Cerebrospinal fluid anti-SSA autoantibodies in primary Sjogren's syndrome with central nervous system involvement

MEGEVAND, Pierre Bastien, et al.

Abstract

Central nervous system involvement in primary Sjogren's syndrome is a matter of controversy, and its diagnosis remains difficult.

Reference


DOI: 10.1159/000098469
PMID: 17213724
Cerebrospinal Fluid Anti-SSA Autoantibodies in Primary Sjögren’s Syndrome with Central Nervous System Involvement

Pierre Mégevand a, Carlo Chizzolini b, Michel Chofflon a, Pascale Roux-Lombard b, Patrice H. Lalive a, Fabienne Picard a

a Service of Neurology, Department of Clinical Neuroscience and Dermatology, and b Service of Immunology and Allergy, Department of Internal Medicine, Geneva University Hospital and School of Medicine, Geneva, Switzerland

Introduction

Sjögren’s syndrome (SS) is an autoimmune inflammatory disorder characterized by xerophthalmia, xerostomia and diverse systemic manifestations, secondary to both cellular and humoral immune responses [1]. Although peripheral nervous system involvement is well described, occurring in about 20% of patients [2], the frequency of central nervous system (CNS) manifestations remains debated [3, 4]. Serum anti-SSA and anti-SSB autoantibodies (autoAbs), used as part of current classification criteria for SS [5], are believed to participate in its pathogenesis [6]. In a study of SS patients with CNS involvement, positive serum anti-SSA autoAbs were associated with severer CNS disease and signs of small-vessel vasculitis on cerebral angiography [7]. However, both anti-SSA-positive and -negative SS patients can develop CNS involvement, and no biomarker has yet been unequivocally associated with CNS involvement. Cerebrospinal fluid (CSF) anti-SSA and anti-SSB autoAbs, in particular, have received little attention. Here, we report 3 patients with primary SS and CNS involvement in whom we studied the presence and significance of anti-SSA and anti-SSB autoAbs in the CSF.
**Materials and Methods**

**Patient 1**

A 45-year-old woman presented with a 1-day history of left-sided body and face paresthesia and a 3-year history of progressive cognitive impairment described by the patient as difficulties in memory and concentration. Primary SS had been diagnosed 14 years before admission based on xerophthalmia, xerostomia, positive serum anti-SSA and anti-SSB autoAbs, pathologic Schirmer’s test and presence of lymphocytic sialadenitis on accessory salivary gland biopsy. Examination showed left-sided body and face hypoesthesia. Neuropsychological testing revealed impairment in word finding, verbal and visuospatial episodic memory, executive functions and attention. Brain magnetic resonance imaging (MRI) showed T2 hyperintensities in the right pons, the left and right thalamus and internal capsule, without any T1 gadolinium enhancement. Diffusion-weighted sequences did not disclose any recent ischemia. No cardiac source of emboli was found. The head and neck arteries were normal. HIV serology was negative. Treatment with hydroxychloroquine was introduced. One year later, neurological examination showed an improvement in memory as well as an amelioration in sensory function, with persistence of residual hypoesthesia of the proximal part of the left arm.

**Patient 2**

A 60-year-old woman presented with a 3-year history of progressive chorea and cognitive dysfunction. She reported xerophthalmia and xerostomia for several years. Three months before admission, she had developed arthritis of the hands and feet, for which prednisone 40 mg daily had been introduced 1 week before admission. Examination showed choreic movements of all 4 limbs, predominating distally. Neuropsychological testing revealed impairment in oral and written language and attention. Brain MRI showed a small T2 left frontal periventricular white matter lesion with no T1 gadolinium enhancement. Genetic testing for Huntington’s disease, serum ceruloplasmin, anti-streptolysin O antibodies and blood smear were normal or negative. Serum anti-SSA autoAbs were positive. Schirmer’s test was pathologic. Accessory salivary gland biopsy, performed 4 weeks after the introduction of corticosteroids, showed minimal fibrosis. Cyclophosphamide was added 2 weeks after corticosteroid introduction. Five months later, strength and urinary function had partially recovered.

**Evaluation of Anti-SSA and Anti-SSB Intrathecal Synthesis**

To assess CSF anti-SSA and anti-SSB autoAbs and to evaluate possible intrathecal synthesis, serum samples were diluted to obtain equal immunoglobulin G (IgG) concentration in the serum and CSF for each patient. Diluted sera and CSF samples were then tested for anti-SSA and anti-SSB autoAbs using the above-mentioned ELISAs. A higher anti-SSA or anti-SSB ELISA optical density (OD) in the CSF sample than in the diluted serum sample represents intrathecal synthesis.

Additionally, the antibody index was calculated as the ratio between the CSF-to-serum concentration ratio of a specific antibody and that of IgG. In case of intrathecal IgG synthesis, the measured CSF-to-serum IgG ratio is replaced by the maximal CSF-to-serum IgG ratio that would be observed in the absence of intrathecal synthesis, taking into account the state of the blood-brain barrier [8]. CSF-to-serum ratios of anti-SSA and anti-SSB autoAbs were estimated by calculating the ratio of their ELISA OD and multiplying by the CSF-to-serum IgG concentration ratio. An antibody index $\geq 1.5$ indicates specific intrathecal synthesis.

**Results**

**Serum and CSF Anti-SSA and Anti-SSB AutoAbs**

All patients had positive serum anti-SSA autoAbs (table 1). Patient 1 also had serum anti-SSB autoAbs. The anti-SSA autoAbs were directed against the 52-kD SSA peptide in all 3 patients. In addition, patients 1 and 2 also had anti-60-kD SSA autoAbs. All patients had anti-SSA autoAbs in the CSF, whereas patient 1 also had CSF anti-SSB autoAbs (fig. 1). Patients 1 and 2 had both anti-52-kD...
and anti-60-kD SSA autoAbs in the CSF; only anti-52-kD SSA autoAbs were found in the CSF of patient 3 (table 2).

Intrathecal IgG Synthesis in Absence of Blood-Brain Barrier Dysfunction

No patient had blood-brain barrier dysfunction, as indicated by normal CSF albumin concentration, normal albumin quotient and absence of $T_1$ MRI gadolinium enhancement. Intrathecal IgG synthesis was demonstrated in all 3 patients by CSF-specific oligoclonal bands on isoelectric focusing or raised CSF IgG index. Furthermore, patients 1 and 3 had an increased CSF cell count together with plasma cells (table 2).

Demonstration of Specific Anti-SSA AutoAb Intrathecal Synthesis in Patients 1 and 3

Anti-SSA and anti-SSB autoAbs detected in the CSF were further analyzed to investigate possible intrathecal synthesis. For patient 3, anti-SSA ELISA OD was higher in CSF than in serum (fig. 1). In addition, the anti-SSA antibody index was raised (table 2). This indicates specific intrathecal synthesis of anti-SSA autoAbs. For patient 1, anti-SSA ELISA OD was slightly higher in CSF than in serum, and the antibody index was raised, indicating anti-SSA intrathecal synthesis. For patient 2, anti-SSA ELISA OD was lower in CSF than in serum, and the antibody index was not raised. There was no sign of anti-SSB intrathecal synthesis in patient 1.

Discussion

Our 3 patients fulfilled the primary SS classification criteria proposed by the American-European consensus group [5]. None of them fulfilled classification criteria for systemic lupus erythematosus (SLE) [9] and all were negative for antinucleosome antibodies, a sensitive and spe-
specific marker for SLE [10]. Patient 1 had a hemisensory deficit with cognitive dysfunction, a CNS presentation often described in SS [3, 4]. Patient 2 presented with chorea, a previously reported atypical SS-related CNS manifestation [11]. Patient 3 had optic neuritis and recurrent acute transverse myelitis, a clinical presentation similar to neuromyelitis optica already described in SS-related CNS disease [12]. In all 3 patients, extensive testing did not reveal any alternate diagnosis for the CNS manifestations. Therefore, we considered CNS involvement as related to SS.

Our 3 patients had neither biological nor MRI signs of blood-brain barrier disruption. The blood-brain barrier is generally intact in SS-related CNS involvement [13]. All patients showed evidence of intrathecal IgG synthesis demonstrated by raised CSF IgG index or CSF-specific oligoclonal bands, which is in accordance with previously published findings [13]. This observation may indicate a specific role of intrathecally synthesized IgG in SS-related CNS manifestations. The raised CSF IgG index in patient 2 indicated intrathecal synthesis, while there were no oligoclonal bands on IEF. CSF-restricted IEF oligoclonal bands are more sensitive than the CSF IgG index in multiple sclerosis (MS; 85 vs. 60%) [14]; the specificity of both methods is similar (92%). However, dissociation between a raised CSF IgG index and the absence of oligoclonal bands on IEF has been reported and is more frequent in patients with neurological conditions other than MS [15, 16]. Since IEF only detects expansion of a small number of B cell populations (oligoclonal IgG bands), it has been proposed that IEF-negative, CSF IgG index-positive cases may indicate a polyclonal more than oligoclonal B cell activation within the CNS. Moreover, polyclonal B cell activation has been described in SS [17]. Therefore, the raised CSF IgG index in the absence of IEF oligoclonal bands in patient 2 could be due to polyclonal B cell activation within the CNS.

All 3 patients had positive serum anti-SSA autoAbs; patient 1 also had positive serum anti-SSB. The reported frequency of serum anti-SSA and anti-SSB autoAbs in SS patients with CNS manifestations is about 50 and 20%, respectively [3, 7]. The relation between presence of serum anti-SSA autoAbs, pathogenicity and severity of CNS involvement remains debated. In one study of SS patients with CNS involvement, positive serum anti-SSA autoAbs were associated with sev erer CNS disease and signs of small-vessel vasculitis on cerebral angiography [7], whereas another group reported no correlation between serum anti-SSA status and neurologic complications [18]. In another study, serum anti-SSA autoAbs were found to be more often positive in patients with recurrent idiopathic acute transverse myelitis than in controls [19]. It was suggested that these autoAbs could be directly pathogenic and may be used as a marker of the pathogenic process.

All 3 patients had anti-SSA autoAbs in the CSF; patient 1 also had CSF anti-SSB Abs. The assessment of CSF anti-SSA and anti-SSB autoAbs in SS-related CNS involvement has yet received little attention. Four SS patients with CNS manifestations were reported to be positive for

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
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<tbody>
<tr>
<td>Leukocytes (&lt;5 cells/mm³)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Albumin (110–320 mg/l)</td>
<td>207</td>
<td>200</td>
</tr>
<tr>
<td>Albumin quotient (&lt;8)</td>
<td>6.20</td>
<td>6.25</td>
</tr>
<tr>
<td>CSF IgG index (&lt;0.7)</td>
<td>1.04</td>
<td>0.85</td>
</tr>
<tr>
<td>Serum and CSF isoelectric focusing</td>
<td>CSF-specific oligoclonal bands</td>
<td>no oligoclonal bands</td>
</tr>
<tr>
<td>Anti-SSA antibody index (&lt;1.5)</td>
<td>1.67</td>
<td>0.92</td>
</tr>
<tr>
<td>Anti-SSB antibody index (&lt;1.5)</td>
<td>1.20</td>
<td>not done</td>
</tr>
<tr>
<td>Anti-SSA peptide specificity</td>
<td>52- and 60-kD</td>
<td>52- and 60-kD</td>
</tr>
</tbody>
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Normal ranges in parentheses. Formulas: albumin quotient = CSF albumin/serum albumin × 1,000. CSF IgG index = (CSF IgG × serum albumin)/(serum IgG × CSF albumin). Antibody index = [(CSF antibody ELISA OD/serum antibody ELISA OD) × (CSF IgG/serum IgG)]/(0.8 × √[(albumin quotient² + 15 × 10⁶) – 1.8 × 10⁻³]) [8]. Anti-SSB antibody index was not calculated for patients 2 and 3 because serum and CSF anti-SSB autoAbs were negative.
serum anti-SSA autoAbs, but no anti-SSA autoAbs were detected in the CSF [20]. However, the double immuno-diffusion method used in that study to detect autoAbs might have lower sensitivity than the ELISA method we used [21]. In a recent case report, an SS patient with myelopathy had positive serum and CSF anti-SSA autoAbs, without any investigation of specific intrathecal synthesis [22].

The antibody index allows detecting intrathecal synthesis of specific antibodies while taking into account intrathecal synthesis of other antibodies as well as the state of the blood-brain barrier [8]. With this method, specific intrathecal anti-SSA autoAb synthesis was demonstrated in 2 out of 3 patients. Although intrathecal synthesis of anti-SSA and anti-SSB autoAbs was reported in a patient with SLE and CNS manifestations [23], this is the first description of intrathecal anti-SSA synthesis in patients with SS and CNS disease.

In our report, all 3 patients had positive anti-52-kD-SSA autoAbs, whereas patients 1 and 2 also had positive anti-60-kD-SSA autoAbs. Pathogenicity of anti-52-kD-SSA and anti-60-kD-SSA autoAbs was suggested in SS [6], and antibodies against neuronal peptides were reported in the serum of SS patients with CNS involvement [18, 24, 25]. Nevertheless, a correlation between anti-SSA autoAb pathogenicity and SS-related CNS disease still remains to be demonstrated.

SS-related CNS involvement can cause diverse manifestations and might be confused with other diseases, especially multiple sclerosis (MS). The prevalence of serum anti-SSA autoAbs in MS patients was found to be 7% [26]. Interestingly, de Seze et al. [27] found a 15% prevalence in patients with primary progressive MS. In their study, 16.6% of the primary progressive MS patients fulfilled diagnostic criteria for SS. According to the authors, whether a subset of patients with primary progressive MS had in fact SS-related CNS involvement or whether SS was associated with primary progressive MS remained undetermined. To our knowledge, CSF anti-SSA and anti-SSB autoAbs in MS have been the subject of only one study. Neither elevation of anti-extractable nuclear antigen autoAbs (a group of autoAbs that includes anti-SSA and anti-SSB) in the CSF nor specific intrathecal synthesis of these autoAbs was found in 22 MS patients [28].

Our findings suggest that CSF anti-SSA autoAbs might serve as a biomarker for SS-related CNS disease. However, several important questions remain unanswered. The prevalence of CSF anti-SSA or anti-SSB autoAbs in patients with other neurological diseases, notably MS, SLE and neuromyelitis optica, as well as in SS patients without CNS involvement, is unknown. Furthermore, a subset of SS patients with CNS manifestations does not have anti-SSA or anti-SSB autoAbs in the serum; whether these patients might have CSF-only autoAbs has not been studied. Answering these questions is necessary before using CSF anti-SSA and anti-SSB autoAbs in the diagnosis of SS-related CNS involvement.

Acknowledgment
We thank Prof. Theodor Landis for helpful discussions and comments on the manuscript.

References


