RECURRENT MYELITIS AND SICCA SYNDROME: A TIME-REVEALED ASSOCIATION

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ABSTRACT

The etiology of transverse myelitis (TM) remains frequently unknown, despite a screening for possible causes like infectious diseases, connective tissue diseases, multiple sclerosis, neuromyelitis optica, paraneoplastic or vascular. An important point for the diagnosis is the follow-up which can reveal by adding new clinical elements an etiology for the spinal disease. We report the case of a 40-year-old male with repetitive cervical and thoracic myelitis who was diagnosed with Sjogren syndrome three years after the onset of neurological impairment. Considerations about the differentials are made, and possible etiological entities are discussed.
Key words: myelitis, Sjogren syndrome, multiple sclerosis, sicca syndrome

INTRODUCTION

Transverse myelitis (TM) is an inflammatory process affecting a restricted area of the spinal cord. The etiology remains frequently unknown, after a screening for possible causes like infectious diseases, connective tissue diseases, multiple sclerosis and neuromyelitis optica, paraneoplastic, vascular, etc. (1,2,4) TM can be recurrent or presenting with single episode (1).

The recurrent character can be an important point of the diagnosis, but overall, classifying TM can be a challenge for the clinician, since sometimes only the active follow-up offers elements suggestive for the diagnosis.

THE CASE

We report the case of a 40-year-old male with repetitive cervical and thoracic myelitis who was diagnosed with Sjogren syndrome three years after the onset of neurological impairment.

He was admitted in the Department of Neurology of Colentina Hospital in March 2007 for paresthesia and dysesthesia of the left lower limb, with sensibility disorder at that level. The recent medical history revealed a similar episode occurring in 2005, involving both lower extremities, spontaneously recovered in one week. At that time, a multiple sclerosis diagnosis was raised, but the patient did not fulfill the diagnostic criteria. Neurological examination showed myelopathy at the T4-T7 level, the CSF had increased protein (106 mg/dl), without oligoclonal IgG profile and normal cellularity. The MRI showed demyelinating lesions at T4-T7 level without enhancement after gadollinium administration, no lesions at the cerebral examination. The clinical and serologic screening did not show any sign of systemic disease such as connective tissue disease (anti ADN dc, anti Sm, anti Ro, anti La, anti U1RNP antibodies were absent, crioglobulins were absent, no sicca syndrome – Schirmer test normal, seric angiotensin converting enzime normal), infectious diseases (VDRL, TPHA for treponema pallidum, serologic tests for Borrelia Burgdorferi, viruses, including HIV, HTLV, EBV, CMV, hepatitis virus B and C were negative), there were no sign of inflammatory systemic disease at that time. Auditive and visual evoked potentials were normal; there were no

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abnormalities of electromyographic exploration ruling out a peripheral nervous disease associated with the TM. The patient was considered as isolated inflammatory CNS syndrome and the pulse therapy with metylprednisolone 1g iv daily for 5 days was followed by complete remission.

After 6 month he returned at the hospital because of paresthesia and dysesthesia of the upper and the lower limbs, the clinical examination indicating cervical and thoracic myelitis, confirmed by the IRM exploration of the spinal cord. He also complained for arthralgias of the knees, hips, wrists and low back pain occurred in the last 4 months. The physical examination revealed arthritis of the knees and the osteo-articular scintigraphy: symmetrical inflammatory changes involving the peripheral joints and bilateral sacroileytis. The clinical and serologic screening was performed again with all the tests mentioned above, and more; there were negative for SLE, Sjogren, rheumatoid arthritis (rheumatoid factor, anti CCP antibodies were absent), sarcoidosis, presence of cryoglobulins, infectious diseases (syphilis, borrelia, mycoplasma, HIV, HTLV, CHV, BHV, etc).

In the presence of systemic involvement, suggesting inflammatory systemic disease, after plasma exchange, pulse therapy with metilprednisolone 5g and cyclophosphamide, with prompt recovery of the neurological changes, oral corticotherapy with 1 mg/ kg/day was initiated, with remission of articular inflammation and neurological signs at 1 month. After 4 applications, hypercorticism and repeated infectious episodes (respiratory, urinary, digestive) in the presence of good evolution of neurological disease, tapering of corticoid doses was initiated and cyclophosphamide administration was stopped after 6 months.

In March 2008, while the dose of oral methylprednisolone was 12mg/day, xerostomia and keratoconjunctivitis Sicca occured, with Schirmer test positive and small salivary gland biopsy revealing lymphoplasmocitic infiltrates suggesting Sjogren syndrome. Anti SS-A and SS-B antibodies, anti-DNAds and anti-Sm, were again negative, searched for the third time. Obviously, none of the conditions that might have been associated with sicca syndrome was present, such as: head-neck radiation, hepatitis C virus infection, AIDS, lymphoma, sarcoidosis, graft versus host disease (GVHD), and anti-acetylcholine drug use.

While the criteria for Sjogren syndrome, according to the international classification criteria, were fulfilled (2), the immunosuppressive therapy was considered advisable to be continued in order to prevent a new episode of active neurological disease, and that was made with azathyoprine, together with monthly plasma exchange therapy followed by pulse therapy with metylprednisolone and IGIV in dose of 400mg/kg/day 5 days. It will be a an option, for the future, if new signs of neurological impairment will appear, to initiate therapy with Rituximab, that have been proved to be very effective in treating Sjogren syndrome (3).

At the time of submitting this manuscript, the patient is fully recovered and reevaluated periodically.

DISCUSSION

The etiology of TM covers an important spectrum of entities: TM can be parainfectious (occurring at the time of and in association with an acute infection or an episode of infection), Viral (herpes simplex, herpes zoster, cytomegalovirus, Epstein-Barr virus, enteroviruses (poliomyelitis, Coxsackie virus, echovirus), human T-cell, leukemia virus, human immunodeficiency virus, influenza, rabies), Bacterial (Mycoplasma pneumoniae, Lyme borreliosis, syphilis, tuberculosis), Postvaccinal (rabies, cowpox). Systemic autoimmune disease can generate TM (Systemic lupus erythematosus, Sjogren syndrome, Sarcoidosis, Mixed Connective Tissue Disease, vasculitis). TM can occur as a Paraneoplastic syndrome or have a Vascular etiology (Thrombosis of spinal arteries, Vasculitis secondary to heroin abuse, Spinal arterio-venous malformation) (4). In our patient, the repeated screening for infectious diseases as for systemic illness was mainly negative, pleading for inflammatory systemic context, being however the articular involvement and sicca syndrome. Repeated MRI didn't sustain malformative or vascular etiology.

One of the entities that must firstly be considered in producing TM esspecialy by the neurologist is multiple sclerosis (MS), but in that case, TM is just a manifestation of dissemination in time and space that inflammation in MS presents. Brain lesions were absent in our patient, as were oligoclonal bands in the CSF.

The relationship between MS and primary Sjogren syndrome (PSS) is ambiguous. It was suggested that some patients diagnosed with MS may instead have PSS. It is considered that MS and PSS may coexist in the same individual, but PSS is not more common among MS patients than expected in the general population (5, 6).

Some MS patients, mainly women over 45 years of age, with progressive spastic paraparesis, antiextractable nuclear antigen antibodies (Ro/SS-A or La/SS-B) negative and with abnormalities in spinal cord MRI, may have SS as an additional or alternative diagnosis (7).

Idiopathic recurrent transverse myelitis (RTM) is an entity that represents a challenge to be distinguished from multiple sclerosis-associated RTM (MSRTM). It is known that idiopathic RTM occurs mostly in male patients and presented more often with acute transverse myelitis than did MSRTM. Today, it is considered that idiopathic RTM might be a disease entity distinct from MSRTM, differing in its male preponderance, absence of oligoclonal bands, frequent multiple relapses, and frequent presentation as acute transverse myelitis (8). Our patient can be a candidate to this diagnosis; however the joint involvement and sicca syndrome leads the considerations towards a systemic associated nervous involvement, in this respect no more "idiopathic".

Recently, there was reported a case with the typical features of a Sjogren myelopathy who was positive for NMO-IgG, a marker of Devic disease (9). The absence of optic neuritis precluded the patient from fulfilling strict diagnostic criteria for the diagnosis of Devic disease, however, as the authors emphasized, this often happens when a new diagnostic marker is discovered and the spectrum of disease associated with the antibody is extended. For example NMO IgG has been described in patients with isolated myelitis and it may be that optic neuritis is not a prerequisite of the pathology associated with the antibody. In another recent large study of 82 patients with neurological manifestations of Sjogren syndrome, 58 had CNS disease and of those 28 (50%), had either an acute or chronic myelitis, but only two had a combination of myelopathy with optic neuritis (10). If in our patient, the search for NMO-IgG (not done) would be positive, that might suggest that Devic disease or a Devic-like syndrome underlies the pathology of Sjögren myelopathy. The opportunity of searching NMO-IgG in patients presenting both sicca syndrome and inflammatory myelopathic features is still controversial and was discussed elsewhere (15).

The true incidence and prevalence of neurological manifestations vary in various series reported in the literature in Sjogren's patients (11). Classically, neurological complications associated with Sjogren syndrome can be divided into neuromuscular manifestations occurring in 10-20% of the patients; central nervous system complications in 25% of the patients, and sub-clinical disease that may be present on laboratory or histological studies, the extent of which is undetermined and may not be predicted in any single individual. Spinal cord disorders can include acute transverse myelitis, chronic progressive myelitis, Brown-Sequard syndrome, neurogenic bladder, and lower motor neuron disease. Cerebrospinal fluid analysis may show elevated IgG index, oligoclonal banding, and cytology showing reactive lymphoid cells (11). In regards to immunopathogenesis of central nervous system disease in Sjogren syndrome, those with serious focal symptoms are more likely to be SSA positive(12,13,14). However, the absence of SSA/SSB is not an exclusion criterion for Sjogren even in the case of our patient, whose antibodies titers were negative.

The histological changes in the central nervous system in primary Sjogren syndrome include lymph mononuclear lymphocytic infiltration in the meninges and parenchyma, microinfarcts and microhemorrhages in the parenchyma, and the presence of vasculopathy. In the peripheral nerves, there can be involvement of mononuclear lymphocytic infiltration in dorsal root ganglia, nerve and muscle, as well as an inflammatory vascular response also affecting dorsal root ganglia, nerve and muscle. No nervous biopsy was realized in our patient (11).

In conclusion, we can consider that this patient has RTM probable associated with Sjogren. The follow-up is mandatory for this kind of cases, and even in this patient the reevaluation of the pathogenical context is recommended if new elements, neurological or others will occur.

The neurological manifestations must be recognized early and aggressively treated so as to avoid long-term complications that would reduce the probability of success with treatment. In the light of the controversial differential diagnosis between Sjogren and MS, this is much more difficult to make when the systemic disease in attenuated, xerostomia and xerophtalmia are absent and also SSA/B are repeatedly negative. It is recommended a systematic diagnostic approach for systemic disease, eventually including small salivary gland biopsy, for patients with demyelinating disease, especially when McDonald criteria are not fulfilled. Finally, we emphasize the need for active follow-up in time for RTM patients, often too hasty classified as MS.

REFERENCES

1.Transverse myelitis consortium working group, Proposed diagnostic criteria and nosology of acute transverse myelitis. *Neurology*, 2002; 59:499-505).

2.Revised international classification criteria for Sjögren's syndrome, Ann *Rheum Dis*, 2002;61:554-558

3.**Pijpe J, van Imhoff GW, Spijkervet FK, et al** – Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study, *Arthritis Rheum.* 2005 Sep;52(9):2740-50

4.**Lynn J** – Transverse Myelitis: Symptoms, Causes and Diagnosis, 2006. The Transverse Myelitis Association.

5.**Sandberg-Wollheim M, Axéllm DDS, Hansen BU** – Primary Sjögren's syndrome in patients with multiple sclerosis. *Neurology* 1992;42:845

6.**de Seze J, Devos D, Castelnovo G, et al** – The prevalence of Sjögren syndrome in patients with primary progressive multiple sclerosis, *Neurology* 2001;57:1359-1363

7.**Pericot I; Brieval L. ; Tintore M et al**. – Myelopathy in seronegative Sjögren syndrome and/or primary progressive multiple sclerosis. *Mult Scler.* 2003,256-259

8.**Kwang-kuk K.** – Idiopathic Recurrent Transverse Myelitis. *Arch Neurol.* 2003;60:1290-1294

9.**Sofat N, Venables PJ.** – Is Sjögren myelopathy Devic disease? *Ann Rheum Dis* 2008;67:730-731

10.**Delalande S, de Seze J, Fauchais AL et al.** – Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. *Medicine* (Baltimore) 2004; 83: 280–91

11.**Soliotis FC , Mavragani CP, Moutsopoulos HM** – Central nervous system involvement in Sjögren's syndrome *Ann Rheum Dis* 2004;63:616-62

12.**Alexander EL, Ranzenbach MR, Kumar AJ, et al.** – Anti-Ro (SS-A) autoantibodies in central nervous system disease associated with Sjögren's syndrome (CNS-SS): clinical, neuroimaging, and angiographic correlates. *Neurology* 1994;44:899–908

13.**Mégevand P, Chizzolini C,Chofflon M, et al** – Cerebrospinal Fluid Anti-SSA Autoantibodies in Primary Sjögren's Syndrome with Central Nervous System Involvement, *Eur Neurol* 2007; 57:166-171

14.**Goëb V, Salle V, Duhaut P, et al** – Clinical significance of autoantibodies recognizing Sjögren's syndrome A (SSA), SSB, calpastatin and alpha-fodrin in primary Sjögren's syndrome, *Clin Exp Immunol*. 2007 May; 148(2): 281–287

15.Neuromyelitis Optica and Sjögren Syndrome : co-occurrence or consequence- Can MNO- IGG make the difference?- a case report- D. Luca, C. Burcin, A. Nicolau, A. Gîtman, M. Ţicmeanu, R. Tănăsescu; 40th International Danube Symposium for Neurological Sciences 21-24 May, Sinaia, Romania. *Rom J Neurol* 2008;VII, Suppl 1:70-71