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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

ROMATOİD ARTRİTTE BİLİŞSEL BOZUKLUĞUN DEĞERLENDİRİLMESİ:
EKLEM YIKIMI VE HASTALIK AKTİVİTESİNİN BELİRLEYİCİ DEĞERİ

EVALUATION OF COGNITIVE IMPAIRMENT IN RHEUMATOID ARTHRITIS: PREDICTIVE VALUE OF JOINT DESTRUCTION AND DISEASE ACTIVITY

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ÖZ

AMAÇ: Romatoid Artrit (RA), oryantasyon, dikkat ve bellek zayıflığı gibi azalmış bilişsel işlevlere neden olur. Sunulan bu çalışmanın amacı RA'da bilişsel işlevlerin bir belirleyicisi olarak eklem yıkımını ve hastalığın diğer parametrelerini değerlendirmektir.

GEREÇ VE YÖNTEM: Bu kesitsel çalışma, 45 hasta ve 40 sağlıklı kontrol içemektedir. RA'lı hastalarda radyolojik progresyon skoru (≥0.5, modifiye Sharp / van der Heijde skorları- MTS'ler), 28 eklemin hastalık aktivite skoru (DAS-28) ve 44 eklemin hastalık aktivite skoru (DAS-44) değerlendirildi. Mini Mental Test (MMSE) ve Hastane Anksiyete Depresyon Ölçeği (HADÖ) değerlendirildi. Sonuçlar, bilişsel işlevleri belirlemek için hasta ve kontrol grubu arasında karşılaştırıldı.

BULGULAR: MMSE skorları açısından gruplar arasında istatistiksel olarak anlamlı fark vardı (p=0.003). RA ve kontrol grupları arasında anksiyete ve depresyon düzeyleri açısından anlamlı farklılık yoktu. MMSE skoru; hastalık süresi (p=0.011, r=-0.371), Sharp skoru (p=0.018, r=-0.350) ve DAS-28(p=0.044, r=-0.296) skoru ile ilişkilendirildi. Depresyon skoru da DAS ile ilişkiliydi (p=0.004, r=0.425). Romatoid faktör düzeyleri, anti-siklik sitrullinat peptid düzeyleri ve bilişsel işlev testleri arasında herhangi bir ilişki bulunamadı.

SONUÇ: Sonuçlar, uzun süredir RA olan hastalarda inflamatuar mediatörlere maruz kalmanın, eklemleri etkilediği sürece merkezi sinir sisteminde de bozulmaya neden olabileceğini göstermektedir. Bilişsel bozulma, hastalık şiddeti ve eklem yıkımı ile ilişkili idi. Dolayısıyla, radyografik eklem hasarı, RA'daki bu kronik süreç boyunca nöronal hasarın ve bilişsel bozulmanın boyutunu yansıtan pozitif bir ön belirteç olabilir.

ANAHTAR KELİMELER: Romatoid artrit, Sharp skoru, Bilişsel bozulma

ABSTRACT

OBJECTIVE: Rheumatoid Arthritis (RA) cause poor cognitive functions including reduced memory, orientation and attention. The aim of the present study is to evaluate joint destruction and other parameters of disease as a predictor of cognitive functions in RA.

MATERIAL AND METHODS: This cross-sectional study included forty five patients and forty healthy controls. Radiological progression score (≥0.5 the modified Sharp/ van der Heijde scores- MTSs), disease activity score of 28 joints (DAS-28) and disease activity score of 44 joints (DAS-44) were evaluated in patients with RA. Mini Mental State Examination (MMSE) and Hospital Anxiety Depression Scale (HADS) were evaluated and the results were compared between patients and control groups to determinate cognitive functions.

RESULTS: There was a statistically significant difference between groups in terms of MMSE scores (p=0.003). There were no significant differences in terms of anxiety and depression levels between RA and control groups. MMSE score was correlated with disease duration (p=0.011, r=-0.371), Sharp score (p=0.018, r=-0.350) and DAS-28 score (p=0.044, r=-0.296). Depression score was also correlated with DAS (p=0.004, r=0.425). No relationship was found between Rheumatoid factor levels, anti-cyclic citrullinated peptide levels and the cognitive function tests.

CONCLUSIONS: The results indicate that exposure to inflammatory mediators in patients with long standing RA may lead to deterioration on central nervous system as long as affecting joints. Cognitive deterioration was correlated with disease severity and joint destruction. Thus, the radiographic joint destruction can be a positive predictor of reflecting the extent of neuronal damage and cognitive deterioration during this chronic process in RA.

KEYWORDS: Rheumatoid arthritis; Sharp score; Cognitive decline

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune disease that causes activation of proinflammatory pathways, resulting in systemic inflammation (1-4). The presence of the blood-brain barrier restricts the passage of dissolved mediators and leukocytes from the periphery to the nervous system. In inflammatory conditions such as RA, the passage of leukocytes into central nervous system (CNS) facilities and causes the formation of oxygen radicals and cytokines. In such cases, blood brain barrier functions get affected either directly or indirectly and enzymes facilitate the migration of cytokines (5).

Cognitive impairment and mood disorders is one of the most complications in RA patients. Pain, physical disability, loss of social activities are the major symptoms and all together can lead to mood disorders(6, 7). The prevalence of depression in RA patients is reported as 5% to 42% (8) and it is associated with a higher risk of suicide (9) The neurological symptoms can be as high as up to 70% when all neurological involvements are included (10, 11). Although currently increasing evidence suggests that RA significantly contributes to the pathogenesis of neuropsychiatric disorders such as depression, there is a lack of evidence about the link between disease severity, joint destruction and cognitive impairment. Furthermore, the aim of the present study is to evaluate the relationship between disease activity, severity of joint destruction and cognitive functions in patients with RA.

MATERIALS AND METHODS

Participants

Fourty-five RA patients (according to the 2010 ACR/EULAR Rheumatoid Arthritis diagnostic criteria) and fourty healthy controls were included (12). Study protocol was approved by the Local Ethics Committee and written consents of the participants were obtained. Patients with neurological, psychiatric, inflammatory or immunological disorders; pregnant women; antiepileptic drug users and those aged under 18 years and over 70 years were excluded.

Assessment Measures

-Disease outcomes:

Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) were measured by collecting each RA patients venous blood samples and results were considered positive if the level was above the cut-off values. Radiological progression score (modified Sharp/van der Heijde scores- MTSs), disease activity score of 28 joints (DAS-28) and disease activity score of 44 joints (DAS-44) were assessed in patients with RA. Demographic and descriptive data were collected.

- Assessment of Cognitive Decline:

Self-administered scales (Mini Mental State Examination-MMSE and Hospital Anxiety Depression Scale-HADS) were administrated in order to assess cognitive functions and the results were compared between rheumatoid arthritis patients and control groups.

Minimental test, which is used to determine global mental status, consists of two parts. The first part includes some questions to evaluate orientation, memory, and attention with a maximum score of 21. The second part tests ability to name, follow verbal and written commands, write a sentence spontaneously and the maximum score that can be received from this part is 9. The cut off scores was evaluated as score below 21 was abnormal for 8 th grade education; below 23 was abnormal for high school education, below 24 was abnormal for collage education (13, 14).

HADS was designed by Zigmond and Snaith (15) in 1983 and is used to determine the anxiety and depression and patient experiences. It is the most appropriate tool to determine the psychological anxiety of patients with physical problems and is under the least influence of other physical ailments. The questionnaire consists of 14 questions, 7 of which relate to anxiety (HADS-A) and 7 relate to depression (HADS-D), respectively. Participants may receive a score ranged between 0-3 (0=never, 1=seldom, 2=sometimes & 3= always) from each question which indicates that each individu-

al's score on anxiety or depression might have a range of 0-21. Scores of 11 or more on the anxiety and depression subscales of this scale indicate anxiety and depression, while scores between 8 and 10 represent a borderline score and scores between 0-7 represent no depression/anxiety. The questionnaire was confirmed in relation to its validity and reliability by Montazeri et al. (16, 17).

Statistical Analysis

All analyses were performed using a commercial software (IBM SPSS Statistics, Version 22.0.; IBM Corp., New York, USA). All continuous data were presented as the mean±standard deviation. All categorical data were presented as frequencies and percentages. Categorical variables were analyzed using Chi square test to determine significant differences between groups. The MMSE was evaluated. Correlation was established using Pearson correlation coefficient. p <0.05 was considered to be significant.

RESULTS

a) *General characteristics and cognitive mental status of RA patients and control groups.*

The study included forty five RA patients (35 female, 10 male) and forty healthy control groups (30 female, 10 male). The mean age of the RA patients was 53.73±10.36 years and mean age of the control group was 53.23 ±13.70 years, respectively. MMSE score was 23.38±3.12, HADS-D score was 8.93±3.72; HADS-A score was 7.98±3.88 in patients with RA. MMSE score was 25.62±2.95, HADS-D score was 7.92±3.29; HADS-A score was 9.10±3.56 in healthy controls. The educational level of RA patients and healthy controls were summarized in (**Table 1**). There were no significant differences between the groups in terms of mean age, educational status or gender distribution (p>0.05).

Table 1: Comparisons of general characteristics between RA patients and control groups.

Patients Characteristics	RA (n=45)	Control (n=40)	p values*
Age (mean, SD)	55.73±10.36	53.23 ±13.70	0.341
Gender (n, %)			
- **Female**	35 (77.8%)	30 (75%)	0.776
- **Male**	10 (22.2%)	10 (25%)	
Educational Status (n, %)			
- **No education or just primary studies**	31 (68.9%)	26(65%)	0.759
	10 (22.2%)	11 (27.5%)	
- **Secondary school**	4 (8.9%)	3 (7.5%)	
- **High school and university**			

***:** There were no significant differences between the groups in terms of mean age, educational status or gender distribution (p>0.05).

b) *Sociodemographic attributes and clinical features of RA patients and control groups.*

Serum RF value was positive in 55.6% and Anti-CCP value was positive in 53.3% of patients with RA. Twenty-two (48.9%) patients have no comorbidity. Co-morbidity's characteristics are summarized in (**Table 2**).

Table 2: Disease characteristics and medications data of RA patients

Patients Characteristics	n=45	%*
Serum Rheumatoid Factor (RF)		
- **RF Positive**	25	55.6
- **RF Negative**	20	44.4
Anti-Cyclic Citrullinated Peptide (anti-CCP)		
- **Anti-CCP Positive**	*24*	*53.3*
- **Anti-CCP Negative**	*21*	*46.7*
Comorbidity		
- **Hypertension**	9	20
- **Diabetes**	2	4.4
- **Hypertension+Diabetes**	5	11.1
- **Throid Disfunction**	4	8.9
- **Cardiological disorders**	2	4.4
- **Other**	1	2.2
Treatment of RA		
- **csDMARD (n,%)**	2	4.4
- **Steroid (n,%)**	2	4.4
- **csDMARD+Steroid (n,%)**	31	68.9
- **b DMARD(n,%)**	10	22.2

* Percentages refer to the percentage of patients with data available. csDMARD: conventional synthetic disease-modifying antirheumatic drug; bDMARD: biologic DMARD.

The mean of disease duration was 10.62±9.49 years in RA patients. Disease activity scores (DAS-28 and DAS-44) and Total Sharp Score of these patients are also presented in (**Table 3**).

Table 3: Disease activity and radiological progression parameters of RA patients

RA Patients Characteristics (n=52)	Mean± SD	Min-Max
Disease duration (year)	10.62±9.49	0.5- 40
Disease activity score of 28 joints (DAS-28)	2.89±1.10	1.46- 5.85
Disease activity score of 44 joints (DAS-44)	3.01±1.07	1.46-5.62
Van der Heijde modified total Sharp score (MTSs)	53.24±42.88	3.00- 181.00

c) *Determination of cognitive status.*

There are 30 RA patients whose mean score indicates depression and 9 patients whose test score indicates anxiety. According to MMSE

score in the reference range 18 patients have abnormal MMSE scores. There was a statistically significant difference between groups in terms of MMSE scores (p=0.003). Test scores and comparisons are summarized for each group in (**Table 4**).

Table 4: The comparisons of cognitive status between groups

Patients Characteristics	RA (n=45)	Control (n=40)	p values
Depression-related scores			
- **(HADS-Depressive, n, %)**	30 (%66.6)	21 (%52.5)	0.267
- **HADS-Normal, n, %)**	15 (%33.3)	19 (%47.5)	
Anxiety-related scores			
- **(HADS-Anxiety, n, %)**	9(%20)	13(%32.5)	0.287
- **HADS-Normal, n, %)**	36(%80)	27 (%67.5)	
Mini Mental State Examination Scores (education-adjusted)			
- **MMSE-Abnormal (n, %)**	18(%40)	4 (%10)	**0.003***
- **MMSE-Normal (n, %)**	27(%60)	36 (%90)	

*: Correlation is significant at the 0.01 level (two-tailed)

d) *Correlation of radiographic progression, disease activity with cognitive mental status in RA patients*

There was a significant correlation between disease activity score-28 and depression-related scores (HADS-D) in patients diagnosed with RA (p=0.004, r=0.425). There was also a significant correlation between disease duration (p=0.011, -r=0.371), Total Sharp Score (p=0.018, -r=0.350) and DAS-28(p=0.044, -r=0.296) with Mini Mental State Examination. There were no significant correlation between serum RF, anti CCP and cognitive status of the patients (**Table-5**)

Table 5: The correlations between disease outcomes and clinical scales

Patients Characteristics	Mini Mental State Examination Scores (MMSEs)	Depression-related Scores (HADS-D)	Anxiety-related Scores (HADS-D)
Disease duration (years)			
- **p values**	**0.011***	0.741	0.547
- **r values**	**-0.371**	-0.051	0.066
Serum Rheumatoid Factor			
- **p values**	0.964	0.097	0.722
- **r values**	-0.007	0.251	0.046
Anti-Cyclic Citrullinated Peptide			
- **p values**	0.454	0.059	0.631
- **r values**	-0.114	0.283	0.062
Disease activity score of 28 joints (DAS-28)			
- **p values**	**0.044***	**0.004****	0.083
- **r values**	**-0.296**	**0.425**	0.262
Disease activity score of 44 joints (DAS-44)			
- **p values**	0.438	**0.007****	0.657
- **r values**	-0.119	**0.397**	0.047
Van der Heijde modified Total Sharp Score			
- **p values**	**0.018***	0.867	0.629
- **r values**	**-0.350**	-0.026	-0.052

*: Correlation is significant at the 0.05 level (two-tailed).

**: Correlation is significant at the 0.01 level (two-tailed).

DISCUSSION

In present study; statistically significant difference was found between RA groups and controls in terms of MMSE scores. There were no significantly differences in terms of anxiety levels between RA and control groups. Significantly negative correlation was found between Sharp score, DAS-28 and MMSE score of the patients. Disease activity scores were also correlated with HADS-D score. No relationship was found between RF levels, anti-CCP levels and cognitive function tests.

RA is a chronic inflammatory disease that suppresses the spontaneous locomotor activity, leads fatigue, and decreases the quality of life. It causes inability for daily activities, managing and planning in patients with RA (18). Although peripheral nervous system pathologies are detected widely in RA, there are many studies regarding changes in the CNS. Clinical presentation of neuropsychiatric disorders may vary from cognitive deficites to fatigue (19, 20). Simos et al., which performed with one hundred RA patients, evaluated anxiety, depression, effect of disease on daily activities and pain severity by using battery of 6 neuropsychological tests yielding 14 cognitive indices and selfreported neuropsychological tests. They found a cognitively impaired in twenty percent of RA patients and they showed a negative associa-tion between cognitive function and measures of perceived disease severity (pain level, impact of disease on daily functionality, and overall health quality). Appenzeller et al., evaluated the frequency of cognitive impairment in patients with RA and according their results cognitive impairment was detected in 30% of patients with RA and in 7.5% of healthy controls (21). The results of our study about cognitive impairment is in line with previous studies. Functional neuroimaging investigations(MRI and SPECT) used in some studies to evaluate behavioral manifestations and cognitive performances in patients affected by RA (21, 22). According to a study conducted by Bartolini M et al., impairment was found in visual-spatial tasks in 71% of the patients with RA and there was a high correlation between Ritchie and Lee index (an index for evaluation of cognitive functions) and disease severity in these patients (22). According to whole literature cognitive impairment

are more frequently observed in visual–spatial and planning functions in RA (22). Although direct comparisons among literature may not be possible due to different assessment methods used, these results underline the significance of cognitive impairment in RA. Also there are some supporting studies about RA leads cognitive decline by causing premature immunosenescence (23). According to Petersen's study, although here were no significantly differences in terms of anxiety levels between RA and control groups, patients were reported more depressed, they had lower MMSE scores and logical and working memories.

Inflammatory processes are in an even more prominent condition over the years and aging present with dementia, depression and such cognitive impairment (24, 25). Most of diseases promote inflammatory process and lead to a disturbance of homeostasis. RA is a one of the chronic inflammatory disorder and its pathogenesis occurs because of genetic and environmental factors leading to innate and adaptive immune response and to systemic inflammation (26, 27). RA causes systemic inflammation and this inflammatory situation is responsible for all articular deformities especially bone and joint erosion, synovitis and other extra-articular complications such as mood disorders and poor cognitive performance (2, 24). All manifestations are associated with disease duration and severity and other comorbidities (21, 27). Radiographic scoring methods are gold standard to measure and determine deformations in RA (28). Radiographic progression in RA has been shown to happen early, and because the first erosions are more often found in the feet than in the hands (29). The best of our knowledge this is the first study using radiographic progression for assessing erosion and it is indicating a negatively significant correlation between cognitive status and erosion scores.

There is some strong evidence about changes in T-cell homeostasis that was accelerated in patients with RA. Recent studies showed that CD4+CD28-T cells express NK-cell surface receptors, which provide the ability to produce larger amounts of cytokines. They have been implicated the rheumatoid arthritis pathogenesis (30) and they indicated that reduced memory performance was correlated with B cells and memory CD8+CD45RO+ T cells reduced (23).

Most of the studies in the literature lead to brain, spinal and peripheral nervous system involvement in patients with RA (10, 31). Clinical manifestations of neuropsychiatric symptoms can be various in these patients. Psychiatric symptoms was reported very often especially depressive manifestations occur directly (because of disease symptoms such as fatigue, pain) or indirectly (cumulative use of corticosteroids) in the literature (10). Possible causes for depression in RA include aging, disease severity, incapacity for work (11, 32). The prevalence of depression in RA may be higher than our knowledge due to there are accompanied the comorbidity and disease severity in it (11, 33). In line with the earlier studies in the literature, there was a positive correlation between DAS-44 score and depression.

According to the recently conducted studies, there is a poor cognitive performance that is frequently seen in patients diagnosed with RA. First, RA diseased by itself caused inflammation, fatigue, weight loss, insomnia and lack of appetite pain and such neuropsychiatric disorders (34). RA causes inflammation and released mediators, cytokines such as TNFa, IL-1beta and IL-6 and they have a major role on psychiatric disorders like depression and anxiety (35). Many studies indicate that proinflammatory cytokine causes affective disorders by impaired neurotransmitter metabolism, neuroendocrine function and regional brain activity (36, 37). Secondly; the systemic inflammation affects all the tissue, especially neural tissue (38). Animal and human studies suggest that antioxidant supplementation might be expressed as improvements in motor and cognitive behaviors (39, 40). Third; cytokines, mediators that are released from inflammatory process can pass the Blood-Brain Barrier and cause neuropsychiatric disorders. Forth; blood brain barrier functions get affected either directly or indirectly because of the inflammatory conditions and enzymes

facilitating the migration of inflammatory cells, cytokines and oxygen radicals (6, 41).

The limitation of our study is initially anti-inflammatory drugs like corticosteroids may contribute moods disorders such as depression. The other limitation is that our cross sectional study indicates that we could not rule out RA patients born with cognitive dysfunctions.

CONCLUSION

Our results emphasized that parameters reflecting the acute process like disease activity and inflammatory markers were mostly correlated with depressive moods. However, erosion/destruction is a result of chronic process. Joint erosion was positively correlated with poor cognitive performance. For this reason, the correlation between MMSE score and joint erosion is an indicator of the chronic inflammation that seems to be more important. Because of this chronic process, the radiographic joint destruction can be a positive predictor of reflecting the extent of neuronal damage and cognitive decline in patients with RA. The findings of our study suggest that the burden of cognitive impairment in RA correlates with joint erosion and future studies should focus on identifying specific etiologic contributors to determine the link exactly.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent Informed consent was obtained from all individual participants included in the study.

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