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RESEARCH ARTICLES

Do age at disease diagnosis and age at symptom onset affect cognitive functions in Sjögren's syndrome?

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ABSTRACT

Objectives: In this study, we aimed to investigate the relationship between the age of onset of disease symptoms, the age at diagnosis, and cognitive function in patients with primary Sjögren's syndrome (pSS).

Methods: Sixty-two patients diagnosed with pSS who presented to the Sakarya Training and Research Hospital Internal Medicine Rheumatology outpatient clinic between November 2021 and November 2022 were included in the study. Parameters such as age at diagnosis, age at symptom onset, fibromyalgia status, Beck Depression Inventory (BDI) score, Beck Anxiety Inventory (BAI) score, insomnia, fatigue, learning disability, and number of comorbidities were recorded. The Montreal Cognitive Assessment (MoCA) score was used to evaluate cognitive function. The scale ranges from 0 to 30, with a threshold value set at 21. Scores of 21 and above were considered normal. Independent samples t-tests, Mann-Whitney U tests, and chi-square tests were used for data comparison.

Results: Patients with MoCA values less than 21 were significantly older. In the study, the age at symptom onset for patients with a MoCA score<21 was significantly higher than for those with a MoCA score ≥ 21 ($p<0.05$). Similarly, the age at diagnosis for patients with MoC<A values<21 was significantly higher than for those with MoCA values ≥ 21 ($p<0.05$). The impaired group (MoCA<21) comprised 20 individuals, representing 32.2%±3% of the cohort, while the non-impaired group consisted of 42 individuals, accounting for 67.7%±4% of the patients ($p<0.001$).

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A negative correlation was detected between age at the onset of symptoms (r=-0.376, p=0.003), disease diagnosis age (r=-0.297, p=0.019), and the MoCA value.

Conclusion: In our study, a negative correlation was found between age at the onset of symptoms, age at diagnosis, and MoCA values. Early diagnosis and treatment of SS can minimize cognitive dysfunction that may develop during the disease process. Maintaining high cognitive function will positively affect the quality of life.

Keywords: cognitive dysfunction, Sjögren's syndrome, disease age

INTRODUCTION

Sjögren's syndrome (SS) is an autoimmune disease characterized by symptoms of dry mouth and eyes resulting from lymphocytic infiltration of exocrine glands (1). Extraglandular involvement of various organs and systems can also be seen in SS. Neurological involvement has been reported in 8.5–70% of patients (2).

In primary Sjögren's syndrome (pSS), neurologic manifestations may be the first sign of the disease and are usually seen within the first two years after diagnosis. The most common neurologic complication is peripheral neuropathy with predominant sensory polyneuropathy. Central nervous system (CNS) involvement is less common. Cognitive dysfunction is one of the neurologic findings seen in patients. Mild to moderate cognitive difficulties are frequently reported in SS patients, a condition often referred to as "brain fog." It has been reported that cognitive impairment in pSS is associated with frontal-subcortical dysfunctions that control executive functions such as attention, memory, and information processing (3).

In patients with cognitive difficulties, symptoms such as forgetfulness, memory loss, mental confusion, decreased verbal fluency, and difficulty in concentration may be observed. Various neurological tests, including imaging techniques, are used to evaluate neurological involvement in pSS patients. However, these methods are expensive and may not always be suitable for daily practice (4). The Montreal Cognitive Assessment (MoCA) is an effective and easily applicable Turkish-validated test used in autoimmune diseases to evaluate cognitive functions (5).

SS can occur at any age, but its incidence increases in the 4th and 6th decades. SS is influenced by multifactorial factors, and age is a significant factor in demographic analyses (6).

Publications suggest that the clinical phenotypes of SS differ with patient age (7,8). Studies show that advanced age at disease onset is an independent predictor of neurologic involvement in SS (9). However, studies evaluating cognitive dysfunction in pSS patients and investigating related factors are limited. In this study, we aimed to investigate the relationship between age at onset of symptoms, age at diagnosis, and cognitive dysfunction in patients with pSS.

METHODS

This study included 62 patients over 18 years of age with pSS who met the 2016 ACR/EULAR criteria at the Sakarya Training and Research Hospital Internal Medicine Rheumatology Outpatient Clinic between November 2021 and November 2022. Parameters such as age at diagnosis, age at symptom onset, fibromyalgia, Beck Depression Inventory (BDI) score, Beck Anxiety Inventory (BAI), insomnia, fatigue, learning disability, and number of comorbidities were recorded. Patients were questioned and recorded regarding the presence of diagnosed fibromyalgia and symptoms such as fatigue, attention deficiency, and learning difficulties. MoCA was used to assess cognitive function. The MoCA is a screening tool used to assess early-stage cognitive impairment. The test takes approximately 10 minutes and covers 6 domains: memory, visuospatial ability, executive function, attention, concentration, language, and orientation. The lowest score is 0 and the highest is 30. The

threshold score was set at 21; scores of 21 and above were considered normal (Turkish version). Exclusion criteria included other neurodegenerative diseases affecting cognitive function, history of cerebrovascular disease, secondary Sjögren's disease, additional rheumatological diseases, mental retardation, and age under 18 years. Comparisons between groups were performed using the independent samples t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were analyzed using the Chi-squared test.

RESULTS

The mean age of the patients was 53.08±11.7 years, with 59 (95.16%) being female and 3 (4.83%) male. Patients with a MoCA score less than 21 were significantly older. The age at symptom onset was significantly higher in patients with a MoCA score less than 21 compared to those with a score of 21 or higher ($p<0.05$). Similarly, the age at diagnosis was significantly higher in patients with a MoCA score less than 21 than in those with a score of 21 or higher ($p<0.05$).

The cohort comprised 20 individuals with a MoCA score<21 (32.2%±3%) and 42 individuals with a normal MoCA score (67.7%±4%), a difference that was statistically significant ($p<0.001$).

A negative correlation was found between the MoCA score and both the age at symptom onset ($r=-0.376$, $p=0.003$) and the age at diagnosis ($r=-0.297$, $p=0.019$).

Table 1. Relationship between the MoCA score and the age at diagnosis and the age at the onset of symptoms

	Montreal Cognitive Score (<21); n: 20	Montreal Cognitive Score (≥21); n: 42	P
Age at symptom onset (year)	50.6±12.0	40.8±11.0	**0.003***
Age at diagnosis (year)	53.7±12.0	44.3±11.1	**0.019***
Beck depression scale	11.6±9.4	12.4±8.1	0.728*
Beck anxiety scale	14 (18) IQR	12 (16.5) IQR	0.768**

*Independent samples t-test; **Mann-Whitney U.

IQR: Inter Quantile Range.

Table 2. Associations between MoCA and fibromyalgia, fatigue, forgetfulness, learning disability and attention problems

		Normal Montreal Cognitive Score; n: 42	Impaired Montreal Cognitive Score; n: 20	P*
Comorbidity	Non	15 (35.7)	7 (35)	0.956
	Yes	27 (64.3)	13 (65)	
Fibromyalgia	non	16 (38.1)	9 (45)	0.604
	Yes	26 (61.9)	11 (55)	
Attention deficiency	non	13 (33.3)	7 (48.3)	0.466
	Yes	26 (66.7)	9 (56.3)	
Learning disability	non	13 (33.3)	8 (47.1)	0.329
	Yes	26 (66.7)	9 (52.9)	
Forgetfulness	non	9 (23.1)	2 (11.8)	0.473
	Yes	30 (76.9)	15 (88.2)	
Fatigue	non	4 (9.5)	4 (20)	0.418
	Yes	38 (90.5)	16 (80)	

*Chi-squared tests.

MoCA: Montreal cognitive assessment score.

Conversely, no significant correlation was observed between the MoCA score and the BDI or BAI scores (Table 1). Furthermore, no significant correlation was identified between MoCA scores and patient-reported symptoms of fibromyalgia, fatigue, forgetfulness, learning disability, or attention disorder (Table 2).

DISCUSSION

Cognitive impairment in pSS has been associated with frontal-subcortical dysfunction affecting attention, memory, decision-making speed, and executive functions (10). Cognitive dysfunction may be the first clinical manifestation in some pSS patients. While studies have reported varying results regarding disease duration, age at diagnosis, and clinical manifestations (such as sicca symptoms, arthralgia, and fatigue), data evaluating the relationship between cognitive functions and age at disease onset are limited (6,11).

In our study, a negative correlation was found between MoCA values and age at symptom onset and age at diagnosis. Blanc et al. reported cognitive dysfunction in 60% of patients in a case-control study of 25 patients aged 30–75 years (12). In our study, cognitive dysfunction was identified in 32.2% of the patients. Dziadkowiak et al. reported that cognitive impairment was associated with disease duration and the severity of inflammatory changes in 30 pSS patients with a mean age of 51 years (13). In a controlled case-control study, the MoCA scores of pSS patients were compared with a healthy control group; no significant difference was found in the total score, though pSS patients showed worse results in visuospatial/executive subtests (14). That study, where the mean age was 56 years, did not provide information regarding the relationship between disease age, age at diagnosis, and MoCA scores (14).

Goulabchand et al. stated that cognitive complaints in pSS patients may be associated with accompanying disorders such as depression, anxiety, or sleep problems (15). In an article published in 2016, Tezcan et al. suggested that cognitive dysfunction might be protective against depression in pSS patients (16). In the present study, however, no significant relationship was found between depression, sleep disturbance, and cognitive functions.

Data in the literature suggest a strong association between cognitive impairment and fatigue in patients with pSS (16,17). In our study, no significant difference was found between cognitive dysfunction and fatigue.

Fibromyalgia is characterized by widespread pain, fatigue, sleep disturbance, and cognitive dysfunction. Studies show that fibromyalgia patients have more cognitive impairment than healthy controls (18). It is suggested that SS patients have a high risk profile for fibromyalgia. The coexistence of fibromyalgia and SS may affect cognitive functions (19). However, no significant relationship was found between cognitive dysfunction and fibromyalgia in this study.

Sleep disturbance is common in SS and affects the quality of life (2,20). Findings generally show that sleep disturbance is associated with cognitive dysfunction (20). In our study, no such relationship was found.

Limitations of our study include the lack of a control group and the absence of cranial MRI scans for patients with cognitive dysfunction. Our data suggest that older age at diagnosis and symptom onset are associated with cognitive dysfunction in pSS. Older age may increase the risk of cognitive dysfunction both independently and by influencing the inflammatory process.

We believe that the MoCA is an easily applicable test in pSS patients and can guide further investigation. Cognitive dysfunction in pSS is an area requiring more research. Larger, controlled studies will better elucidate the effects of age at diagnosis and disease onset on cognitive outcomes.

Ethical approval

This study has been approved by the Sakarya University Rectorate Faculty of Medicine Deanery Faculty Non-Interventional Ethics Committee (approval date 29.11.2023, number 352). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: GD, MKU, SMT; Concept: SBA, SÖ; Desing: AK, DK; Data Collection or Processing: EG, CGA; Analysis or İnterpretation: AK,

GD; Literatüre Search: TA, GY; Writing: GD, NE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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