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Severe Peripheral Neuropathy in a Young Female with Primary Sjogren's Syndrome

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Abstract

Neurological disorders represent one of the most common extraglandular manifestations may be found in patients with Sjogren's syndrome. In this paper we will present the case of a 43-year-old patient with symptomatic onset characterized by paresthesia with "stocking-glove" distribution, evolving with severe ataxia. Clinical examination revealed disturbances of proprioceptive sensitivity in both thoracic and pelvic limbs. The titer of antinuclear antibodies was 1/320, Anti-Ro (SS-A) antibodies were positive, and the biopsy of minor salivary glands showed histopathological changes. The patient underwent repeated electromyography examinations that revealed sensory axonal polyneuropathy. SICCA symptoms started several years after the onset of the first neurological manifestations, and the Schirmer's test was 'borderline'. Corroboration of clinical and paraclinical data led to the diagnosis of primary Sjogren's syndrome with sensory axonal polyneuropathy. The administration of Plaquenil (Hidroxychloroquine sulfate), intravenous immunoglobulin, glucocorticoids, plasmapheresis, Mycophenolate mofetil, Belimumab and Rituximab did not improve neurological complaints, the peripheral neuropathy being refractory to treatment.

Keywords: Primary sjogren's syndrome; Sensory axonal polyneuropathy; Severe ataxia

Introduction

Sjogren's syndrome is an autoimmune disorder affecting the exocrine glands [1], associated with peripheral nervous system manifestations, with sensory neuropathy as one of the most common neurological forms [2].

Sjögren's syndrome, in both primary and secondary forms, is defined as a chronic [3], multisystemic disease of unspecified etiology, and is more common in middle-aged women (aged 40-50) [1]. The primary type is characterized by the involvement of exocrine glands with or without systemic complications, and the secondary form is associated with other autoimmune diseases [1]. Peripheral nervous system involvement is the consequence of neuronal damage by immunological mechanism [2], such as apoptosis, antibody expression, B and T cell changes, and cytokine levels [4,5]. We present a clinical case of primary Sjogren's syndrome with severe sensory axonal polyneuropathy.

Methods and Materials

43-year-old M.I. patient with significant family history (mother-rheumatoid arthritis and mixed connective tissue disease, aunt-rheumatoid arthritis), with dyslipidemia, tenosynovitis in both radiocarpal joints operated in 2005 and 2006, is admitted to a clinical hospital in Bucharest for symptoms started in December 2010, consisting of paresthesia with distal onset, predominantly in the left hemibody, both in the thoracic limbs, "glove"-like (with progression up to 2/3 left arm and right elbow), and in the pelvic limbs, "stocking"-like (with progressive evolution up to the knee), as well as on the face. In 2011, the patient complains of the occurrence of related symptoms such as unsteady gait, intense vertigo accompanied by nausea without vomiting, balance and coordination disorders, dysarthria, decreased concentration, important physical asthenia, right ear tinnitus associated with bilateral hearing loss and visual impairment with 'blurred vision' in the right eye. It also associates muscle twitching and atrophies at the level of the pelvic limbs and hypotonia. To investigate these signs and symptoms, several electromyography examinations were performed in April, June and December 2011, and the diagnosis was axonal sensitive polyneuropathy. The patient also states the presence of Raynaud's phenomenon, urinary urgency and chronic constipation, symptoms with an onset of approx. 2 years.

In 2012, the suspicion of an antiphospholipid syndrome was raised, with positive anti-beta-2 glycoprotein antibodies and neuroborreliosis (based on dark field microscopy), but without increased serum antibody titer, disproved by the cerebrospinal fluid result (cellularity, proteinorrachia, glycorrhachia–within normal limits), for which she received repeated courses of antibiotics that suddenly worsened the symptoms, with significant weight loss, so that the patient was able to move only with the help of another person.

In 2014, the diagnosis of primary Sjogren's syndrome was established based on the presence of anti-Ro antibodies and antinuclear antibodies and on the performed biopsies (of minor salivary gland and sural nerve and gastrocnemius muscle). The histopathological appearance of the salivary gland fragment examined revealed focal sialadenitis with predominantly B lymphocytes. The biopsy of the left sural nerve showed signs of severe axonal polyneuropathy manifested morphologically by decreased density of myelin fibers, at 1,987 fb/mm^2 (N=7,000-11,000 fb/m^2), 34% fibers with myelinic

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ovoids and bullae and 15% fibers with segmental demyelination lesions of the total dissociated myeloid fibers. The microscopy of the left gastrocnemius muscle showed muscle lesions of neurogenic origin with the presence of fibers in necrobiosis.Laboratory tests and investigations for disseminated lupus erythematosus, rheumatoid arthritis, Wegener's granulomatosis, scleroderma, dermatomyositis, polymyositis did not confirm all these diagnoses. Serum protein electrophoresis, immunogram, thyroid hormones, HBs Ag, anti-HVC antibodies, HIV, anti-neuronal antibodies, anti-MAG antibodies, anti-ganglioside antibodies, anti-cardiolipin antibodies Ig M and Ig G, anti-β2 glycoprotein antibodies Ig G, anti-Sm antibodies, anti-La antibodies, anti-p ANCA antibodies, anti-centromere antibodies, anti-SCL 70 antibodies, ndc DNA, C-reactive protein, rheumatoid factor, serum complement C3, C4 were within normal limits with positive result for ribosomal P protein. At the same time, Schirmer's test was 'borderline' and cryoglobulinemia and lupus cells–absent. The patient also performed visual and auditory evoked potentials that revealed long-latency potentials. Cerebral and cervical-dorsal-lumbar spine MRI with contrast agent excluded other presumptive diagnoses, such as multiple sclerosis, with no evidence of central nervous system demyelination. In April 2018, the patient is diagnosed with chronic autoimmune thyroiditis-subclinical hypothyroidism, for which Euthyrox treatment is administered, 25 μg/day. During the same period, manifestations of SICCA syndrome-xerostomia and xerophthalmia (approximately 7 years after the onset of the first neurological complaints) occurred.

The objective examination upon re-admission in September 2019 revealed pale skin, livedo reticularis at the distal extremities, underweight, no joint swelling, no rash, pulmonary auscultation without added crackles, cardiac without added murmurs, no orthostatic hypotension phenomena, supple abdomen, mobile with respiration, spontaneous or palpation painlessness, physiological micturition, negative costovertebral angle tenderness test.

Neurological examination highlighted the following aspects: conscious patient, no neck stiffness, ataxic gait with wide base, with unilateral support, unsystematic positive Romberg, left hemifacial hypoesthesia, left>right brachial tetraparesis, right>left crural, severe crural>brachial sensory tetra-ataxia, right>left, overall abolished osteotendinous reflexes, cutaneous plantar reflexes in bilateral flexion, paresthesia with "glove"-like and "stocking"-like numbness left>right, superficial hypoesthesia up to the elbow of the left thoracic limb and right forearm and crural up to the ½ level of left thigh and right knee and deep left>right, mild dysarthria, muscle atrophies in the hands, forearm, chest, continent sphincters. The Electroencephalography (EEG) showed a dominant alpha rhythm in the posterior derivations, blocked at the spontaneous opening of the eyes and at hyperventilation, no electrical paroxysms, no interhemispheric abnormalities. The numerous EMG examinations which our patient undergone led to the diagnosis of sensory axonal polyneuropathy, with no dramatic evolution in the appearances of the pathways throughout this period (Figure 1). The patient did not show psychopathological symptoms of a particular appearance at the psychological examination, without clinically significant cognitive impairment, with a score of 30 points following the MMSE (Mini-Mental State Examination) test and 13 BDI (Beck's Depression Inventory) points.

Since 2014, several regimens have been tried: Plaquenil 200 mgx2/day (stopped in 2017 for ineffectiveness), 9 courses of IVIg (2g/kg body weight) between 2014 to 2018, 4 plasmapheresis sessions in December 2017 (without clinical-biological improvement), and in 2016 a 4-month period of experimental medication–Belimumab-without efficacy. In 2018, Prednisone 25 mg/day and Mycophenolate mofetil 500 mg-2 capsules/day combination therapy was administered for 5 months; the dose of Prednisone was reduced to 15 g/day due to a myasthenic syndrome and cortisone-induced myopathy. In the early part of 2019, the patient is undergoing treatment with Rituximab 500 mg-2g/week (given as off-label medication under the conditions of Sjogren's syndrome with treatment-refractory polyneuropathy). The first course was performed in July 2018, with the patient reporting an improvement in xerostomia and xerophthalmia, normalization of ATPO (Autoantibodies Thyroid Peroxidase) value, decrease of anti-Ro antibodies titer, the rest of the complaints (especially the neurological ones) remaining unchanged. Since October 2019, the patient has been recommended the following regimen: intravenous immunoglobulin, Mycophenolate mofetil, Arlevert (Cinnarizine and dimenhydrinate)–3 capsules/day, Thiossen (Thioctic acid)-1 capsule/day and vitamin B and D supplements, also without success.

The patient is monitored every 3 months for clinical reassessment, for IV Ig administration and for dosage adjustment of the other drugs from the therapeutic scheme as well. The last readmission in hospital was in January 2020, when the patient described a worsening of neurological symptoms (paresthesia), but cortisone-induced myopathy, myasthenic syndrome, xerophthalmia and xerostomia were remitted.

Disscusion and Results

Sjogren's syndrome is an autoimmune, slowly progressive disorder [7] of unknown cause, involving genetic and environmental factors [8], the main neurological complication being peripheral neuropathy [9].

The prevalence of neurological manifestations can be as high as 70%, but the majority occurs in approximately 20% of patients with primary Sjogren's syndrome [10]. In addition to sensory neuropathy, from the extraglandular manifestations we can mention glomerulonephritis with decrease of C4 fraction, of the serum complement, skin vasculitis, lung or liver damage [11].

The pathogenic mechanism involved in triggering neurological manifestations in primary Sjogren's syndrome is unknown, but we recall peripheral inflammatory infiltrate on the one hand and vasculitis with or without necrosis on the other hand [10]. The role of antibodies is also important, the most commonly involved are:

- Anti-SSA (Ro) and Anti-SSB (La) antibodies
- The first is associated with an increased risk of axonal neuropathy [12] compared to the presence of both anti-SSA and anti-SSB antibodies [13]
- Anti-α antibodies–Fodrin Ig A and Ig G (non-erythroid spectrin)
- Anti GM1 Ig M and Ig G antibodies
- Antineuronal antibodies
- Anti-GW182 antibodies

Table 1: Neurological manifestations in primary Sjogren's syndrome.

Peripheral disorders	
Axonal polyneuropathies	
Symmetric pure sensory peripheral neuropathy	Distal sensory polyneuropathy Distal paresthesias and evidence of large fiber sensory dysfunction [10]
Symmetric sensorimotor peripheral neuropathy	Affects sensory and motor axons [12] Weakening of distal muscles of the limbs [14]
Sensory ganglioneuronopathy	Sensory ataxia due to loss of proprioceptive large fibers [12] Chronic and progressive [15] Damage to the dorsal root ganglia [14]
Motor neuropathy	Normal sensory nerve conductor [14] Atrophy and motor root fibrosis [14]
Small-fiber neuropathy	The most common neuropathy in primary Sjogren's syndrome [12] Damage to the A δ small myelinated fibers +/ unmyelinated C fibers [14] The intraepidermal nerve fiber density is calculated [10] Distal burning sensation, dysesthesia, prickling, allodynia localized both hands and feet [10]
Multiple mononeuritis	Sensory and motor deficits with axonal damage [14] Symptomatology evolves faster and is more invalidating in pSS compared with other diseases [10] Associated with vasculitis and cryoglobulinemia [10] Ischemic mechanism [15]
Trigeminal and other cranial nerves neuropathies	Sensory involvement
Autonomic neuropathies	Ganglioneuronopathy and vasculitis mechanism [10] Is manifested with: Adie's pupils Tachycardia Orthostatic hypotension [10] The orthostatic test and Quantitative Sudomotor Axon Reflex Test (QSART) [14] Antibodies against acetylcholine receptor are present in pSS [16]
Demyelinating polyradiculoneuropathy	Uncommon in pSS Symmetric weakening of upper and lower limbs Sensory dysfunction Elevated CFS protein concentration [14]

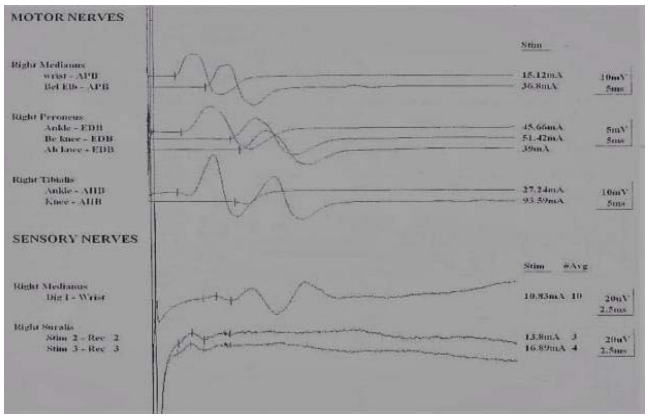

Figure 1: Patient EMG 2019.

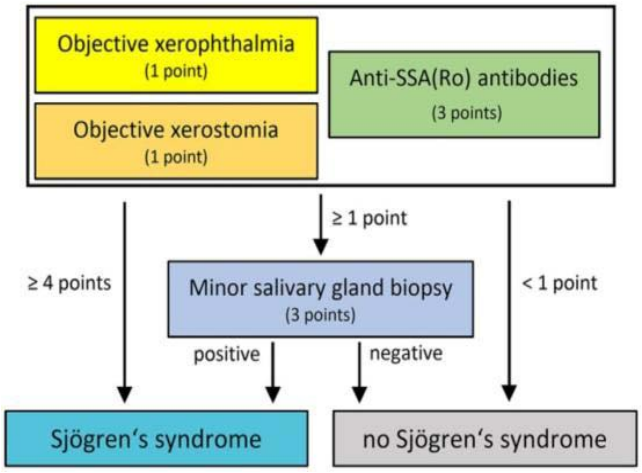

Figure 2: Diagnostic approach for evaluation of Sjogren's syndrome in patients with polyneuropathy [17].

• Antitype 3 muscarinic receptor antibodies [10]

Patients with sensory neuropathy have a low prevalence of ANA, anti-SSA and anti-SSB antibodies [13].

Neurological manifestations in primary Sjogren's Syndrome are described in (Table 1).

In this article, we describe a case of primary Sjogren's syndrome (with xerophthalmia, xerostomia, 'borderline' Schirmer's test, histopathological changes of the biopsy of minor salivary glands, positive Anti-SSA (Ro) antibodies, positive ANA, negative Anti-SSB (La) antibodies, and axonal sensitive polyneuropathy in a 43-year-old patient.

Corroborating the symptoms of SICCA, the presence of anti-SSA antibodies and focal sialadenitis with predominantly B lymphocytes, we can say that the patient meets at least 4 of the 6 diagnostic criteria of a primary Sjögren's syndrome, according to the ACR-EULAR criteria (2016) (Figure 2).

Neurological manifestations may precede xerostomia and xerophthalmia, with patients being diagnosed with primary Sjogren's syndrome after symptoms of peripheral neuropathy [10].

In this case, SICCA symptoms started at 7 years and 2 months

after the onset of the first neurological signs, and the increased anti-SSA (Ro) antibodies levels at 3 years after the onset of "stocking"-like and "glove"-like paresthesias, of the significant ataxia and vertigo. In these situations, patients with paresthesias are investigated and treated in neurology wards, which makes the diagnosis of Sjogren's syndrome almost impossible. It would therefore be auspicious to carry out screening tests for the Sjogren's syndrome to all patients with polyneuropathy so that this condition can be diagnosed at an early stage [17].

In this regard, 2 etiologies were discussed–either vasculitic, or paraneoplastic. Immunoassays showed altered values of anti-SSA antibodies, ANA and β2 glycoprotein. Brain MRI showed no pathological changes, cerebrospinal fluid examination showed normal cellularity, proteinuria, and glycorrhachia values. Flow cytometry, anti-Borrelia antibodies, immunoglobulin index were also unchanged. Paraneoplastic etiology is excluded considering the prolonged progression and absence of evidence of neoplasia. Thus, axonal sensory polyneuropathy was considered to have developed within Sjogren's syndrome with peripheral involvement. The diagnosis was also underlined by the biopsy of the left sural nerve, the microscopic examination showing signs of a severe form of axonal neuropathy.

From a therapy point of view, the purpose of the treatment used is to improve the specific symptomatology of peripheral neuropathy in patients with Sjogren's syndrome, but most of the time the response is inadequate [10].

The 2019 EULAR Recommendations on therapeutic management in neurologically manifested Sjögren's syndrome are as follows:

• For axonal polyneuropathy → symptomatic treatment for 4 weeks

• For ganglionopathy → intravenous immunoglubulin for 4 weeks (First-line therapy), Methylprednisolone for 5 weeks (Second-line therapy) and Cyclophosphamide for 5 weeks as Rescue therapy

• For mononeuritis multiplex → Glucocorticoids 0.5-1 mg/kg of bw/day for 4 weeks (First-line therapy), immunosuppressive agents or Rituximab for 4 weeks (Second-line therapy) and Cyclophosphamide +/- Plasmapheresis for 4 weeks as Rescue therapy [18].

In addition to biological therapy, Rituximab, a monoclonal anti-CD 20 antibody, seems promising in the treatment of patients with severe extraglandular manifestations and also effective in vasculitis manifested by the involvement of the peripheral nervous system in primary Sjogren's syndrome [19].

The Netherlands, France and the UK conducted randomized clinical studies of Rituximab, with improvements in Dutch patients only in terms of SICCA manifestations [20], but with significant results in French patients with associated cryoglobulinemia and peripheral vasculitic neuropathy [10].

In this case, the patient has been treated since 2014 with medication recommended by clinical guidelines, but neurological symptoms persisting despite treatment.

New therapeutic modalities such as IL-1, anti-CD-22, anti-BAFF/Blys, Ig CTLA-4 have been studied, but an optimal result has not been obtained in treating neurological symptoms in Sjogren's syndrome [20].

Current therapeutic strategies depend on the type of neuropathy and the relationship between the presence of antibodies and the development of neuropathy in patients with primary Sjogren's syndrome [12].

Conclusions

The particularity of the case presented is that of neurological manifestations of severe axonal polyneuropathy, refractory to the administration of any therapeutic class, ineffective in alleviating the signs and symptoms described, significantly affecting the patient's quality of life. Neurological manifestations may precede SICCA symptoms, so all patients with polyneuropathy would be tested for Sjogren's syndrome. The involvement of the peripheral nervous system in primary Sjogren's syndrome is an unfavorable prognostic factor, the evolution being more aggressive than in cases where neurological manifestations are not present. Awareness of neurological manifestations in Sjogren's syndrome, a clearer understanding of the mechanism of occurrence of this condition, the development of detailed clinical studies, will lead to effective treatment and a favorable prognosis in patients with this disease.

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