White matter abnormalities in primary Sjögren syndrome

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Summary

Objective: To describe the main characteristics of patients with primary Sjögren syndrome (SS) and white matter abnormalities (WMA) seen by a specialist SS unit.

Methods: The study cohort included 321 consecutive patients fulfilling the 2002 classification criteria for primary SS. We retrospectively analyzed the results of neuroimaging studies performed in patients who presented with neurological symptoms. Patients were further evaluated by three neurologists to determine fulfillment of the McDonald criteria for the diagnosis of multiple sclerosis (MS).

Results: Fifty-one (16%) patients had at least one neuroimaging study, and 25 of these had WMA. WMA were classified as vascular pathological changes in 21 patients: 10 had multiple small focal lesions, 7 had beginning confluence of lesions and 4 had diffuse involvement of the entire region. WMA were classified as inflammatory/demyelinating lesions (MS-like) in 4 patients who fulfilled the MRI Barkhof criteria. Patients with inflammatory/demyelinating lesions were younger (53.7 vs. 73.5 years, \(P=0.001\)) and had a lower frequency of hypertension (25% vs. 86%, \(P=0.031\)) and altered glomerular filtration rate (0% vs. 70%, \(P=0.047\)) in comparison with patients with vascular lesions. The multivariate age–sex adjusted model including the seven variables which were statistically significant in the univariate analysis (antimalarial therapy, leukopenia, anti-La/SSB antibodies, diabetes, hypertension, metabolic syndrome and HDL-c levels) identified hypertension (\(P=0.019\)) and HDL-c levels (\(P=0.032\)) as independent predictors of WMA in primary SS patients.

Conclusion: Neuroimaging studies disclosed WMA in 49% of patients with primary SS and suspected neurological involvement. WMA were identified as vascular pathological changes in 80% of the patients, and hypertension and HDL-c levels as predictive factors for this association.

Introduction

Sjögren syndrome (SS) is a systemic autoimmune disease that presents with sicca symptomatology of the main mucosal surfaces.1 The main sicca features (xerophthalmia and xerostomia) are determined by specific ocular (Rose Bengal staining, Schirmer test) and oral (salivary flow measurement, parotid scintigraphy) tests. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, determined by a biopsy of the minor labial salivary glands.2 The spectrum of the disease extends from...
sicca syndrome to systemic involvement (extra-glandular manifestations) and may be complicated by the development of lymphoma. Patients with SS present a broad spectrum of laboratory features (cytopenias, hypergammaglobulinemia) and autoantibodies, of which antinuclear antibodies (ANA) are the most frequently detected, anti-Ro/SS-A the most specific and cryoglobulins and hypocomplementemia the main prognostic markers.3

Neurological involvement is one of the first systemic manifestations of primary SS. However, whilst peripheral nervous system involvement is well defined, there is little data on central nervous system (CNS) involvement, especially with respect to the prevalence, clinical expression and association with other processes.4,5 One of the most difficult diagnostic issues in primary SS is dealing with a patient in whom neurological imaging studies disclose the presence of white matter abnormalities (WMA). In these patients, physicians usually suspect a diagnosis of active CNS involvement, either of vasculitic origin or in the form of demyelinating inflammatory disease (including multiple sclerosis (MS)) that might lead to aggressive therapies being considered. However, the frequency of WMA increases with age and cerebrovascular risk factors, and WMA are highly suggestive of MS according to specific characteristics of their location (periventricular, corpus callosum and juxtacortical lesions) and morphology (ovoid, well-defined, homogeneous lesions).6 Although some studies have been carried out in primary SS patients referred for specific neurological evaluation,5 there is little information on the prevalence and clinical significance of WMA in large cohorts of unselected patients with primary SS.7

The aim of this case–control study was to describe the main characteristics of patients with primary SS and WMA seen by a specialist SS unit, focusing on the possible associations with the systemic expression of SS, the immunological profile and cerebrovascular risk factors.

Materials and methods

Patients

The study cohort included 321 patients fulfilling the 2002 classification criteria for primary SS8 consecutively evaluated by our unit between January 1995 and December 2009. All patients were considered to have a well-established primary SS defined as fulfillment of at least four of the six 2002 SS classification criteria (including either positive autoantibodies or salivary biopsy as a mandatory criteria). Other possible causes of sicca syndrome (infiltrative processes, infections or neoplasia) and other concomitant systemic autoimmune diseases were excluded. Extraglandular involvement in primary SS was evaluated according to the 2009 clinical guidelines of the Spanish Society of Internal Medicine (SEMI) for the management of primary SS.9 Clinical and laboratory data were collected and computerized according to the standard protocol of the SEMI guidelines.9 Patients were consecutively included when SS criteria were confirmed by our unit and thereafter followed up prospectively with regular visits at 6–12 month intervals. The study design conformed to current Spanish ethical standards. Due to the anonymous nature of the study, informed patient consent was not required.

Neurological evaluation

We retrospectively evaluated the results of neuroimaging studies carried out in the study cohort due to suspected neurological involvement (cerebral tomography—CT and/or magnetic resonance imaging—MRI). Patients with WMA were selected as the study population and those without WMA were included as unmatched controls. One neuroradiologist (J.B.) carried out a blinded re-evaluation of the neuroimaging results to confirm the presence or not of WMA. The age-related white matter changes (ARWMC) scale was applied as described previously:10 white matter changes on MRI were considered as ill-defined hyperintensities ≥5 mm on both T2 and PD/FLAIR images, and in the CT as ill-defined, moderately hypodense areas ≥5 mm.10 WMA were graded according to the ARWMC 4-point scale:10 0, no lesions; 1, focal lesions; 2, beginning confluence of lesions; and 3, diffuse involvement of the entire region, with or without involvement of U fibers. Five different regions were rated separately in the right and left hemispheres: the frontal area, the parieto-occipital area, the temporal area, the infratentorial area and the basal ganglia, as previously described.10 WMA were classified as pathologic vascular changes if they were parenchymal focal areas with low attenuation on CT and/or high signal on T2-weighted MRI not exceeding 15 mm in size, and affecting the basal ganglia, internal capsule, corona radiata and pons and subcortical lesions with the same features >15 mm in size.11 WMA were classified as inflammatory/demyelinating lesions according to the following neuroradiological criteria: (i) ovoid, well-circumscribed, homogeneous foci observed with or without involvement of the corpus callosum, (ii) T2 hyperintensities measuring ≥3 mm and fulfilling Barkhof criteria (at least three out of four) for...
dissemination in space,\textsuperscript{6} and (iii) absence of vascular pattern of lesions.\textsuperscript{12,13}

Neurological disease attributed to abnormal cerebral neuroimaging was defined according to the American College of Rheumatology definition of neuropsychiatric involvement in systemic lupus erythematosus (acute or relapsing encephalomyelitis with evidence of discrete neurologic lesions distributed in place and time).\textsuperscript{14} Patients were further evaluated by three neurologists (A.S., Y.B., F.G.) to determine fulfillment of the McDonald criteria for the diagnosis of MS that includes the MRI Barkhof criteria for dissemination in space and time.\textsuperscript{13,15}

### Cerebrovascular risk factors

The following data were systematically recorded from the medical and laboratory records of patients with primary SS at the time of the last visit to our department: hypertension (defined as a physician diagnosis and/or prior/current antihypertensive medication), smoking (defined as previous/current consumption of more than one cigarette per day), diabetes mellitus (defined as a physician diagnosis of diabetes requiring insulin or glucose lowering agents, and/or the presence in at least two determinations of fasting glycemia >126 mg/dl), obesity (defined as a waist circumference >102 cm for men and >88 cm for women), hypercholesterolemia (defined as a total serum cholesterol level >250 mg/dl on two or more visits), high-density lipoprotein (HDLc) cholesterol (defined as <40 mg/dl), low-density lipoprotein (LDLc) cholesterol (defined as >160 mg/dl) and hypertriglyceridemia (defined as serum triglyceride level >150 mg/dl on two or more visits). Glucose, total cholesterol, LDLc, HDLc and triglyceride levels were measured in fasting blood samples using standardized laboratory tests. Patients receiving specific treatments for any metabolic abnormality were considered to have the metabolic abnormality in question. Information on the use of corticosteroids, antimalarials and immunosuppressive agents was also recorded. The 10-year risk of cardiovascular morbidity/mortality was classified as low, moderate, high and very high according to the 2007 guidelines of the European societies of hypertension and cardiology\textsuperscript{16} as previously reported.\textsuperscript{17}

### Statistical analysis

Categorical data were compared using the $\chi^2$ and Fisher’s exact tests. Continuous variables were analyzed with the Student’s $t$-test in large samples of similar variance and with the non-parametric Mann–Whitney $U$-test for small samples, with results indicated as mean ± standard error of the mean (SEM).

A two-tailed value of $P<0.05$ was taken to indicate statistical significance. When several independent variables appeared to have statistical significance in the univariate analysis, a multiple logistic regression analysis was performed. Multivariate Cox regression analysis using a backward conditional stepwise method allowed adjustment for age, sex and the variables that were statistically significant in the univariate analysis. The hazard ratios (HRs) and their 95% confidence intervals (CIs) obtained in the adjusted regression analysis were calculated. The statistical analysis was performed with the SPSS program (SPSS, Chicago, IL, USA).

### Results

Neuroimaging studies were carried out in 51 (16%) of the 312 patients in our cohort: 25 patients had an ARWMC score $\geq 1$ and were selected as the study population, while the remaining 26 had an ARWMC score $= 0$ and were selected as controls. In 18/51 (35%) patients, only CT results were available.

### Characteristics of patients with WMA

Of the 25 patients with WMA, 22 were female, with a mean age at SS diagnosis of 63 years and at 70 years at the time of identification of abnormal cerebral neuroimaging. Neurological symptoms leading to neuroimaging studies included cognitive impairment in 10 patients, focal neurological symptoms in 6, memory impairment in 3, headache in 3, muscular weakness in 2 and seizures in 1 patient. Neurological symptoms attributable to abnormal cerebral neuroimaging were found in only one patient (a female patient who developed seizures). Three patients were diagnosed with stroke. After a mean follow-up of 39 months (range 6–120 months), no patient developed new clinical symptoms, and a second neuroimaging study performed in 6 patients showed no radiological progression of evolution to MS.

All abnormal cerebral lesions corresponded to WMA, which were isolated ($<3$) in 4 (16%) patients and multiple in 21 (84%) patients. The corpus callosum was involved in 3 patients, the U fibers in 3, the cerebellum in 3, the pons in 2, the basal ganglia in one and the mesencephalons in one patient. WMA were classified as vascular pathological changes in 21 patients: 10 had multiple small local lesions (ARWMC score $= 1$; Figure 1A), 7 had beginning confluence of lesions (ARWMC score $= 2$; Figure 1B) and 4 had diffuse involvement of the entire region (ARWMC score $= 3$; Figure 1C).
Figure 1. Different patterns of demyelinating cerebral lesions in patients with primary SS. (A) Focal multiple small lesions (arrow) seen on axial T2WI MRI (ARWMC score = 1). (B) Beginning confluence of lesions (arrows) on axial FLAIR MRI (ARWMC score = 2). [C(i and ii)] Diffuse involvement of the entire region (ARWMC score = 3), seen on axial unenhanced CT (i); on axial T2WI MRI (ii). [D(i and ii)] Inflammatory/demyelinating disease (MS-like disease) (arrows) seen on axial T2WI MRI (i); on sagittal FLAIR MRI.
WMA were classified as inflammatory/demyelinating lesions in 4 patients who fulfilled the MRI Barkhof criteria of dissemination in space (Figure 1D). Contrast enhancement on postgadolinium T1-weighted images was not observed in any of the 3 patients with available postcontrast study. A follow-up MRI was performed in 2 patients showed no evidence of radiological progression. In addition, we analyzed the association between location (only supratentorial vs. involvement of other regions), size (small vs. confluent/diffuse lesions) and etiological classification (vascular vs. inflammatory/demyelinating) and the main SS-related features, immunological markers and cerebrovascular risk factors (data not shown). The only statistically significant differences were that patients with WMA classified as inflammatory/demyelinating were younger (53.7 vs. 73.5 years, \( P = 0.001 \)) and had a lower prevalence of hypertension (25% vs. 86%, \( P = 0.031 \)) and altered glomerular filtration rate (0% vs. 70%, \( P = 0.047 \)) in comparison with patients with WMA classified as vascular pathological changes.

**Table 1** Epidemiologic features, sicca features included in the 2002 criteria, general features, associated organ-specific diseases, systemic involvement and therapies received in 51 patients with primary SS with and without WMA in neuroimaging studies

<table>
<thead>
<tr>
<th></th>
<th>Absence of WMA, ( n = 26 ) (%)</th>
<th>Presence of WMA, ( n = 25 ) (%)</th>
<th>Bilateral, ( P )-value</th>
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<tr>
<td>Gender (male)</td>
<td>1 (4)</td>
<td>3 (12)</td>
<td>0.350</td>
</tr>
<tr>
<td>Age (mean ( \pm ) SEM)</td>
<td>58.31 ( \pm ) 3.10</td>
<td>70.32 ( \pm ) 2.39</td>
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<td>Xerostomia</td>
<td>26 (100)</td>
<td>24 (96)</td>
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<tr>
<td>Xerophthalmia</td>
<td>25 (96)</td>
<td>24 (96)</td>
<td>1.000</td>
</tr>
<tr>
<td>Positive ocular tests</td>
<td>20/22 (91)</td>
<td>22/24 (92)</td>
<td>1.000</td>
</tr>
<tr>
<td>Severe involvement in parotid scintigraphy (Grades III–IV)</td>
<td>16/21 (76)</td>
<td>15/22 (68)</td>
<td>0.736</td>
</tr>
<tr>
<td>Positive salivary gland biopsy</td>
<td>10/11 (91)</td>
<td>19/19 (100)</td>
<td>0.367</td>
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<tr>
<td>Fever</td>
<td>4 (15)</td>
<td>5 (20)</td>
<td>0.726</td>
</tr>
<tr>
<td>Parotid enlargement</td>
<td>3 (11)</td>
<td>6 (24)</td>
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<td>Arthralgias</td>
<td>13 (50)</td>
<td>18 (72)</td>
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<td>0.726</td>
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<tr>
<td>Raynaud phenomenon</td>
<td>6 (23)</td>
<td>5 (20)</td>
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<td>Cutaneous vasculitis</td>
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<td>5 (20)</td>
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</tr>
<tr>
<td>Ro-associated cutaneous lesions</td>
<td>1 (4)</td>
<td>4 (16)</td>
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</tr>
<tr>
<td>Interstitial lung disease</td>
<td>2 (8)</td>
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<td>Digestive involvement</td>
<td>5 (19)</td>
<td>10 (40)</td>
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<td>Autoimmune liver disease</td>
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<td>4 (16)</td>
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<td>Renal involvement</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td>1.000</td>
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<tr>
<td>Peripheral neuropathy</td>
<td>7 (27)</td>
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<tr>
<td>Cranial neuropathy</td>
<td>3 (11)</td>
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<td>Antimalarials</td>
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<td>Corticosteroids</td>
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<td>13 (52)</td>
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</tr>
<tr>
<td>Immunosuppressive agents</td>
<td>6 (23)</td>
<td>6 (24)</td>
<td>1.000</td>
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\( P \)-values < 0.05 in bold

**Comparison between patients with and without WMA**

Table 1 summarizes the principal differences in the main clinical SS-related features and therapies received by the two groups of patients. Patients with WMA had a higher mean age at the time of identification of WMA (70.3 vs. 58.3 years, \( P = 0.004 \)) and had received antimalarials less frequently (8% vs. 35%, \( P = 0.038 \)) in comparison with patients without WMA. In laboratory parameters (Table 2), patients with WMA had a lower frequency of leukopenia (4% vs. 31%, \( P = 0.024 \)) and anti-La/SS-B antibodies (36% vs. 69%, \( P = 0.025 \)); no significant differences were observed with respect to cryoglobulins, complement levels or antiphospholipid antibodies. Patients with WMA had a higher frequency of cardiovascular risk factors (Table 3), including a higher frequency of diabetes mellitus (68% vs. 31%, \( P = 0.012 \)), metabolic syndrome (40% vs. 8%, \( P = 0.009 \)) and hypertension (76% vs. 23%, \( P < 0.001 \)), and lower mean HDL-c levels (42.0 mg/dl vs. 64.3 mg/dl, \( P = 0.009 \)). Figure 2 shows the classification of cerebrovascular
risk factors according to the presence or absence of WMA. The multivariate age- and sex-adjusted model including the seven variables which were statistically significant in the univariate analysis (antimalarial therapy, leukopenia, anti-La/SSB antibodies, diabetes, hypertension, metabolic syndrome and HDL-c levels) identified hypertension ($P=0.019$) and HDL-c levels ($P=0.032$) as independent predictors of WMA in primary SS patients.

**Discussion**

The exact prevalence of CNS involvement in unselected primary SS patients remains unclear,\(^{18-20}\)
because primary SS patients present a wide spectrum of neurological manifestations that may be difficult to differentiate from other neurological diseases. One of the best examples are WMA, which are associated with a wide variety of disorders, including hypoxic-ischemic vasculopathies and vasculitides, infectious, metabolic and neoplastic processes,\textsuperscript{21,22} although MS is probably the disease most often considered in the differential diagnosis. Therefore, one of the most difficult diagnostic issues is dealing with a patient with sicca syndrome and WMA in whom two clinical

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year</th>
<th>N</th>
<th>Mean age (years)</th>
<th>Clinical profile</th>
<th>WMA (n)</th>
<th>Percentage of lesions</th>
<th>Cardiovascular risk factors</th>
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<tr>
<td>Alexander et al.\textsuperscript{25}</td>
<td>1988</td>
<td>16</td>
<td>NS</td>
<td>NRL involvement</td>
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<td>75</td>
<td>NE</td>
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<td></td>
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<td>NE</td>
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<td>NS</td>
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<td>9</td>
<td>60</td>
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<td>51</td>
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<td>21</td>
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<td>Suspected NRL inv</td>
<td>1</td>
<td>5</td>
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<tr>
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<tr>
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<td>20</td>
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<td>NS</td>
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<td>50</td>
<td>NE</td>
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<td>55.8</td>
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<td>87</td>
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<td>51</td>
<td>64.2</td>
<td>Suspected NRL inv</td>
<td>25</td>
<td>49</td>
<td>HTA 49%, DM 49%, Hcol 45%, HTG 35%</td>
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</table>

**Total**: 361 199 55


**Figure 2.** Classification of the cardiovascular risk factors according to the presence or absence of WMA.
scenarios may be hypothesized: ischemic small vessel disease or inflammatory demyelinating insult (MS-like or true MS). This study found that WMA in patients with primary SS were overwhelmingly associated with concomitant cerebrovascular risk factors. Studies evaluating WMA in primary SS are summarized in Table 4. A total of 199/361 (55%) patients included in 15 studies were found to have WMA, with a prevalence ranging from 5% (28) to 87% (7), compared to the 49% of patients in whom neuroimaging studies were carried due to suspected neurological involvement in our study. These differences may be explained not only by the different setting (neurology or internal medicine departments, specialized SS units), but also by the different prevalences of some processes associated with WMA, hypertension and cerebral ischemic disease. In contrast, Harboe et al. found a higher number of WMA in primary SS patients than in age- and sex-matched controls, although the difference almost disappeared when hypertensive patients were excluded from both groups. In contrast, Coates et al. did not find significant differences in total and regional WMA scores between 68 unselected primary SS patients and 68 age–sex-matched healthy controls.

In primary SS, most studies describe WMA as small rounded lesions, predominantly located in the subcortical or periventricular areas. However, WMA have also been described in the cerebellum, corpus callosum and basal ganglia. As shown by our results, WMA are usually multiple; only four primary SS patients, including one from our study, have been reported to have a single lesion. The etiopathogenesis of the WMA in primary SS patients is not clear. In our study, the presence of WMA was associated with age and cerebrovascular risk factors. In patients without autoimmune disease, the frequency of WMA clearly increases with age, and in the general population are closely associated with cardiovascular disease, hypertension and metabolic syndrome. In our study, >90% of patients with WMA had cerebrovascular risk factors and the age- and sex-matched multivariate model identified hypertension and HDL cholesterol as independent predictors in primary SS patients. Taken together, these data suggest that, in the majority of primary SS patients, WMA are due to nonautoimmune causes.

Identification of WMA in a patient with primary SS requires a differential diagnosis with MS. Delalande et al. found that 40% of patients with primary SS and neurological involvement had WMA suggestive of MS, although the criteria used to define the MRI findings were not described. We found that the prevalence of MS-like lesions in our unselected primary SS population was much lower, probably due to the older age of our patients, the high rate of cerebrovascular risk factors found and the strict definitions used to consider WMA as suggestive of MS. In addition, in our study, neuroimaging was ordered by an SS specialist for screening purposes and not by neurologists, who predominantly evaluate patients with a high probability of having a well-defined neurological disease. This highlights the importance of evaluating the setting (neurological vs. SS unit) when the reported prevalence of CNS involvement in primary SS patients is analyzed.

Some clinical, analytical and imaging features may help to differentiate between ischemic cerebrovascular disease and inflammatory/demyelinating disease–MS. The clinical course is probably the key factor in the diagnosis of MS. In patients with primary SS, WMA are often diagnosed in asymptomatic patients or in those with non-specific neurological symptoms (migraine, memory loss, depression) as reported in the present study. In contrast, a diagnosis of MS requires focal neurological symptoms suggestive of an MS flare, together with the appearance of new clinical episode or MRI lesion during the follow-up (‘dissemination in space and time’). Cerebrospinal fluid (CSF) analysis may aid the differential diagnosis, although elevated IgG and oligoclonal bands are found in both diseases. Higher levels of CSF lymphocytes and proteins are more frequently, but not always, seen in SS patients, although this is not an always valid feature. CSF immunoelectrophoresis may show a lower number of oligoclonal bands in primary SS (less than 5 compared with more than 10 in MS patients). However, the key to the differential diagnosis continues to be cerebral MRI to show the presence, size and location of WMA. Expert evaluation and the application of the MRI Barkhof criteria will lead to a diagnosis of MS.

Our results show that WMA are associated with a less-pronounced immunological pattern (lower frequency of autoantibodies, especially anti-La/SS-B), similar to the results found by Delalande et al. Because fulfillment of SS criteria requires positive anti-Ro/La or salivary biopsy, such a biopsy may be required to confirm SS in patients...
with WMA and negative immunological results; in the study by Delalande, 95% of patients had a positive biopsy in comparison with only 43% who had positive Ro/La antibodies. However, we found no association between WMA and other immunological markers such as antiphospholipid antibodies (aPL) or cryoglobulins. In fact, the frequency of these immunological markers was nonsignificantly lower in patients with WMA, as also reported by Delalande et al. This suggests that the probability of a patient with SS presenting CNS involvement due to overlapping antiphospholipid syndrome or vasculitic cryoglobulinemia is low.

Correct differentiation between ischemic cerebral small vessel disease and inflammatory/demyelinating disease in primary SS patients is of great importance in defining the therapeutic strategy. Our results suggest a complete evaluation of cardiovascular risk factors in primary SS patients with suspected CNS involvement before considering aggressive immunosuppressive therapy. In primary SS patients diagnosed with ischemic cerebral small vessel disease, strict control of cardiovascular risk factors is mandatory due to the increased risk of stroke, dementia and death in patients with WMA. In contrast, the treatment of primary SS patients with severe neurological symptoms due to inflammatory/demyelinating disease requires high-dose corticosteroids and immunosuppressors such as cyclophosphamide. In some patients, it may be difficult to differentiate between an inflammatory demyelinating disease related to primary SS and true MS; in these patients, a therapeutic strategy covering both possibilities, such as corticosteroids associated with azathioprine or even rituximab, may be employed until further clues are revealed by the disease evolution.

Possible concerns in observational retrospective studies include selection bias (in our study, only symptomatic patients were included). This patient profile makes it impossible to extrapolate our results to the whole population of primary SS patients, especially considering that incidental WMA may be found in asymptomatic patients. In addition, in our study, nearly 10% of patients included as controls had no MRI study, and this does not allow the exclusion of small demyelinating lesions not detectable by CT. Nevertheless, in spite of these limitations, we believe that the recruitment of 51 patients with primary SS with neuroimaging studies is significant and permits useful information on the characteristics and outcomes to be obtained.

In summary, neuroimaging studies disclosed WMA in 25/51 (49%) patients with primary SS studied due to neurological symptoms. Lesions were identified as vascular pathological changes in 21 patients and of inflammatory/demyelinating origin (MS-like) in the remaining 4. No patient fulfilled the McDonald criteria for the diagnosis of MS, while 3 were diagnosed with stroke. The multivariate age- and sex-adjusted model identified hypertension and HDL-c levels as independent predictors of WMA. In patients with primary SS with suspected CNS involvement, a multidisciplinary approach involving neurologists, neuroradiologists and specialists in cardiovascular and autoimmune diseases is highly recommended.

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