Montreal cognitive assessment in primary sjogren's syndrome

A brief screening tool

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ABSTRACT

الأهداف : لاستخدام اختبار مونتريال المعرفي لتقييم الخلل المعرفي عديم الأعراض في المرضى الذين يعانون من متلازمة شوغرين الأولية (PSS) وتقييم ارتباط نتائج MoCA بنتائج التصوير بالرنين المغناطيسي (MRI) لهؤلاء المرضى .

الطريقة : أُجري اختبار MoCA بشكل اسْتِباقيّ على 32 مريضًا على التوالي (31 إناث ، 1 ذكور) تم تشخيصهم بـPSS و 30 فرد صحي (29 إناث، 1 ذكر) في مستشفى أنطاليا للتعليم والبحث خلال الفترة من يونيو 2014م وأكتوبر 2015م. خضع 20 مريض PSS للتصوير بالرنين المغناطيسي (T1 ، T2 ، و T2- FLAIR) .

النتائج : كان متوسط العمر 45.84 (مجموعة 24-63) في مجموعة PSS، وكان متوسط مدة المرض 3.5 سنوات (4 أشهر – 18 سنة). كان هناك 22 مريضا (68.80%) مع 8-5 سنوات التعليم و 10 مريضا (31.30%) مع أكثر من 8 سنوات التعليم. كان متوسط العمر 42.8 (28-64)في المجموعة الضابطة. كان هناك 20 فرد من مجموعة التحكم (66.70%) مع 8-5 سنوات من التعليم و 10 فرد من مجموعة التحكم (33.3%) مع أكثر من 8 سنوات من التعليم. كان معدل التذكر المتأخر لمجموعة المرضى مع 8-5 سنوات من التعليم أقل بكثير من مجموعة التحكم، وكان معدل التذكر مع إشارات متعددة الخيارات لنفس مجموعة المرضى أعلى بكثير من المجموعة الضابطة (p<0.05). لم يكن هناك أي ارتباط بين عدد الآفات ومجموع نقاط MoCA أو المجموعات الفرعية.

الخاتمة : نقترح أن اختبار MoCA هو اختبار من صفحة واحدة يسهل إدارته، ويمكن استخدامه لتقييم الإدراك لدى المرضى الذين يعانون من PSS خاصة في المجموعات الكبيرة.

Objectives: To use the Montreal Cognitive Assessment (MoCA) test to assess the subclinical cognitive impairment in patients with Primary Sjögren's Syndrome (PSS) and assess the correlation of MoCA results with magnetic resonance imaging (MRI) findings in these patients.

Methods: The MoCA test was prospectively administered to 32 consecutive patients (31 females, 1 male) diagnosed with PSS and 30 healthy controls (29 females, 1 male) at Antalya Education and Research Hospital between June 2014 and October 2015. Twenty PSS patients underwent a brain MRI (T1, T2, and T2- FLAIR-weighted sequences).

Results: The mean age was 45.84 (range 24-63) in the PSS group, and the mean duration of disease was 3.5 years (4 months - 18 years). There were 22 patients (68.80%) with 5-8 years of education and 10 patients (31.30%) with >8 years of education. The mean age was 42.8 (28-64) in the control group. There were 20 controls (66.70%) with 5-8 years of education and 10 controls (33.3%) with >8 years of education. The delayed recall rate of the patient group with 5-8 years of education was significantly lower than that of the control group, and the recall rate with multiple choice cues for the same patient group was significantly higher than that of the control group ($p<0.05$). There was no correlation between the number of lesions and total MoCA score or subgroups.

Conclusion: We suggest that the MoCA test is a single-page, easy-to-administer test, can be used to assess cognition in patients with PSS especially in large groups.

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Primary Sjögren's syndrome (PSS) is a common autoimmune disease characterized by lymphocytic infiltration of exocrine glands without other systemic autoimmune diseases.[1] Neurological involvement in PSS has been reported to occur in 8.5-70% of cases. This difference was ascribed to the use of different diagnostic criteria in the diagnosis of PSS and different populations with distinct genetic and environmental factors. Neurology studies have also observed high levels of neurological involvement.[2,3]

Neurological involvement occurs in the form of peripheral and central nervous system (CNS) involvement. The type and prevalence of CNS involvement should also be discussed in the evaluation of Sjögren's syndrome. Cognitive impairment is also a common non-focal symptom of CNS involvement.[3-5] Cognitive impairment in PSS was reported to be associated with frontal-subcortical dysfunctions including attention, memory, information processing speed and executive functions.[4-10]

Magnetic resonance imaging (MRI) is a potent predictor of subclinical tissue damage and the spread of CNS involvement in Sjögren's patients.[11] Increased white matter abnormality was defined in PSS patients however in some studies, it was not different from the normal population.[11-13] Similarly, some studies found a relationship between cognitive impairment and white matter lesions (WMLs),[14] whereas this was not supported in other studies.[5,6] Previous studies did not mention a specific test for detecting cognitive dysfunction in PSS; in addition, some cognitive tests are expensive and time-consuming. The Montreal Cognitive Assessment Test (MoCA) test is a one-page, easy-to-administer, short test, which was first developed to detect mild cognitive dysfunction in the elderly.[15] This test evaluates attention, concentration, executive functions, memory, language, visuospatial skills, abstract thinking and calculation, and it has not previously been conducted on patients with PSS. A previous study suggested that it can be used routinely to detect cognitive dysfunction in patients with Systemic Lupus Erythematosus.[16]

The aim of this study was to use the MoCA test to assess subclinical cognitive dysfunction in patients with PSS and also assess the correlation of MoCA results with magnetic resonance imaging (MRI) findings in these patients.

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Methods. *Patients and control subjects.* A total of 32 consecutive patients, including 1 male and 31 females, who were seen at the rheumatology outpatient clinic in the Antalya Education and Research Hospital between June 2014 and October 2015 and were diagnosed with PSS according to the American-European Consensus criteria[17] were included in this prospective study. The consent of the local ethics committee was obtained. Patients were excluded if they had other concomitant connective tissue diseases, previous neurological involvement, and co-morbidities associated with cognitive impairment, alcohol abuse, seizure history or traumatic brain injury. Written consent was obtained from the patients.

Healthy control participants who met the same exclusion criteria were recruited. The control group consisted of a total of 30 age-, gender-, and education level-matched volunteers, including 1 male and 29 females. A standard history and clinical neurological assessment was performed in both the patient and control groups. Their then-current medication, antibody positivity and concurrent diseases were recorded (**Table 1**).

Neuropsychological assessment. MoCA is a screening scale developed by Nasreddine et al[15] to particularly assess the early stages of cognitive dysfunction. A Turkish version of the scale was developed by Selekler et al[18] MoCA, which takes approximately 10 minutes to administer, is a one-page, easy-to-administer and short scale. The scale contains items evaluating attention, concentration, executive functions, memory, language, visuospatial skills, abstract thinking and calculation. The lowest score that can be obtained from this scale is 0, and the highest score is 30. The cut-off score in the Turkish version was set to 21.[18]

The MoCA test was used to assess the patient and control groups. Patients and control subjects were assessed separately according to whether their education level was 5-8 years or more than 8 years (>8 years). Depression was assessed according to the 21-item Beck Depression Inventory (BDI), Turkish validity and reliability of which have been demonstrated.[19,20]

Brain MRI Assessment. Twenty patients underwent brain MRI with a 1,5 Tesla superconducting 8 channels MRI system (Achivea, Philips Medical System, Best, The Netherlands) provided with high speed- gradients. MRI protocols was as followed: Axial T2 turbo spin echo, 5-mm slices and 1- mm gap (repetition time/echo time 4600/100), axial pre- and post constrast T1 weighted images (repetition time/echo time 620/15), axial fluid attenuated inversion recovery (FLAIR) (repetition time/echo time 6000/120) and sagittal T2 weighted (repetition time/echo time 4400/100) images.

Table 1 - The sociodemographic characteristics of PSS patients and the control group.

characteristics	Patients	Control	*P*-value
	n (%)		
Sex			
Female	31 (96.90)	29 (96.70)	inevaluable
Male	1 (3.10)	1 (3.30)	
Age			
n	32	30	0.21
% mean±SD	45.84±9.39	42.8±9.52	
median (min-max)	46 (24-63)	42 (28-64)	
Education n (%)			
5-8 years	22 (68.80)	20 (66.70)	0.861
>8 years	10 (31.30)	10 (33.30)	
Disease duration	32		
% mean±SD	3.45±3.75		
median (min-max)	2.25 (0.25-18)		
SS-A positive	21 (67.70)		
SS-B positive	3 (9.70)		
RO52 positive	16 (51.60)		
Drugs			
Hydroxichloroqine	29 (90.6)		
Pilocarpine	16 (50.0)		
*NSAİD	11 (34.4)		
Prednisolone	4 (12.5)		
**other	8 (25)		
***comorbidity	9 (28)		

*Non-Steroidal Anti-Inflammatory Drug, **antidepressant drugs, antidiabetic, antihypertensive, mood stabilization, ***diabetes mellitus, hypertension, mood disorder, hemifacial spasm, tension type headache

Table 2 - The MoCA results of both PSS and control group according to education level (cut off: ≥ 21).

MoCA 21	n (%)	Control	*P*-value
Education 5-8 years patients			
<21	11 (50)	5 (25)	0.096
≥21	11 (50)	15 (75)	
Education >8 years patients			
<21	0 (0)	0 (0)	None
≥21	10 (100)	10 (100)	

MoCA - Montreal Cognitive Assessment Test, PSS - Primary Sjögren's Syndrome

Pre–and post contrast T1 weighted images was used with and without gadolinium based contrast agents (0.1 mmoL/kg of body weight). For this study, the axial FLAIR were used to evaluate the WMHs according to the semiquantitative rating scale of Scheltens et al.[21] Depending on the spatial localization, size and number of lesions, four regions of cerebral white matter were evaluated: the periventricular (PV) region, subcortical and deep white matter of the frontal, parietal, temporal, and occipital areas (FPTO), the basal ganglia (BG), and the infratentorial (IT) regions. We counted lesions smaller than 3 mm and none of the lesions was confluent and had no predisposition for atherosclerotic WM lesions. WMH were then classified, using a system scored 0–3, depending on their number: (0-1 lesion: 0, 2-3 lesions: 1, <10 lesions: 2, > 10 lesions: 3). MRI was performed within 3 weeks after MoCA test assessment.

Statistical analysis. Descriptive statistics were presented with frequency, percentage, mean, standard deviation (SD) and median, minimum (min) and maximum (max) values. Fisher's Exact Test or Pearson Chi-square test was used to analyze the relationships between categorical variables. To analyze the difference between the measurement values of the two groups, the normality hypothesis was verified with the Shapiro-Wilk test, the Mann-Whitney U test when the sample did not fit a normal distribution, or the Independent Samples t Test when the sample fit a normal distribution. Pearson correlation coefficient was used to test the strength of any associations between MRI and MoCA total scores and subgroups scores. Analyses were performed using the SPSS 22.0 (SPSS, Chicago, IL, USA) software package. A *p*-value of <0.05 was accepted to be statistically significant.

Results. A total of 32 consecutive patients, including 1 male (3.1%) and 31 females (96.9%), were included in the study. The sociodemographic characteristics of the patient and control groups are shown in **Table 1**. The mean age was 45.8±9.39; range=24-63 in the patient group. The mean duration of disease was approximately 3.5±3.75 years, range=4 months-18 years). There were 22 patients (68.80%) with 5-8 years of education, and 10 patients (31.30%) with >8 years of education. The control group consisted of a total of 30 volunteers, including 1 male (3.3%) and 29 females (96.7%). The mean age of the control group was 42.8±9.52, range=24-63. There were 20 controls (66.70%) with 5-8 years of education, and 10 controls (33.3%) with >8 years of education.

In the MoCA test, out of 22 patients with 5-8 years of education, 11 patients (50%) scored 21 points or more, and 11 patients (50%) scored 20 points or less. As for the control group, out of 20 volunteers, 15 volunteers (75%) scored 21 points or more, and 5 (25%) scored 20 points or less (**Table 2**). The difference was not statistically significant. However, the number of subjects who scored 21 points or more in the MoCA

Table 3 - The MoCA subgroup analysis by years of education in PSS and control group.

			5-8 years						>8 years			
	n	mean	SD	min	max	*P*-value	n	mean	SD	min	max	*P*-value
Visuospatial/executive 5 points												
Patients	22	3.82	0.85	2	5	1.158	10	4.5	0.71	3	5	0.121
Control	20	4.2	0.7	3	5		10	4.9	0.32	4	5	
Naming 3-pointsl												
Patients	22	2.27	0.63	1	3	1.55	10	2.9	0.32	2	3	0.317
Control	20	2.55	0.51	2	3		10	3	0	3	3	
Attention 6-points												
Patients	22	3.68	1.84	0	6	0.538	10	5	0.67	4	6	0.872
Control	20	3.5	1.19	1	6		10	4.9	1.2	3	6	
Language 3-points												
Patients	22	1.41	1.18	0	3	0.865	10	2.3	0.67	1	3	0.598
Control	20	1.35	0.88	0	3		10	2	1.05	0	3	
Abstraction 2-points												
Patients	22	1.55	0.6	0	2	0.175	10	2	0	2	2	0.999
Control	20	1.75	0.55	0	2		10	2	0	2	2	
Delayed recall-5 points												
Patients	22	2	1.51	0	5	0.016	10	4.1	1.1	2	5	0.499
Control	20	3.1	1.21	1	5		10	3.8	1.14	2	5	
multiple-choice cue												
Patients	22	1.59	1.22	0	4	0.021	10	0.4	0.52	0	1	0.861
Control	20	0.75	0.72	0	2		10	0.5	0.71	0	2	
category cue												
Patients	22	1.05	1	0	3	0.11	10	0.3	0.48	0	1	0.577
Control	20	0.55	0.6	0	2		10	0.5	0.71	0	2	
Orientation-6 points												
Patients	22	5.86	0.35	5	6	0.347	10	6	0	6	6	0.999
Control	20	5.95	0.22	5	6		10	6	0	6	6	
Moca												
Patients	22	20.64	4.33	10	26	0.348	10	26.8	1.81	24	30	0.787
Control	20	22.35	2.32	18	27		10	26.9	2.13	23	30	
Beck												
Patients	22	13.5	10.16	0	39	0.189	10	12.3	7.06	0	27	0.118
Control	20	9.25	5.99	2	31		10	8.3	4.35	3	16	

test was higher in the control group. All 10 patients (31.25%) with >8 years of education and 10 volunteers (33.33%) with >8 years of education (100%) scored 21 points or more in the MoCA test.

When the MoCA test results were examined by subdividing the test into visuospatial, naming, attention, language, abstract thinking, delayed recall and orientation functions (**Table 3**), delayed recall was significantly lower in the patient group with 5-8 years of education than in the control group (*p*=0.016). Furthermore, the rate of recall with multiple choice clues for the patient group with 5-8 years of education was significantly higher than that of the control group (*p*=0.021). In the other subgroups, there were no

significant differences between the patient and control groups with 5-8 years of education. There were no differences between the patient group and the control group with >8 years of education.

Of the 20 patients (62.5%) who underwent MRI, 16 (80%) had 5-8 years of education and 4 (20%) had >8 years of education. Eleven (55%) of these patients were found to have lesions. Of those with 5-8 years of education, 7 had (43.75%) 0-1 lesion, 3 (18.75%) had 2-3 lesions, 3 (18.75%) had 4-10 lesions, and 3 (18.75%) had 10+ lesions. Of those with >8 years of education, 2 (50%) had 0-1 lesion and 2 (50%) had 2-3 lesions. The correlations between the number of lesions, age, total MoCA scores and subgroups were investigated,

Table 4 - The correlations between the total MoCA and subgroups scores and the number of lesions, age and disease duration.

	Education 5-8 years			Education >8 years		
	Age	Lesion number	Disease duration	Age	Lesion number	Disease duration
MoCA						
r	0.166	-0.144	0.191	0.344	0.236	0.091
p	0.459	0.596	0.394	0.331	0.764	0.802
n	22	16	22	10	4	10
Visuospatial/executive 5 points						
r	-0.358	-0,288	0,231	-0,024	-0,577	-0,304
p	0.102	0,279	0,301	0,947	0,423	0,393
n	22	16	22	10	4	10
Naming 3-points						
r	-0.245	-0.089	-0.076	0.291		-0.473
p	0.272	0.744	0.738	0.415		0.168
n	22	16	22	10	4	10
Attention 6-points						
r	0.413	-0.147	0.086	-0.359	0	0.617
p	0.056	0.587	0.704	0.308	1	0.057
n	22	16	22	10	4	10
Language 3-points						
r	-0.029	0.336	0.215	0.212	0.577	-0.256
p	0.898	0.204	0.338	0.557	0.423	0.475
n	22	16	22	10	4	10
Abstraction 2-points						
r	0.209	-0.101	0.216			
p	0.35	0.71	0.335			
n	22	16	22	10	4	10
Delayed recall-5 points						
r	0.112	-0.019	-0.012	0.408	0.707	0.328
p	0.621	0.945	0.958	0.242	0.293	0.354
n	22	16	22	10	4	10
Orientation-6 points						
r	-0.376	-0.207	-0.085			
p	0.084	0.443	0.707			
n	22	16	22	10	4	10
category cue						
r	-0.117	-0.046	0.124	-0.457	-0.577	-0.348
p	0.605	0.866	0.582	0.184	0.423	0.324
n	22	16	22	10	4	10
multiple-choice cue						
r	-0.046	0.162	-0.149	-0.428		-0.181
p	0.838	0.549	0.508	0.218		0.617
n	22	16	22	10	4	10
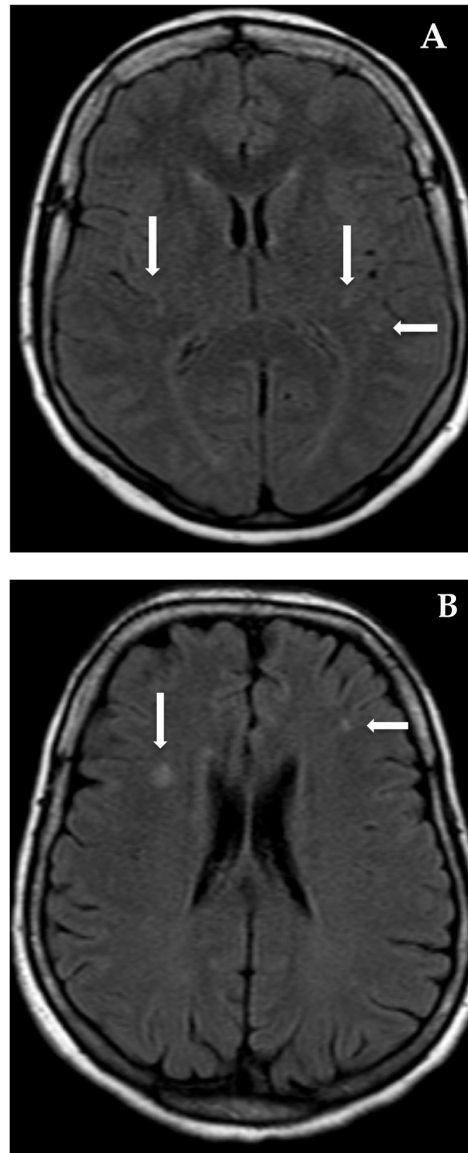
Figure 1 - Axial FLAIR weighted image of brain of a patient with Sjögren's Syndrome. **A)** The image has 2 parietal periventricular white matter hyperintensities at right and left and scored as 1. **B)** The image has 3-4 periventricular hyperintens lesions and one lesion in the subcortical white matter at frontal lobe and scored as 2.

but no correlations were found between them (**Table 4**). The lesions were cortical-subcortical and periventricular lesions localized in the frontal, parietal and occipital regions, and most of them were periventricular lesions in the parietal region (**Figure 1a-b**). None of the lesions were enhanced. There was no lesion in the infratentorial regions and basal ganglia.

Using the Beck depression score measure, the mean BDI value was 13.1±9.2, range=0-39 for 32 patients

in the PSS group and 8.9±5.44, range=2-31 for the 30 subjects in the control group. The average BDI score of the PSS group was higher (*p*=0.037). However, there was no relationship between the BDI score and the MoCA total score, MoCA subgroup score or number of MRI lesions. The MoCA total score and subgroup scores were also analyzed for comorbidities, antibody positivity and medications they took; no differences were found.

Discussion. This prospective study was performed using MoCA test for subclinical cognitive dysfunction in patients with PSS and also investigated the correlation of MoCA results with MRI findings. We found that the delayed recall in the MoCA test was significantly lower in the low-educated group (5-8 years) with PSS than in the control group. There was no difference in the high-educated group. No correlation was established between magnetic resonance imaging (MRI) findings and total MoCA score or subgroups.

Primary Sjögren's Syndrome (PSS) causes different neurological complications including focal, non-focal, cranial, and spinal symptoms in the CNS.[3] Cognitive impairment is a common non-focal symptom.[5] Cognitive impairment in PSS was demonstrated to be associated with frontal-subcortical dysfunctions in attention, memory, information processing speed and executive functions.[4-10]

The low number of sample size can explain no difference between the high-educated group and the control group in the delayed recall of the MoCA test. In the low-educated group, the higher results of the recall with multiple-choice clues might indicate subcortical involvement. No correlation was established between MRI lesions and the lower rate of delayed recall or the higher rate of recall with multiple-choice cues in the low-educated group. Again, the BDI score was higher in the PSS group. However, this high rate was not correlated with the total MoCA test scores, subgroup scores or number of MRI lesions.

Rodriguez et al[10] conducted a short neurological test on 18 PSS patients, 18 Multiple Sclerosis patients and 18 healthy controls and found that patients with PSS scored lower in "executive function and long term memory" tests than healthy controls. Compared with our study, the aforementioned study reported a higher mean age and no information on the duration of the disease. In our study, the mean duration of the disease was short. A study by Martinez et al. conducted on 12 PSS patients, 10 migraine patients and 10 healthy controls investigated whether there was progressive

cognitive dysfunction 8 years apart. Similar to previous studies, they found impairment in visuospatial abilities and executive functions indicating frontal-subcortical dysfunction of PSS patients and migraine patients. However, no significant progression was observed.[7] In that study, the mean duration of the disease (12.5 years) was longer.

Mataro et al. evaluated the correlation of cognitive dysfunction with MRI findings in 15 PSS and 15 migraine patients and found increased ventricular volume in MRIs of patients with PSS compared to the migraine group. They demonstrated correlations between MRI hyperintensities and the degree of ventricular volume and cognitive and psychiatric findings. They also suggested that cognitive dysfunction is related with memory and the frontal lobe.[9] In a 2013 study by F. Blanc et al., similar to Mataro's study, 60% of PSS patients were found to have cognitive deceleration, long term memory impairment, attention deficit and impairment of executive functions. Cognitive impairment was also correlated with the presence of white matter lesions.[14]

In our study, no correlation was established between delayed recall memory impairment and MRI findings, although not all patients (%62.5) had MRI evaluations. Unlike the studies by Mataro and F. Blanc, in our study, the mean age was lower and diseases such as migraine, seizure or neuropsychiatric involvement did not accompany patients with PSS. Eleven patients (55%) with MRI were found to have lesions. The lesions were cortical-subcortical and periventricular localized in the frontal, parietal and occipital regions. Similarly, a previous study reported that MRI abnormalities in PSS patients are largely localized in the periventricular and subcortical regions.[22]

In a study by Harboe et al., white matter lesions (WML) of PSS patients did not differ from those of the control group but cognitive dysfunction was correlated WML. Unlike our study, these study had population-based study and patients had neurological involvement.[13] In addition, Le Guern et al. demonstrated that although the MRI findings of PSS patients did not differ from controls, cognitive impairment was correlated with decreased brain perfusion as detected by 99mTc-ECD single-photon emission computed tomography (SPECT); the authors claimed that SPECT is more sensitive in detection of CNS involvement in PSS patients.[8]

The prevalence of MRI abnormalities in PSS patients with and without clinically diffuse CNS involvement is unknown.[2] Belin et al[6] found no abnormalities in the

MRIs of patients with neuropsychiatric abnormalities. On the other hand, Pierotti et al. reported punctate white matter lesions in 60% of neurologically asymptomatic patients and mild cerebral atrophy in 40% of the patients.[23] However, it should be considered that these findings may be due to age and cerebrovascular risk factors, since PSS is prevalent in the age group of 40-50 years.[24]

With respect to the relationship between the duration of the disease and WMLs, a study by F. Blanc et al[14] established a correlation between WMLs and cognitive impairment, and the authors reported a span of 10 years between the onset of PSS symptoms and cognitive complaints.In our study, there was no difference in cognitive functions, except delayed recall, which can be ascribed to the short duration of the disease.

In our study, the BDI score was higher in the PSS group. However, this was not accompanied by delayed recall impairment or changes in the total MoCA or other subgroup scores. In a previous study by Segal et al[25] , it was suggested that depression and memory impairment are individual parameters of neurological exposure.In another study, Martinez et al[7] reported that the effect of depression on cognition can be controlled with appropriate statistical methods. Similarly, Lafitte et al[5] proposed that cognitive impairment cannot be attributed to affective disorder.

Limitations of our study include the low number of samples, short duration after PSS diagnosis and absence of MRI evaluations for all patients. Further studies with a larger number of patients, MRI and SPECT evaluations, and consideration of various inflammatory diseases and disease duration are needed.

In conclusion, early detection of cognitive involvement in PSS is important for an effective treatment plan without lowering the quality of life of patients. We found that the delayed recall in the MoCA test was significantly lower in the low-educated group. We suggest that the MoCA test is a single-page, easy-to-administer test, can be used to assess cognition in patients with PSS especially in large groups.

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Supplements

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*   Supplements will be considered for work including proceedings of conferences or subject matter covering an important topic
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*   Material in supplements will be for the purpose of teaching rather than research.
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