THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

COMPLEX NEURORADIOLOGICAL AND NEUROPSYCHOLOGICAL ASSESSMENT IN RHEUMATOID ARTHRITIS PATIENTS

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The Examination will be held 11:00 am, December 10,2020

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The PhD Defense will be held 13 pm, December 10, 2020.

Live online access will be provided. If you wish to take part in the discussion, please send an e-mail to olahcs@gmail.com not later, than 12 pm on the day before the discussion (December 9, 2020). After the deadline, for technical reasons , it is no longer possible to join in to the defence.

1 INTRODUCTION

1.1 Cognitive functions, neuropsychological examinations

Cognitive functions and abilities are the basic elements of intellectual functioning. Abilities can be divided into two major groups: direct and indirect cognitive processes. Direct skills are detection (reception), perception and attention (selection). Direct abilities enable the perception and interpretation of momentary reality. Impulses acting on the senses create sensations in the brain. Perception is the interpretation of perceptions. Attention focus on something, we highlight and separate the important stimuli. Indirect skills are memory, imagination and thinking. Indirect abilities make it possible to get to know and perceive a reality that is not currently present. By memory, we can recall our previous perceptions. Through imagination, we create new images based on known elements of reality. Thinking is the highest level of mental ability. Thinking allows to gain new knowledge, understand the contexts of reality, and solve problems. Inductive thinking is one of the most important tools for acquiring new knowledge, it is closely related to problem solving, intelligence, critical thinking, learning potential. Combinatorial thinking plays a key role in various creative activities, discoveries, innovation, and the functioning of imagination.

The two most significant complex cognitive abilities are creativity and intelligence. According to Wechsler's definition, intelligence is the individual's global ability to act purposefully, to function effectively in his environment, to think rationally. Cognitive abilities differ significantly in different age groups, constantly changing with age. In infancy and childhood, cognitive functions develop and improve very quickly. The cognitive parameters of children are only partially determined by inherited factors, the genetic background. Numerous twin studies have demonstrated that family background, school education, and different social components significantly influence children’s cognitive parameters. While cognitive parameters continuously improve in childhood, cognitive parameters deteriorate in elderly parallel with the continuous death of cerebral neurons.

Cognitive tests always measure current status function and are used to measure various cognitive parameters. During the scientific processing, patients' results must always be compared with the same control group in terms of age, gender and education. The effect of diseases on cognitive function is also significantly influenced by the therapies used. At the time of the introduction of new drugs (biological therapies) for the treatment of certain diseases, only the pharmacokinetic and acute pharmacodynamic effects are known by human I-IV phase clinical studies. Over the years, not only the beneficial effects of new drugs on the rheumatic disease, but also their effects on other organs become measurable. These can be beneficial, but even harmful in the long run. The long-term effects of biological treatments on cognitive functions are a very interesting area of clinical pharmacology and clinical research.

Numerous cognitive tests have been included in everyday clinical prectice, and a lot of tests are also used in research. If several different tests are used simultaneously, a more complex picture of the cognitive status of the patient is obtained.

1.2 Cognitive dysfunctions in rheumatoid diseases

Patients with chronic autoimmune rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SS) need normal cognitive function for daily activity in order to thrive in their daily lives and take their medicines properly. Most chronic autoimmune inflammatory rheumatic diseases are associated with varying degrees of cognitive impairment.

1.2.1.Reumatoid arthritis

Reumatoid arthritis exerts various neuro-psychiatric manifestations. There is an increased risk of stroke especially in elderly patients with long-standing disease. Depression or anxiety are present in two-third of RA patients. In cognitive function

tests, RA patients significantly underperform compared to healthy ones. Cognitive impairment can occur in the early stages of RA, even in young patients. Cognitive dysfunction influences patients' pain threshold, the effectiveness of their medicines and overall self-care. RA disease activity through systemic inflammation affects the rate of development of cognitive impairment as well as the rate of depression and anxiety. In depression, concentration and problem-solving ability deteriorate.

Among antirheumatic drugs, methotrexate (MTX) and corticosteroids affect the development and prognosis of cognitive impairment. However, the effect of these drugs is controversial. Both corticosteroids and MTX reduce systemic inflammation, and this may have an indirect beneficial effect on cognitive function. On the other hand, MTX is associated with cognitive impairment, mood disorder, and confusion, while corticosteroids may have a negative effect on memory and hippocampal function. The control of disease activity is the most basic treatment option. Although inflammatory mediators play an important role in cognitive impairment in RA, very few studies have evaluated the effect of RA drugs on cognit ive function.

1.2.2. Systemic lupus erythematosus (SLE)

Neuropsychiatric manifestations in SLE ranging from stroke, transverse myelitis, acute confusional state to nonspecific symptoms such as mood disorders, headache and cognitive impairment. Studies have estimated that cognitive dysfunction influences 3-81% of SLE patients. An interesting aspect of cognitive impairment develops insidiously, may present and progress independently of other SLE symptoms and generally do not respond to standard immunosuppression.

1.2.3. Systemic sclerosis (SSc)

One of the least affected organ systems in systemic sclerosis is the central nervous system. In SSc, cognitive impairment is rare, but depression, anxiety, and mood disorders are common.

1.3 Neurological abnormalities and neuroradiological examinations

The main causes of mortality in RA are cardiovascular and cerebrovascular diseases, which develops primarily on the basis of accelerated atherosclerosis. RA also directly and indirectly affects the nervous system:

- peripheral nervous system - polyneuropathy, tunnel syndromes,
- spine - C.I., C.II. destructive lesions,
- brain - structural and functional abnormalities

1.3.1.Abnormalities of the peripheral nervous system

In RA, polyneuropathy symptoms and compression syndromes may occur. Most commonly, carpal tunnel syndrome is encountered. In addition, tarsal and cubital tunnel syndromes may also occur. Polyneuropathy RA causes glove- and sock-like numbness, less commonly pain.

1.3.2.Spinal abnormalities

The atlanto-occipital and atlanto-axial joints are special spinal levels because there is no intervertebral disc here, only synovial joints. This is the reason that RA affects this spinal segment most often. Erosive pannus formation in RA is also associated with chronic synovitis, which can result in odontoid erosion, ligament weakness, spinal stability, and atlanto-axial subluxation (AAS). AAS can be anterior,

posterior, and vertical. Anterior AAS is the most common form, the main cause being weakness of the ligament. During the course of RA, cervical lesions do not cause clinical symptoms for a long time. Neurological symptoms may not appear up to 10 mm of AAS. The most common sign of AAS is neck pain, although it may be absent in up to half of patients with known instability. Tinnitus, dizziness, and dysphagia may also occur. Functional spine X-ray and MRI may detect asymptomatic abnormalities that may become symptomatic even after trauma, a sudden movement and retroflexion of the neck during anesthesia. The most serious complication is the spinal cord involvement. Myelopathy can cause irreversible neurologic deficit, severe pain, respiratory problem and death.

1.3.3.Brain abnormalities

Stroke morbidity and mortality were significantly increased among RA patients. Ischemic and hemorrhagic stroke are common.

1.3.4. Radiological examinations of the central nervous system

Radiological examinations of the cervical spine include X-ray, computed tomography (CT), and magnetic resonance imaging (MRI). X-ray examination can confirm gross degenerative changes, fractures and instability of the cervical spine. In several previous RA studies the cervical spine has been examined with X-ray. The CT examination shows the degenerative and traumatic abnormalities of the cervical vertebrae more accurately, and the spinal cord and nerve roots are also imaged. The "gold standard" examination procedure for the cervical spine is MR examination. MRI can be the most accurate diagnosis of degenerative, inflammatory, tumorous lesions affecting the cervical region.

CT and MRI are suitable for detecting brain structures. Cerebral MRI examination best depicts abnormalities affecting the cerebrum (emollitions, bleeding, hydrocephalus, tumor, abscess).

Suitable methods for detecting large cervical vessels include magnetic resonance angiography (MRA), computed tomography angiography (CTA), digital subtraction angiography (DSA), and ultrasound (US). US is excellent for the screening of the common and internal carotid arteries. US assess structural and flow parameters witout radiation and contrast material.

CTA, MRA, DSA, and transcranial Doppler ultrasound (TCD) are suitable for detecting cerebral vessels and their pathological changes. TCD is a non-invasive, easy-to-bed examination. TCD provides not only anatomical but also pathophysiological information.

Blood flow rates (peak systolic and end-diastolic), the pulsatility and resistance index reveal many aspects of cerebral circulation. Functional TCD using hyperventilation and respiratory arrest can determine cerebrovascular reserve capacity (CRC) and provide accurate information on the state of vascular autoregulation. If the CRC values decrease, it can be considered a threatening sign for ischemic stroke even if patient is asymptomatic.

2. AIMS

2.1. The basic ideas of our research

Rheumatoid arthritis affects patients' cognitive status.
Biological treatments affect the cognitive parameters of RA patients.
There is correlation between cognitive parameters and cerebrovascular abnormalities in patients with RA.
Biological treatments have effect on upper cervical spine lesions in rheumatoid arthritis.
The 3T MR examination is suitable for the accurate detection of cervical spine lesions in patients with RA who are asymptomatic and asymptomatic for the cervical spine, allowing the screening of at-risk patients prior to special treatments or interventions.

2.2. Aims:

2.2.1. Study 1:

Main aims:
to measure of cognitive parameters in female patients with rheumatoid arthritis,
to determine the relationships between neuropsychological and neuroradiological parameters in patients with RA,
to measure of the effect of biological treatments on cognitive status and cerebrovascular status,

Additional aims:
to assess of depression and anxiety in patients with rheumatoid arthritis,
to assess of life quality parameters in patients with rheumatoid arthritis,
to achieve complex neuroradiological mapping of patients with rheumatoid arthritis,
to assess the effect of biological treatments on psychological status and quality of life,
to analyse of correlations between cognitive parameters and disease activity parameters in patients with RA.

2.2.2. Study 2:

Main aims:
to analyse cervical spine lesions with 3 Teslás MRI in patients with RA

to assess the effects of biological treatments on cervical spine lesions in patients with RA.

to analyse the role of MRI examination in the context of cervical spine lesions in patients with asymptomatic rheumatoid arthritis.

Additional aim:

to analyse the correlations between cervical spine lesions and disease parameters in patients with RA.

3. PATIENTS AND METHODS

3.1. Study 1: complex neuropsychological examination in rheumatoid arthritis

3.1.1 Patients and controls

60 female RA patients undergoing regular follow-ups at the Borsod County University Teaching Hospital, Miskolc were selected. The inclusion criteria were informed consent; female patients aged 18 or over; definitive diagnosis of RA and stable dose of MTX, corticosteroids and biologics for at least 6 months prior to the study. The exclusion criteria were pregnancy and/or breast feeding; implanted metal; claustrophobia; history of skull trauma; any previous vascular events including cerebrovascular diseases, as well as mental disorders; known depression and other mood disorders.

20 patients were biologic naive. They had been receiving MTX for a mean 7.2±4.9 years in an average dose of 14.1 ± 4.4 mg per week. We selected forty female patients receiving biologics [20 infliximab (IFX) and 20 tocilizumab (TCZ)] in combination with MTX, for a mean duration of 4.0±2.0 years. We selected intravenously administered biologics to increase therapy control and compliance. The doses of MTX and biologics had been stable for at least 3 months prior to the study. Disease activity (DAS28 and ESR) was determined in all RA patients every 3 months; thus, the mean values of the past 5 visits (1 year) were calculated.

39 healthy female individuals was chosen as the control group. They participated in a carotid ultrasound screening program by the author. Controls had the same inclusion and exclusion criteria as patients. The age of controls (60.2 ± 6.7 years) was not significantly different from that of RA patients. RA patients' SF-36 scores were compared to the gender- and age-matched Hungarian general population norm. We assessed alcohol consumption, smoking habits during the past 2 years and the number of years in education. All patients and controls signed informed consent. Ethical approval (No. 1046-63/2015) was obtained from Miskolc University Institutional/ Regional Review Board.

3.1.2. Cognitive and psychological tests

During the study we used international tests translated into Hungarian.

Mental capabilities

The Montreal cognitive assessment (MOCA) is a screening test to determine mental capabilities in general and for determining mild-medium cognitive impairment. The higher values indicate better cognitive function (range 0–30).

Attention/concentration

The Digit Symbol subtest of the Wechsler Adult Intelligence Scale (WAIS) provides information on visuo-perceptual functions, fine visual-motor speed dexterity and. The number of correct symbols reproduced within the time limit is measured. Numbers are then converted to Hungarian standard scores.

Trail making test (TMT) measures the mental flexibility, visual attention, executive functions and speed of visual processing. In TMT-A assessing visuomotor processing speed, numbers are presented on a page in random array. The patient is instructed to connect the numbers in ascending order as quickly as possible. TMT-B determines mental flexibility and measures the control and executive function of the frontal lobe of the brain. Numbers and letters are on the sheet and the examinee must alternate connecting numbers and letters one after the other. The score on each part is the time.

Executive function

The Victoria Stroop Test (VST) is a brief version of the Stroop test. VST measures the cognitive control by determining the ease with which a person can maintain a goal in mind and overwhelm a habitual response in favor of a less familiar one (response inhibition). VST contains 24 items in each of the following conditions: naming the color of dots (VST-A), of neutral words (VST-B), and of color words printed in different colors (VST-C). We determined the time in seconds. VST and TMT-B tests assess executive functions.

Memory

The Benton Visual Retention Test (BVRT) was used to assess the patient's immediate visual memory and visuo-constructive skills. 10 geometric figures are shown one after the other and the patient has to draw the designs as accurately as possible. More correct reproductions and less errors indicate intact skills.

Anxiety

The Spielberger State-Trait Anxiety Inventory (STAI) is a commonly used self-scored measure of trait and state anxiety. It is composed of dot, neutral word and color word tasks. Both the time of task completion and the number of errors have been recorded. STAIS indicates state (current status) and STAIT measures trait (general status). Lower STAIS or STAIT values represent less trait and state anxiety.

Depression

The Beck Depression Inventory (BDI) is a self-report rating inventory that measures characteristic attitudes and symptoms of depression. Higher BDI values represent higher degree of depression.

3.1.3 Quality of life test

We used Hungarian validated , paper-based version of the SF-36. SF-36 measures general health status. The SF-36 questionnaire consists of 36 questions and provides scores for 8 individual subscales: physical function (PF), role physical (RP), global health (GH), bodily pain (BP), vitality (VT), role emotional (RE), social function (SF), and mental health (MH). The score range of each scale is between 0 and 100. Higher score means better quality. Domains' scores were combined to form the physical component summary (PCS; PF + RP + BP + GH) and mental component summary (MCS; VT + SF + RE + MH).

3.1.4 Laboratory assessments

Serum IgM RF and high-sensitivity CRP (hsCRP) were measured by quantitative nephelometry (Cobas Mira Plus, Roche), using special reagents (Dialab,

Vienna). RF levels > 50 IU/ml indicated seropositivity and hsCRP levels > 5 mg/l were considered elevated. Erythrocyte sedimentation rate (ESR) was determined by Westergren method (mm/h). Anti-CCP autoantibodies were detected using the second generation Immunoscan-RA CCP2 ELISA test (Euro Diagnostica, Arnhem). A concentration > 25 IU/ml indicated seropositivity. DAS28-ESR was determined in all RA patients and mean of the last 5 ESR and DAS28 values was also calculated.

3.1.5. Neuroradiological examinations

Transcranial Doppler assessment

Transcranial Doppler (TCD) assessment of the MCA vessels was implemented. We used TCD using a Multi-Dop T Digital (DWL Company, Singen) device. Cerebrovascular reserve capacity (CRC) reflects the physiological vasodilatory and vasoconstrictive function of resistance precapillary arteries. Normally, the increase in CRC after stimuli causing vasodilation is bigger than 30%.

Carotid artery ultrasound examination

Common carotid artery (CCA)and internal carotid artery (ICA) assessments were carried out using a duplex ultrasound system (Vivid E, GE Healthcare) using a 8 MHz linear array transducer (GE Probe 8L-RS). Longitudinal high resolution B-mode ultrasound scans were carried out over both right and left CCA and ICA . Carotid artery intima–media thickness (cIMT; mm) was defined as the distance between the first and second echogenic lines from the lumen, taking the average of 5 results on both ICA and CCA. All visible plaques were also detected. Each assessment was performed by a single neurosonolgist.

Brain MRI investigations

Altogether 49 out of the 60 RA patients also underwent brain MRI studies (Siemens Magnetom Verio 3T, Siemens, Munich) to assess atrophy, focal vascular lesions and emollition. All MRI scans were performed by a radiologist and a neuroradiologist. A global cortical atrophy score was used as follows: 3, severe atrophy; 2, moderate atrophy with volume loss of gyri; 1, mild atrophy with opening of

sulci; 0, no atrophy. Vascular lesions were considered hyperintense lesions detected by flair and T2 sequences not characteristic for any white matter diseases.

3.1.6 Statistical analysis

IBM SPSS22 software was used for statistical analysis. Data are expressed as the mean ± SD and frequencies and percentages. Normality of data was assessed by Kolmogorov–Smirnov test. Continuous variables were compared by Mann–Whitney test. Simple correlations weredetermined by Spearman's analysis. Multiple linear regression analysis using the backward method was used to determine independent associations and correlations between parameters. Cognitive tests were the dependent variables and several other parameters were independent variables. *P* values < 0.05 were considered significant.

3.2. Study 2: complex neuroradiological examination in rheumatoid arthritis

3.2.1. Patients and controls

49 RA patients were recruited for the study at the Borsod County University Teaching Hospital. Patients with RA were in stable remission or with low disease activity. None of them had neurological any deficits or pain.

All patients were females, their median age was 60 (43–78) years. Their median disease duration was 9 (0.5–36) years. 71% were IgM RF positive, and 67% were ACPA positive. Among these patients, 15 were biologic free. They had been receiving MTX for 6 (0.5–15) years in an average dose of 15 (7.5–20) mg/ week. 34 patients had treated biologics (17 infliximab and 17 tocilizumab) in combination with MTX. They have got biologic therapy for 5 (1–10) years, the median duration of MTX was 5.5 (0.5–12) years in an average dose of 15 (7.5–25) mg/week.

3.2.2. Cervical spine MRI examination

All 49 RA patients underwent cervical (atlas and axis) MRI imaging. We used Siemens Magnetom Verio 3T MRI instrument. The presence or absence of periodontal

soft tissue thickening, odontoid erosion, and atlantoaxial subluxation were noted. AAS is defined by an increase in the atlantodental interval (> 3 mm). ADI > 3.5 mm means instability and ADI > 10 mm is the indication for surgery.

3.2.3. Hand X-ray examination

All RA patients underwent hand X-rays to assess the degree of disease progression. Erosions were scored according to the modified van der Heijde–Sharp method. Each joint was graded on a score of 0 (normal) to 5 (maximal destruction).

3.2.4. Laboratory assessments

The laboratory parameters described in the first study were measured and evaluated as described there.

3.2.5. Statistical analysis

IBM SPSS25 software was used for statistical analysis. Data are expressed as median and range. The distribution of continuous variables was determined by Kolmogorov–Smirnov test. Differences were evaluated by independent two-tailed *t* test or Mann–Whitney test as appropriate. Nominal variables were compared between groups using the Chi-squared or Fisher's exact test, as appropriate. p values < 0.05 were considered significant.

4. RESULTS

4.1. Study 1: complex neuropsychological examination in rheumatoid arthritis

4.1.1 Basic characteristics of RA patients and controls

Their mean age was 60.7 ± 9.5 (27–78) years and mean disease duration was 11.6±7.6 (2–36) years. Altogether 70% were IgM RF positive and 65% were ACPA positive. 8.3% of RA patients and 25% of controls regularly consumed alcohol. Education level was not different between RA patients and controls. There were more smokers among RA groups compared to controls. CCA plaques were detected in 55% RA patients. 23.5% of controls and 46.9% of RA patients had at least one MRI vascular lesion in their left hemisphere. 20.6% of controls and 46.9% patients had MRI lesions in their right hemisphere. 2.9% of controls and 26.5% of RA patients had cerebral atrophy.

4.1.2 Results of cognitive tests

Most cognitive test results correlated with many others in RA patients. In BVRT, the number of correct reproductions was significantly lower in the RA patients (p = 0.005) and biologic treated patients (p=0.006) compared to controls. There were no differences in BVRT errors. The MOCA total score was significantly lower in RA (p=0.002) and in biologic-treated patients (p=0.001) compared to controls. 25 or less MOCA score was observed in 63%, 50%, 70% and 46% of patients in the total RA, MTX, biologic sub-groups and controls. Total RA (p=0.029) and biologic-treated RA patients (p=0.007) had longer TMT-A times than controls. Biologic treated patients required more time vs MTX treated group (p=0.041). In TMT-B, RA patients needed longer time than controls (p=0.048). In VST-A, RA patients (p = 0.040) and the biologic treated group (p=0.019) needed longer time than controls. In VST-B, biologic-treated RA patients required longer time vs controls (p=0.007) WAIS digit symbol scores were significantly higher in controls compared to the total (p=0.003) and biologic-treated RA groups (p=0.006).

BDI values were significantly lower in controls versus all (p=0.023) and biologic-treated patients (p=0.015). STAIS values were significantly lower in controls

vs. all RA (p<0.001), MTX treated (p=0.012) and biologic-treated patients (p<0.001). STAIT values were higher in all (p=0.004) and biologic-treated RA group (p=0.002) vs controls. SF-36 scores were lower in RA patients vs controls in all domains except RE. Three out of the four mental domains of the SF-36 were impaired in RA patients.

4.1.3 Correlations between cognitive function and other parameters

BDI, STAIS and STAIT values exerted significant inverse correlations with all 8 SF-36 domains (p<0.05). WAIS Digit Symbol values showed positive correlations with 7 SF-36 domains. Disease duration correlated with longer VST-A time (p=0.027). STAIT correlated with DAS28 (p=0.018) and ESR (p=0.006).

4.1.4 Associations between neuropsychological and neuroradiological results

Patients with brain atrophy had lower WAIS scores, while those with MRI vascular lesions had longer VST-A times (p=0.032). RA patients with left carotid plaques had higher BDI, STAIS, STAIT scores, longer VST-C and TMT-A times, and lower WAIS scores (p<0.05). Patients with right carotid plaques had longer VST-C times, higher STAIT, STAIS values, and lower WAIS scores (p<0.05).

Right cIMT inversely correlated with WAIS Digit Symbol scores (p=0.024). Right MCA CRC positively correlated with BVRT values (p=0.033). Left MCA CRC exerted positive correlation with MOCA values (p=0.016) and inversely with BDI result (p=0.008).

4.1.5 Determinants of cognitive function

In the multiple regression analysis, age was independent predictor of WAIS scores (p=0.001), TMT-A (p=0.001), VST-B (p=0.005) and VST-C time (p=0.001). School years determined BVRT total scores (p<0.001) and errors (p < 0.001), MOCA (p=0.006), BDI (p=0.001), STAIS result (p<0.001). MRI lesions determined longer

VST-A times (p=0.001). Left carotid plaques predicted STAIT (p=0.036). Biologics and MTX therapy was an independent predictor of TMT-A times (p=0.016).

In the univariate analysis, a lot of tests correlated with school years and age (p<0.05). TMT-A and VST-C time, STAIT, STAIS, and WAIS Digit Symbol score were associated with carotid plaques (p<0.05). Right cIMT correlated with WAIS scores (p=0.024). The presence of MRI vascular lesions correlated with VST-A time (p=0.006). STAIT correlated with DAS28 (p=0.02) and ESR (p=0.009). Biologic- vs MTX-treated patients had longer TMT-A times (p=0.03). BVRT and BDI scores associated with both MCA CRC (p<0.05).

4.2. Study 2: complex neuroradiological examination in rheumatoid arthritis

4.2.1 Comparative description of RA patient subsets

The total RA cohort, the MTX- and biologic-treated RA subsets did not differ from each other in most clinical and disease activity markers. Biologic-treated patients had significantly lower DAS28 2.59 (0.75–3.69) vs 3.23 (1.86–4.34) than MTX-treated patients (p = 0.036). IFX-treated patients had significantly higher DAS28 2.78 (1.8–3.69) vs 2.2 (0.75–3.29) (p<0.001), ESR 22.38 (9.62–50.86) mm/h vs 9.56 (2.62–24) mm/h (p<0.001) and lower modified van der Heijde–Sharp scores 15 (0–146) vs 26 (3–70) (p=0.040), compared to TCZ treated individuals.

4.2.2 Cervical spine MRI investigations

Anterior AAS developed in 29.4% of the biologic-treated subset, 20.0% of the MTX- and 26.5% of all RA patients. 35.3% of TCZ - and 23.5% of IFX -treated patients had anterior AAS. No posterior or vertical AAS was detected in any patient. Soft tissue thickening was confirmed in 24.5%, 33.3%, 20.6%, 5.8% and 35.3%, of all ,MTX-, any biologic-, TCZ -, and IFX -treated RA patients. Odontoid erosion was observed in 16.3% of all RA patients, 20.0% in MTX and 14.7% of any biologic-treated, as well as in 17.7% of TCZ - and 11.8% of IFX - treated patients. There were no significant differences between biologic and MTX-treated patients with respect to any MRI finding. There were no differences between the TCZ- and IFX-treated subsets.

4.2.3 Associations of cervical spine MRI pathologies with clinical, laboratory and hand X-ray parameters

Patients with anterior AAS had significantly higher CRP compared to patients without AAS 10.17 (2.16–21.8) vs 4.6 (0.16–26.32) mg/l; (p=0.019). Patients with AAS also had a tendency of higher MTX dose and DAS28, but these differences were not significant. Patients with periodontoid soft tissue thickening were significantly younger compared to those without this pathological feature 54.5 (45–63) vs 61 (43–78) years; (p=0.013). There was also a tendency of higher DAS28 and ESR in patients with periodontoid soft tissue thickening. Patients without odontoid erosion had significantly lower vdHSS compared to those with odontoid erosion 16 (0–146) vs 38 (21–86) (p=0.007). With respect to other parameters, such as seropositivity, disease duration, biologic treatment and its duration, MTX dose and duration, TCZ versus IFX treatment, there were no differences between the three patient subsets.

5. DISCUSSION

5.1. Study 1: complex neuropsychological examination in rheumatoid arthritis

A prospective study was performed on female RA patients, comparing their complex cognitive function, depression and anxiety values to gender-and age -matched healthy volunteers using standard validated tests. Our aim was to demonstrate an association between cognitive decline function and RA-related parameters, quality of life, cerebrovascular abnormalities, and treatment modalities. We applied MOCA as a screening tool. We assessed memory (BVRT), concentration /attention (TMT-A, TMTB, WAIS), executive functions (VST, TMT-B). We also compared cognitive dysfunction with anxiety (STAI) and depression (BDI). The novelty of our study was that we examined the cognitive status of patients in a very complex way (using several tests) and in parallel we also used a complex series of neuroradiological procedures including brain MRI, carotid ultrasound and TCD. Various cognitive function tests correlated with each other in RA. BVRT score, MOCA score, WAIS Digit Symbol scores, VST-A, VST-B, TMT-A and TMT-B times were significantly abnormal in RA patients. We confirmed that RA is associated with cognitive dysfunction. Depression and anxiety are common among RA patients. Some domains of cognitive dysfunction did not correlate with STAI or BDI scores, so cognitive impairment cannot be explained by psychological factors alone. A novelty of our study was that cognitive function abnormalities and depression / anxiety scales were examined in a large number of patients and compared to control groups. A similar prospective study has not been reported previously.

3 SF-36 mental domains were impaired in RA patients. The WAIS screening test showed association with 7 SF-36 domains. TMT-A and TMT-B times correlated with some SF-36 domains. BDI, STAIS, STAIT values were associated with all 8 SF-36 domains suggesting that, in RA, both depression/anxiety and cognitive dysfunction may have negative impact on the general health status of RA patients. We have found only one study that analyzed the associations of SF-36 with cognitive function in RA. In our study cognitive function tests were correlated with other parameters, such as ESR, DAS28, disease duration.

As atherosclerosis has been involved in cognitive impairment in RA, we also examined carotid atherosclerosis, intracranial arteries' CRC, cerebral vascular lesions and atrophy. We found correlations between cognitive impairment and vascular pathologic alterations. Cerebral blood flow in association with cognitive function has not yet been examined in RA before. TMT-A times were longer in biologic vs MTX-treated patients. Although some studies suggest that MTX may itself cause cognitive impairment, it is possible that the severity of RA may even be more important in this respect. Although inflammation also plays a major role in cognitive decline in RA, only very few studies have analyzed the longitudinal effect of antirheumatic drugs on cognitive function.

Our study have strengths and limitations. Our study is rather comprehensive applying numerous different cognitive tests in the context of quality of life, laboratory factors, crebrovascular reserve capacity, brain vascular lesions and carotid atherosclerosis.
Modern imaging technologies were used with complex cognitive screening in large patient and control groups, one of the strengths of our study.

The limitations of our study include the relatively low number of healthy controls and patients matched for many relevant characteristics. We suggest to consider our results as explorative rather than conclusive and further examinations involving larger samples, representative for the RA population are encouraged. Given the cross-sectional design, the effect of different therapies on cognitive function could not be longitudinally analyzed; this is an important field for further research.

While laboratory and neuroradiological parameters and quality of life could be numerically determined, we could only roughly interpret smoking habits, alcohol intake and education. Applying measures and categories that allow comparisons with population norms for tobacco and alcohol consumption as well as for educational levels is suggested in further studies.

5.2. Study 2: complex neuroradiological examination in rheumatoid arthritis

Despite modern therapy, we still detect cervical spine abnormalities in the RA. AAS, odontoid erosion, or periodontoid soft tissue thickening may be confirmed even in asymptomatic patients. Anterior AAS may develop early in the disease and it can later be complicated with odontoid erosions and periodontoid soft tissue lesions . Initial symptoms are usually neck pain and headache followed by different neurological symptoms even myelopathy.

As 3 Tesla MRI instruments have become available, we wished to try this examination to assess cervical spine abnormalities in RA. Moreover, there have been only very few studies with respect to cervical spine pathology in biologic-treated RA patients. We included 49 RA patients with no neurological symptoms and cervical spine pain. The most common cervical spine involvement is AAS. We found this lesion in about 25% of our RA patients. Anterior AAS was associated with higher DAS28, CRP and MTX dose. Early onset of RA, seropositivity, erosive disease at baseline, high disease activity scores, and corticosteroids therapy were predictors of AAS. vdHSS was not associated with AAS. Importantly, the progressive damage of peripheral joints with indication of prosthetic implantation was also associated with cervical spine involvement. In RA, patients right before hip or knee replacement surgery, 44–65% demonstrated AAS on preoperative radiographs.

MRI is useful when assessing cervical spine pathologies in comparison to conventional radiography, may also detect odontoid erosions and periodontoid soft tissue thickening. We assessed our patients for signs of synovitis and fibrotic pannus in the joints of atlas and axis, as well as for erosive lesions of the dens. 16% of patients had dens erosions and 25% had soft tissue thickening. Interestingly, odontoid erosions were associated with higher vdHSS while periodontoid soft tissue thickening occurred at younger age. We compared MTX- versus biologic-treated, as well as, IFX- versus TCZ-treated RA patient subsets. We confirmed that MTX- and biologic-treated patients had similar clinical features. Only DAS28 was lower in the biologic-treated group. On the other hand, IFX -treated patients had higher ESR and DAS28 and somewhat higher CRP compared to TCZ -treated patients indicating that IFX and TCZ may have different effects on inflammatory activity. However, TCZ-treated patients had higher vdHSS suggesting that this subset may reflect a more severe patients. Despite these radiological and clinical differences between the RA subsets, no significant differences

were found between subsets with respect to soft tissue thickening, AAS or odontoid erosions.

In 2019, Sandstrom et al. published the NEORACo results. In this study, 99 RA patients received conventional treatment and then they were randomized to receive placebo or IFX. After 10 years, 4.7% patients had upper cervical spine involvement. There were only two cases with AAS, both treated with IFX. In this study AAS is relatively rare compared to our patients with 10–11 years of disease duration. Salli et al. reported successful IFX treatment of periodontoid pannus in a RA case report. We have not found any other articles on the possible effects of biologics on cervical spine pathologies. Kanayama et al. published a study on RA patients receiving IFX for at least 1 year. IFX suppressed the progression of cervical lesions in 83% of patients. We did not find any reports about TCZ treatment in this regard.

Our study has strengths and limitations. Possible limitations include the the cross-sectional nature of our study and relatively small number of patients. The major strength is its novelty studying cervical spine involvement in RA in the era of modern imaging and therapies. We enrolled RA patients with longer disease duration; therefore, cervical spine pathologies are relatively more common than in early stage RA cohorts. In conclusion, 3 T MRI may assess soft tissue involvement and odontoid erosions in addition to AAS. Despite of modern therapy, 15–30% of patients still have preclinical cervical spine abnormalities that may be related with higher degree of structural hand joint changes and systemic inflammation. MRI is a sensitive imaging to assess cervical spine involvement in asymptomatic RA patients.

6. CONCLUSIONS

Several cognitive tests have demonstrated that patients with rheumatoid arthritis have significantly worse cognitive status than age-matched healthy individuals. Depression and anxietas were higher in patients with rheumatoid arthritis than in healthy control group. However, many cognitive impairment do not correlate with the degree of depression and anxiety, so cognitive impairment cannot be explained by psychological factors alone. Deterioration of cognitive factors was associated with disease length and activity, inflammatory markers, mental factors of SF-36, and several neurovascular parameters. Between biologic-vs MTX- treated subgroups there was no significant difference in cognitive impairment. Different biological therapies showed a difference in cognitive functions, but it was not significant. As a result of cognitive impairment, patients' quality of life parameters also deteriorated.

We assessed cerebrovascular lesions and cerebral atrophy (by MR examination), carotid atherosclerosis (by ultrasound examination), cerebral blood flow (by TCD examination). Asssociations have been confirmed between cerebral atrophy, cerebrovascular lesions, carotid atheroclerosis, decreased cerebral vascular reverse capacity and cognitive dysfunctions.

3 Tesla MRI examination accurately confirmed periodontoid soft tissue involvement and odontiod erosion in addition to AAS. Despite biologic therapies, 15-30% of RA patients have asymptomatic cervical spine abnormalities and this is associated with higher degree of systemic inflammation and deformity of the small joints of the hand. There was no significant difference in MRI abnormalities between biologic –vs MTX-treated patients. No significant difference was observed between the 2 biological treatment subgroups either.

Patients with evidence of periodontal soft tissue thickening were significantly younger. There was association between elevated disease activity values and soft tissue thickening. In patients with confirmed odontoid erosion, deformity of the small hand joints was more pronounced.

There was no difference between treatment arms in 3 Tesla MRI parameters considering disease length, seropositivity, MTX treatment time and dose, types and timing of biological treatment, TCZ and IFX treatment arms. MR examination is a

sensitive radiological examination to detect asymptomatic cervical spine pathologies in RA patients.

7. SUMMARY

Cognitive function tests showed impairment in RA vs controls. Depression and anxietas were higher in patients with rheumatoid arthritis than in healthy controls. However, many cognitive impairment do not correlate with the extent of depression and anxiety, so cognitive impairment cannot be explained by psychological factors alone. TMT-A times were longer in biologic-vs MTX-treated patients. Different biological therapies showed a difference in cognitive functions, but the difference was not significant.

Some cognitive functions also correlated with disease duration, ESR and DAS28. Carotid plaques were associated with multiple cognitive parameters, cerebral vascular lesions with VST-A, while CRC with BVRT, MOCA and BDI. Cognitive dysfunction may occur together with depression and anxiety. Deterioration in cognitive function was more pronounced in older and less educated patients. Cognitive screening is a useful tool to identify subgroups of RA patients to be further investigated for cerebrovascular pathologies. There was no significant difference in cerebral MRI abnormalities between MTX-treated and biologically treated patients. No significant difference was observed between the 2 biological treatment subgroups.

Anterior AAS and periodontal soft tissue thickening were observed in a quarter of patients, while odontoid erosion was observed in 16% of patients. There was no significant difference between treatment groups. Posterior and vertical AAS were not confirmed in any of the patients.

Cervical spine abnormalities are more common in RA patients with 10-11 years of the disease. Erosive disease and high disease activity are associated with atlantoaxial involvement.With respect to seropositivity, disease duration, biologic treatment and its duration, MTX dose and duration, IFX versus TCZ treatment, there were no differences between the 3 patient subsets for 3 Tesla MRI parameters. 3 Tesla MRI sensitive method for AAS, periodontoid soft tissue lesions and odontoid erosion.

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List of publications related to the dissertation

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