

Signal Hyperintensities on Brain Magnetic Resonance Imaging in Patients with Primary Sjögren Syndrome and Frequent Episodic Tension-type Headache: Relation to Platelet Serotonin Level and Disease Activity

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ABSTRACT. Objective. To examine differences in number and size of signal hyperintensities (SH) on magnetic resonance imaging (MRI) between patients with primary Sjögren syndrome (pSS) and controls who all had frequent episodic tension-type headache (FETH), and to investigate their relation to platelet serotonin level (PSL), patient age, disease duration, and activity.

Methods. SH in 22 pSS patients with FETH were compared to 20 aged-matched controls with FETH, using the modified semiquantitative rating scale. Spectrofluorimetry was used for determination of PSL, and the European League Against Rheumatism SS Disease Activity Index (ESSDAI) for disease activity assessment.

Results. Statistically significant differences in the total number of SH were noted infratentorially ($p = 0.025$) and in the basal ganglia for lesions of diameter > 5 mm ($p = 0.048$). Significant correlations were found between disease duration and number of overall lesions > 5 mm ($p = 0.04$) and subcortical lesions of diameter 2–5 mm ($p = 0.035$). Number of periventricular SH inversely correlated to PSL ($p = 0.019$) and to patient age ($p = 0.004$), without association with markers of immunoinflammation and ESSDAI.

Conclusion. Our study showed that SH on brain MRI are more common in specific regions of the brain in pSS patients with FETH than in controls with FETH, signifying a more widespread cerebral vasculopathy in SS patients with FETH. Periventricular SH seem to be associated to increased platelet serotonin release in pSS patients with FETH and correlated with disease duration, without correlation to the actual ESSDAI and markers of immunoinflammation, and might be linked with chronic immunoinflammation of low-grade intensity and vasculitis in pSS. (First Release June 1 2013; *J Rheumatol* 2013;40:1360–6; doi:10.3899/jrheum.121132)

Key Indexing Terms:

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This study represents an extension of the authors' previously published study. Central nervous system (CNS) tissue damage associated with primary Sjögren syndrome (pSS) is still a matter of debate among research groups. CNS manifestations in pSS are unusual. The diagnosis is

more difficult in pSS patients with nonfocal CNS disease because of nonspecific symptoms. Prevalence of brain magnetic resonance imaging (MRI) signal hyperintensities (SH) in patients with pSS range from undetectable to quite common^{1,2}. Some findings in the literature have not been

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confirmed in more recent studies, possibly owing to referral bias in the populations studied. In a pSS population with a high percentage of neurologically impaired individuals, pronounced abnormalities on brain MRI, predominantly in periventricular and subcortical white matter, are common^{3,4}. SH in the infratentorial region and in the basal ganglia, compared with periventricular and subcortical lesions in patients with SS, were not addressed or received less attention in previous studies.

Several pathogenic factors may explain CNS tissue damage in pSS: direct infiltration of CNS by mononuclear cells⁵, vascular injury, and noninflammatory thickening of small vessels due to the presence of antineuronal antibodies and anti-Ro antibodies associated with ischemia secondary to small-vessel vasculitis^{3,6,7,8}. Correlation between SH on brain MRI with neuropathological data has shown that some of these SH may be associated with perivascular edema, periventricular gliosis, myelin pallor, or demyelination consistent with lesions in multiple sclerosis, arteriosclerosis, ischemia, small-vessel infarction, or true vasculitis with inflammatory cell infiltrates^{4,9}. Cerebral MRI can detect subclinical tissue injury and determine location and extent of SH in patients with pSS⁴. However, the prevalence, site frequency, and pathogenesis of SH on brain MRI have not been precisely described. Our study offers new information about the extent, size, and location of SH on brain MRI in patients with pSS and frequent episodic tension-type headache (FETH), and age-matched controls with FETH, and relationships between SH, platelet serotonin level (PSL), soluble markers of immunoinflammation, disease duration, and disease activity assessed by the recently developed European League Against Rheumatism (EULAR) SS Disease Activity Index (ESSDAI).

MATERIALS AND METHODS

Patients. Data on patients with definite diagnosis of pSS¹⁰ and who had FETH¹¹, and age-matched controls with FETH, who all had headache severe enough to sustain brain MRI, were evaluated prospectively to determine the location and extent of SH. The study group was composed of 22 outpatient and day hospital pSS patients with FETH (18 women and 4 men), median 58.5 years old (range 43–74), with the median sicca complex duration of 8.95 years and median 6.45 years since diagnosis of pSS was established. They were recruited from 61 consecutive patients with pSS from the Department of Immunology, Rheumatology and Pulmonary Disorders, Internal Clinic, University Hospital Sisters of Mercy, Zagreb, between November 2009 and January 2012. From the total number of 61 patients with SS, 31 patients had headache severe enough to sustain brain MRI. An age-matched and sex-matched control group of 20 subjects (14 women and 6 men), median 57.5 years old (range 44–71), clinically diagnosed with FETH headache, were recruited from the Diagnostic Centre Medikol, Zagreb. Of the 31 patients with SS who had headache severe enough to sustain brain MRI, 22 pSS patients with FETH were recruited after exclusion of 9 individuals: 3 pSS patients with systemic hypertension, 2 pSS patients with diabetes, 1 patient with headache that occurred in association with cardioembolic stroke, 1 patient following cerebral vascular procedures, and 2 patients with migraine with visual aura. All MRI scans were evaluated 15–45 days after initial examination in the Croatian Institute for Brain Research, Zagreb. The patient group and the control

group were assimilated regarding the diagnosis of FETH, after exclusion of individuals with vascular headaches or headaches that occurred in association with ischemic strokes, cervical artery dissections, intracranial aneurysms, and following cervical or cranial vascular procedures. Others were excluded if onset of headache was prior to the manifestation of other neurological deficits, or if headache was coincident after onset of stroke symptoms. Also excluded were patients with a history of cerebrovascular disease, systemic hypertension, diabetes, migraine headaches, and other factors that may have significant relevance to development of brain SH. In subjects with FETH, the pain was typically bilateral, pressing or tightening, nonpulsating, and of mild to moderate intensity, and was not aggravated by routine physical activity. There was no nausea or vomiting, but photophobia or phonophobia were occasionally presented. At least 10 episodes have occurred on ≥ 1 but ≤ 15 days per year or for at least 3 months (≥ 12 and ≤ 180 days per year).

Clinical assessment. The original diagnostic category was checked during the study by reported oral and ocular symptoms, Schirmer test, unstimulated salivary flow, and routine laboratory examinations [erythrocyte sedimentation test (ESR), C-reactive protein (CRP), haptoglobin, serum proteins, gammaglobulins, immunoglobulins, complements C3 and C4]. Specific biological tests were anti-Ro/SSA, anti-La/SSB, antinuclear antibodies (ANA), rheumatoid factor (RF), and the minor salivary gland biopsy, repeated at the time of diagnosis if specific SSA and SSB antibodies were negative. All pSS patients with FETH underwent extensive neurological examination and brain MRI.

Patients and controls presented with complaints of daily occurrence of headache suggestive of FETH, lasting from 30 min to several days. The ESSDAI was used to assess disease activity at the time of brain imaging and laboratory processing, which were conducted within 2–4 weeks after clinical assessment. ESSDAI is used to assess the actual disease activity and systemic complications, and comprises evaluation of 12 organ-specific domains that are predominantly clinical; only 1 domain includes CNS involvement¹². During a study visit, a rheumatologist examined the patients and secured the tests to complete the ESSDAI. Prior to the study, approval was obtained from ethics committees at all centers involved. Written informed consent was obtained from all participants.

Blood sampling and PSL measurement. Venous blood (8 ml) was collected on acid citrate dextrose anticoagulant between 7:30 AM and 10:00 AM. Platelet-rich plasma was prepared by centrifugation of blood samples (200 \times g, 15 min) and aliquoted for platelet counting (0.5 ml; Coulter Counter ZM) and PSL determination (2 \times 1.0 ml) by orthophthaldialdehyde-enhanced fluorimetry (Varian Cary Eclipse), as described¹³. Blood samples of patients and controls were always processed simultaneously. All measurements were performed in duplicate, with differences between parallels amounting to about 10%. Results are expressed as ng 5-hydroxytryptamine (5-HT)/10⁹ platelets.

MRI imaging. All patients and age-matched controls were scanned in a 1.5 Tesla (T) MR unit (GE Medical Systems). MRI images were acquired using T2-FLAIR: imaging time 4.16 min; axial interleaved sections 5 mm with 0.7 mm gap; matrix 224 \times 224 field of view, 24 \times 24 cm. This series had a repetition time of 8000 ms and echo delay time 80 ms. The sequence provided 20 parallel sections in a 224 \times 224 matrix. Axial images were 5 mm thick with a 0.7 mm gap between each section.

MRI analysis. MRI scans were performed and examined by 2 radiologists (TK and MB) blinded to the subject's condition, who counted SH in a randomized order. The presence of SH on brain MRI in the following structures was collected: periventricular, subcortical, basal ganglia, mesencephalon, pons, and cerebellum. We classified SH per location into those in the periventricular, subcortical, basal ganglia, mesencephalon, pons, infratentorial, and supratentorial locations, as well as per regions: frontal, temporal, parietal, and occipital. Hyperintense foci were rated using a modified semiquantitative scale¹⁴ to record prevalence, size, and anatomical distribution. The size of SH was counted according to the largest diameter of 1 lesion in these categories: minor (< 2 mm), moderate (2–5

mm), or major lesion (> 5 mm). This very detailed scale is characterized by good reliability and sensitivity with respect to size, anatomical distribution, and extent of lesions. Significance of brain SH in pSS were analyzed by correlating their number and size in different brain regions with PSL and various soluble markers of immunoinflammation, ESSDAI, the patient's age, and disease duration.

Statistical analysis. Standard descriptive statistics (mean, median, SD, range, proportions) were used in data analysis for description of the study population and the characteristics of SH. In evaluation of differences between groups, Mann-Whitney U test and chi-square test were used, where appropriate. The dependence between variables was evaluated using Spearman R correlation. The statistical significance was set at $p < 0.05$. Data were analyzed using Statistica (StatSoft Inc.) version 8.0.

RESULTS

Our study showed more numerous SH on brain MRI scans in the group of patients with pSS who had FETH¹¹ than in age-matched controls with FETH. Considering the number of SH evaluated by brain region, more lesions were found in pSS patients with FETH than in controls with FETH (Figures 1A, 1B, and Figure 2), but this difference was not statistically significant. However, significant differences in the number of lesions between patients and controls were noted in the basal ganglia for lesions > 5 mm diameter ($p = 0.048$) and infratentorially (Figure 1C) in the total number of lesions ($p = 0.025$; Table 1). As many as 90 hyperintense foci were counted in all screened patients with pSS, with a range of 0–75 (mean 15.1), yet 51 lesions were detected in the control group (range 0–43, mean 8.95), with an insignificant difference ($p = 0.23$) by chi-square test. We found 77 SH (85.56%) located supratentorially and 13 lesions (14.44%) infratentorially, with only 2 foci in the brain stem site (2.2%) in the group with SS. However, none was found infratentorially in the control group. Also, 20 lesions (22%) were counted in the basal ganglia in patients with pSS (range 0–9, mean 0.9); there were only 2 foci in the basal ganglia in the control group. When evaluated by brain

region, SH were more numerous infratentorially ($p = 0.025$) for the total number of lesions and in the basal ganglia only for lesions > 5 mm in diameter ($p = 0.048$) in the SS group compared to controls (Table 1). Clinically insignificant correlation was found between the number of SH in different brain regions and ESSDAI (Table 2). The number of SH was not associated with any measured circulating serum antibodies or other blood tests (Table 2).

Group values of PSL measured in pSS patients with FETH but not controls with FETH were measured (Table 3). As expected, PSL in pSS patients with FETH were significantly lower (pSS patients with FETH 351.1 ± 158.06 ng 5-HT/ 10^9 platelets vs healthy controls 460 ± 157 ng 5-HT/ 10^9 platelets)¹⁵. Correlation analysis of PSL and SH showed statistically significant association ($p = 0.019$) of this platelet measure with the number of SH in the periventricular region. Similarly, reduction in PSL was not associated with the number of SH in other brain regions. Further, no correlations were observed of PSL with any of the measured circulating serum antibodies and different soluble markers of immunoinflammation. Data on the presence of antibodies and other blood tests (ESR, C4, SSA, SSB, RF, and CRP) are given in Table 3. Also, statistically significant correlations were noted between the SS disease duration and lesions > 5 mm and 2–5 mm in diameter in the subcortical location ($p = 0.04$ and $p = 0.035$, respectively), and patient's age ($p = 0.032$) in pSS patients with FETH (Table 3).

DISCUSSION

Our results appear to support an increased prevalence of SH of variable size and locations on brain MRI of patients with pSS with FETH in comparison to age-matched controls with FETH. SH were more numerous in specific brain structures in the SS group: infratentorially, in the basal ganglia, and in

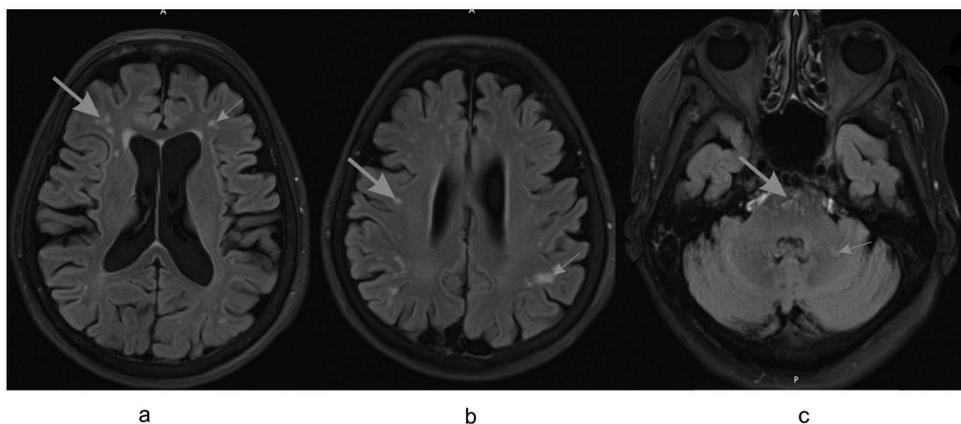


Figure 1. A and B: Axial magnetic resonance imaging 2-Tesla images show signal hyperintensities (SH) in the white matter in a 70-year-old female patient and diffuse cortical atrophy with enlargement of ventricular system. A. Numerous SH in frontal regions, lesion > 5 mm diameter in the right frontal lobe (large arrow) and 2–5 mm lesion in the left frontal lobe (small arrow), along with confluent SH in the periventricular region on both sides. B. Lesion diameter 2–5 mm in the right paraventricular location and lesion > 5 mm, indicative of the minor lacunar infarct in the left parietal location. C. Pontine lesion > 5 mm and cerebellar lesion 2–5 mm.

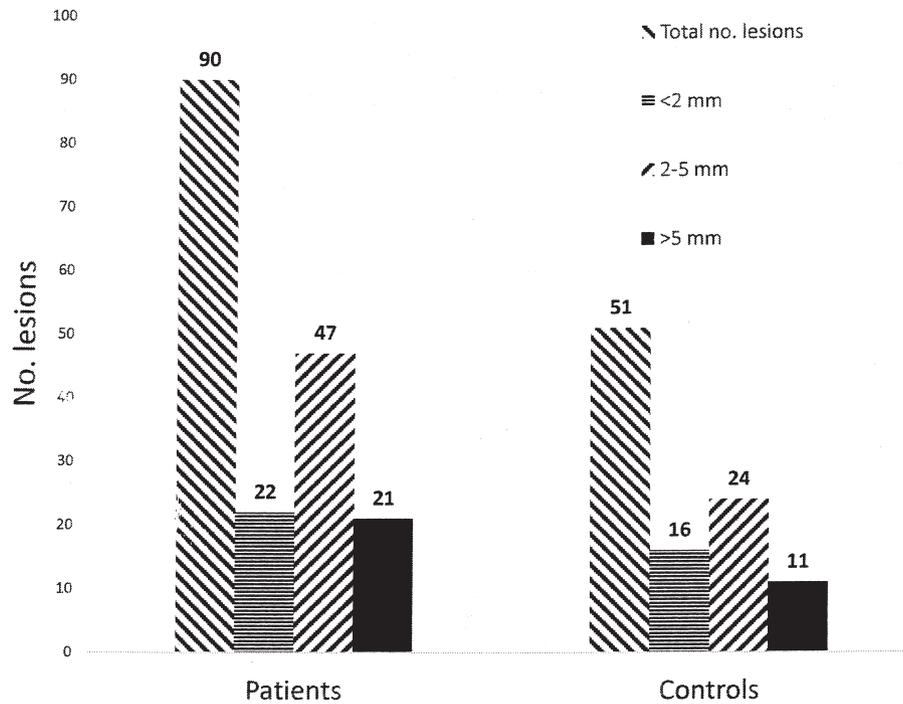


Figure 2. Differences in number of signal hyperintensities between patients with primary SS with frequent episodic tension-type headache (FETH) and age-matched controls with FETH.

Table 1. Differences in number of minor (< 2 mm in diameter), moderate (2–5 mm), and major (> 5 mm) lesions on brain magnetic resonance imaging between patients with primary Sjögren syndrome and frequent episodic tension-type headache, and controls. Between-group differences in signal hyperintensities (SH) are stratified by size and brain region and their relation with the disease activity assessed by the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index.

SH Region	Total No. SH	p		
		SH < 2 mm	SH 2–5 mm	SH > 5 mm
Total	0.23	0.71	0.18	0.29
Periventricular	0.34	0.78	0.61	0.89
Subcortical	0.71	0.81	0.20	0.43
Basal ganglia	0.21	0.34	0.43	0.048
Cerebellum	0.81	—	—	0.81
Mesencephalon	0.34	—	0.34	—
Pons	0.34	0.34	—	—
Infratentorial	0.025	0.17	0.09	0.17

subcortical sites. The number of periventricular SH significantly correlated to PSL, with no association to any markers of immunoinflammation including SSA, SSB, RF, ESR, CRP, and C4. SH correlated to patient's age and to the disease duration. An inverse correlation between SH and the disease activity assessed by ESSDAI at the time of brain imaging was also found, but it seemed to be clinically insignificant, because ESSDAI was statistically significantly higher in younger patients with pSS, who had a decreased number of SH in comparison to elderly patients. The preva-

lence of SH on brain MRI varied substantially in the pSS population, and some findings from the older literature have not been confirmed in more recent studies, possibly because of referral bias in the populations studied^{3,6,16,17,18,19}. When data were stratified by size and brain region, we found a significantly increased total number of infratentorial SH and an increased number of major SH in the basal ganglia of the SS group with FETH. These findings delineated brain regions that have received less attention in previous studies, revealing abnormalities in regions supplied by smaller blood vessels, where the most lacunar infarcts occur²⁰. Pierot, *et al* found numerous punctate areas of high signal in the basal ganglia in 60% of 15 patients with pSS without clinical evidence of CNS involvement, and SH were more frequent in asymptomatic patients with pSS than in age-matched healthy subjects¹⁸. Multiple SH have been detected in up to 80% of patients with pSS who have focal neurological dysfunctions and also in 50% of patients with pSS with the diffuse pattern¹⁹. Several studies reported an increased number of SH in patients with pSS³ and also in migrainous patients²⁰, suggesting the lack of significant differences between them. It is also known that focal infratentorial vascular lesions occurred more frequently among patients with small-vessel cerebrovascular disease, who seem to have more widespread cerebrovascular pathology than those with isolated large-vessel disease.

It should be emphasized that a significant association between SH and patient's age was demonstrated in our

Table 2. Correlations between signal hypertensities stratified by brain region.

	ESSDAI	SS-A	SS-B	RF	CRP	C4	PSL
Total							
p value	0.004	0.057	0.207	0.817	0.957	0.698	0.453
r	-0.58	-0.41	-0.28	-0.06	-0.01	0.09	-0.17
Periventricular							
p	0.07	0.450	0.717	0.605	0.757	0.777	0.019
r	-0.39	-0.17	-0.08	-0.14	-0.07	0.07	-0.49
Basal ganglia							
p	0.033	0.188	0.256	0.799	0.779	0.767	0.749
r	-0.46	-0.29	-0.25	-0.07	-0.06	-0.07	0.07
Subcortical							
p	0.09	0.486	0.738	0.475	0.722	0.908	0.658
r	-0.36	-0.157	-0.08	0.19	-0.08	0.03	0.66
Cerebellum							
p	0.94	0.599	0.649	0.082	0.14	0.27	0.187
r	0.02	-0.118	-0.1	0.45	-0.33	0.259	0.29
Mesencephalon							
p	0.21	0.599	0.649	0.581	0.632	0.616	0.594
r	0.28	-0.12	-0.103	-0.15	-0.11	-0.12	0.12
Pons							
p	0.13	0.599	0.649	0.082	0.422	0.27	0.939
r	-0.33	-0.12	-0.1	0.45	-0.18	-0.26	0.02
Infratentorial							
p	0.53	0.186	0.253	0.277	0.204	0.793	0.113
r	-0.14	-0.29	-0.25	0.29	-0.29	0.06	0.35

ESSDAI: European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; RF: rheumatoid factor; CRP: C-reactive protein; PSL: platelet serotonin level.

study. SH are frequently observed in normal aging, and most elderly individuals have SH on T2 MRI, indicating their association with age and vascular risk factors²¹. This makes the interpretation of our findings for our study population (middle-aged women) rather difficult. However, our results showed that the number of periventricular SH was significantly inversely correlated with PSL, demonstrating an association between number, size, and localization of SH and decreased PSL in pSS patients with FETH, thus indicating possible clinical relevance for our findings. Our results and the literature showed that decreased PSL is a general finding in pSS, as in other autoimmune rheumatic disorders¹⁵. This could reflect increased release of 5-HT during platelet activation due to immunoglobulin/immune complex binding to the platelet surface²² or to factors released by leukocytes²³.

Further, we found that the overall number of lesions of diameter > 5 mm and subcortical lesions size 2–5 mm were statistically significantly correlated to disease duration. We also found a clinically insignificant inverse correlation between the location and extent of SH with ESSDAI and all measured markers of immunoinflammation. In systemic lupus erythematosus (SLE), the disease specificity of SH has been indicated by their association with greater overall disease activity²⁴. The disease activity in pSS is not stable, and disease progression usually continues during the early years after onset; most patients then stabilize despite

continuing B lymphocyte hyperactivity and irrespective of any medical treatment²⁵. Patients with pSS often demonstrate a chronic systemic inflammatory reaction of a low-grade intensity in contrast to patients with other autoimmune disorders such as rheumatoid arthritis (RA) and SLE^{26,27,28}. Because of the variable course of pSS, the cumulative ESSDAI score could be more applicable for describing disease activity. However, absence of immunoinflammatory markers does not preclude CNS involvement in pSS⁶, and > 20% of patients with pSS without peripheral vasculitis have CNS lesions⁷, which may be the only extraglandular manifestation of the systemic disease.

The pathogenesis of SH in pSS could be explained by several mechanisms: the long-lasting non-immune-cell mediated reaction⁴, immune-autoantibody mediated reaction and immune complex deposition that causes vasospasm, or a tendency for platelets to aggregate and secrete vasoactive substances (i.e., serotonin), causing noninflammatory microangiopathy and ischemic CNS injury^{3,6,7,8,21}. Because it is difficult to obtain brain tissue from untreated patients with pSS during active disease, the pathological and pathogenetic hallmarks of SH and their relation to disease activity remain unclear.

The published data on decreased levels of several platelet inflammatory mediators, including PSL in SLE, RA²⁷, and pSS¹⁵ and of subcortical white-matter interneurons that express a variety of vasoactive molecules²⁸ suggest an

Table 3. Characteristics of study participants.

Characteristics	Patients with pSS	Controls
No. subjects	22	20
Sex, female/male	19/3	14/6
Age, yrs, median (range)	51 (43–61)	57.5 (44–71)
Disease duration, yrs, median (range)	6.5 (2–15)	NA
Duration of sicca symptoms, median (range)	8.9 (2–23)	NA
ESSDAI score, median (range)	9.5 (3–19)	NA
Anti-Ro/SS-A antibodies +, n (%)	6 (27.0)	NA
Anti-La/SS-B antibodies +, n (%)	5 (23.0)	NA
ANA, n (%)	12 (0.51)	NA
RF+, n (%)	15 (68.1)	NA
ESR, mm, median (range)	29 (0.4–11.7)	NA
CRP, mg/l, mean (SD)	3.78 (0.4–11.7)	NA
Complement C3, g/l, mean (SD)	1.19 (0.26)	NA
Complement C4, g/l, mean (SD)	0.28 (0.048)	NA
Haptoglobin, g/l, median (range)	1.43 (0.5–2.9)	NA
Serum albumins, g/l, mean (SD)	47.17 (4.01)	NA
Serum gamma globulins, mean (SD)	11.48 (6.22)	NA
IgG, g/l, median (range)	11.61 (8.1–15.12)	NA
IgA, g/l, median (range)	2.5 (1.01–3.85)	NA
IgM, g/l, median (range)	2.5 (0.45–4.51)	NA
IgE, g/l, median (range) n (%)	465.5 (7.55–666)	NA
PSL, ng 5HT/10 ⁹ platelets, mean (SD)	353.1 (158.06)	NA
MSG biopsies focus score ≥ 1	16	NA
MSG biopsy grade 3	11 (50.0)	NA
MSG biopsy grade 4	5 (23.0)	NA

ESSDAI: European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; ESR: erythrocyte sedimentation rate; Ig: serum immunoglobulin; MSG: minor salivary gland; NA: not applicable; ANA: antinuclear antibodies; RF: rheumatoid factor; CRP: C-reactive protein; PSL: platelet serotonin level.

important role of 5-HT in the pathogenesis of inflammatory vascular disease, by increasing vascular permeability, a prerequisite for the deposition of circulating immune complexes. Incomplete knowledge of the longterm course of immunoinflammation makes directions for monitoring disease activity in pSS difficult. Subsequently, clinical and laboratory markers, including circulating cytokines, neurotransmitters, hormones, and neuropeptides, and laboratory tests that indicate polyclonal B lymphocyte hyperactivity need to be investigated to elucidate the pathogenetic mechanisms and to improve management of pSS.

Our findings demonstrated more common brain tissue damage in pSS patients with FETH than in controls with FETH, and highlighted the importance of brain MRI in evaluation of SH in pSS with FETH. Our study supports the potential role of impaired platelet serotonin uptake and/or storage in pathophysiological mechanisms of brain tissue damage in pSS patients with FETH, especially in specific regions of the brain.

Large controlled studies are necessary to provide more information on size, location, and extent of SH in patients with SS and pSS with FETH to explain the pathophysiology of brain tissue damage in patients who have FETH. Our results appear to support PSL as one of the biomarkers of

brain tissue damage in patients with pSS and FETH and potentially as a marker of some specific clinical symptoms and/or complaints in pSS that are still unexplained. The use of PSL in addition to other markers might improve understanding and monitoring of the disease course and manifestations in patients with pSS who have FETH, and help to create better treatment guidelines.

Our study demonstrated that SH on brain MRI are more common in specific brain regions of patients with pSS and FETH than in age-matched controls with FETH, indicating more widespread cerebral vasculopathy in the SS group. Brain MRI represents a sensitive screening tool for detection of SH in patients with pSS who have FETH. PSL is significantly decreased in patients with SS who have FETH, and considering our results and available literature, it seems that reduced PSL is a general finding in pSS as in all major inflammatory rheumatic disorders. An association between PSL and periventricular lesions in our study is in line with the hypothesis of interrelation between increased platelet serotonin release and pathophysiology of brain tissue damage in specific regions of the brain in patients with pSS who have FETH. Positive correlation between SH and the patient's age and the disease duration, and the absence of association between SH and ESSDAI scores and standard soluble markers of immunoinflammation, as contrasted to SLE and RA, may indicate distinct features of pSS with FETH in comparison to other inflammatory rheumatic disorders. It also might indicate that, because of variability of the course of pSS over time, cumulative ESSDAI scores or other disease damage indices^{29,30} that show how disease course is associated to SH on brain MRI should improve our understanding of the pathogenesis of the disease and might lead to better guidelines for estimating distribution and extent of brain SH, and optimal prevention and treatment.

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