Acute encephalitis in primary Sjögren’s syndrome: A case report and literature review

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ABSTRACT

Acute encephalitis is an extremely rare condition in primary Sjögren’s syndrome (pSS), and its characteristics and prognosis remain unclear. Here, we report the case of pSS presented with acute encephalitis. She was admitted to our hospital for acute disturbance of consciousness. Acute encephalitis was diagnosed based on the results of the cerebrospinal fluid test (the increase of leukocyte counts, proteins, and interleukin-6 levels), magnetic resonance imaging, and single-photon emission computed tomography with 99mTc. The infectious aetiologies and underlying malignancies were excluded. Serum anti-Sjögren’s syndrome-related antigen A autoantibody was positive with extremely high titre. The biopsy specimen of her labial salivary gland revealed a focal lymphocytic sialadenitis with a score of grade 4 in the Greenspan grade. She also developed diffuse alveolar haemorrhage during the clinical course. She was diagnosed with pSS complicated with acute encephalitis followed by diffuse alveolar haemorrhage and successfully treated with pulse steroids, high dose of prednisolone and intravenous cyclophosphamide. Our present case and literature review suggest that acute encephalitis associated with pSS can be treatable with the immunosuppressive therapy, and thus early recognition and treatment initiation are important for this life-threatening condition. pSS should be included in the differential diagnosis of unexplained encephalitis. Notably, our case characteristically showed diffuse alveolar haemorrhage, adding new insights into the pathogenesis of acute encephalitis associated with pSS that capillaritis might be the underlying cause of this condition.

KEYWORDS: Acute encephalitis; Sjögren’s syndrome; interleukin-6

Introduction

Primary Sjögren’s syndrome (pSS) is a systemic autoimmune disease that affects lacrimal and salivary glands, resulting in a chronic sicca syndrome [1, 2]. This disease can also involve the extraglandular organs including the central nervous system (CNS) [3–5]. CNS involvement is uncommon in pSS, estimated to be present in 2–5% of the patients [6]. Various types of CNS involvements have been reported in pSS, such as multiple sclerosis–like disorders, neuromyelitis optica spectrum disorders, transverse myelitis, cerebral vasculitis, and aseptic lymphocytic meningitis [6]. So far, there have been only few reports on acute encephalitis associated with pSS, and therefore, their characteristics and prognosis are largely unknown. Here, we present our case of acute encephalitis associated with pSS and reviewed published literature to increase our understanding of this rare but life-threatening condition.

Search strategy

We conducted a literature review on PubMed database using keywords ‘Sjögren’s syndrome’ and ‘encephalitis’ OR ‘meningoencephalitis’ from inception dates until 29 July 2021, according to the search strategy recommended for writing a narrative review [7]. The flow chart of our literature search is shown as Figure 1. We reviewed 72 articles, and a total of 14 articles were included in the analysis [8–21] and summarised in Table 1.

Case report

A 33-year-old Asian female with a past history of dry mouth presented to our hospital for fever, headache, and vomiting. Four days ago, she felt the pain in her right posterior neck, and the antibiotic treatment with amoxicillin 1 g/day was ineffective for her symptom. Two days ago, she had a headache, followed by fever and vomiting. On admission, her consciousness level was normal assessed as E4V5M6 using the Glasgow Coma Scale score. Her body temperature was 38.3°C, blood pressure was 102/68 mmHg, heart rate was 120/min, oxygen saturation of peripheral artery (SpO₂) was 98% (room air), and respiration rate was 12/min. Physical examination found a tender, soft lymph node swelling (~10 mm in diameter) on her right posterior neck. Neck stiffness, Kernig’s sign, and Brudzinski’s sign were absent. There were no oral ulcers, skin rash, alopecia, and arthritis. Laboratory tests revealed leukopenia (2300/μl, normal range 3300–8600/μl), lymphopenia (483/μl, normal range 1190–2975/μl), thrombocytopenia (90,000/μl, normal range 158,000–348,000/μl), and an elevated
<table>
<thead>
<tr>
<th>No.</th>
<th>Authors</th>
<th>Sex, age (years)</th>
<th>Encephalitis prior to pSS diagnosis</th>
<th>Neurologic symptoms</th>
<th>Other extraglandular involvements</th>
<th>Serum autoantibody</th>
<th>CSF</th>
<th>MRI</th>
<th>Findings</th>
<th>Location</th>
<th>Treatment</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>1</td>
<td>Devos et al. [8]</td>
<td>Male, 52</td>
<td>Yes</td>
<td>Disturbance of consciousness, ataxia</td>
<td>No</td>
<td>None</td>
<td>Anti-SSA</td>
<td>63 cells/µl</td>
<td>93</td>
<td>ND</td>
<td>High signal intensity on T2 and FLAIR</td>
<td>Right thalamus and left cerebellum</td>
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<tr>
<td>2</td>
<td>Ide et al. [9]</td>
<td>Female, 35</td>
<td>Yes</td>
<td>Disturbance of consciousness, short-term memory loss</td>
<td>No</td>
<td>None</td>
<td>Anti-SSA, anti-SSB</td>
<td>2 cells/µl</td>
<td>50</td>
<td>ND</td>
<td>High signal intensity on T2 and FLAIR</td>
<td>Bilateral medial temporal lobes</td>
</tr>
<tr>
<td>3</td>
<td>Ide et al. [9]</td>
<td>Male, 33</td>
<td>No</td>
<td>Disturbance of consciousness, seizure</td>
<td>Yes</td>
<td>Pleuritis, interstitial lung disease, circular erythema</td>
<td>Anti-SSA, anti-SSB</td>
<td>620 cells/µl</td>
<td>136</td>
<td>ND</td>
<td>High signal intensity on T2 and FLAIR</td>
<td>Bilateral medial temporal lobes</td>
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<tr>
<td>4</td>
<td>Hirohata et al. [10]</td>
<td>Female, 50</td>
<td>Yes</td>
<td>Coma, forgetfulness</td>
<td>Yes</td>
<td>None</td>
<td>Anti-SSA, anti-SSB</td>
<td>ND</td>
<td>56</td>
<td>ND</td>
<td>High signal intensity on T2 and FLAIR</td>
<td>Cortical and subcortical white matter, including the right occipital cortex and left insular cortices</td>
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<tr>
<td>5</td>
<td>Mouta-ouakil et al. [11]</td>
<td>Female, 25</td>
<td>Yes</td>
<td>Confusion, cerebellar involvement, and spastic tetra paresis</td>
<td>Yes</td>
<td>None</td>
<td>Anti-SSB</td>
<td>162 cells/µl</td>
<td>300</td>
<td>ND</td>
<td>High signal intensity on T2</td>
<td>Around lateral ventricle</td>
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<tr>
<td>6</td>
<td>Collison et al. [12]</td>
<td>Female, 56</td>
<td>Yes</td>
<td>Dysequilibrium, nausea, confusion, short-term memory loss</td>
<td>No</td>
<td>None</td>
<td>Anti-SSA, anti-SSB</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>High signal intensity on FLAIR</td>
<td>Right medial temporal lobe</td>
</tr>
<tr>
<td>7</td>
<td>Hoshina et al. [13]</td>
<td>Female, 50</td>
<td>No</td>
<td>Disturbance of consciousness, headache, nausea</td>
<td>Yes</td>
<td>None</td>
<td>Anti-SSA, anti-SSB</td>
<td>14 cells/µl</td>
<td>55</td>
<td>100 pg/ml</td>
<td>High signal intensity on T2</td>
<td>Posterior horn of lateral ventricle</td>
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<tr>
<th>No.</th>
<th>Authors</th>
<th>Sex, age (years)</th>
<th>Encephalitis prior to pSS diagnosis</th>
<th>Neurologic symptoms</th>
<th>Other extraglandular involvements</th>
<th>Serum autoantibody</th>
<th>CSF</th>
<th>MRI</th>
<th>Treatment</th>
<th>Outcome</th>
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<tr>
<td>8</td>
<td>Chen et al. [14]</td>
<td>Female, 44</td>
<td>Yes</td>
<td>Dizziness, dysphagia, nausea, vomiting</td>
<td>Yes</td>
<td>None</td>
<td>Anti-SSA, anti-SSB</td>
<td>Normal</td>
<td>43</td>
<td>ND</td>
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<tr>
<td>9</td>
<td>Sharma et al. [15]</td>
<td>Male, 64</td>
<td>Yes</td>
<td>Gait disturbance, dizziness, nausea, vomiting</td>
<td>No</td>
<td>None</td>
<td>Anti-SSA, anti-SSB</td>
<td>24 cells/µl</td>
<td>78</td>
<td>ND</td>
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<tr>
<td>10</td>
<td>Matsui et al. [16]</td>
<td>Female, 9</td>
<td>Yes</td>
<td>Confusion, lethargy, difficulty with ambulation</td>
<td>Yes</td>
<td>None</td>
<td>Anti-SSA</td>
<td>48 cells/µl</td>
<td>76</td>
<td>ND</td>
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<tr>
<td>11</td>
<td>Çoban et al. [17]</td>
<td>Female, 47</td>
<td>Yes</td>
<td>Agitation, aggression, paranoid delusions, short-term memory loss</td>
<td>Yes</td>
<td>None</td>
<td>Anti-SSA, anti-SSB</td>
<td>22 cells/µl</td>
<td>Normal</td>
<td>ND</td>
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<tr>
<td>12</td>
<td>Çoban et al. [17]</td>
<td>Female, 60</td>
<td>No</td>
<td>Apathy, disorientation, confusion, agitation, difficulty walking, vomiting, seizure</td>
<td>Yes</td>
<td>None</td>
<td>Anti-SSA, anti-SSB</td>
<td>No cells</td>
<td>Normal</td>
<td>ND</td>
</tr>
<tr>
<td>13</td>
<td>Çoban et al. [17]</td>
<td>Female, 26</td>
<td>No</td>
<td>Confusion, memory loss, visual hallucinations</td>
<td>Yes</td>
<td>None</td>
<td>Anti-SSA, anti-SSB</td>
<td>22 cells/µl</td>
<td>Normal</td>
<td>ND</td>
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(continued)
Table 1. (Continued)

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<th>No.</th>
<th>Authors</th>
<th>Sex, age (years)</th>
<th>Encephalitis prior to pSS diagnosis</th>
<th>Neurologic symptoms</th>
<th>Dry eye or dry mouth</th>
<th>Other extraglandular involvements</th>
<th>Serum autoantibody</th>
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<th>MRI</th>
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<td>14</td>
<td>Shinmura et al. [18]</td>
<td>Female, 52</td>
<td>No</td>
<td>Disturbance of consciousness</td>
<td>Yes</td>
<td>Pleuritis, pericarditis</td>
<td>Anti-SSA</td>
<td>2 cells/μl</td>
<td>39</td>
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<tr>
<td>15</td>
<td>Yoshimura et al. [19]</td>
<td>Female, 25</td>
<td>Yes</td>
<td>Disturbance of consciousness, short-term memory loss, seizure</td>
<td>No</td>
<td>None</td>
<td>Anti-SSA</td>
<td>15 cells/μl</td>
<td>41</td>
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<tr>
<td>16</td>
<td>Mittal et al. [20]</td>
<td>Female, 30</td>
<td>Yes</td>
<td>Altered mental status</td>
<td>No</td>
<td>Tubulointerstitial nephritis</td>
<td>Anti-SSA</td>
<td>1 cells/μl</td>
<td>68</td>
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<td>17</td>
<td>Verma R et al. [21]</td>
<td>Male, 42</td>
<td>Yes</td>
<td>Cognitive decline</td>
<td>No</td>
<td>None</td>
<td>Anti-SSA</td>
<td>10 cells/μl</td>
<td>63</td>
</tr>
<tr>
<td>18</td>
<td>Our case</td>
<td>Female, 33</td>
<td>Yes</td>
<td>Disturbance of consciousness, faecal incontinence</td>
<td>Yes</td>
<td>Alveolar haemorrhage</td>
<td>Anti-SSA</td>
<td>12 cells/μl</td>
<td>359</td>
</tr>
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</table>

Abbreviations: pSS, primary Sjögren’s syndrome; CSF, cerebral spinal fluid; MRI, magnetic resonance imaging; ND, not determined; PSL, prednisolone; IVIg, intravenous immunoglobulin; IVCY, intravenous cyclophosphamide.
Papers from literature search
(n=72)

Duplicates
(n=3)

Remaining papers screened
(n=69)

Unrelated topic (n=55)

Papers included
(n=14)

Figure 1. Flow chart of our literature search.

level of serum C-reactive protein (11.09 mg/dl, normal range ≤0.14 mg/dl). The titre of anti-nuclear antibody (ANA) was 1:40 (homogenous and speckled patterns). Serum anti-Sjögren’s-syndrome-related antigen A (anti-SSA) antibody was positive with extremely high titre (3840 U/ml, normal range <10.0 U/ml), whereas anti-Sjögren’s syndrome-related antigen B (anti-SSB), anti-double-stranded DNA, anti-Smith, anti-ribosomal P, anti-ribonucleoprotein, anti-β2-glycoprotein I, anti-cardiolipin, and anti-neutrophil cytoplasmic antibodies were all negative. Lupus anticoagulant and Coombs tests were negative. Serum immunoglobulin (Ig)G level was within normal range (1477 mg/dl, normal range 861–1747 mg/dl), and cryoglobuline was negative. Serum complement levels were as follows: C3, 124 mg/dl (normal range 73–138 mg/dl), C4 48 mg/dl (normal range 11–31 mg/dl), and CH50 71.3 mg/dl (normal range 31.6–57.6 mg/dl). A urinalysis showed a pH of 7.0 with no proteinuria, occult blood, white blood cells, or casts. Serum complement levels were as follows: C3, 124 mg/dl (normal range 73–138 mg/dl), C4 48 mg/dl (normal range 11–31 mg/dl), and CH50 71.3 mg/dl (normal range 31.6–57.6 mg/dl). A urinalysis showed a pH of 7.0 with no proteinuria, occult blood, white blood cells, or casts.

Soon after admission, her consciousness level became worsened, which was assessed as E4V1M3, and faecal incontinence was observed. Cerebrospinal fluid test showed the slightly increased leucocytes (12/µl with 92% of mononuclear cells) and markedly elevated levels of protein (359 mg/dl), IgG (78.8 mg/dl), and interleukin-6 (IL-6; 229 pg/ml). The IgG index of the cerebrospinal fluid was not measured. Cerebrospinal fluid glucose level was not decreased. Cerebrospinal fluid test showed the negative results, whereas anti-SSA antibody in cerebrospinal fluid was positive (166 U/ml).

As the aetiology of her acute encephalitis, we suspected pSS and performed the biopsy of her labial salivary glands, which demonstrated a focal lymphocytic sialadenitis with a score of grade 4 in Greenspan grade (Figure 3). We diagnosed her with pSS based on the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria [22]. During her clinical course, she also suffered from acute respiratory failure due to the diffuse alveolar haemorrhage (Figure 4(a–c)). The patient’s heart at the timing of alveolar haemorrhage seemed to be enlarged because it was taken in a recumbent position with a portable X-ray. The findings suggestive for pulmonary arterial hypertension were not found; chest CT did not show enlarged diameter of the main trunk of the pulmonary arteries (19.95 mm, <29 mm), and electrocardiogram showed no findings of right heart load such as right bundle branch block or right axis mutation. She was treated with pulse steroids followed by high dose of prednisolone (60 mg/day) and intravenous cyclophosphamide (1 g/body). Her fever, impaired consciousness, and respiratory failure all improved (Figure 4(d)). The counts of blood lymphocytes and platelets and serum C-reactive protein level all turned to be normal. She had dry mouth, and gum test showed 10 ml in 10 minutes, suggesting the decrease of her saliva production. Four months later, follow-up examination for head MRI and SPECT confirmed the improvements of the lesions (Figure 2(c, d)). Prednisolone dose was gradually tapered to 10 mg/day, and the disease recurrence was not observed at the timing of writing this manuscript (6 months after treatment).

Results

The characteristics of the 18 cases of acute encephalitis associated with pSS including our present case are shown in Table 1. The mean age was 40.7 years (range 9–64 years), and 14 of the 18 cases (78%) were female. In most of the cases (13/18, 72%), the presentation of acute encephalitis preceded the diagnosis of pSS. The neurological symptoms were varied such as disturbance of consciousness, confusion, cognitive decline, lethargic, seizure, and focal neurological deficits. Four cases had the other extraglandular involvements (alveolar haemorrhage, pleuritis, pericarditis, interstitial lung disease, circular erythema, and tubulointerstitial nephritis) except for acute encephalitis. All cases except for one case had positive anti-SSA antibody. Eleven of the 18 cases (61%) had positive anti-SSB antibody. Cerebrospinal fluid test was examined in 17 cases; 11 cases (65%) showed mild pleocytosis. In addition, protein level in cerebrospinal fluid was elevated in 14 cases (82%). IL-6 level in cerebrospinal fluid was investigated in three cases, which demonstrated marked elevation. All cases demonstrated high signal intensity on head MRI images.
All cases were treated with the immunosuppressive therapies such as pulse steroids, high dose of prednisolone, intravenous cyclophosphamide, and intravenous immunoglobulins. Neurological symptoms were improved in all cases.

**Discussion**

We presented our case of acute encephalitis associated with pSS, which was successfully treated with the intensive immunosuppressive therapy. Our present case and literature review suggest that acute encephalitis associated with pSS can be treatable with the immunosuppressive therapy. Although acute encephalitis is extremely rare in pSS, we should include
pSS as one of the differential diagnoses of unexplained encephalitis because this condition is life-threatening if the diagnosis and treatment initiation are delayed. Importantly, acute encephalitis can be the initial manifestation of pSS in most cases; therefore, high index of suspicion for pSS is required, and the testing for serum anti-SSA and/or anti-SSB antibodies might be helpful as the initial screening.

Anti-SSA antibody could be pathogenic in the certain organ involvements because this autoantibody is known for its pathogenicity in the fields of neonatal congenital heart block as well as cutaneous lupus erythematosus [23, 24]. The pathogenic role of anti-SSA antibody for autoimmune encephalitis remains unknown. In our present case, cerebrospinal fluid anti-SSA antibody might be detected just as the result of damaged blood–brain barrier. In fact, the cerebrospinal fluid anti-SSA/serum anti-SSA ratio (4.3%: 166/3840) was similar to the cerebrospinal fluid IgG/serum IgG ratio (5.3%: 78.8/1477), suggesting that local production of anti-SSA antibody in the brain is unlikely. Alternatively, the perivascular inflammation and/or capillaritis might be involved in the pathogenesis of acute encephalitis of pSS. The biopsy specimens of the brain from pSS patients with CNS involvements have shown the perivascular inflammation and/or capillaritis with leucocytes into the surrounding brain parenchyma [25–27]. Our present case showed the leucocyte infiltration in the cerebrospinal fluid. Notably, our case also had the diffuse alveolar haemorrhage during the clinical course, which is generally thought to be caused by capillaritis or cryoglobulinemia in pSS [28–30]. In our present case, no cryoglobulin was detected, indicating that capillaritis is more likely to be implicated in the pathogenesis of diffuse alveolar haemorrhage. Thus, capillaritis might be the possible common mechanism contributing to the acute encephalitis and diffuse alveolar haemorrhage in our case.

Elevation of IL-6 levels in cerebrospinal fluid was reported in the autoimmunity-mediated CNS damage such as neuropsychiatric systemic lupus erythematosus (SLE), neuromyelitis optica spectrum disorder, and neuro-Behcet’s disease [31–34]. Our present case showed the markedly elevated level of IL-6 in cerebrospinal fluid. The other case report of acute encephalitis of pSS also demonstrated the usefulness of IL-6 in cerebrospinal fluid as a biomarker of disease activity assessing the serial changes [13]. Importantly, IL-6 blockade therapy was reported to be effective in patients with neuromyelitis optica spectrum disorder and neuro-Behcet’s disease [33, 35]. Thus, the IL-6 level in cerebrospinal fluid might be a biomarker of disease activity of acute encephalitis associated with pSS and one of the potential therapeutic targets.

In patients with neuropsychiatric SLE, it has been reported that MRI and SPECT are the most useful neuroimaging modalities due to their complementary nature of the information [36]. MRI is the first choice imaging modality for the diagnosis of neuropsychiatric SLE because this is useful to exclude the differential diagnoses such as cerebral infarctions, haemorrhages, brain abscesses, infectious meningitis, and mycotic aneurysms [36]. MRI is also useful to detect the focal lesion of the affected brain such as limbic encephalitis [37]. On the other hand, the sensitivity of MRI is lower (50%) than that of SPECT (75%) for detecting the diffuse damage of the brain [38]. Our present case suggest that both MRI and SPECT can be the useful modalities to investigate acute encephalitis associated with pSS, and particularly, SPECT is sensitive to reveal the diffuse damage of the brain.

Both acute encephalitis and diffuse alveolar haemorrhage can be the clinical features of SLE, whereas those features are rare in pSS. Although our present case did not satisfy the SLE classification criteria (2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria and 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria), ANA-negative SLE with secondary Sjögren’s syndrome was the important differential diagnosis [39]. Of note, the prozone effect can occur in cases of high antibody concentrations, resulting in the negative ANA [39, 40]. Therefore, when we face with a negative ANA testing in the cases with suspected SLE, it might be helpful to consider the possibility of prozone effect and repeat ANA testing using different kits and laboratories.

In conclusion, acute encephalitis in patients with pSS is rare but can be treatable with immunosuppressive therapy, and therefore, physicians need to be aware of this rare life-threatening involvement in patients with pSS for the prompt diagnosis and treatment. Capillaritis might be the underlying pathogenesis of acute encephalitis associated with pSS.

Acknowledgements
We appreciate Dr Makoto Yoneeda from Fukui Prefectural University for measuring anti-NAE antibody.

Conflict of interest
All authors have no conflict of interest related to this case report.

Funding
None declared.

Patient consent
Written informed consent for publication of this report was obtained from the patient.

Ethical approval
Not applicable.

References


