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The early diagnosis and differential diagnosis of Alzheimer's disease with clinical methods

By

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INTRODUCTION

Alzheimer's disease (AD) is a progressive and fatal neurodegenerative disorder manifested by cognitive and memory deterioration, progressive impairment of activities of daily living, and a variety of neuropsychiatric symptoms and behavioral disturbances. For 70 years after Alois Alzheimer (1864-1915) described a disorder of tangle-and-plaque dementia in 1907, Alzheimer's disease was a condition of relatively young. Definitions of AD have changed over the past 30 years and under the revised view AD has truly become an age-related disease and has been recognised as a major public health problem.

The pathomechanism of AD has been researched intensively. The novel drugs can slow down the progression of the disorder in the early phase. Histopathological confirmation of AD in vivo is extremly rare, so the diagnosis is probable AD. There is an increasing need for the biological markers, which would detect the fundamental neuropathology of AD.

The characteristic histopathological changes (plaques and neurofibrillary tangles) occur long before the clinical symptoms in AD. The plaques and neurofibrillary tangles were rarely detected in normal ageing, but frequently appear in mild cognitive impairment, which suggests MCI is a transitional state between normal ageing and AD.

Mild Cognitive Impairment (MCI)

MCI can present with a variety of symptoms and when memory loss is the predominant symptom, it is termed "amnestic MCI" (aMCI). Patients with MCI have a memory impairment that is out of proportion to that expected for their age, yet they do not meet commonly accepted criteria for dementia (or AD), and longitudinal outcome results indicate that they are likely to progress to AD at an accelerated rate (10% to 15% per year). Heterogeneity of MCI means that individuals who clinically present mild cognitive symptoms may not all share the same ultimate fate. Some develop AD later, while others may progress to another type of dementia, and still some will never progress to any significant extent.

Memory impairment is usually the initial manifestation of dementia in AD, which can be characterised as MCI. On the other hand, in some cases a small vascular damage may occur in the brain, causing mild cognitive impairment, before VD develops. However, cerebral atrophy or lacunar infarcts do not necessarily go parallel with dementia.

MCI and cerebrovascular disease

Cerebrovascular disease is a common symptom of the ageing process, and several studies suggest that cerebrovascular risk factors are strongly associated with prevalent dementia,

including AD. Individuals identified as having MCI showed significantly increased frequencies of vascular risk factors and evidence of vascular brain injury.

Dementia and depression

In the early phase of AD, depression can mask the cognitive impairment ("pseudodepression"), and late life depression often goes with cognitive impairment ("pseudodementia"). Demented patient can be depressed or comorbid depression may occur beside dementia. All of these make the differential diagnosis difficult.

Neuropsychological symptoms in dementia and depression

In AD neurofibrillary tangles and amyloid plaques were found in mediotemporal lobe, especially in the entorhinal cortex. There is an early cingular atrophy with damage of connection between associate neocortex and mediotemporal lobe, resulting in short term memory loss. The next damage occurs in the associate neocortex, leading to agnosia, aphasia and apraxia. Motor and sensory functions are saved for a long time during the disorder. Executive functions are a complex mental process based on working memory, resulting the information turnover and problem solving, and are disturbed in AD.

Previous studies of cognitive impairment in unipolar depression have demonstrated impairments in psychomotor speed, memory, sustained attention and executive functions, including working memory and complex problem solving, but findings across studies have been somewhat inconsistent. Patients with remitted depression were impaired on tasks of rapid visual information processing, psychomotor performance, and spatial working memory. After correction for residual depressive symptoms, deficit in sustained attention remained significant suggesting it is a good vulnerability marker for major depressive disorder.

Electrophysiological methods in dementia

In the conventional EEG frontal slow waves are present in AD, but in the early phase no characteristic features were found. The late component of the auditory event-related cortical potential (AEP), P300 reflects cognitive processing, such as stimulus registration, attention, stimulus evaluation, and memory. P300 latency is thought to indicate the speed of information processing, delayed latency relates to slowed cognitive function in normal elderly, as well as disturbances of mental functions in patients with dementia. The origin of this electrical component is not well understood, some studies have suggested the involvement of limbic/mesial temporal structures, while others hypothesized the role of cortical areas in its generation. Most authors agree that P300 latency can be considered as a useful screening tool for dementia among patients with suspected cognitive disorders

Biochemical markers in dementia

Recently, several studies have confirmed the role of oxidative stress in the pathogenesis of AD and VD. HDL-associated paraoxonase (PON) is one of the antioxidative enzymes that may reduce LDL oxidation.

Cognitive decline in AD results from neuron degeneration and death. It is widely assumed that neuron loss in Alzheimer type and vascular dementias is a consequence of apoptosis, or apoptosis-related biochemical processes. The concentration of N^{ε}(γ-glutamyl)lysine isodipeptide (IDP) in cerebrospinal fluid might correlate with the intensity of apoptotic cell turnover.

OBJECTIVES

The general aim was to detect AD pathology as soon as possible and different clinical methods were assessed for early diagnosis of AD.

I. Cambridge Neuropsychological Test Automated Battery (CANTAB)

- **a.** Is there characteristic cognitive deficit in AD?
- **b.** Is there detectable cognitive impairment in amnestic MCI (aMCI) and is it similar to the pattern in AD?
- **c.** Is there characteristic cognitive disturbance in major depression (MD) and can it help to distinguish AD from MD?
- **d.** In what way are the cognitive functions change in remission of MD?

II. Auditory evoked potential (P300)

- **a.** Do P300 parameters reflect the severity of dementia?
- **b.** Do P300 parameters help to distinguish AD from VD?
- **c.** Are there any changes of P300 in amnestic MCI?
- **d.** Is P300 sensitive enough to distinguish aMCI with normal CT/MRI from aMCI with positive CT/MRI?

III. Biological methods

- **a.** How will HDL-assotiated paraoxonase activity change in the sera in AD and VD?
- **b.** Does the determination of N^{ε}(γ-glutamyl)lysine isodipeptide (IDP) concentration in the cerebrospinal fluid offer a novel method for the measurement of neurodegeneration in AD or VD?

MATERIALS AND METHODS

The patients were selected from the in- and outpatient units of the Department of Psychiatry, Medical and Health Science Center, University of Debrecen. Patients were diagnosed according to the ICD-10 and DSM-IV diagnostic criteria system, NINCDS-ADRDA and NINDS-AIREN criteria. Dementia caused by other possible diseases was excluded. All participants had laboratory tests: serum ion, enzyme levels, thyroid-, liver-, and kidney function, lipid levels, urine examination, blood count, erythrocyte sedimentation rate, vitamin B12 level, folic acid level, hemostasis, VDRL, apoE genotype, chest X-ray, EEG, CT/MRI examination. Cerebral SPECT and carotid Doppler examination were also performed when it was clinically indicated. The differencial diagnosis between AD and VD was based on the Hachinski Ischemic Scale, laboratory tests, anamnestic data, imaging investigations and attending illnesses. MD patients were assessed by Hamilton Depression Scale. Healthy control subjects were included in the study after general physical examination, and routine laboratory tests, in case of negative neurological and psychiatric anamnesis, and MMSE score between 27 and 30 points. All subjects were informed about the study and gave their written consent to participation. The study was conducted according to the principles of the Helsinki Declaration.

CANTAB

Table 1. Data of AD and aMCI patient

Patient groups	Mean age±SD	MMSE (mean±SD)	CDR (mean±SD)
AD (n=15)	58±6	21±1.2	2.1±1.3
MCI (n=25)	55±6	28±0.6	0.5

Table 2. Data of patients with major depression (MD) and remitted MD (MD rem)

Patient groups	Mean age±SD	MMSE (mean±SD)	HDRS (mean±SD)
MD (n=25)	56.8±8	28±0.2	23±5.4
MD rem (n=11)	55±6	29±1.6	8±3.6

Subjects were asked to perform a series of 13 computerised neuropsychological tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition, Cambridge, United Kingdom). CANTAB has been used and proved to be a useful tool to assess cognitive functions in diverse neurological and psychiatric disorders, such as dementia, schizophrenia, depression, and Parkinson's Disease. Subjects were seated at a comfortable height, approximately 0.5 m from the monitor, and were instructed to carry out the tasks by

touching the screen. After an initial explanation and completing a simple "motor screening task" successfully (touching the centre point of flashing crosses on the screen), subjects were given the following tests in the following order (the technical description of the tests can be found on the Cambridge Cognition's website: http://www.cantab.com): *Big Little Circle* (BLC); *Spatial working memory* (SWM); *Reaction time* (RTI); *Spatial span* (SSP); *Pattern recognition memory* (PRM); *Spatial recognition memory* (SRM); *Paired associate learning* (PAL); *Intra/Extradimensional shift task* (IED); *Match to sample visual search* (MTS); *Delayed matching to sample* (DMS); *Stockings of Cambridge* (SOC); *Rapid Visual Information Processing* (RVP).

Results were compared to the internal normative database of CANTAB, involving 3,000 healthy volunteers, and were matched for age groups and gender. CANTAB tests were previously validated among Hungarian healthy volunteers showing no statistically significant differences in the cognitive performance compared to the internal normative database.

Auditory event related potential

17 (N/F: 10/7) AD, 14 (N/F: 8/6) VD and 20 healthy age-matched control subjects were included. 28 MCI patients, 18 MCI with negative CT/MRI and 10 with positive CT/MRI results (mild cerebral atrophy), were compared to the age matched 20 control subjects. Data of the subjects are shown in the Table 5 and 6. The average P300 wave forms were recorded by a Cadwell Spectrum 32 and compared to the age-matched controls. The apparatus recorded 21 different channels. Event-related potentials were measured during an auditory discrimination task paradigm by presenting a series of binaural 1000 Hz (standard) vs. 2000 Hz tones (target) (target/standard: 40/160) with a stimulus rate of 0,91/sec. Patients were instructed to count the number of non-frequent tones and to report them at the end of each run. EEG activity was recorded with Ag-AgCl electrodes filled with paste and attached to the scalp according to a 10-20 system, referred to mastoids. The filter band pass was 0.5-70 Hz. P300 latency was determined at the centroparietal peak amplitude (Cz) and amplitudes were measured. The mean values of P300 latency and amplitude were calculated based on a peak-to-peak method. The time window was 256-500 ms. The internal artefact-rejector of the apparatus was used during recording to include only artifact-free targets in the calculation of the ERP waveforms. For group comparison analysis, a one-way non-parametric ANOVA was used. The correlation of different variables was analysed by the Spearman non-parametric method. P values less than 0.05 were considered as significant. Statistical calculations were

carried out using the GraphPad Prism 4.00 for Windows software (GraphPad Software, San Diego, CA, USA, http://www.graphpad.com).

Lipid parameters and paraoxonase (PON) activity in the sera

30 (N/F: 20/10) AD, 40 (N/F: 27/13) VD patients and 40 (N/F: 26/14) non-demented consenting healthy control subjects were included (Table 7). Lipid parameters were determined by an autoanalyser. PON activity was measured spectrophotometrically using paraoxon as the substrate.

N^{ε}(γ-glutamyl)lyzine isodipeptide (IDP) concentration in cerebrospinal fluid (CSF)

14 (F/M: 7/7) AD, 11 (F/M: 7/4) VD patients' CSF IDP concentration were compared to 15 (N/F: 6/9) non-demented consenting patients' CSF IDP level (Table 8). Controls were undergoing spinal anesthesia for inguinal hernia operation or varix removal from the lower extremities respectively. Free IDP concentration of CSF was determined from protein-free ultrafiltrate of lumbar CSF using internal ^{3}H-N^{ε}(γ-glutamyl)lysine internal standard tracer and precolumn phenylisothiocyanate derivatization followed by C18 HPLC separation as described.

RESULTS

CANTAB

Table 3. The median *Z*-scores of the CANTAB tests compared to healthy individuals in the AD group (n=15) and MCI group (n=25).

CANTAB tests	AD (n=15)		MCI (n=25)	
	Median *Z*-scores	Significance (*p*)	Median *Z*-scores	Significance (*p*)
Delayed matching to sample (DMS)	-2.641	<0.001	-1.111	<0.05
Intra/Extradimensional shift task (IED)	-1.077	n.s.	-0.9705	n.s.
Matching-to-sample (MTS)	-4.103	<0.05	-0.2235	n.s.
Paired associate learning (PAL)	-7.196	<0.05	-2.942	<0.001
Pattern recognition memory (PRM)	-1.942	<0.01	-0.3715	n.s.
Spatial recognition memory (SRM)	-2.201	<0.001	-2.061	<0.001
Reaction time (RTI)	-1.109	<0.01	-4.520	n.s.
Rapid visual processing (RVP)	-2.735	<0.001	-2.101	<0.001
Stocking of Cambridge (SOC)	-0.5713	n.s.	-0.2675	n.s.
Spatial span (SSP)	-1.212	<0.01	-0.755	<0.001
Spatial working memory (SWM)	-0.968	<0.01	-0.8871	<0.001

n.s.= not significant

Table 4. The median *Z*-scores of the CANTAB tests compared to healthy individuals in the MD group (n=25) and remitted MD (MD rem) (n=25).

CANTAB tesztek	MD (n=25)		MD rem (n=25)	
	Median *Z*-score	Szignifikancia (*p*)	Median *Z*-score	Szignifiancia (*p*)
Delayed matching to sample (DMS)	-2.198	<0.01	-3.095	<0.001
Intra/Extradimensional shift task (IED)	-1.017	n.s.	-0.916	n.s.
Matching-to-sample (MTS)	-1.421	n.s.	-1.346	<0.05
Paired associate learning (PAL)	-4.98	<0.001	-3.024	<0.01
Pattern recognition memory (PRM)	-1.354	<0.05	-2.071	<0.01
Spatial recognition memory (SRM)	-2.892	<0.001	-1.841	<0.01
Reaction time (RTI)	-1.922	<0.01	-0.796	n.s.
Rapid visual processing (RVP)	-1.922	<0.01	-2.498	<0.01
Stocking of Cambridge (SOC)	-1.171	<0.001	0.638	n.s.
Spatial span (SSP)	-1.456	<0.001	-2.083	<0.001
Spatial working memory (SWM)	-1.094	<0.01	-1.398	<0.001

n.s.= not significant

P300

Table 5. Mean P300 latency and amplitude for the AD and VD patients, and control group A.

Subject groups	Mean age ± SD (years)	MMSE score (mean ± SD)	P300 latency (msec) (mean ± SD)	P300 amplitude (μV) (mean ± SD)
Control group A (n=20)	71.2±6.5	27.6±0.8	354±30	12.4±4.8
AD (n=17)	69.1±6.9	21.5±1.2	436±31 p<0.01*	8.9±2.4 p<0.05*
VD (n=14)	75.6±7.5	21.5±0.9	430±33 p<0.01*	6.8±3 p<0.001*

* compared to control group A

Table 6. Mean P300 latency and amplitude in the two groups of subjects with MCI and control group B.

Subject groups	Mean age ± SD (years)	MMSE score (mean± SD)	P300 latency (msec) (mean± SD)	P300 amplitude (μV) (mean± SD)
Control group B (n=20)	51.5±5	29.8±0.1	327±18	14.3±5.1
MCI negative CT/MRI (n=18)	51.7±5.2	28.6±0.5	340±17	11.3±2.6
MCI positive CT/MRI (n=10)	52.6±5.8	27.9±0.6	355±19 p<0.01*	11.7±2.9

* compared to control group B

Table 7. Lipid parameters and paraoxonase (PON) activity in the sera

	AD (n=30)	VD (n=40)	Control (n=40)
Age (átlag±SD) (years)	64.3±11.7	76.1±12.4	72.3±9.6
Sex (N/F)	20/10	27/13	26/14
Cholesterin (mmol/l)	6.52±0.7	6.3±0.8	4.71±0.89
LDL-chol. (mmol/l)	3.84±0.6	3.96±0.8	2.6±0.6
Triglicerid (mmol/l)	1.68±0.1	1.47±0.8	1.06±0.52
HDL (mmol/l)	1.95±0.1	1.43±0.31	1.47±0.1
HDL-associated PON (U/l)	131±40	151±47	188±55

Table. 8. N^{ε}(γ-glutamyl)lyzine isodipeptide (IDP) concentration in cerebrospinal fluid (CSF)

	AD (n=14)	VD (n=11)	Control subjects (n=15)
Sex (N/F)	7/7	7/4	6/9
Age ± SD (years)	66.5±8.5	67.6±9.4	66.1±12.1
MMSE score ± SD	16.4±4.3	13.7±5.2	29.4±0.7
CSF IDP±SD (nM/l)	176.6±77.1	95.6±45.1	37.9±8.7
Plasma IDP (nM/l)	2.3±1.8	3.0±1.4±	2.1±0.9

DISCUSSION

CANTAB

The present results show that several cognitive domains are already impaired in patients with MCI, and in AD patients several other cognitive domains show impairment and the severity of the cognitive dysfunctions is more pronounced.

Visual Paired Associate Learning (PAL test) was significantly ($p<0.05$) impaired among subjects with AD and MCI. A successful performance in the PAL test requires both the elaboration of „frontal strategies" and the „mnemonic processes" of the medial temporal lobe. MCI patients performed poorly on this test, as did AD patients, which suggests that they may already be in the early stage of the disease. Several studies, including functional brain imaging experiments, have shown a dysfunction of the medial temporal lobe in the early phase of dementias and schizophrenia. Furthermore, elderly subjects with major depression also perform poorly on tests of memory, as do AD subjects; thus, the *specificity* of such tests is particularly crucial for being able to differentiate the AD individuals. Refinement of the

sensitivity of neuropsychological tests would allow possible disease-modifying treatments to be employed at the earliest stages of neuronal loss.

P300

In line with the literature the obtained results confirm previously reported findings that P300 latencies are significantly prolonged among patients with both vascular and Alzheimer's dementia, and amplitudo was decreased. Also, no significant differences of mean P300 latencies between the AD and the VD patients were found. Prolonged P300 latency in both types of dementia is associated with the dysfunctions of the neuropsychological processes involved in P300 generation. The present results confirm previous results that the severity of dementia and the prolongation of P300 latency are correlated; therefore, the prolongation of P300 latency reflects the severity of dementia, but not the type of dementia. MCI subjects with mild cerebral atrophy had a prolongation of P300 latency similar to that observed in demented patients, while in MCI patients with normal brain structure, the P300 latency was not altered. This may suggest that P300 latency prolongation can be connected with the structural brain damage detectable in MCI patients and that the complex cognitive disturbances are already present in this group of MCI patients.

Paraoxonase (PON)

Most of the patients with AD had the apoE4 isoform, consistently with other studies. We found significantly higher total-cholesterol and LDL-cholesterol levels in AD and VD patients compared to the control group. The HDL-associated paraoxonase activity was significantly lower in both patient groups, but did not differ in AD from VD. The results suggest that the defect in PON antioxidant capacity plays a role in the pathogenesis both of AD and VD.

N^{ε}(γ-glutamyl)lyzine isodipeptide (IDP) concentration in cerebrospinal fluid (CSF) showed significant elevation in vascular as well as Alzheimer patients. We suppose that IDP released from the apoptotic cells within the central nervous system accumulates in the CSF. The overlap of IDP ranges may reflect the etiological relatedness of the two dementia types. A linear correlation between IDP concentrations in CSF and age of control persons were found: higher age is associated with higher IDP level, which reflects an increasing intensity of apoptotic cell turnover with age.

SUMMARY

Several different clinical techniques were evaluated for the early diagnosis of Alzheimer's disease (AD). The brain has the capacity to compensate for the smaller damages and to retrieve small lesions, therefore the disorder can have a long preclinical phase before the clinical symptoms are present. There is a need for sensitive biological markers to detect AD pathology. The recognition of prodromal and early phase of AD opens possibility for the prevention (i.e. elimination of the vascular risk factors), and for the early treatment.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) showed characteristic changes in early AD and amnestic MCI, which suggests that aMCI may be a prodromal phase of AD. The cognitive deficit appears to be similar in major depression (MD), so it does not give a determined help to differentiate it from AD. There are less cognitive deficits in the remission phase of MD than in the depressed phase. Presumably the underlying process of the cognitive deficit in depression might be rather functional disturbance than structural damage in the brain. Some advantages of CANTAB compared to the other neuropsychological methods are the following: it is independent from language, useful in case of aphasia, and requires shorter time to perform.

The late component of auditory evoked potential, P300, is not widely used in psychiatry, althought it may be a sensitive marker of cognitive impairment. P300 has less value in the differentiation of AD from vascular dementia (VD), because the changes are similar in these two disorders. The longer latency of P300 in amnestic MCI might predict the conversion to AD, and a more extensive use is offered.

The altered serum paraoxonase (PON) activity, a defect in the antioxidant capacity beside lipid metabolism, and the increased oxidative stress all play important role in the pathomechanism of AD and in atherosclerosis, which suggests an overlap in the pathogenesis of AD and VD. The altered PON activity can be a sensitive marker of the defect in antioxidant capacity.

The transglutaminase activation is a marker of apoptosis and elevated isodipeptide concentrations in the body fluids might correlate with the intensity of apoptotic cell turnover. The determination of N^{ε}(γ-glutamyl)lysine isodipeptide (IDP) concentration in the cerebrospinal fluid offers a novel method for measurement of neurodegeneration in primary and mixed dementias.

There is not enough evidence to recommend one specific technique for the prediction and early detection of AD. A combined use of cognitive tests, ApoE genotype, functional and

structural neuroimaging techniques, the serum and cerebrospinal fluid measurements is probably the best option.

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