
- *progressive headache (referring for frequency and intensity),*
- *headache following trauma,*
- *headache associated with fever and confusion,*
- *headache accompanied by neurological symptoms,*
- *headache that changed in quality,*
- *sudden and severe headache developing during physical activity.*

In the first part of this chapter the idiopathic or primary headaches will be discussed.

IDIOPATHIC HEADACHES

Tension headache

Tension headache without any structural damage in the background is the most common type of idiopathic headaches. Almost everyone experiences it during the lifetime, but it occurs more often in women suffering from mild depression. The cause of the pain is unknown, but the disturbances of pain perception and permanent muscle contraction are thought to have an important causative role (referring for the nomination).

The characteristics of tension headache

The headache is diffuse or band-like, and rather dull. The patients describe the pain as if their head were being compressed by a band or cap. The pain in tension type headache is typically bilateral, pressing or tightening (but not pulsating) in quality, mild to moderate in intensity, and can be treated well with common painkillers (metamizole, paracetamol, NSAID, noraminophenazon). The pain does not aggravate with physical activity, and its intensity does not prevent the patient to participate in normal everyday activity. Tension headache is rarely accompanied by vegetative (nausea) or other symptoms (light or sound avoidance). Usually, if the headache develops rarely, the patients use over-the-counter medicines to ease their pain, and most of them do not seek medical help. However, if the pain becomes more frequent, they rather visit the doctor's office. **Chronic tension headache** is defined when tension headache episodes occur 15 days or more a month for at least

3 months. In these cases prophylactic treatment is recommended to reduce the headache frequency. Certainly, preventive therapy does not exclude the use of common painkillers when headache presents.

Prophylactic treatment

The most effective medicine to prevent tension type headache is the tricyclic antidepressant amitriptyline (Teperin 25mg) or clomipramine (Anafranil 10 or 25 mg, Anafranil SR 75 mg). The patients should be informed that in these cases antidepressants are for the prevention of headaches and not for the treating of depression. In order to improve the patients' compliance, it should be highlighted that the prophylactic drugs do not have immediate effect on easing pain, and they should be taken daily, not when experiencing headache. Even if taken regularly, the effects of antidepressants can be expected only after weeks. If they seem to be ineffective, their dose might be increased by 25 mg weekly.

Side effects of tricyclic antidepressant medications involve drowsiness and anticholinergic effects, such as xerostomia (dry mouth) and tachycardia. Tricyclic antidepressants should not be administered to patients with glaucoma and prostate hyperplasia, because they increase the intraocular pressure, and may provoke urinary retention. If the patient does not tolerate amitriptyline, change to other tricyclic antidepressant, e.g. clomipramine, can be tried. Since tricyclic antidepressants inhibit the re-uptake of serotonin, dopamine and noradrenalin non-selectively, concomitant SSRI (selective serotonin reuptake inhibitor) therapy should be avoided because of risk of serotonin syndrome.

If the patient cannot take tricyclic antidepressants due to ineffectiveness, side effects or potential side effects, anxiolytics (alprazolam, clonazepam) or SSRIs could be tried.

Change of lifestyle is at least as important as the medical therapy in the treatment of chronic tension headache. It may include regular physical activity, change of workplace, but also psychotherapy or autogenic training. Besides changing the life habits, acupuncture might be beneficial, too.

Diagnosis of tension type headache can only be established, if other causes are excluded. Besides the carefully elicited medical history, the diagnosis usually requires blood pressure monitoring, laboratory tests, ophthalmological (intraocular pressure!), and otolaryngological examinations. Cranial CT is indicated if the patient has neurological symptoms, progressive headache, or trauma in the anamnesis. If tension type headache is diagnosed, the patient should be reassured about not having serious problem in the background.

Tension headache related diseases

Atypical facial pain and atypical toothache are related to tension headache, at least the quality of the pain and the background supposed are quite similar. After excluding every possible cause of the known facial pain syndromes, patient can be diagnosed with atypical facial pain. Usually, the pain is located deeply in the facial tissues and lasts for hours or days. It involves mainly women between 30-40 years.

The symptoms may start after having minor facial traumas or dental procedures. Half of the patients with atypical facial pain suffer from depression as well. The use of tricyclic antidepressants is usually effective and might be combined with psychotherapy.

Glossodynia and atypical toothache are the special types of atypical facial pain. The patient experiences burning pain affecting the tongue, lips and the oral mucous membrane, and complains of disturbances of smelling and tasting. Minor part of the cases is symptomatic: anemia (due to iron or vitamin B12 deficiency), malnutrition, diabetes, medicines (diuretics!), candidiasis, or smoking can be in the background. Idiopathic cases can be treated with antidepressants and anxiolytics, while symptomatic cases require further investigation.

Atypical toothache is a moderate dull pain lasting for at least 3 months. The patient usually localizes the pain to the place of an extracted tooth or a pulpless tooth with treated root canal. The pain increases from morning to evening, and stops during sleeping. Despite of the pain, dental examination does not reveal any physical or radiological abnormality. Atypical toothache usually affects women between 50 and 60 years. The prevalence may even reach up to 3-6% in root canal treated cases. Therapeutic nihilism and irreversible procedures should be avoided. The local application of 0,025% capsaicin solution may ease the symptoms, and the administration of low dose amitriptyline may be beneficial too.

Migraine

Migraine is also a common idiopathic headache affecting approximately 10% of the population. It develops mainly in women between 20-50 years. In childhood the prevalence of migraine is the same in boys and girls, but after the age of 14 it is about three times more common in women than in men. Besides the hormonal effects, genetics also has an influence on migraine development. The changed serotonin metabolism and the so-called trigeminovascular pathway may also have an important causative role: the trigeminal nerve innervates the vessels of the dura and the proximal part of the Willis' circle. Neuropeptides causing vasodilation and inflammation are supposed to be released from the perivascular nerve endings due to the neuronal activity of the brainstem, and cause migraine attacks. Therefore, both antiinflammatory/analgesic drugs and vasoconstrictor agents are effective in the treatment.

Aura

Migraine headaches are divided into two groups: **migraine with aura** or **“classical migraine”** and **migraine without aura** or **“common migraine”**. The aura is a focal neurological sign preceding the migraine attack. It develops gradually and usually stops within 30 minutes (even in case of combined aura symptoms, they disappear within 1 hour). In most of the cases the aura derives from the occipital lobe and causes visual symptoms. The disturbance of vision often consists of dazzling points (scintillating scotoma), blurred vision (as though

the patient would look through a waterfall), and colorful zigzag lines. During the period of aura the visual signs spread: they start in the center of the visual fields, gradually move to the peripheral areas, and then leave the fields in approximately 20 minutes. The aura can be a somatosensory aura too, originating from the parietal cortex and consisting of a feeling of pin and needles, which also migrates. Somatosensory aura may be present alone or in combination with the visual aura. Aura including other symptoms such as aphasia develops more rarely.

In case of **complicated migraine**, the symptoms of aura persist even after the headache is stopped. The symptoms may last for more than 24 hours. The most familiar types of complicated migraine are the ophthalmoplegic and basilar migraine headaches, which are very difficult to differentiate from ischemic stroke at the first time.

Initially, the symptoms of aura were thought to be related to vasoconstriction, but nowadays, the theory of spreading depression is more supported. It means that depolarization, followed by long-lasting repolarization, originates from certain cortical areas (usually from the visual cortex), and spreads over the cortex with a certain speed. This phenomenon is responsible for the symptoms of aura and possibly causes the vasoconstriction, too.

It is important to know, that the use of oral contraceptives and smoking are contraindicated in patients suffering from classic migraine, as it increases the risk of stroke. Interestingly, the prevalence of persistent foramen ovale reaches up to 50-55% in patients with classic migraine compared to the whole population, where the prevalence of PFO is approximately 25%. **Migraine equivalent** is known as recurring migraine aura without headache.

Migraine headache

Usually, as the symptoms of aura stop, the **migraine headache** starts, which has the same features in classic and common migraines. The headache may last from 4 hours up to 72-96 hours, but usually it lasts for 24 hours. The frequency of attacks is extremely variable, from 6-8 attacks generated in a month to one attack per year, but the average frequency is 1.2 headaches, monthly. The headache is usually unilateral, throbbing and severe (the patients describe its intensity as 8 or 9 in a scale of 10). The pain is often accompanied by other symptoms, such as nausea, vomiting, photophobia or phonophobia. During the migraine attack the patient is unable to continue the everyday work, she/he lies down in a dark and silent room and tries to sleep. The pain is aggravated by physical activity. Some of the patients may experience **prodromal symptoms**, such as emotional instability, predicting the migraine attack a day earlier.

The treatment of migraine

The treatment of migraine involves the acute treatment of attacks and prophylactic medication.

The treatment of migraine attacks

Migraine attacks can be treated with several medicines, however, the common painkillers (e.g. paracetamol, metamizole, noraminophenazon) are usually ineffective. Non-steroid anti-inflammatory drugs (NSAID) belong to the group of the most effective medicines for treating migraine attacks. The administration of 500-1000 mg aspirin might be beneficial, especially if combined with antiemetics (e.g. domperidone, metoclopramide). If aspirin is not effective, other NSAIDs can be tried, such as diclophenac (75-150 mg), naproxen (550-1100 mg), or ibuprofen (400-800 mg). These medicines, such as every drugs used for the acute therapy of migraine, should be combined with antiemetic treatment. (It is well known, that the frequent and excessive use of NSAIDs may cause stomach or duodenal ulcers, but it is less known, that they can induce renal failure too.)

The use of ergotamines is still suggested for migraine treatment. They are alpha-adrenergic agonists with strong serotonin receptor affinity, and have non-selective vasoconstrictor effect. Therefore, they should be administered with utmost care, and should be avoided in patients suffering from peripheral arterial disease, transitory ischemic attack, stroke, angina pectoris, myocardial infarction, untreated hypertension, glaucoma, or tachycardia.

The use of combined medicines is suggested if NSAIDs and/or ergotamines are not effective. These combined medicines usually contain metamizole, caffeine and drotaverine (such as Quarelin or Algopyrin Kompex). The atropine extracted from deadly nightshade (*Atropa belladonna*) is combined with ergotamine, caffeine, and aminophenazone in the medicine of Kefalgin.

Nowadays, the most effective medicines developed for treating migraine attacks are the triptans, characterized by selective serotonin agonist function (serotonin 1B/D receptors), and selective vasoconstrictor and anti-inflammatory effects. Since the first use of sumatriptan, many triptans have been developed in the last years (e.g. zolmitriptan, eletriptan, naratriptan). These medicines have the same therapeutic effect, but their half-life time or elimination half-time may differ. Although the triptans are the most effective drugs in migraine, they are relatively expensive, and are contraindicated in patients with stroke, TIA, angina, myocardial infarction, untreated hypertension and in pregnancy.

It is well known that any medication used for treating migraine attacks is the most effective, if they are administered soon after the first symptom developed. They should be quickly absorbed and able to reach the maximum serum level as soon as possible. Therefore, these medicines are produced not only in the form of pills, but in forms of liquids or solutions, too. As for their use is often accompanied by vomiting, pharmaceutical manufacturers have developed nasal sprays or subcutaneous injections, too.

If triptans are not available in hospitals, the following parenteral treatment can be suggested to relieve the pain in acute migraine attack:

- 300 mg diclofenac in infusion or 1000 mg aspirin, or 1000 mg metamizol intravenously and
- 100 mg of vitamin B6 intravenously and
- 10 mg of diazepam intravenously and
- low dose of steroid intravenously (e.g. 40 mg methylprednisolone) .

Prophylactic treatment

If the number of migraine attacks reaches or exceeds 3 per month, the use of prophylactic treatment in order to reduce the frequency and intensity of migraine attacks should be considered. Preventive treatment has no strict rules. If the patient is suffering from migraine headache with high intensity, and the attacks may last for days, are resistant to the acute treatment, or accompanied by aura, prophylactic therapy is indicated, even in case of one attack per a month. However, prophylactic treatment is not necessary in patients with mild symptoms, which can be treated well with common painkillers, even if he/she experiences 4-5 attacks in a month. The effectiveness and the adverse effects of preventive medication should be considered individually.

Firstly the triggering factors should be eliminated to reduce the frequency of migraine attacks. Foods, beverages, cheese, chocolate, red wine, insomnia, stress and weather changes may provoke the attacks. Preventive treatment should be started with low doses, titrated slowly to the effective dose or side-effects, and used for the appropriate time period (usually for months).

The following medicines are used for preventing migraine attacks:

1. **Beta-blockers** (propranolol 20-80 mg, metoprolol 25-100 mg):

Beta-blockers are indicated in case of normal or slightly elevated blood pressure with normal heart rate or tachycardia, or if the patient suffers from hyperthyroidism or essential tremor too. The use of beta-blockers is contraindicated in patients suffering from bronchial asthma, electrical conduction disorders of the heart, bradycardia or hypotension.

2. **Calcium-channel blockers** (flunarizine 5-10 mg):

Similarly to beta-blockers, calcium-channel blockers are also effective in the prevention of migraine attacks. Their use might be limited by their side effects, because they may increase the appetite and body weight, and induce depression. Therefore, flunarizine is not recommended in patients with obesity or depression. Calcium-channel blockers may cause drowsiness, which is usually well tolerated. To avoid drowsiness, calcium-channel blocker treatment should be started in low doses (e.g. 5 mg flunarizine), and after a week the dose could be increased (e.g. 10 mg flunarizine), and flunarizine should be taken at the evenings. Beside flunarizine, verapamil can also be tried in migraine prophylaxis (240-360 mg)

3. **Valproic acid**, used primarily as anticonvulsant in the treatment of epilepsy, is also effective in the prevention of migraine attacks in the dose of 2x300-500 mg. The side effects of valproic acid include hand tremor, ataxia, temporary hair loss, menstrual cycle disturbances, peripheral edema,

thrombocytopenia and weight gain. It is important to inform the patients about the need of proper contraception during taking valproate, and if pregnancy is planned, the drug should be stopped.

4. Another anticonvulsant drug, namely the **topiramate** was also proved to be effective in migraine prophylaxis, in a daily dose of 100 mg. Main side effects of topiramate are metabolic acidosis and nephrolithiasis, which risk can be decreased by proper hydration.

5. **Amitriptyline** is effective in the treatment of mixed type headache (migraine and tension headache). Regarding the recommended doses and the possible side effects we refer to the treatment of tension headache.

6. Apart from the drugs listed above, many medicines and **alternative methods** (autogenic training, acupuncture) are used in the prophylactic treatment of migraine attacks.

Cluster headache

Cluster headache is a primary headache that develops in clusters, periodically, and affects the young-middle aged population. The prevalence of cluster headache is 0.05-0.5%, and it is approximately 4-5 times higher in men than women. Although its pathophysiology has not been known exactly, hypothalamic abnormalities are supposed to have causative role. The term “cluster” refers to the temporal profile and appearance of headaches in time, and suggests that the pain develops in clusters lasting for 4-12 weeks, interrupting the remission period, which may last for months or years.

The characteristics of cluster headache

In cluster period 1-3 headaches develop daily. The pain is always unilateral without “side-shifting” in a period (but in the next period it may affect the other side). The pain is always localized in or around one eye, and radiates to the temporal and frontal areas. The pain is shooting in quality, usually lasts for 15-180 minutes, and has the intensity of 10 on the 0-10 numeric pain intensity scale. According to a survey, 40% of patients suffering from cluster headache have already thought for suicide because of an intolerable pain during the attacks. These patients are unable to stay in lying position, restless, keep on walking, roll on the floor, hit or rub their head. Cluster headache is provoked by alcohol, cold weather and sleeping, therefore, it often develops at nights or dawns, usually in the same hours of the day. It is always accompanied by unilateral autonomic symptoms affecting the side of the pain. These symptoms may include conjunctival injection, lacrimation, nasal congestion, rhinorrhea, ptosis, pupillary abnormalities, facial edema, unilateral sweating, and facial blushing. The former name of cluster headache (erythropsoplagia) refers to facial pain and blushing.

The acute treatment of cluster headache

It is important to know that vasodilators (alcohol, nitrates) and cold may provoke the symptoms in the cluster period, so these factors should be avoided.

In the treatment of cluster headache both the intensity of the pain and its relatively short duration should be taken into consideration. Therefore, medicines with fast absorption and high effectiveness should be recommended. Since cluster period is rarely over after 3-4 headache attacks, prophylactic therapy should be considered already at the beginning of the period.

Oxygen therapy is effective in the acute treatment in about 75% of the cases. Inhalation of 100% oxygen is recommended at the beginning of the cluster attack for 15 minutes in the dose of 6-8 l/min through facial mask. Sumatriptan, which is also known to be effective, is usually administered subcutaneously (6 mg) or in form of nasal spray to increase its absorption. Xylocaine or 4% Lidocaine solution may ease the symptoms, if dropped in the nostril of the same side while the patient positions his/her head laterally with 40-45 degree. The drug solution is expected to reach the ipsilateral sphenopalatine fossa.

The disadvantage of the oxygen treatment is that it is usually available only in hospitals, while the use of sumatriptan is limited by its high price.

Prophylactic treatment of cluster headaches

After the patient has experienced 2-3 cluster headaches, we can be sure, that other attacks would develop in the next few weeks, and prophylactic treatment would be necessary. The most effective medicines in prevention are verapamil and steroid. The **verapamil** dose should be increased gradually till the effective or maximal dose (480 mg). During verapamil treatment ECG control is necessary! Concerning the steroid, 40-80 mg **prednisone** should be administered for 3-5 days, after that the dose could be decreased gradually at 3-day intervals. During the treatment, prevention of gastric ulcers, potassium supplementation, and the management of blood pressure and serum glucose levels should not be forgotten. Steroid usually stops the cluster period, but certainly do not prevent the next attacks several months or years later.

If the medicines, listed above, are ineffective, **methysergide** can be recommended, but the treatment cannot last for more than three months due to the risk of its severe side effects (retroperitoneal and/or pleuropulmonary fibrosis).

If cluster headache becomes chronic, i.e. cluster attacks present for more than a year without or with an asymptomatic period lasting for less than 1 month between the attacks, administration of **lithium carbonate** is recommended. The total daily dose of lithium carbonate is between 600-1500 mg, which should be divided into three equal parts. Since the therapeutic and toxic doses are close to each other, monitoring of serum lithium levels is essential during the treatment. The dose may be reduced after a two-week asymptomatic period.

When the above mentioned therapies do not relieve the pain, deep brain stimulation of hypothalamus as a last resort can be considered.

Table 1 summarizes the main differential diagnostic questions of the 3 most common types of primary headaches.

Table 1
The characteristics of most common primary headaches

Characteristics	Tension headache	Migraine	Cluster headache
<i>Aura</i>	absent	might be present	absent
<i>Duration</i>	variable	2-72 hours	15-180 minutes
<i>Intensity (on a scale of 10)</i>	3-6	8-9	10
<i>Is the patient able to continue the everyday work?</i>	yes	no	no
<i>Is the pain aggravated by physical activity?</i>	no	yes	no
<i>Pain characteristics</i>	dull	throbbing, pulsating	extremely intense, shooting
<i>Localization</i>	band-like, diffuse	unilateral, temporal	unilateral, periorbital
<i>Autonomic symptoms</i>	absent	present	present, unilateral
<i>Acute treatment</i>	common painkillers	NSAID, triptans	oxygen, triptans
<i>Prophylactic treatment</i>	amitriptyline, clomipramine	propranolol, flunarizine, valproate, topiramate, amitriptyline	verapamil, steroid, (lithium carbonate)

Other primary headaches

Cases of unilateral periorbital paroxysmal pain associated with ipsilateral vegetative signs may show different temporal profile. These diseases have collectively been called trigeminal autonomic cephalalgias. Its most common form is the cluster headache, but paroxysmal hemicrania and SUNCT syndrome also belong to this form of headache.

The **episodic or chronic paroxysmal hemicrania** affects mainly women, usually lasts for a few minutes (2-45 min), and presents at least 5 times a day. The symptoms otherwise are similar to that of cluster headache, and they are also accompanied by one of the following symptoms: lacrimation, conjunctival hyperemia, nasal congestion rhinorrhea, ipsilateral eyelid edema, unilateral facial sweating, partial Horner triad (miosis and/or ptosis). The headache always reacts well to a daily dose of 75-150 mg indomethacin, therefore this disease is also called as indomethacin sensitive headache.

SUNCT (short-lasting unilateral neuralgiform attacks with conjunctival injection and tearing) syndrome also belongs to the trigeminal autonomic cephalalgias. The symptoms, which are quite similar to the paroxysmal hemicrania, are described in the name of the disease, however, the attacks are even briefer (5-240 seconds) and more frequent in the SUNCT syndrome (5-200/day) than in the chronic paroxysmal hemicrania, and the headache does not respond to indomethacin in SUNCT syndrome.

Hemicrania continua is characterized by continuous unilateral headache lasting for more than 3 months. Although the characteristics of the pain in hemicrania continua are quite different than in the trigeminal autonomic cephalalgias, the headache is accompanied by at least one autonomic symptom also in this type of headache (e.g. rhinorrhea, lacrimation, conjunctival injection, ptosis or pupillary differences). Hemicrania continua does not belong to the autonomic trigeminal cephalalgias, but, similarly to the paroxysmal hemicrania, responds well to indomethacin.

SYMPTOMATIC OR SECONDARY HEADACHES

Symptomatic headaches are not discussed in detail here, except for a few notable cases.

Posttraumatic headache

In case of posttraumatic headache the pain is often accompanied by dizziness, concentration disturbances, insomnia and irritability. The symptoms usually appear within a week after the trauma, and decrease within 3 months, however in **chronic posttraumatic headache** the pain may be present for much longer. The quality of pain is similar to that of tension headache. It is important to know, that the severity of trauma does not correlate with the severity of the posttraumatic syndrome. The

headache can be treated acutely with NSAIDs, but in chronic cases prophylactic amitriptyline treatment is recommended.

After a head trauma, cranial CT might be necessary to exclude intracranial hemorrhage (contusion, subdural bleeding, epidural hematoma).

Headaches attributed to traumatic intracranial haemorrhage (subdural or eoidural haematomas, cerebral contusion)

Eighty percent of patients with chronic subdural hematoma experience headache. Many of them do not even remember for suffering trauma, or it might have been so insignificant, that they simply do not attach any importance to it. Patients receiving anticoagulant treatment or suffering from alcoholism or Parkinson's syndrome with frequent fallings should be taken with utmost care. Headache is also common symptom of epidural hematoma, but the pain is usually accompanied by rapidly worsening neurological symptoms and disturbance of consciousness. In case of subdural or epidural hemorrhage urgent neurosurgical intervention is indicated. Cerebral contusion is also characterized by focal neurological signs and headache after head trauma.

Headaches caused by vascular disorders

Headache is a common symptom of subarachnoid hemorrhage and arterial dissection. In case of **subarachnoid hemorrhage** patients describe their pain as the worst they had ever experienced. The headache is often accompanied by nausea, vomitus, photophobia, phonophobia, meningeal signs and increased body temperature. Twenty percent of patients having **intracranial aneurysm without rupture** complain about headache. Headache often develops in **parenchymal hemorrhage**, while only 15-35% of patients with **ischemic lesions** experience it. In ischemic lesion, the pain mostly develops in vertebrobasilar vascular disorders, and is localized to the nuchal area. The onset of the pain in vascular disorders correlates with the onset of the vascular disease.

The symptoms in the **carotid artery dissection** are sudden headache, neck and facial pain, which might be accompanied by Horner triad, stroke, pulsatile tinnitus and lesion of the inferior cranial nerves.

Headache is present in 80-90% of **cranial venous or sinus thrombosis**, and the pain is often associated with focal neurological signs, epileptic seizures, disturbance of consciousness, papillary edema, or any of them.

More than half of the patients suffering from **arteriovenous malformation** experience migraine headache, and in case of bleeding this rate may reach 80-90%.

The **carotido-cavernous fistula** has the symptoms of painful ophtalmoplegia and pulsating exophthalmus. The arterio-venous fistula is accompanied by headache and pulsatile tinnitus. In case of **cavernoma** headache rarely develops, and epileptic seizures or hemorrhage may refer to the diagnosis. In case of bleeding the

headache is more common. CT, MRI, CT angiography or MR angiography is needed to ensure the diagnosis of the conditions listed above.

Temporal arteritis is significant enough to be detailed here. Temporal arteritis is also known as giant cell arteritis or cranial arteritis. It is an autoimmune inflammatory disease of blood vessels commonly involving the branches of external carotid artery. It rarely affects the internal carotid artery. The inflammation consisting of the so-called giant cells and granulomas affects the tunica media and adventitia of the large and medium vessels.

Temporal arteritis usually affects elderly patients above the age of 50-60 years. It is characterized by more and more intense and frequent **headache** irregularly accompanied by unilateral sharp pain on the affected side. The pain, which is usually worse in the evenings, lasts for days. The vessels of the scalp and the temporal region become enlarged, tender and sensitive, but they do not pulsate. One third of the patients complain about jaw claudication (when chewing) due to the inflammation-induced stenosis of the maxillary artery. Ischemic nodular lesions may develop on the scalp and they may ulcerate too.

Temporal arteritis is a deteriorating disease accompanied by bad mood, weakness, loss of appetite, weight loss, increased body temperature or low fever. The polymyalgia rheumatica often causes pain in the shoulders and hips. The early diagnosis is necessary, because blindness may develop due to the thrombosis of ophthalmic artery or posterior ciliary arteries, which may be preceded by amaurosis fugax.

The erythrocyte sedimentation rate (Westergreen) is elevated in most cases (above 50 mm/h), and it may reach up to 100 mm/h or more. The neutrophil count may also be elevated.

If the patient becomes blind, the vision rarely improves. Thus, if cranial arteritis is suspected, the patient should be treated immediately. The most important treatment is the steroid, which should be administered for weeks (prednisone 40-60 mg intravenously, daily). The initial dose of steroid should be decreased gradually to 10-20 mg, which dose should be taken continuously as long as the symptoms decrease. The steroid therapy may even last for 1 or 2 years. The headache and the erythrocyte sedimentation rate should decrease significantly soon after the steroid treatment has been started. If these symptoms do not decrease, the diagnosis should be questioned. In the last years high resolution duplex ultrasound was shown to reliably detect the thick, inflamed vessel wall of the superficial temporal or vertebral artery in patients with temporal arteritis. However, the gold standard in the diagnosis of temporal arteritis is still the biopsy and histological examinations. The main advantage of the ultrasound that it gives immediate result, may guide the site of the biopsy, and follow the therapeutic effectiveness. It has to be highlighted that if the diagnosis is probable, steroid administration should be started immediately even if the histological results are pending.

Headaches caused by non-vascular intracranial diseases

The increased or decreased pressure of the cerebrospinal fluid, aseptic meningitis and intracranial tumors may also cause headache.

Cerebrospinal fluid fistula, lumbar puncture and idiopathic hypotension may result in **decreased pressure of the cerebrospinal fluid**. It is characterized by the symptoms of headache developing and aggravating in sitting or standing position, nausea, hearing loss, tinnitus, photophobia, and nuchal rigidity. The pressure of the cerebrospinal fluid is under 60 mm H₂O in lying position.

The **pressure of the cerebrospinal fluid may be increased** in hydrocephalus, hormonal, metabolic or toxic diseases, and pseudotumor cerebri (benign intracranial hypertension). It is notable, that sinus or intracranial venous thrombosis was revealed in almost half of the cases of intracranial hypertension that used to be considered as idiopathic. The permanent, diffuse and non-throbbing headache is accompanied by papillary edema, enlarged “blind spot”, visual field abnormalities and abducent nerve palsy. The pain is aggravated when performing Valsalva maneuver by inhibiting the venous flow. The pressure of the cerebrospinal fluid is at least 200 mm H₂O in lying position.

Headache caused by tumors is characterized by progressive pain, which might be accompanied by nausea and vomiting later. According to the tumor localization the pain can be unilateral, bilateral or diffuse, or it may affect the forehead (anterior skull base) or the nuchal region (posterior skull base). The localization of the tumor does not always correlate with the localization of the pain, therefore, tumors in the posterior area may cause forehead pain too. Cerebral tumors may induce neurological symptoms according to their localization. Superficial tumors affecting the cortical areas can provoke epileptic seizures, while tumors causing mass effect or being in the frontal lobe can cause personality changes, apathy and drowsiness, beside the headache.

Headaches provoked by chemicals, or the administration or withdrawal of medicines

If discussing headaches provoked by chemicals or the administration or withdrawal of medicines, headaches induced by vasodilator nitrates and dipyridamole should be emphasized. To avoid headache in patients treating with dipyridamole, its dose should be increased gradually. Similarly to dipyridamole, other phosphodiesterase inhibitors, e.g. sildenafil, may also provoke headache.

There are many drugs that are able to induce headache, like triptans, ergotamines, caffeine, and common painkillers. After the provoking agent is omitted and the patient is examined carefully, the headaches can be treated with prophylactic medicines, including amitriptyline, valproic acid, topiramate, or propranolol. If severe headache develops after withdrawing a medicine, NSAIDs can be administered to ease the pain. The headache will decrease within 7-10 days.

Headaches caused by homeostatic imbalance or metabolic disturbances

Hypoglycemia (starving), hypotension or hypertension can induce headache, too. Usually, mild hypertension does not cause pain, but the sudden and pronounced increase of the blood pressure (hypertensive crisis) may result bilateral, pulsating headache aggravating by physical effort. The pain usually decreases an hour after the blood pressure is normalized.

Hypertensive encephalopathy is often diagnosed without knowing its proper definition. Hypertensive encephalopathy develops if the blood pressure exceeds the upper limit of the autoregulation range, and the vasoconstriction of arterioles is unable to compensate the increased perfusion. In these cases vasogenic cerebral edema develops, and the diffuse, pulsating headache is accompanied by disturbance of consciousness, vision impairment and papillary edema. MR imaging may reveal edema in parieto-occipital region.

Non-specific infections accompanied by fever may often cause headache, which stops after the fever decreases. Headaches induced by the infection of the central nervous system are discussed elsewhere. Acute or subacute headache develops in almost every cases of meningitis or meningoencephalitis, and is often associated with fatigue, confusion, disturbance of consciousness, nausea, photophobia, phonophobia and meningeal signs.

Headaches caused by the diseases of neck, nose, sinuses, teeth and temporomandibular joints

Odontogenic pain is the most common facial pain. Caries, pulp degeneration, pulpitis or irritation caused by periodontal abscess may induce the discomfort of maxillary and/or mandibular area. The pain resulted from the dental nerves is throbbing, and more severe at night. It is often accompanied by sensitivity to cold, hot, and pressure above the dental root. The pain can be treated by the denervation of the affected tooth.

The facial pain caused by the **diseases of the nasal cavity and the paranasal sinuses** is not rare, though the significance of chronic sinusitis is often overestimated. The pain is generated by the hyperemia and edema of the mucous membrane lining the inner wall of the sinuses, thus, antihistamines are usually effective. Situations increasing the cephalic venous pressure (e.g. bending forward, effort, coughing or wearing tight collars) or the hyperemia of the nasal mucous membrane (e.g. anxiety, menstruation, cold air, alcohol, etc.) may provoke the facial pain and headache. The pain increases after the patient wakes up, and decreases when he/she goes to bed. The ethmoid and maxillary sinus infections are the most common forms of acute sinusitis. Sinusitis is characterized by mild or moderate pain, which is rather dull or smart. It is usually accompanied by the sensation of fullness. The disease can be diagnosed by using X-ray, CT and MR imaging. Asymptomatic sinusitis can be an additional finding on cranial CT and MR scans. If it cannot be verified by imaging techniques, the pain should be

investigated further. The pain can be treated well with non-steroid anti-inflammatory drugs; otherwise sinusitis should be treated according to the otorhinolaryngological guidelines.

The possible causes of **eye pains** can be divided into two major groups: the first group is characterized by the symptoms of inflammation involving the cornea, sclera, conjunctiva and episclera ("**red eye**" or "**inflamed eye**"), while these symptoms are absent in the other group ("**quiet eye**"). The symptoms listed above can be evoked by many ophthalmological diseases, which are not detailed here. In case of eye pain, consultation with an ophthalmologist is necessary. In neurological practice the differentiation of eye pain caused by cavernous sinus thrombosis, glaucoma, cluster headache or giant cell arteritis is a marginal field. Cavernous sinus thrombosis, cluster headache and giant cell arteritis have been discussed previously. Glaucoma can be verified by eye pressure measurement. Significance of the eye pain or headache induced by **eyestrain** is often overestimated. Eyestrain can be caused by accommodation disorders, and the imbalanced function of extraocular muscles. The symptoms are often related to stress and continuous concentration. The pain usually radiates to the frontal, temporal or occipital area, and it has mild or moderate intensity, but it can be sharp or throbbing, too.

Ear pains affecting the facial area are usually caused by inflammation (e.g. external otitis, otitis media). The rare non-otogenic otalgia can be neuralgia, or the pain originating from the primary tumors of the face and neck can radiate to this area. In rare cases, ear pain can be purely psychogenic, too. The differential diagnosis and effective treatment may require the involvement of otorhinolaryngologist, neurologist, psychiatrist, and neurosurgeon.

The term **temporomandibular dysfunction (TMD - Costen's syndrome)** refers to the dysfunction of the temporomandibular joints and the muscles of mastication, which is accompanied by pain. The pain is located unilaterally to the masticatory muscles, the preauricular region and the temporomandibular joint, and sometimes, it can be experienced only while chewing. In other cases chewing may promote the pain, which can radiate to the temporal region, face, head or even the neck. Temporomandibular dysfunction often involves young or middle-aged women (the women/men ratio is 4:1). It is often characterized by limited mouth opening and asymmetrical jaw movements with crepitation. The joint is sensitive to pressure. Besides the disorders of dental malocclusion and joint diseases, the symptoms of TMD can be caused by stress and anxiety. CT imaging may be necessary to the diagnosis. The consultation with dentists and oral surgeons is essential, but sometimes, psychological examination is also needed. If dental intervention is not required, the administration of NSAIDs, muscle relaxants, and amitriptyline is suggested.

Other facial pains

Tolosa-Hunt syndrome is a granulomatous disorder of the third, fourth and sixth cranial nerves and the sensory ophthalmic nerve, which can develop variously in the cavernous sinus and the superior orbital fissure. The cranial nerve signs

(third, fourth and sixth cranial nerves and the sensory ophthalmic nerve can be affected) are accompanied by pain occurring behind the eye. It can be treated well with steroids, which has diagnostic value too.

Gradenigo's syndrome is characterized by facial pain and abducent nerve palsy. Gradenigo discovered the paresis of the lateral rectus muscle associated with the presence of ipsilateral facial pain in connection with purulent otitis media in 1904. In that case, the symptoms were caused by inflammatory edema reaching the apex of the petrous portion of the temporal bone, which irritated the abducent nerve and the Gasserian ganglion located near the pyramid apex. The pain is usually severe, sharp or throbbing, worsens at night. It can be provoked by pressing the tragus or pulling the auricle. The syndrome can be caused by tumors or other solid lesions located near the pyramid. It occurs rarely due to the spread of antibiotic treatment.

NEURALGIA AND DEAFFERENTATION PAINS

Neuralgias form a different main group when classifying headaches.

Trigeminal neuralgia (tic douloureux, prosopalgia)

Trigeminal neuralgia mainly affects middle-aged or elder patients. It has the incidence of 4-5/100000/year, and the prevalence of 30/100000. The men-women ratio is 2:3. Hypertension, multiple sclerosis and diabetes are the risk factors of trigeminal neuralgia.

The disease, which is interestingly much more frequent on the right side, usually affects the area supplied by the mandibular or maxillary branch of the trigeminal nerve, and only rarely (<5%) involves the ophthalmic nerve. The pain is described as intense, severe and sharp, and feels like an electric shock. The attack suddenly starts and ends, and lasts for seconds. The symptoms localize to the area of the affected branch of the trigeminal nerve. During the attack, because of the very intense pain, the patient touches his/her face and grimaces (tic douloureux = painful tic). The frequency of painful attacks is variable. The pain may appear more than 100 times a day, but it can even disappear for weeks or months. If not being treated properly, trigeminal neuralgia can ruin the patient's life, and has the risk of suicide. The touching of the so-called trigger zones (e.g. skin of the face, lips, gingiva, or certain areas of the tongue) can provoke the pain. The same can occur during the everyday tasks, like shaving, tooth brushing, speaking, eating, swallowing or yawning. The attacks are followed by refractor periods lasting for 2-3 minutes, while the pain cannot be triggered again.

In the symptomatic cases of trigeminal neuralgia, neurological disorders can be revealed in the pontine area (e.g. lesion in multiple sclerosis), the posterior skull base (e.g. basilar aneurysm), the cerebellopontine angle (e.g. acoustic or trigeminal neurinoma, meningioma, epidermoids, etc.), the apex of the pyramid, the cavernous sinus, the superior orbital fissures, the orbits and in the skull base (e.g.

nasopharyngeal carcinoma, etc.). The major part of the trigeminal neuralgia cases was considered **idiopathic**, as for the causative agents were unknown. Nowadays, it is revealed that the **demyelination of trigeminal nerve fibers due to microvascular compression** is in the background of the significant numbers of trigeminal neuralgia cases. Either venous or arterial vessel loop (superior cerebellar artery, inferior anterior cerebellar artery, primitive trigeminal artery) may result the compression.

Trigeminal neuralgia and the other neuropathic pain syndromes (e.g. painful diabetic neuropathy, post-herpetic, post-traumatic and post-stroke neuralgia) cannot be treated well with common painkillers (e.g. aspirin, NSAIDs) and opioids, but they may respond well to **anticonvulsive drugs** or **antidepressants**. The treatment should be started with low-doses, which can be titrated to the effective dose or to the upper limit. The dose of anticonvulsive drugs can be increased in 2- or 3-day intervals, as long as the patient experiences significant improvement or side effects.

The administration of **carbamazepine** is recommended firstly, which initially is very effective in 70-80% of patients with trigeminal neuralgia, but unfortunately, after a few months or years drug tolerance develops in half of the patients. Thus, carbamazepine should be combined with lamotrigine having verified additive effects. **Oxcarbazepine**, having the same effects as carbamazepine, has fewer side effects, but it is expensive and larger doses (with 50%) are needed. Patients not tolerating carbamazepine can be treated with **baclofen**, which also belongs to the first line drugs. Other GABAergic medicines, such as **gabapentin** and **pregabalin**, are also effective. (Unfortunately, gabapentine and pregabalin is not licensed in Hungary for treating trigeminal neuralgia, and their use is limited due to their high costs.)

In at least 25% of the patients with lifetime lasting trigeminal neuralgia the drugs become ineffective, thus **non-medical treatment might** also be necessary. One of the simple interventions performed on the peripheral nerve endings is the **lidocaine infiltration** of the affected branches (infraorbital and supraorbital nerves, mental nerve). The additive effects of lidocaine may decrease the frequency and intensity of the painful attacks, and if being applied together with this technique the effect of medicines may become sufficient. Years before, the nerve function was cut off by using **chemical exhairesis** (infiltration of lidocaine or 50-50% solution of concentrated alcohol and phenol to the nerve endings) or **mechanical exhairesis** (the removal of nerve endings), however these techniques have no longer been used. The disadvantage of the method was that after a few months the nerves regenerated, and the pain inevitably re-occurred.

Nowadays, **percutaneous radiofrequency trigeminal gangliolysis (PRTG) and microvascular decompression** are the most common surgical procedures. PRTG is performed under local anesthesia. Although, it can ease the pain in almost 100%, hypaesthesia often remains, and the pain can relapse in 25% of the cases. The rare complications of PRTG are cornea anesthesia and weakness of the masticatory muscles. The advantage of this one-day surgical procedure is that it has minimal risk even in patients over the age of 65.

Microvascular decompression is rather performed on younger, otherwise healthy patients having trigeminal neuralgia. This method is preferred, if the ophthalmic nerve or all branches of the trigeminal nerve are affected. Craniotomy is performed under general anesthesia via a small 3 cm long incision, and a teflon sponge is placed around the vessels connected to the trigeminal nerves arising from the pontine area. Microvascular decompression has complications in 1-5% of the cases (e.g. permanent dizziness, hear loss, cerebrospinal fluid leakage, meningitis and cerebellar stroke). Its mortality is less than 1%. After the procedure, the patients usually do not experience significant sensory loss. Microvascular decompression provides better results and long-term loss of pain than PRTG.

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia has many common features with trigeminal neuralgia, but it develops more rarely. It is characterized by an intense and paroxysmal, sharp or burning pain, localized to the pharynx, Eustachian tube and middle ear. Swallowing commonly triggers the pain, but speaking, chewing, yawning, and laughing can also provoke it.

Glossopharyngeal neuralgia is called idiopathic, when there is no apparent cause. In these cases it is revealed that the posterior inferior or anterior inferior cerebellar arteries often compress the nerve, and this compression may contribute to the symptoms of neuralgia. The most common causes of secondary glossopharyngeal neuralgia are styloid process elongation, cerebellopontine tumor, arteriovenous malformation, metastasis in the petrous portion of the temporal bone (breast cancer!), compression causing disorders of the parapharyngeal area, peritonsillar abscess, nasopharyngeal carcinoma and epithelioma. Therefore, in case of glossopharyngeal neuralgia rhinoscopy and pharyngoscopy should be performed. The treatment of secondary neuralgias depends on their causes. The same medicines are used for the treatment of idiopathic type, as we use in the therapy of trigeminal neuralgia.

Occipital neuralgia

Occipital neuralgia is characterized by paroxysmal pain localized to the suboccipital, occipital and posterior parietal areas, which are supplied by the major and minor occipital arteries. The pain is unilateral, permanent or paroxysmal, burning or sharp. Dysesthesia often develops on the affected area, and the regions, where the occipital nerves cross the superior nuchal line, can be sensitive, too. The treatment involves repeated courses of the occipital nerve blocking via local anesthesia.

Post-herpetic neuralgia

Herpetic eruptions and post-herpetic neuralgia caused by varicella zoster virus infection may involve not only the spinal roots, but also the sensory cranial nerves. It has two main forms affecting the facial area: the **herpes zoster oticus** or **auricular herpes zoster** and the **ophthalmic herpes zoster**. Both types can be very painful in the acute period of the infection.

In case of herpes zoster oticus the eruptions are located to the external auditory canal and the auricle. It is characterized by severe, permanent and burning pain, which may even last for more than half year. If the inflammation affects the surrounding cranial nerves (such as the facial nerve or the vestibulo-cochlear nerve) the pain can be accompanied by peripheral facial nerve paresis, loss of hearing, tinnitus and vertigo (also known as Ramsay Hunt syndrome). The syndrome is likely to be caused by the infection of the **geniculate ganglion** receiving the special sensory fibers of the facial nerve.

In most of the cases the herpetic infection of **Gasserian ganglion** affects the first branch of the trigeminal nerve causing **ophthalmic herpes zoster**. Four or five days after the pain developed, eruptions usually appear. The acute discomfort related to the herpetic eruptions decreases in a few weeks, but it may last for months. Acyclovir treatment can shorten the period of pain and vesicles, but there is not any drug, which could prevent the development of chronic post-herpetic neuralgia. The **chronic postherpetic neuralgia** is characterized by a permanent burning sensation with temporary sharp pain. The affected skin becomes very sensitive even to mild tactile stimuli.

Malignant diseases or weakened immune system can be in the background of herpes zoster, so the patient should be investigated for tumors as well. The **treatment** of postherpetic neuralgia is the most challenging field of pain therapy. The use of mechanical vibratory techniques, local anesthesia or capsaicin may ease the symptoms. Primarily, gabapentine or pregabalin, as well as carbamazepine can be suggested among the medicines, and they can be combined with tramadol. The combination therapy of antidepressants (such as amitriptyline and/or fluoxetine) can be useful, while in other cases antidepressants can be combined with valproate effectively.

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The dizzy patient

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Definition, classification

Beyond headache, dizziness and vertigo are the most frequent complaints of patients seeking neurological help. We can find different definitions for vertigo. "Vertigo is a total or partial loss of spatial orientation, feeling of rotation of the environment." (*Révész*). "Vertigo is a discrepancy between objective and subjective spatial relations." (*Horányi*) "Vertigo is an illusoric feeling of movement of the body or the environment."

The experience and the well-known symptoms of vertigo appear, when the vestibular, somatosensory and optical afferentations provide conflicting information for the central nervous system.

The patients with different complaints are classified into four major categories.

Vertigo: a systemic experience of movement, rotation or tilt, e.g. vestibular neuritis, Menière's disease, positional vertigo.

Dysequilibrium is an experience of general imbalance, e.g. in patients suffering from Parkinson's disease or polyneuropathy.

Lightheadedness is usually a manifestation of an underlying psychiatric disorder. Most frequent causes are anxiety, depression, alcohol intoxication and hyperventilation syndrome.

Presyncope is caused by different disorders affecting the cerebral circulation, e.g. orthostatic hypotension, arrhythmias, myocardial infarct, carotid stenosis, or different medications.

By the localization of the underlying pathology, we must differentiate central and peripheral vertigo.

Peripheral vertigo (originating from the vestibular organs) **usually appears as a harmonic vestibular syndrome:**

- direction of tilt, past pointing, deviation during blind walking and direction of the slow component of nystagmus are identical,
- nystagmus is horizontal or horizonto-rotatory, and never vertical,
- direction of nystagmus is independent from the direction of gaze (I.-II.-III. grade nystagmus),
- symptoms may worsen by changing head or body position,
- usually very heavy vegetative symptoms (vomiting, sweating, pale skin),
- mortal fear can develop,
- vestibular excitability may decrease on the lesion side.

Central vertigo usually appears as disharmonic syndrome:

- direction of tilt, past pointing, deviation during blind walking and direction of the slow component of nystagmus usually discordant,
- direction of nystagmus can be changed with the gaze direction,
- nystagmus can beat to any direction (even upbeat or downbeat), or can be dissociated,
- the complaints are not always rotatory,
- changing of the head or body position usually does not affect the severity of the symptoms,
- vegetative symptoms are usually not prominent or may be missing,
- *other, typically brainstem derived neurological signs develop: double vision, dysarthria, dysphagia, sensory loss, paresis, ataxia etc.*

Symptoms are discussed in detail at the specific syndromes, these enumerations are only generally true. Dizziness or vertigo can have a lot of different causes. That's why we cannot restrict the examination on some physical or instrumental tests. In many cases specific, detailed history taking and specific examinations lead us to the correct diagnosis.

Examination of the dizzy patient, diagnostic tools

During history taking we always have to clarify the questions listed here:

- *Type of the dizzy complaints:* rotatory (e.g. vestibular neuritis), disequilibrium (e.g. Parkinson's sy, polyneuropathy), presyncope, postural (e.g. phobic postural vertigo), or atypical, lightheadedness (e.g. anxiety, intoxication).
- *Duration of the attacks:* seconds, minutes (BPPV, vestibular paroxysmia), hours (Menière, migraine), continuous (vestibular neuritis, brainstem stroke, MS), recurrent (Menière, migraine).
- *Trigger:* no (vestibular neuritis), walking (phobic postural vertigo, bilateral vestibulopathy), head turn (vestibular paroxysmia), certain head positions (BPPV), coughing, pressing, loud sounds, certain frequencies (perilymph fistula), life situations (phobic postural vertigo).
- It is very important to clarify the *circumstances* (time, place, activity) of the first vertigo episode and whether these features resemble during the recurrent attacks!
- *Accompanying symptoms:* hypacusis, tinnitus (e.g. Menière), double vision, ataxia, nystagmus, oscillopsia, brainstem, cerebellar symptoms (vertebrobasilar stroke), headache (migraine, stroke).

Neurological examination is compulsory in dizzy patients, because the presence or absence of the neurological symptoms is crucial for the diagnosis. Many times neurological testing alone leads to the diagnosis (e.g. polyneuropathy, complex symptoms of brainstem stroke, signs of MS). In other cases, specific auxiliary examinations are necessary. Most of these tests do not require special

equipment, this way they can be performed in any consulting room. The specific auxiliary tests are the following ones:

Eye movements

Saccades should be conjugated, fast and accurate. Slow, hypometric saccades are usually caused by intoxication, degenerative disorders, or brainstem lesion. Hypermetric saccades are the signs of cerebellar (vermis) lesion, particularly in patients with multiple sclerosis.

Smooth pursuit eye movements are driven by the cooperation of multiple supra- and infratentorial structures. They are considered to be abnormal when the eye movements become saccadic or asymmetric.

Examination of the nystagmus

We should search for spontaneous, gaze-evoked, hyperventilation-, head shaking- or Valsalva maneuver- induced nystagmus. Visual fixation, which suppresses the spontaneous nystagmus, should be eliminated by Frenzel glasses.

Halmágyi-Curthoys manoeuvre (head impulse test)

This test is suitable for the examination of the horizontal vestibulo-ocular reflex (VOR). The patient should fix a target (e.g. the examiner's nose), while the examiner is rapidly rotating the patient's head horizontally to the left and the right directions. This rapid head movement in a healthy subject effects rapid compensatory eye movement in the opposite direction. In cases of unilateral labyrinth (horizontal semicircular canal) lesions, the normal contraversive eye movement is missing. Eyes go with the head during the rapid turn and a visually driven, corrective and saccadic eye movement (catch-up saccade) is seen at the end. The test can be performed in all the six directions of the different semicircular canals.

Dix-Hallpike manoeuvre

This test is performed to diagnose benign paroxysmal positional vertigo (BPPV). The patient is sitting on the examination bed, and his/her head is turned 45° left or right (left or right sided posterior canal testing) then the patient is rapidly reposed to supine position with the head hanging over the end of the bed, about 15° below the bed level. If BPPV of the posterior canal is present, after a 5-10 seconds latency a crescendo-decrescendo nystagmus is seen beating upwards and towards the affected and examined lower ear (the plane of the eye movement is identical with the plane of the posterior canal). The duration of the nystagmus and the accompanying vertigo is typically about 20-30 seconds. After sitting up, a reversed directional nystagmus with the same time course can be seen in about 1/3 of the cases.

Statokinetic tests

Romberg test, blind walking, star walking, Unterberger's test, Bárány's test (past pointing) are used to detect asymmetry of the vestibular function. Unilateral cerebellar lesion also results in tilt or deviation towards the affected side. If we suspect psychogenic reasons in the background of the dizziness, we should divert the patient's attention by writing numbers on the forehead or make her calculate difficult mathematical tasks. In psychogenic cases the tilt and body sway will be reduced or ceased by these tricks.

Labyrinth stimulating tests

Head shaking: the patient's head is rapidly rotated from left to right 20-30 times, after stopping we search for nystagmus. Provoked nystagmus denotes latent asymmetry between the two-sided vestibular systems due to central or peripheral cause. *Caloric stimulation* is thought to be the gold standard of vestibular (horizontal semicircular canal function) testing, because it provides quantitative information, repeated examinations allow follow-up of the patient's state. The tympanic membrane should be intact. The patient's head is tilted backwards by 30° the outer ear is irrigated with 30°C cool water for 30 seconds on each side. With 5 minutes breaks between, the irrigation is repeated with 44°C warm water. If the eardrum is not intact, stimulation is performed with tempered air. Normally, cold stimulus provokes nystagmus to the opposite and warm to the ipsilateral direction for about 120 seconds. Asymmetry above 25% is considered as abnormal. In well-equipped laboratories eye movements are registered by electro- or videonystagmography, where the slow phase velocity of the nystagmus is measured in order to use it in quantitative formulas.

Effects of pressure change

These tests help to diagnose perilymph fistula and superior canal dehiscence syndrome. We can change the pressure of the outer and the middle ear by using a Politzer balloon (a rubber balloon with a small tube that fits to the outer ear), or by applying compression on the tragus. Nystagmus and complaints can be induced by a Valsalva manoeuvre or by coughing, sneezing, pressing. The pressure change of the middle ear induces pressure change in the labyrinth via the fistula, causing vertigo.

Hyperventilation

In patients with cerebellar lesion downbeat nystagmus can become more intensive. Vertigo attack can be provoked in patients with vestibular paroxysmia via changing the blood pH level.

Further laboratory, instrumental examinations in dizzy patients

To answer the questions of differential diagnosis, sometimes blood laboratory tests are necessary. Ultrasound (Doppler) examination of the cervical arteries (vertebral artery dissection), cerebrospinal fluid examination (meningeal carcinomatosis), brainstem-evoked potentials (brainstem lesion) can be useful. CT and MRI are mostly performed to find the cause of the central vertigo (ischemic lesion, hemorrhage, tumors). Thin-slice high resolution CT of the pyramidal bone is suitable to find tumor of the inner acoustic channel, cholesteatoma, pyramid bone fracture, labyrinth ossification, superior canal dehiscence and other diseases affecting the bony parts. Three-dimensional MR imaging using true 3D data acquisition strategies on the posterior fossa helps to diagnose neurovascular compression, Cogan's syndrome, and inflammatory diseases of the labyrinth and the cochlea. In spite of the availability of the modern high-tech radiological examinations, the diagnosis of some diseases is still based mostly on correct physical examination and history e.g. BPPV, vestibular neuritis or Menière's disease.

Most frequent causes of vertigo and dizziness

Based on the patient population of 4 years (almost 5000 patients) of the vertigo ambulance of the Munich Neurology Department, the causes of vertigo and dizziness in decreasing order of frequency are: benign paroxysmal positional vertigo (BPPV) 18,3%; phobic postural vertigo (PPV) 15,9%; central vestibular vertigo 13,5 %; vestibular/basilar migraine 9,6 %; vestibular neuritis 7,9%; Menière's disease 7,8%; bilateral vestibulopathy 3,6%; psychogenic vertigo (excluding PPV) 3,6%; vestibular paroxysmia 2,9 %; perilymph fistula 0,4%; other 12,3%; unknown 4,2%.

The most frequent central causes are the brainstem ischemia, multiple sclerosis, basilar/vestibular migraine, posterior scala tumors, syringobulbia, Arnold–Chiari's malformation, cerebellar atrophy or degeneration, and temporal epilepsy.

General therapeutic rules for treating dizzy patients

In patients with severe vertigo, beyond making the diagnosis, the most important measure is the symptomatic treatment of the severe complaints of vomiting, vertigo and malaise. We can administer vestibular suppressants and antiemetics. These drugs are needed most commonly in acute peripheral vestibular

lesion, acute brainstem lesion, and kinetosis and for premedication before BPPV liberatory manoeuvres.

Vestibular suppressants: benzodiazepines (diazepam, clonazepam, alprazolam); dimenhydrinate; promethazine; hydroxyzine; cinnarizine; flunarizine.

Antiemetics: Anti-dopaminergic drugs: thiethylperazine, haloperidol, sulpiride, metoclopramide, and domperidone. Anticholinergic-antihistamines: dimenhydrinate, promethazine. Anti-serotonergic drugs: ondansetron. These drugs should not be applied longer than 2-3 days, because vestibular suppressants can retard central compensation procedure, which is the final solution for the patient's complaints. As the vomiting is usually very profuse, the administration of the drugs should preferably be parenteral or per rectum (suppository). We should take special care on parenteral fluid supplementation of the profusely vomiting patient. The specific therapy of the different syndromes is discussed below.

As the intense acute symptoms calm down, we can start the balance training and the vestibular rehabilitation to enhance the central compensation. During this procedure the central nervous system makes a new balance state by substituting the missing function with the afferentations from the different healthy sensory organs (the vestibular system of the other side, visual, somatosensory).

Surgical therapy is indicated only in very selected cases when conservative therapy does not help: brainstem and posterior fossa tumors, cavernomas, neurovascular compression, and perilymph fistula. Intractable Menière's disease is solved by chemical denervation of the affected side. The severe BPPV is sometimes treated by plugging the affected channel.

Psychological and psychiatric therapies are recommended in phobic postural vertigo and acrophobia. Behavioral therapy involving desensitization mostly helps. Drugs (SSRIs, tricyclic antidepressants) are usually less effective.

Characteristics, diagnosis and therapy of the most frequent vertigo syndromes

Vertigo of peripheral origin

Benign paroxysmal positional vertigo (BPPV): *the most frequent cause of vertigo.* It can appear in any age, but more frequent in elderly patients. It is caused by canalolithiasis. Small calcium crystals called otoconia peel off the cupula due to degeneration, inflammation or trauma, and form a conglomerate usually in the posterior semicircular canal. If the size of the conglomerate is close to the diameter of the semicircular canal, it functions as a piston and make the endolymph move until it sediments at the lowest point determined by the actual head position. Therefore the vertigo attack lasts maximum 30-60 seconds, and is provoked by a certain head position: mostly laying down, getting up from bed, turning in bed to one side, bending over or watching upwards. Vertigo and nystagmus appear after a latency of some seconds, and their direction is constant during the attack, and their intensity is of crescendo-decrescendo type. *The first attack usually develops during*

the first position change after waking up in the morning (when the patient is getting up), very intense, sometimes associated with vomiting. Later the symptoms improve spontaneously (as the conglomerate brakes up) or may persist for months.

Physical examination does not reveal spontaneous nystagmus, hearing loss or abnormality of the caloric test. *The diagnosis* is based on the anamnesis and the Dix-Hallpike manoeuvre. Bilateral involvement is seen in 10-20% of the cases and sometimes the horizontal canals are involved too. *Therapy: drugs are not necessary, as they do not help!* Applying the liberatory (repositioning) manoeuvres (Semont, Epley) canalolith can be forced to move from the semicircular canal to the utricle, where it does not provoke endolymph movement any more. These manoeuvres are usually successful in 80-90% for the first attempt. If the liberation is failed, we advise the patient to perform the Brandt-Daroff manoeuvre at home regularly, which brakes up and disperses the otolith into small crystals, which do not function as a pump any more, plus central compensation is assisted. Patients mostly do not require hospitalization, we can send them home right after the liberation. Sometimes transient observation and symptomatic therapy (or premedication) is indicated due to the intense symptoms during or after the liberation. *Differential diagnosis:* central positional nystagmus, vestibular paroxysmia.

Vestibular neuritis: It appears as a harmonic vestibular syndrome with heavy rotatory vertigo, very intense vegetative symptoms, and I-III grade nystagmus. It is predicted a few days before the attack by short rotatory vertigo episodes. Complete recovery of the affected vestibular system is seen only 40% of the cases. A few weeks later the symptoms disappear in a stable head position by means of the central compensation, but a sudden head movement, running, or walking may provoke vertigo, nystagmus or oscillopsia. Later BPPV or PPV may develop. Viral infection is suspected in the background as in Bell's facial nerve palsy. *Therapy:* vestibular suppressants, antiemetics applied as long as the patient is vomiting. Methylprednisolone within 3 days of symptom onset (100 mg /die, tapering by 20 mg every 3 days) significantly improves the long-term outcome and vestibular function. *The circulation enhancing infusions are ineffective!* The gradual vestibular rehabilitating exercises help the central compensation after the acute phase. Hospitalization is mostly indicated because of the intense vomiting and necessity of parenteral fluid supplementation, otherwise the disease itself would not require it. *Differential diagnosis:* Menière's disease, vestibular migraine, vestibular paroxysmia, herpes zoster oticus, labyrinthitis, borrelia infection, multiple sclerosis, brainstem stroke, and ictus cochlearis (with or without cerebellar infarct).

Menière's disease: It is a disease with attacks lasting for usually 1-2 hours (>20 min, max. 12 hours, exceptionally 24 hours) presenting with rotatory vertigo, tilt, vegetative and cochlear symptoms, and later hypacusis in the affected ear. It is caused by the hydrops of the endolymphatic labyrinth and periodic rupture of the membrane located between the endolymph and perilymph. The potassium-rich endolymph depolarizes the vestibulocochlear nerve. Later it causes a conduction block, which lasts for hours. Thus, during a typical attack, a harmonic syndrome is present with direction change, as the excitation turns to the blockage. (This can be

seen only if we catch and follow the attack in a very early phase). Tinnitus, hearing loss, fullness, and congestion in the affected ear are typical prodromal and accompanying symptoms. The disease typically develops in the 4-6th decades with a male predominance. In the beginning it is unilateral, but after 1-2 decades, bilateral involvement is found in 30-60% of the cases. The frequency of attacks is increasing, then decreasing, but finally, the patient will have symptoms due to the cochlear and vestibular involvement. Rarely, as the first symptom of the attacks, the so-called vestibular drop attack (Tumarkin's otolith crisis) is seen, the patient is suddenly falling to the ground. It is caused by otolith shifting, which is resulted by the hydrops. In many cases it is misdiagnosed as epilepsy. *The diagnosis* is based on the symptoms, the presence of recurrent attacks, measurable hearing loss (typically in the low frequency range), electrocochleography results and the exclusion of other etiologic factors. *Therapy*: The therapy is symptomatic during acute attacks. Betahistine and diuretic agents are used to prevent further attacks. The effectiveness of betahistine is still debated, because its recommended dose is 3x40-48 mg/day for 6-12 months! The combination of hydrochlorothiazide and triamterene can be added. If these are ineffective, chemical vestibular denervation with intratympanic gentamycin injection is recommended. The surgical and circulation-enhancing medications are usually ineffective. *Differential diagnosis*: basilar migraine, vestibular neuritis, multiple sclerosis, brain stem stroke, ictus cochlearis, Cogan's syndrome, and vestibular paroxysmia.

Vestibular paroxysmia: Short lasting (seconds, or maximum minutes), recurrent rotatory or postural vertigo attacks presenting many times per a day. Intense rotatory nystagmus, sometimes tinnitus, and hypacusis are the usual accompanying symptoms. Vestibular and cochlear deficit can develop in advanced stages. *Triggers*: certain head position, sometimes hyperventilation. Carbamazepine eases or abolishes the attacks. No brainstem sign is seen. Sometimes, the signs of the facial nerve excitation are seen during the attacks. It is most frequently seen in males in the 5-7th decades. *Causes*: spontaneous discharges of the vestibular (and cochlear) nerve due to neurovascular cross-compression. Most frequently the anterior inferior cerebellar artery (AICA) is the compressing one, but arachnoid cysts, aneurysms, and vascular malformation can also be in the background. *Therapy*: low dose carbamazepine 200-600 mg/day has a quick effect, which is also diagnostic for the disease. Valproic acid, gabapentin, and phenytoin are the possible alternatives. Surgical decompression of the arterial cross-compression should be avoided because it increases the risk of deafness and stroke. In cases of other pathologies (cyst, or tumor), the surgical decompression can stop the symptoms. *Differential diagnosis*: BPPV, basilar migraine, phobic postural vertigo, and vertebral artery compression caused by head position change.

Bilateral vestibulopathy: It is characterized by oscillopsia and blurred vision during walking and head movements (recognition of faces, street signs make a problem), gait instability (especially in darkness and on uneven ground), spatial memory problems and difficulties of orientation. The patient is asymptomatic in resting position. The symptoms are produced by the bilateral loss of the vestibulo-ocular reflex, caused by bilateral vestibular lesion. Head impulse test is pathological in both directions. The (usually asymmetric) vestibular deficit can be

quantified by using bilateral caloric stimulation. Romberg's test is expressly positive, and can be associated with hearing loss. The etiology is unknown in 20-30% of the cases. Ototoxic medications (aminoglycoside, aspirin, diuretics, chemotherapeutic agents), meningitis, labyrinthitis (bacterial, TBC, HIV), tumors (neurofibromatosis, meningeal carcinomatosis), autoimmune diseases (Cogan, Bechet, SLE, RA, PAN, giant cell arteritis), neuropathies, chronic phase of bilateral Menière's disease, Paget's disease, and bilateral pyramid bone fracture can be in its background. *Therapy*: prevention is the most important. The careful administration of the aminoglycoside antibiotics is essential. In autoimmune cases the use of immunosuppressants and corticosteroids may help. Vestibular exercises and physiotherapy may help the CNS to develop such central compensation, which uses somatosensory and visual information instead of the lost vestibular afferentation. *Differential diagnosis*: cerebellar lesion, phobic postural vertigo, vestibular paroxysmia, intoxication, perilymph fistula, and orthostatic hypotension.

Perilymph fistula: Attacks, which are evoked by pressure changes, last for seconds to days, and associated with rotatory or postural vertigo, oscillopsia, and vertical-rotatory nystagmus. The presence of hearing loss is not rare. *Triggering factors*: pressure change, such as coughing, sneezing, Valsalva's maneuver, loud sounds (Tullio's phenomenon), bending over, or high altitude. Barotrauma and ear or head traumas are usually reported in the medical history. The most frequent cause is the dehiscence of the anterior (superior) semicircular canal. A part of the bony coverage of the labyrinth is missing, and labyrinth membrane is practically in the epidural space. The classic form is caused by the presence of a fistula located between the perilymphatic space and the middle ear, near the round or oval window. The pressure of the middle ear or the intracranial space is transmitted to the labyrinth, which causes excitation. *The diagnosis* is based on the symptoms and Valsalva's maneuver, tragus compression, Politzer balloon test, high resolution CT, and tympanoscopy. The course of the disease and the attack frequency are different. The attacks usually break off and may return after a new trauma. *Therapy*: bed rest for 1-3 weeks with a slightly elevated head position, laxatives, moderate physical activity for some weeks usually release the symptoms. Surgical closure of the fistula is rarely indicated and rarely successful. *Differential diagnosis*: BPPV, central vertigo, phobic postural vertigo, Menière disease, vestibular paroxysmia, bilateral vestibulopathy, labyrinth commotion.

Vertigo and dizziness of central origin

Basilar/vestibular migraine: Recurrent vertigo attacks accompanied with the various combinations of the symptoms below: truncal or limb ataxia, visual disturbance, other brainstem signs, occipital headache, nausea, vomiting, disturbed consciousness, mood change, and decreased psychomotility. In the monosymptomatic cases of vertigo and hearing loss we talk about vestibular migraine, while basilar migraine is characterized by accompanying brainstem signs. In 75% of cases only vestibular symptoms develop, thus the diagnosis is problematic. The diagnosis is easier if headache is present or the patient had other type of migraine in the history. The duration of the attacks can vary between

seconds to days. The symptoms can develop in any age, most frequently in the 3-6th decades (contrary to the misbelief, that basilar migraine is the disease of young women). The average age is 38 in women and 42 in men at the onset of the attacks. *The diagnosis* is based on the presence of the attacks associated with the symptoms detailed above, and the exclusion of other causes (especially brainstem stroke). *Therapy*: the drugs used in migraine with aura, antiemetic and NSAID (ibuprofen, diclophenac) medication. Triptans are relatively contraindicated, as they increase the risk of stroke due to their vasoconstrictive effect! Triptan therapy can be effective in certain cases. For prophylactic treatment, metoprolol is the first and valproic acid is the second recommended agent. The use of vestibular suppressants, carbamazepine and other anticonvulsive drugs are ineffective. *Differential diagnosis*: brainstem ischemia, cerebellar ischemia and hemorrhage, vertebral artery dissection, Menière's disease, vestibular paroxysmia. *During the first basilar migraine attack(s) it is extremely important to exclude brainstem ischemia (basilar artery occlusion) and other severe, life-threatening pathologies of the posterior fossa (cerebellar ischemia, hemorrhage, tumor)!* If the symptoms ease and the course of the subsequent attacks are similar we can make the diagnosis of basilar migraine.

Ictus cochlearis: The internal auditory artery derives from the anterior inferior cerebellar artery (AICA) in 80% of the cases. The occlusion of the auditory artery can develop alone or as the part of the AICA occlusion. The occlusion of the auditory artery presents with severe hearing loss, and harmonic vestibular syndrome due to cochleo-vestibular deficit. AICA occlusion may also cause ipsilateral facial nerve paresis, gait- and limb ataxia, tactile hypaesthesia of the ipsilateral face and contralateral body, ipsilateral Horner's syndrome, and ipsilateral horizontal gaze disorders. The affected areas are the middle cerebellar peduncle, the infero-lateral part of the pons, the anterior inferior part of the cerebellum, the cochlea, and the labyrinth. In the waste majority of the acute labyrinthitis cases mentioned at vestibular neuritis, the occlusion of the auditory artery is suspected. *The possibility of the occlusion of the auditory artery should be suspected in patients with vertigo and acute hearing loss experienced on the side of the vestibular lesion, and should be examined by a neurologist!* If the brainstem involvement is proven, the patient should be admitted to a stroke ward. *Differential diagnosis*: Menière's disease, vestibular neuritis, labyrinthitis, and vestibular/basilar migraine.

Other types of central vertigo develop if the connection between the vestibular nuclei in the medulla oblongata and the mesencephalic oculomotor nuclei, vestibulocerebellum, thalamus, temporoparietal vestibular cortex or the vestibulospinal pathways is damaged. The syndrome can be very different, depending on the site of the lesion, which may be suggested by the accompanying symptoms. It is usually caused by ischemic stroke, multiple sclerosis, other inflammatory diseases (encephalitis) or developmental disorders (Arnold-Chiari malformation, syringobulbia), degenerative diseases (e.g. spinocerebellar ataxia), or temporal epilepsy. *If the dizzy patient's symptoms do not fit into the above detailed benign vertigo syndromes, and/or other brainstem- or cerebellum-derived symptoms are found (paresis, eye movement disorder, sensory abnormality), the*

patient should be sent to neurological emergency department immediately, especially, if the symptoms are severe, abrupt or progressive!

Psychogenic vertigo

In everyday medical practice vertigo and dizziness are very frequent complaints and in many cases psychogenic background is suspected. Usually, anxiety, depression and somatoform disorders are found in the background. The complaints of dizziness appear without obvious physical signs. Later, diverse accompanying symptoms can develop, such as concentration problems, decreased performance, tachycardia, nausea, sweating, feeling of asphyxia, lack of appetite, weight loss, and sleep disorder. Psychotherapy and the administration of psychiatric medication can be considered. The most frequently seen psychogenic syndrome is discussed in detail.

Phobic postural vertigo is characterized by subjective postural dizziness and gait unsteadiness, attacks of fear of falling without any real falls, anxiety, and vegetative signs. The dizziness is atypical, and the patient cannot define the complaints, which are not visible by the observer. The attacks often occur in typical situations (crowd, bridge, hypermarket, car driving, etc.), but more typically, they develop without any specific trigger. In many cases organic vestibular illness (BPPV, vestibular neuritis) or psychosocial stress situations are reported in the patient's medical history. Later, the complaints become more generalized and an avoiding behavior develops. These patients often exhibit obsessive-compulsive or perfectionistic personality and self-observing behavior. Physical and instrumental examinations are all negative. Phobic postural vertigo can manifest in any age, but most often it develops in the second and fifth decades. *Its diagnosis* is based on the presence of the symptoms and the exclusion of other causes. *Therapy:* psychoeducational assessment, the patient should be relieved from the fear of organic illnesses. Desensitization with repeated self-exposure to triggers and regular exercises is recommended. If the complaints persist, behaviour therapy with or without pharmacotherapy (SSRI, tricyclic antidepressants, sometimes tranquillizers) may help. The earlier is the diagnosis and treatment, the better improvement rate can be expected. *Differential diagnosis:* panic disorder, bilateral vestibulopathy, vestibular paroxysmia, perilymph fistula, basilar migraine, central vertigo, and orthostatic dysregulation.

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Epilepsy

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Definition

Epilepsy is a chronic disease of the central nervous system (CNS). It is caused by the hyperexcitability of the neurons. The epileptic seizure manifests itself in neurological and/or psychiatric symptoms depending on which part of the brain is involved. It is the biological nature of the CNS that it reacts for certain stimuli with epileptic seizure. Epileptic seizure can be provoked in everyone by appropriate electric stimuli or chemical agents. Five percent of the population has a lower threshold, thus certain provoking factors can elicit epileptic seizures in them (e.g. fever, sleep deprivation or scintillating lights). In these cases we are talking about provoked (acute) seizures, and not about epilepsy. Metabolic disturbances (e.g. hyperglycemia), acute cerebral damages (e.g. encephalitis, trauma, stroke) can cause acute seizures too. The later ones are risk factors for epilepsy (post-stroke epilepsy, posttraumatic epilepsy). Epilepsy is diagnosed when the seizures appear and repeat spontaneously without any provoking factor. The prevalence of the epilepsy is 0.5% in adults and 1% in the pediatric population.

Classification

According to the etiology we can differentiate *idiopathic (primary)* (20-25%) and *symptomatic (secondary)* (75-80%) epilepsies (Figure 1). The majority of the idiopathic epilepsies have a polygenic inheritance. If one parent is affected, the risk is 4 to 5 times higher comparing to the general population. If both parents are affected, the risk of epilepsy is 8 to 10 times higher. Every effect harming the brain can induce epilepsy. The risk is high for patients with cortical dysgenesis, hippocampal sclerosis, or low-grade tumors. Perinatal injury, stroke and trauma are associated with medium risk.

According to their onset and EEG signs epileptic seizures are classified into *focal (partial)* and *generalized types*. Focal seizures originate from a well-circumscribed area of the brain. In case of generalized seizures a circumscribed anatomic localization cannot be verified.

There is no disturbance of consciousness during a *simple partial seizure*. It can be motor, sensory, vegetative, or visual etc., depending on the involved brain area.

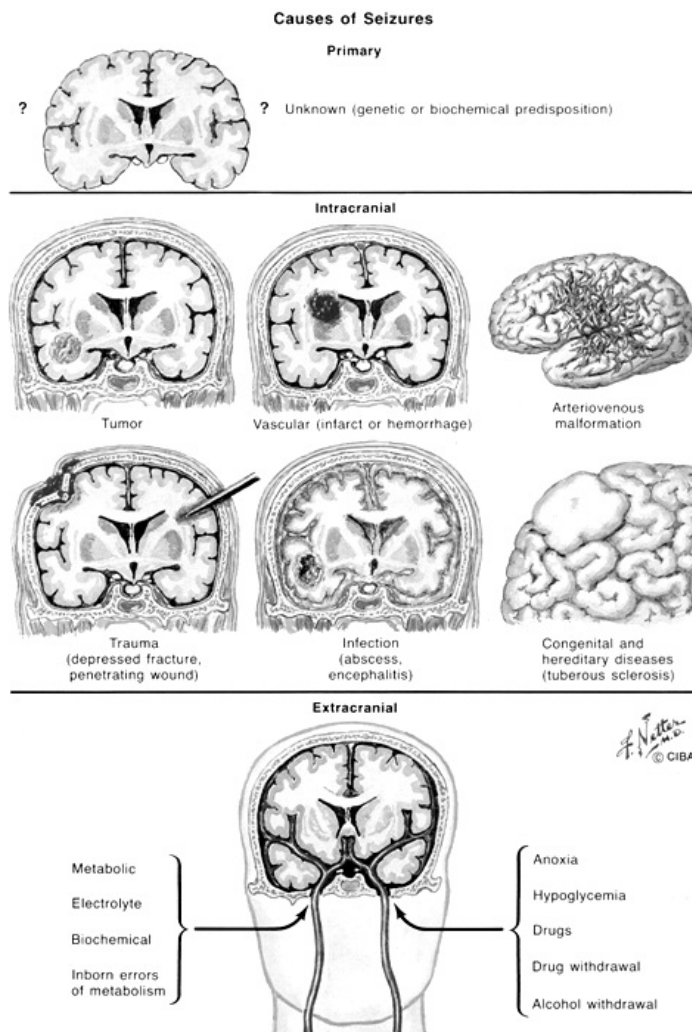


Figure 1
Causes of seizures
(Netter Collection of Medical Illustrations, Volume 1, Part 2: *Nervous System: Neurologic and Neuromuscular Disorders*, Saunders, 1986, page 41.)

Disturbance of consciousness is present in *complex partial seizures* (frontal lobe, temporal lobe epilepsy), and sometimes automatisms can appear, too. Oral automatisms can be observed frequently, such as chewing, swallowing, or munching, and sometimes thrumming, aimless gesticulations may appear. The disturbance of consciousness is usually non-hypnoid, so the patient is alert, but

confused, and does not cooperate. Focal seizures can evolve to secondarily generalized seizures accompanied by loss of consciousness, and sometimes the clonus of the extremities.

The types of the *generalized seizures* are absence, myoclonic, clonic, tonic, tonic-clonic, and atonic seizures (epileptic fall).

Absence seizure (petit mal): frequent in childhood. The patient stares ahead for 10-30 sec, but does not lose his/her consciousness, and does not collapse. Fine myoclonus can appear in the periorbital and periocular regions. There is no tenebrosity (confusion) after the seizure, and the patient continues his/her previous activity.

Myoclonus: short, rapid contraction of a smaller or larger muscle group. It can also be observed in other disorders.

Clonic seizure: quickly repeating myoclonus.

Tonic seizure: tonic (sustained) contraction of the axial and limb muscles.

Tonic-clonic (grand mal): it starts with a tonic phase, which mainly affects the anti-gravitational muscles (arms in flexion, legs in extension). It lasts for 10-20 sec. The clonic phase starts with the clonus of the extremities. The heart rate and the blood pressure increases. In the tonic part apnea is present, which causes cyanosis and perspiration, and increases the tracheobronchial secretion. During the clonic phase the expirations whip the secretions and cause frothing at the mouth. Usually the patient sleeps after the seizure (postictal sleep). Postictal tenebrosity, headache and muscle strain are also frequent.

Atonic: the sudden, brief, generalized loss of muscle tone causes the fall of the patient, and risks trauma. Usually, the patient remains conscious, and tries to stand up quickly.

Epileptic state (Status epilepticus)

The seizure lasts longer than 30 minutes or the patient cannot regain his/her consciousness during the seizure. Nowadays it is widely accepted that epileptic state should be considered even after 5 minutes, because the convulsive epileptic state may be fatal or result in permanent brain damage. The non-convulsive epileptic state endangers the patient or his/her environment, because the patient is confused, and may suffer accidents or harm others. The diagnosis of non-convulsive epileptic state is difficult, but EEG can verify it.

Epilepsy syndromes

According to their etiology, pathomechanism, seizure type, EEG, accompanying neurological and psychopathological symptoms, therapy and prognosis, epilepsy syndromes can be defined (Table 1).

Table 1
The most frequent epilepsy syndromes

	Idiopathic	Symptomatic
<i>Partial</i>	benign centrotemporal	temporal, frontal, occipital, parietal
<i>Generalised</i>	absence, juvenile myoclonic epilepsy	West, Lennox-Gastaut sy

Diagnosis

Anamnesis

The most important part of the diagnostic process is the auto- and the heteroanamnesis, because many seizures may impair the consciousness. What happened during the seizure? Did aura or postictal confusion develop? How long did the seizure last? Can the patient remember the event? Previous diseases, perinatal events, traumas, medications and provoking factors are also important. **Nowadays the relatives and friends can record the seizure by mobile phone or camera.** It can be very helpful for the diagnosis.

Physical examination

Record the neurological and psychical states. Judge the somatomental development of infants and children.

Laboratory parameters

The followings are obligatory to check: blood cell counts, serum sodium, potassium, calcium, magnesium, phosphor, urea, creatinine, glucose, AST, ALT, GGT, and AP. In childhood epilepsies special examinations are necessary e.g. lactate, genetics. If inflammatory disease is suspected, the examination of the cerebrospinal fluid is recommended.

Electroencephalography (EEG)

Interictal (between seizures) or ictal (during a seizure) epileptiform activity can be verified. Even in the postictal phase the sensitivity is only 40-50%, so **a negative EEG does not exclude epilepsy. Some percent of the population can have epileptiformic signs on EEG without epilepsy.** Ictal EEG pattern during a seizure verifies the epileptic origin of that seizure. Negative EEG during a seizure excludes the epileptic origin of that seizure (some patients can have both epileptic

and non-epileptic seizures). The EEG can help the classification of the seizures (focal or generalised). During a video-EEG registration we can record simultaneously the EEG and the course of the seizure, which is very helpful to diagnose psychogenic seizures. It is also helpful for the localization and analyses of the seizures. Ambulatory EEG is also available, by which we monitor the patient while he/she is performing his/her routine daily activities. Routine provoking methods during the EEG is hyperventilation, photo-simulation, and sleep deprivation.

Radiology

In emergency (e.g. first seizure) cranial CT should be performed. The epilepsy protocol prefers MRI, because small lesions can be verified only with MRI (hippocampal sclerosis, cortical dysgenesis). In special cases, especially when epilepsy surgery is indicated, PET, SPECT, functional MRI, or MR spectroscopy is necessary.

Neuropsychological test

It should be performed if cognitive or psychopathological symptoms are present, and during pre-surgical evaluation.

Differential diagnosis

After the first seizure it is difficult to decide whether it was a provoked seizure or epilepsy. Thus, we usually establish the diagnosis only after observation, or a second episode.

Febrile seizure is a special provoked seizure. It is present in 5% of the children between the age of 3 months and 5 years, and is accompanied by fever. It recurs in 30% of the patients. Epilepsy develops in 2 to 10%, so the majority of children with febrile seizures will not suffer from epilepsy.

Non-epileptic paroxysmal events: syncope, psychogenic seizure, TIA, events during sleep (periodic limb movements, sleep apnea), extrapyramidal disorders, migraine. It is important to emphasize that some abortive movement can be present in syncope (Table 2).

	Syncope	Epileptic seizure
<i>Prodrome</i>	frequently pale, sweat, blurred vision	rarely special aura
<i>Onset</i>	slow, progressive	sudden, quick
<i>Vegetative</i>	decreased blood pressure (BP) heart and breathing rate	tachycardia, high BP
<i>Body position</i>	standing	any
<i>Motor activity</i>	no movement, or some abortive	tonic and/or clonic, automatisms
<i>Consciousness</i>	quickly resume	gradually
<i>Incontinency</i>	rarely	frequently
<i>Tongue bite</i>	very rare	frequent

Table 2
Differential diagnosis of syncope and epileptic seizures

Therapy

Around 70% of the patients respond well to pharmacological therapy. The aim of the therapy is to make the patient free from seizures. Antiepileptic drugs (AED) are usually not indicated after the first seizure, because it is unsure that the patient really had epilepsy and not a provoked (acute) seizure. Monotherapy is recommended to avoid side effects and to achieve a better compliance. The doses of AEDs should be increased gradually. The extended release formulas are better, because they maintain a more stable serum level.

There are old (e.g. carbamazepine, valproate, phenytoin) and new (e.g. lamotrigine, gabapentine, levetiracetam, zonisamide, topiramate) AEDs. Generally speaking the newer medications are not more effective than the old ones, but they have less side effects. The majority of the AEDs cannot be used in every types of epilepsy, because in some cases they can be ineffective or even harmful. For example the phenytoin and carbamazepine are not effective in several generalized epilepsies, and they can provoke myoclonus and absence. If the diagnosis is uncertain, it is recommended to use drugs that are effective in generalized epilepsies.

In case of bi- or polytherapy interactions may appear. The enzyme-inducers (e.g. carbamazepine) increase the metabolism of those AEDs (phenytoin,

lamotrigine, valproate) and other medications (warfarin, contraceptives, several antipsychotics, etc.) that are eliminated by the liver, therefore they decrease their effects. It is worth to know that lamotrigine and valproate mutually elevate serum levels of each other.

The first choice of drugs according to the international guidelines

Partial epilepsy: first carbamazepine, valproate

Absence: ethosuximide, valproate

Other generalized epilepsy: first valproate, lamotrigine

West's syndrome: vigabatrin

The duration of pharmacotherapy is generally 3 years after reaching the seizure-free state. The therapy should be stopped gradually. In certain epilepsy syndromes lifelong treatment is recommended despite the seizure-free state (e.g. juvenile myoclonic epilepsy).

Side-effects

Every AEDs have dose dependent side effects, including sleepiness, dizziness, and psychomotor slowness.

Individual side effects

Carbamazepine: leukopenia, hepatopathy, hyponatremia.

Valproate: thrombocytopenia, hepatopathy, weight gain, problems of the menstruation, polycystic ovaries.

Phenytoin: leukopenia, hepatopathy, arrhythmia, gingiva hyperplasia, and after years: irreversible cerebellar atrophy, polyneuropathy.

Lamotrigine: adjust its dose gradually, because severe skin symptoms may appear.

Topiramate: weight loss, nephrolithiasis, hepatopathy, leucopenia.

Vigabatrin: visual field abnormalities.

Oxcarbazepine: hyponatremia.

Routine check of the serum levels of the antiepileptics is not recommended. It should be checked if intoxication, the lack of compliance, or drug interactions are suspected and in case of pregnancy.

It is necessary to check the blood cell counts and the liver enzymes after the administration of carbamazepine and valproate. They should be checked after 2 weeks of therapy, later monthly for half a year, and once in a year afterwards. It is recommended to do a general laboratory check up once in a year for every epilepsy patient. If the patient takes vigabatrin, visual field examination should be performed in every 6 months.

Treatment of the epileptic state

The epileptic state is frequently (if convulsive, it is always) a life-threatening event. It requires ICU management.

1. Check the vital parameters, treat the primary cause (if possible), and administer thiamin and glucose to patients suffering from alcoholism.
2. Iv. benzodiazepine (diazepam, clonazepam or lorazepam).
3. If the seizure continues: valproate/phenytoin/levetiracetam should be administered iv.
4. If necessary, general anesthesia is the next step (midazolam/propofol/barbiturate), usually with endotracheal intubation and mechanical ventilation.

It is important to emphasize that first, the dose of the medication should be gradually increased, and later we can change for another drug. It is no use to give little amounts from many drugs.

Surgery

Approximately 70% of the patients react well to the pharmacotherapy. It is obligatory to consider surgery if the patient is resistant to drugs. Surgery is indicated if the epileptic focus can be identified (video-EEG during seizure, MRI) and removed without causing neurological/neuropsychological deficit. The good compliance of the patient and/or his/her relatives is essential. The planned intervention should improve the quality of life.

Pre-surgical evaluation should be performed in specialized epilepsy centers. Video-EEG of at least one typical seizure and MRI are obligatory. Sometimes invasive monitoring (e.g. subdural electrodes) is necessary. Epilepsy surgery is performed most frequently in temporal lobe epilepsy, and 60-90% of the patients become seizure-free.

Prognosis

- Excellent (approximately in 20%): in these syndromes the seizures are rare, the pharmacotherapy is usually avoidable and spontaneous remission develops (e.g. benign neonatal syndromes).
- Good (10-15%): the patients taking medications become seizure-free, later the therapy can be omitted (e.g. childhood absence).
- Therapy-dependent (30-40%): the patients taking medications become seizure-free, and the therapy cannot be omitted (e.g. most of the idiopathic generalized epilepsies, some symptomatic partial epilepsies).
- Bad (20-30%): drug-resistant cases.

Special issues

Driving license

The rules are different in every countries. In Hungary after an accidental seizure 1 year observation is obligatory. If the provoking factors are still present, the patient cannot drive despite of having seizure-free state.

In case of epilepsy individual assessment is recommended. Generally, in idiopathic generalized epilepsies with benign clinical course and good compliance, one year observation is recommended. In focal epilepsies, if the patient has good compliance and takes the AEDs regularly, the observation of two to three years is recommended.

If the patient still has seizures, he/she can get driving license after individual judgment, e.g. if the patient has seizure only when he/she is sleeping.

If the epilepsy is cured (after 3 years seizure-free period with medication, plus 2 years without therapy) the patient can get driving license (except for public transport).

Contraception

Any kind of method can be applied. It should be considered that the enzyme-inducer drugs (carbamazepine) increase the metabolism of the hormonal contraceptives.

Pregnancy

Pregnancy is not contraindicated. Usually the pregnancy does not increase the seizure frequency. The epileptic seizure endangers the mother and the fetus too (especially in case of grand mal). The risk of complications is higher if the epilepsy is not treated, comparing to the risk of the therapy. The serum level of the antiepileptic drugs usually decreases in the second and third semester, but it is usually not necessary to change the dose of medications. Vitamin K supplementation is indicated in case of enzyme-inducer AEDs. Carbamazepine, phenobarbiturate, phenytoin, and valproate increase the incidence of major developmental disorders to 2-3 folds. Polytherapies including valproate are associated with higher risk. There is insufficient experience with the new drugs. To decrease the teratogenic risk, monotherapy is recommended in the lowest effective dose. The serum level peaks should be avoided (extended release formulas, dividing the daily dosage). Folic acid supplementation is very important, as early as 3 months before the planned pregnancy (1-5mg/day). The pregnancy can be managed optimally only if it is planned! The delivery per vias naturales is possible, if there is no other contraindication. Mothers taking AEDs can breastfeed their babies. The phenobarbiturate and primidone may cause somnolence of the baby, if their serum level is high. In this situation alternating breastfeeding and nutrition is recommended. Sleep deprivation can provoke the seizure; therefore, the adequate help for the mother is important.

Special issues for general practitioners

When the epilepsy patient should be sent to a specialist or hospital?

Urgently to a hospital:

- first seizure, or not first but the patient was not examined previously,
- repeating seizures or epileptic state,
- severe injury during a seizure,
- severe psychiatric symptoms,
- new neurological or general symptoms (e.g. fever).

To a specialist:

- the seizure frequency is increased, or a new type of seizures appears (sometimes emergency),
- side-effect of the AED (sometimes emergency),
- the diagnosis is unclear,
- regular control recommended by the specialist.

Treated epilepsy patient with a „usual” seizure should not be sent to hospital if there is no other indication. General laboratory check up as recommended.

Take home message and common misbeliefs

Generally, after the first seizure the epilepsy cannot be diagnosed. Accidental seizure could happen.

There can be some abortive clonus in syncope too.

Negative EEG does not exclude epilepsy. In case of many epilepsy patients the interictal EEG is negative. Epileptic signs can be present in the EEG of healthy persons too.

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Sleep disorders

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About the sleep...

Each of us will spend about 27 years of our lifetime sleeping, and one third of the population complains about sleep disturbances. The non-refreshing sleep is associated with negative daytime consequences, such as fatigue, mood disturbances, irritability, and daytime sleepiness. The chronic and non-restorative sleep increases the risk of accidents at work or while driving.

Based on electroencephalographic activity (EEG), muscle tone and eye movement, the normal human sleep is comprised of two distinct states, which are known as non-rapid (NREM) and rapid eye movement (REM) sleep. NREM sleep takes up the 75-80% of the sleep time. The NREM phase is divided into four stages (stage 1-4) based on the pattern of the brainwaves detected by EEG. Stage 3 and stage 4 are called together as *slow wave sleep*. The REM sleep takes up to 20-25% of the sleep time. It represents an active form of sleep and is characterized by low voltage cerebral activity associated with muscle atonia and rapid eye movement. Most of the dreams occur during this phase of sleep. The NREM-REM *sleep cycle* lasts for 90 minutes, and approximately four to six cycles occur per a *major sleep episode* (per night).

Sleep time and *sleep pattern* change throughout the life. Newborns may spend asleep 16-18 hours of the day, young adults 8 hours, while old people 5-6 hours. The slow wave sleep period declines after adolescence.

Sleep disorders

More, than 80 sleep disorders are known based on the International Classification of Sleep Disorders Version 2.

The eight categories used by the ICSD-2 include:

1. Insomnias
2. Sleep-related breathing disorders
3. Hypersomnias
4. Circadian rhythm sleep disorders
5. Parasomnias
6. Sleep-related movement disorders
7. Isolated symptoms, normal variants
8. Other sleep disorders

We discuss only those sleep disorders, which are important for the physicians in the everyday practice.

Insomnias

Insomnias are the most common sleep disorders, 30 to 50% of the population is affected. The prevalence of insomnia increases with age, and it is more common in women than men.

Definition

- A complaint of difficulty in initiating or maintaining sleep, or waking up too early, or a complaint of sleep that is chronically not restorative or poor in quality.
- The sleep difficulty mentioned above occurs despite of the adequate opportunity and circumstances for sleep.
- At least one of the following daytime complaints is present: fatigue, attention, concentration or memory impairment, mood disturbance or irritability, daytime sleepiness, motivation or initiative reduction, tension headaches or gastrointestinal symptoms, social or vocational dysfunction, poor school performance.

Insomnia is classified on the basis of features such as symptoms, frequency, duration, severity and presumed etiology.

Acute insomnia: transient insomnia, stress-related insomnia. Insomnia is present in association with an identifiable stressor. This sleep disturbance has a relatively short duration, typically a few days to a few weeks (in definition it lasts less than 3 months). The sleep disturbance resolves when the specific stressor resolves, or when the subject adapts to the stressor.

Psychophysiological insomnia: chronic insomnia, primary insomnia. The physiological arousal is associated with emotional reactions, which causes cognitive hypervigilance. Hypervigilance results mental arousal.

Paradox insomnia: pseudo-insomnia, subjective insomnia. The essential feature of paradoxical insomnia is a complaint of severe insomnia that occurs without evidence of objective sleep disturbance and without daytime impairment.

Idiopathic insomnia: childhood-onset insomnia, life-long insomnia. Patients suffering from idiopathic insomnia complain of life-long sleep difficulty beginning in infancy or childhood. The specific features may include difficulty falling asleep, repeated awakening, and short overall sleep duration. This sleep disturbance cannot be explained by another sleep disorder, medical or mental disorder, psychosocial stressors and medications. The insomnia causes functional impairment including daytime fatigue, mood symptoms, and cognitive complaints, such as poor attention and concentration. There is no identifiable triggering factor or cause of insomnia.

Insomnia due to mental disorder: psychiatric insomnia. As discussed in the Diagnostic and Statistical Manual of Mental Disorders, a variety of mental disorders have insomnia as a symptom (it is mainly observed in depression or anxiety disorders). The difficulty of falling asleep is typical in patients with anxiety

disorders, while patients suffering from depression often have frequent awakenings during the night and early morning awakenings with difficulty in returning to sleep.

Inadequate sleep hygiene: bad sleep habits, poor sleep hygiene, excessive napping. This insomnia associated with daily living activities that are inconsistent with the maintenance of good quality sleep, or with failure to maintain a comfortable sleeping environment. Excessive alcohol, nicotine, or caffeine intake, physical or emotional activities close to bedtime, and improper sleep scheduling, which consists of frequent daytime napping are the more common bad sleep habits.

Insomnia due to drugs or substances: the sleep disturbance occurs during periods of use, exposure, or discontinuation of the substance (drugs, prescribed medication, caffeine, cocaine, alcohol or exposure to an environmental toxin). In some individuals the chronic use of sedative-hypnotic medications may lead to tolerance, dependence and loss of efficacy. The discontinuation of these medications may cause rebound insomnia characterized by sudden worsening of the sleep disorder.

Insomnia due to medical conditions: many medical and neurological disorders may give rise to chronic problem of sleep initiation or maintenance, especially those disorders that cause pain, breathing problems (COPD, asthma) or limited motility.

Diagnosis

Complete medical assessment should be obtained, including questioning about medical disorders – especially psychiatric disorders -, medication and substance use, sleep schedule and regularity, sleep-related behaviors, and predisposing and precipitating factors. After the physical examination the patients receive a so-called *sleep diary*. They have to note their daily activities (bedtime, eating, exercise, medication intake) in the sleep log for two weeks. The sleep diary is probably the most helpful diagnostic tool in the assessment of insomnia, as well as in the follow of the treatment response. Polysomnography is not indicated routinely for the evaluation of insomnia, but suggested in those cases, when sleep-related breathing disorders or periodic limb movement disorders are suspected.

Treatment

The duration of treatment differs in insomnia variants: it lasts for three weeks to one month in acute insomnia, while in chronic cases it may last for even a year. Depending on the treatment of the concomitant diseases and the reason of the insomnia, the pharmacological and non-pharmacological treatments are also important in the management of insomnia.

The non-pharmacological treatment includes proper sleep hygiene, psychotherapy (relaxation therapy, behavioral or cognitive therapy), sleep restriction therapy, stimulus control and light therapy. The application of non-pharmacological treatment lasts for long time, and requires patience from both the subjects and physicians, too. That is why the short-term **hypnotic treatment** should be supplemented with behavioral and cognitive therapies. The modern

hypnotics are the GABA-A receptor selective agonists, namely Z-hypnotics, causing low dependence and tolerance. The short-acting zolpidem (5-10 mg/day) is a sleep promoting medication, while the intermediate-acting zopiclone (3.75-7.5 mg/day) is effective for the maintenance of the sleep. The main side effects of these medications are amnesia and morning drowsiness, but both conditions develop rarely. The current guidelines suggest that most of the Z-hypnotics should be used only for short periods (1-3 month). Intermittent use is recommended for 2 weeks after the effective therapy to avoid rebound insomnia, which appears after the abrupt withdrawal of the hypnotics. In case of drug abuse, myasthenia gravis, acute stroke and sleep-related breathing disorders, the use of sleeping pills is contraindicated. These drugs should be used in lower doses in elderly, who may have nycturia. The hypnotic side effects may also increase the risk of falls at night in old people.

Sleep-related breathing disorders

It is the second most common disorder and affects 2-40% of the population. The term of sleep-related breathing disorder is used to describe a spectrum of respiratory disturbances from benign snoring to obesity-hypoventilation (Pickwickian) syndrome causing high cardiovascular risk. Based on the waveform of the polysomnography, three main types of sleep-related breathing disorders are known:

Central sleep apnea syndromes: are possibly caused by the abnormalities of the ventilation control system. The central sleep apnea syndrome is characterized by recurrent episodes of apnea during sleep and in the absence of any upper airway obstruction. Central sleep apneas cause hypoxemia and frequent arousals. The Cheyne-Stokes respiration is a form of central sleep apnea, which occurs in certain medical conditions such as heart failure or acute cerebrovascular diseases.

Obstructive sleep apnea (OSA) syndromes: the muscle tone decreases during the sleep, the pharyngeal muscles collapse, and the obstruction of the upper airway causes apnea, consequently. The temporary absence of breathing results in repetitive hypoxemia and increased arterial pCO₂ level. The stimulation of the respiratory receptors terminates the apnea, and causes arousals and frequent awakenings, which lead to daytime symptoms such as sleepiness and impaired concentration.

Sleep-related hypoventilation syndromes: are typical in patients suffering from emphysema, chronic bronchitis or extreme obesity. The obstruction of the lower airways without apnea leads to nocturnal hypoxemia, and hypercapnia at awakening. The consequences of sleep-related hypoventilation include pulmonary hypertension, cor pulmonale, polycythemia, daytime sleepiness and neurocognitive dysfunction.

The predisposing factors of the sleep-related breathing disorders are age, male gender, smoking, alcohol consumption in the evenings, use of sleeping pills,

obesity – especially central obesity – hypothyroidism, abnormal upper airway anatomy and menopause in women.

Diagnosis

The subjective symptoms and clinical features, what are characteristic for sleep-related breathing disorders, can occur at nights or during the day. The snoring, observed apneas and gasping, frequent awakenings, sweating, palpitations and nycturia are the most common symptoms developed at night. Patients often feel sleepy in the morning; they might have morning headache or gastro-esophageal reflux disease. Because of the non-refreshing sleep, the neurocognitive functions are impaired, and the patients complain excessive daytime sleepiness or mood disturbances. Hypoxemia during the night may result in cardiac arrhythmia. The increased sympathetic activity increases the blood pressure too. The decreased blood pressure, which is normal during sleep, is absent in patients with obstructive sleep apnea, which is called as “non-dipper type”. That is why the patients visit the sleep laboratory after having ECG or ABPM monitoring.

Attended full-night polysomnography is a gold standard for confirming the objective diagnosis. Polysomnography is a multichannel monitoring during the night. Based on the results of EEG, EMG (muscle tone) and electrooculography (eye movement), we determine the sleep stages, while the ECG, movements of the thoracic and abdominal bands, nasal airflow, microphone, and O₂ saturation detect the periods of apneas.

The severity of the sleep-related breathing disorders is defined by the apnea-hypopnea index (AHI), which means the total numbers of apneas and hypopneas divided by the hours of sleep.

normal: <5/h

mild: 5-15/h

moderate: 15-30/h

severe >30/h

Treatment

Non-specific treatment: The consultation with the patient should address obesity, lifestyle issues, tobacco, alcohol and the use of sedatives. Successful dietary weight loss may improve the apnea-hypopnea index in obese obstructive sleep apnea patients. The positional therapy consists of a method that keeps the patient in a non-supine position. It is an effective secondary therapy, or can be supplementary to primary therapies for those patients, who have a low AHI in the non-supine versus the supine positions.

Surgical treatments (uvulo-palato-pharyngoplasty or maxillo-mandibular advancement) can improve the symptoms, in case of the anatomical obstruction of the upper airways. The best candidates for these types of surgeries are patients who are not obese and have abnormal anatomy including enlarged tonsils, adenoids and small pharyngeal inlet.

Oral appliances move the mandible forward to increase the size the upper airways. Oral appliances are indicated for patients with mild to moderate OSA, who do not prefer continuous positive airway pressure (CPAP) treatment, do not respond to it, or cannot receive it, or who fail treatment attempts with CPAP or treatment with behavioral measures such as weight loss or sleep position change AND have not got any severe comorbidity such as non-dipper hypertension, diabetes mellitus or cardiovascular event in his/her case history.

If moderate to severe obstructive sleep apnea exists, **nasal CPAP** should be initiated. CPAP is a non-invasive procedure that maintains the airway patency during sleep. Nowadays, it is the established evidence-based treatment for obstructive sleep apnea. CPAP has been shown to decrease the frequency of apneas and oxygen desaturation during sleep, and to reduce the severity of daytime sleepiness. CPAP prevents certain cardiovascular diseases and may reduce mortality due to cardiovascular causes.

Hypersomnias

In modern societies the most common cause of excessive daytime sleepiness is secondary, it probably develops due to the combination of insufficient sleep, inadequate sleep hygiene, and work schedules. A variety of sleep disorders are associated with excessive daytime sleepiness. The examples include sleep-related breathing disorders, circadian rhythm sleep disorders, medication-induced sleepiness, periodic limb movement disorder, and sleepiness associated with insomnia. One of the primary hypersomnias is narcolepsy. Excessive daytime sleepiness is an important public health issue among individuals working in conditions where the lack of attention can result in injury to self or others such as transportation.

Diagnosis

Subjective measure of sleepiness is the Epworth Sleepiness Scale. It consists of a simple self-administered questionnaire asking the patients to rate the likelihood (from 0 to 3) of dozing or falling asleep in eight situations. Scores from each of the eight situations yield a total score ranging from 0 to 24, greater than 12 suggests pathological sleepiness. Multiple Sleep Latency Test (MSLT) measures *objectively* the sleep latency – what is the time from lights out until the first 30-second of any stage of sleep. The test is performed in sleep laboratory during the day in standard environment using polysomnography, and it consists of four nap opportunities performed with 2-hour intervals. Mean sleep latency less than 5 minutes indicates pathologic sleepiness.

Narcolepsy

It is a primary hypersomnia, where genetic predisposing factors are suspected. Narcolepsy is associated with the HLA subtypes DR2/DQB1 0602. The loss of hypothalamic neurons containing the neuropeptide hypocretin-1 results in low

hypocretin-1 level in the CFS, and the regulation of sleep-wakefulness cycle is impaired. The symptoms usually begin at the age of 15-25 years.

Excessive daytime sleepiness is usually the most disabling symptoms and the first to occur: it is characterized by repeated episodes of naps or lapses into REM sleep across the daytime (involuntary sleep episodes). Patients with narcolepsy typically sleep for a short duration (10-30 minutes), awaken refreshed, but within 2 or 3 hours they begin to feel sleepy again.

Another frequent symptom is *cataplexy*, which is a sudden loss of bilateral muscle tone provoked by strong emotions such as laughing, pride, surprise or anger. Patients fall due to the skeletal muscle atone, but they remain awake. Cataplexy can be localized: the lower or upper limbs, neck or eyelids may be affected regionally.

Sleep paralysis is a rare symptom: it is a transient (usually lasts for 10-20 minutes), generalized inability of moving during the transition between sleep and awakening. These episodes often occur with *hypnagogic hallucinations*. Narcoleptic patients may report *nocturnal sleep disruption*, *automatic behavior* and *psychopathological symptoms too*.

Treatment

Psychostimulants, such as methylphenidate and modafinil, have been used to treat excessive daytime sleepiness. Cataplexy is treated by antidepressants, such as SSRI-s or tricyclic agents. Benzodiazepines or Z-hypnotics are used for maintaining nocturnal sleep.

Circadian rhythm sleep disorders

The 24 (25)-hour circadian rhythm is maintained by the endogenous melatonin produced by pineal gland. Light suppresses the melatonin secretion through the suprachiasmatic nucleus, whereas darkness has the opposite effect. Melatonin levels are low during the day, and begin to rise just before sleep onset. It reaches its peak during the night, and maintains the sleep. Human adaptation to light/dark cycle is ensured by the melatonin.

Delayed sleep phase type: it is more common in adolescent and young adults. There is a delay in the phase of the major sleep period. Patient complains about the inability to fall asleep at a desired time, and difficulty waking up in the morning. The sleep structure and duration remain normal. The 24-hour sleep-wake pattern is not impaired. Patients have to adapt to the socially acceptable morning time, that is why they feel sleepy in the morning.

Advanced sleep phase type: it typically begins during middle age. There is an advance in the phase of the major sleep period; the patient has recurrent complaint of inability to stay awake until the desired conventional clock time.

Irregular sleep/wake type: there is no 24-hour circadian rhythm; the sleep-wake rhythm is chaotic. It is typical in Alzheimer disease, in psychosis, or in metabolic (hepatic) encephalopathy.

Jet lag type: it is characterized by a misalignment of the endogenous sleep-wake cycle with the external environment because of a change in time zone. The symptoms of jet lag are often worse with increasing number of time zones crossed and more severe on eastward- versus westward-bound flights. The complaints are temporary, the subjects adapt to new environment after 2-4 days.

Shift work sleep disorder: there is a complaint of insomnia or excessive sleepiness that is temporally associated with a recurring work schedule that overlaps with the usual time of sleep. Decreased alertness can also lead to cognitive deficiency.

Diagnosis

The diagnosis usually can be made on the basis of detailed clinical presentation. Sleep diary for 2-4 weeks or actigraphy may be useful in documenting the sleep-wake cycle. Actigraphy is an objective measurement of sleep-wake cycle. The actigraph is an accelerometer, which detects wrist movement. The movements are reduced during sleep and increased, when the patient is awake.

Treatment

Light therapy: the therapeutic intensities of light should be between 2500-10000 lux. Nowadays the pale blue (450-470 nm) light with 2500-lux intensity is used. To apply in the evening in advanced sleep phase type and in the morning in delayed sleep phase type is effective.

Melatonin: exogenous melatonin (5-10 mg/day) is effective for the treatment of jet lag and after night shift, to promote daytime sleep.

Parasomnias

Parasomnias are undesirable physical events or experiences that occur during sleep initiation, sleep periods, or arousals. Parasomnias may include abnormal movements, behaviors, emotions and autonomic activities, and may be the manifestations of the central nervous system activation. The ICSD-2 subdivides parasomnias into arousal disorders (arousal from NREM sleep), parasomnias associated with REM sleep and other parasomnias.

Disorders of arousal

Somnambulism (sleepwalking): it originates from slow wave sleep and is common during the first third of the night. It occurs in children aged between 5 to 12 years. Sleepwalking consists of a complex behavior, which is presented during

the slow wave sleep. It results in sitting up, walking and rarely, escaping. On waking up, the patient is confused and amnesic about the events happened during the episode. The patient's environment should be safe to avoid falls and injuries during the sleepwalking episodes. In severe cases benzodiazepines or tricyclic antidepressants may be effective with reducing the time spent in slow wave sleep.

Pavor nocturnus (sleep terrors): is most common in pre-pubertal children. It is characterized by a sudden arousal from slow wave sleep with piercing screams or cry and extreme panic attacks accompanied by severe autonomic symptoms (tachycardia, tachypnea, mydriasis). The patient is amnesic about the episode, and can fall asleep after it.

Parasomnias usually associated with REM sleep

Nightmares: they occur during the last third of the night causing patients to arouse from REM sleep. The sympathetic activation and confusion are not typical. The presence of vivid dreamlike feature is essential in differentiating it from sleep terror. The patient cannot fall asleep after the episode.

Sleep related movement disorders

Restless Legs Syndrome

Restless legs syndrome is the most frequent among the sleep related movement disorders. (RLS, Ekbom's sy, Elvis's legs). Its prevalence is 5-15% in the general population. In addition to the primary form, secondary forms are also known: RLS is common in pregnancy, uremia, microcytic anemia, polyneuropathy, and in the early stages of Parkinson syndrome, or it can appear as the side effect of certain medications (SSRI-s, tricyclic antidepressants, antiemetics).

Diagnosis

Four essential criteria are required for the diagnosis of RLS:

1. The unpleasant leg sensations that usually occur before sleep onset, begin or worsen during periods of rest or inactivity such as lying or sitting;
2. Irresistible urge to move the limbs;
3. Partial or complete relief from discomfort on leg movement, such as walking or stretching and return of the symptoms on cessation of leg movement;
4. The urge to move otherwise the unpleasant sensations are getting worse, or they only occur in the evening or at night.

RLS symptoms have been described as arising at rest, and the symptoms are present only just before the patient falls asleep. That is why the patient will complain the difficulty in initiating sleep. RLS is characterized by a circadian tendency for symptoms to be maximal in the evening and increasing in intensity toward the early sleep period. Primary form is explained by dopaminergic

hypofunction, thus dopaminergic therapy is also effective. Another hypothesis concerns iron storage deficiency in the brain: for example, iron deficiency anemia can result in reversible RLS.

After detailed history is taken, the secondary forms should be excluded or proven with laboratory examinations: red and white blood cells counts, serum iron level, renal and thyroid function and blood sugar level. ENG can confirm polyneuropathy or radicular lesion. Actigraphy and polysomnography are useful to confirm the RLS diagnosis in sleep laboratories.

Treatment

Elimination of the predisposing and precipitating factors is important: the patient should avoid taking medications that may provoke RLS, such as SSRI-s, tricyclic agents, neuroleptic and antiemetic drugs. Caffeine, alcohol and nicotine cessation are necessary.

Sleep hygiene: hot and cold shower before bedtime, brief walk or massage of limbs may be useful.

Pharmacologic therapy:

- Iron substitution
- Dopamine agonists (pramipexole 0.125-1.5 mg/day, ropirinole 0.25-6 mg/day)
- Anticonvulsants (gabapentin 300-2700 mg/day)
- Opioids (tramadol 100-400 mg/day, oxycodone 5-20 mg/day)
- Benzodiazepines (clonazepam 0.5-4 mg/day)

Messages

Sleep disturbances are common complains. The detailed case history, including information on medical and psychiatric disorders, medication use, behavior and the sleep-related environment, is necessary for the diagnosis. The sleep diary containing information at least on 2 weeks can be useful.

Obstructive sleep apnea syndrome is a cardiovascular risk factor. Polysomnography is necessary to confirm diagnosis. Its evidence-based treatment is the CPAP.

Restless legs syndrome is often secondary. Detailed laboratory examinations are necessary.

The sleep disorders are treatable.

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The inflammation of the central nervous system

TÜNDE CSÉPÁNY MD.

Terminology

According to their extent, inflammations of the meninges, brain and spinal cord are called as **meningitis**, **encephalitis** and **myelitis**, respectively. Meningo-encephalomyelitis is the general term for the inflammation affecting these structures together. Solid inflammations include **abscesses**, sinus **thrombophlebitis**, and epidural or subdural **empyema** localized outside the brain. Infective agents, autoimmune or malignant diseases can cause the inflammation, which can be acute or chronic. The clinical picture depends on the type and amount of the infective agent, the resistance of the host, the presence of concomitant diseases, and the treatment, of course.

The classification of meningitis

Meningitis can be classified many ways depending on their origin and the type of the infective agent. Although the types may overlap, according to their origin the following types can be differentiated:

1. Acute meningitis
 - a. purulent (septic or bacterial) meningitis
 - b. non-purulent (aseptic or lymphocytic) meningitis
2. Chronic meningitis

Acute meningitis

The significance of **septic, purulent meningitis** is important, as treatment delay may cause the patient's death. The incidence of purulent meningitis is 3-4/100000 yearly. Since Hemophilus influenzae vaccines are available, the number of meningitis caused by Hemophilus influenzae has decreased significantly, but the incidence of meningitis caused by penicillin and cephalosporin resistant Streptococcus pneumoniae is rising. The risk factors of meningitis are the patient's age (childhood or old age), immunodeficiencies with different origin, diabetes, malnutrition, chronic renal diseases, alcoholism, malignancies and neurosurgeries. Usually, the infective agents spread via the bloodstream from a purulent lesion of the body into the subarachnoid space. The secondary inflammatory reactions (inflammatory factors, interleukins, tumor necrosis factor α , thrombocyte activating factor) play an important role in the development of clinical symptoms. The blood-brain barrier is damaged. The inflammation inhibits the absorption and circulation of the cerebrospinal fluid, and infiltrates the cerebral vessels. It causes obstructive hydrocephalus, edema and increased intracranial pressure. If not being treated, the

inflammation spreads to the brain via the cortical vessels. Neurological symptoms may develop due to the presence of vasculitis, disturbed autoregulation and cortical hypoxia; therefore, the term meningo-encephalitis is more accurate in this phase.

The diagnosis of acute meningitis

Symptoms

Fever, headache and stiff neck (nuchal rigidity, meningismus) are the classical symptoms of meningitis, but they may develop in other inflammations too, such as bronchopneumonia. The presence of nausea, vomitus, light sensitivity, fatigue, general weakness and back or muscle pain refers for meningeal irritation.

During the early phase (the so called direct “meningitis”) the patient is aware, or drowsy. If the meningitis is not treated, confusion, delirium-like condition, stupor and coma may develop due to the diffuse cerebral damage caused by the spread of the infection to the cortical area and white matter. If this occurs, we cannot obtain anamnestic data from the patient furthermore. Fever in the early phase is an important diagnostic sign. In 40% of the cases focal or generalized epileptic seizures may develop, in 20% of the cases cranial nerve or focal neurological symptoms are present.

In severe cases seizures or epileptic state may develop due to the presence of fever, hyponatremia, anoxia, decreased cerebral blood flow, and toxins secreted by infective agents. The characteristic symptoms of meningitis usually develop in a few days or a week, but in case of rapid course they may appear and become serious within 24 hours and even cause death.

Physical examination

Neck stiffness is the most common and reliable meningeal sign. The examiner feels resistance when tries to flex forward the patient’s head passively in the supine position, and the flexion is unsuccessful. Kernig’s sign is elicited with the patient in the supine position. The thigh is flexed on the abdomen, with the knee flexed. Attempts to passively extend the leg elicit pain at the lumbar region of the spinal column, when meningeal irritation is present. If we try to have the patient sit upright, he/she flexes the hip and knees. The spinal column tightens in concave position; the head is dorsalflected and the patient supports himself/herself with his/her arms stretched. Intense pain develops along the spinal column. The position may refer to meningeal irritation, too. We may observe during the inspection that the patient is lying on his/her side with flexed lower extremities in the hip and knees. Petechiae on the chest, lower extremities, palms or feet refer to meningococcal infection.

Additional examinations

If meningitis is suspected, urgent lumbar puncture is needed (if focal neurological signs and papillary edema are present, always perform cranial CT or MRI before the puncture). In bacterial meningitis the color of the cerebrospinal fluid is yellowish, and turbid (like cabbage juice). The granulocyte count is increased (thousands or ten thousands/ μ l), the protein level is elevated, and the

glucose level is decreased. In this case urgent antibiotic treatment is necessary (third-generation cephalosporin and vancomycin). Besides the routine examinations, quick tests, Gram staining and culturing are required to identify the infective agent. Depending on the result of culturing, it may be necessary to modify the therapy.

The source of infection should be screened (sinus X-ray, chest X-ray, cranial X-ray, otolaryngological, cardiologic examinations, skin).

Prognosis

In case of acute bacterial meningitis delay in the diagnosis and antibiotic treatment may cause the patient's death or severe impairment. If meningitis is suspected, the patient should be transferred to hospital immediately.

The fever is absent in 10% of severe purulent meningitis cases. If the patient is homeless, always think for the presence of meningitis. Chronic inflammations of the middle ear may be the source of intracerebral abscess and otogenic meningitis. Otogenic meningitis may be hyperacute, if it is not diagnosed and treated within 24 hours, the patient may die or have extremely severe impairment.

The differential diagnosis of acute meningitis

Bacterial meningitis should be differentiated from viral meningoencephalitis including herpes encephalitis, brain abscess and subarachnoid hemorrhage.

Herpes simplex encephalitis

The incidence of encephalitis caused by herpes simplex virus (HSV) is 0.5/100000 yearly. Without treatment the mortality rate is more than 70%, so the proper diagnosis if this rare disease is important. The main symptoms of herpes encephalitis are unilateral headache and continuously high fever, which are associated with one or more of the following signs: changes in the behavior (irritability, personality changes), focal or generalized epileptic seizures, focal neurological signs (speech disorders, rarely hemiparesis, which is more severe on the face and upper extremities, and visual field abnormalities of the upper quadrant). If the patient is unable to give information on his/her medical history due to dysphasia, he/she could be admitted to psychiatric ward. The symptoms of herpes encephalitis develop in days; therefore the patients visit their general practitioners after at least a week. In advanced cases hypnoid unconsciousness may develop. If the symptoms of encephalitis are suspected, the patient should be transferred to neurological ward immediately. Immediate acyclovir treatment significantly reduces the mortality. The irreversible damage of the temporal regions can cause permanent impairment, even if the patient survives the disease.

In herpetic encephalitis cranial MRI can reveal the lesions of the limbic area of the temporal lobe and insula. Lumbar puncture is essential for the diagnosis. The cerebrospinal fluid is characterized by lymphocytic pleiocytosis referring to moderate inflammation and increased protein levels. The presence of the herpes simplex virus should be verified by using polymerase chain reaction (PCR)

technique. Acyclovir treatment should be continued, until the herpes simplex virus infection is refuted.

The PCR usually shows positive result in the early phase of the infection, but decreases after a week, and it can be false positive too, if the cerebrospinal fluid contains blood by traumatic puncture. Simultaneously to the examinations of cerebrospinal fluid, serum samples should be tested for HSV IgG. The presence of antibodies verifying the diagnosis can be detected 8-12 days after the onset of symptoms, and lasts for 30 days.

Viral meningitis

Viral meningitis is in the differential diagnosis only if the clinical presentation is limited to fever, headache, and stiff neck. Patients with viral meningitis do not have focal neurological deficits, new-onset seizure activity, or an altered level of consciousness. In the early phase polymorphonuclear cells dominate in the cerebrospinal fluid, but later lymphocytosis and normal glucose level are detected. The identification of infective agent, which is based on the detection of antiviral antibodies, usually takes a long time and is expensive in the everyday practice. The incidence of viral meningitis is 11-27/100000/year. The disease is usually benign, and most of the patients become asymptomatic after receiving the treatment.

Focal intracranial infections

Purulent meningitis should be differentiated from focal intracranial infections including abscess, subdural empyema and epidural abscess. *Cerebral abscesses* usually are detected due to their intracranial mass effect. It is characterized by headache, which is permanent and tension or sharp, it can be unilateral or diffuse and usually increases. 50% of patients have mild fever when the disease is diagnosed. In 25-30% of the cases epileptic seizures of recent origin develop. Focal neurological signs are present from the onset in 60%. Focal intracranial infections are more frequent under the age of 30, when purulent sinusitis and middle ear infections are common. Untreated bacterial endocarditis and pulmonary abscess also increase the risk. Cranial CT can reveal focal or multifocal space-occupying lesions, which are surrounded by contrast media (ring-enhancing lesions). Brain biopsy may be indicated, but neurosurgery may disseminate the infection.

Subdural empyema is characterized by fever and progressive headache. As the empyema increases, focal neurological signs, seizures and the symptoms of increase intracranial pressure may appear. Headache is the most characteristic symptom, and it starts on the side of empyema and later becomes diffuse and more intense. If not treated, subdural empyema may cause increased intracranial pressure, consciousness disturbances, stupor and coma.

Intracranial epidural abscess is characterized by intense unilateral headache and fever. Imaging techniques help the differential diagnosis of focal infections. The surgical and antibiotic treatment can save the patient's life.

Septic thrombosis of cerebral venous sinuses

The dural sinus thrombosis and the septic venous thrombosis of the cortical veins are usually the complications of bacterial meningitis, subdural empyema or

epidural abscess, and the infections of the face, sinuses, middle ear and mastoid process. Venous sinus thrombosis can imitate everything on CT scans, including hemorrhage. The symptoms are usually mild. It often develops during the puerperium. If epileptic seizure develops, which cannot be explained by other causes, always think for the presence of sinus thrombosis. Perform MRI or cerebral angiography, which can visualize the venous circulation.

Subarachnoid hemorrhage

Subarachnoid hemorrhage is characterized by sudden and intense headache. The headache may develop after the patient experienced temporary loss of consciousness. Nuchal rigidity and vomitus are common symptoms; therefore subarachnoid hemorrhage should be differentiated from bacterial meningitis.

Chronic inflammations of the nervous system

Chronic inflammations of the nervous system including chronic meningitis are rarely developed in people with normal immune system. It usually develops in patients suffering from AIDS due to HIV infection or other immunodeficiency or immunosuppressed conditions. Their significance is increasing in these conditions.

Aseptic meningitis

Chronic meningitis is characterized by headache lasting for weeks and months, intermittent and moderate fever, slowly progressive confusion, mild meningeal signs and progressive paresis of the cranial nerves. The lumbar puncture is essential for the diagnosis. Increased mononuclear cell count and protein levels can be detected by routine examinations. Chronic meningitis may have several causes, including bacterial (syphilis, neuroborreliosis, tuberculosis, mycoplasma, brucellosis), fungal (Candida species, Cryptococcus neoformans, Nocardia, Aspergillus species), viral (enterovirus, Herpes simplex virus 2 and 6, Varicella Zoster virus, Epstein-Barr virus, CMV), and protozoon infections (Toxoplasma gondii), non-infective conditions (autoimmune CNS vasculitis, SLE, Wegener's granulomatosis, Bechet's syndrome) and malignancies (leukemia, neurosarcomatosis, bronchus and breast neoplasms). It should be differentiated from the complications of their treatment too, which may cause similar symptoms due to meningeal irritation.

Tick transmitted infections

Lyme neuroborreliosis (LNB)

It develops in patients with normal immune system, thus we detail it.

Clinical symptoms

Borrelia burgdorferi, a spirochete transmitted by ticks, can cause chronic infections of multiple organs. There is no difference between genders, but it mainly affects children between the age of 5-9 and adults over 30 years. Its incidence is 9/100000/year in Europe. The manifestations of skin, nervous system, heart and joints may follow each other, but they may pass without treatment too. Not every patient has organic symptoms. The antibiotic treatment of the skin symptom developed after the tick bite (early localized inflammation: erythema chronicum migrans) can cure the infection and prevent the secondary manifestations. If the infection is not treated, the neurological symptoms appear within 1-12 weeks (usually 4-6 weeks) after the tick bite in approximately 10-15% of the cases. Only 50% of the patients remember for the tick bite, and 20-30% remember for the local skin symptom. The 95% of the symptoms referring to the damage of the nervous system is classified as early LNB signs, and last for not more than half a year. In 5% of the cases the symptoms last for more than 6 months or even years, and called as late LNB signs (late persisting inflammation).

Early disseminated inflammation

The painful meningoradiculitis (also called as Bannwarth's syndrome) is the most common form of the early neuroborreliosis. In 86% of the patients it is characterized by intense radicular pain, and peripheral limb paresis (61%). The intensity and localization of pain change from day to day, and increase at night. The damage of motor cranial nerves may also occur including facial, abducent and oculomotor nerves. Peripheral facial paresis developed due to radiculitis may be followed by the damage of the opposite side. If facial diplegia develops quickly, always think for *Borrelia* infection. Patients experience headache in 43%, and the intense headache is often accompanied by radicular pain and paresis. Symptoms referring to the damage of the central nervous system are rare, but myelitis or encephalitis may occur. The presence of fever and meningeal signs is not characteristic in neuroborreliosis. Acute peripheral facial paresis and lymphocytic meningitis associated with fatigue and loss of appetite often develop in children with Lyme neuroborreliosis (in 55%).

Late persisting inflammation

Late LNB is often called as chronic neuroborreliosis. It is characterized by mononeuropathy, radiculopathy and polyneuropathy, and often associated with late skin symptoms (acrodermatitis chronica atrophicans). The peripheral symptoms are accompanied with tetraspasticity and spastico-ataxic walking referring for Lyme encephalitis and encephalomyelitis.

The diagnosis of LNB

The examination of the cerebrospinal fluid

The detection of inflammatory signs in the central nervous system, the intrathecal antibody production, and the verification of the presence of anti-*Borrelia* antibodies in both serum and CSF samples taken in the same time are necessary to establish the diagnosis of neuroborreliosis.

The verification of central nervous system inflammations

In Lyme neuroborreliosis the cell count is increased (10-1000 leukocyte/ μ l), lymphocytes and plasma cells dominate, the protein levels are increased, and oligoclonal bands are present. In polyneuropathy accompanied by acrodermatitis chronica atrophicans the cerebrospinal fluid is often normal.

The detection of Borrelia burgdorferi (BB-) antibody in the serum and cerebrospinal fluid

The examination should be performed in two steps. The positive result of ELISA should be verified with immunoblot technique (Western blot). IgM antibodies can be detected in the early phase, while IgG antibodies are present when the complications have developed. In some cases of LNB antibodies were detected in the cerebrospinal fluid only. Antibodies detected only in the serum have low diagnostic value, because 14-20% of the normal population is seropositive. Anti-borrelia IgG and IgM antibodies may persist for years even after the successful treatment.

Contrary to the common opinion the verification of spirochetes from cerebrospinal fluid is not recommended with dark field microscopy.

Definite neuroborreliosis* <i>All criteria are fulfilled</i>	Possible neuroborreliosis <i>Two criteria are fulfilled</i>
1. Neurological symptoms referring for LNB without any other explanation	
2. Pleiocytosis in the cerebrospinal fluid	
3. Intrathecal production of Borrelia burgdorferi antibodies	

*Referring to all groups except from late LNP with polyneuropathy, because in this case the presence of acrodermatitis chronica atrophicans and BB antibodies in the cerebrospinal fluid is also required for the diagnosis.

The treatment of LNB

Two-week antibiotic treatment is recommended occasionally for adults having definite or possible **early** neuroborreliosis with the symptoms of Bannwarth's syndrome (symptoms localized to the meninges, nerve roots and peripheral nerves). Oral doxycycline (200 mg daily) or intravenous ceftriaxone (2 g daily) is equally effective. Doxycycline is contraindicated during pregnancy and breastfeeding. If central symptoms are present (myelitis, encephalitis), ceftriaxone should be administered intravenously for 14 days.

Three-week antibiotic treatment is recommended for adults having definite or possible **late** neuroborreliosis with symptoms localized to the peripheral nerves (or skin). Oral doxycycline (200 mg daily) or intravenous ceftriaxone (2 g daily) is

recommended. If central symptoms are present, ceftriaxone should be administered intravenously for 21 days.

The prognosis of LNB

The symptoms of LNB respond well to antibiotic treatment. Post-Lyme disease syndrome may develop in patients, who were treated appropriately. The syndrome is characterized by subjective symptoms including fatigue, paresthesia, sleep disorders, cognitive dysfunction, headache, and joint or muscle pain, which last for more than 6 months after the patient received standard treatment. Researches proved that in this stage further antibiotic treatment was not recommended, as it did not decrease the complaints.

Tick-borne encephalitis

Tick-borne encephalitis may also develop after a tick bite, but the inflammation may be localized to the meninges too. The infective agent, an RNS virus, comes from rodents. The infection can be prevented with vaccination. The course of infection is characterized by fever developed in two phases. The first period of fever lasts for 7-14 days, and characterized by influenza-like symptoms (fever, headache, bad mood, muscle pain). The second period of fever is developed after an asymptomatic interval lasting for a week. During this period symptoms referring for meningoencephalitis may be present. The paresis of the abducent nerve may be the only symptom.

Syphilis related neurological disorders

The incidence of syphilis has increased among drug-addicts, and the disease is more common in heterosexuals. If the *Treponema pallidum* gets into the mesenchymal system directly from the blood flow, focal vascular syphilis or luetic vasculitis develops. If the spirochete infects the nervous system through the choroid plexus, diffuse luetic meningitis develops. The two conditions are often associated with each other. It may happen, that the development of symptoms takes years after the infection. In early stages, syphilis has poor clinical symptoms. The signs of meningeal irritation are not characteristic for syphilis, but headache localized to the top of the head and oculomotor nerve palsy (the pupils do not react for light) may develop at night. Epileptiform signs, focal neurological symptoms, hydrocephalus or subarachnoid hemorrhage may be present. In the cerebrospinal fluid low glucose level and oligoclonal gammopathy can be detected, but the pleiocytosis and increased protein levels are not significant. The specificity of the **Fluorescent Treponemal Antibody-Absorption test (FTA-ABS)** reaches 100%.

Metasyphilis developed decades after the *Treponema* infection has two different types. In case of progressive paralysis the non-specific chronic inflammation of the cerebrum damages the frontal lobes, and causes dementia and psychosis. In case of tabes dorsalis or spinal ataxia, the degenerating nerves are in the dorsal columns of the spinal cord. This condition can be differentiated from the

toxic polyneuropathy developed in chronic alcoholism by the absence of pupillary reactions. Syphilis is still treated with penicillin.

Septic meningitis developed in immunosuppressed conditions

It is characterized by the symptoms described previously: headache, mild or severe fever, progressive consciousness disturbance (confusion), mild or absent meningeal signs (nausea) and progressive cranial nerve palsies. The diagnosis is based on the result of lumbar puncture. The increased mononuclear cell count and high protein levels are common findings. Among the imaging techniques cranial MRI may help the diagnosis. Contrast enhancement on the area of the basal meninges refers to inflammation.

Tuberculosis of the nervous system

In tuberculous meningitis exudate is found mainly in the basal cisterns, but through the sulci it can spread to the surface of the brain and cerebellum too. Due to the adhesion of meninges disorders of the liquor circulation and consequent internal hydrocephalus may develop. The disease was called as basilar meningitis referring for the localization of the inflammation. The infection derives from an active focal lesion located in the body and spreads hematogenously.

The clinical symptoms are characterized by anorexia, sweating at night, headache, nuchal rigidity, depression and fever lasting for 4-8 weeks. In $\frac{1}{4}$ of the cases symptoms referring to cranial nerve damages are present. In the cerebrospinal fluid the protein level is increased (1-5 g/l), pleiocytosis is present (10-500 cell/ μ l). The glucose level is usually lower than the normal range. Due to the large amount of protein the cerebrospinal fluid may coagulate (Froin's syndrome). The Ziehl-Nielsen staining of the CSF remnant and the direct identification of the infective agent provide the diagnosis of tuberculous meningitis. The last fraction of lumbar puncture should be examined, and the result is positive in 10-40%. As for the culturing takes long weeks, in case of suspected tuberculous meningitis the treatment should be started immediately, even if the result of culturing is not available.

Cryptococcal meningitis

Cryptococcus neoformans is a common fungal species found in the soil, but it often appears for example in the nest of pigeons. It is believed to be acquired by inhalation. *Cryptococcus* rarely causes disease in healthy people. Similarly to the tuberculous infections cryptococcosis has a slow onset too. The patient may experience the early symptoms of headache, nausea and vomitus. The granulomatous inflammation of the basal meninges develops, which causes increased intracranial pressure. Later focal neurological signs, cerebellar ataxia, spastic paresis and severe dementia may develop. The cerebrospinal fluid is characterized by mild pleiocytosis, increased protein and decreased glucose levels. The direct identification of the *Cryptococcus neoformans* (India ink staining) and the detection of fungal antigens are necessary for the diagnosis. The disease is

lethal without treatment, but despite of the combined antifungal therapy 40% of the patients suffering from cryptococcosis die.

Non-infective aseptic meningitis

Sarcoidosis

Sarcoidosis is a multisystemic granulomatous disease, in which bilateral hilar lymphadenopathy is present in 90% besides the skin and eye symptoms. The diagnosis of sarcoidosis is based on the biopsy of the affected lymph node. It is accompanied by neurological symptoms is 17%. Peripheral facial paresis (diplegia facialis) is a common finding, and it can be associated with headache and meningism. The presence of lymphocytic pleiocytosis in the cerebrospinal fluid is a recurrent problem, but the decreased glucose levels, increased IgG synthesis and the presence of oligoclonal band also verify the diagnosis. The increased level of angiotensin converting enzyme detected in the blood and cerebrospinal fluid is caused by neurosarcoidosis in 50-70% of the cases. Positive chest X-ray, and biopsies of the lymph nodes or skin lesions, or transbronchial lung biopsy are necessary to confirm the diagnosis. Sarcoidosis can be treated with steroids.

Leptomeningeal carcinomatosis

The carcinomatous meningitis develops due to the dissemination of malignant cells originated from the adenocarcinoma of the breast or bronchus, malignant melanoma, or hematological disorders (acute lymphoid or myeloid leukemia, non-Hodgkin-lymphoma). The presence of malignant cells among inflammatory cells in cerebrospinal fluid samples confirms the diagnosis.

Wegener's granulomatosis

The necrotizing granulomatous vasculitis of the respiratory system can be associated with the granulomatous inflammation of the nervous system. Its typical symptoms are cough, chest pain, hemoptoe, nose bleeding and sinusitis, which possibly damages cranial nerves II, VI, VII and VIII resulting in hearing loss, ptosis, ophthalmoplegia and facial palsy. In 90% of the cases the immunoserology (c-ANCA) supports the diagnosis.

Reactive aseptic meningitis developed due to treatment

It can be caused by many medicines, such as non-steroid anti-inflammatory drugs, antibiotics (trimethoprim-sulfamethoxazole), IVIG, CellCept and isoniazid. Beside the presence of fever and meningeal symptoms, arthralgia, myalgia, rashes, and abnormal liver function can be detected. It often occurs in SLE. The exclusion of bacterial, viral and fungal infection and the differentiation from lupus activity require a lot of examination.

Encephalitis

Encephalitis may spread from the soft meninges to the parenchyma (usually purulent), thus causative agents listed previously may cause them, but it can develop independently. It is recognized by the presence of focal neurological symptoms developed due to the localization and extent of the inflammation. It is characterized by general symptoms (malaise, fever, fatigue, headache) and epileptic seizures. The inflammation damages the cortical area (white matter) primarily, which causes the initiating focal symptoms. In case of diffuse encephalitis the presence of somnolence, stupor or coma is necessary. Encephalitis usually develops subacutely. According to their localization we can differentiate polioencephalitis localized to the gray matter, panencephalitis affecting both the gray and white matters, and leukoencephalitis affecting only the white matter. Imaging techniques and the examination of the cerebrospinal fluid are necessary for the diagnosis.

The classical type of **poliomyelitis** has not developed since the vaccination is introduced in Hungary, but practicing physicians can meet remnant symptoms of former diseases. The paresis of the lower extremities is more significant than the paresis of the upper ones, and the asymmetrical palsy of muscles extending the knees and elevating the legs is more expressed. The function of gluteal muscles is often affected too. The paresis is peripheral and characterized by the following symptoms: atrophy, the absence of reflexes, and atonia. No treatment is needed. Rabies (Lyssa virus) and new arbovirus ("West Nile virus") infection may cause similar diseases with peripheral palsies. The latter is transmitted from birds to humans by mosquitos, and its risk is increased in people over 80 years. Symptoms include flaccid weakness due to involvement of anterior horn cells.

Herpes simplex, measles virus and JC virus infection are the most common causes of **panencephalitis**. The mechanism of encephalitis caused by HSV infection is still unknown, though the virus can be detected in almost everyone. Despite of its rare development doctors should be familiar with herpes encephalitis. The occurrence of subacute progressing panencephalitis has been ceased practically, since the vaccination is introduced. This is caused by persistent defective measles virus infection. Clinical presentations are variable including behavioral-cognitive change, myoclonic seizure, visual problem, spasticity or abnormal movement. Progressive multifocal leukoencephalopathy (PML) caused by the polyomavirus JC virus, which latent form is usually activated in patients suffering from immunosuppressed conditions deserves the attention, because the biological therapies introduced in the latest years has just revealed its risk in immunocompetent patients too. The focal white matter lesions in an immunocompromised patient should always raise the possibility of PML. The onset is insidious with progressive cognitive impairment combined with symptoms of white matter involvement such as visual deficits, language deficits, weakness and ataxia. Differentiation between Human Immunodeficiency Virus Encephalopathy (HIVE) and PML is important.

In **leukoencephalitis** the myelin fibers forming the white matter are damaged. Encephalomyelitis can be parainfectious, postvaccinal and autoimmune (multiple

sclerosis, acute disseminated encephalomyelitis). Parainfectious and postvaccinal encephalomyelitis usually develop within 8-10 days after the infection and vaccination, respectively, and cause the palsy of the ocular muscles, pyramidal signs, and consciousness disturbances. They can develop due to rubella, measles, smallpox and chickenpox. Varicella zoster virus causing chickenpox in children persists in the sensory ganglia, and its reactivation results in the symptoms of herpes zoster. In adults itching and vesicles develop in the dermatome belonging to the affected ganglia. After an illusory recover pain may develop in the affected dermatome. According to its localization herpes zoster can be zoster ophthalmicus (it can be accompanied by the palsy of the extraocular muscles), zoster oticus and zoster generalisata. It occurs more often in elderly patients, immunosuppressed conditions and malignant diseases. It may affect more dermatomes. Encephalitis is a rare complication, and in 0.1% the cerebellar symptoms dominate (cerebellar ataxia, seizures, hemiplegia). In case of complication the rashes developed in the ear are accompanied by peripheral facial paresis on the same side, the eruptions may appear on the palate and the first two-third of the tongue (Ramsay-Hunt's syndrome), and in case of progression brainstem symptoms might be present. If the rashes appear in the back dermatomes, the development of paraparesis indicates that the inflammation has spread to the posterior radix and the spinal cord. The examination of cerebrospinal fluid may verify the diagnosis. No special treatment is needed, but in most of the patients acyclovir therapy may cease the symptoms.

The differential diagnosis of encephalitis

Viral encephalitis should be differentiated from metabolic encephalopathy and acute disseminated encephalomyelitis. After the prodromal symptoms are revealed the diagnosis of Jacob-Creutzfeldt disease starting with personality changes, extrapyramidal symptoms initiated by progressive dementia, myoclonus, ataxia and dysarthria, is not problematic.

We should consider the followings while taking the **medical history**: recent travels to abroad, known hepatic or renal diseases, transplantation, diabetic complications, toxic effects of alcohol. Vaccination and rashes, gastrointestinal infection, or the infection of the upper airways developed within a month should be investigated. Work, living conditions or contact to animals should be investigated too. In case of severe consciousness disturbances there is no way to take anamnestic data from the patient, but family doctors may have important clues about the prodromal period.

The **physical examination** may reveal systemic impairment (affecting the respiratory and gastrointestinal tracts) and rashes.

Neurological examination: focal neurological signs, fronto-temporal lesion, aphasia, focal seizures besides herpetic encephalitis, combination with symptoms referring to the damage of the peripheral nervous system and myelitis indicate herpetic encephalitis.

Laboratory examinations: Among the routine hematology and biochemistry examinations, leukocytosis is a common finding in ADEM, while relative lymphocytosis is present in viral encephalitis. Increased erythrocyte sedimentation

rate suggests tuberculosis and malignancies. Toxicology and urine examination may provide relevant results. It is necessary to perform X-ray, as positive results may refer to tuberculosis, malignancies, mycoplasma and legionella infections. The serology does not help the acute diagnosis as the analysis usually takes weeks.

Imaging techniques: cranial CT or MRI often is the primary examination excluding intracranial tumors and abscesses. In viral encephalitis MRI can reveal temporal infiltration even in the early phase of herpes encephalitis, but it can be normal too. SPECT may provide additional data, for example temporal hypoperfusion may indicate HSE. The EEG is useful in the differential diagnosis of viral encephalitis and metabolic encephalopathies. If viral encephalitis is suspected, the examination of the cerebrospinal fluid is necessary after intracranial space-occupying processes and severe cerebral edemas have been excluded. In case of HSE the increased cell count (10-200/ μ l) and protein levels (0.6-6 g/l) are typical findings. The chance of detection HSV-RNS with PCR is 95% in the first week; the results can be false positive in the first 24-48 hours and after 10-14 days.

The treatment of encephalitis

There is no specific treatment of encephalitis, except if caused by herpes viruses (i.v. acyclovir). As the mortality rate of herpetic encephalitis is extremely high without treatment, every case should be treated with intravenous acyclovir, if different origin is not proven. Beside this, patients with encephalitis should receive high dose intravenous steroids due to vasogenic edema.

Myelitis

The isolated inflammation of the spinal cord may be present in infectious diseases, allergic reactions and autoimmune demyelinating disorders. It can be the rare complication of viral diseases.

Acute transverse myelitis

It is a rare disease with the incidence of 13/10000000. It mainly affects people between 10-20 and above 40 years. Fever, myalgia, back pain and band-like pain initiate the symptoms of the complete or partial transverse lesion. Sometimes, the symptoms appear within a few minutes, sometimes it takes a week. They improve within a week, but after three months recovery is unlikely. In one third of the cases the neurological symptoms are preceded by an infection, e.g. infection of the upper respiratory tract. The examination of the cerebrospinal fluid performed after spine MRI verifies the presence of inflammation. The origin of some cases remains unclear. Acute transverse myelitis should be differentiated from multiple sclerosis, optic neuromyelitis, Guillain-Barre's syndrome, complications of systemic autoimmune diseases, spinal ischemia, epidural abscesses and other spinal compressions. The treatment is mainly supportive, but high dose corticosteroids are useful.

Spinal epidural abscess

The spinal epidural abscess is a very rare disorder. Among 10000 admittances to hospital there is only one case with spinal epidural abscess. It is characterized by fever, intense back pain in the affected segment, impaired spinal movements, weakness of the extremities, sensory dysfunction and incontinence. Delay in treatment may cause permanent impairment, thus it should be recognized immediately. The CRP level is often increased. Spinal MRI performed in the level of the lesion is mandatory, according to its result immediate surgical decompression and long-term antibiotic treatment are needed. The most common causative agent is *Staphylococcus aureus*. The risk factors of spinal epidural abscess are diabetes, severe renal disorders, malignancies, long-term corticosteroid treatment, alcoholism, permanent urinary catheter, local spinal trauma and surgery. The prognosis depends on the patient's age, the extent of spinal compression, the level of epidural abscess, the time since the onset, and the septic symptoms presented at the diagnosis. There is hope for recovery if the surgery is performed within 72 hours after the symptoms have developed.

Acquired Immune Deficiency Syndrome (AIDS)

In Acquired Immune Deficiency Syndrome the virus (HIV) itself can damage different parts of the nervous system, so the symptoms depend on the presence of aseptic meningitis, leukoencephalitis (HIVE: subcortical progressive dementia followed later by pyramidal and cerebellar dysfunction), spinal myelopathy, peripheral polyneuropathy and myositis. The neurological signs are accompanied by various infective symptoms, because those agents, who - due to their low virulence - can rarely infect people with normal immune system (e.g. *Toxoplasma*, *Cryptococcus*, Tuberculosis, neurosyphilis, JC virus, CMV etc.), become more frequent in AIDS.

If the general symptoms of meningitis are present (e.g. fever, newly developed headache, nausea, light sensitivity, confusion), always consider the diagnosis of meningitis, even if the meningeal signs are absent.

In case of fever, personality changes, epileptic seizures and confusion always consider to possibility of encephalitis even if definitive neurological signs, such as hemiparesis or aphasia have not developed yet.

Always provide historical data about the events happened right before the symptoms have developed (previous diseases, infections, travels to abroad, animals).

The imaging techniques cannot provide the diagnosis by themselves.

The examination of the cerebrospinal fluid is necessary, including routine tests, cytology, culture, serology and immunology performed both on liquor and blood samples.

If purulent meningitis or herpes encephalitis is suspected, the empirical antibiotic or acyclovir treatment should be started immediately even if the results of the laboratory tests are not available.

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Multiple Sclerosis

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Definition and pathomechanism

Multiple sclerosis (MS) is defined as a chronic inflammatory disease of the central nervous system, which leads to focal inflammatory demyelinated lesions with secondary neurodegeneration. However, this concept has recently been challenged by several observations suggesting that in this disease neurodegeneration might occur independent of inflammation.

Demyelination and axonal degeneration is located in the white matter and have different levels of damage. Calling multiple sclerosis a demyelinating disease is not correct, because in many cases demyelination can occur without inflammation, for instance in toxic damage and avitaminosis. The glia - supporter of the central nervous system - , the mesenchymal cells and the blood cells also take part in the pathomechanism, therefore it is rightful to call the disease encephalomyelitis or leukoencephalitis. The pathological, degenerative, insidious process is the loss of axons formed in foci or plaques. There are many foci of different age can be found in the white matter. The damage of the axons is different in dimension and speed. Perivascular lymphocyte infiltration can be seen in the acute foci as an inflammatory component. The destruction of the myelin sheath (demyelination) is supposed to be caused by T-cells and macrophages or by B-cells (antigen or complement system). Inflammatory (proinflammatory Th1 cytokines, IFN gamma, TNF alpha) and antiinflammatory (antiinflammatory Th2 cytokines, IL-4, IL-5, IL-10, TGF beta) molecules relapse under this process. The oligodendroglia, which is responsible for the production of myelin, also falls a victim to this process (by the mechanism of apoptosis or dystrophy) and the myelin repair (capacity for remyelination), which can be seen at the beginning, is exhausting. Macroglia (astrocytes) swells around the chronic foci and the fibrous matrix (scar) made by them forms the sclerotic foci. These sclerotic foci that are located in the central nervous system, are perceptible to the naked eye, the new ones are oedemic, the old ones are different in colour and they feel hard (that's why the disease called: "multiple sclerosis" by Charcot). The extent of the foci is different, sometimes they can be fused and can damage huge areas. To understand the clinical symptoms we should know, that the foci of multiple sclerosis have favourite locations. These are the spinal cord, the territory of the fourth ventricle, the cerebellum and lateral corner of cella media located in the lateral ventricles and in the neighborhood of the posterior horns. The direct cause of the symptoms is the loss of myelin sheath (demyelination, loss of insulation) which causes a conduction block. As far as the axons of the neurons are intact, the remyelination can cease the symptoms. Over the years of the chronic disease the axon damage becomes more severe: this makes symptoms irreversible.

The pathomechanism of multiple sclerosis is not clear and the etiology is unknown. Animal experiments support that the central nervous system determines an alkaline protein of the myelin sheath (myelin basic protein, MBP) as an antigen.

Besides MBP many other antibody can be detected in multiple sclerosis. Besides this the gammaglobulin content is increased in the liquor, which might derive from B-cells and gets from the nerve tissue to the liquor. Swelled IgG and activated complement can be demonstrated from the plaques, from the damaged myelin. Otherwise, the IgG specific antigen, produced by the cerebrospinal fluid, couldn't have been identified. There is evidence that the process starts at the peripheral nervous system, not in the central nervous system. The survival T-cell, which escapes from the control of the thymus, becomes „autoreactive” by the effect of an environmental factor (for instance they can be activated by a microbiological antigen due to a virus infection) and these activated T-cells can get through the blood – brain barrier. From this very moment these T-cells react the components of the myelin sheath and trigger series of immunological cascades.

Regarding to the etiology many infectious, toxic, avitaminosis theory came up. It is a multifactorial disease. Genetic and environmental factors all together can be responsible for the pathomechanism. The complete genom studies signed explicit associations only at the MHC II locus of the sixth chromosome. Like every autoimmune disease, twice as many women are affected as men, and people of Northern European origin appear to be at the highest risk for the disease. It has a prevalence that ranges between 2 and 150 per 100,000 worldwide. Multiple sclerosis affects an estimated 300,000 people in the United States and probably more than 1 million people around the world.

Clinical symptoms

This multifocal disease is characterized by optic nerve, cerebellum and spinal cord symptoms. The presence of objective neurological symptoms is essential for the diagnosis. We rarely meet cases when we couldn't find pyramidal signs referring to corticospinal tract lesions. If we detect muscle weakness of the extremities, that occurs with spasticity most of the time. Central facial lesion is also frequent.

If diplopia is present, the lack of coordination between the eyes or jerky eye movements, we should think about brainstem damage. The speech becomes nasal regarding the foci in medulla oblongata. They may also cause dysphagia.

Coordination disorders and ataxia – which can be seen by voluntary movements – are typical and become more significant. Ataxia is characterized by limb movements with equal amplitudes around a virtual axis, which is also called *intention tremor*. It can be explained in cases when the foci are in the posterior columns and the cerebellum. Ataxia of the muscle parts of the speaking mechanism leads to a special change of the speech: the patient talks slower and monotone than usual like an articulate explosion and there are breaks between the syllables. We call this as *scanning speech*, and it is related to cerebellum disorders.

The optic nerve involvement is characterized by unilateral blurred vision and pain around the eye. You might not see anything on the optic disc in the early phase of the disease, despite of the presence of loss of vision, regarding the colour vision some scotomas in different sizes can be seen. We call it *retrobulbar neuritis*. As the disease progresses, temporal pallor (temporal decoloration) can be seen on the disc due to the optic nerve fibers degeneration, which is a very important diagnostic sign in the recognition of multiple sclerosis. The connections of vestibular nerve often damage, leading to nystagmus and dizziness. Patients often experience subjective sensory dysfunctions: numbness, tingling starting in the feet and spreading up to the waist, curious warm sensation, feeling of a tight band wrapped around the trunk or limbs, or swelling of limbs as well as the electric shock-like sensation down the back on flexing the neck (*Lhermitte's sign*).

If the pins and needles sensation affecting the lower limb spreads up to the upper limb and the contralateral upper limb, we might think of cervical spinal cord lesion. Impaired vibration sense and joint position sensation are more frequent between objective sensory dysfunctions.

Considering the vegetative functions, the dysfunction of the bladder and bowel usually occurs if the lumbosacral innervation is impaired. Urgent micturition, urgent incontinence and retention can be diagnosed. The sexual reflexes are frequently disturbed too. The damage of supranuclear neurons causes *compulsive crying and laughing*.

The cognitive performance is getting worse, and sooner or later dementia develops. The elevated mood, called euphoric dementia, is the characteristic feature of the progressive phase. Depression is more frequent in the earlier phase than in the normal population.

The localizations of sclerotic lesions may vary causing the clinical symptoms of multiple sclerosis.

Not all newly developed foci cause clinical symptoms. People attributed significant relevance to symptoms described by Charcot in the second part of the 19th century and in the first part of the 20th century: *nystagmus, scanning speech and intention tremor*.

Later it has been found that the *Charcot triad* occurs only in 10% of the cases. The loss of superficial abdominal reflex and the decoloration of the temporal disc are valuable diagnostic signs.

In the knowledge of the predirection of loci is not surprising that some symptoms are markable. Regarding the clinical picture – which can be related to the localization of foci– we can speak about localization forms, such as:

1. *Bulbo-pontin (brainstem) form*, which can be recognised by the dysfunction of cranial nerves and symptoms related to the damage of the corticospinal tract in the brainstem.
2. *Cerebellar form*, in which the signs of cerebellar damage are the most spectacular.
3. *Spinal form*, in which the cervical or the lumbosacral segments are damaged primarily. Regarding this the loss of motor and sensory function and the ataxia of the upper limbs or the lower limbs are the most

remarkable symptoms. The consequence of the damage of the lumbosacral segment is the sympathetic and parasympathic dysfunction.

4. *Hemiparetic form*, in which the hemi-pyramidal symptoms are the most remarkable.
5. *Brainstem and cerebellar* damage symptoms are also associated.

Diagnosis

Multiple sclerosis hasn't got any typical clinical, laboratorical or radiological signs. The diagnosis is based on chronic, multifocal inflammation. The chronicity is based on the follow-up of the dissemination of the lesions in time. We can verify the multifocal damage in the central nervous system firstly by the clinical symptoms, the objective neurological signs of long tract damage and secondly with paraclinical tests. In the acute phase the disease is characterised by neurological signs; if the neurologist does not detect neurological symptoms despite the complaints, it denies the presence of multiple sclerosis.

The course of multiple sclerosis

The first sign of the disease appears typically between at the age of 20-40, it starts rarely in childhood or above 50 years. The disease could start with any kind of (CNS) neurological symptoms: blurred vision (retrobulbar neuritis), paraesthesia, muscle weakness, dizziness and double vision could be the first complaints. According to the progress of the disease subgroups can be distinguished. For 60-85 percent of the patients fluctuating is characteristic in the first phase of MS. The symptoms come and go, which means that *relapses and remissions* follow each other. After further and further relapses (clinical episodes, exacerbations, attacks, relapses, shubs) residual symptoms could arise. This period with relapses and remissions could last from a few years to even 10-20 years. MS is a complex and heterogeneous disease. Without treatment after 10 years about 40 percent of the patients get to the phase of *secondary progressive MS*, when there are no relapses and the disease will worsen with the slow increase of the clinical disability. About 10-15 percent of the patients have no relapses, but their symptoms are deteriorating insidiously, continually persistent and more and more severe from the beginning: this is the *primary progressive form* of the disease. In this form frequently spastic paraparesis is the dominant symptom. The previous history of the patient could include some curious paresthesia, gait disturbances or abnormal fatigue. Besides the earlier specified typical multiple clinical symptoms, aphasia, homonym hemianopia, peripheral type of stepping gait, focal atrophy of the muscles are rare symptoms in MS. The clinical diagnosis is based - on the observance of gender and age - on the careful analysis of the clinical signs. It's important to detect, which were the first symptoms, when they occurred and how they formed.

Demyelisation has to be suspected in every paresthesia of unusual localisation (especially when the trunk is affected, sometimes only at one side) and procession, double vision in young age and clumsiness of the extremities; the patient has to be sent to a specialist. It's important not to mark the patient with MS based on one relapse with optic lesion.

Physical examination

The purpose of the examination is the objective detection of the damage of the long tracts. For example in the early phase of the disease, when there are no complaints about the weakness of the extremities, a pyramidal sign or the decoloration of the temporal disc without any sign of optic lesion in the case history could be a really valuable diagnostical sign.

Paraclinical examinations

After the physical examination MRI investigation has to be chosen first, because it demonstrates sensitively the multifocal damage of the white matter, which is characteristic for the disease (Figure 1). But the multiple demyelinating lesions in the radiological finding do not mean MS, if there are no specific symptoms of the disease. The examination of the cerebrospinal fluid is a suitable method to detect the autoimmune inflammation. Its diagnostical significance is much smaller since the introduction of the MRI, but in the early diagnostical phase, especially in the onset of the disease, it's still a very valuable additional examination. In the case of liquor test mild cell-increment can be detected with generally normal protein content and the determination of the IgG-index and the oligoclonal gammopathy (OGP) is essential. Subclinical damage of the optic nerve can be diagnosed with the registration of visual evoked potential (VEP) and with ophthalmological (colour vision, visual field) examination.

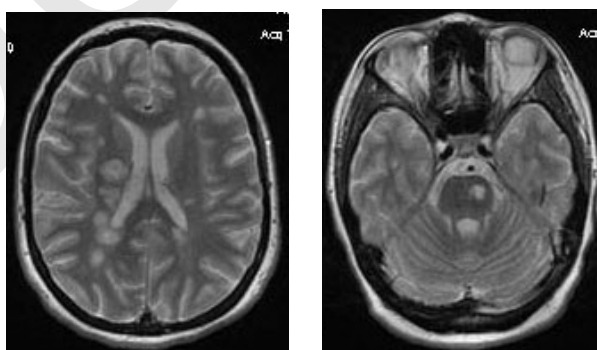


Figure 1
Multifocal demyelinating white matter lesions on axial T2 images.

Prognosis

MS is thought to be a more sinister disease than it is reality by the lay person and often the first thought about the disease is a wheelchair. Fortunately it's not true. At 20-30 percent of the patients MS has a mild progression, patients are moderately handicapped physically after 10-15 years and they can work in jobs with light physical load. Unfortunately 10-20 percent of the patients have the malignant type of the disease and the patient will be bedridden two years after the first symptoms develop. In the remaining cases patients will be physically handicapped after 10-15 years and unilateral assistance has to be used to their walking. In the first phase of the disease patients with relapsing and remitting form will suffer from incalculable episodes with rapid worsening of the neurological symptoms, which are followed by remissions. Frequent relapses, multi-symptomatic onset and the permanent lesion of functions means significantly frequent adverse disease course. In the last few years it became certain in spite of the previous approaches that the oral anticonceptives and the pregnancy have no negative effect on the long-term outcome.

Treatment

Although there is no known cure for multiple sclerosis, several therapies have proven helpful. In case of acute relapse of MS symptoms will improve faster with *corticosteroid*. Although generally effective in the short term for relieving symptoms, corticosteroid treatments do not appear to have a significant impact on long-term recovery. The clinical progression of the disease is variable and heterogeneous. The function of the immune system can be modified in MS (beta interferons, glatiramer acetate, natalizumab), which can significantly decrease the number of relapses in the relapsing-remitting phase and delay the development of the permanent neurological damages. The frequent relapses mean adverse disease course, that is why we treat these patients with *immunomodulatory therapy*. In the first line of options, interferons and glatiramer acetate therapy could be administered for the patients by self-injections optimally through the years. These medications are indicated by MS specialist and the specialised staff could teach the administration technique. The efficacy of these products are almost the same, they decrease the number of relapses approximately by one third and they moderate the progression of the brain damage caused by MS. Patient with two or more attacks in the last two years and are able to walk 100 meters without any assistance should apply one of these drugs. If the disease is still active, the immunomodulatory treatment should be changed. Both natalizumab and fingolimod appear to be more effective than the interferons and glatiramer acetate, but both have more safety problems. Natalizumab should be administered monthly intravenously, fingolimod is the first approved drug with oral availability. The treatment with natalizumab is associated with a risk of patients developing progressive multifocal leukoencephalopathy (PML), which the JC virus causes. The cardiac effects and

potential immunosuppressive side effects of fingolimod require intensive monitoring. Mitoxantrone should be considered for non-responder cases.

Recently there are no special medicines that could delay the progression of the symptoms in chronic cases without relapses (primary-, or secondary progressive MS). Some part of the patients can accept this fact, but others want to take medicines and do something against the disease.

Permanent symptoms of the MS could be moderated with various treatments. The excessive muscle spasm can be reduced, urinary problems can be influenced efficiently, neuralgiform pain can be relieved, depression and some forms of the sexual dysfunctions can be treated and there are lots of therapeutic equipments to use. The excessive use of vitamins is not useful, moreover it could be dangerous. There are no approved methods in the alternative medicine, which can be used for the therapy of MS.

Due to the new treatments the MS patients' expected disease course is more favourable, than 10 years before. The disease is the most common in the USA and in the most advanced countries, accordingly numerous and high standard scientific researches are in progress to develop medicines that are more effective than the current ones. Effective oral immunomodulatory drugs can be introduced in the immediate future.

Lifestyle

Active lifestyle is proposed by possibility in the light of the current symptoms and the invalidity. Exhaustion should be avoided. Aerobic, swimming, yoga, Tai-Chi and muscle lengthen activities could be beneficial. There is some information about the favourable effect of magnetic treatment.

Pathological fatigability (fatigue) is a frequent symptom. That is why physical tolerance and remedial gymnastics are advisable, which also has a good effect on the muscle spasm. During the physiotherapy maximum 80 percent of the efficient strain must keep in mind. The physical load of patients with interferon beta treatment should be modified individually depending on the side effects on the day of the injection. It is not recommended for even workable patients to work in jobs with hard physical load, night work or shift work. The complex attendance should expand to the treatment of the psychological symptoms.

Increasing of body temperature (hot bath, sauna, sunbathing) should be avoided. Reducing the fever is also important. Chronic foci (dental, gynaecological, urological etc.) should be eliminated.

Diet, rich in multiple unsaturated fatty acids (linolenic acid) could be beneficial. Fish oil, sunflower seed, corn, soya been oil are rich in linolenic acid.

Vaccination against flue is not contraindicated.

Psychical stress can have a negative effect.

Differential diagnosis

Neuromyelitis optica (Devic's disease): The name of the disease (neuromyelitis optica) refers to the inflammation of the optic nerve and the spinal cord. The complaints which are characteristics for the recurrent myelitis and the retrobulbar neuritis without any treatment could lead to blindness and paralysis. MRI and cerebrospinal fluid examination could help to differentiate it from MS. If aquaporin-4 antibody can be demonstrated from the serum of the patient, the diagnosis is definite. Neuromyelitis optica often associates with other autoimmune diseases (SLE).

From the MS variants **acut disseminated encephalomyelitis** has a practical significance. It has to be separated from optic neuritis and transverse myelitis. Acut disseminated encephalomyelitis (ADEM) is primarily the disease of children and young adults. Multiple demyelinated damage develops in the CNS after an infection or rarely after vaccination. Mainly it is a monophasic disease. Headache, fever and meningism (lacking in adults) can help us to differentiate it from the multiple symptoms of the brainstem, spinal cord, cerebellum and hemisphere in children.

Multiple demyelinating foci in MRI scans can help us to differentiate - with the assistance of anamnesis, laboratory examinations and lack of objective neurological signs - from autoimmune diseases (antiphospholipid antibody syndrome, systemic lupus erythematosus), hypertensive encephalopathy and infectious diseases (in the case of the central nervous symptoms of Lyme neuroborreliosis).

Granulomatous diseases (sarcoidosis, Wegener granulomatosis).

Spinal cord syndromes (spinal cord compression, cervical myelopathy, vitamin B12 deficiency).

Genetic diseases (leukodystrophies, Leber's hereditary optic atrophy).

Summary

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, which leads to focal inflammatory demyelinated lesions with a different grade of axonal damage in the white matter. MS is the most frequent neurological disease among young adults, which results in two third of the cases after 10-15 years permanent disability and early retirement. Clinically two major forms can be defined: relapsing-remitting (which in most of the cases turns into secondary progressive) and primary progressive forms. The common symptoms are numbness, weakness, visual impairment, loss of balance, dizziness, urinary bladder urgency, fatigue, and depression. The diagnosis of multiple sclerosis should be made by a physician with experience in identifying the disease. Diagnosis should be based on objective evidence of two or more neurologic signs that are localized in the brain or spinal cord and are disseminated in time and space. There is no known cure for multiple sclerosis. There are no universal therapies and it's hard to make a prognosis. Symptom-specific drugs can relieve spasticity, bladder

dysfunction, depression, and fatigue. Six disease-modifying treatments for multiple sclerosis have been approved by the U.S. Food and Drug Administration. These treatments are partially effective in reducing exacerbations and may slow the progression of disability in patients with relapsing-remitting phases. Patients with MS are at the forefront of current research. Nowadays the expected disease progression of MS patients is better than ten years before. That is why it is important to make an early diagnosis and send the suspicious cases to MS care center.

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Tumors of the central nervous system

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Taking all age groups into consideration the frequency of brain tumors is 15/100,000 individuals in the industrialized countries. Every year 18,000 – 20,000 primary intracranial neoplasms are diagnosed in the United States, which takes approximately 2% of tumors in adults. Most of the intracranial tumors in adults are growing in the anterior cranial fossa. The posterior cranial fossa is mainly involved in children.

The origin can be a neural structure, these are the primary neural neoplasms. Glial cell tumors constitute 45-50% of this category, meningiomas, neurinomas are present in 7-15%. Secondary spreading and metastatic tumors are originating from other organs or tissues. Metastases can involve the brain and spinal cord, getting into the central nervous system or its coverings via lymphatic or blood circulation. Extraneural neoplasms do not only cause symptoms by direct compression, infiltration or giving metastasis but as a remote effect, by immunological mechanism. Paraneoplastic syndrome is often the first or only clinical manifestation of the tumor.

Etiology

The exact cause of brain tumor is not known yet, genetic and environmental factors may also play a role in the development. Age is very important, medulloblastomas, spongioblastomas, optic gliomas, pinealomas usually develop before the age of 20, although meningiomas, glioblastomas are typically seen around the sixth decade. There is clear evidence of inheritance in case of neurofibromatosis, tuberous sclerosis or Von Hippel-Lindau disease and familial accumulation was described in gliomas and astrocytomas. Tumor processing and inhibiting factors were described in a few cases. Oncogenes and tumor suppressor genes may also have a role in the tumorigenesis. Deletion of the short arm of chromosome 17 including the p53 gene, is present in more than 50% of malignant astrocytomas. Mutation of the well-known tumor suppressor retinoblastoma gene have not only found in retinoblastoma but also in 30% of malignant gliomas. Molecular analyses showed that excess of 7p or lack of 10q are typical gene abnormalities in glioblastoma multiforme (GBM), lack of 1p and 19q have very often found in oligodendrogliomas. Mutant or overexpressed form of epidermal growth factor (EGF) or tumor growth factor (TGF) is present in approximately 50% of gliomas, which suggests the importance of trophic factors in tumorigenesis.

Up to now there is no clear evidence for the connection between different viruses and development of central nervous system tumors. According to the results of epidemiological and animal studies human papillomavirus, hepatitis B, Epstein-Barr and human T lymphocytotropic viruses are suspected. Among environmental factors the role of irradiation and different chemical materials were also examined.

Patomechanism

The precise determination of the date of tumor formation is very difficult. Most of the brain tumors are recognised when neurological symptoms appear. The volume of the skull is determined, filled with brain tissue, cerebrospinal fluid (CSF) and blood. According to the Monroe-Kellie rule if something grows inside the skull, it will push and damage other structures. The tumor compresses the healthy brain tissue and CSF spaces, causes dislocation of brain structures and blood vessels. If the brain cannot compensate the compression anymore, the intracranial pressure starts to increase. This increased intracranial pressure inhibits the axonal transport in the optic sheath and due to the retinal vein occlusion edema of the papilla appears.

Damage of the blood-brain barrier causes increased capillary permeability which results vasogenic edema in the white matter. If CSF circulation is also blocked by the mass, hydrocephalus may develop.

According to the size and surgical treatment of the tumors 3 phases can be differentiated:

1. Beginning (latent) phase of the growing: the tumor is already present, but does not cause clinical symptoms, and is only recognised accidentally or by screening. Depending on the location these tumors are usually small in diameter and can be removed easily.
2. Manifestation of the tumor: because of continuous growing the tumor has connections with neighbouring structures causing excitement (epilepsy) or suppression (symptoms of focal deficit) calling the attention as warning sign. Subjective complains may also appear, like headache, psychiatric complications. Examinations reveal the problem. Chance for surgery in this stage is good, but there is a risk of temporary or permanent stabilisation or progression of symptoms.
3. Phase of decompensation: continuous growing of the tumor causes increased intracranial pressure and appearance of clinical symptoms as a remote effect beside local deficits. Sooner or later the whole function of the central nervous system deteriorates, which has an effect on the total body. The risk of surgical removal and mortality at this stage is the highest.

Primary brain tumors have 4 essential features, which distinguish them from other neoplasms in the body.

- Histologically benign tumor may also be lethal if total surgical removal is not possible because of the location (eg. ependymoma in the fourth ventricle).
- Infiltration of the neighbouring structures is typical for parenchymal neoplasms in general, but especially for atocytomas. There is no sharp border around the lesion, impossible to distinguish the healthy and involved tissue neither by eyes nor microscopically.
- Appearance of remote metastases in other organs are very rare even in case of the most malignant brain tumors as well. Sometimes after surgical procedures damaging the dura mater remote metastasis may appear in

those cases when the primary tumor is glioblastoma multiforme or medulloblastoma. Dissemination inside the central nervous system goes via the CSF.

- Some of the tumors have typical anatomical localisation (anatomical predilection) and in some cases age predilection is also seen (eg. medulloblastoma typically develops in the cerebellum in the first decade, but GBM or anaplastic astrocytoma are more common in middle aged or old people).

Clinical symptoms

Occurrence of neurological symptoms depends on the location and histological origin of the tumors. The following statements are true in general:

Because of the tumor progression neurological symptoms usually develop **slowly, gradually**. Comparing to the circulation deficit (stroke) sudden onset of symptoms only rarely seen, and so huge mass lesion surrounded by edema causing large midline shift or high number of intracranial metastases can result very poor clinical picture with small neurological deficit.

Headache is an early sign **in approximately 1/3 of the patients**, usually diffuse, more severe in mornings and gets better during the day.

Signs of increased intracranial pressure:

- Papillary edema: mostly occurs in case of tumors growing inside the posterior fossa, but is not necessarily present if the tumor progression is slow especially in elderly.
- Vomiting: especially in children in case of involvement of the posterior fossa, sudden onset of jet vomiting may occur without any initiating symptom.
- Double vision: is usually the result of the abducent nerve lesion which is caused by nerve compression as a consequence of the increased intracranial pressure.
- Increasing circumference of the head and neck stiffness can be present in children.
- At advanced stages Cushing reflex occurs: bradycardia, increased systolic but decreased diastolic blood pressure and decreased frequency of breathing.

Cognitive and mental deterioration, memory deficit, fatigue: symptoms of frontal and temporal lobe involvement, neoplasm in the third ventricle or in the thalamus can mimic real psychiatric condition and causes difficulties in the differential diagnosis.

Slowly progressing tumors in the hemispheres damage the cortex and cause **epileptic seizure** (focal or generalized) **in 20-50% of cases** as the first symptom of the disease, which might occur months before the other symptoms of the increased intracranial pressure, **so in case of first seizure in adults, brain tumor always should be excluded!**

Diagnosis

Beside the physical examination imaging methods have a leading role in the diagnosis of brain tumors. **Negative CT scan do not always exclude the neoplasm (eg. low grade glioma), if there is a suspicion MRI study should be done!** X-ray of the skull and angiography are additional methods. The role of EEG is also restricted. CSF examination can be normal or if the tumor reaches the surface of the brain or ependyma, increased cell number and protein content can be detected and sometimes tumor cells are directly seen in the CSF by microscopy.

Therapy

Symptomatic and curative therapy are differentiated.

Symptomatic therapy means treatment of the vasogenic edema around the tumor by administration of corticosteroid (4-40 mg dexamethason daily), which relieves the patient's symptoms very fast and may render the use of more aggressive antitumor treatment possible. Antiepileptic drugs are not suggested for prevention, only in case of seizures.

Curative therapy means destroying or removal of the tumor by use of different methods, like whole brain irradiation therapy, stereotaxic radiosurgery (gamma knife), traditional neurosurgery and chemotherapy. Extension of surgical removal depends on the location and diameter of the tumor. *Total extirpation* of glioblastomas is usually not possible because of the infiltration of white matter, only decompressive surgery can be done in such cases. *Postoperative irradiation* of tumor bed makes the therapy more effective. In case of soliter metastasis if it is close to the surface of the brain, easy to reach and the patient's general condition is good, it is worth to remove surgically. Postoperative irradiation is also suggested. *Whole brain radiation therapy* is recommended when the patient has multiple (more, than 3) metastases, or 1-2 metastasis but too big for radiosurgery and in case of recidiv tumor or progression after surgical removal. *Stereotaxic radiosurgery* is a good option for patients, who have less than 4 tumors and the diameter of the tumors are less than 3 cm, especially if the operation is hazardous because of the location. It has relatively good effect on controlling of the tumor with minimal invasivity and without need of general anesthesia, so the mortality decreases and the patient's quality of life improves. The role of *chemotherapy* is restricted, mainly used as additional therapy besides the other treatment options or adjuvant therapies. Cytostatic agents are not really effective in the treatment of neoplasms with glial origin. Comparing to other alkilating agents the FDA approved temozolomide extends the survival with a mean time of 5.8 months in case of glioblastoma and anaplastic astrocytoma.

Newer therapeutic options are trying to improve the permeability of blood-brain barrier, decrease the vascularisation of the tumor and in this way inhibit its progression. Different anti-angiogenetic factors are working like this and also inhibition of blood circulation inside the tumor mechanically by preoperative

embolisation. Immunological methods, protection against tumor cells using antigens or dendritic cells are in research phase at the moment.

Classification

Classification of tumors of the central nervous system based on the histological feature and location according to the WHO 2007:

1. Tumors of neuroepithelial tissue:
 - a. astrocytomas,
 - b. oligodendrogliomas,
 - c. ependymal tumors,
 - d. choroid plexus tumors,
 - e. other neuroepithelial tumors,
 - f. neuronal and mixed neuronal-glial tumors,
 - g. tumors of the pineal region,
 - h. embryonal tumors.
2. Tumors of cranial and paraspinal nerves:
 - a. schwannoma,
 - b. neurofibroma,
 - c. perineurinoma,
 - d. malignant peripheral nerve sheath tumor.
3. Tumors of the meninges:
 - a. tumors of meningotheial cells (meningioma),
 - b. mesenchymal tumors,
 - c. primary melanocytic lesions,
 - d. other neoplasms related to the meninges (haemangioblastoma).
4. Lymphomas and haematopoietic neoplasms.
5. Germ cell tumors.
6. Tumors of the sellar region.
7. Metastatic tumors.

From the clinical point of view astrocytoma, glioblastoma multiforme, oligodendroglioma, ependymoma, meningioma, primary central nervous system lymphoma and metastases have the greatest importance.

Astrocytoma: the most common tumor with glial origin. It has the highest incidence between the 3rd and 5th decades. It is usually localised in the supratentorial region in adults, the typical localization is the hypothalamus and optic nerve/chiasm in children. The growth of the tumor is slow but it may infiltrate relatively large area and the appearance is often cystic. The clinical picture is relatively poor, with only a few symptoms.

The occurrence of recidive tumors after radical surgery is very common, because histologically they are benign tumors, but their behaviour is malignant. Their typical feature is the presence of glial fibrillar acid protein in the tumor cells. Their malignant form is the anaplastic astrocytoma, which is mainly found in

hemispheres in adults. Recidive tumor appears in relatively short period of time after surgical removal, so postoperative irradiation or chemotherapy is also suggested.

Glioblastoma multiforme (GBM, Grade 4 astrocytoma): occurrence is 50% among gliomas. Highly malignant, quickly progrediating tumor. It is the most common in the 5th-6th decade, usually is found in the hemispheres but can spread through the corpus callosum into the contralateral hemisphere (*butterfly tumor*) and can involve basal ganglia as well. Irregular shape and typical girland like contrast material enhancement is seen on the CT scan, necrosis can be present in the middle and marked perifocal edema around the lesion. In most cases only partial resection of the tumor is possible. Total exstirpation is performed in case of lobar involvement although the tumor can regrow in that cases too. Sometimes recidiva appears in other lobes or also in other hemispheres. Besides the postoperative irradiation and chemotherapy most of the patients die in 12-month period from the diagnosis.

Oligodendroglioma: commonly occurs in 35-45 years old patients, usually in the hemispheres, in the neighbourhood of basal ganglia and thalamus. It grows slowly, epileptic seizure is the first symptom in more than half of the patients. Survival time after total resection is over 5 years, but implication of adjuvant chemotherapy is also suggested.

Ependymoma: tumorous growth of the ependymal cells, mainly seen in children and in young adults. The most common place of its occurrence is the region of the fourth ventricle, but can be found anywhere from the frontal horn of the lateral ventricle to the conus medullaris. The tumor blocks the CSF circulation and the symptoms of the increased intracranial pressure will attract the attention to this problem. Tumor cells may be detected in the CSF. The prognosis is relatively good, after surgical removal and irradiation the survival rate is approximately 70% at 10 years. Unfortunately total exstirpation of the tumor is rarely possible because of the location.

Plexus papilloma: intraventricular neoplasm originating from the chorioid plexus. Rare, usually benign tumors, but can cause hydrocephalus by increased CSF production. The surgical removal is the effective treatment.

Medulloblastoma: it mainly affects children, grows in the cerebellar vermis penetrates into the fourth ventricle. This tumor can disseminate in the CSF space and give metastases. Highly malignant and recidive tumors are frequently seen after surgical removal in spite of using irradiation therapy. Combination with chemotherapy may increase the 2 years survival rate to about 50%.

Meningioma: benign tumor of the meninges, mostly characterized by slow growth. It takes 12-20 % of intracranial tumors. The incidence is twice higher in women than in men, probably caused by hormonal background. Because of the slow progression the brain may compensate for a while, so relatively large mass can be experienced at the time of diagnosis. Small meningiomas (below 2 cm in diameter) are usually found accidentally. 50% of the meningiomas localized at the convexity of the brain, in the parasagittal region or in the falx, others in the olfactory, sphenoidal and suprasellar region or next to the tentorium. Sometimes they are found inside the ventricles or intradurally in the spinal part of the CNS.

Looking at the shape, it can be globosus (round shape) or en plaque (flat). There are different forms from the histological point of view, meningotheelial, fibroblastic, transitional, angiomatous and malignant forms like sarcomatous and anaplastic meningioma. It appears on the CT scan as a well circumscribed tumor, sometimes containing calcification, separating from the brain tissue but compressing and displacing it with contrast material enhancement. If it is located on the surface of the brain, it can make the bone of the skull thinner or can cause destruction of the sphenoid bone as well, which can be recognised on x-ray scans. The therapy is surgical extirpation but if it is only subtotal resection, recidiv tumor commonly occurs.

Acoustic neurinoma: Originates from Schwann cells of the vestibulocochlear nerve growing from the internal acoustic meatus and it takes place in the corner of the cerebellum and the pons. Mainly found in adults, usually on one side, bilateral presentation is rare, but can be seen as a part of the Von Recklinghausen type neurofibromatosis. Symptoms are generated by the expansion of the tumor: when it is inside the meatus, tinnitus, hearing loss on the affected side or sometimes vertigo can be present. In the extrameatal phase compression of the facial nerve and other neighbouring cranial nerves (V, IX, X, XI) are responsible for the symptoms. Further expansion causes compression of the brainstem and cerebellum, results pyramidal tract lesion, nystagmus, ataxia or hydrocephalus. Special X-ray (Stenvers) can frequently detect the enlargement of meatus, but MRI of the head can give correct diagnosis. It is important to know, that protein content in the CSF is elevated in almost every cases. Surgery is the appropriate treatment, but the risk of damage of the neighbouring structures (facial nerve) is very high, so alternatively stereotaxic radiosurgery (gamma-knife) can be also considered as a therapeutic option especially in cases of small tumors.

Hypophyseal adenoma: benign tumor from the cells of the anterior lobe of hypophysis. Its incidence is increasing by age. Symptoms are caused by the pressure of neighbouring structures from one side (bitemporal hemianopia, decreased visual acuity, papillaedema are the most common) endocrin problems caused by overproduction or decreased hormone production on the other side (amenorrhea-galactorrhea syndrome, acromegalia, Cushing disease). Headache is a common symptom, at the beginning irradiating towards the nose. According to the diameter micro- (< 10 mm) or macroadenoma (> 10 mm) should be differentiated. Symptoms of hormonal disturbance, results of the imaging methods and laboratory investigations (hormon levels) can help in the diagnosis. Therapy can be pharmacological or surgical, stereotaxic radiosurgery significantly decreases the frequency of complications comparing to manual removal.

Apoplexia of the hypophysis is a serious clinical condition, which means bleeding inside the hypophysis adenoma. The volume of tumor is increasing suddenly, severely decreased vision and headache appears. Larger bleeding can be lethal.

Empty sella is usually detected accidentally on imaging examinations as a result. Origin could be primary when CSF gets through the hiatus of the diaphragma sellae and widens it or secondary, which means intrasellar arachnoidal cyst formation after surgical removal of the hypophysis.

Craniopharyngioma: tumor of the embryonal tissue around the handle of the hypophysis, it occurs in children and adults both. It usually grows in the sella, sometimes in the suprasellar region. Main symptoms are similar to the hypophyseal adenomas. Often they are relatively large in diameter, the compression of the third ventricle or hypothalamus results in occlusive hydrocephalus. Calcification or cholesterol crystals inside the tumor can be frequently seen. This is a benign tumor from the histological point of view but total surgical removal has very high risk because of the location, in that case postoperative irradiation is necessary.

Lymphomas: primary central nervous system lymphoma is a rare form of extranodal non-Hodgkin lymphoma, affecting the brain, meninges, spinal and intraocular compartment. At the moment the only well known risk factor is immunodeficiency (inherited or acquired). Most commonly occurs in men between 50-60 years. Often slow progression of behavior disturbance, mood or mental impairment may occur, but headache, signs of increased intracranial pressure or focal neurological deficits can be present. Usually uni- or multifocal infiltrative gadolinium enhancing lesion especially in the periventricular region is seen, biopsy and histological examination provide the correct diagnosis. The cytology of the CSF is positive only in 15-31 % of cases. Prognosis is worse comparing to systemic lymphoma. Surgical removal is usually not possible because of the involvement of deep structures next to the midline. Methotrexate based chemotherapy is the standard treatment completed by irradiation. Autologous stem cell transplantation or other methods of immunotherapy (intrathecal rituximab administration) seem to be an option in case of refractory or relapsing disease in young patients.

Metastases: the most common intracranial tumors in adults, their incidence is **10 times higher comparing to primary brain tumors**. They are present in 10-40% of patients suffering from any kind of tumor and the incidence is increasing continuously. Metastases usually originate from 3 types of malignancy: **lung** (40-50%), **breast** (15-25%) and **melanoma malignum** (5-20%). Sometimes colorectal and germ line cancers, non-Hodgkin lymphomas, ovarian and kidney cancers are responsible for occurrence of brain metastases. Gastrointestinal tumors usually give metastases into the liver and lung first, before reaching the brain, metastasis of prostatic cancer often occurs in the vertebra and spinal cord reached it by veins of the plexus. Although lung cancer is responsible for the highest number of brain metastasis, **melanoma is the most potent tumor to give intracranial metastasis**.

Presence of symptoms are depending on the location of the tumor or are the consequence of the increased intracranial pressure. Some metastases tend to be cystic and often seen bleeding inside. The occurrence can be single or multiple. In case of solid tumor 37-50% of patients have single but 50-63% have multiple brain metastases at the time of diagnosis. If only single mass is seen on the CT scan, MRI can reveal multiple lesions.

Patient's survival period without treatment in case of brain metastasis can be measured only in weeks, but definitive treatment makes it longer with 4 months in general. The most important symptomatic treatment is decreasing the vasogenic edema surrounding the tumor by administration of corticosteroid (4-40 mg dexamethason daily), which usually helps quickly and makes the initiation of more

aggressive antitumoral therapy possible. Starting an antiepileptic drug from the prophylactic point of view is not suggested only in case of seizures. Methods of curative therapy are the whole brain radiation therapy (WBRT), stereotaxic radiosurgery (gamma-knife), traditional manual surgical removal and chemotherapy. Decision about their application or combination is individual in case of a particular patient. The more important prognostic factors are the Karnofsky score (KPS), age, control of primary tumor and extension of the tumor in space. KPS70 or higher, age below 65, appropriate treatment of the primary tumor without extracranial metastases and single brain lesion are determining the best chance for survival.

Special form of multiple brain metastases is the **leptomeningeal carcinomatosis**, which **occurs in 5-8% of tumor patients**. Most commonly caused by breast or lung cancer, melanoma, lymphoma and leukemia, but in some cases the tumors of the head-neck region and gynecological, renal or bladder cancer was also described. Malignant cells reach the meninges by hematogen, lymphatic spreading or direct infiltration. Clinically headache, nausea, damage of the cranial nerves and spinal roots are typical but behaviour changes, menigeal irritation signs, epileptic seizures and other focal neurological deficits can be present too. The most important thing in the diagnosis is detection of tumor cell directly in the CSF, but increased CSF pressure, high protein content and decreased sugar content also support the diagnosis in 50-70% of cases. MRI with contrast material is more sensitive than CT scan in imaging. Despite the use of systemic or intrathecal chemotherapy and irradiation patients' prognosis suffering from leptomeningeal carcinomatosis is very poor. The mean survival period in solid tumor is 4-11 weeks but worse in hematological conditions.

Tumors of the spinal cord

Tumors of the spinal cord can be found in the epidural space (extradural), inside the dura (intradural) but outside the spinal cord (extramedullar) or inside the spinal cord (intramedullar). Presence of symptoms in time is depending on the location of the mass, symptoms of compression of the spinal cord occur early in case of cervical, but late in lumbar lesion.

- a. **Extradural tumors:** symptoms are caused by bone destruction, compression of the cord and radicles. Most of the patients complain about increasing pain in the back and later, symptoms of spinal cord compression occur. Local sensitivity to hit can be present above the lesion and gibbus can develop at the affected level. Most commonly carcinoma metastases (lung, breast, prostata) myeloma, lymphoma are in the background. Very often simple X-ray can detect osteolytic lesion or pathological compression and can help in the diagnosis. CT and MRI describe the extent of lesion and the level of compression more precisely. In therapy the decompressive surgery performed in time improves the neurological status, but indication of operation of spinal cord compression in case of metastasis is not absolutely clear. After the surgery usually irradiation is necessary.

- b. **Intradural, extramedullar tumors:** most commonly are solid tumors (meningiomas, neurinomas). They are usually seen at the thoracic level, but can be detected in the cervical and lumbar region as well. Based only on the clinical picture they are not differentiated clearly from the extradural tumors. Symptoms usually develop gradually during a longer period. The first sign of neurinomas is radicular pain. Originating from the posterior radix it enlarges the intervertebral foramen and spreads through the radix (sand-glass tumor). Myelography, CT and MRI describe the correct diagnosis. Treatment means radical surgical removal.
- c. **Intramedullar tumors:** can be astrocytoma, ependymoma, sometimes angioblastoma or metastasis. Astrocytoma mainly occurs at cervical level, ependymoma involves the cauda equina and the lumbar region. Growth is slow, difficult to differentiate clinically from the extramedullar tumors. Segmental pain commonly occurs, and lesions located in the midline can cause dissociated sensory deficit (superficial sensation problem but preserved deep sensation or on the contrary). Surgical removal using microsurgery became possible. Postoperative irradiation can decrease the rate of progression. Angiomas cause neurological deficit not only by cord compression but by circulation problem, furthermore bleeding originating from their rupture can result symptoms of spinal cord transection.

Paraneoplastic syndrome

This entity is not connected directly to the tumor or the consequences of the oncological therapy, but is an **autoimmune disease** based on molecular mimicry. It affects approximately 1 % of patients suffering from malignancy. Cytotoxic T cells and antibodies produced against particular proteins on the surface of tumor cells penetrate across the blood-brain barrier and react with different neuronal proteins which are normally present inside the nervous system and result in neurological deficit. Symptoms may develop in the central or peripheral nervous system but retina and muscles can also be involved. Symptoms can develop rapidly, within days or weeks, sometimes mimic stroke because of the rapid onset, but can progress slowly, suspected for chronic degenerating condition. **In 60-80% of cases neurological symptoms occur months or years before the diagnosis of tumor.** Detection of antineuronal antibodies in the serum or CSF is the most important factor in the diagnosis. Most commonly small cell lung cancer, breast, ovary, kidney tumor or lymphoma is in the background. In case of suspicion of neurological paraneoplastic syndrome MRI of the head should be performed.

There are classic paraneoplastic syndromes, such as cerebellar degeneration which causes subacute cerebellar symptoms, limbic encephalitis typically appears with memory deficit, behavioural changes and epileptic seizures, paraneoplastic sensory neuropathy or Lambert-Eaton myasthenic syndrome. Therapy usually means treatment of the basic condition (tumor) and use of methylprednisolone, intravenous immunoglobulin, plasmapheresis or other immunosuppressive agents

(azathioprin, cyclophosphamide, cyclosporin). Unfortunately none of these can improve the prognosis of the degenerative process.

Summary

- *Brain tumors have their own special feature, different from other malignancies of the body.*
- *Headache is not necessary!*
- *First onset of epileptic seizure in adults can be suspicious for tumor and indicates CT scan of the head with administration of contrast agent.*
- *Brain metastases are 10 times more common in adults than primary brain tumors.*
- *In spite of complex treatment protocol the prognosis is poor.*
- *In case of unusual neurological symptoms and negative CT scan paraneoplastic origin should be considered.*

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Movement disorders (Disorders of the extrapyramidal system)

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Definition

Extrapyramidal system involves those centers and tracts (except for pyramidal tracts), which have an important role in the organizing of movements. The extrapyramidal system is responsible for controlling and modulating movements, and it ensures properly arranged, fluent and “gracile” moves. The extrapyramidal system has the following parts:

- a) cortical centers (located in every cerebral lobes),
- b) subcortical centers: caudate and putamen (the striatum is composed of caudate and putamen), pallidum, subthalamic nucleus (Luys), nucleus ruber, reticular formation, and cerebellum.

The damage of the extrapyramidal system causes different movement disorders.

Classification

The symptoms of extrapyramidal injuries can be divided into two main groups:

1. hypokinetic-hypertonic (rigid), and
2. hyperkinetic-hypotonic symptoms.

HYPOKINETIC-HYPERTONIC (RIGID) SYNDROMES

Parkinson’s disease, Parkinsonisms

- Primary or idiopathic form: *Parkinson’s disease*. It is the second most common progressive neurodegenerative disorder. Its prevalence is 1% at the age of 65, but by the age of 85 it reaches up to 4-5%. It occurs sporadically, but in 10% of the cases it is hereditary and attributed to known genetic factors (more than 16 chromosome mutation is known, which can be either autosome dominant or recessive).
- Secondary or symptomatic form: *Parkinson’s syndrome*. It can be caused by head injury (e.g. multiple commotions in box fighters), tumors damaging the nigrostriatal area, inflammation, stroke (ischemic or hemorrhagic), and intoxication (carbon-monoxide, side effects of neuroleptics).

In some neurodegenerative disorders the parkinsonian movements are dominant, but we can detect other characteristic symptoms too, which help the

diagnosis. These are called *Parkinson plus syndromes*, which involve the following disorders: multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration.

Etiology and symptoms

According to the classical theory Parkinson's disease is caused by the degeneration and dysfunction of substantia nigra and striatum. Lewy bodies (eosinophilic cytoplasmatic inclusions, that are composed of accumulated protein) appear in the cells of the affected regions. The symptoms are caused by the dopamine-acetylcholine imbalance, decreased dopamine levels and cholinergic excess.

According to the modern neuropathological theory (named after Braak in 2003) the symptoms are caused by the progressing dysfunction of the central nervous system. Firstly, the medulla oblongata (cranial nerve IX, dorsal motor nucleus) and the anterior olfactory nucleus are damaged; later the pontine tegmentum (raphe nuclei, locus ceruleus), the mesencephalon (compact part of the substantia nigra), the basal prosencephalon and mesocortex (enthorinal region, temporal mesial cortex, CA2) become injured; and finally the neocortex (advanced sensory association symptoms, prefrontal cortex) loses its function, too.

The main symptoms of Parkinson's disease are rigidity, tremor, hypo- or bradykinesia, and postural instability.

- *Rigidity*: Both the agonist and antagonist (flexors and extensors) muscles are affected, and the body and the extremities are in semiflexed position. During passive movements resistance develops ("lead-pipe" and "cogwheel" rigidity). Rigidity is often unilateral and asymmetrical, especially in early stages.
- *Tremor*: It is characterized by the repeated contraction of the agonist and antagonist muscles with the frequency of 6-8/min. It is usually maximal when the limb is in rest, but emotional distress may increase it too. The tremor decreases or disappears with voluntary movements and sleep. It is often unilateral and asymmetrical, especially in early stages.
- *Hypo- and bradykinesia*: The whole course of movement and walking becomes slower, the patient shuffles and has difficulty when changing the position or turning. Freezing may occur during the movements.
- Patients suffering from Parkinson's disease may have several additional symptoms, which can help the diagnosis. If the syndrome is suspected, we should ask directly if these symptoms are present. These additional symptoms are the followings: on-off phenomenon, pulsing symptoms, less expressive face, slow blinking, monotonous speech, micrographia, oily skin, sialorrhea, excessed sweating, smelling or tasting disturbances, orthostatic hypotension, gastrointestinal disorders (obstipation), depression and sleep disorders.

Parkinson plus disorders mentioned above often cannot be differentiated easily from Parkinson's disease. The medical history, complaints and the presence of characteristic symptoms can help the diagnosis.

The characteristic features of *multiple system atrophy* are: less asymmetrical parkinsonian symptoms, early falls, autonomic dysfunctions (orthostatic hypotension, impotence, incontinence, respiratory stridor), "dropped head", pyramidal signs, cerebellar symptoms, and poor response to levodopa.

The characteristic features of *progressive supranuclear palsy*: postural instability, early falls, axial rigidity, freezing, supranuclear gaze paresis (vertical downward gaze is affected dominantly), ocular apraxia, frontal symptoms (liberation signs, apathia, frontal dementia).

The symptoms and complications of the *Parkinsonian crisis* are the following: complete loss of moving ability, inability to swallow or speak, extreme rigidity, fever, circulatory insufficiency, decubital ulcers, pneumonia, deep vein thrombosis and pulmonary embolism. **The Parkinsonian crisis can be fatal!**

The treatment of Parkinson's disease

The modern treatment of Parkinson's diseases provides stable dopamine level in the central nervous system.

Medications

Substitution with levodopa

- L-DOPA+DOPA decarboxylase inhibitor (carbidopa, benserazide)
 - standard drugs with quick absorption and long lasting effect
 - duodenal infusion
- L-DOPA+DOPA decarboxylase inhibitor+COMT-inhibitor (levodopa+carbi-dopa+entacapone)

The administration of COMT inhibitors without L-DOPA is contraindicated!

L-DOPA should be administered at least 3 times daily, but the recommended dose should be divided into 4-5-6 portions.

Dopamine agonists

- Ergotamine type: e.g. bromocriptine (its use is not recommended due to its severe side effects, such as pericardial, retroperitoneal, pulmonary fibrosis, heart valve insufficiency).
- Non-ergotamines: pramipexole, ropirinole, rotigotine, apomorphine.

MAO-B inhibitors

- selegiline, rasagiline

Amantadine

- In form of infusion amantadine can save the patient's life in parkinsonian crisis.

Anticholinergics

- biperiden, metixene, procyclidine

The most common side effects of antiparkinsonian medications are dullness, drowsiness (sleep attacks may develop during the day), sleep disorders, nightmares, hallucinations, orthostatic hypotension, nausea, vomitus, obstipation and symmetrical edema on the legs, which does not respond to diuretics.

Patients should take care not to miss any drugs during the day (especially if L-DOPA should be administered 4-6 times a day). Protein intake should be limited. The intake of vitamin B₆ does not improve the bioavailability of L-DOPA. L-DOPA should be taken approximately 30-60 minutes before eating with liquid.

Surgical treatment

DBS: (deep brain stimulation) the most common target is the subthalamic nucleus.

Thalamotomy, pallidotomy. It can be used, if drugs are ineffective in the treatment of severe Parkinson's disease. These procedures can improve the quality of life in patients selected and examined carefully. The well-trained staff and adequate postoperative care are necessary.

Physiotherapy, psychotherapy

The symptoms of extrapyramidal diseases are aggravated by stress and depression. The psychological care is the essential part of the treatment. Patients often receive DVDs containing special exercises developed for patients suffering from Parkinson's disease, and can do exercises at home too. The help of a physiotherapist may be useful. Walking exercises can improve the postural instability. Nowadays the well-planned anti-parkinson therapy improves both the survival and quality of life of the patients.

Primarily, general practitioners should recognize the symptoms and send the patient to neurologists, or specialist practice. The detailed medical history and the recognition of the characteristic signs (slow movements, loss of expression, difficulty in turning, hand tremor, micrographia, and the other additional symptoms that are listed before) are essential in the diagnosis of Parkinson's disease and Parkinson's syndromes.

Specialists dealing with patients suffering from Parkinson's disease have more experience in the field of differential diagnosis and treatment than general physicians. Today, we have many efficient treatments with potential side effects, thus, a modern, well-chosen therapy is essential to the patients' quality of life. It is also important that general practitioners should not modify the patient's medicines prescribed by specialists. If it is necessary, they should consult with specialists.

Specialists provide the date of follow-up visits. These follow-up examinations may be more frequent while the diagnosis is confirmed and the appropriate medication is selected in order to control the symptoms of the disease. During this period patients may be required to visit specialists in every two weeks. Later, when the state of stabilisation has been reached, patients using the appropriate and effective medications should visit their doctors in every six months. There might be

exceptions: yearly follow-up visits are acceptable if the patient has severe difficulty in moving or he/she is totally confined to bed. Doctors should make this decision individually for every patient. According to the experiences patients suffering from Parkinson's diseases visit the specialist practice regularly, but general practitioners may help this by checking if the patient has been to follow-up visit in the last half year.

Parkinsonian crisis needs immediate admission to hospital, because it can be fatal. The ambulance should transfer these patients to neurological wards, or intensive care units, if available. In patients suffering from Parkinson's disease or MSA orthostatic hypotension may develop due to progression or adverse events. In this situation patients should be admitted to general internal medicine wards.

Psychosis often developing in elderly patients or in advanced disease is a severe complication, and usually it is the side effect of medication. Patients may experience acoustic or visual hallucinations, and auto- or heteroaggression. In this case patients should be admitted to psychiatric ward.

HYPERKINETIC-HYPOTONIC SYNDROMES

Etiology

These syndromes can be primary or idiopathic, if despite of the diagnostic methods the causative agent remains unknown. In these cases genetic disorders are suspected. The positive results of genetic examinations confirm the diagnosis, but negative results do not exclude it (the disease could have been caused by other mutations not tested in laboratory). In case of secondary or symptomatic syndromes imaging techniques (brain MRI is recommended) can reveal ischemic or hemorrhagic lesions, complications of trauma, or tumors in certain areas of the brain. Movement disorders can be caused by side effects and dysmetabolism too.

Specifications

The most important clinical symptoms, etiology, diagnostic tests, treatment.

A. Chorea

Characteristic symptoms: irregular, unexpected and fast movements especially in the distal parts of the extremities, but it may affect the muscles of the trunk, head or tongue. Emotional stress provokes the movements.

Anatomically, it is caused by the damage of the putamen and caudate nucleus (striatum).

Types:

- primary, genetic (Huntington's chorea, autosomal dominant);
- secondary (chorea minor or Sydenham's chorea): a reversible movement disorder induced by Streptococcus infection, which is often

associated with arthritis, rheumatic fever, and carditis. Chorea gravidarum: reversible movement disorder, which is a complication of pregnancy. Trauma, tumor, inflammation, ischemic, or hemorrhagic lesions might be present in the affected region.

Diagnosis: careful medical history, physical examination, brain MRI (atrophy of the striatal region, trauma, tumor, inflammation, ischemic, or hemorrhagic lesions), genetic test may confirm or exclude the diagnosis of Huntington's chorea (CAG-trinucleotide repeat analysis).

B. Ballism

Characteristic symptoms: intense, flinging motions in the proximal muscles of the extremities, and because of this the patient may fall.

Anatomically, it is caused by the damage of subthalamic nucleus.

Types:

- primary, idiopathic,
- secondary (trauma, tumor, inflammation, ischemic , or hemorrhagic lesions in the affected region).

Diagnosis: careful medical history, physical examination, brain MRI (atrophy of the subthalamic region, trauma, tumor, inflammation, ischemic, or hemorrhagic lesions).

C. Athetosis

Characteristic symptoms: involuntary convoluted, writhing movements of distal muscles of the extremities.

Anatomically, it is caused by the damage of striatum and pallidum.

Types:

- primary, idiopathic,
- secondary (trauma, tumor, inflammation, ischemic , or hemorrhagic lesions in the affected region).

Diagnosis: careful medical history, physical examination, brain MRI (atrophy in the region of striatum and pallidum, trauma, tumor, inflammation, ischemic, or hemorrhagic lesions).

The treatment of chorea, ballism and athetosis

These syndromes cannot be cured, but treated (except for chorea minor and chorea gravidarum). The treatment may ease the symptoms, and decrease the movement disorders. Huntington's chorea is a progressive, lethal condition, which is characterized by severe dementia too.

Medications

- dopamine agonists: tiapride
- tetrabenazine
- chlorpromazine
- haloperidol
- clonazepam
- amantadine

Physiotherapy, psychotherapy

Emotional stress or depression aggravates the symptoms of extrapyramidal diseases, thus, the appropriate psychiatric care is essential. The help of a physiotherapist may be useful.

D. Dystonia

Generalized types:

- primary or idiopathic: dystonia musculorum deformans (Oppenheim's dystonia), DOPA responsive dystonia.
- secondary or symptomatic: Wilson's disease (hepatolenticular degeneration) – disorder of copper metabolism; Hallervorden-Spatz's disease – disorders of iron metabolism; ischemic or toxic cerebral damage; tardive dyskinesia or dystonia – side effects of neuroleptics.

Among the diseases listed above Wilson's disease has practical significance due to its prevalence. **If an extrapyramidal movement disorder of unknown etiology develops in young patients, always investigate for Wilson's disease, the disorder of the copper metabolism.** Wilson's disease can be diagnosed (brain MRI, ophthalmologic examinations, the detection of copper and ceruloplasmin levels in the serum, liver enzymes, copper excretion with the urine) and treated with chelation therapy.

Focal types:

- blepharospasm, hemifacial spasm, oromandibular dystonia (Meige's syndrome);
- cervical dystonia (torticollis, antero-, latero-, and retrocollis); focal hand dystonia (also known as musician's or writer's cramp).

Focal dystonias can be the side effects of certain medicines: thiethylphenazine, metoclopramide, domperidone. **If general practitioners prescribe one of the medicines listed above, they should always consider their extrapyramidal side effects.** In case of dystonia the prescribed drug should be stopped, and ½-1 vial of diazepam i.v. should be administered slowly, which immediately eases the symptoms.

Diagnosis: careful medical history, physical examination, brain MRI (atrophy in the basal ganglia, trauma, tumor, inflammation, circulatory insufficiency, metal depositions in the affected area), MRA (abnormal vessel compression the brainstem – neurovascular compression – can cause blepharospasm or hemifacial spasm).

Genetic tests.

Laboratory examinations: ceruloplasmin and copper in the serum, copper excretion.

Ophthalmological examinations: Kayser-Fleischer's ring.

The treatment of dystonia

Medications

- L-DOPA (in L-dopa responsive cases),
- anticholinergics/antihistamines: trihexyphenidil, procyclidine,
- ethopropazine,
- baclofen,
- clonazepam,
- antiepileptics: carbamazepine, gabapentin, levetiracetam,
- agents reducing the dopamine levels: tetrabenazine, reserpine,
- dopamine agonists: tiapridal,
- chelation therapy: D-penicillamine in Wilson's disease,
- botulinum toxin – local intramuscular infiltration to the affected muscles in focal dystonias. Botulinum toxin inhibits the neuromuscular junction reversibly, thus, patients should be treated in every 3 months.

Surgical treatment

Unilateral or bilateral DBS (deep brain stimulation), the targets are the basal ganglia, subthalamic nucleus, thalamus or pallidum.

Thalamotomy, pallidotomy.

Physiotherapy, psychotherapy

Emotional stress or depression aggravates the symptoms of extrapyramidal diseases, thus, the appropriate psychiatric care is essential. The help of a physiotherapist may be useful.

E. Myoclonus

Characteristic symptoms: a brief, involuntary twitching or arrhythmic movement affecting the distal or axial muscles, or the muscles of the soft palate.

Anatomically, it is caused by cerebral or spinal lesions, or the damage of the so-called “myoclonus triangle”: nucleus ruber, dentate nucleus and inferior olive.

Types:

- primary, idiopathic,
- epileptic,
- secondary (damage of the central nervous system caused by ischemic, toxic or metabolic reasons, inflammation, tumor).

Diagnosis: careful case history, physical examination, brain and spinal MRI, EEG.

The treatment of myoclonus:

- clonazepam
- carbamazepine
- levetiracetam
- valproate
- piracetam

F. Tic

Characteristic symptoms: sudden, repetitive, non-rhythmic, stereotypic motor movements, or the stereotype repetition of vulgar words (Tourette syndrome). Tourette syndrome is defined by the presence of motor and vocal tics, and various symptoms lasting for more than a year. Its onset is below the age of 21.

Types:

- primary, idiopathic,
- secondary (trauma, tumor, inflammation or circulatory insufficiency in the region of the basal ganglia).

Diagnosis: careful medical history (psychiatric disorders are more common in these families, especially compulsive disorders), physical examination, brain MRI (atrophy in the region of the basal ganglia, trauma, tumor, inflammation, circulatory insufficiency).

The treatment of tic:

- dopamine receptor antagonists: haloperidol, risperidon,
- ziprasidone,
- α_2 agonists: clonidine,
- agents, decreasing monoamine levels: tetrabenazine,
- clonazepam,
- SSRIs: paroxetine, citalopram, venlafaxine, etc.

Physiotherapy, psychotherapy: Emotional stress or depression aggravates the symptoms of extrapyramidal diseases, thus, the appropriate psychiatric care is essential. The help of a physiotherapist may be useful.

If general practitioners diagnose the symptoms listed above, they should direct the patient to neurologists or specialist practices dealing with extrapyramidal disorders. The selection of the proper treatment can be very intriguing even for neurologists. **The therapeutic management of extrapyramidal movement disorders is the responsibility of the neurologists, thus, general practitioners should not make decisions about the patients' medication.** The most common side effects of these medications are dullness, drowsiness (sleep attacks may develop during the day), sleep disorders, nightmares, hallucinations, orthostatic hypotension, nausea, vomitus and obstipation. Local infiltration of botulinum toxin may cause temporary muscle weakness (ptosis, double vision, peripheral facial paresis, dysphagia), which eases spontaneously within 2 weeks.

Patients suffering from advanced Huntington's chorea may require immediate admission to hospital, if they become confused, anxious or aggressive because of having severe dementia. Patients with Tourette syndrome are likely to become psychotic and decompensated. In both cases psychiatric treatment is necessary.

Intense or permanent involuntary movements can cause cardiac insufficiency, especially in elderly patients or patients with cardiac history. These patients should be admitted to general internal medicine wards, or intensive care units.

Dystonias can be painful, as the joints can take positions, which differ from the physiological ones. These positions can last for minutes or can be permanent too.

Patients should be directed to specialist trained in extrapyramidal movement disorders immediately, because concerning the patients' quality of life the quick decisions on examinations, diagnosis and treatment are essential. If medicines are ineffective, DBS or surgery is recommended. If the treatment is delayed, painful contractures develop in the joints, which are almost impossible to be relaxed in this stage.

Parkinson's disease is the second most common neurodegenerative disorder. Nowadays, its prevalence is 200 000 in Hungary, which is a considerable number. The diagnosis of Parkinson's disease is an important task of general practitioners, and they should direct the patients to neurologists as well. The early and appropriate treatment improves the patients' lifespan and quality of life.

In case of hypotonic-hyperkinetic movement disorders the patient should be directed to neurologist, as the early and professional treatment can prevent the development of somatic and psychical impairment, e.g. in Wilson's disease.

Medicines used in the general practice may cause sudden, temporary movement disorders; therefore, these medicines should be prescribed with care.

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The most common types of dementia

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Definition

Conditions characterized by the deterioration of cognition are called dementias. According to the current DSM-IV, the diagnostic criteria of dementia are the following:

- The development of multiple cognitive deficits manifested by memory impairment, and
- one or more of the following cognitive disturbances are present: aphasia, apraxia, agnosia and disturbance in executive functioning; and
- these cognitive deficits cause significant impairment in everyday life (in social or occupational functioning).

It is important to emphasize that the loss of cognitive abilities represent a significant decline from a previous level of functioning, and the course is characterized by progressive cognitive impairment. Therefore, the congenital oligophrenia should not be classified as dementia, because the memory impairment itself does not fulfill the diagnostic criteria of dementias.

It is important that dementias should be differentiated from delirium. In case of delirium the symptoms develop suddenly, and both the awareness and the capacity of coherent thought fluctuate. The symptoms of delirium, which are often accompanied by autonomic signs, are usually reversible, if the causative agent (mostly exogenous) is ceased.

Dementia has many classifications, as in many cases it is difficult to define what is considered to be normal. Currently, the DSM-IV classification for dementias is generally accepted.

The classification of dementias

Many disorders can cause cognitive impairment. In *primary dementias* the cognitive impairment is the characteristic symptom of a cerebral degenerative disorder. In *secondary dementias* the cognitive impairment is secondary, and develops as the complication of a cerebral or an extracerebral disorder.

Dementias can be classified by other features, too. Considering the primarily affected brain regions, we differentiate *cortical* (e.g. Alzheimer, fronto-temporal), *subcortical* (dementia in Huntington's and Parkinson's diseases) and *mixed* (vascular dementia, Lewy body dementia) dementias. According to the outcome dementias can be *reversible* (e.g. dementias caused by subdural hematomas or tumors) or *irreversible* (every primary dementia). On the basis of their histological pattern, dementias can be classified as so-called *synucleinopathies* or *taupathies*. The severity of dementias can be assessed by using certain scales.

In the clinical practice we commonly use the following categories to define dementias: primary-secondary and reversible-irreversible. In many cases the primary goal is to find a detectable and potentially reversible cause in the background of the process.

Table 1
Reversible conditions, which may cause dementia

Vitamin B ₁₂ deficiency
Thiamin deficiency (Wernicke-Korsakoff syndrome)
Hepatic encephalopathy
Paralytic dementia (neuroleues)
Cerebral tumors
Subdural hematomas

Table 2
The most common primary dementias

Alzheimer's dementia
Lewy body dementia
Fronto-temporal dementia
Creutzfeldt-Jacob's disease

Epidemiology

Dementia is a common symptom. According to the available epidemiological data in the USA 4 million people are suffering from severe dementia, and 50-60% of these patients have Alzheimer's disease. The prevalence increases exponentially with age, from 6-7 percent of those aged 65, to 15-20 percent of those aged 75 and 25-50 percent of those aged 85. As for the life expectancy is increasing all over the world, the number of patients suffering from dementia will increase significantly as well. Considering the facts above 200 000 patients may suffer from dementia in Hungary.

The distribution of primary and secondary dementias is different in the scientific literature due to the inaccuracy of clinical data. According to some opinions the prevalence of dementia may vary with populations and countries. In 2001 more than 24 million people suffered from dementia in the world, and according to the expectations this number will be doubled in every 20 years. Therefore, in 2040 this number will reach up to 81 million. Considering the data of

the Western-European countries and the USA, the most common type of dementia is Alzheimer’s disease (35%). There is a significant overlap between the vascular dementia and Alzheimer’s disease; thus, the second most common type is the so-called “mixed” dementia showing the symptoms of both Alzheimer’s and vascular dementias (15%). The third is the Lewy body dementia; the fourth is the vascular type. The fifth most common type shows the symptoms of Alzheimer’s dementia and Lewy body dementia together (5%). The sixth type is the fronto-temporal dementia (formerly called as Pick’s disease), and the rest involves those diseases, where the dementia is secondary. Nowadays, every scientist shares that opinion, that Alzheimer’s disease is the most common type of dementia.

Table 3
The prevalence of dementias

Alzheimer’s disease	35%
Alzheimer’s disease AND Vascular dementia	15%
Alzheimer’s disease AND Lewy body dementia	5%
Lewy body dementia	10%
Vascular dementia	10%
Fronto-temporal dementia	5%
Dementias associated with movement disorders	6%
Dementias of toxic and metabolic origins	4%
Dementias associated with psychiatric disorders	4%
Dementias of infective origin	3%
Normal pressure hydrocephalus	2,5%
Other causes	<1%

Source: Cummings J.L.: *Dementia: A Clinical Approach*, 2003.

General symptoms

The symptoms of dementia are classified into three main groups. These symptoms usually occur together, but may vary according to the type and stage of dementia. The first group involves the cognitive symptoms, which usually initiate the disease, including memory loss, impairment of language ability (aphasia), loss of the ability to execute or carry out learned movements (apraxia), the loss of ability to recognize things (agnosia) and the disorders of executive functions carried out by the frontal lobe (such as providence and planning). The second group contains the so-called non-cognitive symptoms, such as mood disorders

(affectivity), personality and behavior changes (e.g. agitation, aggression, hallucinations, delusions). The third group of symptoms contains the extrapyramidal symptoms, impairment of walking and incontinence, which are late symptoms in primary dementias, and dominate in the secondary types. The dynamics of symptom development and their combination determine the diagnosis and the classification of dementias.

The general diagnostics of dementias

The appropriate medical history is essential. Though, it should be emphasized, that during the examination the presence of another person living in the same household or in close relationship with the patient is necessary to ensure the reliability of anamnestic data. Patients suffering from moderate and severe dementia are usually not aware of their disease (they often underestimate the severity of their symptoms), while patients suffering from depression usually overestimate their symptoms. It is important that the examination should be performed in calm circumstances (avoid phone rings) to decrease the patient anxiety.

After taking the medical history, general and neurological physical examinations are necessary including cognitive tests and tests on lobe functions.

Among the cognitive tests the Mini Mental State Examination (MMSE) is used widely due to its simplicity, relative shortness and good reproducibility. The conventional MMSE test has the maximal score of 30 points. A score of 23 to 15 suggests mild dementia, 14 to 10 suggests moderate dementia, and less than 10 indicates severe dementia. This test has an extended version, where the maximum score is 100 points, and scores below 85 points suggest dementia. The MMSE by itself is not eligible to set up the diagnosis of dementia.

The standardized clock-drawing test may be useful too (patients are asked to draw a clock face showing half past two). The criteria for scoring includes the integrity of clock face, the organization of numbers and the use of clock hands. This test primarily assesses the visual spatial organization, praxis and perceptual functions. There are many other tests, including DemTect, which are more sensitive in the assessment of cognitive deficit than the MMSE, so in doubtful cases they may help the diagnosis of dementia. According to the Hungarian guidelines, beside the MMSE the Hachinski scale should be assessed too, which helps to decide whether the patient has Alzheimer's disease, vascular or mixed type dementia. The Hachinski scale is based on the dynamics of symptoms and the presence of vascular risk factors.

The Alzheimer's Disease Assessment Scale - Cognition (ADAS-Cog) is one of the most common tests used in the assessment of Alzheimer's disease, which evaluates cognitive impairment. Besides the cognitive tests, the functions of the lobes should be assessed too (e.g. proverb interpretation, conception), including both the parietal (autotopagnosia – inability to recognize or correctly orient the parts of one's own body, counting, orientation in space, writing, reading, praxia, gnostic functions) and frontal functions (memory functions, aphasia tests).

Tests assessing the cognitive functions may be followed by tests on affectivity including geriatric depression scale and Hamilton depression scale (not mandatory, it should be assessed individually).

Based on the examinations and tests listed above, we may have orientation in the type of dementia, but in many cases we may have not. That is why beside the anamnesis and cognitive tests laboratory examinations are also essential (including sodium, potassium, creatinine, urea, glucose, AST, ALT, GGT, CK, LDH, hematology, ESR, CRP, sTSH, SeB₁₂ and VDRL). In certain cases lumbar puncture is required, especially in atypical cases, if the patient is young, immunosuppressed, or the infection of the central nervous system is suspected. In Alzheimer's disease the sensitivity of biological markers in the cerebrospinal fluid may reach up to 90%. This method may help the diagnosis, if available, but is not part of the routine examinations.

Beside the laboratory examinations imaging is also essential. Actually, every patient suffering from dementia should be assessed by MRI, but due to its limited availability and the long waiting period we have to content ourselves with CT in clinically unambiguous cases. In vascular dementias carotid Duplex should be performed to assess the state and risks. The EEG is an important additional examination, and it can be specific for certain diseases (e.g. Creutzfeldt-Jacob disease). SPECT may be required to verify the diagnosis and predict the outcome in those uncertain cases, where the diagnosis of dementia is probable due to the presence of mild symptoms, but cannot be confirmed. PET is more reliable than SPECT in this indication, especially, since amyloid deposits can be detected directly in the brain by using appropriate tracers. When this chapter is written, the National Health Insurance does not cover PET examinations in this indication in Hungary.

Among the functional imaging techniques fMRI is notable, but so far it is used only for experimental purposes.

Alzheimer's disease and related dementia

Alois Alzheimer described a case in Tübingen in 1911, which was named after him. During his work Alzheimer described those clinical symptoms and neuropathological findings that are considered to be the characteristics of Alzheimer's disease today (amyloid plaques, neurofibrillary tangles). Alzheimer's dementia is the most common type of dementias, and is responsible for 50-60% of the cases. Its prevalence increases with age.

The risk factors of Alzheimer's diseases are:

- age,
- the size of the brain,
- low educational level,
- impaired physical and mental activity in middle and older ages,
- head injury in the medical history, and
- vascular risk factors.

It is still unclear if they activate processes leading to the development of amyloid plaques or tau fibers directly, or they aggravate the symptoms of the disease secondary due to cerebrovascular pathological processes, and the parenchymal damage caused by vascular injury makes the symptoms of the clinically silent disease apparent.

The factors that may reduce the risk of Alzheimer's disease are:

- moderate alcohol consumption (250-500 ml wine of good quality daily),
- vitamin intake related to homocysteine metabolism (vitamin B₁₂, folate), antioxidants (vitamin C, E).

It is well known, that environmental factors may increase the risk of Alzheimer's dementia, but the disease has a significant genetic background too.

Alzheimer's dementia is a heterogeneous group of disease, which can be sporadic or familial.

The familial type of Alzheimer's dementia typically initiates before the age of 65 and is rare. The prevalence is under 0,1%, and only approximately 5-10% of the Alzheimer's dementia cases is genetically determined. The first case that was described was attributed to mutations in amyloid precursor protein (APP) gene located in the chromosome 21. This mutation involves only a few cases. Most of the familial cases are related to the mutations of presenilins 1 and 2.

The results of the genetic examinations showed that genetic variants of apolipoprotein E (Apo E) functioning as cholesterol transporter are also associated with an increased risk. The mechanism is still unclear, and there are contradictory results too, thus, the automatic screening of the patients is not recommended in the everyday practice.

Pathogenesis

Histologically, the Alzheimer's dementia is characterized by the presence of senile or amyloid plaques and neurofibrillary tangles. The neurons and their synapses degenerate, and their numbers are decreased. Initially the plaques and tangles are located in the medial structures of the temporal lobe and the basal cortical areas, but later they can appear in everywhere in the cortical areas. Many processes have been investigated in connection with the development of protein deposits, including amyloid beta aggregation and deposits, tau hyperphosphorylation, neurovascular dysfunction, inflammations, oxidative stress and mitochondrial dysfunction.

According to the central or amyloid cascade hypothesis accepted by many, the accumulation of amyloid beta (A β) proteins (containing 40 or 42 amino acids) derived from the degeneration of a transmembrane protein called amyloid precursor protein (APP) is responsible for the development of Alzheimer's disease, because these are the main component of the amyloid or senile plaques. Firstly, the production and clearance of A β become imbalanced, causing neurodegeneration, neuronal loss and dementia. The mechanism is still unclear.

According to our actual knowledge (2011), the development of amyloid plaques precedes the appearance of tau-positive helical tangles (neurofibrillary

tangles), though this is being challenged, and many other theories are published on the pathomechanism of Alzheimer's disease.

Some theories are based on the pathology of the hyperphosphorylated tau-proteins contributing to the stabilization of neural axons, and consider this as primary reason. According to other scientist Alzheimer's disease is a vascular disease, and the histological findings are caused by the general cerebral hypoperfusion. There are many scientific pro and contra arguments on this topic. The time and the success or failure of therapeutic attempts based mainly on the amyloid pathology will decide which theory is correct.

Clinical features

Alzheimer's dementia characterized by the gradual impairment of the episodic memory initiates insensibly and progresses slowly. Later the cortical lobe symptoms, aphasia, apraxia, and agnosia are accompanied by general cognitive impairment, incoherence of thoughts, altered judgment, and disorientation in time and space. These symptoms are associated with affective disorders (usually depression), delusions (often delusions of stealing) developed due to the impaired thinking processes, hallucinations, and the symptoms of complete psychosis. In the advance stage of the disease apathy and extrapyramidal symptoms including parkinsonism and incontinence dominate. Finally, the patient becomes bed-ridden, and dies from its complications (pneumonia, urinary sepsis, pulmonary embolism, etc.).

At first, the term Alzheimer's disease was used for those patients, who were pre-senile (below the age of 65) when the disease had started. Senile dementia was considered to have affected patients over the age of 65. Scientific examinations have suggested that the number and extent of plaques and neurofibrillary tangles are similar in both forms, thus, nowadays pre-senile and senile dementias are considered to be a homogenous entity and called as Alzheimer's disease.

In Alzheimer's disease the neurodegeneration starts 20-30 years before the development of the clinical symptoms. In this so-called preclinical phase the amount of plaques and tangles increases gradually, and as it reaches a threshold, the neurological and psychiatric symptoms appear. This phase is often indicated as the phase of mild cognitive impairment (MCI), in which it is the patient who reports his/her mild cognitive impairment. In this phase usually the short-term memory is disturbed, and the relatives and the cognitive tests confirm the patient's complaints. These symptoms do not affect the everyday life, and social functions. Etiologically, MCI is a heterogeneous condition, because it can initiate the prodromal phase of the Alzheimer's disease, but in other cases, if the symptoms does not aggravate, it can be the part of the normal aging, too. It can even initiate other types of dementias, such as vascular dementia.

The diagnosis of Alzheimer's dementia

The diagnosis of Alzheimer's dementia is based on the auto- and heteroanamnesis, general physical and neurological (psychiatric) examinations. In

the very early phase detailed neuropsychiatric examination might be needed to assess the loss of memory functions objectively. Laboratory tests and imaging techniques (CT, MRI) may help the diagnosis by excluding secondary dementias and vascular diseases. The NINCDS-ARDA criteria (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria) accepted generally is more than 20 years old (see Table 4). The criteria were based on the exclusion of secondary dementias.

Table 4
The NINCDS-ADRDA Alzheimer's Criteria

Unlikely AD:
Dementia with a sudden onset. Focal neurologic signs, or seizures or gait disturbance early in the course of the illness.
Possible AD:
Dementia syndrome. Atypical onset, presentation or progression. The etiology is unknown; but no co-morbid diseases capable of producing dementia are believed to be in the origin of it.
Probable AD:
Progressive and compound cognitive deficit. The onset is between the ages of 40 and 90 years. There must be an absence of other diseases capable of producing a dementia syndrome.
Definite AD:
The patient meets the criteria for probable Alzheimer's disease. Histopathologic evidence is present.

Currently, the diagnosis of Alzheimer's disease should be confirmed by neuropathological examinations, this is the gold standard. Histological findings listed above should be present.

Biomarkers of the central nervous system

The accuracy of biomarkers detected in the cerebrospinal fluid (T-tau, P-tau, A β 42) has been verified by many examinations, and confirmed in cases with neuropathological evidences. Currently, they are not part of the routine examinations, though they can increase its sensitivity and specificity.

The treatment of Alzheimer's disease

Symptomatic treatment

Acetylcholinesterase inhibitors

According to the cholinergic hypothesis of the Alzheimer's disease the degeneration of cholinergic neurons located in the nuclei of the basal prosencephalon causes the changes of the presynaptic cholinergic terminals in the hippocampus and neocortex, and consequent memory loss and cognitive impairment.

Therefore, this therapeutic approach tries to enhance the cholinergic transmission by inhibiting the acetylcholinesterase enzyme (which degrades the acetylcholine in the synaptic space) and increasing the amount of acetylcholine.

Currently there are three acetylcholinesterase inhibitors used: rivastigmine, galantamine and donepezil (when this chapter is written, galantamine is not available in Hungary). They have moderate effect on the cognitive functions in mild and moderate Alzheimer's disease. They can halt the disease progression, and delay the appearance of new, more severe symptoms with 2-3 years. There are no evidence for that these drugs would have significant differences in their effect.

They can be used safely, and usually have gastrointestinal side effects, such as nausea, vomitus, and loss of appetite.

Memantine (Ebixa)

Glutamate is the main excitatory transmitter of the brain. Normally, the glutamate and the N-methyl-D-aspartate (NMDA) receptors play an important role in learning and memory processes. In certain abnormal conditions (e.g. in Alzheimer's disease) the increased glutamate activity continuously activates the NMDA receptors, which may damage the normal neuronal function.

Memantine is a non-competitive NMDA receptor agonist, which protects the neurons against the glutamate-mediated excitation, without inhibiting the normal NMDA receptor function required for physiological cognitive abilities. According to the results of the available studies the use of memantine can be beneficial only in those cases, where the Alzheimer's disease is advanced. It does not affect the cognitive symptoms, but can improve the behavior disturbances, and the patients will require less antipsychotics.

The treatment of behavior disturbances

Behavior disturbances (aggression, psychomotor agitation, hallucinations, delusions) are common, especially in the late phase of dementias. These symptoms affect not just the patient, but the relatives too, and may require considerable expenses (e.g. in case of institutionalization, if the family members can not tolerate the patient).

Atypical antipsychotics having less significant extrapyramidal side effects are recommended to reduce the symptoms of psychosis and agitation (e.g. risperidon, olanzapine). Valproate and carbamazepine can be used alternatively, to stabilize the patient's mood or in case of maniac symptoms.

Drugs with potential effect

According to the results of epidemiological examinations, many drugs could be beneficial in the treatment of Alzheimer's disease. Although, when these drugs were studied in randomized and controlled circumstances, they were not proved to be effective. These drugs are the followings: NSAIDs, drugs lowering the cholesterol levels, estrogen-derivatives and antioxidants.

Lewy body dementia

Lewy body dementia (LBD) is the group of neurodegenerative disorders. It used to be considered to develop rarely, but nowadays, it is the second most common primary degenerative dementia in the elderly population. According to the autopsy results the 10-15% of dementia cases is LBD.

Apart from the information based on autopsy results, we do not have accurate epidemiological data on the prevalence of LBD, thus, we do not know which gender or years it is most common, and we are not familiar with its risk factors either.

*Clinical features***Cognitive symptoms**

Typically, recurrent confusion initiates the disease hiding progressing dementia. Lewy body dementia is characterized by cortical and subcortical cognitive deficits, disturbances of attention and disorientation in space. Patients with LBD perform the speech tests better than Alzheimer patients, but they have more severe impairment in the field of visuospatial perception.

The fluctuation of the cognitive performance is also diagnostic, which is related to the changes of arousal and attention.

Psychiatric symptoms

The psychiatric symptoms are common in Lewy body dementias. The visual hallucinations, delusions, apathy, and anxiety dominate the disease, usually from the beginning. These are the first symptoms that make the patients to visit their doctors, too.

Neurological symptoms

In 25-50% of the cases extrapyramidal symptoms (mainly parkinsonism) are present when the diagnosis of LBD is confirmed. In the major part of the cases (75%) these symptoms appear later, as the disease progresses. According to certain opinions Parkinson's disease without dementia, Parkinson's disease with dementia and the Lewy body dementia are spectrum disorders, and they are the different forms of the same disease.

Sleeping

The rapid eye movement (REM) sleep behavior disorder is a type of parasomias, which is common in LBD. The affected person is usually vivid and suffers from frightening nightmares, which is accompanied by simultaneous motor symptoms. The patient usually “plays” the dream: he/she can escapes or defends himself/herself actively while dreaming, or can even attack his/her partner sleeping next to him/her.

Vegetative disorders

Vegetative disorders including orthostatic hypotension and carotid sinus hyperesthesia, are more common in LBD, than in Alzheimer’s disease or healthy people of the same age. The patient often complains about dizziness or accidental falls, but complete syncope can develop as well. Urinary incontinence is common even in the early stage of LBD, and is a late symptom in Alzheimer’s disease.

Clinical diagnosis

The clinical diagnosis of LBD, similarly to that of the Alzheimer’s dementia, is based on the exclusion of other diseases. The guidelines and steps, which have been already discussed before, are necessary for the diagnosis. However, it is important to mention the main symptoms of the disease. If the following symptoms are present, always consider the diagnosis of LBD: fluctuating cognitive impairment, parkinsonism and recurrent visual hallucinations. The so-called suggestive symptoms are falls, depression, other types of hallucinations and REM sleep behavior disorders. Always consider the diagnosis of LBD if REM sleep behavior disorder is present, or sensitivity to neuroleptics administered for behavior disturbances develops (significant parkinsonism after the administration of low-dose neuroleptics).

The diagnosis of LBD is based on the diagnostic criteria listed in Table 5. The following diseases should be excluded: Alzheimer’s disease, vascular dementia, Parkinson’s disease with dementia, Parkinson plus syndromes (multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration), and Creutzfeldt-Jacob’s disease.

Table 5
The diagnostic criteria of possible and probable LBD.

Central feature (essential for a diagnosis of possible or probable LBD):	
–	Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function.
–	Prominent or persistent memory impairment may not necessarily occur in the early stages but usually is evident with progression.
–	Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.
Core features (two core features are sufficient for a diagnosis of probable LBD or one for possible LBD):	
–	Fluctuating cognition with pronounced variation in attention and alertness.
–	Recurrent visual hallucinations that typically are well formed and detailed.
–	Spontaneous features of parkinsonism.
Suggestive features:	
–	recurrent falls,
–	syncope,
–	temporary unconsciousness,
–	severe neuroleptic sensitivity,
–	organized delusions,
–	other types of hallucinations,
–	REM sleep behavior disorder (RBD),
–	depression.
Non-suggestive features:	
–	Stroke in the medical history.
–	Any other disease or cerebral damage, which is able to cause cognitive dysfunction.

Pathological diagnosis

The pathological criteria of LBD are based on the presence of ubiquitin-positive Lewy bodies in the central nervous system, and their classification into three groups.

Earlier, three types were differentiated according to the number and distribution of the Lewy bodies: brainstem-dominant, limbic and neocortical types. In the latest years α -synuclein immunohistochemistry has been proved to be more efficient in the detection of Lewy bodies than ubiquitin histochemistry, and has been able to identify other histological abnormalities, such as the presence of Lewy neuritis, which was unknown earlier.

The treatment of Lewy body dementia

The so-called non-medical treatment of the disease involving the management of help providing and care, and the establishment of appropriate caring environment is the same to that of in other types of dementia.

Though the evidences on medical treatment are limited, it is generally accepted, that antiparkinsonian medication should be administered in the lowest effective dose for treating extrapyramidal symptoms. The D2 receptor antagonists (especially the conventional antipsychotics) are contraindicated, because they can cause severe rigidity, which may double or triple the mortality rate. If needed, the use of atypical antipsychotics is recommended.

Univocal evidences prove that acetylcholinesterase inhibitors developed for the treatment of Alzheimer's disease are more efficient in the treatment of LBD, especially if the patient suffers from visual hallucinations.

Frontotemporal lobar degeneration Frontotemporal dementia complex

Pick's atrophy

The frontotemporal lobar degeneration (FTLD) develops more rarely than Alzheimer's disease or Lewy body dementia, though it takes considerable amount of degenerative dementias. According to autopsy results 5-7% of dementias is FTLD, but it can reach up to 8-17% in patients with dementia below the age of 70. It has the same prevalence in men and women. In 1892 Arnold Pick described a type of dementia with circumscribed lobular atrophy and aphasia, and the disease was named after him (Pick's atrophy). For many years dementias with prominent frontal lobe signs and personality changes was simply called as Pick's disease. In the latest years our knowledge on these degenerative diseases has been completed with many clinical, pathological and genetic data.

Terminology

The scientific literature of FTLD is rather difficult, because the authors use different terms for the same clinical and pathological entities. Additionally, clinical features not tested regularly during the routine examinations are required to understand these articles (apraxia, agnosia, behavior, etc.). Fortunately, the Neary criteria summarize these opinions and emphasize four clinical syndromes according to the involvement of the frontal and temporal lobes, the dominant and subdominant hemispheres, and the clinical features:

1. Frontal lobe dementia – the behavioral symptoms dominate, the frontal or temporal lobe of the dominant hemisphere is affected.

2. Progressive motor aphasia – the deterioration of language function (expressive aphasia) dominates, the frontal lobe of the dominant hemisphere is affected.
3. Progressive sensory aphasia (also called as semantic dementia) – the ability to comprehend words is disturbed, the temporal lobe of the dominant hemisphere is affected.
4. Prosopagnosia – the disorder of face recognition dominates (sometimes the recognition of objects is also disturbed), the temporal lobe of the subdominant hemisphere is affected.

Every syndrome listed above is classified as frontotemporal lobar degeneration. The most common type is the frontal lobe dementia.

Clinical features

In the clinical practice the following areas are affected: behavior, cognitive functions, sensory aphasia, expressive aphasia and neurological physical signs.

Behavior changes

The abnormal changes of behavior are a characteristic symptom of FTLT. This form of dementia can be differentiated well from Alzheimer's diseases and vascular dementia due to the change of emotional life and the absence of disease awareness and interest. The basic emotional reactions including sadness, sympathy and empathy are absent in these patients. The disease is characterized by repetitive, stereotype behaviors (unused movements, perseveration and repetition of a particular response, such as a phrase, or sentence, or complex behavior pattern). The eating habits are also changed. Some patients may addict to certain foods, others become gluttonous or can even take up odd eating habits, which was unlikely to them. Detailed examination may reveal abnormal response to sensory stimuli, e.g. pain.

Patients may be hyperactive or socially unscrupulous, idiots, extremely apathetic, indolent or emotionally colorless.

Cognitive changes

The disturbances of the executive functions are common. The planning, judgment, solution of problems, organization skills, attention, abstract thinking and mental flexibility are significantly impaired.

The visual perception, orientation in space and memory are preserved, which may help to differentiate the disease from Alzheimer's dementia, especially in the advanced stages.

When performing the cognitive tests, the patients are usually inattentive and impulsive (they often response without thinking), and often give the same answers for the questions.

Patients suffering from FTLT are unable to recognize emotions expressed on the face, or communicated by voice.

Speech changes

The thinking is concrete, and the verbal stereotypes, echolalia and perseverations are common. In case of slowly progressing motor aphasia, the

paraphasia, anomia and agrammatism are common symptoms, and often accompanied by stuttering, deterioration in the repetition of words, alexia, agraphia, and in advanced stage, mutism. Progressive sensory aphasia (semantic aphasia) is characterized by slowly worsening fluent speech, that lacks meaning, and impaired auditory comprehension. In those cases where the subdominant hemispherium is affected at the early phase of the disease, dys- or aprosodia can develop. (Prosody means melody of language. More specifically, prosody refers to the pitch, volume, rate, and tempo of speech). In these cases the speech becomes monoton, colorless or robotic.

Physical findings

In early phases neurological signs are absent. As the disease progresses, the symptoms of frontal degeneration appear (liberation signs), later rigidity develops. In some patients having motoneuron disease focal muscular atrophy and fasciculation might be present.

Imaging techniques

In early phase the conventional CT and MRI do not reveal any abnormalities, but they are important to exclude silent frontal space-occupying processes. In advanced stages the asymmetrical atrophy of the frontal and/or temporal lobes is usually significant, but its extent often does not correlate with the clinical severity of the disease. Functional imaging (SPECT, PET) may help the diagnosis in the early stages.

Pathological background

FTLD is characterized by the atrophy of the prefrontal and anterior temporal cortical areas. The localization of atrophy usually correlates with the clinical symptoms. The routine histology is usually poor: microvacuolation or rarely transcortical gliosis might be present in the outer cortical layers due to the loss of neurons.

Four types can be differentiated by immunohistochemistry:

1. Microvacuolation without neuronal inclusions.
2. Microvacuolation with ubiquitinated rounded intraneuronal inclusions and dystrophic neurites within the second layer of frontal and temporal neocortex and hippocampal dentate gyrus cells.
3. Transcortical gliosis with tau-reactive rounded intraneuronal inclusions (Pick's bodies) and swollen achromatic neurons (Pick's cells).
4. Microvacuolation and taupositive neurofibrillary tangles or Pick-like bodies in neurons, and sometimes tangles in glial cells of the cerebral cortical white matter. This is associated with familial FTLD because of mutations in the tau gene.

Unfortunately, clinical features cannot predict the histological findings. Every histological type can be associated with every clinical symptoms and the other way around.

Genetics

According to our present knowledge less than 10% of the FTLT is familial. In some of the familial FTLT cases the gene of the tau-protein located in the chromosome 21 is damaged. So far more than 35 different mutations of the tau-gene have been verified, in approximately 100 families. Genetic-clinical correlations were not detected in any of the tau-mutations. They are likely to be the part of a neurodegenerative cascade resulting in impaired microtubule formation and disturbed axonal transports.

Therapy

There are no specific pharmacological therapies approved for use in any of the FTD syndromes. The efficiency of acetylcholine esterase inhibitors is not proven. Behavior disturbances are treated with neuroleptics, antidepressants, and antiepileptics, while rigidity is treated with dopamine agonists. According to the recommendations the use of SSRIs is beneficial in the treatment of behavior disturbances, even if the patient does not suffer from depression.

The decision on driving licence should be made in the early phase of the disease due to the patient's impaired judgment. An expert speech therapist may help to preserve the ability of speech and to develop alternative strategies for communication.

Vascular dementia

Vascular dementia is a complex neuropsychiatric disorder with changes in behavior and cognitive functions, developed due to cerebral ischemia or hemorrhage. The course of vascular dementia is progressive, typically fluctuating. Physical examination usually reveals focal neurological signs, but imaging techniques help the diagnosis. Cerebrovascular disorders are common in elderly ages, and the abnormalities caused by ischemia or hemorrhage are often combined with the pathological abnormalities of other neurodegenerative disorders, such as Alzheimer's disease, frontotemporal lobar degeneration, Lewy body dementia or Parkinson's disease. The senile cognitive impairment is often caused by vascular dementia, which is responsible for the 15-50% of dementia cases according to clinical studies. The risk factors of stroke and vascular dementia are the same.

There are many known diagnostic criteria for the diagnosis of vascular dementia, but most commonly the NINDS – AIREN criteria are used.

The NINDS – AIREN criteria introduced in 1993 mainly assess the presence of three criteria including the presence of neurological findings by physical examination, the evidence of relevant cardiovascular disease by brain imaging, or

the presence of close relationship between the development of stroke and onset of dementia (less than 3 months). This theory has high specificity but low sensitivity. According to the DSM-IV criteria the dementia is not necessarily correlates with the stroke in time, but due to this fact, the number of patients with vascular dementia is generally overestimated.

Table 6
NINDS – AIREN criteria for the diagnosis of vascular dementia

Probable vascular dementia	
1.	Dementia manifested by impairment of memory and of two or more cognitive domains.
2.	Cerebrovascular disease, defined by – the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria. – evidence of relevant CVD by brain imaging (CT or MRI) including multiple large vessel infarcts or a single strategically placed infarct, as well as multiple basal ganglia and white matter lacunes, or extensive periventricular white matter lesions, or combinations thereof.
3.	A relationship between the above two disorders, manifested or inferred by the presence of one or more of the following: – onset of dementia within 3 months following a recognized stroke; – abrupt deterioration in cognitive functions; or – fluctuating, stepwise progression of cognitive deficits.
4.	Clinical features consistent with the diagnosis of probable vascular dementia include the following: – Early presence of gait disturbance, history of unsteadiness and frequent, unprovoked falls; early urinary incontinence; pseudobulbar palsy; and personality and mood changes.
Possible vascular dementia	
1.	dementia with focal neurologic signs in patients in whom brain imaging studies to confirm definite CVD are missing;
2.	dementia with focal neurologic signs in the absence of clear temporal relationship between dementia and stroke;
3.	dementia with focal neurologic signs in patients with subtle onset and variable course (plateau or improvement) of cognitive deficits.

By reviewing the diagnostic criteria, three aspects can be emphasized and applied in the everyday practice to diagnose vascular dementia:

1. A relationship between the development of stroke and onset of dementia (within 3 months).
2. Bilateral infarcts affecting the frontal, temporal or parietal cortical areas, or infarcts affecting the basal ganglia or thalamus.
3. Neurological signs detected by physical examinations referring to the symptoms of former strokes.

Another important fact should be emphasized additionally to that of listed above: sometimes it is difficult to decide whether the lacunar lesions or the extended lesions of the white matter are related to dementia or not; if their numbers or extent reach that limit, which above they are considered to be responsible for cognitive impairment.

Vascular dementia often has sudden onset and fluctuating course. Stroke is often reported in the medical history, and focal neurological signs are also present. If the patient reaches seven or more point on the Hachinski-scale, the diagnosis is unambiguous, but it should be confirmed by imaging techniques. Stepped progression is also characteristic for vascular dementia.

In some cases of dementia caused by cortical or large subcortical infarcts, the deficit of cognitive functions does not affect homogeneously the whole intellectual performance, which helps to differentiate it from Alzheimer's disease.

Imaging techniques

Imaging techniques are essential for the diagnosis of vascular dementia. If imaging is not performed, the diagnosis of vascular dementia cannot be confirmed. Among the available techniques MRI is the most effective, and more sensitive than CT in the detection of small ischemic lesions or bleedings (see the relevant chapter).

Pathology

We do not discuss the cerebrovascular pathological abnormalities being responsible for the development of vascular dementia. See the relevant chapter for more information on this. The abnormalities cover the whole spectrum of stroke etiology.

Therapy

The medication of vascular dementias involves more dimensions. The appropriate method for stroke prevention should be chosen for these patients, and the risk factors and complications should be treated too, including impaired mobility and functional deficits caused by stroke. The first three factors do not differ from that of applied in patients with dementia. The treatment of apathia, depression, anxiety, agitation and psychosis is also the same. Studies on large

number of patients have not proved the efficacy of nootropics, vinpocetin, ginkgo-derivatives or nicergoline administered for cognitive disorders yet. They may have beneficial effect in some cases. It is not surprising that acetylcholine esterase inhibitors developed originally for the treatment of Alzheimer's disease are as effective in vascular dementia just as in patients with clinically diagnosed Alzheimer's dementia. This could be resulted by the combined pathology represented in most of the patients.

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Traumas of the central nervous system

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Head injuries

The major causes of traumatic head injuries are traffic accidents, work and home accidents, sports injuries, and violent acts. Each case must be considered potentially as polytrauma (chest and abdominal injuries, fractures of large bones, internal bleedings, etc.).

Pathomechanism

Primary lesions: lesions developed at the moment of trauma by the direct injury of the brain (hit, shot, depressed skull fractures), vascular lesions, diffuse axonal injury. Secondary lesions are caused by extracerebral (shock, respiratory insufficiency) and intracerebral (intracranial bleedings, brain edema, increased intracranial pressure) reasons.

Hospitalisation

In case of head injury – even in asymptomatic cases – the patient must be transferred immediately to neurotraumatology ward. If it is not available, depending on the type of the injury and symptoms, the patient must be transferred to traumatology, neurology or neurosurgery wards.

Diagnostic imaging

Native cranial CT and bone window CT are preferred. If the CT is performed with bone window, skull X-ray is not required. If brain CT is not available native skull X-ray is recommended, although it has limited diagnostic value, because only depressed fractures (fracture of the bone, where the fragment is dislocated inwards) or basal skull fractures can be seen by this method effectively. If the fracture of the posterior fossa is suspected bi-directional X-ray examination should be combined with an additional third direction showing the occipital region. In case of skull fracture bi-directional X-ray of the cervical spine is required too. In polytrauma further imaging examinations are recommended: chest X-ray, abdominal and pelvic ultrasound, etc. (See further details in the diagnostic chapter).

Skull fractures

Definition

The fractures of skull bones can be open or closed. The term "open skull fracture" is strictly used when the continuity of the skin is interrupted as well. Basal skull fractures with CSF (cerebrospinal fluid) leakage due to the tear of dura are also called open skull fractures.

Typical forms

1. Depressed fractures: Neurosurgical operation is needed if they are open or the degree of depression is greater than the thickness of the skull. If the degree of depression is less than the thickness of the skull, but air can be seen intracranially (dural tear), it also requires urgent operation. Skull fracture lines crossing the middle meningeal artery can cause epidural hematomas, especially in the temporal region (see details below).

2. Basal skull fractures: usually they are connected with the fractures of calvaria.

a.) basal skull fractures in the anterior fossa can result in raccoon or panda bear hematoma, CSF rhinorrhea, and smelling disturbances (due to the tear of the fila olfactoria);

b.) basal skull fractures in the middle fossa or fractures of the pyramid may result in CSF otorrhea, ear hemorrhage, mastoid ecchymosis (Battle's sign), hemotympanum, peripheral facial palsy, and deafness. Rarely, the pituitary gland is damaged too, causing hypopituitarism as a late complication. Carotid-cavernous fistula (between the internal carotid artery and the cavernous sinus) is also a rare complication. Symptoms: pulsating exophthalmus, chemosis, pain, ophthalmoplegia. Murmur can be heard over the eye-socket. The venous stasis causes retinal ischemia, which can lead to severe vision loss. It can be detected by angiography and requires immediate surgical intervention.

c.) basal skull fractures in the posterior fossa cause blood and CSF leakage in the throat.

◀ Liquorrhea can be detected by using radio-labelled albumin. The chronic liquorrhea increases the risk of meningitis therefore urgent surgical intervention is indicated. The risk of infections is high in every open head injury; therefore, antibiotics should be administered!

Cerebral commotion

Definition

Reversible injury caused by blunt force impact. It is mainly characterized by usually short period of unconsciousness, temporary loss of memory and the absence

of focal neurological signs. Loss of consciousness develops immediately after the head trauma, and lasts for a few minutes or rarely for 1-2 hours. Heteroanamnesis is very important in defining the exact duration. Amnesia may relate to the time of the accident (congrade), to the period before the accident (retrograde), or to the period after the accident (anterograde).

Symptoms

Nausea, vomitus, dizziness, nystagmus, headache, orthostatic hypotension. **There is no pathological sign on the cranial CT.** The post-commotional syndrome can be its late complication: headache, dizziness, decreased daily activity, irritability, and depressive mood.

Treatment

4-5 days of bed rest and step-by-step mobilisation. If post-commotional symptoms develop, symptomatic treatment is needed. The prognosis is good, the patient can start to work again no later than 4 weeks after the accident.

Cerebral contusion

Definition

Skull injury caused by blunt force impact with destruction of the superficial brain tissue and focal neurological signs. Usually there is blood in the CSF. In contrast to the cerebral commotion there is always definitive brain lesion visualized in cranial CT.

Localisation

The presence of neurological symptoms depends on the localisation of the cerebral injury. The most common locations are the frontal and temporal regions. If the traumatic impact is associated with intense acceleration, the brain suffers direct damage on the side of the force („coup” contusion), and the contralateral side („contrecoup” contusion) too, due to the inertia (the brain collide to the opposite side of the skull), which causes cortical damage mainly.

Symptoms

Cerebral contusion is not always associated with unconsciousness. Depending on their localisation the focal neurological signs can be mild (visual field defects, central facial or hypoglossal palsies, latent or mild hemiparesis). In other cases severe hemi- or tetraparesis, aphasia develops partly due to the large edema.

Focal or generalised epileptic seizures are frequent, and sometimes they can

be the first alarming signs. Loss of consciousness, delirium and traumatic Korsakoff's psychosis may occur also.

The most severe form of cerebral contusion is brainstem contusion developed due to a great blunt force trauma of the cranio-cervical region. In this case the mesencephalon and pons are affected, which is usually fatal: coma and decerebrate rigidity develop quickly, whereas the reticular formation being responsible for the alertness is damaged directly.

Cerebral contusion may be associated with parenchymal bleeding. **Note:** only 80 % of the hemorrhages can be seen in the first 48 hours on cranial CT scans, and the further 20 % develop between the second and sixth day after the trauma (*delayed traumatic cerebral hemorrhage, DTCH*).

Gradual losing of alertness is observed when the size of the edema or the hemorrhage provoked by the contusion increases. If the symptoms are getting worse, the cranial CT examination should be repeated.

Treatment

The treatment includes careful observation, bed rest and dehydration in severe cases. In case of space-occupying parenchymal hemorrhages in the posterior fossa with hydrocephalus and rapidly developing loss of consciousness urgent neurosurgical operation is indicated. Conservative treatment is recommended if the patient is awake, there are no signs of brainstem involvement and in case of cerebellar hemorrhage, its diameter is smaller than 3 cm. Urgent operation is needed if deteriorating mental status and progressive symptoms are detected, even if the diameter of cerebellar bleeding is smaller than 3 cms. When hydrocephalus develops, endoscopic ventriculostomy of the third ventricle should be performed. If this option is not available, an external ventricular drain should be inserted.

Despite of a successful surgery, severe symptoms may remain in cases with the damage of the brainstem or particularly important cortical areas. Regardless of the severity of the contusion epilepsy and dementia can be the late complications.

Subdural hematoma

Definition

The venous blood detected between the dura mater and the arachnoid mater originates from the tear of bridging veins, and leads to the compression of the brain parenchyma. It occurs in the 10-15 % of head injuries. On cranial CT scans, hypodense (darker than the brain parenchyma), isodense (same density) or hyperdense (lighter than the brain parenchyma) lesions can be seen depending on how much time has passed since the onset.

Forms

Acute: the symptoms develop within 72 hours after the injury. Cranial CT shows a hyperdense, and often crescent-shaped lesion around the convexities. In case of quickly increasing mass effect, rapidly developing unconsciousness is the leading symptom. In addition to the focal neurological symptoms (anisocoria, hemi- or tetraparesis, pyramidal signs), epileptic seizures, and the symptoms of the increased intracranial pressure are characteristic too.

Subacute: the symptoms appear 3 to 15 days after the trauma. On cranial CT scans a slightly hyperdense or isodense lesion is shown. Increased intracranial pressure is the leading symptom.

Chronic: diagnosed on the 20th day or subsequently. It is more frequent in elderly patients or patients suffering from epilepsy or chronic alcoholism, or taking anticoagulants. It is often caused by relatively minor trauma. Approximately half of the cases of head injuries cannot be found in the anamnesis. As the degradation and absorption of the blood begin, the hematoma gradually builds over a xanthochromic hygroma. CT scan shows a hypodense lesion around the convexities. The symptoms are often trivial: fatigue, mild dizziness, headache, discrete and slowly progressing focal neurological signs (cranial nerve symptoms, latent or mild hemiparesis, pyramidal signs), memory loss, psychomotor slowness.

Treatment

In case of acute and subacute subdural hematoma immediate surgical evacuation is recommended. The mortality rate of acute hematomas is about 40-50 %, even if craniotomy was performed in time.

For chronic subdural hematoma surgical intervention is suggested, but depending on the patient's general condition the operation can be elective. The patient should be observed carefully.

Epidural hematoma

Definition

Arterial hematoma originating from the traumatic tear of the branches of the middle meningeal artery between the skull and the dura mater can quickly cause mass effect by compressing the surrounding brain parenchyma. Rarely, it can be caused by the damage of the sinuses. The chronic epidural hematoma is a special form, originating from the slow leakage of the diploid blood vessels.

Localisation

Most commonly it develops in the temporal region. On cranial CT scans a typical biconvex (lenticular), sharp-edged, and **hyperdense** lesion is detected.

Symptoms

Rapidly developing unconsciousness, anisocoria, severe hemiparesis, pyramidal signs and symptoms of acute increased intracranial pressure develop. The lucid interval (after a sudden loss of consciousness the patient becomes alert and then loses his/her alertness again), which was previously thought to be a characteristic sign, occurs only in 10 % of the cases.

Treatment

Immediate surgery is recommended. If the operation is performed in time and there is no significant brain injury, the prognosis is good.

Traumatic subarachnoid hemorrhage

Definition

It is a bleeding in the subarachnoid space after head injuries. Rarely it can be isolated, but usually it is associated with other head injuries mentioned above. The therapy is primarily determined by the treatment aspects of the concomitant brain damage.

General aspects of management for patients with head trauma

On the spot treatment

Detailed case history and documentation should include the following: the circumstances of the accident, external injuries, accompanying injuries, loss of consciousness, etc. The patient's general condition and the changes in the **level of consciousness** must be recorded in every minute in the first period.

The prophylaxis of hypoxia and hypotension can prevent secondary damages. Free airways should be ensured. If the patient has the score of 8 on the Glasgow Coma Scale, on-site intubation and respiratory support is required. Resuscitation may be needed (A: airway; B: breathing; C: circulation). In case of shock, use intravenous infusion of isotonic and colloidal solutions. Our goal is to keep the mean arterial blood pressure over 70 mmHg. Sedation and analgesia may be needed too. In case of imminent herniation, dehydration and hyperventilation are important.

Institutional care

Head injuries require intensive care and monitoring (ECG, BP, heart rate, body temperature, blood gas parameters, the measurement of intracranial pressure, laboratory examinations).

Airway: always assume that the stomach is filled, therefore vomiting and aspiration can occur at any time.

Monitoring of neurological status: the size and light reaction of the pupils, brainstem reflexes (corneal, vestibulo-ocular, cough reflex, etc.), responses to painful stimuli. Glasgow Coma Scale: score is 13-15 in mild, 9-12 in moderate, 3-8 in severe cases.

Control the fluid and electrolyte balance and glucose metabolism. Support the adequate calorie intake by using parenteral nutrition. Avoid hypovolemia, hyperglycemia, and hyperthermia. According to recent studies, mild hypothermia can be beneficial.

Analgesia and sedation.

Prevention of complications: pneumonia, urinary tract infections, deep vein thrombosis, pulmonary embolism, and decubital ulcers.

Treatment of the increased intracranial pressure (see details below).

Increased intracranial pressure

Definition

The volume of the brain parenchyma and/or the cerebrospinal fluid increases disproportionately in relation to the available intracranial space. According to the Monroe-Kellie's hypothesis, the skull is a nearly enclosed area and the volume of one component (brain/blood/CSF) can only grow at the expense of the other two. In case of head injuries associated with space-occupying lesion (hematoma, edema) the intracranial pressure usually increases rapidly. It deteriorates the blood flow by reducing the perfusion pressure in the brain, and can cause brainstem or other herniation due to its mass effect.

Cerebral perfusion pressure = mean arterial blood pressure - intracranial pressure.

Symptoms

The early symptoms are usually non-specific: headache, nausea, vomiting, papillary edema, dizziness, and ataxia. Bilateral and diffuse damage of the cerebral hemisphere causes decorticate posture: flexion of the arms, wrists, fingers, together with the extension of the lower extremities. The signs of brainstem herniation are rapidly developing unconsciousness, nuchal rigidity, pupillary abnormalities, decerebrate rigidity (arms in extension and adduction, forearms in pronation, wrist and fingers in flexion, lower limbs in extension), increased blood pressure, decreasing heart rate, alteration in breathing (Cheyne-Stokes). Uncal herniation occurs in case of unilateral supratentorial mass lesion. Its typical symptom is the ipsilateral oculomotor paralysis (miosis, later mydriasis, ptosis, absence of light reactions, the eye turns laterally and somewhat inferiorly). If the pyramidal tract is

injured, contralateral hemiparesis develops (rarely it can be ipsilateral due to the compression of the contralateral cerebral peduncle!).

The most important symptoms is the **loss of consciousness**, so if it is possible, we should avoid administering drugs that affect alertness.

Intracranial pressure (ICP) monitoring

The monitoring of ICP can be epidural or intraventricular. We can control the effectiveness of the therapy by performing CT imaging or by measuring the intracranial pressure. The ICP monitoring often indicates the deterioration of the patient's condition earlier, than the clinical picture does it. The prognosis is extremely poor, if the intracranial pressure is greater than 40 mmHg for a long time period (or if the difference between the mean arterial blood pressure and the intracranial pressure is less than 40 mmHg permanently). If the intracranial pressure is less than 20 mmHg, the prognosis is usually good. TCD (transcranial Doppler) may also be suitable for monitoring the pressure. If the intracranial pressure increases with 10 mmHg, the pulsating index of TCD rises with 20-50 %.

Therapy

Intubation and careful hyperventilation are recommended, because overventilation can cause hypocapnia, which depresses the brainstem respiratory activity.

Dehydration with mannitol or sorbitol (if the ICP is increased by trauma, glycerin is not recommended) is suggested. In case of therapy resistance administration of sodium chloride solution can be useful.

Stabilization of the systolic blood pressure around 160 mmHg with volume expansion (use dopamine if necessary).

The head and the upper body should be elevated to aid the venous outflow.

The level of blood $p\text{CO}_2$ should be kept around 28-35 mmHg.

The prognosis of herniation

Despite of the operation half of the patients with brainstem herniation die. If neither of the pupils reacts to light, the mortality rate is up to 90%.

If the patient survives the critical period, the prognosis depends on the damage of the ponto-mesencephalic midline structures and the reticular formation. The prognosis of traumatic brain hemorrhages and the epidural hemorrhages is usually poorer than the outcome of subdural hematomas.

Brain death

Definition

Brain death is diagnosed if every function of the central nervous system is completely and irreversibly lost, cranially from the foramen magnum.

Symptoms

1. Coma, lasting at least six hours
2. Dilated and fixed pupils.
3. Absent cough reflex while stimulating the trachea by suction or moving the intratracheal tube.
4. The complete absence of spontaneous breathing. Positive apnea test is required: the patient is ventilated with 100% oxygen for 10 minutes to ensure tissue oxygenation. During the test an endotracheal catheter is inserted to provide pure oxygen in order to prevent tissue hypoxia. The ventilation is discontinued for approximately 5-10 minutes and we check the presence of spontaneous breathing continuously and the arterial $p\text{CO}_2$ level in every 2-3 minutes. If the **arterial $p\text{CO}_2$ is 60 mmHg** and the spontaneous breathing is still absent, the respiratory system cannot be stimulated. After establishing the absence of spontaneous breathing the mechanical ventilation must be continued if we plan organ transplantation.
5. Absent brainstem reflexes
 - a) Absent corneal reflex;
 - b) No movement or increasing heart rate to painful trigeminal stimuli;
 - c) Missing vestibular-ocular reflex evoked by caloric stimulation. During the examination 30-40 ml of icy water is injected slowly into the external ear canal. After a two-minute waiting period, conjugated deviation and nystagmus towards the direction of the tested ear appear normally. We can also use Chlorethyl instead of ice water.
 - d) Doll's eye phenomenon: while the patient's head is turned suddenly, in healthy individuals the eyeballs move to the opposite direction to compensate. In severe brainstem damage the compensatory movements are missing and the eyes move together with the head (= doll's eye - phenomenon). Because of confusing nature of this term, the preferred definition is that oculocephalic reflex is present or absent.
 - e) Absent coughing reflex.
6. Hypotonic muscles.
7. No response to noxious stimuli.
8. Polyuria develops due to diabetes insipidus.
9. Absence of the circadian rhythm of body temperature.
10. The blood pressure becomes unstable.

Symptoms that make the diagnosis uncertain

1. Spinal reflexes, such as complex limb movements, are present, while the Babinski's sign is evoked.
2. Soft movements of the intratracheal tube, which are synchronous with the heart rate, refer to breathing.
3. During the apnea test the $p\text{CO}_2$ does not rise to the expected level, although there is no spontaneous breathing. This can be caused by metabolic acidosis and the apnea test needs to be repeated after administration of bicarbonate.
4. Pupillary constriction caused by fluid loss.
5. False positive atropine test: if the patient receives dopamine at the same time, relative tachycardia may be observed. Administration of atropine without dopamine can help the diagnosis.
6. EMG artifacts caused by spontaneous muscle activity on the isoelectric EEG due to denervation.
7. It is necessary to exclude the temporary absence of brain functions:
 - medication (intoxication by sedative drugs affecting consciousness; relaxation),
 - shock,
 - metabolic coma should be excluded: laboratory parameters should be in the normal ranges, or close to that (glucose, ions, urea, creatinine),
 - hypothermia,
 - brainstem encephalitis.

Diagnostic tools helping the diagnosis of brain death

CT/MRI: may show morphological abnormalities supporting the diagnosis of irreversible brain damage. Warning: the severity of the lesion and the clinical condition do not correlate!

EEG: the lack of bioelectric activity for more than 30 minutes. The difficulty of evaluation: it provides no information about the brainstem.

Carotid angiography: extracerebral accumulation of contrast media.

TCD: pendular flow; the systolic peak velocity is less than 60 cm/sec.

BAEP: in healthy persons after an auditory stimulus 5-6 clearly identifiable waves can be elicited. If there are at least 2 or 3 peaks, the brain death cannot be confirmed. The test is invalid in inner ear or auditory nerve damage, which is common in head injuries.

SSEP: shows the integrity of the cortex and the brainstem. The evaluation can be difficult if there is a complete spinal cord injury at the same time.

SPECT: is not used routinely.

The indication of brain death determination

The brain death can be determined, if the patient is clearly considered as brain dead and no improvement is expected from further intensive treatment. When the

determination of brain death is established for organ donation, a special committee appointed by the medical director of the same medical institution completes it. The designates should participate on a training organized by an accredited institute, and perform an exam. The representatives of the following specialties are in this committee: internist, neurologist and anesthesiologist.

Brain death can be determined if all members confirm the diagnosis! The members of the team are not allowed to participate in the transplantation process. The doctor, who is responsible for the conditioning of the donor, cannot be involved in the determination of the brain death, nor in the removal or the transplantation of the organs.

Ethical and legal considerations of organ transplantation

1. According to the current provisions in Hungary, organs cannot be used for transplantation, if the potential donor made a protesting statement in his/her life. To clarify this we have to answer the following questions:
 - a) Is there a written protest in the potential donor's personal documents?
 - b) Does the local and competent Institute of National Public Health have a written statement of protest?
 - c) Ask the relatives, if the patient made this statement in writing or verbally?
2. As provided by law the consent of the relatives is not necessary for the transplant. The doctor managing the donor conditioning should respect the feelings of the relatives and the considerations of piety. Although, it is not necessary to involve the family members in the decision, in the everyday clinical practice the discussion with the relatives in quiet circumstances usually solves this problem. After confirming the brain death, we have to explain to the relatives that the patient has died, and the vital functions can be maintained only by using machine support. It should be emphasized that according to our present medical knowledge, the status of the patient is final and irreversible. It should be told that the organ donation helps to other people.
3. The relatives can get no information about the recipient at all.

Absolute contraindications

1. Malignant tumor, except for primary brain tumors
2. Septic state
3. AIDS
4. Viral hepatitis
5. Viral encephalitis
6. Drug-addiction

Relative contraindications

1. Sustained hypertension
2. Donor over the age of 70
3. Alcohol abuse
4. Chronic renal failure: anuria
5. High doses of catecholamines
6. Curable infections

Spinal cord injuries

The most frequent causes are accidents. The spine can damage also: fractures, subluxation, and luxation (the detailed description is the subject of neurosurgery) may occur. In severe accidents we should assume spinal cord injury. The patient should be transported immediately to neurotraumatology or neurosurgery department.

Symptoms

The most severe form of spinal injuries is the complete transection of the spinal cord, which causes spinal shock: below the level of injury hypotonic plegia, areflexia, anesthesia, fecal and urinary retention, impotence and thermal dysregulation develop. After the cessation of spinal shock (takes a few weeks) spastic paraparesis, hyperreflexia, pyramidal signs, triflextion and spinal automatisms develop associated with the presence of autonomic bladder.

Pathomechanism

Spinal cord injuries can be caused by external compression, hematomyelia, ischemia, tear of the spinal cord, traumatic disc herniation or a displaced bone fragment.

Imaging diagnostics

X-ray should be performed in three views (anteroposterior, lateral and open mouth of the odontoid). Combined CT and MRI are preferred, because CT demonstrates the bone, and MRI visualizes the spinal cord and the soft tissues.

Commotion of spinal cord

The neurological symptoms disappear within a few hours. Treatment: careful observation, perhaps dehydration.

Contusion of spinal cord

Within a few hours heavy edema develops, which compresses the spinal cord by vicious circle. Petechias may occur centrally and after their absorption, fibrosis and void formation can develop. The aggressive and immediate reduction of edema is recommended by using high-dose steroids (in 30 mg/kg dose within the first hour, followed by 5 mg/kg per hour).

Bleedings

Epidural, subdural and intramedullary hemorrhages can develop. All of them are associated with severe spinal cord damage or complete transection.

The treatment of spinal cord injuries

On the spot treatment

In case of serious accidents spinal cord injury should be assumed. The severity, the level of the injury, and the stability of the vertebral column should be clarified on the site of the accident. If serious spine and spinal cord injury is suspected, the patient can be moved only, if the entire spine is stabilized (several helpers are needed to turn or to raise the patient). During transportation the spine should be fixed firmly (e.g. by using vacuum mattress). If there is no concomitant traumatic shock, circulatory or respiratory failure or severe accompanying injury, the administration of high dose steroid is recommended. We should pay attention to easing the pain and inserting urinary catheter to prevent retention. The patient should be transported by using vehicles having less traumatic effect (e.g. helicopter).

Institutional care

In case of spinal cord compression immediate surgery is indicated. If the spine is unstable due to fracture or luxation, stabilizing surgery is required, too.

Prognosis

In case of complete spinal cord lesions the prognosis is poor, usually there is no hope for significant improvement. Complete spinal cord lesion at the level of C3 is fatal due to the paralysis of the respiratory muscles. Temporary spinal shock develops immediately in incomplete spinal cord damages, but later some improvement is possible. In the future the damaged segments can be replaced by using stem cell therapy.

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Neurological consequences of alcoholism and internal medicine diseases

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Neurological consequences of alcoholism

Alcohol consumption causes many problems in modern societies. Ten percent of adults are either alcohol abusers or alcohol dependent and alcohol-related causes are responsible for about three percent of the death cases. *Alcoholism* is defined as both a chronic disease and a disorder of behavior, characterized by chronic, repetitive drinking to an extent that interferes with the drinker's health and interpersonal relations. By another definition, alcoholic is that person whose thoughts and activities aim getting and drinking alcohol, and in lack of alcohol withdrawal symptoms develop, which requires medical help. Problems related to alcoholism can be divided into 3 groups:

1. Acute effects of alcohol (alcohol intoxication);
2. Consequences of chronic alcohol consumption;
3. Effects of alcohol withdrawal (withdrawal syndromes)

1. Alcohol intoxication

Ethyl alcohol, or ethanol is absorbed unaltered from the gastrointestinal tract, may already be detected in the blood 5 minutes after drinking, and the maximum concentration is reached in 30 to 90 minutes. It is well known that the metabolism of alcohol begins already in the stomach by alcohol dehydrogenase, but the main site of alcohol metabolism is the liver, where different enzyme systems oxidize alcohol to acetaldehyde. The most important enzymes are alcohol dehydrogenase (ADH) and its isoenzymes which are responsible for more than 80 percent of ethanol oxidation. Then, acetaldehyde is converted by aldehyde dehydrogenase to acetate that is metabolized further in the Szentgyörgyi-Krebs cycle. (It is important to know that oxidation of 1 g alcohol leads to 7 kcal energy production which may cover the energy demand of the body. However, alcohol contains neither vitamins nor proteins and thus, chronic alcohol consumption may result in nutritional deficiency.) Aldehyde dehydrogenase is inhibited by disulfiram, therefore, patients taking both disulfiram and alcohol will accumulate acetaldehyde, leading to nausea, vomiting, and hypotension, which may be severe or even fatal. This pharmacological effect of disulfiram explains the use of this drug in the treatment of alcohol addiction. Certain other drugs such as sulfonylurea and metronidazole may also inhibit the aldehyde dehydrogenase, therefore, alcohol consumption is not allowed when these medicines are administered.

Similarly to the general anesthetics, alcohol acts directly on neuronal membranes. Signs and symptoms of alcohol intoxication depend on the amount of alcohol consumed. At low or moderate concentration excitement, loss of restraint,

irregularity of behavior, slurred speech, incoordination of movement and gait, irritability, drowsiness are the main symptoms, while at higher ethanol concentration and in advanced cases, stupor and coma may develop. The phenomenon of tolerance is well known and means that a chronic alcoholic patient can drink more and show fewer effects than an abstainer. In those people who died because of alcohol intoxication, autopsy revealed hyperemia of leptomeninx, petechia-like bleeding in the brain parenchyma, and non-specific degeneration of neurones.

Alcohol intoxication in cases of mild to moderate degrees of intoxication require no special treatment, although resting and forced diuresis might be suggested. However, in severe cases with extremely high blood alcohol concentrations and acidosis leading to coma, use of hemodialysis should be considered. (Because of potential legal consequences, blood test is always recommended to determine alcohol concentration.) It is very important to pay increased attention to alcoholic patients, since comorbidities, including head injury and gastrointestinal bleeding, are frequently present, and diagnosis of these diseases are difficult because signs and symptoms of alcohol intoxication may cover the original symptoms.

On rare occasions, alcohol has rather an excitatory than a sedative effect. This reaction is known as **pathological intoxication** (also called *atypical* or *idiosyncratic alcohol intoxication*), which is characterized by an outburst of blind fury with assaultive and destructive behavior. The attack terminates with deep sleep, and on awakening, the patient has no memory of the episode. The diagnosis of pathological or idiosyncratic intoxication has important legal implications. While a person suffering from usual forms of drunkenness is responsible for all consequences of his/her drinking, a person with pathological intoxication is considered irresponsible at the time. Considering the differential diagnosis, patients with temporal lobe seizures may have similar signs and symptoms.

Poisoning with methyl alcohol usually happens due to mistakes, namely the failed differentiation between alcohol and methyl alcohol. The oxidation of methyl alcohol to formaldehyde and formic acid is relatively slow, therefore, signs of intoxication appear several hours or day after the ingestion. The toxic effects are similar to those of ethyl alcohol, but in addition methyl alcohol poisoning may produce serious degrees of acidosis (the pH of the blood is often below 7.0), Kussmaul breathing, blindness due to damage of retinal ganglion cells, and disturbance of consciousness. The patients' pupils are usually dilated and the pupillary reflexes are absent. Survivors may be left blind and Parkinson syndrome may also develop because of putaminal damage. The treatment should be started as soon as possible and includes hemodialysis and intravenous administration of large amounts of sodium bicarbonate.

Poisoning with ethylene glycol is also not rare. Ethylene glycol is a commonly used industrial solvent and antifreeze solutions also contain it. At first the patient seems to be drunk after ingestion of ethylene glycol, but several hours later other signs and symptoms develop due to severe metabolic acidosis (the pH is often below 7.0) and renal insufficiency. Acidosis occurs because ethylene glycol is converted into glycolic acid by alcohol dehydrogenase. The main symptoms are

hyperventilation, severe confusion, convulsions, coma, and renal failure. Since the ethanol inhibits the alcohol dehydrogenase competitively, alcohol is used as a treatment strategy, however early hemodialysis and intravenous infusion of sodium bicarbonate are more important.

2. Consequences of chronic alcoholism

Depending on the site of damage, chronic consumption of alcohol may cause myopathy, neuropathy, myelopathy, Wernicke encephalopathy, Korsakoff psychosis, central pontine myelinolysis (indirectly), cerebellar and cortical atrophy.

Alcoholic myopathy mainly affects the proximal muscles. Two main forms of alcoholic myopathy are known: the first is accompanied with muscle pain, edema and elevated creatinine kinase value, the second is painless and characterized by hypokalemia. In rare cases, alcoholic myopathy is associated with rhabdomyolysis and consequent myoglobulinuria. Isolated alcoholic myopathy is a rare condition; the symptoms of myopathy are usually mixed with the symptoms of polyneuropathy.

Alcoholic polyneuropathy is one of the most frequent forms of polyneuropathy. Polyneuropathy is caused by the toxic effect of alcohol and B₁ vitamine (thiamine) deficiency. The type of alcoholic polyneuropathy is usually axonal, but demyelinating and mixed forms were also reported. The symptoms are distal type of paraesthesia and pain, disturbance of superficial and deep sensation, decreased deep reflexes, trophic changes, distal type of paresis, perspiration, and orthostatic hypotension. The polyneuropathy can be so severe that the patient cannot walk alone. The treatment includes parenteral administration of high dose B₁ vitamine (100-200 mg a day), and electrotherapy and exercises when paresis is present. Certainly to avoid relapse abstinence is essential.

Alcoholic myelopathy is very rare consequence of chronic alcoholism. It results in pyramidal signs and spastic paraparesis of lower extremities. Imaging techniques including MR examination do not reveal structural abnormality.

Wernicke's encephalopathy was named by Carl Wernicke, who described the disease in 1881 by symptoms of 2 alcoholic male patients and a female patient who suffered from esophagus stenosis. Carl Wernicke called the disease "encephalitis haemorrhagica superior". Wernicke's syndrome includes: 1) **disturbance of eye-movement or gaze** (paresis of external eye-muscles, gaze disturbance, horizontal and vertical nystagmus), 2) **ataxia**, and 3) **confusion, memory-disturbance**, and somnolence. The improvement occurs in a certain order; at first the eye-movement disturbance improves, then the ataxia, and finally the memory disturbance. According to the autopsy results of patients died in Wernicke's encephalopathy, bleeding and leukocyte infiltration were described in the midline grey matter structures, thalamus, mamillary bodies, and nuclei of III-rd and IV-th cranial nerves. **The underlying cause is thiamine deficiency**, which may develop not only in alcoholics but also in patients suffering from hyperemesis gravidarum, gastric cancer, and chronic gastric ulcer. The treatment requires

parenteral administration of high dose B₁-vitamin (100-300 mg thiamine) and supplementation of other types of B vitamin.

Korsakoff's psychosis was described some years later (1887) and the underlying cause was shown to be the same, namely the deficiency of thiamine. However, in Korsakoff's psychosis the **damage of the mamillary bodies** is the main feature. Therefore, the symptoms are **retrograde amnesia to the previous events of near-past, inability of learning, and confabulation** with which the patients try to compensate their memory disturbances. The histological findings and the treatment options are the same as in Wernicke's encephalopathy.

Central pontine myelinolysis develops most frequently in alcoholic patients, because those metabolic changes, which are responsible for the disease, occur most frequently in alcoholics. This disease, characterized by tetraplegia and pseudobulbar palsy, was first described in 1950 in young alcoholics. Autopsy and histological investigation revealed **demyelination**, which was most pronounced **at the centre of the pons**, but the gray matter was preserved, and histological investigation did not show inflammatory changes. Since the pyramidal tract, corticopontine and corticobulbar fibres pass through the pons, the patients have tetraparesis, they are unable to swallow, chew, speak, and move their facial muscles. Usually, the horizontal gaze is also affected. This combination of symptoms is called as locked-in syndrome, because the patient is alert, but cannot communicate only with vertical gaze (fibres running to the vertical subcortical gaze centres, oculomotor and trochlear nuclei are preserved). It has to be mentioned that the symptoms of the disease are not always so severe, and demyelination may affect extrapontine structures as well (thalamus, striatum, internal capsule, lateral geniculate body, corpus callosum, cerebral and cerebellar white matter).

The disease affects males and females equally, and was also described in children, especially after burning injuries. Concerning the **pathomechanism**, two theories are known: the first theory claims that **fast correction, sometimes overcorrection of hyponatremia** is in the background, while the second theory supposes **hyperosmolarity** as the causative factor (this conclusion was drawn in patients with burning injuries).

In **alcoholic cerebellar degeneration (cerebellar atrophy)** the atrophy of the vermis is the most prominent leading to trunk ataxia and dysmetria, which is more pronounced in the upper than the lower extremities.

Cerebral atrophy is a well-known consequence of chronic alcoholism. The atrophy was described in both the grey and white matters, but was the most prominent in the cerebral cortex, where neuronal loss and astrocytosis were observed. The main symptoms of the disease are the memory disturbance, dementia, gait disturbance, and dysarthria. Cerebral CT reveals widened sulci and dilated ventricles.

Fetal alcohol syndrome is partly due to the direct effect of alcohol that passes through the placenta, and partly caused by the disturbed absorption and vitamin deficiency of the mother. Infants of those mothers who are regularly drinking alcohol develop slower, and consequently, their weight and height are smaller than normal. The mortality rate of these infants is double of the usual rate, moreover,

mental retardation, behaviour problems and other developmental disturbances of the brain are also found with increased frequency.

3. *Withdrawal syndromes*

Chronic alcoholism may cause neuropsychiatric disorders not only due to alcohol consumption, but also because of relative or absolute abstinence from alcohol. Every physician should know these syndromes, since patients after admission cannot get alcohol in the hospital, therefore, these syndromes may occur at any ward. The most common manifestation of the withdrawal syndrome is **tremulousness**. This symptom first appears in the morning, after abstinence during the night. Many patients experience that the tremor disappears after a few drinks in the morning. However, the symptoms usually return on the next morning with increasing severity. The tremor is usually generalized and increased by motor activity or emotional stress. Sometimes the tremor is so strong that the patient cannot stand without help, or speak clearly. If the patient does not get alcohol the symptoms are accompanied by general irritability, tachycardia, hyperemic conjunctiva and face, and nausea and vomiting. The patient is fully awake and complains of insomnia. Increased adrenergic hyperactivity is supposed as a causative factor, and indeed, the concentration of norepinephrine and its metabolites are elevated in both the blood and CSF. The symptoms reach their peak intensity 24 to 36 hours after the complete cessation of alcohol consumption. The tremor can be relatively well treated by beta-blockers and high dose of meprobamate or other anxiolytics.

If the patient does not get ethanol, **hallucinosi**s occurs in about one-quarter of the hospitalized tremulous patients. The patients sometimes complain of bad dreams, which are difficult to differentiate from the real experience. They see mostly animals, but the hallucinations can be not only visual, but also auditory, mixed visual and auditory, or rarely tactile in type. Since the patients usually misinterpret sounds and pictures or shadows of different objects, the symptoms are more illusions than hallucinations in the strict sense.

Auditory hallucinosis typically develops 24-48 hours after the cessation of alcohol consumption. Usually elementary (ringing, clicking or gunshots) or complex auditory hallucinations occur, however the most common hallucinations are human voices, which may speak to the patient, but mostly discuss him in the third person. In the majority of cases the voices are malignant and threatening in nature, and the patients feel the voices so real that they usually respond to the voices, and may call help for protection. The hallucinations are the most prominent during the night, and their duration varies from seconds to hours.

Withdrawal seizures ("Rum fits") are not rare between 12 to 48 hours after cessation of alcohol consumption. The seizures are grand mal in type, i.e., generalized, tonic-clonic convulsions. Sometimes there is only 1 seizure, but in the majority of cases the seizures are repeated, moreover, epileptic status may also develop. Cerebral CT and interictal EEG usually show no abnormalities. Focal seizures are not typical and always suggest focal lesions. Clonazepam or diazepam can be administered during the epileptic seizures, however, most cases do not

require the use of anticonvulsant drugs, since the seizure usually terminates before the patient is seen by medical team. The long-term administration of anticonvulsants is usually not necessary: if the patients remain abstinent, they will have no seizures; if they continue drinking, they usually omit their medicines. Therefore, the aim is to maintain abstinence instead of long-term administration of anticonvulsants. However, if an antiepileptic is still given, carbamazepine or oxcarbazepine can be suggested, which decreases the hunger for alcohol besides their antiepileptic potentials. Certainly, if epileptic status develops, it should be managed like any other epileptic status.

Delirium tremens develop in almost 20 percent of patients who had withdrawal seizure. This is the most severe disease among the alcohol-related syndromes. It is characterized by tremor, agitation, insomnia, severe confusion, hallucinations, and accompanied by the signs of overactivity of autonomic nervous system, including hyperthermia, tachycardia, perspiration and dilated pupils. Delirium tremens develops 2 to 4 days after the cessation of alcohol consumption. In the majority of cases the duration of delirium tremens is 72 hours or less and it is ending as suddenly as it begins. At the end of delirium the patient falls into a deep sleep and has no memory of the events of the delirious period. Although the mortality rate of delirium tremens was decreasing in the last decade, approximately 5 to 10 percent of cases are still fatal. The cause of death is usually an associated infectious disease or head injury, but in many cases hyperthermia or peripheral circulatory collapse was supposed to lead to the fatal event. Before discussion of **treatment of delirium tremens**, the importance of a very careful examination has to be underlined. At first, associated injuries (head injury, skull fracture, subdural hematoma, cerebral contusion), infections (pneumonia or meningitis), gastrointestinal bleeding, pancreatitis, and liver disease have to be excluded. In order to recognize these complications in due time, skull and chest X-rays, cerebral CT should be performed routinely, and hepatic enzymes, serum lipase and amylase, ions, glucose, blood urea nitrogen, creatinine and C-reactive protein levels, blood gases, as well as full blood count have to be determined. Furthermore, lumbar puncture should also be considered to exclude infection of the central nervous system. In severe forms of delirium tremens, temperature, pulse, and blood pressure should be monitored at 30-minute intervals to prevent potentially fatal complications including peripheral circulatory collapse and hyperthermia. The **treatment** includes correction of fluid and electrolyte imbalance, administration of antibiotics, beta-blockers, and high dose of thiamine. Severe degrees of agitation and perspiration should be taken into consideration when the amount of parenteral fluid intake is calculated. The occurrence of hyperthermia requires the use of antipyretic drugs and cooling mattress in addition to specific treatment for any infection. Confusion, agitation and hallucinations have to be treated, in which meprobamate and haloperidol or other antipsychotics are still the first choice drugs. In the case of shock, one must act quickly, utilizing fluids, vasopressor drugs, and whole-blood transfusions, if necessary.

At the end of this chapter, it has to be highlighted that alcoholics require special attention because 1) they suffer head trauma frequently with no memory to the event, 2) due to the altered immune-reactivity they react to diseases in an

unusual way (e.g. infections including pneumonia or meningitis without fever), and 3) their compliance is usually poor. Therefore **treatment of alcoholic patients is always a complex and difficult challenge**. It is important to know that successful treatment of an acute complication of alcoholism does not mean the end of the treatment. Alcoholic patients have to recognize that they are alcoholics i.e., their drinking is beyond their control, therefore they need help. The successful treatment of an alcoholic patient requires the recognition of the causes, which have led to the alcoholism. Moreover, the patient has to be convinced about the importance of the treatment and abstinence, the family has to support and motivate the patient on his or her way, and the bias of the society has to be overcome. Besides the proper treatment of the disease, the relapse has to be prevented. This is one of the most difficult tasks in medicine, which can be successful only with **involvement** of the patient, patient's family, general practitioner, specialists, and the society.

Neurological consequences of the major internal medicine diseases

Classification

One of the major neurological consequences of the internal medicine diseases is the so-called **secondary encephalopathy**, which indicates a global cerebral dysfunction caused by failure of some other organ system (heart, lung, liver, kidney, pancreas, endocrine glands etc.), electrolyte, metabolic and hormonal disturbances, blood gas alterations, or nutritional deficiencies. Since these abnormalities may lead not only to secondary encephalopathy but also to other neurological disorders (e.g. polyneuropathy, myopathy, central pontine myelinolysis, etc.), for convenience, these consequences will be discussed together.

Secondary encephalopathies

Secondary encephalopathies are at the border of internal medicine and neurology. Although the neurologic symptoms are only consequences of the internal medicine diseases in secondary encephalopathies, they may be more informative than the symptoms related to the organ primarily involved, and thus, may be a clue to the diagnosis of the systemic disease. In general, secondary encephalopathies are caused by metabolic, hormonal, electrolyte or blood gas alterations, as well as nutritional deficiencies. These changes frequently result in headache, irritability, inattention, confusion, and may be accompanied by asterixis, tremor, myoclonus, and convulsion. Later, this state may progress to disturbance of consciousness (somnolence, stupor, coma). Focal neurological signs are usually not found, and cerebral CT and CSF are also normal. In a patient with suspicion of secondary encephalopathy, laboratory examinations, including erythrocyte sedimentation rate, blood count, serum Na, K, Ca, glucose, BUN, NH₃, pH, P_{CO}₂,

P_{O_2} , sTSH, thyroxin level, C-reactive protein, and osmolality, may provide reliable clues to most of the causes. Besides laboratory examinations, EEG may be helpful in the diagnosis. Although EEG alterations are not specific to secondary encephalopathies, slowing of the background rhythms indicates the severity of the metabolic disturbance. If an exogenous toxin is suspected, a toxicology test should also be performed! It is important to know that the severity of symptoms of secondary encephalopathies depends not only on the severity of the metabolic changes but also on the speed of development. Fast development of metabolic abnormality usually leads to severe, while gradual onset of abnormality results in mild neurological symptoms. Secondary encephalopathies are usually reversible if the systemic dysfunction can be controlled. However, if the abnormality is very severe and lasts for a long period, the brain may suffer an irreversible damage, leading to persistent neurological dysfunction even after control of the metabolic abnormality. Intoxication and overdose of medicines should be considered in differential-diagnosis of secondary encephalopathies.

Hypoxic-ischemic encephalopathy

Hypoxic-ischemic encephalopathy means that the oxygen does not reach the neurons in proper amount. In case of hypoxic encephalopathy the main pathomechanism is the lack of proper oxygenation of the blood, while ischemic encephalopathy is caused by a global decrease or cessation of cerebral blood flow. The main causes are listed below:

- there is not enough oxygen (mistake during anaesthesia, mountain-climbing in high altitudes);
- the pathway of oxygen is obstructed (strangulation, foreign body, trachea compression);
- the oxygen does not reach the lung because of weak respiratory muscles (myasthenia gravis, Guillain-Barre syndrome, ALS);
- the oxygen change is blocked in the lung because the respiratory surface is significantly decreased (bilateral pneumonia or aspiration) or because of apnoea
- the oxygen reaches the blood but due to an inappropriate circulation (heart arrest, myocardium infarction, severe hypotension, shock) it does not reach the brain;
- the oxygen reaches the blood, the circulation is also normal, but there is not enough hemoglobin (severe anemia) or it is not able to bind and transfer the oxygen to the brain (carbon-monoxide poisoning).

In case of hypoxia, depending on its severity, the compensatory increase of cerebral blood flow may maintain the proper oxygen supply.

When the cerebral perfusion pressure is slightly reduced, a compensatory dilation of resistance vessels may keep the normal cerebral blood flow (autoregulation). When the perfusion pressure falls below a critical level (approximately 60 mmHg), the cerebral blood flow decreases, but even in this case the increased oxygen extraction may maintain the oxygen supply necessary for the

normal energy metabolism. Further decrease of perfusion pressure, however, leads to decreased tissue oxygenation and consequent tissue damage. In complete ischemia, the cerebral tissue suffers irreversible damage already after 5 minutes, although hypothermia or barbiturate treatment may prolong this period by decreasing the brain metabolism.

If the ischemia is incomplete (e.g. systemic hypotension), the main damage occurs in the borderzones located between the major cerebral arteries or between the centrifugal and centripetal arteries, while in anoxia neurons in certain parts of the hippocampus are especially vulnerable. In severe degrees of either ischemia or hypoxia the cortical neurons damage firstly, and later, the basal ganglia, and the cerebellum. Nuclei of the brainstem are relatively resistant to hypoxia and hypotension and show dysfunction only after the cortex has been severely damaged.

Mild degrees of hypoxia induce headache, inattentiveness, confusion, and motor incoordination. It is a general rule that if hypoxia does not cause unconsciousness, irreversible damage cannot be expected in the central nervous system. In case of anoxia or severe global cerebral ischemia (e.g. cardiac arrest), consciousness is lost within seconds, but if breathing and circulation are restored within 4-5 minutes, complete recovery may occur. However, if the anoxia or severe global cerebral ischemia lasts longer than 5 minutes, the risk of permanent cerebral injury is significantly increasing. (As it was mentioned before, decreased cerebral metabolism under hypothermia or barbiturate treatment may increase the tolerance of the cerebral tissue.) In unconscious patients, the presence or absence of the brain-stem reflexes may predict the outcome; the intact brainstem reflexes (normal pupillary light, oculoccephalic, corneal, and vestibulo-ocular reflexes) indicate a more favourable prognosis, however, absence of these reflexes predicts poor outcome for recovery of consciousness and for life expectancy.

In case of cortical damage with preserved brainstem functions, hypotonic extremities or decorticated rigidity (increased tone of flexors in the upper, and extensors in the lower extremities) may develop. Myoclonus and epileptic seizure may occur. In case of more severe damage, when the brainstem is also affected, decerebrated rigidity may be observed (increased tone of extensors in all extremities), and is often accompanied by bilateral Babinski signs. In this form of the disease, hyperthermia, deepening coma, and circulatory collapse may develop within several days, and may lead to death. In the most severe form, brain death may develop, when all brainstem reflexes, breathing, and electrical activity in the EEG are absent.

Patients, who have suffered less severe hypoxia or ischemia, may regain their consciousness after a certain period of coma. In this posthypoxic phase, confusion and involuntary movements including myoclonus and choreoathetosis may be present. Some of these patients may show complete recovery, while others are left with different degrees of permanent disability, such as persistent coma or stupor, and, with less severe cerebral injury, choreoathetosis, ataxia, myoclonus, dementia with or without extrapyramidal signs, visual agnosia, parkinsonian syndrome with cognitive impairment, and epileptic seizures. These symptoms rarely occur alone; usually they are present in various combinations.

The treatment of hypoxic-ischemic encephalopathy aims the restoration of proper oxygen supply as fast as possible in order to prevent the development of a severe hypoxic injury. After a clear airway is secured, the use of cardiopulmonary resuscitation, proper oxygenation, and control of myoclonus and seizures are the most important. Once the cardiac and pulmonary functions are restored, cerebral metabolic demand should be reduced by control of seizures, hypothermia and barbiturate medication.

Regarding the further therapeutic strategies, the possible causes of the hypoxic-ischemic encephalopathies should be considered.

- Is there enough oxygen? (The lack of oxygen in the inhaled air is very rare).
- Is there an airway obstruction (foreign body, trachea compression)? Therefore, the respiratory tract should be checked, and the airway obstruction, if present, has to be overcome with either intubation or tracheostomy.
- Are the respiratory muscles functioning properly (respiratory muscles may be weaker in myasthenia gravis, Guillain-Barre syndrome, ALS...)? (Chest elevation during deep breath has to be checked!)
- Is there any disease, which may decrease the respiratory area (bronchopneumonia, aspiration)? If there is enough oxygen, no airway obstruction can be detected, the respiratory muscles are not weak, and the circulation is intact, chest X-ray and measurement of oxygen saturation should be used for the assessment of respiration.
- Is there a circulatory collapse, which may prevent the oxygen transfer to the cerebral tissue? Cardiac arrest, myocardial infarction, severe hypotension, and shock may cause circulatory failure, which have to be treated promptly by resuscitation, administration of fluid, or sympathomimetics.
- Is there enough hemoglobin in the blood and can it bind the oxygen appropriately? In case of severe anaemia, transfusion should be initiated.

Hypercapnia

Chronic emphysema, fibrosing lung disease, restrictive pulmonary diseases, weakness of respiratory muscles may result in the elevation of P_{CO_2} . The clinical syndrome consists of headache, drowsiness, confusion, action tremor, flapping tremor, papillary edema, and finally, stupor and coma. The most effective therapy is the artificial ventilation with positive-pressure devices, using proper amount of oxygen. The administration of drugs depressing the respiratory center should be avoided. The danger of 100% oxygen inhalation has to be known, because the respiratory center is insensitive to CO_2 in hypercapnia, and 100% oxygen inhalation may eliminate the major stimulus to the respiratory center in these circumstances.

Hypoglycemia

The normal brain has considerably low glucose reserve (1 to 2 g) that is able to maintain cerebral activity only for 15-30 minutes when glucose is no longer

available. Therefore, severe functional and structural impairment may develop under conditions of hypoglycemia. The major difference between hypoglycemic and hypoxic encephalopathies is the speed of evolution of the neurologic disorders. While the neurologic signs develop in a few seconds in hypoxic encephalopathies, it takes minutes in hypoglycemia. The most common causes of hypoglycemic encephalopathy are accidental, or the deliberate overdose of insulin, or an oral antidiabetic agent. Depletion of liver glycogen in alcoholic patients or after starvation may also contribute to development of hypoglycemic encephalopathy, while insulin-secreting tumor of the pancreas (insulinoma) is the very rare cause of hypoglycemia.

When the level of blood glucose declines below a critical value (2 mmol/L), the initial symptoms, including hunger, anxiety, sweating, trembling, and headache, appear. After these symptoms, confusion and drowsiness develop, and the risk of epileptic seizures increases. In the more severe form, hypnoid disturbance of consciousness (somnolence, stupor, coma) as well as epileptic seizures may occur. Blood glucose levels below or equal to 0.5 mmol/L cause coma, hypotonicity on all limbs, shallow respiration, and dilated, unreactive pupils, however, severe hypoglycemia may result in the most variable neurological symptoms including hemiplegia. This is the reason, why the measurement of blood glucose level is mandatory in stroke patients.

Certainly, the treatment of hypoglycemia is the very rapid correction of blood glucose level. If glucose is administered in due time, the patient can be restored to normal state. However, when hypoglycemia is severe and lasts for a long period before correction, only partial or delayed recovery can be expected. A severe and prolonged episode of hypoglycemia may result in memory disturbance or impairment of intellectual functions, and in the most severe cases, even coma may persist.

Hyperglycemia

Two forms of hyperglycemia can be differentiated: hyperglycemia with, and without ketoacidosis. The **ketoacidotic form** is associated with Kussmaul type of breathing, fatigue, weakness, headache, abdominal pain, dehydration, and in severe cases, stupor or coma. Urine analysis always reveals pronounced glycosuria and acetonuria. This form of hyperglycemia develops over days. The blood glucose level is usually more, than 20 mmol/L and the blood pH is less, than 7.2. The treatment consists of administration of insulin and infusions to rehydrate the patient.

In **hyperosmolar nonketotic hyperglycemia**, the blood glucose is extremely high, over 30 mmol/L, and the osmolality is usually around 340 mosmol/L, however ketoacidosis does not develop. This form of hyperglycemia usually occurs in elder diabetic patients with simultaneous infection, enteritis, pancreatitis, but administration of drugs known to disturb diabetic control (prednisone, phenytoin, thiazides) may also cause severe hyperglycemia. The main symptoms are fatigue, polyuria, confusion, and disturbance of consciousness. The mortality rate is high, around 30%. The correction of the elevated blood glucose requires

relatively small amounts of insulin, because these patients are relatively sensitive to insulin.

NEUROLOGICAL CONSEQUENCES OF HEPATIC DISEASES

Hepatic encephalopathy

Hepatic encephalopathy is usually caused by chronic hepatic insufficiency (parenchymal decompensation) or development of portocaval shunting (vascular decompensation). The most widely accepted hypothesis of hepatic encephalopathy relates to hyperammonaemia. Protein, derived from food, breaks down to amino acids, and due the urease-containing organisms, ammonia (NH_3) is released in the bowel and carried to the liver by the portal circulation. Within physiological conditions the ammonia is converted into urea (blood urea nitrogen, BUN) in the liver, and the urea is excreted with the urine. However, when ammonia fails to be converted into urea, either because of impaired function of hepatic cells (parenchymal decompensation) or due to portal-systemic shunting of the blood (vascular decompensation), high concentration of NH_3 reaches the systemic circulation, and thus, the brain, leading to neurologic dysfunction. Although the concentrations of serum ammonia is compared to that of control subjects, mild increase of ammonia level is defined between 50-100 $\mu\text{mol/L}$, while severe increase is assessed above the concentration of 100 $\mu\text{mol/L}$.

In mild forms of hepatic encephalopathy, decreased psychomotor activity, impairment of cognitive functions, confusion and slurred speech are the main symptoms, while in more severe cases, progressive drowsiness, stupor, and coma may occur. The confusional state is frequently combined with the so called asterixis, or flapping tremor (sterixis: Greek word, means “fixed position”, asterixis means “no fixed position”). Asterixis, or flapping tremor indicates that the patient is not able to sustain a fixed joint position (usually extension) requiring continuous muscle contraction caused by a sudden drop of muscle tone. Therefore, the sustained position will be interrupted by an opposite movement leading to a repetition of extension and flexion, resembling to tremor. This sign can be demonstrated by asking the patient to hold his arms outstretched with the wrists extended. Since this position cannot be sustained in asterixis, the wrist will be flexed. This tremor can be seen not only in the wrist, but also in any sustained posture. The other characteristic sign in hepatic encephalopathy is an EEG abnormality showing paroxysmal bilateral synchronous triphasic waves in the delta range. Besides the above mentioned signs (confusion, asterixis, EEG abnormality, and disturbance of consciousness), fluctuating rigidity of the trunk and limbs, sucking and grasping reflexes, Babinski's signs and seizures may be observed.

Hepatic encephalopathy usually evolves over days to weeks and may be fatal or regress partially or completely. In mild forms, the disturbance of consciousness does not develop, only mild mental dullness and confusion with asterixis and EEG changes can be found.

Treatment strategies include restriction of dietary protein, inhibition of bowel bacterium flora by oral administration of neomycin or rivaximin (due to its nephro-

and ototoxicity neomycin is rarely used and instead of it rivaximin is recommended), and use of lactulose (lactulose acidifies the colonic contents and leads to the change of ammonia to ammonium ion that leaves the body by the stool). Certainly, treatment of the underlying hepatic disease has to be continued, and if there is no improvement, liver transplantation may be considered.

In **acute hepatitis with fulminant hepatic failure**, confusional, delirious, and comatose states also occur, and although the blood NH_3 may be elevated, it does not explain all the symptoms. The main pathomechanism of the neurological disturbances in fulminant hepatic failure seems to be the severe cerebral edema. The early diagnosis of cerebral edema (before the development of stupor and coma) and enormously increased intracranial pressure have to be highlighted, because patients may survive the fulminant hepatic failure if liver transplantation is performed in due time. The cerebral edema can be detected by computed tomography, transcranial Doppler, and by invasive monitoring of the intracranial pressure. The combination of rapidly evolving hepatic failure and massive cerebral edema was also described in the **Reye's syndrome**. Reye's syndrome is a special type of non-icteric hepatic encephalopathy, which occurs in children after viral infection combined with administration of aspirin. The mortality rate of Reye's syndrome decreased from 50 to 5% due to the early recognition and treatment. The treatment consists of correcting the metabolic abnormalities and reducing intracranial pressure. It includes administration of lactulose and neomycin or rivaximin, temperature control, glucose control, maintenance of fluid and electrolyte balance, nasotracheal intubation and controlled ventilation, control of intracranial pressure by continuous monitoring and the use of hypertonic solutions (e.g. mannitol).

In case of hepatic disease, the hemostatic parameters should be checked (spontaneous increase of INR!), since hepatic failure can be associated with inadequate synthesis of coagulation factors increasing the risk of bleedings, including cerebral hemorrhages.

NEUROLOGICAL CONSEQUENCES OF RENAL DISEASES

Uremic encephalopathy

The cerebral symptoms caused by uremic state are most frequently observed in patients with rapid development of renal failure. The major symptoms are fatigue, inattentiveness, apathy, and later, irritability, confusion, hallucinations, dysarthria, asterixis, and in the most severe forms, disturbance of consciousness. In renal failure, these symptoms nearly always associated with tremor, myoclonus, or convulsion. The EEG usually shows diffuse slow activity, which improves slowly after dialysis. It is important to keep in mind that uraemia is frequently associated with hypertension, hemostatic abnormalities, and ionic changes (calcium, magnesium, potassium), which may also influence the neurologic function.

Pathophysiological data show direct relationship between the neurological symptoms and the high urea level. Restoration of renal function completely corrects the neurologic syndrome, indicating that mainly functional and not

structural disturbances predominate in uremia. Indeed, cerebral CT and MRI usually do not show abnormalities except for cerebral shrinkage, and the intracranial pressure is also normal.

Concerning the treatment, dialysis should be started as soon as possible and the indication of renal transplantation should be considered. Improvement of encephalopathic symptoms may take 1-2 days after start of dialysis. Since the serum albumin concentration is decreased, and thus, the unbound, therapeutically active portion of drugs is increased in uremia, lower dose of anticonvulsants may also be effective in control of epileptic seizures. The altered excretion of drugs may lead to their accumulation, which should also be taken into consideration during the treatment.

Dialysis encephalopathy (Dialysis Dementia)

Dialysis encephalopathy is characterized by dysarthria, dysphasia, and apraxia of speech leading to a dysfluent speech pattern. Besides these signs, myoclonus, seizures, personality and behavioral changes can be observed. The signs and symptoms are transient at the beginning of the disease, however, later they become permanent and show a subacute progression within several months. The dialysis encephalopathy was explained by aluminum intoxication, but due to purifying the water used in dialysis and removal of aluminium from the dialysate resulted in disappearance of the disorder.

Consequences of Renal Transplantation

Since immunosuppression is necessary after renal transplantation, its effects including the increased the risk of fungal infections and development of primary cerebral lymphoma and progressive multifocal leucoencephalopathy should be taken into consideration.

With administration of cyclosporin and other immunosuppressants, encephalopathy was described by MRI examination, which was characterized by widespread edema of the cerebral white matter seen predominantly in the occipital region (**posterior, reversible encephalopathy syndrome, PRES**). This form of encephalopathy, however, not specific since it was also described in patients with preeclampsia and eclampsia or hypertensive encephalopathy. The symptoms include headache, visual field defect (sometimes cortical blindness), confusion, epileptic seizures, and disturbance of consciousness. Regarding the pathophysiology, several theories were published, but according to the most widely accepted theory endothelial damage and/or hypertension and disturbance of autoregulation cause the hyperperfusion, which leads to the vasogenic edema.

Although the disequilibrium syndrome does not belong to the encephalopathies, it is also discussed in this chapter.

The "Disequilibrium Syndrome"

The so called disequilibrium syndrome may occur during and following the dialysis, mainly in the early stages of the dialysis program or during a rapid dialysis. The symptoms, which typically develop in the third or fourth hour of the

dialysis and last for several hours, include headache, irritability, muscular cramps, convulsions, and sometimes agitation or drowsiness. Disequilibrium syndrome is usually explained by the rapid lowering of serum urea, which is followed slower in the extracellular and much slower in the intracellular space in the brain. It results in a higher concentration of urea in the brain as compared to the serum leading to a shift of water into the brain cells according to the osmotic gradient (intracellular edema). In the last years, inappropriate secretion of antidiuretic hormone was also supposed in the background of the water shift.

Uremic polyneuropathy

Peripheral neuropathy, which is probably the most frequent neurologic complication of chronic renal failure, is discussed elsewhere.

Encephalopathy associated with sepsis

Reversible confusion and drowsiness are frequently observed in severely septic patients, but could not be explained by hypotension, hepatic, pulmonary or renal failure, drug intoxication, or electrolyte imbalance, and neither a primary lesion of the brain can be detected in the background of the symptoms. Although, the exact pathomechanism is not known, the causative role of endotoxins or circulating cytokines is supposed. The therapy includes the treatment of the underlying disease(s), and correction of fluid and electrolyte disturbances, body temperature and blood pressure, if necessary.

Other Metabolic Encephalopathies

The limited extent of this chapter permits only a brief list of the other important metabolic disturbances causing episodic confusion, stupor, or coma.

- Severe hypercalcemia, which may be caused by hyperparathyroidism, bone metastasis, multiple myeloma, sarcoidosis, and excessive intake of vitamin D.
- Metabolic acidosis resulting in drowsiness, stupor, and coma, and associated with Kussmaul breathing.
- Addison's disease.
- Hyperviscosity syndrome, caused by multiple myeloma, Waldenström macroglobulinaemia, polycythemia, or extreme hyperlipidemia.
- Encephalopathies associated with endocrine diseases (steroid encephalopathy, thyroid encephalopathy, pancreatic encephalopathy) will be discussed in the next subdivision.

NEUROLOGICAL CONSEQUENCES OF ENDOCRINE DISEASES

Hypoparathyroidism

Earlier, the usual cause of hypoparathyroidism was the accidental surgical removal of the parathyroid glands during thyroidectomy. This form, due to changes in surgical techniques, became rare. However, the damage of the parathyroid glands and consequent absence or decreased level of parathormone, can also be caused by irradiation of thyroid diseases, as well as infections or tumor

metastasis. The clinical manifestations, which mainly relate to **hypocalcemia** and increased neuromuscular excitability, are paresthesias of the extremities or face, muscle cramps, tetany, myoclonus, but convulsions may also occur.

Hypocalcemia may also develop in malabsorption, pancreatic insufficiency, and vitamin D deficiency, but the most frequent cause of the low level of free calcium ions is due to the hyperventilation. During hyperventilation the CO₂ level decreases, and the blood pH becomes alkalotic. As a result, protons leave the protein and the negative charges on the protein surface bind the calcium ions, leading to hypocalcemia. The therapy includes intravenous administration of calcium and the treatment of the underlying disease.

Hyperparathyroidism

The hyperparathyroidism is associated with **hypercalcemia**. Although the neurological consequences of hypercalcemia are less pronounced, it may cause fatigue, weakness, myoclonus, headache, nausea, drowsiness, confusion, as well as disturbance of consciousness.

Cushing's disease, corticosteroid induced psychosis

Some patients, receiving ACTH or steroid, report a sense of wellbeing and decreased tendency to become tired. At higher doses (80 units per day of ACTH and 60 mg per day of prednisone), patients may show overactivity, emotional lability and complain of insomnia. In more severe cases mood changes like euphoria and hypomania may be accompanied by confusion, but rarely hallucinations and delusions can also be observed resembling to psychosis. The withdrawal of steroids, or significant decrease of steroid dose usually results in improvement, but the full recovery may take several days or even weeks. Wider ventricles and sulci were revealed by imaging techniques, however, the cause of the steroid-induced psychotic symptoms is still unclear.

Thyreotoxicosis, thyroid encephalopathy, and other neurological consequences of hyperthyroidism

Thyroid crisis can be recognized by the pronounced increase of the symptoms and signs of hyperthyroidism (tachycardia, fever, action tremor, restlessness, perspiration, vomiting and diarrhea). However, besides the general symptoms, mental confusion, irritability, seizures, hallucinations, delirium, and finally, disturbance of consciousness may also occur (**thyroid encephalopathy**). In the past, thyreotoxicosis was a not rare postoperative complication in patients, who were not properly prepared for thyroid surgery. Now, it is quite rare, and mainly seen in patients with untreated thyreotoxicosis complicated by serious medical comorbidity.

Encephalopathy (confusion, myoclonus, seizure, altered consciousness) was described in Hashimoto's disease as well. The encephalopathic symptoms responded well to steroid therapy and antithyroid antibodies decreased too.

Neurological complications were described not only in **thyreotoxicosis** but also in simple hyperthyroidism. One of these symptoms is the **endocrine ophthalmopathy**, which is associated with exophthalmus, edema of the periorbital

tissues and eye muscles, and sometimes diplopia. **Tremor** is almost universal, which is best seen in the outstretched fingers of the pronated hand. Besides endocrine ophthalmopathy and tremor, chorea, **myopathy**, muscular weakness, periodic paralysis, and myasthenia-like symptoms were also described.

Hypothyroidism

The most common symptoms of hypothyroidism are the **reduced and slow psychomotor activity**, apathy, inattentiveness, and drowsiness. Besides these symptoms, hypothyroidism can be associated with hypothermia, **myopathy**, **peripheral neuropathy**, **cerebellar ataxia** and **dementia**. Regarding the laboratory abnormalities, elevated CK, hyponatremia, and higher CSF protein value were described. The clinical symptoms and laboratory abnormalities are usually reversible when thyroid hormone is supplemented, however, the improvement may take several days after the proper treatment.

We do not aim to discuss the pediatric relations of hypothyroidism, but we feel important to mention, that thyroid hormone, thyroxin, is necessary for the normal intrauterine development. If the thyroxin level is low during the intrauterine period, the forming of cochlea and the migration of neurons may be disturbed, causing deafness, spasticity in the lower extremities, delayed psychomotor development, microcephaly, and mental deficiency (cretinism). It can be prevented by taking iodine and/or thyroxin in the first and second trimesters, however, if the treatment is started in the third trimester, it may only attenuate the symptoms. The **psychomotor development of children suffering from hypothyroidism is retarded**, and the closure of fontanelle is delayed too.

Pancreatic Encephalopathy

Although it is uncertain whether pancreatic encephalopathy is a different entity, encephalopathic symptoms including agitation, confusion, hallucinations, disturbances of consciousness and dysarthria were described in patients with severe pancreatitis, and could not be explained by any other abnormality. Since alcoholism is often associated with pancreatitis, delirium tremens and ionic changes with their consequences should be excluded before establishing the diagnosis of pancreatic encephalopathy.

DISORDERS OF ELECTROLYTE AND FLUID BALANCE

Hypo- and hypernatremia

Among the many causes of **hyponatremia**, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is of special importance, since it may occur in many neurological diseases, including head trauma, subarachnoid hemorrhage, meningitis and encephalitis, neoplasm, and even cerebral infarction. The diagnosis of SIADH should be suspected in any critically ill neurologic or neurosurgical patient with hyponatremia, when urine is hypertonic relative to the plasma. Since the low serum sodium level is not associated with similar decrease of intracellular sodium concentration, water will enter from the extracellular to the

intracellular compartment according to the osmotic gradient, and thus, leads to intracellular edema. Hyponatremia is characterized by drowsiness, confusion, epileptic seizure, and later severe disturbance of consciousness may also develop. It is a general rule in the metabolic encephalopathies that the severity of symptoms is related to the rapidity of development of metabolic abnormality. It is also true for the development of hyponatremia: the fast decline of serum sodium level is associated with severe symptoms, while the slow, gradual development is relatively well tolerated.

Treatment of hyponatremia is not an easy task, and it usually requires consultation with well trained internist. Since central pontine myelinolysis is a real risk in hyponatraemia, the rapid correction of low sodium concentration should be avoided. Although the first therapeutic consideration is usually an intravenous administration of NaCl, if the increased ADH secretion is proved, restriction of fluid intake could be the first therapeutic action. The daily fluid intake of only 500 mL is suggested when the serum sodium level is less than 120 mmol/L, and it should not exceed 1000 mL when the serum sodium concentration is between 120-130 mmol/L. Administration of sodium is recommended only, if the patient is comatose, suffers from epileptic seizures, or has a very low serum sodium level. If sodium is administered, particular attention has to be paid not to increase the serum sodium concentration faster than 10 mmol/L in the first 24 hours in order to avoid development of central pontine myelinolysis.

Certainly, not all neurological or neurosurgical patients with hyponatremia have SIADH, and different causes may require different treatment. Renal diseases (renal loss of salt), certain drugs (carbamazepine, oxcarbazepine), water poisoning, as well as the inadequate correction of salt loss may also result in hyponatremia. In differential diagnosis, measurement of serum and urine sodium concentration and osmolarity is necessary to establish the correct diagnosis.

Hypernatremia can be caused by decreased ADH secretion (diabetes insipidus), excessive sodium and restricted water intake (dehydration). The severity of the neurological consequences depends on the rapidity of development of hypernatremia. Slow elevation of sodium concentration, up to the level of 170 mmol/L, is usually well tolerated. However, fast and pronounced increase of sodium level may cause myoclonus, seizures, asterixis, and in severe cases, disturbance of consciousness. Hypernatremia, which is more severe in the serum than in the intracellular space, causes diffusion of water from the intracellular toward the extracellular compartment, leading to the decrease of the intracellular volume, and the consequent decrease of the brain volume. The shrinkage of the brain leads to retraction of the cerebral cortex from the dura, and thus, may result in rupture of the bridging veins and consequently subdural hematoma.

Hypo- and hyperkalemia

Both hypo- and hyperkalemia may cause generalized muscular weakness, although in case of hyperkalemia the cardiac complications (including the risk of cardiac arrest) are the most important. Hypokalemia may occur as a result of vomitus, diarrhoea, renal disease, Cushing's syndrome, hyperaldosteronism, as well as administration of certain drugs such as insulin, diuretics, and steroids. The

main causes of hyperkalemia are the renal failure, Addison's disease, hemolysis, but combination of angiotensin-converting enzyme inhibitor and potassium saving diuretics (spironolacton, amilorid) may also result in high serum potassium level espically in patients with chronic renal insufficiency.

Neurological consequences of hypo- and hypercalcemia were discussed above (Neurological consequences of endocrine diseases).

NEUROLOGICAL CONSEQUENCES OF CARDIOLOGICAL DISEASES

The discussion of cardiogenic stroke can be found in the relevant chapter, while the hypoxic-ischemic encephalopathy was discussed above, in this chapter. Briefly, different degrees of **global cerebral ischemia** may develop as the result of the decreased cardiac output, which might be the consequence of heart-valve diseases (aortic valve stenosis), decreased pump function (myocardium infarction, severe cardiomyopathy), or cardiac arrest (sick-sinus syndrome, atrio-ventricular block, ventricular fibrillation, carotis-sinus hyperesthesia, vaso-vagal syncope). Hypoxic-ischemic encephalopathy, as the neurological consequence of the cardiac arrest, was discussed above, at the beginning of this chapter.

The **neurological consequences and the differential diagnostic questions of short-lasting cardiac arrest or hypotension** are discussed below. Since the patient loses his/her consciousness transiently during both the epileptic seizure and the short lasting cardiac arrest or hypotension, the question of transient loss of consciousness stands at the interface of cardiology and neurology, and the neurologist is usually asked to confirm or exclude epilepsy. The differentiation of these diseases is especially difficult if there is no eyewitness, since the patient usually does not remember to the episode. Still, the next differences may help to differentiate syncope and epileptic seizures (see the table). Tongue biting, enuresis, convulsion, long-lasting postictal confusion and tenebrosity support the diagnosis of epilepsy, although it should be known that enuresis and certain abortive jerks may occur also in syncope. Repeated EEG examinations, Holter ECG, and detailed cardiological examination may also help the differentiation. However, it is important to know that negative interictal EEG does not exclude epilepsy, similarly, negative ECG does not exclude the cardiac origin either. As a general rule, the neurological and cardiological examinations have to be made parallelly, nevertheless, the cardiological examination takes priority. Its explanation is that the repeated cardiac arrest may cause death, while the epileptic seizure has no so severe consequences. If neither cardiological, nor neurological origin can be found, but the attacks are repeated from time to time, ex juvantibus administration of anticonvulsants can be tried (e.g. 2x500 mg valproic acid).

Table 1
The differentiation of syncope and epilepsy

	Syncope	Epilepsy
<i>Body position</i>	Mostly, but not exclusively, in standing position	Independent of body position
<i>Initial symptoms</i>	Nausea, turning pale, fatigue, blurred vision	Rarely aura sign
<i>Pulse, blood pressure</i>	Low blood pressure, pulse could be normal, but mostly weak; Bradycardia supports vaso-vagal syncope	Tachycardia, hypertension
<i>Tongue biting</i>	Rare	Frequent
<i>Enuresis</i>	Rare	Frequent
<i>Convulsion</i>	Rare, but 1-2 myoclonus, jerks may occur	Frequent
<i>Postictal confusion</i>	Usually does not occur	Postictal tenebrosity is a frequent finding

Neurological consequences of malignancies

The neurological consequences of malignant diseases include metastases of the central nervous system, paraneoplastic syndromes, and neurological complications of chemotherapy/radiotherapy. Metastases may affect 1) the parenchyma of the central nervous system, 2) the meninges, 3) and the bones, including vertebra, which fracture may cause compression of the myelon. Neurological complications of chemotherapy/radiotherapy include polyneuropathy, encephalopathy, opportunistic infections of the central nervous system, etc. The detailed discussion can be found in the relevant chapter of this book.

Neurological consequences of other internal medicine diseases

The limited extent of this chapter does not allow the discussion of the neurological consequences of all internal medicine diseases. The diseases of the nervous system due to vitamin or nutritional deficiencies are not discussed here. For example, B12 vitamin deficiency, which is not rare in vegetarians or in patients suffering from anemia perniciosa, may cause subacute combined degeneration of the spinal cord, dementia, and polyneuropathy. We did not deal with thrombophilic conditions, which considerably increase the risk of stroke and sinus thrombosis. Neurological consequences of intoxications and overdose of different medicines (carbamazepine, warfarin, etc.) could neither be discussed in details. Concerning these and other questions, we refer to the internal medicine and neurological handbooks.

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Bedside differential diagnosis of acute disturbances of hypnoid type of consciousness

LÁSZLÓ CSIBA MD.

Introduction

The causative diagnosis of consciousness disturbances is one of the most important and difficult clinical tasks. While an incipient renal failure can have vague symptoms, the primary (e.g. commotion) or secondary (e.g. cardiac arrest) insults of the brain provoke a quick disturbance of consciousness, due to the significant oxygen and energy demand of the brain. Sooner or later, every practicing physician will provide emergency care for a patient suffering from disturbances of consciousness, and will meet the difficulty of the differential diagnosis, too.

Hypnoid types of disturbances of consciousness (HDC)

This chapter discusses the **hypnoid types of disturbances of consciousness**. This patient is similar to a sleeping healthy person. In everyday practice these conditions can be divided into two groups:

A. The patient becomes unconscious very *suddenly* (usually in seconds). Because the pathological event is transient (such as epileptic seizure or transient cardiac arrhythmia), the patient regains his/her awareness *quickly*.

The possible causes:

- a) Central nervous system
 - i. mild head injury resulting only in reversible damage in neurons and axons (concussion without structural impairment).
 - ii. epilepsy
 - iii. psychogenic mechanism
- b) Heart: temporary dysfunction of the pump function of the heart (e.g. cardiac arrest) or transient arrhythmias.
- c) Reflex vasodilation with or without the presence of “b” mechanisms (see also Figure 1)

B. The HDC's caused by metabolic dysfunction (e.g. uremia, hypo- or hyperglycemia, barbiturate intoxication etc). Belong to another group, the group of *slowly* developing HDC, because longer time (minutes, hours, sometimes days) is needed to reach the critical level of blood concentration (e.g. glucose, barbiturate, ammonia) for the dysfunction of the brain. The returning speed of consciousness

depends on the normalization of blood concentration of the metabolic factor responsible for the HDC.

The differential diagnosis of *slowly* (mostly metabolic) and *quickly* (mostly epilepsy and cardiac/reflex origin) developing of disturbances of consciousness is also an important topic of neurology and will be discussed in another chapter.

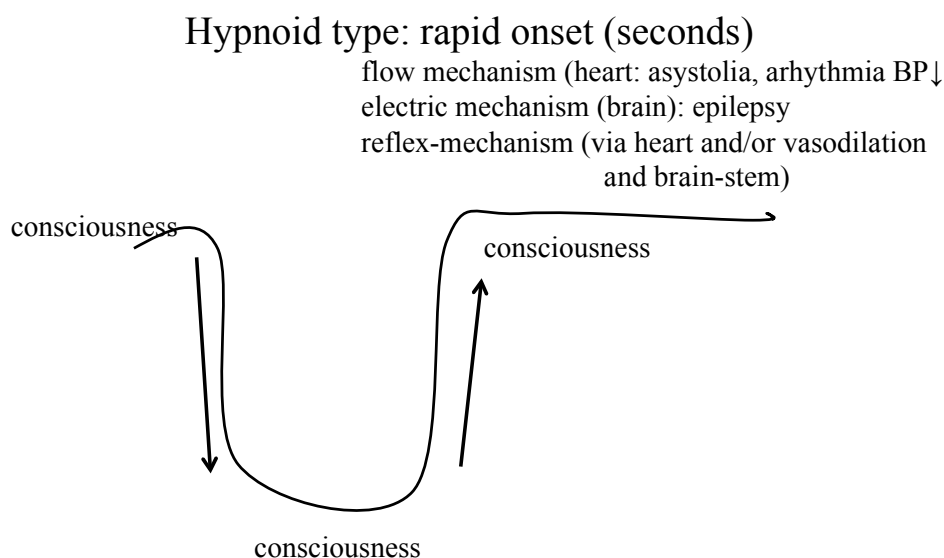


Figure 1

The causes might be in the central nervous system (e.g. epilepsy), heart (arrhythmia, cardiac arrest), or caused by reflex-mechanism (peripheral vasodilation with consequent ischemia in the central nervous system).

This chapter does not deal with *HDCs developing and disappearing quickly* (Figure 1), but with those developing *slowly in minutes or hours* (Figure 2), and not struck as lightning.

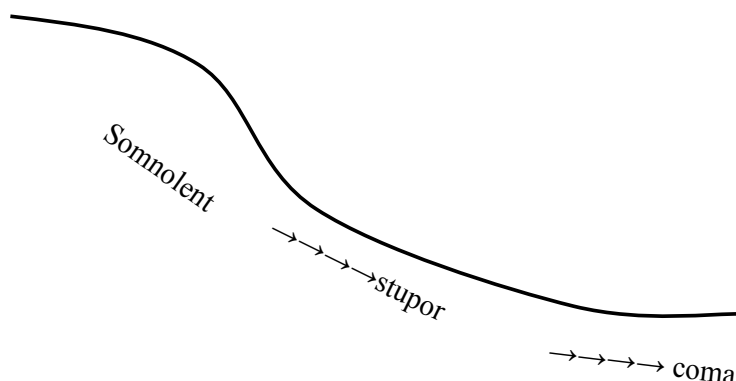


Figure 2

The relatively slowly developing HDC is a frequent finding on ICUs treating intoxicated or metabolic failure (diabetes, liver, kidney etc.) patients or patients with increasing intracranial pressure.

Typical example of slowly developing HDC is the barbiturate intoxication, where drowsiness, deep sleep and coma develop parallel to the drug absorption.

Coma is the most severe stage of hypnoid unconsciousness, in which the patient cannot be woken up and does not response to stimuli. There is no evidence of awareness of self and environment. The patient with continuously *closed eyes* does not react to external stimuli. The most important symptoms are the absence of spontaneous eye opening and the circadian rhythm of sleep cycles.

The *spontaneous* or provoked eye opening may return in patients suffering from permanent unconsciousness. The *reoccurrence of eye opening and the absence of conscious responses* refer to vegetative state (VS, also called as apallic syndrome or coma vigil, incorrectly).

According to the American Academy of Neurology the criteria of vegetative state are the following:

1. No evidence of sustained, reproducible, purposeful or voluntary behavioral responses to visual, auditory, tactile or noxious stimuli.
2. No evidence of language comprehension or expression.
3. Return of sleep-wake cycles (periodical eye opening).

The vegetative functions are intact in patients suffering from vegetative state, even responsive or spontaneous movements may occur, but these are always *purposeless*. They can make sounds or grimace, but inadequately. Patients suffering from vegetative condition are not likely to recover, which is difficult to explain to the family members.

In *minimal conscious state (MCS)* limited but clearly discernible evidence of self and environmental awareness is demonstrated comparing to the vegetative state.

To make the diagnosis of MCS, one or more of the following criteria must be fulfilled:

1. Obeying simple commands.
2. Gestural or verbal yes/no responses (regardless of accuracy).
3. Intelligible verbalization.

A few examples:

- crying, smiling, laughing in response to the linguistic or visual content of emotional but not to neutral topics or stimuli,
- vocalizations or gestures that occur in direct response to the linguistic content of questions,
- reaching for objects that demonstrates a clear relationship between object location and direction of reach,
- touching or holding objects in a manner that accommodates the size and shape of the object,
- pursuit eye movement or sustained fixation that occurs in direct response to the moving object.

In the latest years, some patients considered being in minimal conscious state for years or decades were reported to have regained the awareness and ability of communication.

The classification of the severity of hypnoid types of disturbances of consciousness (HDC)

This large group of consciousness disturbances **does not involve only the coma**, but it contains also the state of somnolence and stupor too. *All patients* suffering from any type of hypnoid unconsciousness are alike sleeping people, who are healthy otherwise. If not provoked by pain or any other stimulus, the patient is lying *with his/her eyes closed*.

Somnolence: the patient can be woken up easily, but sleeps away right after being left alone.

Stupor (also known as sopor): the patient seems to be sleeping abnormally deeply, but reflects with motor or verbal responses for motor or verbal stimuli.

Coma (from a greek word meaning deep sleep): The patient does not react for strong pain stimuli, but both the spontaneous breathing and circulation are intact.

In the everyday practice, the terms somnolent-stuporous and stuporo-comatose are also widely used for indicating the severity, but cannot be used for quantitative assessments. Instead, we use different coma scales to record the level of consciousness.

Table 1
The Glasgow Coma Scale.
The lowest possible score of Glasgow Coma scale is 3, while the highest is 15 (fully awake person).

Eye-opening	Spontaneous	4
	In response to voice	3
	In response to painful stimuli	2
	No response	1
Motor response	Obeying command	6
	Localizes to pain	5
	Withdraws to pain	4
	Abnormal flexor response	3
	Extensor posturing	2
	No response	1
Verbal response	Oriented	5
	Confused conversation	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No verbal response	1

A recommendation published in 2010 compared the scales, which are commonly used to assess the disorders of consciousness. The use of Coma Recovery Scale-Revised (Table 3) is recommended with minimal limitations. The total score range is between 0-23, and the assessment takes 25 minutes.

Table 2

The most frequently used scales in the assessment of consciousness disturbances

CRS-R	Coma Recovery Scale-Revised
CLOCS	Comprehensive Levels of Consciousness Scale
CNC	Coma/Near-Coma Scale
FOUR	Full Outline of UnResponsiveness Score
GCS	Glasgow Coma Scale
GLS	Glasgow-Liege Coma Scale
INNS	Innsbruck Coma Scale
LOEW	Loewenstein Communication Scale
RLS85	Swedish Reaction Level Scale-1985
SMART	Sensory Modality Assessment Technique
SSAM	Sensory Stimulation Assessment Measure
WHIM	Wessex Head Injury Matrix
WNSSP	Western Neuro Sensory Stimulation Profile

We can find *confused* patients in every hospital ward who are desoriented in space and time, especially at night hours, but can be contacted, and communicate well (no aphasia!). In these cases *desorientation and consequent agitation or aggression* dominate and these patients do not suffer from HDC.

Delirium due to alcoholism or other causes is characterized by *hallucinations and agitation* and intense autonomic symptoms. Patients suffering from delirium are also **alert** and also do not belong to the group of HDC.

Table 3
The Coma Recovery Scale-Revised

1. Auditory function scale 4 Consistent movement to command 3 Reproducible movement to command 2 Localization to sound 1 Auditory startle 0 None
2. Visual function scale 5 Object recognition 4 Object localization: reaching 3 Visual pursuit 2 Fixation 1 Visual startle 0 None
3. Motor function scale 6 Functional object use 5 Automatic motor response 4 Object manipulation 3 Localization to noxious stimulation 2 Flexion withdrawal 1 Abnormal posturing 0 None/Flaccid
4. Oromotor/Verbal function scale 3 Intelligible verbalization 2 Vocalization/Oral movement 1 Oral reflexive movement 0 None
5. Communication scale 2 Functional: accurate 1 Non-functional: intentional 0 None
6. Arousal scale 3 Attention 2 Eye opening without stimulation 1 Eye opening with stimulation 0 Unarousable

The examination of patients suffering from HDC

The reliable data on medical history and risk factors are very important. Information should be collected not just about the previous diseases, such as hypertension, diabetes, cardiovascular or hematological disorders, depression, fever, but the medications too. Life habits are very important (medication? alcohol/drug consumption? problems in the private life or at work?).

It should be investigated if the family members experienced any change in the patient's behavior, difficulty in his/her verbal communication and self-expression, or the signs of lightheadedness. Did the patient complain about numbness, visual problems or double vision? Did he/she experience any trauma? Painful stimuli should be used to assess the severity of the consciousness disorder.



Figure 3

Painful stimuli are applied either on the supraorbital area, sternum or on both mastoid processes. The symmetrical or asymmetrical movements of the extremities can be assessed.

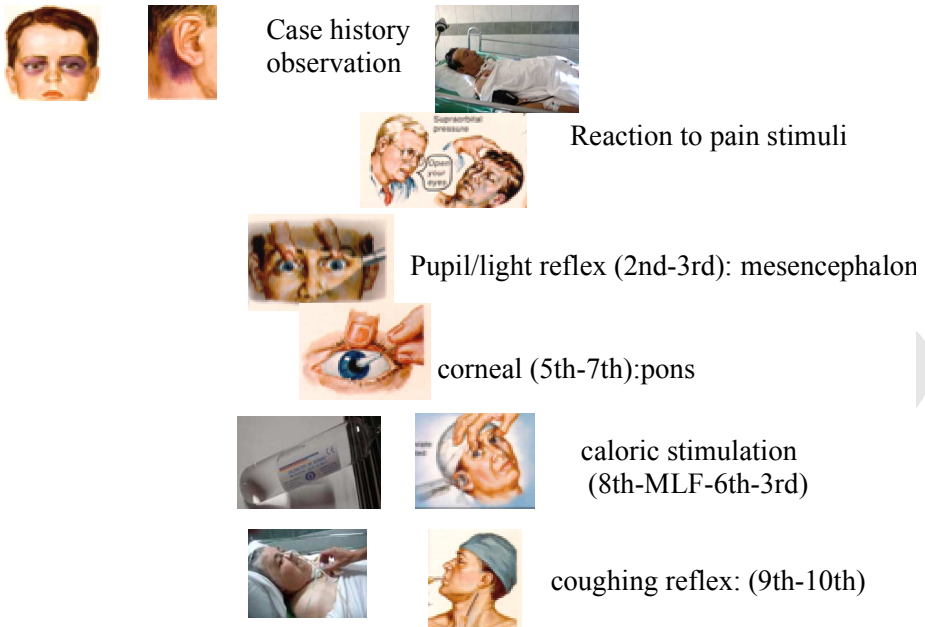


Figure 4
The most important steps of neurological examination in HDC

Bedside differential diagnostic considerations of patients suffering from acute HDC

The normal conscious state requires the intact function of the reticular formation located in the brainstem and the intact function of the supratentorial region activated by the reticular formation. These facts help us to understand the differential diagnosis of consciousness disorders.

Many agents can harm the supratentorial region directly or indirectly, but an isolated brainstem lesion can also cause coma (e.g. occlusion of the basilar artery affecting the brainstem reticular formation).

It is essential to understand that whatever damages the supratentorial region, hypnoid unconsciousness develops only if the pathological process has diffuse/extended effect in the supratentorial area.

Accepting this postulate it is easy to understand why an acute viral encephalitis or barbiturate intoxication will result in disturbance of consciousness while a large territorial cerebral infarct *without mass effect* will not alter the consciousness. E.g. always look for other reason of unconsciousness, if CT or MRI reveals focal supratentorial ischemia without mass effect!

With other words: an *acute supratentorial focal ischemia or bleeding* without mass effect (without midline shift, without increased pressure etc.) will NOT result in HDC, but an acute event with space occupying effect can be accompanied with HCD. *Last but not least, all of our statements are valid only for acute events!*

A *slowly growing tumor* or subdural hematoma does not necessarily result in disturbance of consciousness although the CT reveals space occupying/mass effect with midline shift etc.

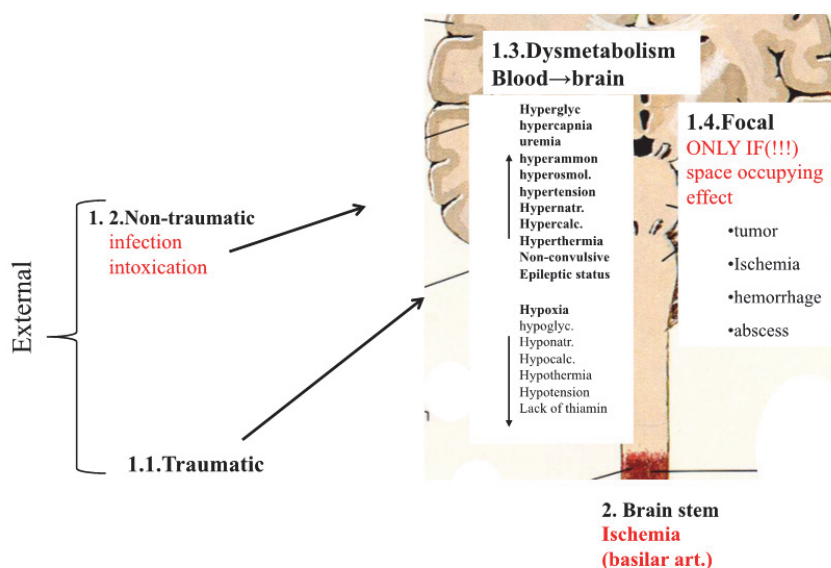


Figure 5

The first group (1.1-1.4) contains those acute external and internal agents, which can cause hypnoid unconsciousness due to the diffuse damage/impact on the supratentorial region. Ischemia of the brainstem or hemorrhage (2) can cause hypnoid unconsciousness by damaging the reticular formation in the brainstem. Of course, the mechanism 1.1-1.4 and 2 can be combined.

The diagnostic procedures involving the examination of the relevant agents are summarized in Figure 6.

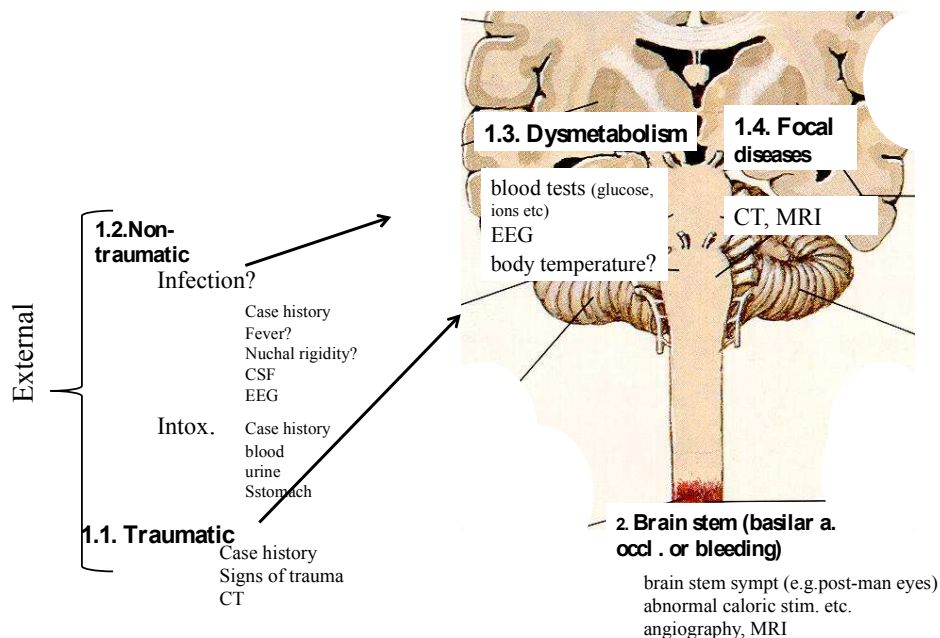


Figure 6
Possible causes and diagnostic steps in HDC patients

Now, we can understand that **every** condition listed in 1.1-1.4 might have negative impact on the function of the whole supratentorial region (even a mild brain concussion, without any apparent CT or MRI abnormality can result in transient loss of consciousness because of the transient colloidal changes of neurons caused by the head trauma (mild and transient but also diffuse impact on the supratentorial region!).

It is also easy to understand that viral encephalitis impairs diffusely both gray and white matter, and barbiturate intoxication, electrolyte imbalance, hypoglycemia, hyperglycemia, hormonal defects and hypothermia result in also diffuse dysfunction of the supratentorial region.

Example (epidural hematoma): transient disturbances of consciousness may develop immediately after trauma because of the diffuse brain concussion (energy impact) provoking colloidal changes in the neurons. The patient regains his/her consciousness (lucid interval) as the colloidal changes disappear, but after some hours, the increasing intracranial arterial hematoma compresses the ipsilateral and contralateral hemisphere, then HDC develops with hemi- or tetraparesis, coma and brainstem herniation.

It is important to emphasize again, that in *acute cases* the mass effect caused by supratentorial processes correlates well with the severity of consciousness disturbances. *If the mass effect evolves very slowly* (e.g. in case of tumors or chronic subdural hematoma increasing slowly for weeks), even a significant midline shift or considerable mass effect might remain with intact consciousness!

Diagnosis

We can identify the cause of HDC (listed in 1.1-1.4 or 2 sections of Figure 5) responsible for the unconsciousness by knowing the medical history and using examinations indicated on Figure 6.

Brainstem is probable the lesion's site if the patient

- had no trauma,
- no intoxicated,
- no sign of infection,
- normal labor parameters,
- normal supratentorial CT or MRI finding, or the CT/MRI show lesions without any mass effect.
-

The anisocoria, diverging eyes, tetraparesis, absence of brainstem reflexes may also suggest the causative role of brain stem, which can be confirmed by basilar artery angiography and brainstem MRI.

The therapy depends on the causative agent, so we do not provide further details about it. In case of basilar artery occlusion thrombolysis is indicated, if HDC developed due to intoxication, detoxification is needed, etc.

Important! If CT or MRI reveals ischemia or hemorrhage without any mass effect, and the patient has normal conscious state, but hours later he/she shows the signs of any consciousness disturbances, such as somnolence, the hemorrhage is likely to have increased suddenly, or malignant ischemic cerebral edema could have developed, especially if the patient has normal laboratory result, did not experience fever, and did not get any sedatives. In these cases imaging should be performed again!

Prognosis

The prognosis depends on the causative agent, the patient's age and general condition. According to the survey of the American Academy of Neurology, patients suffering from coma caused by cardiac arrest (hypoxia and ischemia) are likely to have poor prognosis after 3 days, if any of the followings is present:

- absent pupillary, corneal, coughing reflexes, absent reaction to caloric reflex test, absent or extensor motor responses (evidence A), the presence of seizures or myoclonus status epilepticus (evidence B);

- bilateral absence of the cortical component of the SSEP predicts a poor outcome (evidence B);
- burst-suppression pattern or generalized epileptiform activity are associated with poor outcome (evidence C);
- serum neuron-specific enolase (NSE, only this marker has verified diagnostic value!) levels $>33 \mu\text{g/L}$ at days 1 to 3 predict poor outcome (evidence B).
- There are insufficient data to support or refute whether the measurement of intracranial pressure, the oxygenisation of the brain, and neuroimaging (MRI, CT) are indicative of poor outcome or not.

Summary

In case of consciousness disturbances the following examinations are essential:

1. Analysis of the detailed medical history including the information obtained from family members.
2. General physical examination, neurological examination, and the examination of external injuries, including:
 - responses to painful stimuli,
 - the isocoria of the pupils, eye positions and movements, the presence or absence of pupillary, corneal, and coughing reflexes.
3. The physical examination, the analysis of the imaging and laboratory results may provide the bedside diagnosis of the causative agents listed in Figure 5-6.

The treatment of consciousness disturbances can be operative or conservative depending on the causative agents.

Brain death

We would like to call the attention to **some** diagnostic criteria of brain death (the irreversible loss of all brain functions above the level of foramen magnum). It is diagnosed if the patient does not have spontaneous breathing, and the pupillary, corneal, coughing reflexes and the caloric reactions are also absent.

There are numerous mandatory investigations, here we draw your attention to the **apnea-test**:

- The level of CO_2 should be in the range of 38-42 mmHg.
- Ten minutes inhalation of 100% oxygen.
- After disconnection of the ventilator a small catheter with 100% oxygen (6 L/min) should be placed into the intubation tube (for adequate tissue oxygen supply).
- Blood samples is drawn for **testing arterial pCO_2 level**.

- If the repeated sampling with increased CO₂ level (60 mmHg or above) cannot return the spontaneous breath, the respiration center of the brain is damaged irreversibly.

The diagnosis of brain death primarily is based on clinical criteria, but we can perform other examinations too, such as imaging techniques, evoked responses of the brainstem, transcranial Doppler, EEG, angiography and scintigraphy.

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Neuromuscular disorders

FERENC MECHLER MD.

The neuromuscular disorders include three groups:

- I. Myogenic muscle diseases or myopathies
- II. Neurogenic muscle diseases
- III. Diseases of neuromuscular transmission

I. Myopathies

The myopathies are primary muscle diseases, where the cause of the symptoms of muscle lesion is in itself the muscle. They could be classified as follows:

- A. Genetically determined myopathies
- B. Inflammatory myopathies
- C. Myopathies associated with endocrine and metabolic diseases

We discuss the more important diseases in clinical practice.

A. Genetically determined myopathies

A1. The muscular dystrophies are genetically determined muscle diseases with progressive muscle weakness and atrophy.

A1a. Their most well known and tragic form is the *Duchenne muscular dystrophy*, which is an X-linked recessive inherited disease. The prevalence is one in 3500 newborn boys.

The *clinical symptoms*: in the first years of life the boy has a peculiar, so called waddling gait, he has difficulties climbing stairs and falls frequently. On neurological investigation the weakness of the proximal muscles (shoulder and pelvic girdles, as well as proximal upper and lower limb muscles) is found, later the muscles will be atrophied. The lumbar lordosis and the pseudohypertrophy of calves are also striking. The progression is very fast, they are forced to use wheelchair at about 10 years of age. They develop severe contractions and spine deformity and they die at 15-25 years of age, usually in pneumonia.

The extremely high serum CK value is characteristic already in the first months of life: one or two hundred folds of the normal value. The EMG investigation shows a severe myogenic lesion with the decrease of duration and amplitudes of motor unit action potentials as well increase of polyphasic potentials. The muscle biopsy shows a great variety of fiber diameter, atrophic fibers and increase of connective tissue.

A1b. The allelic form of Duchenne dystrophy is the more benign *Becker type muscular dystrophy*. The onset is later, about between 5 to 15 years of age. The clinical and laboratory characteristics are similar to those in Duchenne, but the progression is slower.

The genetic background: the gene responsible for the disease is located on Xp21 locus, one of the biggest gene in the human genome, containing two and half million base pairs with 69 exons and coding a subsarcolemmal protein, the so called **dystrophin**. The molecular genetic studies detected, that about 2/3 of the Duchenne and Becker patients show the deletion of one or more exons, the rest have point mutations. The deletions could be detected by PCR. In Duchenne dystrophy the mutation results in a stop codon, therefore the dystrophin is missing from the muscle, while in Becker dystrophy the result is a semifunctional dystrophin in lack of stop codon. In cases of point mutation, immunohistochemistry is used from muscle biopsy.

Diagnostics: clinical investigation, serum CK determination, EMG, muscle biopsy -histology and immunohistochemistry-, molecular genetics (deletion screening).

Therapy: the causal therapy would be the gene therapy, however in spite of the intensive research work, there are no clinically useful gene therapies available, up till now. The usual procedures include symptomatic, palliative treatments: E vitamin against free radical damage in atrophic process, uridine triphosphates, creatine monohydrate, but there are no evidences for their real effectiveness. The intentionel physiotherapy has an important role in treatment.

The unique confirmed but transient therapeutic intervention is the *use of steroid in the early period of Duchenne muscular dystrophy*, with a dose of 0,75 mg/kg/day. This prevents the progression for 1 to 4 years, transiently the symptoms may improve, however, after this period the progression proceeds. Its drawback is the early presence of severe steroid side effects.

A1c. Limb-girdle muscular dystrophies.

They represent autosomal dominant or recessive diseases.

Clinical symptoms: the weakness and atrophy of the proximal muscles in upper and lower limbs as well as in shoulder and pelvic girdles. The onset is in the second or third decade. The progression is slower than in Duchenne or Becker, they are able to walk till 40 years of age.

The serum CK value is usually increased, but not so high as in Duchenne disease. The EMG shows myogenic lesion. The prevalence is 1: 20000. The genetic studies showed that in majority of patients there are mutations of several autosomal genes coding numerous muscle proteins, usually membrane glycoproteins, like *sarcoglycans*, *dysferlin*, *dystroglycan*, *caveolin-3*, *laminin*, etc.

For genetic diagnosis, immunohistochemical investigations are used from muscle biopsy. The diagnostic procedures include serum enzyme and EMG investigations, too.

Therapeutic procedures as in dystrophinopathies.

A1d. Facioscapulohumeral muscular dystrophy (FSH)

FSH is an autosomal dominant disease with a similar prevalence to the limb girdle types. The onset is usually in the middle of the second decade.

Clinical symptoms: weakness and atrophy in the shoulder and proximal upper limb muscles as well as in facial muscles. The mimic and whistling is poor, the scapula alata presents. There is a progressive difficulty elevating the arms. In the lower limbs only the tibial anterior muscle is affected for a long time. The progression is slow. The EMG is myogenic.

Genetic background: the gene responsible is located on 4q35, but the gene is not entirely identified yet. However, it turned out that there is an 3.2 kb tandem repeat in this gene region which is deleted in FSH patients, so the direct genetical diagnosis is available.

The diagnostic and therapeutic procedures are similar to the previous ones.

A2. Myotonic diseases

Myotonia is the disorder of muscle membrane manifested in increased contraction and delayed relaxation of muscle fiber. The patients are complaining that their muscles are rigid and stiff, they have difficulties in starting movements.

The genetically determined myotonias include three entities:

A2a. Myotonia congenita

A2b. Paramyotonia congenita

A2c. Dystrophia myotonica

A2a. The onset is present in the first decade: the movements of the child are slow and rigid, they could start movements with difficulty, can not run properly. Cold provokes myotonia, while repeating the movements alleviates it. The inheritance pattern is autosomal dominant.

A2b. Paramyotonia differs from the previous one that repeating of movements increases myotonia and the provoking effect of cold is stronger.

In the diagnosis of myotonias the *EMG investigation is essential*: either spontaneously or moving the electrode, high frequency discharges, so called *myotonic salve* could be recorded which sounds in the loud-speaker as a diving bomber, and may have a diagnostic value. The electrophysiological and molecular genetic studies confirmed that these myotonias are *channelopathies*. Myotonia congenita is the result of mutation of the gene coding muscle *chloride channel*, while paramyotonia is caused by point mutation of the gene coding the muscle *sodium channel*.

A2c. Dystrophia myotonica

This is a multisystemic disease with autosomal dominant inheritance. The two basic symptoms are muscle dystrophy and myotonia, however, the patients have many other symptoms, too: ptosis, endocrine disturbances like testis or ovarium atrophy, cataracts, frontal boldness, dysarthria, dysphagia, immune disturbances, mental retardation.

The *genetic background*: The gene responsible is located on 19q13 and codes a protein kinase enzyme which is present in almost every cell types. The gene mutation is a CTG triplet expansion and results in a very wide symptomatology.

Therapy: Acetazolamide and mexiletine is used for alleviating myotonia.

B. Inflammatory myopathies (myosites)

The myosites can be classified as

1. idiopathic or autoimmune myositis,
2. symptomatic myositis.

In the clinical practice the *autoimmune myosites* have prominent importance.

They include:

- B1. Polymyositis (PM)
- B2. Dermatomyositis (DM)
- B3. Inclusion body myositis (IBM)

B1. The clinical symptoms of *polymyositis* usually start at the middle age. The weakness of the proximal muscles is characteristic in addition to the affection of neck muscles. Dysarthria and dysphagia are frequent. Most of the patients complain about muscle pain and tenderness. The deep reflexes are normal or decreased. Half of the patients show muscle atrophy, too.

Diagnostics: the inflammatory markers (sedimentation rate, CRP) and se-CK values are increased in acute cases. *EMG* shows myogenic lesion, and fibrillation potentials in acute cases. *Muscle biopsy* shows peri- and endomysial mononuclear infiltration, on *immunohistochemistry* CD⁺ T-cells are characteristic.

B2. The clinical symptoms of *dermatomyositis* are consistent with those of PM, in addition to skin signs, mainly erythemas on the different parts of the body. Concerning the onset, there are two age groups: childhood and old age.

The laboratory and EMG findings are similar to those in polymyositis.

Muscle biopsy: mononuclear infiltrations with perifascicular muscle fiber atrophy are characteristic. *Immunohistochemistry* shows CD⁺ T-cells.

B3. *Inclusion body myositis* is different from the previous myosites.

The onset is in the elderly age, usually above 50. The muscle weakness and atrophy is conspicuous in the distal muscles, the muscle pain is not frequent. The affection of the forearm flexors and the quadriceps muscle is characteristic.

The muscle biopsy findings are very different: rimmed vacuoles are present in the muscle fibers in addition to mononuclear infiltrations. Electronmicroscopy can detect inclusions in nucleus and cytoplasm. The autoimmune origin of this form is debated by several specialists.

Therapy: Polymyositis and dermatomyositis are well treatable diseases.

The first choice is steroid (Medrol), in a dose of 60–100 mg per day. Usually we start with infusion, than continue orally until the symptoms essentially improve,

then is gradually decreased to a maintaining dose which should be given long-lasting.

If the response to steroid is insufficient other immunosuppressive drugs can be indicated: cyclosporin, cyclophosphamide or iv. immunoglobulin (IVIG).

IBM is resistant to immunosuppression, the only exception is IVIG: about 30 % of IBM patients react practically well to IVIG.

II. Neurogenic muscle disorders

They could be divided into 2 big groups:

- A. Diseases of the motor neuron cells in the anterior horn of spinal cord
- B. Peripheral nerve damages, neuropathies

A. Diseases of the motor neuron cells in the anterior horn of spinal cord

Among the group A, *amyotrophic lateral sclerosis (ALS)* has an outstanding importance in clinical practice.

The pathological basis of ALS is the progressive degeneration of the upper and lower motor neurons. The 90 % of patients are sporadic, about 5 – 10 % are familial. The onset of the clinical symptoms is usually at 40 – 60 years of age, very rarely in young age. Generally the first symptoms are painless weakness and atrophy in the small hand muscles which progress proximally. Then the signs of upper motor neuron lesions appear, usually in lower limbs, followed by bulbar paresis, dysarthria, dysphagia, finally by the weakness of respiratory muscles. Diffuse fasciculation is characteristic. The vegetative functions and the consciousness are spared. The duration of the disease process is usually 3 – 5 years, in case of bulbar onset it is shorter.

Etiology: The etiology of *sporadic ALS* is not known. It is generally accepted that ALS is a multifactorial disease as a common result of several factors like glutamate excitotoxicity, oxidative stress, lacking of neurotrophic factors, disturbances of immune system, genetic factors, etc, leading to the degeneration of motor neuron cells. The most accepted and studied factor is the *glutamate excitotoxicity* which gave the basis for the therapeutic use of a glutamate antagonist, *riluzole* in ALS. It was found that the drug slows down the progression for a few months.

The *molecular genetic basis in certain familial cases* is known: the gene is located in 21q22 locus coding the superoxide dismutase enzyme and its point mutation leads to the disease.

Diagnostics: The routine laboratory findings are normal. *EMG* shows denervation signs in muscles and widespread fasciculations. The changes in the parameters of motor unit action potentials are characteristic to motoneuron lesion. The progression of the process can be followed by *EMG*. On *ENG* the motor and sensory nerve conduction velocities are normal, the amplitude of motor potential is decreased but sensory amplitude is normal. The *magnetic evoked potential (MEP)*

studies may detect subclinical pyramidal lesion. In *muscle histological investigation* the grouping of atrophic fibers and of the fiber types are characteristic.

Differential diagnosis: First of all the *pathological processes in the cervical spinal cord* should be excluded (intramedullar neoplasms, myelopathies, severe spondylosis, etc.) because they can mimic the symptoms of ALS, therefore *cervical MRI* investigation is obligatory. Multifocal motor neuropathy should be also excluded.

Therapy: in addition to riluzole, symptomatic, palliative procedures are used.

Messages

Careful investigation of the musculature of patients complaining muscle weakness to detect possible local or global muscle atrophy.

In case of small hand muscle atrophy and diffuse fasciculation there is strong possibility of ALS.

Molecular genetic screening is necessary in several muscle diseases.

Literature recommended

Karpati G. et al: *Disorders of Voluntary Muscle*, Cambridge Univ. Press, 2002.

III Disorders of neuromuscular transmission

Amongst the disorders of neuromuscular transmission the most important diseases are the myasthenia gravis and the Lambert – Eaton syndrome.

III 1. Myasthenia gravis

Autimmune disease, where autoantibodies attack the postsynaptic Ach receptors resulting their gradual degradation and destruction. Thus, few motoneuron action potentials evoke action potential on muscle fibers leading muscle weakness. The thymus plays an important role in producing autoantibodies.

Three clinical forms are known in myasthenia gravis: *ocular, bulbar and generalized.*

The *clinical symptoms in ocular myasthenia:* ptosis and paresis of the extraocular muscles. The ocular forms have a tendency to generalize.

In the *bulbar form* the patients show tiredness and weakness of muscles performing speech and swallowing leading to hypophonia, dysarthria and dysphagia.

In the *generalized form* a widespread muscle weakness is characteristic, the affection of proximal muscles is more prominent than the distal ones. The weakness of respiratory muscles may lead to respiratory insufficiency.

The fluctuation of symptoms are characteristic in every forms, they are mild in the morning and worsen in evening.

Diagnosis:

Bilateral symptoms, ptosis, dysphonia, dysphagia, generalized weakness are suspicious to myasthenia gravis.

The necessary *diagnostic procedures*:

- a. Increase of *antibody titer against Ach receptors*.
- b. *Tensilon test*: iv Tensilon (short-acting Ach-esterase inhibitor) improves the symptoms dramatically.
- c. *Repetitive stimulation test*: the amplitude of muscle evoked response to 3 Hz nerve stimulation decreases significantly. After tetanic stimulation (20-30 Hz) a posttetanic exhaustion can be observed.
- d. *Single fiber EMG* shows expressed jitter increase.
- e. *Chest CT* may show the possible thymus hyperplasia or tumor.

Differential diagnosis:

Myasthenic syndrome which is characterized by vegetative symptoms in addition to generalized weakness.

Polymyositis, usually with high CK value.

Therapy:

Ach-esterase inhibitors, like pyridostigmin (Mestinon) in a dose of 120-480 mg/day, ambenonium (Mytelase) in a dose of 5-30 mg/day.

Immunsuppression: corticosteroids, azathioprine, cyclosporin, cyclophosphamide.

Plasmapheresis, iv.immunoglobulin (IVIG).

Thymectomy, in case of thymoma.

Myasthenic crisis indicates urgent intensive care unit admission, plasmapheresis, IVIG.

Several patients need a maintaining, slow dose corticosteroid therapy.

III 2. Myasthenic syndrome, Lambert-Eaton disease

Autoimmune disease, associated with small cell lung carcinoma in half of the patients. The autoantibodies attack the presynaptic voltage-gated Ca channels and inhibit the Ach release which results in weakness and tiredness mainly in the proximal muscles. In addition to these symptoms, vegetative signs could be observed: mouth dryness, obstipation, potency disturbances, urinary dysfunction.

Diagnostic procedures:

- a. *Repetitive stimulation test*: contrary to myasthenia gravis, the amplitudes of evoked responses are low. Tetanic stimulation (20-30 Hz) results in an intense facilitation (100-200%) of amplitudes.
- b. *EMG* shows no myogenic lesion.
- c. The *VGCC antibody* titer is high.
- d. *Chest CT* for confirmation or exclusion of lung tumor.

Differential diagnosis: myasthenia gravis, early phase of ALS.

Therapy: pyridostigmine, diaminopyridine, guanidine.

Immunomodulation: corticosteroids, azathioprine, plasmapheresis, IVIG

The chronic course of the disease needs a long-standing therapy.

Summary

Repetitive stimulation test is indicated in the following clinical symptoms:

- *tiredness, weakness progressing to evening, particularly with dysphonia and dysphagia,*
- *ptosis and diplopia appearing suddenly, perhaps with fluctuation during the day.*

Pain in the low back, neck and extremities

KLÁRA FEKETE MD, AND LÁSZLÓ CSIBA MD.

Introduction

The pain is the most common disorders/diseases of the spine and needs a team work of the rheumatologist, orthopedist and neurologist, but the general practitioners meet also both acute and chronic patients. The prevalence of low back pain is high up till 60% of the population, the fifth most common cause of patient's visits (but only 1% has root symptoms). Patients usually present to their primary care physician but are commonly referred to a neurologist. When back pain persists, and/or if neurologic symptoms develop, or it may be the first sign of a serious disease (ie, malignancy).

The low back pain can be diffuse, or the pain can be localized onto the distribution of one or more nerve roots with associated weakness, sensory disturbances and loss of reflexes. Studies did not show significant differences in the geographical spreading. Acute pain lasts 4 weeks, subacute more than 4 weeks, and chronic more than 12 weeks. Acute pain often responds well to pharmacotherapy whereas chronic pain may be difficult to treat.

We have to emphasize, that not only disc herniation but numerous other diseases can provoke cervical, thoracic or lumbar pain (spondylosis, spondylolisthesis, Facet-diseases, ankylosis, metastasis etc). Consequently, the pains mentioned above need multidisciplinary approach and many times follow up with repeated investigations.

Spinal disc

Simplifying the structure of the disc, it is composed of two parts: a soft inner core containing a loose network of fibers suspended in mucoprotein gel (i.e. nucleus pulposus), and a tough collagen fiber containing annulus fibrosus surrounding it. The discs are connected to the vertebrae with hyaline-end-plates. Since the water-content of the disc is very high, it can flexibly adapt to the spine's carrying out movements in different directions, and at the same time it is resistant to compression – this way maintaining strength and pliability of the spine. In case of damages of the spinal disc the nucleus pulposus through the loosened annulus fibrosus compresses the anatomical structures localized in the area.

According to the severity protrusion, prolapse, and prolapse with a sequester, herniation can be differentiated (Figure 1). If the herniation tends to the midline, it can cause cauda-syndrom, if to lateral, it can cause radicular lesion. On the Figure 1 you can see the lateral herniation and Spurling sign of a cervical disc, while Figure 2 shows the anatomical distribution of lumbar region.

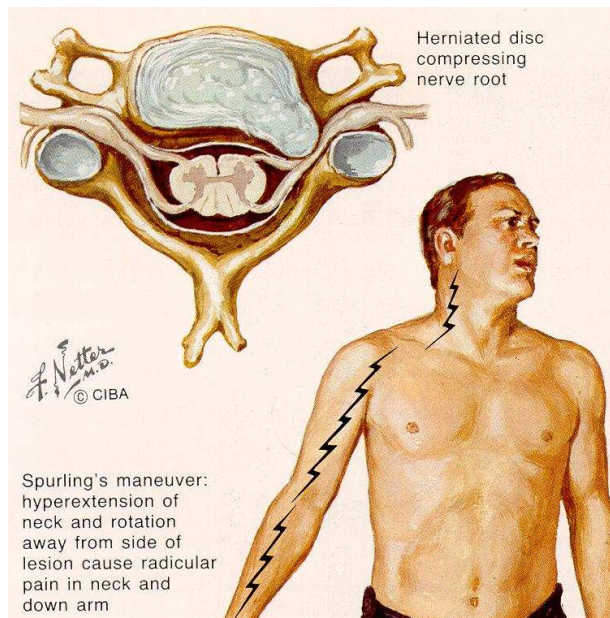
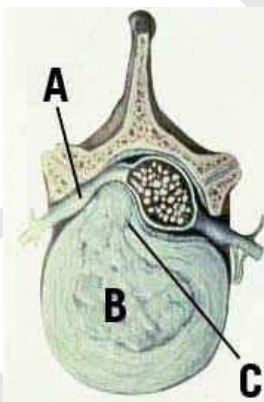


Figure 1
*Lateral compression of a cervical disc herniation
(part of Netter's illustration)*



- A. Exiting nerve root.
- B. Inner core of disc (nucleus pulposus).
- C. Torn outer core of the disc (annulus fibrosus).

Figure 2
*Lumbar herniated disc
(by: Peter F. Ullrich, Jr., MD)*

Diagnosis

Case history questions must be asked about the onset and characteristics of the pain. PQRST mnemonogram can be useful: P:provocating/palliating factors? Q-quality of the pain? R-region of the pain? S-severity? T-time course?

A. Pain, paraesthesia, sensory abnormalities

Localization – radiation of the pain? – *character* – *time* – how it started? (suddenly, movement-provoked, injury, etc.) – *progression* – did the pain increase/decrease to abdominal pressure? – *sensory abnormalities* (numbness, pins and needles, lack of cold/warm sensation, etc.).

B. Paresis/paralysis of the extremities or fingers

Problems with buttoning/lifting, extension, flexion the arms and legs, the feet, fingers? – *involuntary muscle movements* (i.e. fasciculation)?

C. Vegetative symptoms

Signs of incontinency – problems with urine and stools – *impotency* – sexual dysfunction?

Physical examination

The patient should be investigated undressed, evaluate the presence of fasciculation, claudication, abnormal body position, palpate the paraspinal muscles. The patient's range of motion in all directions: flexion, extension, lateral bending, and rotation should be also tested (Figure 3). The low back pain can be diffuse, or the pain is localized onto the distribution of a nerve root with associated weakness and loss of reflexes. The patients with compression of the spinal cord may have upper motor neuron signs like spastic muscle and hyperreflexia (the lesion should be above the L1/2, because spinal cord ends at that level). Patients with low back pain worsening with walking and relieved in a recumbent position may have spinal canal stenosis.

Spine

Painful palpation? Antalgic posture? How is the tone of the paravertebral muscles? Is the lumbar lordosis normal? Are the movements of spinal column painful? – In case of lumbar pain: Lasègue, inverse Lasègue, pressure of the Valleix points must be checked. Is the hip painful e.g. for rotation? Has the height of the patient been changed?

Sensory disturbances

Subjective (paresthesia, spontaneous pain) or objective (touch, cold/warm, pain, vibration sensation, dermolexy, position sense), localized to a dermatome (Figure 4-5)?

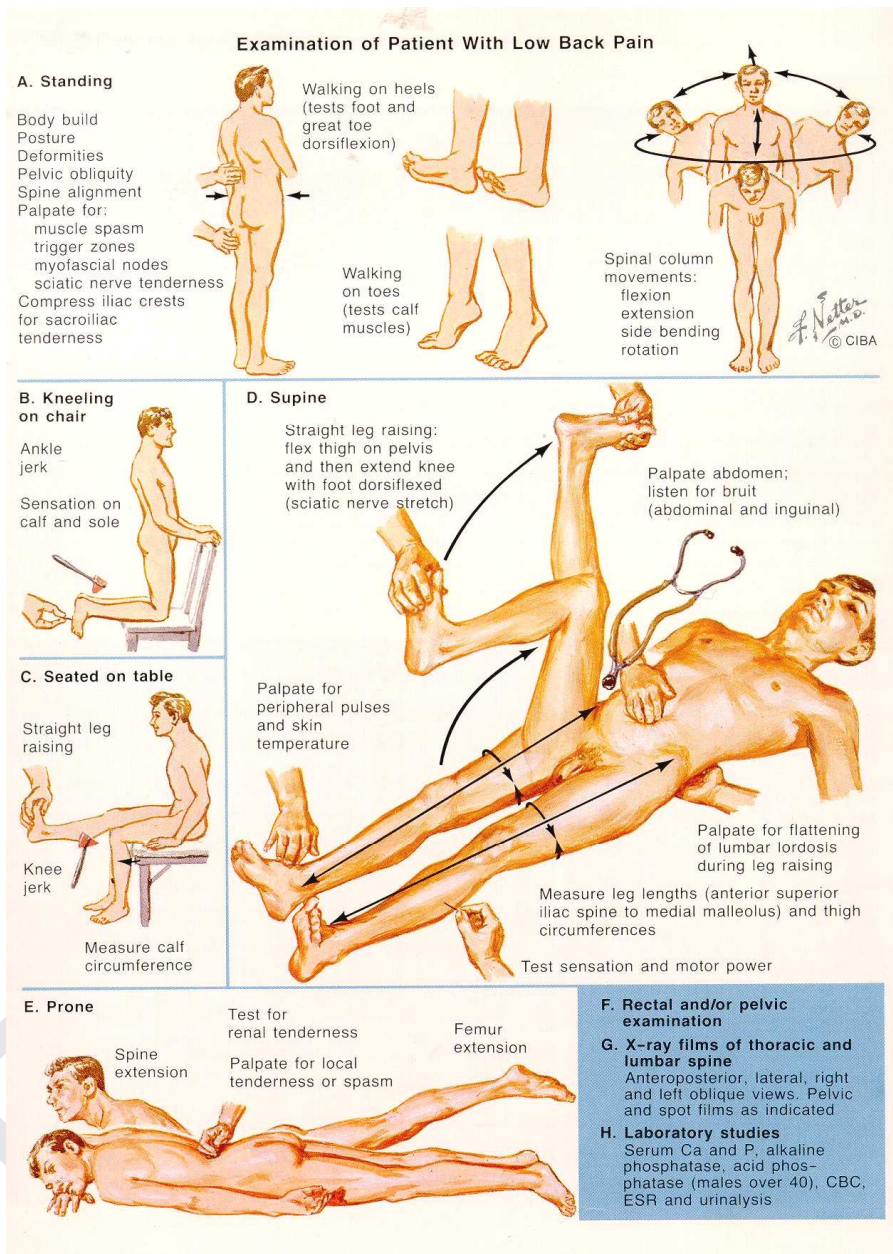


Figure 3
Netter's examination of patient with back pain

Motor system, reflexes

Is the patient able to carry out stepping on heels and toes – squatting and standing up – grabbing the hands, buttoning. Dropping foot? Atrophy of muscles? Presence or absence of patellar and ankle reflexes? Pyramidal signs (if the spinal cord lesion is above the L1-2) (Figure 3).

Vegetative system

Incontinency (urinary and stools)/urinary retention/sexual dysfunction?

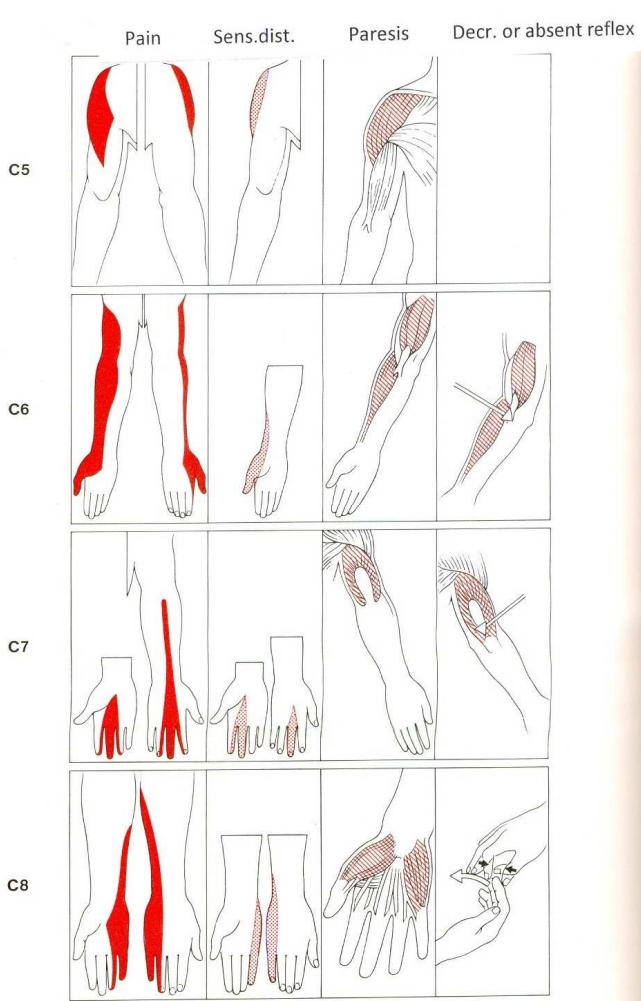


Figure 4
*Pain, paresis and sensory abnormalities in cervical disc patients
(Stöhr's and Riffel's modified figure)*

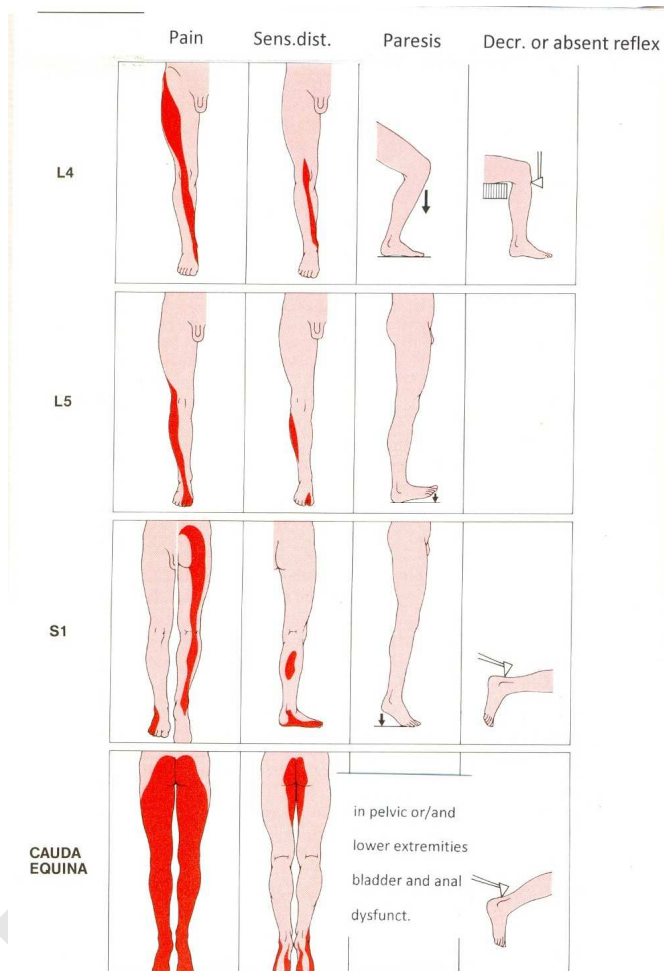


Figure 5
Pain, paresis and sensory abnormalities in lumbar disc disease patients
(Stöhr's and Riffel's modified figure)

Imaging

The majority of patients with low-back pain feel better after a month regardless of whether they get imaging or not. Less than 1% of imaging finds causative background.

- They can detect harmless abnormalities.
- Imaging for acute back pain often leads to unnecessary surgery.

The majority of guidelines does not recommend imaging for lower back pain within a few weeks of the onset as the pain is likely to disappear. The patient can be treated first and waiting a few weeks.

Diagnostic imaging might help to identify the specific cause of the symptoms in non-improving patients. Disc degeneration may result in back pain with root symptoms. Arthritis, spondylosis may narrow nerve root foramen and the canal itself, resulting in radicular or myelopathic symptoms.

The possible causes:

- Degenerative disease (disc, vertebrae),
- Infections (e.g. abscess),
- Tumours (primary and metastatic),
- Vascular causes (malformations),
- Autoimmune diseases.

X-ray, CT, MRI are satisfying in 90% of the cases. Very seldom myelo-CT, myelography can be also useful. In case of myelography non-ionic water-soluble contrast material is injected in the cerebral-spinal fluid. It can be helpful if we suspect for intramedullary/extramedullary/intradural tumors and degenerative disorders of the spine.

Special attention if:

- recent trauma,
- weight loss,
- fever,
- immunosuppressed patient,
- previous or current malignancy,
- osteoporosis,
- onset in age greater than 50 years,
- focal neurological deficit,
- duration of pain longer than 6 weeks.

Electrophysiology

Electroneurography: F-wave, H-reflex: may diagnose radicular lesion. F-wave: electrical stimulus is applied to the skin surface above the distal portion of a nerve, the impulse travels both distally (towards the muscle) and proximally (back to spinal cord). H-reflex (Hoffman reflex): reflex-response of muscles after stimulation (electric) of sensory fibers in their innervating nerves (Ia afferents coming from muscle spindle). The H-reflex is a valuable tool in assessing modulation of monosynaptic reflex activity in the spinal cord.

Electromyography: separates myogen from neurogen lesion.

Somatosensory evoked potentials (SSEP) are elicited by tactile or electrical stimulation of a sensory or mixed nerve. Conventional SSEPs monitor the functioning of the part of the somatosensory system involved in sensations such as touch and vibration. One part of the somatosensory system that is responsible for

pain and temperature is monitored by laser evoked potentials (LEP). LEPs are evoked by focused, rapidly rising heat to bare skin.

The presence of myelon compression can be evaluated also by means of transcranial magnetic stimulation (TMS) that measures the impulse, starting from the cerebral cortex and ending at the anterior horn cells of the cervical, thoracic or lumbar spinal cord. Useful e.g. in patients with two or more cervical disc diseases.

Differential diagnosis

- Degenerative diseases (disc herniation, spondylosis etc.)
- Tumours (primary or metastatic)
- Inflammatory, infective (arthritis, abscess etc)
- Congenital (development abnormalities)
- Psychogenic (personal, existential or family problem may trigger or sustain pain-syndromes, rarely financial benefit). Use this diagnosis only if all possible organic diseases can be excluded and the patient has no neurological symptoms (Figure 6).

Divisions of the spine

Cervical division

Causes: although it is the second most affected (lumbar is the first) part of the spine, but the herniations are less common than in the lumbar part, and spondylosis, osteochondrosis, spondylarthrosis are more frequent. The C6-7-8 radiculopathy occur most frequently.

Cervicocephalic-syndrome: due to the affected plexus, clinically cervical or occipital headache appears.

Cervicobrachialgia: the pain radiates to the arm.

Vertebrogen cervical myelopathy: gradually progressing spinal cord lesion (pyramidal signs, mono- or paraparesis with or without sensory disturbances) due to narrow spinal canal, spondylosis, osteochondrosis and (rarely) vascular lesion of spinal cord.

Symptoms: cervical pain radiating to the arms, shoulders, head – paracervical defense leading to e.g. torticollis. Seldom, the median herniation may result in spastic lower leg paraparesis (depending on the localization) tetraparesis, brisk deep tendon reflexes and pyramidal signs.

Diagnosis:

Spurling maneuver: turn the neck to the affected side, hyperextend the arm pressing the vertex at the same time (Figure 1). Do not test Spurling maneuver after trauma!

Imaging: X-ray from 4 directions, MRI (Figure 7), if needed myelography.

Electrophysiology: ENG, EMG, SSEP, TMS (see above).

Differential diagnosis: e.g. brachial plexus lesion, Pancoast tumor, spinal tumors, humeroscapular periarthritis, cervical myelopathy, anterior spinal artery syndrome.

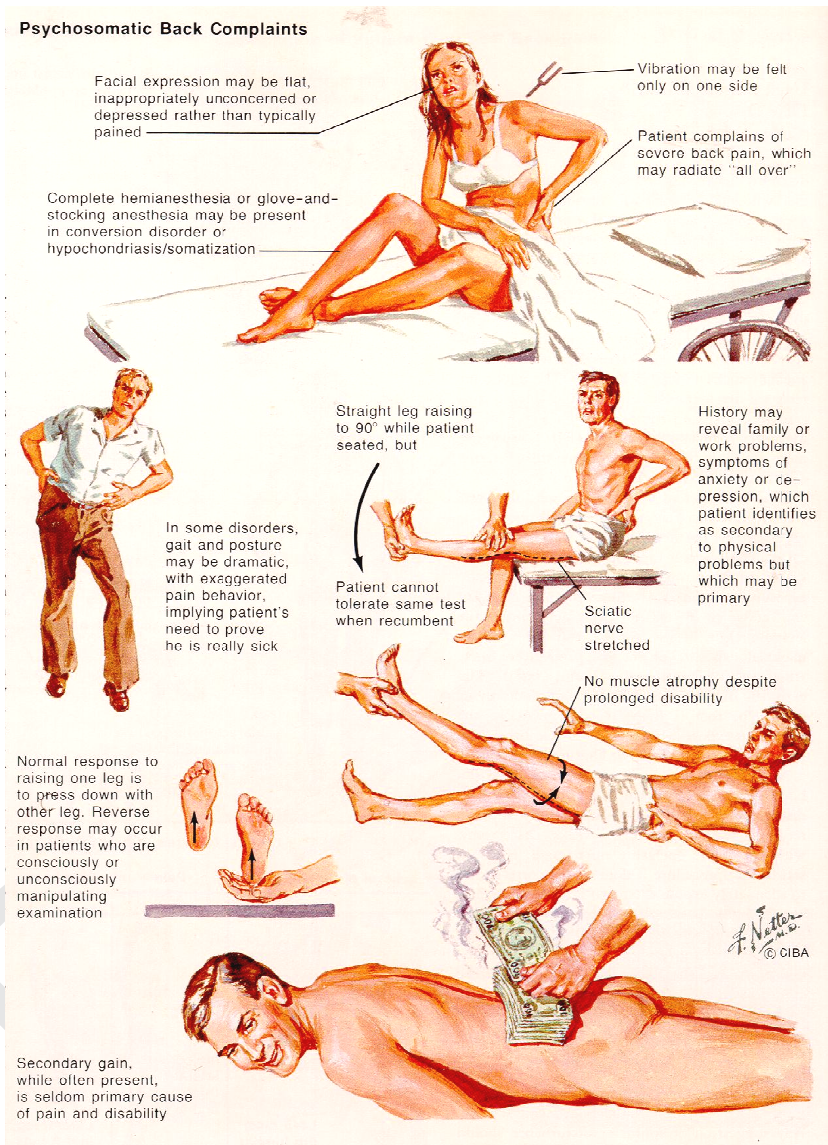


Figure 6
Psychosomatic back complaints
(Netter's figure)

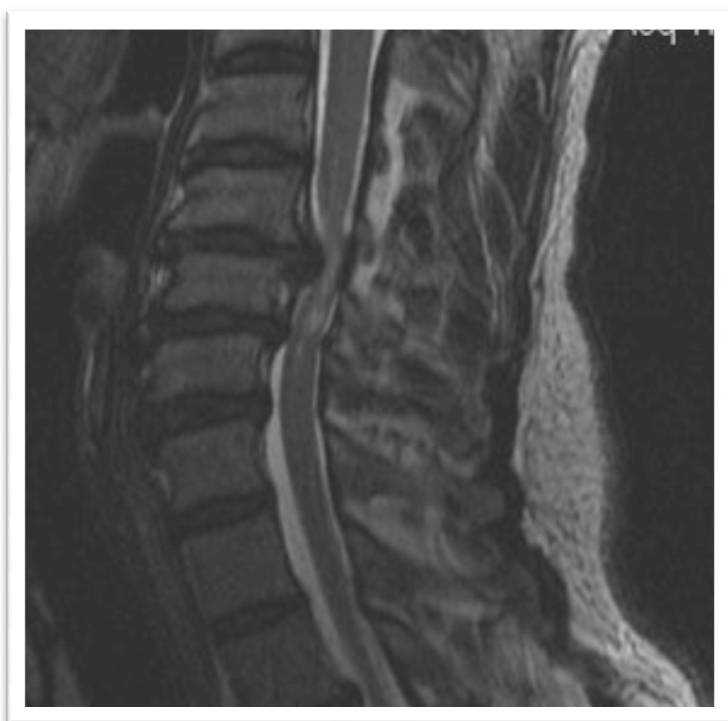


Figure 7
Cervical spine MRI

The white arrow shows the severe disc degeneration compressing the spinal cord. The herniated disc compresses the arteries on the surface of spinal cord resulting in (secondary) ischemic damages in the spinal cord. The secondary damages in the spinal cord explain the lack of clinical improvement after a successful disc operation. Our patient had progressive, very severe, spastic lower leg paraparesis before and after the operation.

Table 1
Important cervical radiculopathies

Radix	Sensory disturbances (hypesthesia, anesthesia, hypalgesia, pain, numbness)	Paretic muscles	Impaired movement	Absent or diminished reflex
C5	lateral surface above the posterior deltoid muscle	deltoid	abduction of the arm	radial
C6	the pain radiates to the radial part towards the pollex, hypesthesia in the I-II finger	biceps, brachioradial	flexor of the elbow	biceps, radial
C7	II-III-IV finger, mainly the III.	triceps, extensors of forearm and sometimes of the wrist		triceps
C8	IV-V finger	hypothenar, intrinsic hand muscles	flexor of the small finger	

Thoracic division

Causes: the most stable part of the spine, herniation is rare. If symptoms occur in this region, always think of space-occupying procedures (trauma, tumor, epidural bleeding).

Symptoms: pain in the thoracic area with band-like or sickle form irradiation. If Th 5-12 is affected the abdominal reflexes are absent or diminished.

Diagnosis:

Imaging: X-ray from 4 directions, MRI, if needed, myelography, myelo-CT.

Electrophysiology: ENG, EMG, SSEP, TMS (see above).

Differential diagnosis: e.g. intercostal neuralgia, tumor, shingles, fracture of the vertebra, aorta dissection, multiple sclerosis, abscess, inflammation.

Lumbar division

Causes: *Herniation and radiculopathy* are most common in this part of the spine. The LIV/V and LV/SI are the most frequently damaged. Stenosis of the spinal canal is common in elderly, caused by degenerative diseases. Besides disc herniation, *spondylosis* plays an important role in low back pain. Degeneration of the spinal disc and the edges of the vertebrae are responsible for the development of spondylosis. If the spinal discs become flat due to the compression – the shape of the nucleus pulposus and annulus fibrosus is also modified – and the long ligaments stabilizing the spine will be distended and calcified. This procedure leads to narrowing of spinal canal and foraminae. The risk factors of spondylosis are advanced age, kyphosis, scoliosis, trauma, overburden of the spine. The severity of the X-ray findings does not always correlate with the severity of the complaints. Vice versa: mild radiological abnormalities can be accompanied with severe clinical complaints.

Diagnosis:

Lasègue maneuver: (stretching the sciatic nerve) the patient is lying on his back, and his stretched lower limb is lifted until he feels pain in his lower back. The angle between the lower limb and the bed is calculated. Frequently positive in L4, L5, S1 radiculopathies.

Bragard sign: like Lasègue sign but with dorsiflexed hallux.

Inverse Lasègue maneuver: (stretching of the femoral nerve) the patient is lying on the abdomen and the lower limb is lifted and stretched. The pain will be localized in the middle part of the lumbar division and inguinal region. Positive in L3, L4 radiculopathies.

Crossed Lasègue sign: lifting the not-affected limb of the patient will provoke pain on the affected side. Positive in case of disc herniation.

Valleix points: the sciatic nerve is painful on pressure in the gluteo-femoral region.

Schober-index: the patient leans forward with stretched knees. The distance between the spinous process of the LV vertebra and the point 10 cm above it must be measured after leaning (normal: 10/15).

Imaging: X-ray from 2 directions (especially in osteoporosis, fractures, spondylosis), CT, MRI, if needed myelography, myelo-CT, abdominal and pelvic ultrasonography.

Electrophysiology: ENG, EMG, SSEP, TMS (see above).

Symptoms: lumbar pain radiating to the different dermatomes, which is usually knife-like stab type. The lumbar lordosis can be flat, defense in the paravertebral muscles, antalgic posture is seen. Paresis, vegetative syndromes can accompany the above mentioned ones in severe cases. In case of disc herniation clinical symptoms are almost diagnostic (sciatica, sensory disturbance in special dermatoma, tendon reflex impairment, muscle weakness), but neuroimaging techniques are mandatory.

Differential diagnosis: e.g. retroperitoneal abscess or bleeding, degenerative hip disorders, coxarthrosis, sacroileitis, tumor, adnexitis, extrauterine gravidity, renal calculus, cystitis.

Lumbago: local lumbar pain, if there is no sign of radiating pain, reflex abnormalities, vegetative disturbance.

Table 2
Important lumbar radiculopathies

Radix	Sensory disturbances (hypoesthesia, anaesthesia, hypalgesia, pain, numbness)	Motoric symptom, and paretic muscles	Impaired muscle movement	Special examination	Reflex absent or diminished
L3	anterior part of the thigh radiating to the medial part of the knee	psoas, quadriceps	thigh adduction, flexion of the hip	inverse Lasègue sign	-
L4	lateral part of the thigh, and medial part of the shine radiating to the medial ankle	anterior tibial, quadriceps	paresis of the thigh muscles, muscle stretchers (staggering)	Lasègue and inverse Lasègue signs	patella
L5	lateral part of the shine, dorsal surface of the foot radiating to the hallux	long peroneal, anterior tibial, long extensor hallucis	dorsiflexion of the toe (standing on heels)	Lasègue, crossed Lasègue sign	-
S1	posterior part of the thigh, shine, lateral surface of the foot	gastrocnemius	plantar-flexion of the foot (standing on toes)	Lasègue sign, Valleix points painful on pressure	Achilles

Cauda and conus syndrome, stenosis of the spinal canal

The spinal cord ends at the L1-II vertebrae in adults, the radices run down in a pony-tail shape (cauda equine).

Cauda-syndrome:

Cause: the damage of the radices running in the spinal canal.

Symptoms: sensory disturbances in S3-S4 coccygeal dermatomes, must be considered in paraesthesia, hypaesthesia in the anal region. Absent reflexes in the lower limbs, anal and cremaster reflex are absent as well. Urinary retention with overflow, problems with stools.

Conus-syndrome:

Cause: the lesion is in the altitude of L1, both the medullar cone and the cauda equine are affected.

Symptoms: sensory disturbances in S3-S4 coccygeal dermatomes, must be considered in paraesthesia, hypaesthesia in the anal region; L3-S2 radiculopathy can occur; urinary bladder and anal sphincter paralysis; absent reflexes in the lower limbs.

In case of anal region sensation disturbances, urinary or anal retention operation is needed in 24 hours!!

Stenosis of the spinal canal:

Cause: bony narrowing of the spinal canal, usually seen in the cervical and lumbar divisions.

Symptoms:

Cervical: spastic tetraparesis can occur, with ascending sensation disturbances.

Lumbar: (also known as neurogen claudication) the pain increases with strain. It has to be differentiated from herniation and arteriosclerosis of the lower limb. If the patient leans forward (e.g. on a bicycle) in case of neurogen claudication, the pain relieves, although the lower limbs are strained. Running up the stairs will not cause severe pain in neurogen claudication, while running downwards – due to the stretching of the radices-the patient will complain about pronounced pain. If it compresses the radicals it can even cause paralysis.

Diagnosis: CT/MRI (the cross diameter is <10 mm absolute stenosis, 10-12 mm relative stenosis)

Therapy: operation on more segments of the spine; in case of radiculopathy, symptomatic treatment

Treatment

Conservative

Acute pain (<4 weeks)

Medication: muscle relaxants, non-steroid anti-inflammatory drugs (gel, suppositories, ointment, tablets).

Carbamazepine, oxcarbazepine can be useful in radicular pain.

In severe cases epidural steroids and opioids.

Physiotherapy and rest: it must be carried out very carefully, because if the patient does not feel pain, they might strain the spine improperly, which may lead to further damages.

TENS (transcutan electric nerve stimulation) useful in radiculopathy, can be continued at home.

Guidelines from the USA emphasize early physiotherapy and mobilization.

Chronic pain (>3 months)

Medication: as in chronic pain tricyclic antidepressants, SSRI-s, valproate, carbamazepine, oxcarbazepine.

Medical aids: eg. Schanz collar, flexible girdle

Physiotherapy: stretching and underwater exercises to learn the proper posture.

Pain relief can be achieved with TENS diadynamic electric therapy, sonotherapy, galvan therapy.

Muscle relaxation can be achieved with massage, sonophoresis (iontophoresis = transdermal medication+ultrasound), sonodynator (ultrasound + diadynamic electric therapy).

USA guidelines emphasize the role of cognitive therapy and yoga.

Surgery

Absolute indication: leg or finger paresis/paralysis –urinary or anal incontinence-cauda or conus syndrome.

Relative indication: no improvement after 4-6 weeks conservative therapy.

It is important to be aware of the failed back surgery syndrome (10%) when the complaints of the patient persist after the operation as a consequence of inappropriate wound healing, scar, or indication.

Surgery may be indicated when conservative treatment is not effective in reducing pain or when the patient develops neurologic symptoms such as urinary or anal incontinence. No better outcomes could be seen in patients with chronic low back pain by spinal fusion.

Possible interventions: microdiscectomy, discectomy, laminectomy, foraminotomy, or spinal fusion. By fusing two vertebrae together (spinal fusion), they will function as a solid bone. The goal of spinal fusion is to eliminate that extra motion, decreasing pain. If scoliosis or degenerative discs is the problem, the spinal fusion process may be recommended. Lumbar artificial disc replacement is a newer surgical technique. Benefits of spinal surgery are limited when treated degenerative discs.

Cave! Four randomized clinical trials showed that the benefits of spinal surgery are limited when treating degenerative discs with spinal pain (no sciatica).

Physiotherapy after operation

Even if the symptoms are decreased, physiotherapy must follow the surgery. Learning the appropriate posture (stabilizing the pelvic, strengthening the paravertebral and abdominal muscles), taking strain down from the spine will prevent inappropriate wound healing. In case of paresis/paralysis electrical therapy,

active exercises must be done. According to the experiences of neurosurgeons and rehabilitation teams, 10-12 weeks are necessary to learn a new healthy lifestyle.

Summary

By knowing the anatomical structure of the spine the syndromes of the spine can be localized.

Radiculopathy:

- *sensory disturbance (numbness, paraesthesia, pain etc.) in the appropriate dermatome (Figure 8);*
- *may be accompanied with the decrease or absence of tendon reflex relevant to the affected sensory or motor root;*
- *paresis can be also affected in the muscle innervated by the affected motor root.*

Most commonly, protrusion and herniation of the spinal disc and/or spondylosis could be diagnosed. In the huge majority of patients conservative therapy relieves the symptoms. Not the radiological abnormalities but the patient's complains are decisive for conservative or surgical therapy.

If one recovers after conservative therapy, no surgery is needed even in the presence of radiologically verified disc herniation. Surgery can be indicated if there is no improvement after 6 weeks of conservative therapy. Emergency intervention is necessary in case of urinary retention or incontinence, paresis/paralysis, cauda or conus syndrome.

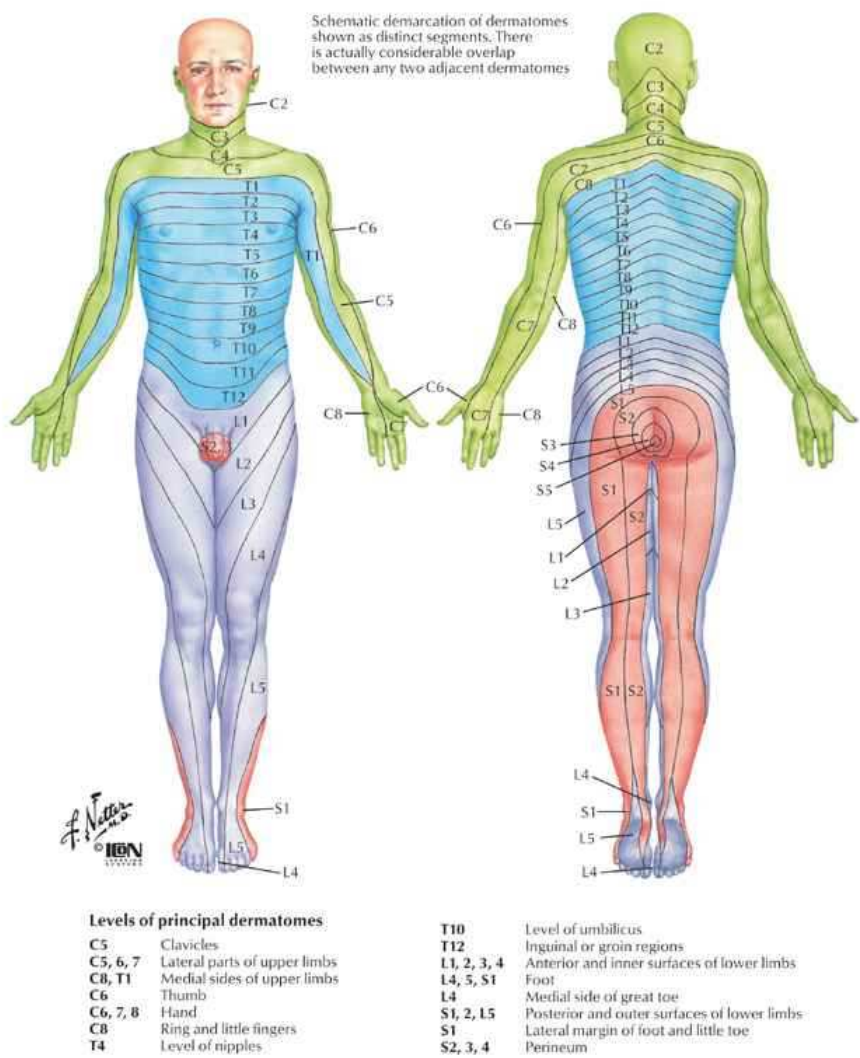


Figure 8
Dermatomes

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The neurology of aging

ISTVÁN FEKETE MD.

Morphologic and physiologic changes in the aging nervous system

The neuron cells are not able to proliferate, so no new cells will develop, which is an important difference between the central nervous system and other organs. The damaged neuron cells become atrophied and die. The number of neurons decreases in case of physiologic aging as well, but the degree differs depending on the affected region (basal ganglia: less atrophy). After the third decade, the weight of the brain decreases gradually in a mild extent (it decreases approximately with 10%), and the size of the ventricles may increase 3-4 folds. But there is no close relationship between the development of dementia and the size of the ventricles, and the volume of the brain. In the neuron cells pigments accumulate such as lipofuscin granules do in the cytoplasm, amyloid does in the arteries. Senile plaques, and rarely neurofibrillar fibres are detected in the brain tissue, even without the presence of Alzheimer dementia. Considering the neurotransmitter levels, it is generally agreed that the concentrations of acetylcholine, norepinephrine, and dopamine decline in the course of normal aging. The concentration of GABA may decrease with age, particularly in the frontal cortex. The enzyme activity is altered (the cholin-actelyse activity increases, and the monoaminoxidase activity decreases). These changes of the neurotransmitters probably reflect the depletion of cells that occurs with age.

The symptoms caused by pathological alterations may be compensated by the fact that more neurons are available than needed (redundancy). The central nervous system is capable of partly compensating loss of function due to its plasticity. Parallel to the necrosis of neuron cells, the number and the length of dendrites of the surviving neurons grow, thus the loss of neurons is compensated by new connections/junction system.

Although peripheral nerves are able to regenerate slowly and aging causes few changes, conduction velocity decreases both in the motor and sensory nerves, leading to diminished deep tendon reflexes.

Physiologic alterations of aging

Cranial nerves: hyposmia, sometimes even parosmia can occur. Presbyopia is the result of aging. Pupils can be more constricted than in younger age, their reactions are decreased to light and on accommodation. The insufficiency of convergence is not rare. These alterations are seen in almost 50% of the population over 85 years. Rarely, the absence of the pupillary light reaction and convergence are observed. The upward gaze, in smaller extent the downward gaze can be mildly limited too. There is frequent loss of Bell's phenomenon (voluntary forceful

closure of the eyelids results the eyeballs move upwards reflexively). The progressive perceptive hearing loss (presbycusis) is a common symptom in old age, especially for high tone, but even deafness is not rare.

Changes in tendon reflexes: The tendon reflexes of the upper extremities are usually intact, but over the year of 80, they might be diminished or absent. Patella reflex can be diminished or absent in 50% of the cases. Achilles reflex decreases (or is absent) over the age of 50, due to the reduction of tendon flexibility and nerve conduction velocity. If the reflexes are absent, it has to be symmetric. The umbilical reflex is not likely to be evoked in elderly patients. In the background of “spontaneous or pseudo- Babinski’s sign” is usually tendon or muscle abnormality, Babinski’s sign is always pathological. Archaic reflexes such as grasping, snout reflex (sucking, biting) can be evoked in case of the Brodmann 6a region lesions in adults. Usually organic lesion causes hyperactive palmomental reflex, but it can be part of the physiological aging.

Motor system, coordination: reduced speed and amount of motor activity, slowed reaction time, impairment of the fine coordination and agility, reduced muscular power (legs are affected more often than arms and proximal muscles more than distal ones). During flexing and extending the elbow, bilateral mild increment in muscle tone can be detected, especially if the patient is not relaxed. If muscle atrophy (particularly affecting the dorsal interossei, thenar and anterior tibial muscles) is not related to functional deficiency, it should be considered as normal in old age. A progressive decrease in the number of anterior horn cells is responsible for these changes. Of course, there can be a spondylarthrosis in the background as well. Muscle strength (especially in women) may be weaker against force. If the muscle weakness is symmetrical, and does not disturb the patient in every-day life, it is not considered as pathological. Elderly patients may be in bad somatic state, which can be caused by non-neurological diseases; in this case take care with the diagnosis of paresis.

Sensory system: usually no abnormality is seen, except for diminished vibration sense under the knees in patients over 50 years (or it can be absent in patients over 80 years). But it is never accompanied by loss/decreased of joint movement and position sense or dermatographia. In 25% of the elderly patients the pain and heat sensation are disturbed, and the tactile sensation can be uncertain and patchy, too.

If **vegetative disturbance** is seen, in women urinary bladder prolapse, in men prostate diseases should be excluded. Dry skin with itching is not rare in old age.

Psychic status: the reaction time is longer, impaired memory function or mild cognitive decline can occur. In normal cases the intellectual performance remains even in patients over the age of 80, but the learning and performing tasks take longer time, and mild forgetfulness is also noticed. In establishing the degree of cognitive decline, several abbreviated tests of mental status have been developed and are of practical value, so they can be assessed at the bedside within 5 to 10 min. Personality changes are more difficult to be measured than cognitive functions, but elderly patients are prone to this, which may seriously disturb the their lives and that of their family members.

To **summarize** the above mentioned, in case of a neurological examination it is essential to consider the history, age, other symptoms and finding together. Symmetrically occurring symptoms without any other sign can be normal variants. The follow-ups are necessary in order to identify the changes and new complaints.

Typical neurological symptoms in elderly

In this chapter only the most common neurological disorders that are special problems of the elderly are discussed. Attention is being drawn to those diagnostic and therapeutical aspects which should be kept in mind.

Neurological diseases can be divided as follows:

- Diseases, which are more typical and common in elderly than in the young (e.g. cerebrovascular diseases, some degenerative disorders and dementia).
- Diseases, which are not more common, but their aetiology and processes are different and their symptoms may be different in elderly than in young patients (e.g. epilepsy, inflammation).
- Diseases that are not typical in old patients, but still can occur (muscle dystrophy, multiple sclerosis, migraine).

It is also important to mention that with aging medical diseases are usually accompanied by other neurological and psychiatric disorders (heart rhythm anomalies, pathological orthostatic reaction, diabetes mellitus, lung and renal dysfunction, diseases).

A/ Symptoms and causes of the cranial nerve lesions

If **visual acuity** is impaired besides the correction, the possibility of hypertension, diabetes, arteriosclerosis, anemic retinopathy, cataract and glaucoma increases. If the patient complains about unilateral, suddenly developing blindness, then amaurosis fugax, occlusion of the central retinal artery, or thrombosis of the central retinal vein should be considered. Urgent ophthalmological and neurological examination is necessary.

Injury of the III-IV-VI cranial nerves: Diabetic neuropathy is the most common cause in this age group. If anisocoria develops after head trauma (the patient falls, hits his head in the wall), the presence of acute/subacute/chronic subdural bleeding should be excluded. The development of space-occupying haemorrhage does not depend on the size of the head trauma. The acute and subacute symptoms are usually easy to diagnose. In case of uncertain sickness, fainting, and anisocoria, thorough case history should be taken, and chronic subdural haematoma should be excluded.

The irritation or the injury of the **cochleovestibular nerve** is common in old age. It is correct to start with an otolaryngological examination, because hypacusis starting in old age can be in its background. The use of hearing devices improves life-quality. In case of tinnitus otolaryngological examination, and neurological examination should be done (if needed).

B/ Impaired consciousness

In case of old, isolated, depressed patients living alone, no unequivocal reason (syncope with low brain blood perfusion, myocardial infarct, hypoglycaemia, diabetes mellitus, acute cerebrovascular disease, and tumor) is detected, which may cause the impaired consciousness, medication or alcohol **intoxication** should always be excluded, and doctors should investigate their symptoms, too. The cause of intoxication can be dementia or forgetfulness.

Epileptic seizures: the patients can be known to have epilepsy, but tongue biting and enuresis can draw our attention to the disease too.

Head trauma: old people fall easily. Even in those cases when the cause of the impaired consciousness is clarified, we should look for the signs of injuries, because attacks could cause head injuries as well (cerebrovascular ictus, epilepsy). Edema of the head-skin draws attention to skull fracture, just as bleeding or liquorrhoea from the nose, ear, and pharynx refers to it. Anisocoria is the typical sign of space-occupying bleedings.

In case of **cerebrovascular diseases or brain tumors**, focal neurological signs and pathological reflexes can be seen.

Aphasia plays an important role in legal procedures e.g. signing informed consent or last will.

The cause of **delirium** may be the decreased fluid intake, dehydration, or disturbance of the electrolytes. In the treatment of delirium haloperidol (0.25 mg or 5-10 drops), thioridazine (5-10 mg) or short/intermediate benzodiazepines are preferred. If agitation is over, their doses can be decreased.

Characteristics of diseases affecting mainly elderly patients

A/ Cerebrovascular diseases

Cerebrovascular diseases discussed in the stroke chapters.

B/ Meningitis

The incidence of meningitis is 10% in elderly, but the mortality rate is higher (53-79%), which can be explained by the presence of other diseases, or by the late diagnoses as well. The pathomechanism of the inflammation is the same as in younger ages but the proportion of infectious agents is different. In 55% of the cases, **Streptococcus pneumoniae** is responsible for the meningitis and bacteraemia originating from otitis media, fracture of the skull base. Meningitis caused by **Gram-negative aerobic bacteria** (8%) develops in case of sore/decubital ulcers, osteomyelitis and urosepsis (permanent catheter), or after skull fracture. The most common agents in hospitalized patients are **Staphylococcus aureus** and **Staphylococcus epidermidis** after shunt implantation, and **Haemophilus influenzae** if the patient has low antibody level.

The presence of anaerobic bacteria is common in upper respiratory tract infections, tumors of the neck-head region, or after neurosurgical interventions. Viral meningitis rarely develops in elderly. In case of long-lasting fatigue, exhaustion, higher temperature and intermittent headache, **Tuberculous meningitis** should be suspected.

In patients suffering from diabetes mellitus and cardiopulmonary diseases, the symptoms of meningitis can be atypical. Insidious onset, fatigue, meningeal irritation and the absence of fever are typical. Therefore it is an important rule, that in old patients suffering from cognitive impairment and having the symptoms listed above, the examination of cerebrospinal fluid is mandatory to exclude the presence of meningitis. Bronchiectasis and pneumonia occur more frequently in elderly resulting in **metastatic focal encephalitis**. In these cases endocarditis should be excluded.

C/ Extrapyrarnidal movement disorders

Stiff and bent posture, rest tremor, rigidity, hypokinesia, and gait instability with the lack of attending limb movements are typical for the **Parkinson's disease/Parkinson's syndrome of elderly patients**. The asymmetric symptoms are characteristic for Parkinson's disease. Other features are discussed in the chapters on movement disorders.

Senile tremor starts after the seventh decade, but it is not the part of the physiological aging and usually affects the head and the upper limb. In case of senile tremor no muscle tone abnormality is present. Beta-blockers may help, or if it is severe, mild sedatives can be effective.

Senile chorea (isolated chorea-like movement, fast complicated involuntary jerks) can develop over the age of 60. The symptoms are acute and unilateral, and do not progrediate. The prognosis is relatively benign. The cognitive impairment and familial predisposition are not characteristic.

Bucco-facial-lingual dyskinesia is typical in elderly patients, and sometimes provoked by medications. It can be treated with 300-600 mg tiapride effectively. Tricycle antidepressants, antipsychotics can cause dystonia, tardive dyskinesia, tardive acathisia in the elderly patients too. Local infiltration with botulinum toxin seems to be efficient in **blepharospasm**.

The lesion of subthalamic nucleus (Luys) results in **hemiballism**. It is mainly caused by vascular lesion, rarely tumors or infections. It should be differentiated from epileptic seizures. Stormy movements of big amplitude and throwing-type, affecting the proximal parts of the limbs, can lead to exhaustion or even death. These pathological movements usually cease spontaneously if they are caused by cerebrovascular diseases. Tiapride, haloperidol, valproic acid can be effective in their treatment.

Myoclonus can be the concomitant symptom of encephalopathy caused by hypoxia, uraemia, hypercapnia, liver malfunction, hypoglycaemia, hyponatraemia, chronic haemodialysis, or focal cerebral lesions. **Nocturnal myoclonus** and **restless leg syndrome** are rare, but typical for the elderly. They occur during the

night and they are disturbing though being benign. They are sometimes mistaken with seizures.

Summary

Physiological anomalies, which are typical for the elderly, can suggest different neurological diseases.

Symmetrical symptoms without any accompanying neurological sign are usually normal variants.

Certain diseases are typical for old patients.

The therapy of specific neurological diseases can differ from that of in younger patients.

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