Sjogren's Syndrome with Acute Cerebellar Ataxia and Massive Lymphadenopathy : a Case Report

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Abstract-

Purpose: Common etiologies of acute acquired cerebellar ataxia include cerebrovascular diseases, toxin or drugs, infections/para-infections, and autoimmune diseases. It is a rare manifestation of Sjögren's syndrome, which is a common autoimmune disease but is often missed as a differential diagnosis.

Case Report: This is a report of a patient with acute onset cerebellar ataxia for one month. She also had massive neck lymphadenopathy. After a series of studies and the exclusion of other common causes of acute cerebellar ataxia, she was diagnosed as having Sjögren's syndrome. Patients with Sjögren's syndrome have higher risk for lymphoma, which leads to poorer prognosis. After lymph node biopsy, the patient was proven to have sinus histiocytosis, which is another rare finding in Sjögren's syndrome.

Discussion: For patients with acute acquired cerebellar ataxia, immune-mediated cerebellar ataxia should be an important differential diagnosis aside from the more common causes like stroke or drugs.

Key Words: cerebellar ataxia, Sjögren's syndrome, sinus histiocytosis

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INTRODUCTION

Common etiologies of acute acquired cerebellar ataxia include cerebrovascular diseases (i.e., infarction or hemorrhage), toxin or drugs, immune-mediated diseases, and infectious/para-infectious diseases (e.g., abscess or cerebellitis). Herein is a case that presented as acute cerebellar ataxia and massive neck lymphadenopathy.

CASE REPORT

A 44-year-old female was admitted to the Neurology Ward for acute onset dizziness and unsteady gait for one month. Three weeks prior to admission, she consulted at the emergency department for dizziness, vertigo, and unsteady gait. Brain computed tomography (CT) was unremarkable but she was referred to the Neurology Clinic after some medical treatment. Initial neurologic exam demonstrated unilateral, horizontal nystagmus towards the left during left lateral gazing. There was an unsteady gait but without motor weakness or bulbar sign. Brain magnetic resonance imaging (MRI) showed no lesion in the cerebellum or brainstem (Fig. 1) although there were several ill-defined hypointensities on T-1 weighted imaging and iso-intensity on

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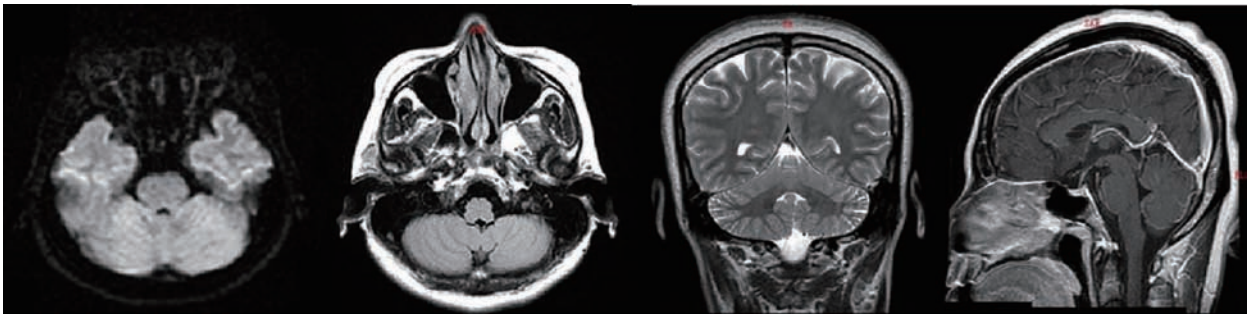

Figure 1. There was no abnormal signal intensity or enhancing lesion in the brainstem and bilateral cerebellar hemispheres.

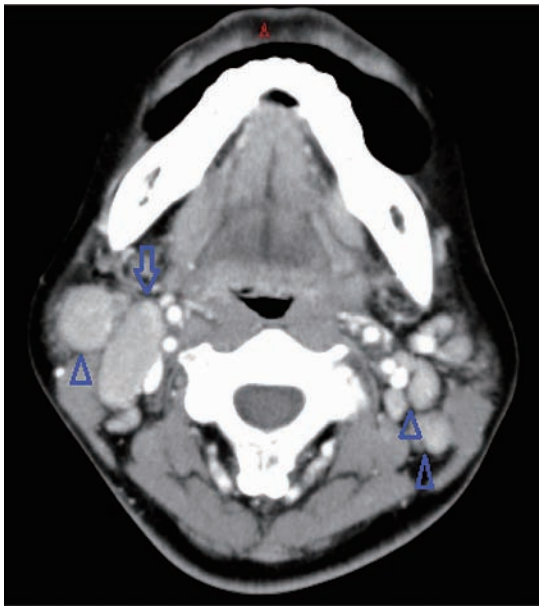

Figure 2. Head and neck computed tomography (CT) showed multiple enlarged lymph nodes over the bilateral parotid and carotid areas, and the posterior triangle of the neck regions (arrowhead). The largest one was about 3.2 cm in diameter (arrow).

Table 1. Laboratory data of autoimmune survey

Test	Value	Unit	Normal range
C3	111.4	mg/dl	86-160
C4	15.3	mg/dl	17-45
Rheumatoid F	296.9	IU/ml	0-18
ANA	Speckled (1:1280)		≤1:40X(-)
Anti-dsDNA	Negative	IU/ml	Negative (<10)
ENA-I SSA	Positive (>240)	U/ml	Negative (<7)
ENA-I SSB	Positive (125)	U/ml	Negative (<7)

T-2 weighted imaging, with lesions by FLAIR imaging over the bilateral parotid space and posterior cervical space. Head and neck CT revealed multiple large lymph nodes over the bilateral parotid and carotid areas, and the posterior triangle of the neck (Fig. 2). The largest lesion was about 3.2 cm in diameter while some had a confluent appearance. Lymphoma or inflammatory lymphadenopathy was suspected.

The patient returned to the Neurology Clinic two weeks later without improvement of symptoms. During neurologic re-evaluation, she still had unilateral nystagmus, as well as vertical double-vision while looking straight in front or downward. There was still no focal weakness while finger-to-nose test showed no dysmetria or intention tremor. She had poor performance of the heel-knee-shin in the left lower limb and severe ataxia during walking. Under the impression of acute cerebellar ataxia, she was admitted to the Neurology Ward for further evaluation.

After admission, the patient had swelling of the bilateral parotid glands. According to her, this condition waxed and waned for over a period of time. She also experienced dry eye and dry mouth in the last year.

A series of laboratory tests revealed abnormal results in the autoimmune survey (Table 1). Shirmer's test and salivary scintigraphy were all positive. Based on the Revised International Classification Criteria for Sjögren's Syndrome, primary Sjögren's syndrome (PSS) was diagnosed. Repeat brain MRI showed no cerebral or cerebellar lesion while cerebro-spinal fluid (CSF) study showed normal cell count with mild elevation of CSF

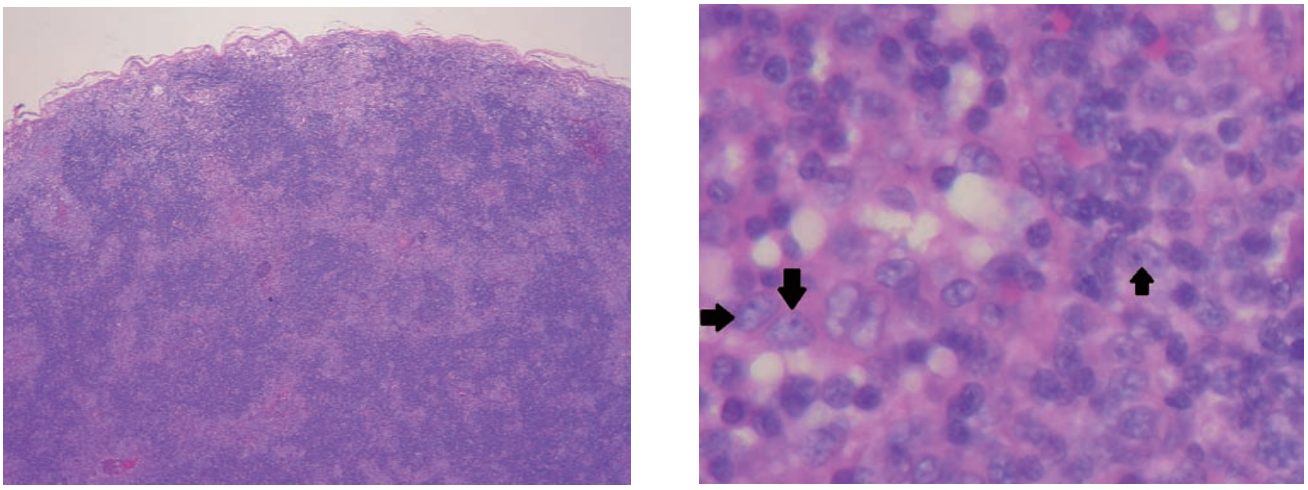

Figure 3. Excision biopsy of the neck lymph nodes revealed bland histiocytes (arrow) aggregating in the sub-capsular, trabecular, and medullary sinuses without malignancy.

total protein level (48.1 mg/dl, reference 8-32 mg/dl).

After lymph node biopsy, the pathology report demonstrated sinus histiocytosis without malignancy (Fig. 3). Primary Sjögren's syndrome with central nervous system involvement (cerebellar ataxia) and sinus histiocytosis with massive lymphadenopathy was diagnosed. Methylprednisolone pulse therapy was given during admission but provided no clinical improvement. Oral steroid was initiated and the patient was referred to the Rheumatologic clinic for further management after discharge.

DISCUSSION

Sjögren's syndrome is an autoimmune chronic lymphocytic inflammatory disease involving the exocrine glands (Arthritis Care Res (Hoboken) 2012;64:911-918). It can occur alone as primary Sjögren's syndrome (PSS) or in conjunction with other connective tissue diseases (secondary Sjögren's syndrome). The 2002 American European classification criteria for PSS is adopted by most studies and include subjective symptoms of dry eyes/dry mouth, objective signs of ocular or salivary gland involvement, pathologic examination and elevated serum titers of anti-Ro or anti-La autoantibodies (Table 2) (Ann Rheum Dis 2002;61:554-558).

Primary Sjögren's syndrome may have extra-glandular manifestations, including the neurologic system, with the prevalence of 10-60% (Curr Opin Neurol 2010;23:509-513). The central nervous system is less commonly compared to the peripheral nervous system (Curr Opin Neurol 2010;23:509-513; Clin Rheumatol 2011;30:485-490; Brain 2005;128:2518-2534; Rheum Dis Clin North Am 2008;34:885-906, viii). Sensory neuropathies, multiple mono-neuropathies, and poly-radiculopathies are common findings in patients with peripheral nerve system involvement (Curr Opin Neurol 2010;23:509-513). Non-focal symptoms like memory loss, cognitive dysfunction, visual disturbance, dizziness, and reduced concentration and attention are frequent symptoms while the central nervous system is involved (Rheumatology (Oxford) 2010;49:1540-1549). Cerebellar ataxia has been mentioned in patients with autoimmune diseases, including Sjögren's syndrome (J Neurol 2007;254:1609-1611; J Clin Neurol 2012;8:155-159; Ryumachi 1995;35:107-111; Neurology 2004;62:2332-2333) and systemic lupus erythematosus (Lupus 2008;17:1122-1126; Lupus 2011;20:1312-1315; Lupus 2012;21:324-328; Ann Rheum Dis 1988;47:954-956; N Y State J Med 1983;83:983-984; Clin Neurol Neurosurg 2000;102:37-39).

Although substantial effort has been exerted to clarify the underlying pathophysiologic mechanisms of autoimmune disease-related neurologic manifestations,

Table 2: Revised international classification criteria for Sjögren's syndrome

I. Ocular symptoms (at least one of the following questions):
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?
II. Oral symptoms (at least one of the following questions):
1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs (positive finding in at least one of the following two tests):
1. Schirmer's test, performed without anesthesia (≤5 mm in 5 minutes)
2. Rose Bengal score or other ocular dye score
IV. Histopathology: focal lymphocytic sialoadenitis in minor salivary gland biopsy (obtained from normal-appearing mucosa).
V. Salivary gland involvement: (positive result for at least one of the following diagnostic tests):
1. Unstimulated whole salivary flow (≤1.5 ml in 15 min)
2. Parotid sialography (showing the presence of diffuse sialectasias without evidence of obstruction in the major ducts)
3. Salivary scintigraphy (showing delayed uptake, reduced concentration and/or delayed excretion of tracer)
VI. Auto-antibodies:
Antibodies to Ro(SSA) or La(SSB) antigens, or both

*Adapted from Ann Rheum Dis 2002;61:554-558.

there is still no conclusive evidence. Some studies have shown that immunologic markers may play roles in the pathophysiology (Curr Opin Neurol 2010;23:509-513; Medicine (Baltimore) 2002;81:270-280; Rheum Dis Clin North Am 2008;34:885-906, viii; Ann Rheum Dis 2004; 63:616-620). One cohort study demonstrated the presence of immunologic markers (i.e., anti-nuclear antibody, rheumatoid factor, anti-Ro/SSA, anti-La/SSB, cryo-globulins) were statistically related to increased risk of extra-gland involvement (Medicine (Baltimore) 2002;81:270-280).

Patients with Sjögren's syndrome have high risk for lymphoma (Arch Intern Med 2004;164:1275-1284). This severe complication occurs in 5-10% of patients with primary Sjögren's syndrome who are followed for more than 10 years. The clinical findings include massive lymphadenopathy with or without splenomegaly, accompany with pathology proved neoplastic lymphoid cells in lymph nodes or bone marrow. This is a serious complication and patients with Sjögren's syndrome should be evaluated and followed for this problem. Another distinct but benign disorder related to Sjögren's syndrome is Rosai-Dorfman disease, characterized by sinus histiocytosis with massive lymphadenopathy (SHML), fever, lymph-node enlargement, high erythrocyte sedimentation rate (Equine Vet J; 41:153-159) and polyclonal hyper-gammaglobulinemia. (Scand J Rheumatol 2004; 33:119-122; Head Neck 2011). Our patient has massive neck lymphadenopathy and pathology-proved sinus histiocytosis, but there was no fever or elevated erythrocyte sedimentation rate.

Current management for Sjögren's syndrome is mainly directed at relief of symptoms and the prevention of complications. Preservative-free tear substitutes are recommended for xerophthalmia and ocular lubricating ointment are suggested for nocturnal use. Maintenance of good oral hygiene, saliva replacement, and salivary stimulation products (like sugar-free chewing gums) are useful for decreasing the complication of xerostomia. Some oral form muscarinic agonists like pilocarpine and

cevimeline are effective in increasing tear production and for the transient increase of salivary flow. According to previous retrospective studies, hydroxychloroquine may be useful for the associated arthralgia and fatigue. The anti-CD20 monoclonal antibody Rituximab may improve the severe inflammatory manifestation of Sjögren's syndrome (Am Fam Physician 2009;79:465-470; JAMA 2010;304:452-460).

For the management of Sjögren's syndrome with central nervous system involvement, there is no conclusive evidence to suggest specific therapy and many kinds of therapies have been mentioned, including steroids, immunoglobulins, plasmapheresis, and D-penicillamine (Curr Opin Neurol 2010;23:509-513; Arch Intern Med 2004;164:1275-1284; Brain 2005;128:2518-2534; JAMA 2010;304:452-460). In one case report, the authors mentioned a patient of cerebellar ataxia combined with Sjögren's syndrome who improved after using high-dose corticosteroids. They used quetiapine for the patient's psychiatric symptoms (J Clin Neurol 2012;8:155-159).

To date, this case is the first case report on an atypical and rare manifestation of primary Sjögren's syndrome - acute onset cerebellar ataxia combined with massive neck lymphadenopathy. Immune-mediated ataxia is one of the differential diagnoses for acute acquired cerebellar ataxia. This patient had typical oral and ocular symptoms, positive results of Shirmer's test and salivary scintigraphy, and elevated titers of auto-antibodies to Ro and La antigens, thereby fulfilling the diagnostic criteria for Sjögren's syndrome. The patient had no sensory symptoms. The deep tendon reflexes were well preserved and the joint position sense was normal during the neurologic examination. Sensory ataxia was less likely to be the cause of ataxia. Imaging and laboratory studies, including CSF study, have excluded other frequent causes of acute cerebellar ataxia. Thus, Sjögren's syndrome with acute cerebellar ataxia is the most reasonable diagnosis. Lymphoma was initially suspected because the patient initially had massive neck lymphadenopathy. Histo-pathology of the lymph node biopsy confirmed sinus histiocytosis without malignancy.

CONCLUSIONS

For patients with acute acquired cerebellar ataxia, immune-mediated cerebellar ataxia should be an important differential diagnosis aside from the more common causes like stroke or drugs. Sjögren's syndrome may have extra-glandular manifestations, including the nervous system. Although the peripheral nervous system is more commonly involved, central nervous system, including the cerebellum, may also be affected. Lymphadenopathy is a common manifestation of Sjögren's syndrome. Such patients have higher risk of developing lymphoma so they should be evaluated and followed-up carefully.

REFERENCES

1. Appenzeller S, Cendes F, & Costallat LTL. Cerebellar ataxia in systemic lupus erythematosus. Lupus 2008;17:1122-1126.
2. Chai J, Logigian EL. Neurological manifestations of primary Sjögren's syndrome. Curr Opin Neurol 2010;23:509-513.
3. Chattopadhyay P, Dhua D, Philips CA, Saha S. Acute cerebellar ataxia in lupus. Lupus 2011;20:1312-1315.
4. Collison K, Rees J. Asymmetric cerebellar ataxia and limbic encephalitis as a presenting feature of primary Sjögren's syndrome. J Neurol 2007;254:1609-1611.
5. Drosos AA, Georgiadis AN, Metafratzi ZM, Voulgari PV, Efremidis SC, Bai M. Sinus histocytosis with massive lymphadenopathy (Rosai Dorfman disease) in a patient with primary Sjögren's syndrome. Scand J Rheumatol 2004;33:119-122.
6. Garcia Carrasco M, Ramos Casals M, Rosas J, Pallares L, Calvo Alen J, Cervera R, Ingelmo M. Primary Sjogren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore) 2002;81:270-280.
7. Gono T, Kawaguchi Y, Katsumata Y, Takagi K, Tochimoto A, Baba S, Yamanaka H. Clinical manifestations of neurological involvement in primary Sjögren's syndrome. Clin Rheumatol 2011;30:485-490.
8. Iwasaki Y, Okamoto A, Shoda H, Takahashi Y, Fujio K,

Kawahata K, Yamamoto K. Subacute cerebellar ataxia and atrophy developed in a young woman with systemic lupus erythematosus whose cerebrospinal fluid was positive for antineuronal cell antibody. Lupus 2012;21:324-328.

9. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjogren syndrome. Arch Intern Med 2004;164:1275-1284.
10. Kim MJ, Lee MC, Lee JH, Chung SJ. Cerebellar degeneration associated with Sjögren's syndrome. J Clin Neurol 2012;8:155-159.
11. Kruszka P, O'Brian RJ. Diagnosis and management of Sjogren syndrome. Am Fam Physician 2009;79:465-470.
12. Lai KL, Abdullah V, Ng KS, Fung NS, van Hasselt CA. Rosai-dorfman disease: Presentation, diagnosis, and treatment. Head Neck 2011.
13. Malladi AS, Sack KE, Shiboski SC, Shiboski CH, Baer AN, Banushree R, Criswell LA. Primary Sjogren's syndrome as a systemic disease: a study of participants enrolled in an international Sjögren's syndrome registry. Arthritis Care Res (Hoboken) 2012;64:911-918.
14. Massara A, Bonazza S, Castellino G, Caniatti L, Trotta F, Borrelli M, Govoni M. Central nervous system involvement in Sjögren's syndrome: unusual, but not unremarkable clinical, serological characteristics and outcomes in a large cohort of Italian patients. Rheumatology (Oxford) 2010; 49:1540-1549.
15. Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H, Sobue G. The widespectrum of clinical manifestations in Sjögren's syndrome associated neuropathy. Brain 2005; 128:2518-2534.
16. Oobayashi Y, Miyawaki S. [Ataxic sensory and autonomic neuropathies associated with primary Sjögren's syndrome: a case report]. Ryumachi 1995;35:107-111.
17. Ramos Casals M, Tzioufas AG, Stone JH, Siso A, Bosch X. Treatment of primary Sjogren syndrome: a systematic review. JAMA 2010;304:452-460.
18. Segal B, Carpenter A, Walk D. Involvement of nervous system pathways in primary Sjögren's syndrome. Rheum Dis Clin North Am 2008;34:885-906, viii.
19. Singh RR, Prasad K, Kumar A, Misra A, Padmakumar K, Malaviya AN. Cerebellar ataxia in systemic lupus erythematosus: three case reports. Ann Rheum Dis 1988;47:954-956.
20. Solano AM, Valverde A, Desrochers A, Nykamp S, Boure LP. Behavioural and cardiorespiratory effects of a constant rate infusion of medetomidine and morphine for sedation during standing laparoscopy in horses. Equine Vet J 2009; 41:153-159.
21. Soliotis FC, Mavragani CP, Moutsopoulos HM. Central nervous system involvement in Sjögren's syndrome. Ann Rheum Dis 2004;63:616-620.
22. Tuchman AJ, Daras M, David S. Cerebellar ataxia in systemic lupus erythematosus. NY State J Med 1983;83:983-984.
23. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Weisman MH. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American European Consensus Group. Ann Rheum Dis 2002;61:554-558.
24. Wong S, Pollock AN, Burnham JM, Sherry DD, Dlugos DJ. Acute cerebellar ataxia due to Sjogren syndrome. Neurology 2004;62:2332-2333.
25. Yaginuma M, Suenaga M, Shiono Y, Sakamoto M. Acute cerebellar ataxia of a patient with SLE. Clin Neurol Neurosurg 2000;102:37-39.