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Primary Sjogren's Syndrome: Cognitive Symptoms, Mood and Cognitive Performance

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Abstract

Objective—to investigate the relationships between self-reported cognitive abilities, psychological symptoms and neuropsychological outcomes in PSS.

Methods—PSS patients and healthy controls completed a comprehensive neuropsychometric battery and questionnaires: the Centers for Epidemiological Scale-Depression, the Profile of Fatigue- mental domain (Prof-M) for cognitive symptoms, Fatigue Severity Scale and the Short-Form McGill Pain Questionnaire.

Results—Female PSS patients (N=39) were similar to controls (N=17) in estimated pre-morbid intellectual function, age and education. Depression ($p=.002$), cognitive symptoms ($p=.001$), fatigue ($p=.000003$) and pain ($p=.024$) scores were greater in the patient group. PSS patients demonstrated inferior performance relative to controls in psychomotor processing ($p=.027$) and verbal reasoning ($p=.007$). PSS patients with and without depression had similar performance on multiple tests, but depressed patients had significantly lower scores for executive function ($p=.041$). Cognitive symptoms correlated with verbal memory ($p=.048$), whereas pain correlated with executive function measures (Stroop, $p=.017$) and working memory (Trails B, $p=.036$). In the regression model, depression and verbal memory were independent predictors that accounted for 61 % of the variance in cognitive symptoms.

Conclusion—The Prof-M is a simple self-report measure which could be useful in screening PSS subjects who may benefit from detailed psychometric evaluation. Our results are consistent with the hypothesis that depression and verbal memory impairment are overlapping but independent aspects of neural involvement in PSS. While pain and depression are significant

confounders of cognitive function in PSS, this study suggests that impaired verbal reasoning ability in PSS is not attributable to pain or depression.

Keywords

Cognition; Central nervous system disorders; Depression; Sjogren's syndrome

Primary Sjogren's syndrome (PSS) is a chronic systemic autoimmune disease characterized by exocrine gland inflammation and symptoms of oral and ocular dryness. Females are affected more frequently than males in a ratio of nine to one with onset of symptoms typically in the fifth decade of life. In addition to the cardinal symptoms of oral and ocular dryness, patients also commonly experience fatigue, pain and cognitive symptoms. The prevalence of depression in PSS is between 30 to 50%. (1,2) Cognitive dysfunction, often experienced as problems with memory, attention or information processing is disturbing to patients and poses a vexing issue for clinicians as a variety of factors can underlie these symptoms.

While cognitive dysfunction is commonly experienced and psychological distress is frequent, published data regarding cognitive function in PSS is sparse. Patients with mild cognitive impairment are often not classified as CNS Sjogren's, hence the relationship of cognitive dysfunction to pathologic processes specific to PSS, has not been adequately investigated. (3–5) Cognitive deficits can arise from depression, however both cognitive and affective disorders could also be the result of immune mediated brain dysfunction, and hence patients with affective and cognitive complaints present difficult therapeutic challenges.

Data on the neuropsychological function of patients with PSS is difficult to interpret due to differences in patient selection between centers and lack of standardized cognitive assessment. (3,6) Frontal and subcortical brain involvement characterized by shortened attention span, poor concentration, memory deficits and cognitive slowness, has been reported in patients referred to tertiary care centers, many of whom had overt central nervous system manifestations and depression. (6,7) To date, there is no data in PSS regarding the relationship of specific neuropsychological outcomes to measures of pain or depression. The aim of this study was to investigate the relationship between perceived cognitive dysfunction, depression and objective cognitive impairment in PSS patients who had no history of central nervous system disorder other than cognitive complaints. We investigated the validity of patient-reported cognitive problems by comparing self-reports with the results of objective tests, and we explored the contribution of pain and depression to objectively measured cognitive abilities.

Methods

Patients

All PSS patients were between 18 years of age and 70 and met American European Consensus Group (AECG 2002) criteria for classification as PSS.(8) Anti-Ro/SSA and anti-La/SSB antibody titers were determined using enzyme-linked immunoabsorbent assay (Immunovision, Springdale, Arizona). A positive test for either antibody fulfills serological criteria for PSS. Sixty percent to 80% of primary Sjogren's patients have circulating anti-Ro/SSA and 40% to 60% are positive for anti-La/SSB antibodies. Cardinal features of the disease such as sicca severity and fatigue do not seem to be linked to antibody status, whereas lymphoproliferative disorders are associated with elevated antibody titers. A total of 39 PSS patients were evaluated. Nineteen consecutive female patients with PSS from the University of Minnesota Sjogren's syndrome cohort were referred for neuropsychometric

evaluation because of cognitive complaints (Cohort 1) and an additional 20 subjects with PSS (Cohort 2) were recruited to participate in a study of cognitive function. The PSS subjects who comprised Cohort 2 were invited to participate from among 74 individuals with PSS who were residents of the greater Minneapolis metropolitan area. The first twenty-two PSS subjects who indicated interest in participating were contacted and screened to determine eligibility. Twenty PSS subjects met inclusion criteria. Seventeen healthy non-autoimmune disease controls were recruited from the university community and from a database. Subjects were excluded who had co-morbidities known to be associated with cognitive impairment: alcohol abuse, seizure history, traumatic brain injury or prior cardiac surgery. No subject had a history of CNS disorder other than mild “mental fatigue” i.e. subjective memory and concentration difficulties. The study was approved by the Institutional Review Board of the University of Minnesota and all subjects gave informed consent.

Questionnaires

Previously validated questionnaires were used to assess psychological symptoms.(9–12) The profile of fatigue, mental domain (Prof-M) was used to assess subjective cognitive function. Respondents are asked to rate their difficulties with memory and concentration (“Not thinking clearly, feeling it’s hard to concentrate, forgetting things, making mistakes”) in the past 2 weeks on a scale of 0 to 7 where 0=no problem at all and 7=as bad as imaginable. The domain score is the mean for the four items. The range is from 0 to 7. The Fatigue Severity Scale (FSS) consists of nine-items that focus on the behavioral consequences of fatigue with higher scores indicating increased fatigue. Scores range from 1 to 7. The Centers for Epidemiologic Studies Depression Scale (CES-D) is a 20-item questionnaire that measures mood on a scale of 0= “rarely or no one of the time” to 3, “most or all of the time” and provides a single score that can range for 0 to 60. A score of ≥ 16 indicates clinical depression and correlates well with results of a structured psychiatric interview. Scores in the range of 16–25 reflect mild depression, whereas > 25 is suggestive of moderate to severe depression. The Short-Form McGill Pain Questionnaire provides a qualitative and quantitative assessment of pain. It contains 15 pain-related words divided into sensory and affective categories in a pain-rating index. Individuals are asked to give each description of pain rating from 0 (“none”) to 3 (“severe”) based on the degree to which they feel that type of pain. Total pain is calculated by adding up these ratings. The range is from 0–45.

Neuropsychological Measures

A comprehensive battery of tests was used to screen subjects across a range of cognitive domains: executive function; attention and cognitive efficiency; visual spatial processing and language. The following tests comprised the test battery: Hopkins Verbal Learning Test-Revised (HVLTR); a brief list-learning task that addresses verbal learning and memory (13); Stroop Interference Test (Stroop) (14), a test of selective attention considered a measure of executive function; the Trail Making Test, Parts A and B which evaluate attention span, speed, working memory and executive function. Part A is a simple timed test of visual attention; whereas Part B is considered a measure of working (short-term) memory and executive function as it requires shifting of attention between two sets of stimuli.(15) The Wisconsin Card Sorting Test (WCST) is an executive function test that requires planning rather than speeded processing. The Digit Symbol subtest of the Wechsler Adult Intelligence Scale 3 (WAIS-3) is a substitution task. The test assesses both visual tracking and sustained attention unaffected by memory or learning and is regarded as a test of psychomotor processing.(16) The Controlled Oral Word Association test (COWAT) is a standard measure of verbal fluency that is used to assess recall of facts and knowledge about the world.(17) The Boston Naming Test (BNT) is a measure of confrontation naming.(18) The Similarities subtest of the WAIS-3 is a measure of verbal abstract reasoning abilities

and is strongly correlated with total and verbal IQ. (19) BNT and Similarities are considered tests of language ability. Visual spatial processing was assessed with the Benton Judgment of Line orientation (JLO). (20) The Reading subtest of the Wide Range Achievement Test-Revised [WRAT-3] was included to estimate pre-morbid levels of intellectual function.(21)

All the tests included in the cognitive battery are standard measures for which normative values are available. The test battery was administered in a single session by a trained psychometrist. For each of the measures, a cut-off score for abnormality was defined as a standardized score of ≤ 1.5 SD from the reference mean. The cut-off of -1.5 SD allowed us to optimize sensitivity for detection of mild cognitive dysfunction while maximizing discrimination between patients and controls. Cognitive dysfunction was classified as mild if there were deficits in 1–2 domains, moderate if there were deficits in 3 or 4 domains.

Statistical methods

Neuropsychological measures assess multiple skills and potentially reflect somewhat overlapping aspects of cognitive function; therefore we performed a principle components analysis to ascertain whether the outcome measures used in this study were clustered into the anticipated cognitive domains prior to conducting other analyses. The principle components analysis confirmed the following groups: Executive Function: Stroop, Trails B, WCST; Verbal memory and Learning: HVLt-R total, HVLt-R per cent retained and delay; Cognitive Efficiency: Controlled Oral Word Association Test, Trails A, Digit Symbol; Language: Similarities and Boston Naming Test.

Raw scores on each test were converted to age corrected T scores, with a mean of 50 and a standard deviation of 10, for comparison of PSS subjects and controls. Comparisons between patients and controls, and between depressed and not-depressed patients, were made using student's t-tests unless there was evidence of non-normality, in which case Wilcoxon rank-sum tests were applied (significance level $p=.05$.) Effect size (ES) was calculated using Cohen's d statistic.(22) Spearman correlation coefficients were calculated to examine the relationship among neuropsychological measures and behavioral variables. To test whether depression and age moderated the relationship between cognitive symptoms and verbal memory, partial correlations were conducted.

Results

All PSS subjects met current American European Consensus Group criteria: 71% were seropositive for anti-SSA/anti-Ro and /or anti-SSB/La. Minor salivary gland biopsies were performed in 2/3 of the patients of which 90% were positive. Extra-glandular manifestations of Sjogren's included: neuropathy in six PSS subjects; vascular purpura in 3 PSS subjects, history of anti-phospholipid antibody in 3 PSS subjects, history of idiopathic thrombocytopenic purpura (ITP) in 3 PSS subjects and lymphoma in one subject. Characteristics of the subjects in each group are reported in Table 1. Patients and controls were similar in age and education as well as estimated pre-morbid intellectual function and were therefore comparable. Subjective cognitive function (Prof-M), depression (CES-D) and fatigue (FSS) were significantly worse in both patient groups relative to controls. The prevalence of depression did not differ between the two PSS cohorts. A physician diagnosis of fibromyalgia was reported by 31% of the PSS patients and 6% of the controls. The prevalence of depression was significantly greater in the combined PSS patient group (47%) compared to the controls (6%). The prevalence of depression was similar in the two patient groups: 55% of cohort 1 and 40% of cohort 2 ($p=.3510$).

Results of the neuropsychometric evaluation are shown in Table 2. There were group differences between PSS patients and controls on two measures: psychomotor processing

(DST) and verbal reasoning (Similarities). A small effect was also noted between patients and controls in selective attention (Stroop); verbal fluency (COWAT) and verbal memory (HVLt-R); although the mean test scores were not significantly different. Mild cognitive dysfunction was present in 12/39 (30%) of the PSS patients and 3/17(18%) of the controls ($p=.317$).

Neuropsychological outcomes in depressed and not-depressed patients are compared in Table 3. Depressed PSS patients had mean CES-D scores in the moderately severe range. The performance of depressed and not-depressed PSS patients was similar for all the tests in the cognitive battery except executive function as measured by the Wisconsin Card Sorting test (WCST). There were also modest effects on working memory (Trails B) and verbal memory tests.

When all subjects (PSS patients and controls) were included in the comparison of depressed to not-depressed subjects (data not shown), there were group differences for multiple tests: Similarities ($p=.0233$); WCST ($p=.0060$) and verbal memory tests: HVLt –total ($p=.0334$); HVLt delay ($p=.0411$) and HVLt % retention ($p=.0430$).

We repeated the analysis for psychomotor processing (DST) and verbal reasoning (Similarities) including only the not-depressed patients and not-depressed controls. Verbal reasoning performance remained significant lower ($p=0.030$) in not-depressed PSS patients ($N=20$) relative to not-depressed controls ($N=16$) Psychomotor processing (DST) was not significantly different (p -value of 0.112).

Correlations between neuropsychological measures and psychological symptoms are shown in Table 4. Higher Prof-M (cognitive symptom) scores indicate worse cognitive function and were strongly correlated with depression and with fatigue. Cognitive symptom severity was also correlated with lower performance on verbal memory. Pain severity was negatively correlated with executive function as reflected by Trails B and Stroop. Partial correlations are shown for the relationship between verbal memory and cognitive symptoms in Table 5. In a linear regression model, with age and depression as adjusters, verbal memory was a significant predictor of cognitive symptoms.

Discussion

The major finding of this study was that cognitive symptoms reported by PSS patients were correlated with verbal memory. Our data suggests that self-report may be a reliable and rapid screen for cognitive dysfunction in PSS. We also found that depression and verbal memory were independent predictors of cognitive symptoms. Hence, this study is consistent with the hypothesis that depression and memory impairment are overlapping but independent aspects of neural involvement in PSS.

We found significant group differences between PSS patients and controls in psychomotor processing (DST) and verbal reasoning (Similarities). The effect of depression on both psychomotor processing and verbal reasoning was small. Verbal reasoning ability in depressed relative to not depressed PSS patients was similar. The deficit in verbal reasoning in the not-depressed PSS subjects relative to not-depressed controls, suggests relative compromise of left hemisphere function not attributable to depression in PSS.

The results of our study are comparable to data in the literature regarding the effects of depression on cognition in lupus.(23,24) Depression was associated with significantly poorer function in several cognitive domains in patients with newly diagnosed SLE. (23) However, several previous studies of SLE indicate that depression and anxiety are not the primary cause of cognitive impairment in SLE.(25,26) Deficits in processing speed and

working memory in SLE that are not attributable to disease activity, disease duration, depression, fatigue or corticosteroid use, in SLE patients without a history of overt CNS disturbance, have been described.(27) Interestingly, in SLE patients without a history of CNS involvement, deficits in processing speed and new learning were accounted for by plasma levels of IL-6, after controlling for the effects of depression and steroid treatment, suggesting a role for inflammatory cytokines in mediating cognitive dysfunction.(28)

The Similarities test is regarded as a good measure of general mental ability and is strongly correlated with total verbal IQ. Lower scores tend to be associated with left temporal and frontal involvement. The deficit in verbal reasoning reflected by the lower scores on the Similarities test in the PSS patients in this study is intriguing, and is consistent with data suggesting dominant hemisphere dysfunction reported in several previous studies of PSS. (6,7,29–31) Malinow found lower verbal IQ scores in PSS patients who also had deficits in attention and concentration.(7) Lafitte found subcortical frontal dysfunction in 8/25 patients defined as attentional deficits, deficits in executive function, and deficits in the Block Design test and Similarities.(6) In a small study of 19 unselected females with PSS and 21 controls, Jennings found group differences with decreased verbal IQ and verbal memory deficit in the PSS patients.(31)

In SLE deficits in attention, recall, psychomotor processing speed as well as visual spatial processing are typically described, a pattern of brain involvement presumed to arise from abnormalities in connectivity between subcortical structures and prefrontal cortex.(32) Effect sizes reported in this study in the comparison of patients and controls on tests of verbal fluency, verbal memory and executive function are comparable to those previously reported in patients with SLE and Multiple Sclerosis(MS).(33) Subcortical frontal cognitive disorders are, however, nonspecific.

Approximately one-third of our PSS patients reported a previous physician diagnosis of fibromyalgia and one-half had symptoms of depression. The frontal subcortical type of involvement previously reported in patients with PSS, MS and SLE, is in fact characteristic of many types of cognitive disorders, particularly those associated with depression and chronic pain including fibromyalgia(FM). The precise mechanisms underlying frontal subcortical cognitive impairment are unknown and multiple different pathological processes could contribute.

Fibromyalgia is an important confounder in studies of cognitive function in both patients with SLE and in those with PSS. Impairments in working (short-term) memory, verbal memory and verbal fluency in fibromyalgia patients have been demonstrated that mimic about 20 years of aging, but the neurobiology underlying these abnormalities is not yet known.(34) While we did not specifically assess subjects for fibromyalgia, our study does suggest an association of pain with memory and attention consistent with current neurobiological models of cognition.(35)

The correlation of McGill pain scores with measures of selective attention and working memory is especially noteworthy. Painful stimulation is attention-demanding and activates brain areas associated with cognitive attention.(34,35) Additional research is needed to assess the effect of neuropathic pain, as well as the effect of fibromyalgia, on cognition in PSS.

The strengths of the current study include access to a large community-based cohort of PSS patients who were rigorously evaluated and classified as meeting current criteria for PSS. We oversampled individuals with PSS who were concerned regarding their cognitive status, and therefore our cohort may not be reflective of the neuropsychological status of the general population of PSS patients, although their demographics, serological and clinical

characteristics were otherwise representative. This study was exploratory. Larger sample size and appropriate control groups are needed to better understand the effects of factors such as anxiety, depression and chronic pain on specific aspects of neuropsychological function in PSS. We evaluated depression with a questionnaire rather than a structured psychiatric interview which might have altered the results. We did not assess subjects for fibromyalgia with a tender point count and therefore cannot assess the contribution of fibromyalgia to the cognitive data. The cross sectional design is also a limitation of the current study. In future studies, it will be important to address the temporal relationship between mood and cognition, and to evaluate whether patients with cognitive deficits progress to more serious cognitive dysfunction over time.

In summary, cognitive symptoms reported by PSS patients were correlated with verbal memory performance. A brief questionnaire, such as the Prof-M could be useful in clinical practice to select those patients who might benefit from thorough neuropsychological evaluation. Our study also suggests that subtle cognitive deficits, particularly in verbal reasoning are not attributable to primarily to depression, although depression and chronic pain are important confounders of cognitive function. Detailed cognitive assessment combined with high resolution neuroanatomic and functional brain imaging are needed to clarify the neurobiology of cognitive symptoms and guide the development of new therapies in PSS.

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Table 1

Clinical Characteristics of PSS Subjects and Controls

Variable	All PSS	Controls N=17	Cohort 1 N=19	Cohort 2 N=20	P Values [†]
Age	50.85 (11.54)	49.24 (9.29)	48.10 (13.08)	53.45 (9.47)	0.614
Education [◆]	14.97 (2.24)	15.76 (0.97)	14.47 (1.95)	15.47 (2.43)	0.169
WRAT-3	105.67 (8.52)	108.94 (6.08)	104.94 (8.23)	106.32 (8.95)	0.173
Prof-M	3.91 (2.07)	2.01 (1.40)	4.13 (2.19)	3.71 (1.99)	0.001
CES-D	16.02 (11.94)	6.11 (5.89)	17.83 (11.39)	14.40 (12.48)	0.002
FSS	5.28 (1.45)	3.26 (1.04)	5.11 (1.48)	5.44 (1.43)	0.000003
McGILL [*]	-----	4.85 (9.68)	-----	12.76 (10.47)	0.024

Results are given as mean (SD).

[†] P-values are given for all PSS subjects combined vs. controls.

[◆] Education given as years in school.

^{*} McGill pain scores were available only in the Cohort 2

Table 2

Cognitive Performance in PSS patients and Controls*

Test**	All PSS Mean (SD)	Controls Mean (SD)	P Value	Effect Size (Cohen's d)
Trails B	56.56 (5.56)	58.21 (9.73)	0.424	0.234
Stroop	53.50 (9.84)	58.13 (9.16)	0.114	0.472
WCST	47.91 (9.24)	50.07 (6.99)	0.422	0.248
Similarities	57.13 (8.446)	64.12 (8.703)	0.007	0.772
Boston Naming test	54.08 (12.93)	56.94 (8.17)	0.406	0.245
DST	52.85 (8.52)	58.04 (6.02)	0.027	0.636
Controlled Oral Word Association	44.21 (8.69)	47.95 (8.38)	0.143	0.398
Trials A	58.02 (5.62)	59.63 (7.22)	0.371	0.263
Verbal Memory				
HVLT-R Total	49.47 (7.62)	52.06 (8.27)	0.267	0.301
HVLT-R Delay	49.19 (8.83)	53.24 (8.45)	0.121	0.458
HVLT-R % retained	48.81 (9.13)	52.76 (7.82)	0.130	0.446

* T scores were calculated using the standardized norms corrected for age and education available from test manuals. T scores have a mean of 50 and a SD of 10.

** Stroop= Stroop Interference Test; WCST = Wisconsin Card Sorting Test; DST= Digit Symbol Test; HVLT-R= Hopkins Verbal Learning Test-Revised, total;

Table 3

Comparison of Psychological Symptoms and Cognitive Performance in Depressed and Non-Depressed PSS patients*

	CES-D$\geq$16 N=18 Mean (SD)	CES-D<16 N=20 Mean (SD)	P value	Effect Size (Cohen's d)
Prof-M	5.45 (1.12)	2.45 (1.67)	<0.000001	1.441
CES-D	25.89 (9.55)	7.15 (4.60)	<0.000001	1.569
FSS	6.07 (0.94)	4.75 (1.36)	0.001	0.984
Similarities	55.71 (10.01)	58.25 (7.06)	0.379	0.299
Boston naming test	54.88 (9.71)	53.01 (15.52)	0.670	0.144
Trails B	55.19 (6.34)	57.67 (4.73)	0.178	0.441
Stroop	53.00(8.66)	54.60(10.69)	0.64	0.165
WCST	44.25 (10.99)	50.60 (6.82)	0.041	0.680
DST	51.69 (7.86)	54.18 (9.22)	0.378	0.290
COWAT	43.81 (9.89)	44.25 (7.91)	0.882	0.0500
Trails A	58.21 (4.44)	58.38 (6.27)	0.925	0.031
HVLT-R total	47.38 (8.66)	50.89 (6.48)	0.179	0.459
HVLT –R delay	47.00 (10.73)	50.79 (6.89)	0.216	0.425
HVLT-R retained	46.31 (10.37)	50.58 (7.85)	0.175	0.464

* Prof-M= Profile of fatigue-Mental domain; CES-D = Centers for Epidemiology Scale –Depression; FSS= Fatigue Severity Scale; McGill= Short Form-McGill Pain Inventory; HVLT-R= Hopkins Verbal Learning Test-Revised, totalscore; DST= Digit Symbol Test; Stroop= Stroop Interference Test; COWAT= Controlled Oral Word Association Test.

Table 4
Correlation between Neuropsychological Symptoms and Cognitive Tests in Patients with PSS[†]

	Prof-M	CES-D	FSS	HVLT-R	DST	Trails B	Stroop	COWAT	Similarities
Prof-M	-----	0.782	0.583	-0.337	-0.314	-0.286	-0.180	-0.140	-0.154
p-value		<0.001	<0.001	0.048	0.059	0.086	0.294	0.415	0.370
CES-D	0.782	-----	0.609	-0.304	-0.301	-0.284	-0.217	-0.025	-0.192
p-value	<0.001		<0.001	0.075	0.066	0.084	0.197	0.883	0.263
McGill	0.663	0.723	-0.802	-0.375	-0.310	-0.569	-0.510	0.075	0.172
p-value	0.004	0.001	<0.001	0.784	0.226	0.017	0.036	0.158	0.509

[†] Prof-M= Profile of fatigue-Mental domain; CES-D = Centers for Epidemiology Scale -Depression; FSS= Fatigue Severity Scale; McGill= Short Form-McGill Pain Inventory; HVLT-R= Hopkins Verbal Learning Test-Revised, totalscore; DST= Digit Symbol Test; Stroop=Stroop Interference Test; COWAT= Controlled Oral Word Association Test.

Table 5

Linear Regression Model for Cognitive symptoms (Prof-M) Adjusted for Age and Depression in PSS Patients

	R²	R² change	P-value
Adjustors: Age and Depression (CES-D)	0.108	---	.053
Verbal Memory(HVLT-R) +Adjustors	0.614	0.506	0.000002