CASO CLÍNICO/CASE REPORT

Charcot-Marie-Tooth Type 2 Disease and Relapsing-Remitting Multiple Sclerosis Coexistence

Coexistência de Charcot-Marie-Tooth Tipo 2 e Esclerose Múltipla Forma Surto-Remissão

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Abstract

Multiple sclerosis (MS) and Charcot-Marie-Tooth disease (CMT) association has been reported, namely in CMTX and CMT1A.

A 37-year-old woman with CMT type 2 (*MFN2* mutation) developed subacute brainstem syndrome (left internuclear ophthalmoplegia, facial palsy and ataxia). Brain magnetic resonance imaging revealed infratentorial, periventricular and subcortical lesions, typical of MS (positive CSF oligoclonal bands, negative anti-aquaporin 4 and anti-MOG antibodies). Patient underwent natalizumab, reaching NEDA-3 – no evidence of disease activity - (3-years follow-up).

Patients with *MFN2* mutations may disclose optic atrophy and periventricular white matter T2 signal changes mimicking MS. Notwithstanding, this is, probably, the first report of proven concomitance between both conditions.

Resumo

A associação entre esclerose múltipla (EM) e doença de Charcot Marie Tooth (CMT) foi reportada previamente, nomeadamente em casos de CMTX e CMT1A.

Uma mulher de 37 anos com CMT tipo 2 (mutação *MFN2*) desenvolveu uma síndroma do tronco cerebral (manifesta com oftalmoplegia internuclear esquerda, parésia facial e ataxia) de forma subaguda. A ressonância magnética (RM) cerebral mostrou lesões desmielinizantes infratentoriais, periventriculares e subcorticais típicas, estabelecendo-se o diagnóstico de EM (bandas oligoclonais positivas no LCR e anticorpos anti-MOG e anti-AQP4 negativos). A doente foi tratada com natalizumab tendo atingido NEDA 3 – sem evidência de doença ativa - (em seguimento há 3 anos).

Doentes com mutações *MFN2* podem apresentar atrofia do disco óptico e alterações de sinal na RM na ponderação T2, que mimetizam EM. Contudo este é, provavelmente, o primeiro caso reportado de concomitância das duas entidades.

Introduction

Primary hereditary motor sensory neuropathies or Charcot-Marie-Tooth disease comprise a complex heterogeneous spectrum of neuropathic disorders,[1] classically divided into: type 1 (CMT1) predominantly demyelinating, most frequently caused by a 1.4 MB tandem duplication comprising the *PMP22* gene on chromosome 17p11.2-12 (CMT1A); and type 2 (CMT2), predominantly axonal, related to mutations of the mitochondrial fusion protein mitofusin 2 gene, *MFN2*, on chromosome 1p36.2 (CMT2A).[2,3] It also includes: Dejerine-Sottas disease, the severe infantile-onset CMT; type 4 (CMT4), autosomal recessive; and the X-linked inheritance type 1X (CMT1X).[2] Although CMT represents a group of exclusive neuropathic hereditary disorders, it is known the association with several systemic and neurological entities, multiple sclerosis (MS), yet rarely, being one of them. This latter association has been reported with CMT1A and CMTX, with some patients with *MFN2* mutations presenting optic atrophy and periventricular white matter T2 signal changes mimicking MS.[4,5] Moreover, there is evidence supporting the possibility of white matter disease in CMT patients that does not meet MS criteria making correct diagnosis a challenge. Here, we aim to report a clinical case in which we have found the coexistence of CMT2 and MS.

Case Report

A 37-year-old female presented with dizziness and imbalance for 3 days, no mention of other recent complains including fever or trauma. Two years before the patient had been diagnosed with CMT type 2, having an axonal type motor sensory neuropathy associated with *MFN2* mutation – heterozygote for c.2119C>T (p.(Arg707Trp)) variant (previously associated with dominant and recessive forms of CMT). The diagnosis was made in our neurology department, where she was followed on a regular basis. She had pes cavum and steppage gait since childhood. Two siblings had the same phenotype. Parents were healthy and not relatives. There was no family history of MS or other autoimmune diseases. Patient was otherwise healthy. Neurological examination disclosed left internuclear ophthalmoplegia, nystagmus, left peripheral facial palsy and axial ataxia, aside previous known arreflexia and steppage gait. Brain magnetic resonance imaging (MRI) (**Fig. 1**) showed T2/FLAIR, hyperintensities, non-gadolinium-enhanced, right mesencephalic and upper pons, periventricular and juxtacortical white matter, MS characteristic demyelinating lesions, spinal cord was spared. She had 10 CSF-specific-oligoclonal bands and high IgG index (1.16) in otherwise normal CSF. Serum anti-aquaporin 4 and anti-MOG antibodies were negative as autoimmune and infectious work-up, except serum EBV IgG positive, positive antinuclear (1/1280) and anti SSA antibodies (64 U/mL) but with no sicca syndrome, negative Schirmer test and no pathological Sjögren features after biopsy of minor salivary glands. Relapsing remitting MS diagnosis was diagnosed in agreement with 2017 revisions of the McDonald criteria.[6] Neurological examination resumed to previous status after steroids (MPev 1 g/d 5 days). Considering brain MRI lesion burden and negative JCV status, patient started natalizumab. She experienced no further relapses or de novo MRI lesions, remaining in the same neurological CMT related dysfunction, after 3 years follow-up.

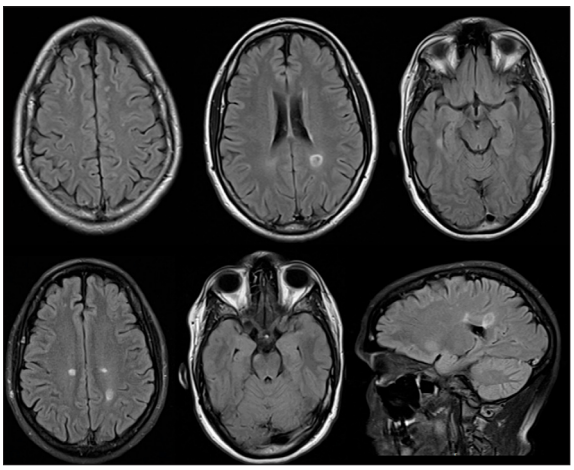

Figure 1. Brain MRI at the diagnosis. Axial T2 FLAIR Images (A-E): Hyperintense lesions in the right mesencephalic and upper pons, periventricular and juxtacortical white matter. Sagittal T2 FLAIR (F): Perpendicular lesions in the corpus callosum, "Dawson's fingers".

Discussion

Here, we report, to our knowledge, the first case of coexistence of MS and CMT type 2. Other authors have presented cases of MS patients who also had CMT – however, only demyelinating variants have been described.[7] Namely, CMT1A and CMT1X have been linked to MS not only in case reports but also as a conceptual idea. Apart from four described patients in the literature regarding the former, authors have tried to establish a link between these two entities. It was theorized that

the explanation might reside in a common pathogenic mechanism on the *PMP22* gene[8,9] that is expressed in myelinating Schawnn cells of the of the peripheral nervous system and shares partial homology with other CNS proteins like the proteolipid protein (PLP). The authors proposed that genetic aberration could be the cause of simultaneity of CMT1A and MS. However, given the axonal features of CMT type 2, this model fails to provide a rationalization for the case we report therefore making it more exquisite.

On the broader side, there have been some studies about polyneuropathies (PNP) and MS. Here, the focus being on the demyelinating ones since they might share pathophysiology with MS. Central demyelination has been found in peripheral demyelinating diseases, such as chronic idiopathic demyelinating polyneuropathy (CIDP). Either presenting with symptoms, in 5%-8% of patients, or as findings in brain MRI of demyelinating lesions in 17%-37% of patients.[10,11]

However, independently of the PNP's etiology in MS individuals, it is known that the diagnosis can be delayed because there is some overlap of symptoms and neurologic signs between the entities. In our case, the PNP diagnosis was made previously and since it was a congenital condition the course was much slower and progressive making it extremely different from the subacute attacks seen in MS. Moreover, the case we report also highlights the importance of a thorough neurologic examination in identifying signals not matching with a "MS only" phenotype such as hypo/arreflexia – a helpful feature when trying to analyze these complex patients.[12]

Diagnosing both pathologies is difficult and challenging since, as previous explained, there is evidence for white matter disease in CMT patients, unrelated to MS. CMT diagnosis has genetic evidence and characteristic features making it easier. For MS, our patient met the criteria for classic typic syndrome of brainstem in regards to time evolution, semiology and objective examination findings. Brain MRI showed lesions of white matter that fulfilled MS characteristics in regards to size and topography distribution as well as being in line with presenting symptoms.[6] Paraclinical features, such as positive CSF-specific-oligoclonal bands, also favor MS diagnosis. Therefore, we agree on the coexistence of entities, although being aware of its uncertainty.

Regarding MS treatment in this particular case, the choice of disease modifying therapy followed the standard MS principles about disease activity however, we also took in consideration the fact that the patient already had disability secondary to CMT so we opted for a high-efficacy therapy with proven results in CMT patients[13] – natalizumab - considering JC virus negative status.

In conclusion, we report what we believe is the first known case of coexistence of CMT type 2 and MS. This might be coincidental and we cannot, with present data, establish any kind of association or relation between the two entities specially with CMT type 2 being an axonal PNP and MS a demyelinating disorder. We, nevertheless, think that is important to pay careful attention to these patients regarding symptoms and temporal pattern of installation as well as neurological findings in examination. ■

Contributorship Statement / Declaração de Contribuição
AJM, JPG: Pesquisa e elaboração do manuscrito.
AFM, AV: Avaliação clínica do doente.
AJM: Revisão do manuscrito.
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AJM, JPG: Research and draft of manuscript.
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