

Devic's syndrome and mixed connective tissue disease: an unusual association

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ABSTRACT

Devic's disease or neuromyelitis optica (NMO) is an autoimmune, inflammatory and demyelinating pathology of the central nervous system that affects the optic nerve and the spinal cord. Diagnosis confirmed by imaging, magnetic resonance (MR) and the presence of the anti-aquaporin 4 antibody (anti-AQP4). We describe two cases of patients with mixed connective tissue disease (MCTD) and Devic's disease, who had anti-AQP4 positive and areas with neuroaxis MR abnormalities, showing this rare association.

Keywords: Devic's syndrome; Mixed connective tissue disease; Optic nerve; Spinal cord.

INTRODUCTION

The neuromyelitis optica (NMO), also known as Devic's disease is a demyelinating inflammatory disease of the central nervous system (CNS), that affects the optic nerve and bone marrow¹. In 1894, Eugène Devic identified the association of optic neuritis and transverse myelitis as independent entities². The NMO has a striking characteristic: the presence of the antibody against the aquaporin water channel 4 (AQP-4) that differentiates this disease from multiple sclerosis³.

Mixed connective tissue disease (MCTD) is an overlap syndrome, which combines findings of three autoimmune diseases, associated with high titers of anti-ribonucleoprotein antibody (anti-U1-RNP)⁴. The neurological manifestations are less common than the involvement in other organs⁵.

In the literature, association between NMO and systemic lupus erythematosus, Sjogren's syndrome and juvenile dermatomyositis have already been described^{6,7}. There are few reports of association of MCTD and Devic's Syndrome^{8,9}. We describe two patients with MCTD, who evolved with neurologic manifestations and diagnosis of NMO, showing this rare association.

CASE 1

Female patient, 19 years old, with the diagnosis of MCTD 9 years ago, by the criteria of Alarcón-Segovia: anti-U1-RNP 1:12.800, Raynaud's phenomenon, synovitis and myositis. Receiving mycophenolate mofetil (MMF) 1.5 g/day for three years. In April 2016, after a viral prodrome, a burning pain in the foot sole region started, with pruritus and bilateral paresthesia, with ascending progression up to level of T6, associated to visual turbidity and urinary retention. Physical examination showed atypical gait and muscular force degree IV in the lower limbs (LL). Cranial nerves: left hemianopsia, sensitivity and preserved cephalic motricity, absence of dysphagia and dysarthria. Fundoscopy: ill-delimited optical disc and tortuous vessels in the eyes. Laboratorial examinations: hemoglobin 11.4g/dL, hematocrit 35.7%, leukocytes 3870 mm³ (segmented 1.900, lymphocytes 1.188), platelets 206,000/mm³, erythrocyte sedimentation rate (ESR) 30mm/1sth, c-reactive protein (CRP) 9 mg/L (baseline value < 6,0), anti-nuclear antibodies (ANA) 1:1280 nuclear large/coarse speckled, serology of cytomegalovirus (CMV), human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV): negative. Cerebrospinal liquid (LCS): 12 cells, protein: 53 mg/dL, glucose: 36 mg/dL. Electroneuromyography of LL: sensitive polyneuropathy of demyelizing nature, and alterations in the magnetic resonance (MR) of the thoracic column and orbits (Figure 1A, B.) Diagnosis of NMO that was con-

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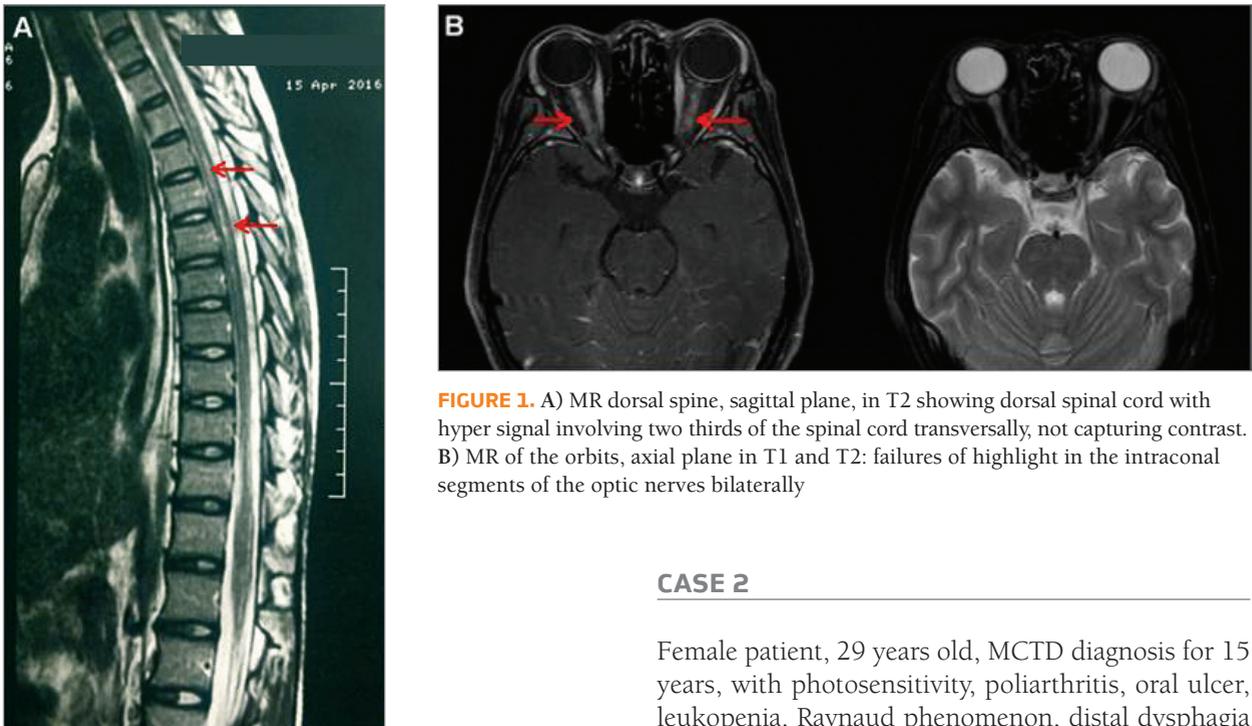


FIGURE 1. A) MR dorsal spine, sagittal plane, in T2 showing dorsal spinal cord with hyper signal involving two thirds of the spinal cord transversally, not capturing contrast. B) MR of the orbits, axial plane in T1 and T2: failures of highlight in the intraconal segments of the optic nerves bilaterally

firmed with the positivity for antibody anti-AQP4 IgG. The patient received pulse treatment with methylprednisolone (MP) 1g/day/five days, followed by plasmapheresis/seven days, and was started on intravenous (IV) cyclophosphamide (CYC) 750mg/m² monthly. After the first month from the beginning of the treatment, the patient revealed a significant improvement of the visual and neurological symptoms. In the third dose of CYC, it presented new NMO attack, confirmed by the MR of spine, but without ocular complaints, carried through new course of IV steroids and plasmapheresis. Hospital discharge with rituximab 2g every 6 months and MMF 1g/day with clinical improvement. In the fifth month of treatment the patient presented an allergy to the MMF, being suspended, at the time, in the absence of bilateral visual deficit and a new ophthalmologic new evaluation revealed well delineated optical disc, slightly paleness in the right eye. The patient evolved with a third neurological crisis, with no visual manifestations, proven by MR of the skull: injuries with hypersignal in T2 and FLAIR involving the left thalamus-capsular region and the posterior branch of the internal capsule to the right. The patient was admitted, performed pulsotherapy with MP and maintenance rituximab and azathioprine. Currently the patient is in remission of the disease.

CASE 2

Female patient, 29 years old, MCTD diagnosis for 15 years, with photosensitivity, polyarthritis, oral ulcer, leukopenia, Raynaud phenomenon, distal dysphagia and pulmonary interstitial disease, ANA 1:1280 nuclear large/coarse speckled, antibodies anti-Sm, SSA/Ro, SSB/La: negative and anti-U1-RNP 600 U/ml. Treated with CYC pulses (750mg/m²) monthly for 12 months, with good clinical response and maintenance therapy with azathioprine. Six years ago, she started an acute condition of paresthesia and symmetrical hypoesthesia of LL, ascending up to level of T8, paraparesis, pulsatile holocranial chronic headache of moderate intensity and urine retention. Physical examination showed Raynaud's phenomenon and reticular livedo in LL. Neurological observation highlighted unspecific paraparetic gait, muscle force grade IV in the four limbs, but with slight predominance of the proximally deficit in LL. Cranial nerves showed absence of acuity deficit, left homonymous hemianopsia, preserved sensitivity and facial motricity, in the absence of dysphagia and dysarthria. Ophthalmologic examination identified atrophy of right optic papilla, in the absence of alterations in papilla and left macula, but an photomotor reflex indicating afferent pupillary defect of the left eye. MR of cervicodorsal spine and skull (Figure 2 A, B). Retinography is showed in Figure 3. LCS evidenced cytometry of 10 cells, rare lymphocytes, protein 70.2 mg/dL and glucose 40 mg/dL. Serologies: HBV, HCV, HIV, CMV, herpes simplex were negative. Anti-AQP4 IgG positivity 1:80, confirmed the diagnosis of Devic's disease. She received pul-

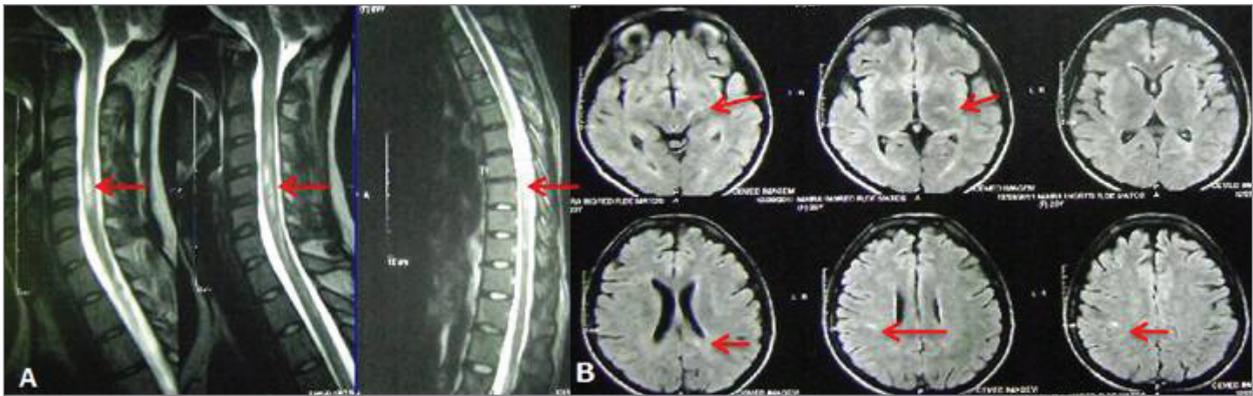


FIGURE 2. A) MR of cervicodorsal spine, sagittal cut, in T2; areas of signal alteration, in the segment between C3-C4 and C7-T1, prevailing in the central and left anterolateral region and medullar segment between T3-T4 to T-10. B) Brain MR, axial cut, in T1 post-contrast: areas of signal change in the peri-ventricular white substance, bilateral and semi-oval center to the right, right insular, cortex brain peduncle and thalamus-capsular region to the left, of unspecific aspect.

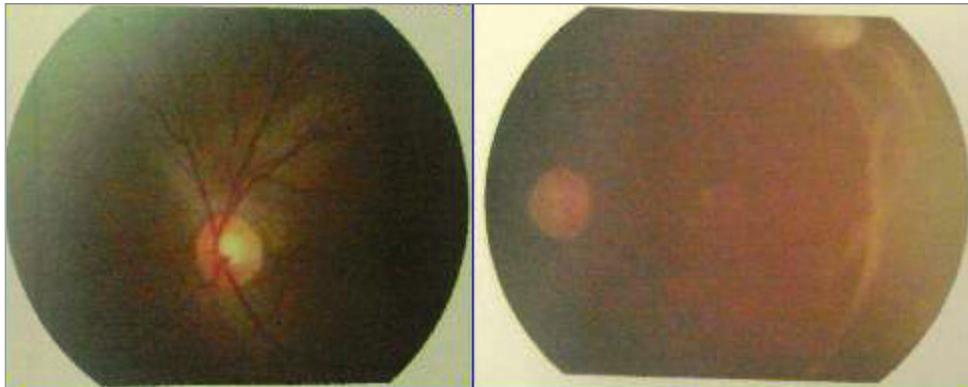


FIGURE 3. Retinography: papilledema and scar of temporal corioretinitis at macula of right eye

sotherapy with MP 1g/day/3 days, evolving with onset of brainstem, especially bulbar and several episodes of emesis and tachypnea, lead to perform plasmapheresis with improvement and partial recovery of the motor deficit and maintenance with CYC/750mg/m² monthly. After 2 months, patient abandoned treatment and got pregnant. In the sixth month of pregnancy, the patient presented fetal loss and a second surge of NMO with bilateral total amaurosis and paresthesia in LL. Received a new course of MP followed by plasmapheresis/5 days and subsequent CYC 1g/monthly for six months with improvement in the sensitive symptoms, but without eyesight recovery (total atrophy of the optical nerve), and then was maintained with rituximab 2g every 6 months and MMF 3g/d. Currently with disease controlled and bilateral visual acuity without luminous perception.

DISCUSSION

The NMO in patients with MCTD is a rare entity with few published reports^{8,9}. This association is not yet well established, but some mechanisms may be implied, such as the presence of immunogenetic and/or environmental factors that predisposes to autoimmunity⁶.

Devic's disease is a condition of the CNS in particular of the spinal cord, in which the optic neuritis is associated with transverse myelitis, therefore, also called NMO. Initially it was described as a single-phase syndrome, currently it is considered as multiphase in 85% of the cases¹.

In literature, the relapses can occur in 2 to 3 years, and the characteristics that predict a relapse course are: advanced age, female gender, evidence of systemic autoimmunity and positivity of anti-AQP4¹⁰. The larger

the number of recurrences, the lesser the chance of full recovery. More than 50% of the patients with recurring NMO, after 5 years from the onset of the disease, have partial or full visual deficit¹¹. In the first case, after the fifth month of evolution, the patient had good visual acuity, in spite of presenting slightly pallid optical disk in the right eye. The patient of the second case evolved with bilateral blindness, because she was older, had more time of disease and little response to the therapy. Kim and collaborators, in 2013, in a retrospective study with 184 patients, evaluated which factors were associated with the interval of time for a new attack of NMO and demonstrated that those patients in use of azathioprine, prednisone or rituximab have a longer period of time between relapses¹². Moreover, it is known that viral infections can act as a trigger for the onset of a crisis in patients with anti-AQP4 positivity¹³. The surges of NMO are preceded by infection or vaccination in up to 20 - 30% of the cases¹⁴.

In the first case reported, the patient presented several relapses in one year (three surges of neurological manifestations) and had two risk factors for a relapse form: female gender and autoimmune disease¹⁰, and the first attack was preceded by viral symptoms, as described in the literature^{12,14}.

In the exacerbations of Devic's disease, LCS shows to unespecific abnormalities such as neutrophilic pleocytosis (> 50cells/mm³), high protein levels and oligoclonal bands may be present (17- 43% of the cases)¹⁰.

Wingerchuk et al, in 2015 proposed new diagnostic criteria for NMO, defined a new nomenclature enclosing spectrum disorders of the NMO (NMOSD), subdivided in two groups: with or without anti-AQP4 positivity. In the positive anti-AQP4 group it is necessary at least one of the following typical neurological syndromes (after exclusion of other pathologies): optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with typical injuries in the MR and symptomatic cerebral syndrome with NMOSD-typical brain lesions. In the group of anti-AQP4 negative or with unavailable test, more rigorous clinical criteria are needed, with additional findings of neuroimage¹⁵.

The brain MR, at the beginning of the disease, can be normal or with unespecific injuries that involve predominantly the hypothalamus, being able to extend around the third and fourth ventricles and aqueduct of Sylvius, regions that correspond to the areas of localization of the AQP4 channel, a water channel in the cel-

lular membrane and expressed in an abundant form in vascular structures of the CNS, responsible for homeostasis of fluids^{6,16}.

In the cases reported, the specific anti-AQP4 marker was positive. The auto-antigen for NMO-IgG is an antibody against AQP4 with 73% sensitivity and specificity of 91% for the diagnosis of the Devic's disease³. The specificity of the anti-AQP4 extended the clinical specter, allowing the identification of the disease in initial phases, when the specific therapy is more effective^{3,10}.

The neurological manifestations in the MCTD include headache, convulsion, psychosis, encephalopathy, peripheral neuropathies and myelitis, being the trigeminal neuralgia the most frequent, and may even be the initial manifestation of the disease⁵. The suggested mechanisms to explain the condition of myelitis in MCTD include vasculitis and thrombosis of small arachnoid arteries of the spinal cord or the presence of antiphospholipids antibody^{8,17}.

The therapeutical strategy of NMO and MCTD is not well defined due to the rarity of the case. In acute surges, the first line of treatment consists of plasmapheresis with MP, followed of immunoglobulin and plasmapheresis in the refractory cases^{7,8}. Immunosuppressive drugs are used in the maintenance treatment, being azathioprine and rituximab considered first-line treatment for NMO, with safety, good long-term response and higher interval between relapses¹⁴.

In short, the authors call attention to a rare association of Devic's disease in patients carrying MCTD, and emphasize the importance of early diagnosis with precise therapy.

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