CASE REPORT

Cerebellar degeneration in primary Sjögren syndrome

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SUMMARY

Neurological manifestations are reported as a consequence of primary Sjögren syndrome (PSS). Any part of the brain and peripheral nervous system can be involved in PSS. However, cerebellar degeneration and atrophy associated with PSS have been rarely reported. Our report describes a 22-year-old woman who presented with cerebellar ataxia, arthritis and arthralgia. Evaluation of her symptoms, autoantibodies and salivary gland pathology was in favour of the diagnosis of Sjögren syndrome. Also, her brain MRI revealed cerebellar degeneration. There are only four patients reported to be affected by cerebellar atrophy associated with PSS. Administration of high doses of methylprednisolone and cyclophosphamide leads to substantial improvement in the cerebellar symptoms of this case. In addition, after 2 months of follow-up, the patient's ataxia recovered significantly. It could be concluded that in addition to neurological degenerative disorders, in some cases cerebellar atrophy could also be associated with autoimmune conditions such as PSS.

BACKGROUND

Sjögren syndrome (SS) is a chronic autoimmune inflammatory disorder characterised by diminished lacrimal and salivary gland secretion and associated with mononuclear cell infiltration in the exocrine glands. The usual presentation for SS is xerophthalmia and xerostomia.^{1–4} Studies have shown that women are more affected by this disease (female to male ratio of about 9:1).^{5–7} The overall incidence of SS is estimated at 7 per 100 000 people.⁸

SS may occur as a primary condition or in association with other rheumatic disorders (secondary). The most common diseases associated with secondary SS are rheumatoid arthritis and systemic lupus erythematosus (SLE), respectively. About 35% of patients with primary Sjögren syndrome (PSS) suffer from systemic manifestations⁹; nevertheless, the prevalence of neurological manifestations of PSS remains controversial.^{10–12}

Both the peripheral nervous system (PNS) and the central nervous system (CNS) are involved in PSS. While PNS involvement is more common, several studies have reported a variable prevalence of CNS manifestations ranging from 2.5% to 60% in patients with PSS.^{1 10–12} In addition, ataxia due to PSS has also been reported in these patients,^{10 13–15} although marked cerebellar atrophy associated with PSS is rarely reported. In this report, we describe a patient with PSS who presented with ataxia and cerebellar degeneration.

CASE PRESENTATION

A 22-year-old woman was admitted to the neurological clinic with gait disturbance 11 months before admission. She had no familial history of gait disturbance, no familial history of neurological disorders and no exposure to toxins and drugs. Her neurological examination had revealed gait disturbance. She was unable to walk without assistance, due to cerebellar ataxia. The patient also has had dysmetria, dysarthria and mild intention tremor of the four limbs, especially her hands.

Motor forces and sensory examinations were normal. Her deep tendon reflexes were normoactive, and her plantar responses were flexor bilaterally. She had no nystagmus and no cognitive impairment. General examinations were otherwise normal and lab tests revealed no impairment. Brain MRI showed no abnormality and she had received no treatment at that time. However, she was advised for regular follow-up.

She was admitted to our rheumatology clinic due to arthralgia and progressive gait disturbance. The patient mentioned that 9 months before admission, she developed arthritis in both wrists and ankles, with spontaneous recovery after several weeks only using non-prescribed non-steroidal anti-inflammatory drugs. She described the development of progressive gait worsening after that period. She also mentioned a history of dryness of both eyes and mouth since 5 months ago.

INVESTIGATIONS

Our neurological findings were positive for cerebellar ataxia, intentional tremor and dysmetria. She also had abnormal finger to finger test, tandem gait and also gait ataxia.

At the time of admission, her lab tests were positive for Anti-Sjögren's-syndrome-related antigen A (anti-Ro-SSA) antibodies, having a significant value of 183 U/mL, with the normal range being <15 U/mL. Antinuclear antibodies were positive (1/80) and the speckled pattern was detected on immunofluorescence evaluation. In addition, Rheumatoid factor (RF) was positive (1/320). On the other hand, the test for antidouble-stranded DNA antibodies was negative.

Her erythrocyte sedimentation rate was 27 (normal range <15). Complete blood count, creatinine, serum electrolytes, blood glucose, coagulation tests, liver function tests, lactic dehydrogenase, serum protein electrophoresis, lipid levels, thyroid function test, vitamin E level, ACE level, Creatine Phosphokinase (CPK), serum folate and complement values were all normal.

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Figure 1 Brain MRI coronal view: Although initial brain MRI was unremarkable, follow-up brain MRI performed 11 months after the first presentation revealed cerebellar atrophy with no evidence of space-occupying lesion.

Coeliac evaluations were performed, and IgA and IgG anti-tissue transglutaminase antibody and IgA endomysial antibody were all negative. Also, assays for ss-B (anti-La), antiphospholipids (cardiolipin and β_2 glycoprotein), anti-cyclic citrullinated peptide (anti-CCP), anti-HIV antibody, Hepatitis B surface antigen (Hbs antigen), Hepatitis C virus (HCV) antibody and antiOglutamic acid decarboxylase (anti-GAD) were all negative.

Brain MRI showed cerebellar atrophy especially in the left hemisphere, presenting as decreased folia thickness and increased gyri width (figures 1 and 2). Cervical and spinal MRI was normal. Electromyography (EMG) Nerve Conduction Velocity (NCV) of the four limbs showed axonal predominant sensory polyneuropathy.

Biopsy of the salivary glands was performed and revealed lymphocytic infiltration and chronic inflammation with a focus score equal to 8 (figure 3). The result of Schirmer's test was positive as the patient had moderately dry eyes.

Considering all these findings the patient was diagnosed with PSS according to the American-European Consensus Group criteria.¹⁶ The patient was treated with intravenous methylprednisolone (1 g/day), administered for 5 days. She also received 1 g of cyclophosphamide.

DIFFERENTIAL DIAGNOSIS

Cerebellar ataxia represents a very rare and severe complication of PSS. It also represents a diagnostic challenge to the clinicians especially when classic glandular symptoms do not exist. Differentiation between diagnosis of PSS with CNS involvement and classical multiple sclerosis may be sometimes difficult. Auto-immune ganglionopathy, coeliac disease, SLE and neuro-Behçet's are disorders that must be considered as other important differentials.

Figure 2 Brain MRI sagittal view: Similar to the coronal view, the sagittal view revealed cerebellar atrophy with no evidence of space-occupying lesion.

Figure 3 Histopathological assessment of salivary gland revealed lymphocytic infiltration and chronic inflammation (magnification $\times 100$).

Ganglionopathy is characterised by paresthesia, ataxia, difficulty with fine motor movements due to impaired proprioception, reduced vibration sense, reduced or absent reflexes, and the presence of Romberg sign. Autonomic dysfunction may also be found in this disease.^{17 18} MRI has been used as a sensitive diagnostic technique in this impairment especially in patients with long disease duration. Hyperintense T2-weighted lesion at the posterior columns and volumetric reduction in the cervical area resulting from dorsal root degeneration of their projections in the gracile and cuneate fasciculi are well-known MRI findings of this disease.¹⁹

Several reports have described an association between coeliac disease and neurological or psychiatric symptoms such as headache, peripheral neuropathy, ataxia, depression, dysthymia, anxiety and epilepsy.^{20 21} Also, coeliac disease may initially present as a neurological disorder.

TREATMENT

The patient was treated with intravenous methylprednisolone (1 g/day), administered for 5 days. She also received intravenous 1 g of cyclophosphamide.

OUTCOME AND FOLLOW-UP

In contrast to the previous studies,^{22 23} our patient's ataxia improved significantly after treatment with five doses of 1 g methylprednisolone and 1 g cyclophosphamide. Her follow-up showed that she could walk without assistance after about 8 weeks of treatment.

We did not use rituximab for the treatment as its efficacy has not been proven to date.²⁴ However, there is no consensus on a specific therapy for the management of SS with CNS involvement. Hence, more studies are needed to identify the best treatment for cerebellar degeneration in PSS.

DISCUSSION

This report shows that cerebellar degeneration and ataxia could be seen in PSS. As we know, this is the fifth patient with PSS who presented with cerebellar degeneration and ataxia.

This presentation could be really challenging for clinicians. At first, we evaluated the common causes of primary cerebellar degeneration in our patient, including alcohol, drug abuse, nutritional deficiency and also HIV infection, all of which were negative.²⁵ After negative screening results of all possible aetiologies

such as coeliac disease, and according to her symptoms, her antibodies and salivary gland biopsy, we assumed that her cerebellar degeneration was strongly related to PSS.

Our patient had both PNS and CNS involvement (sensory neuropathy and cerebellar ataxia). She had arthralgia and arthritis as well. Studies have shown that the prevalence of neurological manifestations of PSS varies from 10% to 60%. Several neuropathic manifestations have been described in patients with PSS. Especially, sensory or pure sensory neuropathies are the most common (about 50%–60%).^{1 26–28} The CNS is less commonly affected than the PNS in PSS.

Despite the wide prevalence of PNS involvement, a highly variable prevalence of CNS manifestations ranging from 2.5% to 60% of all patients with PSS had been reported.^{5 6 29} In one study, the most frequent presentation of CNS involvement was a recurrent subacute encephalopathy characterised by memory loss, cognitive dysfunction, visual disturbances and dizziness,¹⁵ and in another study seizure and cerebral vasculitis were reported as the most common.³⁰ Pure sensory neuropathy is reported to be the most common presentation of PNS involvement in these patients.^{1 26 27}

The results of the biopsy showed a focus score of 8 in our case. It has been shown that higher focus scores (focus score ≥ 1) might be associated with the more severe presentation of the disease and potential extraglandular involvement.³¹ Although none of the previous studies have mentioned the focus score of PSS associated with cerebellar degeneration and ataxia, further studies on several similar cases are necessary to determine if there is an association between focus scores and the neurological manifestations.

The first description of the cerebellar syndrome in association with PSS was defined by Attwood and Poser in 1961.³² Primary cerebellar degeneration is rarely associated with PSS. To our knowledge, only four cases of PSS causing cerebellar atrophy have been reported.^{15 33 34} The pathophysiology of CNS involvement in PSS is still unclear. Some studies have recommended that antibodies and ischaemia may play a significant role, resulting in microinfarcts or macroinfarcts.^{12 35}

The patient in the current study has had arthralgia and intermittent, self-limited arthritis of both wrists showing no deformity or erosion on plain radiography. According to research, approximately half of the patients with PSS experience arthralgia with or without arthritis.³⁶ Arthropathy is usually symmetric, intermittent, non-erosive and most commonly affects the hands, wrist and knees.³⁷ As this patient, RF is positive in about 40% of PSS cases and is more common in patients who have articular symptoms.³⁸ On gait examination, the patient was unable to walk without assistance, and she had ataxia. Her ataxia was progressive and began 11 months ago, and the cerebellar test was positive. Also, there was cerebellar degeneration on her MRI. Finally, it could be concluded that any part of the brain may be involved

in PSS, which includes ataxia due to cerebellar degeneration, as a very rare presentation of this disease.

Contributors MH contributed to taking the clinical history and examination of the patient while helping SA in the management and treatment of the patient. KA contributed to writing and final editing and submission of the manuscript. Also, both SA and MH contributed to the writing of the manuscript and its submission.

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Learning points

- Rheumatological diseases could be considered as a cause of neurological symptoms.
- Assessment of autoantibodies can help in differentiating rheumatological diseases from neurological disorders.
- Cerebellar degeneration due to Sjögren syndrome could be responsive to glucocorticoid and immunosuppressive therapy.
- Coeliac and Sjögren ganglionopathy must be considered as a potential cause of cerebellar ataxia.

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