CASE REPORT

Case of primary Sjogren's syndrome preceded by dystonia

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Accepted 10 May 2018

SUMMARY

There are only six cases in literature that describe development of dystonia with Sjogren's syndrome (SS). We describe a case of a 43-year-old woman who presented with symptoms including movement disorder, sensory neurogenic bladder, sensory loss and neuropathic pain, migraine like headaches, musculoskeletal pain, Raynaud's phenomenon and dysautonomia. Symptoms started in 2000, with weakness that progressed to dystonia in 2003. Diagnostic work-up was inconclusive with negative inflammatory serologies, cerebrospinal fluid and MRI for many years. After patient developed sicca syndrome with dry eyes and mouth in 2009, her rheumatoid factor titre was elevated (550 IU/mL), erythrocyte sedimentation rate, anti-Sjogrens syndrome-related antigen A (anti-Ro/SSA) and anti-SSB/La: anti-Sjogrens syndrome-related antigen B (anti-La/SSB) became positive. Lip biopsy confirmed diagnosis of SS. She was diagnosed with primary SS with neurological involvement. Her symptoms responded well to intravenous methylprednisolone. Symptoms stabilised with trials of immune-suppressive therapy. This is a case that demonstrates the delay of diagnosing SS with preceding unique neurological association.

BACKGROUND

Sjogren's syndrome (SS) is a chronic autoimmune disease which mainly affects exocrine glands and cause dry eyes and dry mouth (sicca complex). Primary SS (pSS) is characterised by sicca complex and extraglandular symptoms without any additional connective tissue disorder. In 20% of the patients, pSS is complicated by neurological involvement.¹ Neurological complications can be the only extra glandular manifestations and the presenting symptoms in pSS since mild sicca symptoms can be subtle. Nervous system involvement is classified into two groups: CNS (central nervous system) and PNS (peripheral nervous system) involvement. PNS involvement most frequently arises as sensory neuropathies. CNS involvement can be focal such as optic neuropathy, hemiparesis, transverse myelitis, movement disorders, aphasia, ataxia or diffuse including dementia, migraine and encephalopathy.² With this variety of symptoms, there is no specific syndrome definition for CNS-pSS. Half of the patients with CNS-pSS are negative for anti SS-A. On the other hand, CT and MRI can be negative.³ Also, involvement of the CNS may mimic many other neurological diseases, often presenting with similar clinical symptoms of

multiple sclerosis. This makes the process of diagnosing pSS challenging.

The prevalence of the CNS involvement is widely heterogeneous, in the range of 0.3%–48%.¹ The prevalence of PNS involvement was reported up to 20%. Even though the exact mechanism is not clear, there are many theories for the CNS complications of SS including: vasculopathy, pathological autoantibodies, endothelial dysfunction of the cerebral microcirculation or potential inflammation mediated shift in the neurovascular coupling.^{4 5} The primary pathology in PNS involvement can be located in the cell body in the dorsal root or perivascular endothelial wall.⁴

CASE PRESENTATION

We describe a case of a 43-year-old woman who presented initially in 2006 with history of dystonia on left side, sensory neurogenic bladder requiring self-catheterisation, presyncopal episodes and migraine like headaches. She had musculoskeletal pain suggestive of fibromyalgia diagnosis, Raynaud's phenomenon, fatigue and depression which was under control with medication. She also reported intermittent electrical like sensation in the head, face and extremities. Her symptoms started in 2000, with mild weakness mainly in the upper left extremity that progressed to dystonia in 2003. The dystonic movements showed as curling of her hands with hand grips and flexion of her left elbow along with curling on her left foot, and sometimes the right foot. Dystonia was both resting and stimulus induced, including temperature changes. These movements lasted anywhere between minutes and hours. On physical examination, she had spontaneous movements described as dystonic flexion and pronation of the elbows and flexion of the wrist with dystonic big toe extension bilaterally, more pronounced on the left side. She had 80% decreased temperature and pin prick sensation in the lower limbs, and mild decrease in vibratory sense in the left upper and lower limbs. Gait was abnormal due to the presence of the left foot dystonic movements.

She was under treatment with amitriptyline, baclofen, fluoxetine, doxazosin, triamcinolone, lorazepam and pain relievers.

She used to work as an accountant assistant until 2005. She was on disability at the time of presentation. There was no history of drug abuse or smoking.

There was no significant related family history except for deep vein thrombosis.

To cite: Ararat K, Berrios I, Hannoun A, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223468

Figure 1 Brain MRI 2007 was unremarkable with no signs of demyelinating or enhancing lesions.

INVESTIGATIONS

Initial investigations including vitamin D, vitamin B₁₂, folate, TSH, creatine kinase, comprehensive metabolic panel, rheumatoid factor (RF) and C reactive protein were within normal limits (WNL). Antinuclear antibodies (ANA) was negative and erythrocyte sedimentation rate was 17. Lumbar puncture showed WCC of 2/mm³, with glucose 56 mg/dL, protein 52 mg/dL and absence of oligoclonal bands in the cerebrospinal fluid. It showed increase IgG in both serum and cerebrospinal fluid, as well as normal IgG index and synthesis rate, which ruled out primary CNS inflammatory process, supporting the assumption that this is a systemic inflammatory condition with secondary neurological involvement and not primary CNS inflammation. Work-up for Lyme, syphilis, HIV and hepatitis panel was WNL. Brain MRI was unremarkable with no signs of demyelinating or enhancing lesions (figures 1 and 2). C-spine MRI showed mild cervical spondylosis and thoracic MRI was unremarkable. Electroencephalogram was unremarkable. Electromyogram showed no evidence of polyneuropathy. Tibial/median somatosensory evoked potentials were WNL B/L. She was diagnosed with dysautonomia after autonomic testing. Neuropsychological testing for worsening memory showed mostly lack of attention due to chronic fatigue, mood instability and medication effect without typical impairment seen in neurodegenerative disorder. In 2009, there were no significant changes in MRI results and most of the initial blood test results except for ANA, RF and erythrocyte sedimentation rate which were elevated (1:160, 550 and 22, respectively). Tests for anti-La/SSB and anti-Ro/SSA were positive with negative results for anti-Scl: scleroderma antibody (anti-Scl), anti-dsDNA: Double Stranded DNA antibody (anti-dsDNA), anti-centromere, anti-Jo-1, Ribosomal P Ab: Antibodies to Ribosome P (ribosomal P Ab), RNP Ab: Ribonucleoprotein antibody (RNP Ab), anti-Sm: Smith antibodies (anti-Sm), VGKG Ab: Voltage Gated Potassium Antibodies (VGKC Ab), phospholipid Ab. Tests for phospholipid IgG/IgA/IgM, anti-cardiolipin IgA/IgM were negative in 2013. (table 1) A lower lip biopsy showed minor salivary glands with local

Figure 2 Brain MRI 2007 was unremarkable with no enhancing lesions.

fibrosis and atrophy with chronic inflammation with grade 4 on Chisholm-Mason classification consistent with SS (figures 3 and 4). A diagnosis of pSS with neurological involvement was made on the basis of clinical features, and positive serology and lip biopsy according to the American College of Rheumatology classification criteria for SS.⁶ Despite her previous negative MRIs, a few non-specific FLAIR hyperintense, non-enhancing foci in the bifrontal periventricular white matter was seen in a study performed in 2014 (figures 5 and 6).

Table 1 Immunology workup			
Immunology	2007	2009	2013
ANA	Negative	Detected	
RF (UI/mL)	<20	550	
CRP (mg/dL)	<2.5	7.8	
ESR (mm/hour)	17	22	
Anti-SSA (A.I.)		>8	
Anti-SSB (A.I.)		3.2	
Centromere Ab (A.I.)		<0.2	
JO-1 Ab (A.I.)		<0.2	
Anti-Scl 70 (A.I.)		<0.2	
Anti-RNP Ab (A.I.)		<0.2	
Smith Ab (A.I.)		<0.2	
Phospholipid Abs	Negative		Negative
Anti-cardiolipin Abs	Negative		Negative

ANA, antinuclear antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

Figure 3 Lip biopsy pathology slide (1) showing minor salivary glands with local fibrosis and atrophy with chronic inflammation with grade 4 on Chisholm-Mason.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of her clinical presentation included idiopathic dystonia, spinocerebellar ataxia type 3, multiple sclerosis or connective system disease with neurological complications.

TREATMENT

After initial presentation, the patient was started on carbidopa/levodopa followed by trihexyphenidyl in a trial to treat the dystonic movements without benefits. Intermittently, her dystonia responded to baclofen. After the diagnosis of pSS, she received 5 days of intravenous methylprednisolone, which improved frequency of her dystonic movements by 80%. Bladder symptoms did not improve. Her sicca symptoms responded to cevimeline. Later in the course of dystonia, there was good response to maintenance cyclophosphamide. Bladder dysfunction was also noted to be improving, but response lasted only 2 weeks. She had 11 infusions of cyclophosphamide in total. The dose was decreased due to leucopenia, and eventually, cyclophosphamide was discontinued due to the development of shingles. She

Figure 4 Lip biopsy pathology slide (2) showing minor salivary glands with local fibrosis and atrophy with chronic inflammation with grade 4 on Chisholm-Mason.

Figure 5 Brain MRI 2014 showed few FLAIR hyperintense foci in the bifrontal periventricular white matter.

had worsening of symptoms after discontinuation of cyclophosphamide, and received two doses of rituximab without good response. When cyclophosphamide was reintroduced, there was

Figure 6 Brain MRI 2014 showed no enhancing lesions.

no profound response. Mycophenolate was started and shortly after, discontinued due to worsening depression. She is currently on azathioprine with moderate response with no progression of symptoms.

OUTCOME AND FOLLOW-UP

Currently, she is on azathioprine for SS and receives botulinum injections for dystonia in the lower extremities. She is on pyridostigmine, midodrine and fludrocortisone for dysautonomia with mild positional lightheadedness and stable BP readings. She does self-catheterisation intermittently. She is on topiramate for migraine like headaches, warfarin for idiopathic PE and fluoxetine for depression. Her neuropathic pain is stable on gabapentin.

DISCUSSION

The diagnosis of pSS in patients presenting with CNS involvement can be challenging. PSS should be suspected in patients with atypical neurological presentation and imaging studies suggesting an inflammatory process.

Our patient's neurological presentation was demonstrated in resting and stimulus-induced multifocal dystonia, which is an unusual, and seldomly reported, association to SS in literature. Additionally, the associated collective central and peripheral involvement, such as neurogenic bladder, autonomic dysfunction and sensory neuropathy, which is more frequently reported, was chronologically matching the presence of dystonia, and preceding the appearance of the SS manifestations.⁷ This is the first reported case that describes the development of neurological symptoms involving primary dystonia prior to sicca syndrome and positive serology. van der Berg *et al*⁸ reported the first patient with SS and dystonia. This patient presented with painless fixed dystonic posture of the left hand with hyperflexion of the left third and fifth fingers and wrist. There was no numbness, paraesthesia or autonomic disorders. He had dry eyes and dry mouth at the time of presentation. Serum ANA was positive but disease-specific antibodies such as anti-dsDNA, anti-Ro/SSA or anti-La/SSB were negative. There were no abnormalities on brain MRI but Single proton emission computed tomography (SPECT) showed decreased striatal uptake demonstrating loss of D2 receptors in the R striatum. Dystonia resolved with steroid treatment and follow-up SPECT showed normal availability of D2 receptors in the striatum. Reduction of prednisone dose led to recurrence of dystonia. Cyclophosphamide plus low-dose prednisone daily resolved dystonia. van der Berg *et al* argued that local CNS vasculitis due to SS could decrease striatal perfusion and it led to D2 receptor loss and dystonia. The appearance of functional changes that prior to structural ones can result in normal MRI results.

Jabbari and Salardini⁹ claimed a different mechanism for this pathology. They reported three patients with SS presenting with dystonia. Patients had clinical findings suggesting spinal cord involvement such as, unilateral motor/sensory disorder, gradual motor and sensory deficits leading to quadriplegia and weakness in both lower extremities with brisk deep tendon reflexes. Two of the patients had lesions in spinal cord on MRI. One patient was treated with prednisone plus phenytoin that diminished the frequency of dystonic movements. They proposed that involvement of spinal interneurons or propriospinal pathways might explain patients' dystonia. Similarly, transverse transmission of neuronal activity from the motor to an adjacent sensory pathway might explain some of their sensory symptoms.

In 2007, involuntary dystonic contractions of the facial and perioral muscles was reported in a patient with SS and celiac disease.¹⁰ ANA titres and RF levels were elevated, but anti ds-DNA, anti-Ro/SSA, anti-La/SSB were negative. MRI Brain was normal, and SPECT was negative for blood flow abnormalities. Treatment with dopamine, clonazepam and levetiracetam failed to control the symptoms. Methylprednisolone infusion dramatically improved the dystonia which confirmed underlying immunological process.

Alonso-Navarro *et al*¹¹ reported a patient with sudden episodes of dystonic posturing of the right arm. Initially, patient received a diagnosis of idiopathic paroxysmal dystonia and failed to improve with carbamazepine, gabapentin, phenytoin, valproic acid, lamotrigine, acetazolamide and topiramate. Eventually, dystonic movements were controlled with clonazepam. RF, anti-Ro/SSA and anti-La/SSB were positive at that time. Biopsy confirmed the diagnosis of SS. Brain MRI showed multiple hyperintense lesions in the white matter and in the grey-white matter border, both on T-2 and FLAIR sequence. She received only symptomatic therapy for sicca symptoms.

Lin *et al*¹² described dystonic tremor in a patient with dry mouth accompanied by paraparesis, glove-stocking distribution of sensory deficits, sensory ataxia and pseudochoreoathetosis of bilateral hands.¹² Schirmer's test was pathological. Anti-Ro/SSA antibodies were positive, but anti-La/SSB antibodies were negative. Salivary scintigraphy showed impaired uptake and excretory functions of bilateral parotid glands and she was diagnosed with SS. MRI brain and spinal cord was unremarkable. They concluded that dystonia in SS can result from peripheral nerve injuries. Impaired somatosensory afferents in SS, might cause abnormalities in sensorimotor integration and lead to dystonia.

Moreover, a case of bilateral blepharospasm in a patient with SS and negative for anti-Ro/SSA and La/SSB was reported.¹³ She had MRI hyperintense and non-enhancing multiple lesions in the basal ganglia, thalamus, the periventricular white matter and brainstem bilaterally. Her symptoms moderately improved with methylprednisolone infusion.

As we learn from the literature and our experience, there are different mechanisms and forms in which the nervous system is involved with SS. The unusual presentation of dystonia without sicca syndrome can make the diagnosis of SS challenging and not clinically suspected. As previously described, there are a handful of cases of SS-associated dystonia in the literature. As the aetiology of this presentation is not yet well defined, we suggest this association based on the chronological appearance of symptoms and positive objective clinical findings. However, possible causes according to the reported cases, range from loss of D2 receptors by decrease in striatal perfusion secondary to CNS vasculitis, disruption of spinal interneurons or propriospinal pathways, to abnormalities in sensorimotor integration causing impairment in somatosensory afferents. Unfortunately, due to the rare presentation and inconsistency

Learning points

- ▶ Neurological presentation can precede the typical serological changes associated with primary Sjogren's syndrome (pSS).
- ▶ Neurological involvement in SS can include rare symptoms such as dystonia.
- ▶ Sicca symptoms can be so subtle in pSS while nervous system involvement can be the only presenting symptoms in pSS. Consider pSS in patients with quite non-specific and diffuse neurological symptoms.

in the associated symptoms, immunological profile and MRI findings, diagnosis of this syndrome can be challenging.

Treatment of dystonia in SS is currently based on individual experience. The unusual response of focal dystonia to an immunosuppressive therapy such as cyclophosphamide and methylprednisolone, seen in the literature as well as our case, suggests causality with an underlying immunological process associated with SS.¹⁴

Due to the rarity of primary dystonia without sicca syndrome in SS, there is no consensus in diagnosis and treatment. Additionally, delay or absence of radiological findings could be seen in the presence of clinically fitting pictures.³ Our case demonstrates a unique presentation of SS with CNS involvement. Diagnosis requires high clinical suspicion, consistency in repeating inflammatory markers as well as imaging studies. Treatment with immunosuppressive therapy may be an option to treat symptoms and delay disease progression, but more studies are necessary to corroborate this anecdotal response.

Contributors KA participated in data gathering, review of literature, writing and reviewing the manuscript. IB participated in data gathering, review of literature, writing and reviewing the manuscript. AH participated in data gathering, writing and reviewing the manuscript. CI participated in data gathering, review of literature, writing and reviewing the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests CI: Biogen Idec and Genzyme. She has received compensations for consulting and advisory boards from Genzyme and TEVA. IB has received compensation for consulting in advisory board from Genzyme.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Massara A, Bonazza S, Castellino G, *et al*. 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* 2010;49:1540–9.
- 2 Govoni M, Padovan M, Rizzo N, *et al*. CNS involvement in primary Sjögren's syndrome: prevalence, clinical aspects, diagnostic assessment and therapeutic approach. *CNS Drugs* 2001;15:597–607.
- 3 Alexander EL, Beall SS, Gordon B, *et al*. Magnetic resonance imaging of cerebral lesions in patients with the Sjögren syndrome. *Ann Intern Med* 1988;108:815.
- 4 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.
- 5 Morreale M, Marchione P, Giacomini P, *et al*. Neurological involvement in primary Sjögren syndrome: a focus on central nervous system. *PLoS One* 2014;9:e84605.
- 6 Vitali C, *et al*. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554–8.
- 7 Delalande S, de Seze J, Fauchais AL, *et al*. Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. *Medicine* 2004;83:280–91.
- 8 van den Berg JS, Horstink MW, van den Hoogen FH, *et al*. Dystonia; a central nervous system presentation of Sjögren's syndrome. *Mov Disord* 1999;14:374–5.
- 9 Jabbari B, Salardini A. Painful tonic/dystonic spasms in Sjögren's syndrome. *Mov Disord* 1999;14:860–4.
- 10 Papageorgiou SG, Kontaxis T, Bonakis A, *et al*. Orofacial dystonia related to Sjögren's syndrome. *Clin Rheumatol* 2007;26:1779–81.
- 11 Alonso-Navarro H, Arroyo M, Parra A, *et al*. Paroxysmal dystonia associated to primary Sjögren's syndrome. *Mov Disord* 2009;24:788–90.
- 12 Lin WY, Huang CC, Chang HS, *et al*. Various movement disorders in a patient with Sjögren syndrome. *Mov Disord* 2009;24:786–8.
- 13 Kargiotis O, Papatheanasopoulos P, Efstathios T, *et al*. Bilateral blepharospasm as the presenting symptom of Sjögren's syndrome with evidence of central nervous system involvement. *Acta Neuropsychiatr* 2010;22:263–5.
- 14 Ozgocmen S, Gur A. Treatment of central nervous system involvement associated with primary Sjögren's syndrome. *Curr Pharm Des* 2008;14:1270–3.

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