Primary Sjögren’s Syndrome or Multiple Sclerosis?
Our Experience Concerning the Dilemma of Clinically Isolated Syndrome

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The authors present the case of a 50 years old woman who during 3 years had a transient right limbs palsy, and numerous episodes of unilateral/bilateral optic neuropathy. The CSF and MRI examinations did not sustain the diagnosis of multiple sclerosis (MS). After 2 years from the onset, she presented bilateral trigeminal neuropathy, and after 9 months the anti-SS-A and anti SS-B antibodies were positive. The sialography and the minor salivary ducts biopsy (in the absence of xerostomia and xerophthalmia) have established the diagnosis of primary Sjögren’s syndrome (pSS). Subsequently, the patient presented spastic paraparesis, the clinical and imagistical features have suggested the diagnosis of acute transverse myelitis C4-T4. The treatment administered (corticosteroids and IGIV) improved the clinical state. The authors analyse then cases with SLE and cases with pSS, whose initial diagnosis was MS possibly with no evidence of collagen tissue disorders (CD) for many years. In conclusion, screening for biomarkers of SLE or pSS should be systematically performed in a case of acute or chronic myelopathy. Some laboratory tests as CSF examination, the antibodies type, cranial and spinal MRI, are useful for the differential diagnosis with MS. In a neurological clinically isolated syndrome (CIS) the diagnosis of MS should be cautiously established; the close follow-up of patients is always necessary, those with atypical neurological symptoms for MS, relapsing-remitting form, or lack of response to the common treatment for MS, should be examined for CD.

Key words: primary Sjögren’s syndrome (pSS), systemic lupus erythematosus (SLE), multiple sclerosis (MS), clinically neurological isolated syndrome (CIS).

Sjögren’s syndrome is a systemic autoimmune disease that mainly affects the exocrine glands, defined by the principal symptoms-xerophthalmia and xerostomia. About 50% of cases occur in isolation and represent primary Sjögren’s syndrome (pSS). The spectrum of the disease extends from an organ-specific autoimmune disease (autoimmune exocrinopathy) to a systemic process with different extraglandular manifestations.

Optic neuropathy (ON) and/or transverse myelopathy (MT)-acute isolated neurological syndromes, may be the first manifestation of many disorders like multiple sclerosis (MS) or collagen tissue disorder (CD), raising a diagnostic problem. In patients with a relapsing-remitting or primary progressive collagen tissue disorder central nervous system involvement may be indistinguishable from MS [1].

Sjögren’s syndrome is underrecognized. Recognition and diagnosis can be very difficult, particularly early in the case of the disease [2][3].
revealed possible demyelinating lesions. Progressive reduction of visual acuity was associated;

– in May 2008 a cerebral MRI reevaluation was done which visualized demyelinating areas in the white matter with non-specific aspect;

– in November 2008 she underwent a neurological examination in a clinic in Vienna, the cerebral MRI was similar to the previous one, the anti-aquaporin 4 antibodies were negative, the IgG index was normal, and no oligoclonal bands were identified;

– in December 2008 the patient presented facial angioedema, edema of the inferior limbs, paraesthesias in the area of the maxilar branches of the trigeminal nerve bilaterally;

– in October 2009 the cerebral MRI showed non-specific areas of T2/FLAIR hypersignal predominant subcortically;

– Antinuclear, anti-SS-A and anti-SS-B antibodies were positive;

– Skin biopsy did not reveal aspects suggestive for SLE or dermatomyositis;

– in March 2010 a spinal MRI was done-non-specific transverse myelitis, probably of inflammatory nature was revealed;

– in May 2010 she was hospitalized in a rheumatologic clinic in Bucharest, the diagnosis established was Cerebral vasculitis, and the diagnosis of Sjögren’s syndrome was biologically, sialographic and by minor salivary ducts biopsy confirmed (Photo 1);

– the treatment administered was many cures of solu-medrol and a cure of cyclophosphamide;

– in July 2010 an electrophysiological study was done, that revealed normal values of motor conduction velocities (MCVs) and of sensitive conduction velocities (SCVs) recorded bilaterally at median, cubital, peroneal and posterior tibial nerves;

– the antinuclear, anti-dsDNA, anti β2-glycoprotein I (β2-GPI), anti-SS-A antibodies were positive;

– in October 2010 she was hospitalized at “Prof. Dr. Matei Balș” Institute of Infectious Diseases for fever, headache, vomissments. Cephtriaxone and corticosteroids were administered. After 18 hours from admission the patient presented urinary retention, low back pain, weakness of the inferior limbs, the gait was impossible;

– in October 2010 she was hospitalized at the National Institute for Neurology and Neurovascular Disorders (INNBNV) presenting paraparesis, superficial hypoaesthesia with the upper level at T3-T4, sensation of thoracic constriction. The vertebrospinal MRI revealed edema and demyelinating hypersignal at C4-T2. The established diagnosis was: Retrobulbar neuritis. Paraparesis. Probably ophthalmoneuromyelitis;

– anti-Borrelia antibodies were positive in sera (ELISA IgG and Western blot), non-conclusive at Cantacuzino Institute, negative in the CSF, negative at a laboratory in Hungary; the treatment with cephtriaxone, ciprofloxacin and methylprednisolone was started, the symptoms improved slowly, she was transferred at “Prof. Dr. Matei Bals” Institute of Infectious Diseases; the suggested diagnosis was Neuroborreliosis;

– at “Prof. Dr. Matei Balș” Institute of Infectious Diseases the CSF examination was done—this was normal, from which all reactions were negative for Borrelia (Western blot), b.K. (PCR), atypical Mycobacteria, toxoplasma; an infectious cause was infirmed, the autoimmune context imposing the transfer at the Clinic of Internal Medicine of “Colentina” Hospital, after administration of 10 grammes of IVIG (the patient evinced the sensation of “generalized illness” after their administration);

– from October 29th till November 8th she was hospitalized at the Clinic of Internal Medicine of “Colentina” Hospital.
The general clinical examination showed a feverless, normal weight patient, with a discrete muco-cutaneous palor, without peripheral edema, without xerophthalmia, without xerostomia, without bronchial rales, the blood pressure (BP) was 100/60 mm Hg, the heart rate was 90 beats/minute, and she had constipation.

The neurological examination at admission revealed spastic paraparesis, extensor plantar responses, the gait was possible only with bilateral assistance, superficial hypoesthesia with the upper level at T1-T2, urinary retention (catheterized bladder), discrete psycho-motor agitation.

The biological exams showed: simple chronic type moderate anemia, discrete modification of the glucose tolerance, negative serology for HIV, Treponema pallidum, B-and C-virus hepatitis.

ECG-sinus rhythm, the QRS axis was at +60°, the ventricular rate was 100 beats/minute, rare extrasystoles.

On November 4th a plasmapheresis was done; it was well tolerated. From November 5th algoparasthesias relapsed at the inferior limbs, then at the upper limbs too, profuse sweatings in the absence of fever, tonic discharges in the inferior limbs were present. The ascent of the sensory level to C4 decided the transfer to the Clinic of Neurology of “Colentina” Hospital on November 8th.

At this time the patient presented a well clinical state, the BP was 120/70 mm Hg, the ventricular rate was 72 beats/minute.

The neurological examination revealed bilateral reduction of visual acuity, spastic paraparesis (left > right), rotulian and achilean reflexes diminished at the left side, extensor plantar responses, right plantar clonus, extensor plantar responses, superficial hypoesthesia with the upper level at T4, catheterized bladder, the patient was alert, well oriented, anxious, and with a depressive mood.

The biological examinations revealed persistence of moderate microcytic hypochromic anemia, hypoproteinemia, moderate inflammatory syndrome (moderate increase of CRP values), anti-SS-A antibodies present, urinary infection with E. coli sensitive at colistin and amoxicillin with clavulanic acid.

The final diagnosis for this patient was:

Two cures of IGIV 0.4 g/kgw/d for 5 days/monthly, corticotherapy (sulomedrol 1 g/d-5 days, then medrol 32 mg/d), plaquenil, anticoagulants (LWMH), antiaggregants, drugs against muscular spasticity (baclofen/lyoresal), proton pump inhibitors, antibiotics, B-group vitamins, statines, pregabalin (lyrica), anxiolytics and sedatives were administered.

The patient’s clinical state slowly improved, including the visual acuity, she was ambulatory with bilateral aid at her discharge home, she presented spontaneous mictions and normal intestinal transit.

We recommended to continue at home the treatment with medrol 32 mg/d, plaquenil/hydroxychloroquine, vessel due/sulodexide, omez/omeprazole, lyrica/pregabalin, lyoresal/baclofen, sortis 20 mg/atorvastatin, milgamma, thiogamma, coxil/tianeptine, to monitor the glycemia, the lipids level, the neurological, ophthalmological, and internal medicine clinical states. Massages and kinetotherapy were also encouraged.

Keeping in mind the presented case, we studied patients with systemic lupus erythematosus (SLE) and patients with primary Sjögren’s syndrome (pSS), whose initial diagnosis was possible multiple sclerosis (MS) with no evidence of collagen tissue disorders (CD) for many years.

Seven patients with the final diagnosis of SLE and five patients with pSS were evaluated based on detailed anamnesis, systemic and neurological examinations, and laboratory tests.

All the patients presented neurological symptoms and magnetic resonance imaging (MRI) abnormalities that did not fulfill clinic or imaging criteria for MS based on McDonald’s criteria or CD. Atypical features for MS were classified as severe unilateral/bilateral visual loss, severe transverse myelopathy with abrupt onset, resistance to corticosteroid therapy, absence of oligoclonal band positivity, and MR imaging features atypical for MS.

Patients were evaluated based on detailed anamnesis, systemic and neurological examinations, and repeated laboratory tests. The latest included total blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver and renal function test, including also urine analysis and microproteinuria, serologic markers such as antinuclear antibodies (ANA), anti-SS-A antibodies, anti-SS-B antibodies, antiphospholipid antibodies (aPL): anti-cardiolipin antibodies (aCL), anti-ß2-glycoprotein I (ß2-GPI) antibodies IgM and IgG, lupus anticoagulant (LA), anti-dsDNA, investigations for concomitant autoimmune diseases.

In patients with xerostomia or xerophthalmia biopsy of minor salivary glands and Schirmer’s test were done.

The diagnosis of SLE was based on the American College of Rheumatology revised classification criteria for SLE, and disease activity was...
measured with the SLE disease activity index (SLEDAI) [4][5].

The diagnosis of pSS was based on the European Study Group on Classification Criteria for pSS, proposed by Vitali et al. [6].

Cranial and spinal MR examination included sagittal and transverse fluid-attenuated inversion recovery (FLAIR), transverse T1 weighted (W) spin echo (SE) and T2W turbo SE and post-contrast transverse and coronal T1W SE. Diffusion-weighted imaging (DWI) was done to determine acute and small ischemic lesions from old lesions. The spinal MRI imaging used sagittal and transverse T1W SE and T2W turbo SE imagine with a repeat of T1W SE imaging following intravenous administration of Gd-based contrast material.

On evaluation of the cranial MRI imaging, the presence of: 1) acute/chronic cortical/white matter lesions in the brain, brainstem, and the cerebellum, 2) leptomeningeal involvement, 3) optic neuropathy, and 4) volume loss of the brain, brainstem, and the cerebellum were recorded. For volume loss only visual evaluation was performed.

For spinal MRI imaging the presence of: 1) acute myelopathy suggested by cord swelling and contrast enhancement; 2) chronic changes suggested by signal changes without cord swelling with volume loss; 3) leptomeningeal involvement; 4) contrast enhancement of the spinal cord and 5) spinal cord atrophy were recorded.

Characteristics of SLE patients are presented in Table I.

Table I
Characteristics of SLE patients
There were seven patients in this group, they presented as principal neurologic problem severe bilateral optic neuropathy (ON), slightly responsive to corticosteroid therapy. None of them recovered normal visual acuity. The number of ocular attacks varied from 12 (patient no: 1) to 1 (patient no: 3).

In this group of patients, 5 presented aCL and 2 presented anti-β2-GPI antibodies.

Patient 7 (female) presented 3 episodes of paraparesis due to transverse myelopathy within an interval of 9 years. Twenty eight months after the first transverse myelopathy episode she described systemic symptoms and her autoimmunity tests became positive. Immunosuppressive treatment for SLE was started; during the follow-up she remained asymptomatic. On the second year of the therapy, she interrupted the treatment and the monitoring. Similar to her first episode, her paraparesis gradually improved with cyclophosphamide and corticosteroids therapy. Other neurological manifestations at the onset in our group of patients were ataxia (2 patients) and seizures (1 patient). The follow-up period was between 1 and 15 years.

The cerebral and spinal MRI findings of SLE group are shown in Table II.

One patient showed imaging features of acute optic neuritis (Figure 1A). The same patient (no: 1) was the only one who had acute focal cortical infarcts in the SLE group (Figure 1B) in addition to small white mater lesions (Figure 1C). Four out of 5 patients with SLE had punctate T2 hyperintense lesions thought to be old ischemic origin (Figure 1D). In one patient, bilateral chronic cortical infarcts were observed (Figure 1D). In one patient (no: 3) a patchy irregular lesion in the periventricular white matter with strong and irregular contrast enhancement was noticed (Figures 1E, F). Partial and almost complete resolution of the lesion with
minimal residual signal abnormality was seen on follow-up brain examination after 3 and 6 months, respectively.

A lesion in the brainstem was found in only one patient (no: 4).

Brain atrophy was observed to a mild degree in 1 patient and severely in 1 patient. None of the patients had a lesion in the cerebellum or atrophy of the brainstem or cerebellum.

No leptomeningeal involvement was observed in any patient.

Two patients had no spinal MR imaging abnormality (no: 2, 4), whereas 5 patients (no: 1, 3, 5, 6, 7) had a longitudinal myelopathy at a segment of > 2 vertebrae (Figures 3A, B).

One patient (no: 1) had two more episodes of acute myelopathy at different segments on spinal MRI other than the initial one: at 17-and 19 months follow-up although chronic changes with no contrast enhancement were observed on the 12-months follow-up MRI. The other patient’s spinal cord changes suggestive of acute myelopathy were partially resolved on the 3-month follow-up spinal MRI and re-occurred at 6 months.

Only one patient (no: 1) had chronic residual changes with spinal cord atrophy and T2 hyper-intensity.

Pial contrast enhancement was observed in one patient, which could be attributed to a recent lumbar puncture (no: 5).

Clinical and laboratory features of primary Sjögren syndrome group (Table III)

There are 5 patients in the group with pSS. All patients were female and all presented with transverse myelopathy. Their systemic symptoms occurred a long time after their initial neurological presentation.

Two patients (no: 1 and no: 4) suffered two and four optic neuropathy attacks, respectively.

Craniospinal MRI findings of the pSS group are shown in Table IV.

Three patients (no: 2, 3, and 4) had cranial imaging abnormalities. All of them had T2-hyper-intense lesions suggestive of chronic small-vessel ischemic disease in the cerebral white matter (Figures 2A, B) and one patient (no: 3) had a punctate acute ischemic lesion in the left parietal white matter shown by DWI (Figure 2C). One patient (no: 4) presented irregularity on the inferior surface of the corpus callosum simulating MS (Figure 2D).

Two patients (no: 2 and no: 3) had additional lesions in the brainstem and one patient had them in the cerebellum (no: 4).

Moderate (no: 3) and severe cerebral atrophy (no: 2) was present in 2 cases.

No leptomeningeal involvement was observed in any of the patients.

Two patients had acute myelopathy shown by cord swelling and contrast enhancement at a segment of ≥ 2 vertebrae at presentation (no: 1 and no: 5).

Patient no: 1 had also chronic changes to the cervical spinal cord.

Holocord atrophy, predominantly caudal to the level of C6 vertebrae, was observed in one patient with pSS (no: 3).

No meningeal enhancement was observed in any of the patients (Figures 3C, D).

Table II
Cranial and spinal MR imaging findings of SLE patients
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Cranial MRI</th>
<th>Spinal MRI</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Abundant hypointense foci in the ST WM (Fig. 1C)</td>
<td>Acute myelopathy from T1 to the conus medullaris with CE</td>
</tr>
<tr>
<td></td>
<td>Acute right frontal cortical infarcts (Fig. 1B)</td>
<td>Chronic changes with T2 signal abnormalities in the SC on 1 year follow-up MRI</td>
</tr>
<tr>
<td></td>
<td>No lesion in the BS and cerebellum</td>
<td>No SC lesion</td>
</tr>
<tr>
<td></td>
<td>No CE of the parenchymal lesions</td>
<td>No SC atrophy</td>
</tr>
<tr>
<td></td>
<td>No atrophy of the brain, BS, or cerebellum</td>
<td>No leptomeningeal involvement</td>
</tr>
<tr>
<td></td>
<td>No leptomeningeal involvement</td>
<td>No leptomeningeal involvement</td>
</tr>
<tr>
<td></td>
<td>Thickening and CE of the intracranial segments of the left optic nerve: ON (Fig. 1A)</td>
<td>Acute myelopathy at the level of T3-T5 vertebrae, on 17 mo follow-up MRI with sequelae at other levels from the previous ataxia</td>
</tr>
<tr>
<td></td>
<td>Bilateral frontal and parieto-occipital chronic cortical infarcts</td>
<td>Acute myelopathy at the level of T7-T10 vertebrae with diffuse background thoracic SC atrophy on 19 mo follow-up MRI</td>
</tr>
<tr>
<td>2</td>
<td>Abundant T2 hypointense foci in the ST WM</td>
<td>No new lesion at 6th month follow-up</td>
</tr>
<tr>
<td></td>
<td>No lesion in the BS and cerebellum</td>
<td>Acute myelopathy at the level of T4 to T8 vertebrae with CE at the level of T5-T6 vertebrae</td>
</tr>
<tr>
<td></td>
<td>No CE of the parenchymal lesions</td>
<td>No SC atrophy</td>
</tr>
<tr>
<td></td>
<td>Severe brain atrophy</td>
<td>No leptomeningeal involvement</td>
</tr>
<tr>
<td></td>
<td>No atrophy of the BS, cerebellum</td>
<td>Partial resolution of the lesion and its enhancement on 3 mo follow-up MRI</td>
</tr>
<tr>
<td></td>
<td>No leptomeningeal involvement</td>
<td>Acute myelopathy at the level of T2-T8 vertebrae with CE at the level of T4-T8 vertebrae on 6 mo follow-up MRI</td>
</tr>
<tr>
<td>3</td>
<td>Chronic cortical and subcortical infarcts (Fig. 10)</td>
<td>No new lesion at 6th month follow-up</td>
</tr>
<tr>
<td></td>
<td>Large patchy area of T2-hypointense periventricular lesion with irregular borders (Fig. 1B)</td>
<td>Acute myelopathy at the level of T4 to T8 vertebrae with CE at the level of T5-T6 vertebrae</td>
</tr>
<tr>
<td></td>
<td>CE of the lesion very strong (Fig. 1D)</td>
<td>No SC atrophy</td>
</tr>
<tr>
<td></td>
<td>No lesion in the BS and cerebellum</td>
<td>No leptomeningeal involvement</td>
</tr>
<tr>
<td></td>
<td>Brain atrophy</td>
<td>Partial resolution of the lesion and its enhancement on 3 mo follow-up MRI</td>
</tr>
<tr>
<td></td>
<td>No atrophy of the BS, cerebellum</td>
<td>Acute myelopathy at the level of T2-T8 vertebrae with CE at the level of T4-T8 vertebrae on 6 mo follow-up MRI</td>
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<tr>
<td></td>
<td>No leptomeningeal involvement</td>
<td>No SC atrophy</td>
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<tr>
<td></td>
<td>Partial resolution of the lesion and its enhancement on 3 mo follow-up MRI</td>
<td>Partial resolution of the lesion and its enhancement on 3 mo follow-up MRI</td>
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<tr>
<td></td>
<td>Resolution of the lesion with minimal residual T2 signal abnormalities with no CE on 6 mo follow-up MRI</td>
<td>Acute myelopathy at the level of T2-T8 vertebrae with CE at the level of T4-T8 vertebrae on 6 mo follow-up MRI</td>
</tr>
<tr>
<td>4</td>
<td>Abundant T2 hypointense foci in the ST WM</td>
<td>No SC lesion</td>
</tr>
<tr>
<td></td>
<td>1 parietal lesion</td>
<td>No SC atrophy</td>
</tr>
<tr>
<td></td>
<td>No lesion in the cerebellum</td>
<td>No leptomeningeal involvement</td>
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<tr>
<td></td>
<td>No CE of the parenchymal lesions</td>
<td>No leptomeningeal involvement</td>
</tr>
<tr>
<td></td>
<td>No atrophy of the brain, BS, or cerebellum</td>
<td>Acute myelopathy at the level of T3-T7 and T11-T12 vertebrae at two discrete segments with CE at T3-T6 and at the conus medullaris (Fig. 3A, B)</td>
</tr>
<tr>
<td></td>
<td>No leptomeningeal involvement</td>
<td>No SC atrophy</td>
</tr>
<tr>
<td>5</td>
<td>Abundant T2 hypointense foci in the ST WM</td>
<td>Mild post-enhancement around the SC</td>
</tr>
<tr>
<td></td>
<td>No lesion in the brain, BS, or cerebellum</td>
<td>Acute myelopathy at the level of T4 to T8 vertebrae with CE at the level of T3-T6 vertebrae</td>
</tr>
<tr>
<td></td>
<td>No atrophy of the brain, BS, or cerebellum</td>
<td>No SC atrophy</td>
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<tr>
<td></td>
<td>No leptomeningeal involvement</td>
<td>No leptomeningeal involvement</td>
</tr>
<tr>
<td></td>
<td>Partial resolution of the lesion and its enhancement on 3 mo follow-up MRI</td>
<td>Partial resolution of the lesion and its enhancement on 1 mo follow-up MRI</td>
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<tr>
<td></td>
<td>Resolution of the lesion on 6 mo follow-up MRI</td>
<td>Acute myelopathy at the level of T2-T8 vertebrae with CE at the level of T4-T8 vertebrae on 6 mo follow-up MRI</td>
</tr>
<tr>
<td>6</td>
<td>Chronic cortical infarcts</td>
<td>Acute myelopathy at the level of T4 to T8 vertebrae with CE at the level of T3-T6 vertebrae</td>
</tr>
<tr>
<td></td>
<td>T2-hypointense periventricular lesion with irregular borders</td>
<td>No SC atrophy</td>
</tr>
<tr>
<td></td>
<td>CE of the lesion</td>
<td>No leptomeningeal involvement</td>
</tr>
<tr>
<td></td>
<td>No lesion in the BS and cerebellum</td>
<td>Partial resolution of the lesion and its enhancement on 1 mo follow-up MRI</td>
</tr>
<tr>
<td></td>
<td>Brain atrophy</td>
<td>Acute myelopathy at the level of T2-T8 vertebrae with CE at the level of T4-T8 vertebrae on 6 mo follow-up MRI</td>
</tr>
<tr>
<td></td>
<td>No leptomeningeal involvement</td>
<td>No SC atrophy</td>
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<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>Resolution of the lesion on 6 mo follow-up MRI</td>
<td>Acute myelopathy at the level of T2-T7 and T11-T12 and CE at T3-T6</td>
</tr>
<tr>
<td>7</td>
<td>Abundant T2 hypointense foci in the ST WM</td>
<td>Acute myelopathy at the level of T2-T7 and T11-T12 and CE at T3-T6</td>
</tr>
<tr>
<td></td>
<td>No lesion in the brain, BS, or cerebellum</td>
<td>No SC atrophy</td>
</tr>
<tr>
<td></td>
<td>No atrophy of the brain, BS, or cerebellum</td>
<td>No SC atrophy</td>
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</table>
Figure 1A. Cranial MRI-from the SLE patient group. Postcontrast T1-W SE image of patient no: 1 with SLE, showing thickening and contrast enhancement of the left prechiasmatic optic nerve compatible with acute optic neuritis.

Figure 1B. Cranial MRI (axial FLAIR image) of patient no: 1 with SLE. A right frontal acute cortical infarct.

Figure 1C. Cranial MRI (axial FLAIR image) of patient no: 1 with SLE. Small hyperintense foci in the subcortical white matter.

Figure 1D. Cranial MRI (axial FLAIR image) of patient no: 3 with SLE. Chronic cortical and subcortical infarcts.

Figure 1E, F. Cranial MRI (axial T2W turbo SE) of patient no: 3 with SLE. Irregular patchy hyperintense lesions in the periventricular white matter extending through the corpus callosum (E), which enhance strongly on postcontrast T1W SE axial imaging.
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Figures 2A, B. Cranial MRI from the patients with primary Sjögren’s syndrome.
A – The axial FLAIR image (patient no: 2) – shows abundant periventricular white matter lesions and brain atrophy.
B – Subcortical small infarcts in the cerebral white matter (patient no: 3).

Figure 2C. MRI-DWI. One punctate acute ischemic lesion (patient no: 2).

Figure 2D. Cranial MRI – sagittal FLAIR image of patient no: 4. Irregularities on the inferior surface of corpus callosum simulating multiple sclerosis.

Figures 3A, B. Spinal MR images from a patient with SLE (no: 5) – sagittal T2W turbo SE (A) and postcontrast T1W SE (B). Long segment myelopathy at the level of T2-T7 and T11-T12 vertebrae and two discrete segments with contrast enhancement at T3-T6 and at the conus medullaris. There is also mild pial enhancement around the spinal cord.
DISCUSSION

Neurological presentation is found in about 3% of SLE patients [7–10].

Additionally, there are reports of pSS with neurological disorders as the initial manifestation [11–14].

Our data are from the long term follow-up of 10 female patients presenting with an acute isolated neurological syndrome without any systemic complaints.

Optic neuropathy, an important neurological entity, can herald the diagnosis of MS. However, it also has a rare, but well described association with autoimmune diseases [15–17].

Its relation with SLE has been documented by a systematic review which described variable clinical pictures ranging from acute retrobulbar neuritis to ischemic optic neuropathy and slowly progressive visual loss [17].

Although ON occurs in only 1% of patients with SLE, it has also been documented as a presenting sign in patients who later would meet diagnostic criteria for SLE [17][18].

Optic neuropathy associated with SLE is often painless, subacute, and progressive, and commonly very severe [18].

Our patients with SLE had recurrent unilateral or bilateral severe ON. None of the patients had a well-established setting of SLE during ON.

The prognosis of ON in the SLE group was not favourable and this was one of the clues for our clinical suspicion for a differential diagnosis. In one of them, findings such as swelling and contrast enhancement of the optic nerve in the intracranial segments, suggestive of acute optic neuropathy, were also observed on cranial MRI (Figure 1A).

Optic neuropathy may also be a rarely presenting neurological feature of pSS and may occur before or at the same time as the diagnosis of pSS [12][19][20].

None of the patients in the pSS group had previous/simultaneous sicca symptoms.

When spinal cord involvement as a presenting sign has been reviewed it is a more common finding in MS patients, but it has also been reported in patients with SLE and pSS. TM in SLE is infrequently reported, i.e., in only 1–2% of patients [21].

There were described three different types of onset: 1) a smoothly progressive onset with ascending neurological symptoms; 2) a subacute, gradually progressive onset; 3) a hyperacute, catastrophic onset type [22].

The clinical course can resemble the relapsing-remitting or primary progressive form of MS. All our patients had a relapsing-remitting course. In some cases, TM may be an initial manifestation of SLE [23][24].

In our SLE group patient no: 5 had an interval of two years between TM and systemic symptoms.

TM was the initial manifestation in 39% of SLE patients and it presented in the first 5 years [25].

The prognosis is generally poor and depends on such factors as rapidity of diagnosis, extent of
spinal cord involvement, and prompt treatment with high-dose corticosteroids, and pulse cyclophosphamide [26][27].

There are also case reports of pSS with acute TM as the initial manifestation [13][14].

The time between diagnosis of pSS and the onset of acute TM has been reported to vary widely [14].

In our pSS group, the interval between neurological and systemic symptoms ranged from 2 to 11 years.

When changes on cranial MRI are concerned, the two groups of patients were similar in that the most common abnormality was numerous small T2-hyperintense foci, some of which tended to coalesce in the periventricular cerebral white matter. DWI was helpful in the patient with pSS in the differentiation of acute punctate ischemic lesion from old lesions by showing restricted diffusion.

A distinguishing feature in the SLE group was the presence of cortical infarcts in two patients, either acute or chronic.

Hemorrhage in the lesions, which is a known feature in SLE patients, was not observed in this series.

### Table III

Characteristics of patients with primary Sjögren syndrome

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Clinical presentation</th>
<th>Neurological symptoms</th>
<th>Systemic symptoms</th>
<th>Interval between neurological and systemic symptoms (year)</th>
<th>Laboratory features</th>
<th>Diagnostic criteria</th>
<th>Disease course/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/P50</td>
<td>Recurrent optic neuropathy, transverse myelopathy</td>
<td>Facial edema</td>
<td>3</td>
<td>ENA SS-A (+)</td>
<td>ENA SS-A (+)</td>
<td>Paroxysms</td>
<td>Xerophthalmia</td>
</tr>
<tr>
<td>2/P23</td>
<td>Transverse myelopathy, astasia</td>
<td>Arthralgias, sicca symptoms</td>
<td>2</td>
<td>ENA SS-A (+)</td>
<td>Xerophthalmia</td>
<td>Xerophthalmia</td>
<td>ENA SS-A</td>
</tr>
<tr>
<td>3/P36</td>
<td>Transverse myelopathy</td>
<td>Arthralgias, sicca symptoms, oral aphasia</td>
<td>11</td>
<td>ENA SS-A (+)</td>
<td>Xerophthalmia</td>
<td>Xerophthalmia</td>
<td>Ena SS-A</td>
</tr>
<tr>
<td>4/P27</td>
<td>Recurrent optic neuropathy, transverse myelopathy</td>
<td>Oral aphasia, sicca symptoms</td>
<td>9</td>
<td>ENA SS-A (+)</td>
<td>Xerophthalmia</td>
<td>Xerophthalmia</td>
<td>ENA SS-A</td>
</tr>
<tr>
<td>5/P21</td>
<td>Transverse myelopathy</td>
<td>Sicca symptoms</td>
<td>3</td>
<td>ENA SS-A (+)</td>
<td>Xerophthalmia</td>
<td>Xerophthalmia</td>
<td>Schirmer (+)</td>
</tr>
</tbody>
</table>

The spinal cord involvement pattern was indistinguishable between the two groups: swelling and increased T2 signal intensity of the involved spinal cord in acute phase and partial resolution of the lesions with residual signal changes and cord atrophy on follow-up imaging.

Some were enhanced homogeneously and moderately, while one had no enhancement despite the swollen cord. One patient with SLE (no: 5) showed intense enhancement of the upper thoracic cord lesion, while a homogeneous mild enhancement was observed in the conus medullaris lesion (Figure 3B).

A typical dorsal medullary location with a well-defined border and homogeneous Gd enhancement of MS lesions were not features of myelopathy with collagenous tissue disorders in our case series.

Our cases also showed long segment myelopathy (≥ 2 vertebrae high) without predilection of the dorsal spinal cord.

Sometimes a clear distinction between MS, pSS SLE patients can be difficult, because clinical and laboratory features and MRI lesions can be indistinguishable.

In such conditions, cerebrospinal fluid findings, especially oligoclonal band positivity, help to confirm the MS diagnosis.

In CNS lupus oligoclonal bands analysis is positive in up to 50% of patients, although, interestingly and unlike MS, these changes can resolve with successful immunotherapy [10].

**Table IV**
MRI findings of primary Sjögren’s syndrome patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Cranial MRI</th>
<th>Spinal MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No lesion in the brain, BS, or cerebellum</td>
<td>Acute myelopathy at the level of C4-T4 vertebrae (Fig. 3C, D)</td>
</tr>
<tr>
<td></td>
<td>No atrophy of the brain, BS, or cerebellum</td>
<td>No leptomeningeal involvement</td>
</tr>
<tr>
<td></td>
<td>No leptomeningeal involvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No interval change on 1 year follow-up MRI</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Abundant T2 hyperintense foci that coalesce in the ST WM, diffuse white matter involvement (Fig. 2A)</td>
<td>A chronic T2-hyperintense lesion in the dorsal SC at the level of T1-T2 vertebrae without CE</td>
</tr>
<tr>
<td></td>
<td>1 lesion in the pons</td>
<td>No SC atrophy</td>
</tr>
<tr>
<td></td>
<td>No lesion in the cerebellum</td>
<td>No SC atrophy</td>
</tr>
<tr>
<td></td>
<td>No CE of the parenchymal lesion</td>
<td>No leptomeningeal involvement</td>
</tr>
<tr>
<td>3</td>
<td>Severe brain atrophy</td>
<td>Holocord atrophy, predominantly caudal to the level of C6 vertebrae,</td>
</tr>
<tr>
<td></td>
<td>No atrophy of the BS, cerebellum</td>
<td>No acute SC lesion</td>
</tr>
<tr>
<td></td>
<td>No leptomeningeal involvement</td>
<td>No CE of the SC</td>
</tr>
<tr>
<td>4</td>
<td>Abundant T2 hyperintense foci in the ST WM</td>
<td>No leptomeningeal involvement</td>
</tr>
<tr>
<td></td>
<td>A punctate acute ischemic lesion in the left parietal WM on DWI (Fig. 2C)</td>
<td>No SC lesion</td>
</tr>
<tr>
<td></td>
<td>1 lesion in the midbrain</td>
<td>No SC atrophy</td>
</tr>
<tr>
<td></td>
<td>No lesion in the cerebellum</td>
<td>No CE of the SC</td>
</tr>
<tr>
<td></td>
<td>No CE of the parenchymal lesion</td>
<td>No leptomeningeal involvement</td>
</tr>
<tr>
<td></td>
<td>Moderate brain atrophy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No atrophy of the BS, cerebellum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No leptomeningeal involvement</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Abundant T2 hyperintense foci in the ST WM</td>
<td>Acute myelopathy at the level of C1-T6 vertebrae and chronic changes with SC atrophy at the level T2-T11 vertebrae</td>
</tr>
<tr>
<td></td>
<td>Irregular and T2 hyperintense CC inferiorly (Fig. 2D), CE in 1 lesion in the CC</td>
<td>No CE even in the swollen segments</td>
</tr>
<tr>
<td></td>
<td>1 lesion in the cerebellum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No atrophy of the brain, BS, or cerebellum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No leptomeningeal involvement</td>
<td></td>
</tr>
</tbody>
</table>

ST WM-supratentorial white matter, BS-brainstem, SC-spinal cord, CE-contrast enhancement, CC-corpus callosum
In our group with the final diagnosis of SLE or pSS, the patients did not have any oligoclonal band positivity from the beginning.

Although higher prevalence of aPL antibodies has been reported especially in SLE [29], they have also been reported with variable frequency in MS patients [29]. Some authors found an aPL prevalence of 5.7% in patients with classic MS [30].

Neurological involvement in SLE is frequently associated with aPL [31–34]. Several reports indicate that there is a significant association between TM and the presence of aPL [35][36]. The prevalence of aPL in SLE – including asymptomatic patients – is approximately 30–50% [32].

In our SLE group, 4 patients were positive for either aCL or β2-GPI.

In the pSS group, 2 displayed aCL positivity. Prevalence of aCL and β2-GPI in pSS was 35% and 38%, respectively.

Variable prevalences (2-44%) of aCL or aPL have been reported in patients with MS and some of these trials reported that MT and ON are common in aCL or β2-GPI positive patients.

Some authors reported 27 patients referred to their unit with the diagnosis of probable or definite MS, all patients had aPL in this atypical MS presentation [37][38].

In our study, aCL or β2-GPI were positive in 4 of 5 SLE and in 2 of 5 pSS patients.

aCL or β2-GPI are not useful for the differential diagnosis of CD and SM; however, the presence of aPL should be a warning for the prognosis of neurological involvement.

In a prospective study, a high prevalence of ANA (22.5%) was detected [30], whereas anti-Ro/SSA antibodies were reported in a prevalence of 7% in MS [40][41].

ANA has a high sensitivity but low specificity for the diagnosis of SLE.

27% of MS patients have ANA positivity and these results were confirmed in other prospective trials [42].

Despite these results, CD should be considered when ANA titers are high (> 1:160) and persistent; therefore, the persistence of high ANA titers and anti-dsDNA should alert the clinician to SLE (Collard) [39].

ANA positivity in pSS was reported at a rate of 72.8% [43].

On the other hand, anti-dsDNA is highly specific for SLE and all of our patients with SLE had these antibodies, whereas none of the patients with pSS had anti-dsDNA antibodies.

Anti Ro (SS-A) or anti La (SS-B) antibodies are present up to 75-80% of pSS patients [10][44].

Some authors have found significative values of auto-antibodies to ribosome P in SLE patients with neurological involvement [45] and of anti-endothelial cell antibodies in SLE patients with acute ischemic stroke [46].

For the patients presenting with TM or ON, there is a tendency to start intravenous corticosteroid treatment as soon as possible. However, steroid treatment may also suppress other clinic and laboratory manifestations of CD leading to confusion in the diagnosis.

In our study, the interval between neurological and systemic symptoms was 8 and 9 years in 2 SLE patients and 9 and 11 years in 2 pSS patients.

Steroid treatment suppresses systemic findings and physician may make mistakes in the exact diagnosis.

Those patients who have possible MS diagnosis, but incomplete response to steroid treatment and atypical radiological findings should be examined further for CD.

During follow-up, these patients, who all had relapsing-remitting clinical profile with neurological signs resembling MS, showed limited response to intravenous corticosteroids. Their MRI findings never fulfilled the criteria for MS [47–51][57–59].

Although the autoantibody profile was screened several times no seropositivity was detected, probably due to the suppressive effect of repeated intravenous corticosteroid treatment. Over several years, all developed some systemic symptoms unexpected in MS, like arthritis, arthralgia, dry mouth and eyes, and headache. Repeated laboratory evaluations of vasculitic markers revealed positivity, leading to the final diagnosis of SLE or pSS.

Returning at our case with pSS, we consider necessary to highlight the many ways in which SS can affect the nervous system.

Recent studies revealed a key role of apoptosis in the destruction of glandular tissue. Some authors suggested that there is a large amount of apoptosis seen in acinar ductal epithelial cells than in the infiltrating lymphocytes; the initial apoptotic event (prior to infiltrating lymphocytes) may have
a viral source; in this case, the cells would stage a normal response to viral infection but would then be unable to control apoptosis, resulting in tissue damage and the clinical presentation of SS [52].

Sjögren’s syndrome related central nervous system is due to cell mediated neuronal injury resulting in inflammation [53–55].

Neurological involvement in pSS is wide, including peripheral nervous system abnormalities with a reported prevalence ranging from 10% to 20% [56][58][60][61].

Pure sensory neuropathy (PSN) is recognised as a characteristic neurological complication of pSS caused by damage of sensory neurones of the dorsal root and gasserian ganglia. There are three differentiated clinical courses for PNS: subacute progression in less than 1 month (7%), late acceleration some years after an initial indolent onset (20%), and a very long term insidious, chronic evolution (73%). Clinically, PNS usually responds poorly to treatment with corticosteroids or immunosuppressive agents, although stabilisation of symptoms (spontaneously or after treatment) during very long periods is often seen [60][62–64].

Autonomic neuropathy is reported in pSS patients, including autonomic cardiovascular abnormalities [65], cystitis-like symptoms [66][67] and parasympathetic nervous system dysfunction which have a role in xerostomia and xerophthalmia [68].

Several authors reported a higher prevalence of autonomic neuropathy in a small series of patients with pSS, with abnormal responses to cardiovascular tests in 69% and severe autonomic cardiovascular neuropathy in 87.5% [68]. Other authors observed in pSS patients signs of both sympathetic and parasympathetic dysfunction, especially those with anti-Ro/SS-A and anti-La/SS-B antibodies, and they had an abnormal blood pressure reaction to the tilt test [69].

Several studies reported no differences in the sympathetic and parasympathetic control function, comparing the cardiovascular regulation between patients with pSS and controls, and also no correlation between the results of clinical tests for parasympathetic dysfunction and decreased salivation or tearing [70][71][56].

New researches discovered that in pSS salivary glands there were found an increased number of muscarinic receptors in the synaptic cleft which bind acetylcholine (M3AChR), which may be secondary to two possible mechanisms: a) disturbed release of ACh, which might be inhibited by cytokines, or b) receptor blockade by specific anti-bodies. Both mechanisms have been proposed in the pathogenesis of pSS [72].

Irreversible binding of the antibody to M3AchR may lead to progressive receptor blockade – probably through desensitisation, receptor internalisation, and intracellular degradation – resulting in down-regulation of the exocrine secretion [73].

Antibodies to M3AchR may also damage the exocrine glands by the activation of NO synthetase and accumulation of NO in the acinar cells [73][74].

Muscular involvement consists in a predominance of subclinical myositis [75], rather than other types of myopathies such as inclusion body myositis [76].

Sensorineural hearing loss (SHL) was observed in some pSS patients, associated with aPL, ANA, anti-SS-A or anti-SS-B [77].

On the other hand, central nervous system abnormalities occur in pSS with a variable prevalence [78–81].

Central nervous system involvement can include disorders involving the brain (focal or multifocal) and the spinal cord.

Those focal disorders in the brain can include motor and sensory loss with hemiparesis, aphasia, dysarthria, seizures, movement disorders, cerebellar syndrome [58][82–84], and very rarely intracranial hypertension [85][86] or central pontine myelinolysis [87].

Neuropsychological abnormalities include deficits of attention, concentration, verbal intelligence greater than non-verbal intelligence, signifying a subcortical dementia, or dysnomia.

Affective disorders include somatization, depression, dysphoria, anxiety, panic, hysteria, and hypochondriasis [88–93].

TM has been reported in pSS and in patients with pSS and primary biliary cirrhosis (94). It has a low prevalence in patients with pSS (<1%).

The pathology of findings in the CNS in pSS include mononuclear lymphocytic infiltration in the meninges and parenchyma, microinfarcts and micro-hemorrhages 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.

Possible etiopathogenesis of TM in pSS patients are vasculitis, immunological injury of spinal vessel and/or spinal cord driven by reactive T cells,
and/or the presence of antineuronal antibodies [95] [96].

Nervous system involvement in SS, just by the position and nature of lesions and infiltrates that may develop, can mimic many other diseases. The relationship between MS and SS is controversial, some MS patients with progressive spastic paraparesis, SS-A or SS-B antibodies negative and with abnormalities in spinal cord MRI may have SS as an additional or alternative diagnosis [97][98].

The diagnosis of pSS with neurologic involvement is sometimes difficult. 30% of patients with CNS involvement have oligoclonal bands [99]. Several authors concluded that anti-aquaporin 4 antibodies (AQP 4) are highly specific for the diagnostic of neuromyelitis optica in the context of several autoimmune and infectious diseases, there is no association of anti-AQP 4 antibodies with neurological manifestations in SS [100].

A study demonstrated that pSS patients with recurrent CNS involvement have brain abnormalities characteristic of NMO and anti-AQP 4 antibodies [101].

Nervous system involvement in SS closely resembles MS clinically. Not only can symptoms be similar, but test results from brain MRI scans, brain electrophysiologic studies (evoked response tests) and CSF exams can be indistinguishable, presenting a real diagnostic dilemma [102–105].

The CNS symptoms may be due to the unique blood vessel inflammation that can occur in SS rather than demyelination which occurs in MS. Some authors suggested that CSF anti-SS-A autoantibodies could serve as a biomarker for SS-related CNS involvement [106].

Therapy in neuroSjögren is directed toward the vasculopathy associated with the neurological manifestation. These can include corticosteroids, cyclophosphamide, azathioprine, chlorambucil, and IGIV [107–111], in refractory cases the treatment with rituximab is recommended [111][112].

CONCLUSION

Screening for biomarkers of SLE or pSS should be systematically performed in a case of acute or chronic myelopathy. Some laboratory tests such as CSF examination, the antibodies type, cranial and spinal MRI, are useful for the differential diagnosis with MS. In a neurological clinically isolated syndrome the diagnosis of MS should be cautiously established; the close follow-up of patients is always necessary, those with atypical neurological symptoms for MS, relapsing-remitting form, or lack of response to the common treatment for MS, should be examined for CD.
neurologic atipice pentru SM, forma cu pusee și remisiuni, sau lipsa răspunsului la tratamentul uzual pentru SM, trebuie examinate pentru BC.

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