Cerebral large vessels vasculitis following Guillain-Barré syndrome as first clinical manifestations of primary Sjogren’s syndrome: a case report and review of the literature

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Case Report

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Abstract

Background:

Primary Sjogren’s syndrome (pSS) is an autoimmune exocrinopathy in which sicca syndrome of the exocrine glands represent the main clinical manifestation.

Severe extraglandular signs of pSS are determinant for the prognosis of this disease. Involvement of both peripheral and central nervous system (CNS) are known to be among the sites of high systemic activity in pSS.

Case presentation:

We, herein, report a case of a 57-year-old female patient with pSS presenting with typical Guillan-Barré syndrome (GBS), shortly followed by acute headaches accompanied by cortical blindness. Cerebral magnetic resonance imaging (MRI) demonstrated T2 signal abnormalities on the occipital region with narrowing and irregularities of the cerebral arteries, suggestive of CNS vasculitis.

Subtle sicca symptoms occurring prior to neurological symptoms by 8 months together with immunological disturbances (anti-SSA, anti-SSB antibodies positivity, type II cryoglobulins positivity, and C4 hypocomplementemia) allowed us to retain the diagnosis of pSS. Recovery of motor symptoms was possible under the combined use of immunoglobulins and corticotherapy during the initial phase. A three-years follow-up confirmed progressive motor recovery and disease stabilization under 6-months cyclophosphamide cycles relayed by azathioprine immunosuppressive therapy. However, severe residual visual loss persisted.

Conclusions:

Neurological complications can be inaugural in pSS and they lead to urgent investigations and treatment. Peripheral and central neurological manifestations can coexist. The approach should integrate careful clinical assessment, as well as radiological and immunological findings.

Background:

Sjogren’s Syndrome is an autoimmune exocrinopathy. Its main clinical presentation is sicca syndrome with dryness of the mouth and eyes. This syndrome can be primary (primary Sjogren’s syndrome (pSS)) or secondary if associated with other connective tissue diseases. Systemic signs during pSS may inaugurate the disease or they may appear after sicca symptomatology. It can be involved all systems, and it is estimated that up to 75% of patients exhibit extraglandular signs of variable severity (1).

Severe extraglandular manifestations of pSS are known to vary between 10 and 20% and they habitually occur late in the disease course (2). They are an important determinant for prognosis in pSS patients (3).
Involvement of peripheral nervous system (PNS) in pSS is well-established, and axonal sensoriomotor polyneuropathies are the most described manifestations (4). However, the type and prevalence of central nervous system (CNS) manifestations of pSS are still controversial (5, 6) including CNS vasculitis (6). The pathogenesis and the characteristics of CNS involvement in pSS are varied and poorly-understood (7). Both peripheral and CNS involvements have been reported among the sites of high systemic activity (8) in pSS patients with severe and life-threatening forms of the disease.

We, herein, report the case of a female patient presenting with typical Guillan-Barré syndrome (GBS), rapidly followed by bilateral cortical blindness related to CNS vasculitis. Careful anamnesis revealed that systemic symptoms shortly preceded neurological features. Based on the aforementioned findings and a detailed work-up, diagnosis of pSS was made.

**Case presentation**

A 57-year-old female patient with no significant past medical history, presented complaining of ascending weakness of four limbs, followed by speech and swallowing disorders for 15 days before admission. One week prior to admission, she reported symptoms of upper respiratory infection. On examination, facial diplegia, impaired swallowing reflexes, and paralytic dysarthria were noted. Motor examination revealed symmetric flaccid quadriplegia with diffuse areflexia. The plantar response was flexor. The patient was apyretic and eupneic. Cerebrospinal fluid (CSF) analysis revealed hyperproteinorachia (0.67 g/l), normal glycorachia (2.8 mmol/l) and normal cytological findings (2 cells/mm$^3$). A Nerve conduction study showed slowing of conduction velocity, and prolonged distal and F-wave latencies on the median and peroneal nerves bilaterally. Diagnosis of the acute inflammatory demyelinating form of GBS was retained. The patient was first treated with intravenous immunoglobulins (0.4 g/Kg weight) for 5 days. No improvement of the neurological symptoms was noted.

Twenty days after the onset of symptom, the patient developed sudden simultaneous headaches and bilateral blindness. On ophthalmic examination, visual acuity was limited to the perception of light bilaterally. The patient's pupil responses were normal with no afferent defect, which is consistent with a cortical origin of symptoms. Bilateral exposure keratitis was also identified. Careful anamnesis revealed that the patient exhibited mouth dryness and arthralgia of the large joints eight months before the current episode which was neglected by the patient. The idiopathic origin of GBS was therefore reconsidered.

Brain magnetic resonance imaging (MRI) demonstrated bilateral T2-weighted hyperintense signal lesions located in the cortical and subcortical regions of the temporal and occipital lobes (Fig. 1a,b). Some lesions showed restriction of diffusion, on the diffusion weighted sequences. Angiographic sequences revealed segmental narrowing and irregularities of the cerebral arteries, suggestive of CNS vasculitis (Fig. 1c).

Biological investigations revealed lymphopenia (count :0.9×10$^9$/l). The C-reactive protein level was 15 mg/l. Albuminemia was normal (40.52 g/l). No proteinuria was detected. Serological markers of infection
with hepatitis viruses B, and C, HIV were negative. The anti-nuclear antibody titer was 1/1600 and antibodies against DNA (deoxyribonucleic acid) were absent. The extractable nuclear panel was strongly positive for anti-SSA antibodies (RO-52, 60) and anti-SSB (La). Hypocomplementemia (of C4) was detected. Type II cryoglobulins were identified. Testing for anti-neuromyelitis optica antibodies was negative. The biopsy of the minor salivary glands (performed after initiating corticotherapy) did not reveal abnormalities. The Salivary gland scintigraphy revealed decreased function of the right parotid gland and the bilateral submandibular glands. Schirmer’s test was positive (< 5mm³ min in the two eyes). A restrictive spirometric defect was identified.

Based on the American College of Rheumatology /European League Against Rheumatism classification criteria for pSS(9). Both peripheral neuropathy (GBS) and CNS vasculitis (with both cerebral parenchymal and large-vessel involvement) were considered to be secondary to pSS in our patient.

Plasma exchange was initiated forty-five days after the first symptom. However, the patient presented breathing difficulties on the second day, forcing us to stop this treatment. Intravenous methylprednisolone (1 gr/day for 5 days) followed by oral corticosteroids (1mg/kg/day) were therefore initiated. A gradual improvement in muscle strength and swallowing difficulties was noted. A check-up brain MRI, performed 22 days after the onset of corticotherapy, demonstrated repermeabilization of the medium and posterior cerebral arteries, despite the persistence of some arterial stenosis especially in the posterior circulation.

Moreover, as a complication of the immunosuppressive therapy, the patient developed a corneal abscess caused by Pseudomonas germ, requiring specific antibiotic treatment and a rapid steroid tapering dose. A check-up ophthalmic examination revealed visual acuity limited to counting fingers in both eyes with bilateral corneal opacity vascularized on the left.

The patient was discharged two months after the first symptoms on a treatment dose of 20 mg of prednisolone. A monthly intravenous cyclophosphamide cycle regimen was then initiated and it was maintained for 6 months. Immunosuppressive therapy was continued with 20 mg oral daily doses of azathioprine. Physical rehabilitation was applied.

One year later, the patient had an important recovery of motor function. She was able to walk independently. Only a mild residual decrease in muscle strength of the four limbs was observed. Nevertheless, severe visual loss persisted. The one-year check-up MRI (not shown) demonstrated arterial repermeabilization and volume reduction of the brain parenchyma lesions. A check-up electromyography was carried showing improvement of the latency responses and the conduction velocity of the median and the peroneal nerves (Table 1).
Table 1
Motor Nerve Studies on check-up electromyography performed 1 year after hospital discharge (Abnormal results are shown in bold and the reference range in parentheses).

<table>
<thead>
<tr>
<th>Studied Nerves</th>
<th>Distal latency (ms)</th>
<th>Amplitude (mV)</th>
<th>Conduction Velocity (m/s)</th>
<th>F-waves Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Median</td>
<td>3.69 (&lt; 3.7)</td>
<td>9.1</td>
<td>51.3</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(&lt; 40)</td>
</tr>
<tr>
<td>Right Ulnar</td>
<td>3.67 (&lt; 3.2)</td>
<td>7</td>
<td>49.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(&gt; 40)</td>
</tr>
<tr>
<td>Right Tibial</td>
<td>5.08 (&lt; 5.5)</td>
<td>3.5</td>
<td>-</td>
<td>59.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(&lt; 40)</td>
</tr>
<tr>
<td>Left Tibial</td>
<td>5.42 (&lt; 5.5)</td>
<td>2.2</td>
<td>38.8</td>
<td>51.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(&lt; 40)</td>
</tr>
<tr>
<td>Right peroneal nerve</td>
<td>4.17 (&lt; 5)</td>
<td>1.72</td>
<td>32.9</td>
<td>58.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(&lt; 40)</td>
</tr>
</tbody>
</table>

Discussion and conclusions

We, herein, report the case of a female patient presenting with a typical GBS, rapidly followed by cerebral vasculitis manifested by bilateral cortical blindness. Mild systemic symptoms shortly preceded GBS. A detailed work-up allowed us to retain the diagnosis of pSS with severe neurological features as the main extraglandular manifestations. The clinical outcome was partially favorable. An important residual visual loss persisted.

pSS is a complex systemic autoimmune disease primarily affecting the salivary and lachrymal glands. However, in some cases, extraglandular severe manifestations including, neurological manifestations may occur (2). Peripheral or CNS features can also be observed. While the prevalence of PNS in pSS is estimated at about 20%, the frequency of CNS involvement is widely variable (5). The underlying pathophysiological mechanisms are also not fully understood (10–12).

The nervous system involvement in pSS can be associated with an unfavorable outcome (13). Indeed, in a large series of Spanish pSS patients (the GEAS-SS Registry) (8), both CNS and PNS were reported among the severe and potentially life-threatening systemic sites of the disease activity.

In pSS patients, distal axonal sensory and sensitivomotor polyneuropathy are the most common manifestations of PNS involvement (1). In a French prospective cohort (ASSESS cohort) including 392 pSS patients, PNS involvement was identified in 16.1% of the patients and only one patient, noticeably, presented a polyradiculoneuropathy (3).
Chronic polyradiculoneuropathy is rather reported when a demyelinating process is involved (14). However, the acute form of polyradiculoneuropathy presenting during pSS was rarely reported before (10, 12) and once reported, various forms of GBS were described.

When focusing on subclinical neuropathy associated with pSS, Gøransson et al. (15) showed, through nerve conduction studies and epidermal nerve fiber densities, the presence of subclinical demyelinating motor neuropathy in 27% of a cohort involving 62 patients with pSS.

GBS with underlying axonal mechanisms were also reported. Acute motor axonal neuropathy in the absence of sicca signs and positivity to SSa and GM1 gangliosides antibodies were described in a young patient (10). Mochizuki et al. (12) reported motor dominant axonal GBS form concomitant with cervical edematous myelitis as inaugural for both CNS and SNP manifestations of pSS with anti-SSA antibodies positivity. Tanaka et al. (11) reported a mixture of polyneuropathy as GBS and multiple mononeuropathy as inaugural neurological symptoms in a 57-year-old Japanese male patient. These findings were endorsed by electrophysiological studies (prolonged terminal latencies, decreased nerve conduction velocity, and decreased compound muscle action amplitude) and histopathological findings (segmental demyelination and axonal degeneration with variable severity in the teasing fiber analysis of sural nerve biopsy). The authors speculated that GBS is a trigger factor for multiple mononeuropathy in the included pSS patient and that a pre-existing pSS related neuropathy could explain the severity of the clinical and electrophysiological findings (11).

To explain the observed GBS in our patient based on the aforementioned data, it is possible to speculate that a subclinical neuropathy in a pSS patients could be a worsening factor of GBS in this specific population (11), which could explain the severity of PNS features in our report.

CNS manifestations, including acute onset of headaches and cortical blindness, following the initial typical GBS signs by 3 weeks and the detailed significant anamnestic data for sicca syndrome directed our investigations to condition associated to GBS in the present report.

In the ASSESS cohort, cerebral vasculitis was reported to be one aspect of CNS involvement in pSS. It manifested, among others, by headaches, optic neuritis, and multiple lesions on cerebral MRI (3). The reported visual disturbance of CNS manifestations in pSS was issued from different CNS lesions. Bilateral optic neuropathy as an initial symptom of pSS with significant improvement under cyclophosphamide was reported (16). Homonymous hemianopsia associated with sensory polyneuropathy was described in one of the 16 patients included in the original cohort reported by Alexander et al. (17), focusing on CNS manifestations of pSS along with the presumed role of anti-SSA antibodies. On the other hand, Jeong et al. (18) described posterior reversible encephalopathy syndrome in a young female patient with pSS with identified T2-weighted disturbances in the frontal and occipital lobes. The authors attributed the syndrome to severe generalized autonomic disturbances related to pSS. This diagnosis could be discussed in the present case given the cortical blindness, parenchymal occipital involvement, and narrowing of the cerebral arteries. However, rapid artery repermeability visualized on the
second cerebral MRI, performed only 3 weeks after the appearance of CNS symptoms, argued against posterior encephalopathy syndrome.

Large-vessel cerebral-related vasculitis is another particularity in the present case. This was indeed rarely reported (6). Headaches associated with convulsions are the main manifestations of vasculitis (6). Unnikrishnan et al. (19) proposed the detection of wall thickening using high-resolution MRI vessel technique as a non-invasive method to detect cerebral vasculitis involving large cerebral vessels in pSS.

The precise degree of CNS involvement in pSS is not fully outlined (20). The reported frequency ranges from 0.3 to 48% (5). In an Italian series involving 120 patients, headaches were the most common feature of CNS involvement, followed by cognitive and psychiatric disturbances. Focal CNS signs were less observed in their study (20).

Cognitive disturbance and multiple sclerosis-like symptoms, including optic neuritis, are among the most observed signs. Notably, lung involvement is more observed in CNS-pSS patients and it is the strongest risk factor for CNS involvement (21). This is consistent with the clinical findings in the present case.

The immunological disturbances observed in the present case were significant with low C4 serum levels, detection of anti-SSA and anti-SSB antibodies, and the presence of cryoglobulinemia type II.

Antibodies to SSA and SSB are associated with long disease duration, systemic manifestations (including vasculitis), and type II cryoglobulins (22). They play a pathogenic role in pSS through direct tissue damage. Among the earliest works are the studies from the 1980s conducted by Alexander et al. (17). Antibodies to SSA were detected in 7 from 8 pSS patients with CNS involvement, highlighting a possible specific pathogenesis role of these antibodies. In addition to antibodies to SSA and SSB, our patient also presented lymphopenia. This is in accordance with the early reported association of antibodies to SSA and SSB positivity with, among others, lymphopenia (23). Subsequently, in 1994, Alexander et al. (21) demonstrated a significant association between the presence of antibodies to SSA response and both the clinical CNS active pSS involvement disease and the radiological abnormalities, including T2 signal and/or cerebral angiograms abnormalities consistent with cerebral angiopathy (21). A high prevalence of anti-SSA and SSB antibodies in pSS patients with neurological involvement was subsequently confirmed. In the study of Delalande et al. (24), among pSS patients with neurological involvement, these antibodies were detected in 43% of the cohort during a mean follow-up of 10 years. Cryoglobulinemia was also detected in all patients with PNS involvement.

Concerning complement disturbances, in a large cohort involving 1115 pSS patients, Baldini et al. (2) demonstrated that the presence of low C4 levels and the presence of cryoglobulins are among the biological markers of the disease severity. Neurological complications are one aspect of this evolution. This serological profile reflects a status of chronic B cell activation in pSS patients with severe extraglandular manifestations (2). Also, in a large cohort of Spanish patients, hypocomplementemia was reported to be associated with higher frequency of vasculitis (25). More specifically, as observed in the present case, decreased C4 level was also reported by Massara et al. (5), demonstrating a direct and
independent correlation between decreased C4 levels and CNS involvement in pSS. Both the detection of activated terminal complement pathway and the evidence of intrathecal synthesis of IgG in cerebrospinal fluid are the arguments reinforcing the immunologically mediated mechanisms in pSS with CNS involvement.

The presence of both anti-Ro and anti-La in pSS have a prognostic value since they can alert to the possible association with systemic manifestations, including vasculitis and peripheral neuropathy (26).

**Conclusions**

The present case illustrates a rare but a life-threatening neurological complication of pSS. First, it emphasizes that acute polyradiculoneuropathy can be an initial manifestation of pSS and that a careful clinical and paraclinical evaluation should be performed to rule out any associated systemic condition. However, it was not possible to confirm a direct physiopathological link between GBS and the subsequent CNS involvement in the present case. Secondly, even with severe clinical presentation, associated CNS involvement can rapidly respond to an early immunosuppressive therapy. Thirdly, the present case highlights that clinicians must take into consideration the immunological disturbances associated with the neurological manifestations of pSS, which are thought to be involved in the pathogenic process of neurological involvement during pSS. This is helpful to plan the therapeutic approach and to improve estimates of prognosis for such serious condition.

**Abbreviations**

- GBS: Guillan-Barré Syndrome.
- CNS: central nervous system.
- CSF: Cerebrospinal fluid.
- MRI: magnetic resonance imaging
- pSS: primary Sjogren Syndrome.
- PNS: peripheral nervous system.

**Declarations**

*Ethics approval and consent to participate: not applicable*

*Consent Statement for publication:*

Written informed consent was obtained from the patient involved in this report.

*Availability of data and materials:*

The datasets analysed during this case report are available from the corresponding author (Dr Zakaria Saied).
**Competing interests:**

the authors declare no competing interests.

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  - writing—review and editing : Dr Ben Sassi Samia
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**References**


Figure 1

(a) Initial magnetic resonance (MRI) of the brain. The initial MRI scan showed hyperintense white matter lesions involving right occipital regions and left subcortical occipital, periventricular regions in the axial T2 Flair ponderation (Arrows).

(b) The initial MRI scan of the brain, axial T2 Flair ponderation showed hyperintense lesion involving the left parietal lobe (Arrow).

(c) The initial Angio-MRI 3D-TOF (time-of-flight) showed the narrowing of the M 1 and M 3 segments of the right middle cerebral artery and M 1 segment of the left middle cerebral artery (Arrows).