Working Up Relapsing Optic Neuritis: A Patient with Undiagnosed Chronic Relapsing Optic Neuritis

Investigação da Neurite Óptica Recorrente: Um Doente com Neurite Ótica Inflamatória Crónica Recorrente Não Diagnosticada

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ABSTRACT

Chronic relapsing inflammatory optic neuropathy (CRION) presents itself as a challenging clinical diagnosis, due to its rarity, mimicking clinical entities and workup required to obtain a well-substantiated diagnosis, deliver adequate treatment, and exclude potentially life-threatening differential diagnoses. A male patient presented with various episodes of optic neuritis. A full work-up was performed, including magnetic resonance imaging, lumbar puncture, and serologies for infectious and autoimmune diseases. Temporarily elevated levels of angiotensin-converting enzyme hampered the correct diagnosis, as repeat blood work was normal. After excluding multiple sclerosis, neuromyelitis optica, infectious and other autoimmune etiologies, the most likely diagnosis remained CRION. CRION should be kept as a differential diagnosis early during the disease course and repeat exams should be done whenever they do not match the clinical picture. CRION should be thought of whenever presented with a steroid dependent optic neuritis with decreased ganglion cell layer thickness and negative anti-myelin oligodendrocyte glycoprotein antibodies.

KEYWORDS: Neuromyelitis Optica/diagnosis; Optic Neuritis/diagnosis; Tomography, Optical Coherence.

RESUMO

A neurite ótica inflamatória crónica recorrente (CRION) apresenta-se como um diagnóstico clínico desafiante, devido à sua raridade, semelhança com outras patologias e à investigação necessária para obter um diagnóstico bem fundamentado, instituir um tratamento adequado e excluir diagnósticos diferenciais ameaçadores de vida. Um doente apresentou vários episódios de neurite ótica, realizou uma investigação completa que incluiu ressonância magnética do neuroeixo,

punção lombar e serologias infeciosas e autoimunes. Níveis temporariamente elevados da enzima de conversão da angiotensina atrasaram o diagnóstico. Após a exclusão de esclerose múltipla, neuromielite ótica, causas infeciosas e outras etiologias autoimunes, o diagnóstico mais provável manteve-se como CRION. CRION deve ser considerada como um diagnóstico diferencial, deve-se repetir exames sempre que estes não correspondam ao quadro clínico. Deve-se pensar em CRION sempre que haja uma neurite ótica dependente de corticosteroides, com redução da espessura da camada de células ganglionares e anticorpos anti-glicoproteína de oligodendrócito de mielina negativos.

PALAVRAS-CHAVE: Neuromielite Óptica/diagnóstico; Neurite Óptica/diagnóstico; Tomografia de Coerência Óptica.

INTRODUCTION

Chronic relapsing inflammatory optic neuropathy (CRION) is characterized by recurrent bilateral episodes of optic neuritis of demyelinating nature that are markedly steroid dependent.[1,2] It was first described in 2003 by Kidd *et al* in a cohort of patients that presented with episodic optic neuritis in the absence of brain magnetic resonance imaging findings or signs suggestive of systemic sarcoidosis.[3] Its mechanism of disease is thought to be related to the presence of anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibody.[4] Current diagnostic criteria are based presence of a steroid dependent relapsing optic neuritis in the absence of neuromyelitis optica antibodies (NMO-IgG).[1] Due to the relapsing nature of this clinical entity, long term immunosuppression is needed to maintain disease control.[1–3] Despite being a rare disease, it is most likely underdiagnosed as well as mistaken for similar diagnosis.

CASE REPORT

A male patient in his early twenties presented to the neuroophthalmology clinic with unilateral decreased vision and painful left eye movements. The patient had a previous episode of optic neuritis (ON) of the left eye 8 years ago. He presented decreased visual acuity (best corrected visual acuity (BCVA) +0.1 LogMAR). A relative afferent pupillary defect of the eye was evident. The left eye's optic disk was pale at fundoscopic evaluation. The right eye examination was unremarkable, as was the remainder of the neurological examination. The patient was treated with a 1000 mg intravenous methylprednisolone pulse followed by 20 mg daily oral prednisolone.

The patient underwent standard automated perimetry (SAP) and optical coherence tomography (OCT) of the macula. OCT imaging (Fig. 1) shows a globally decreased ganglion cell layer (GCL) thickness of the inferior retina on the left eye and a mild decrease in GCL thickness of the inferonasal retina of the right eye. Blood work, neuroaxis magnetic resonance imaging (MRI) with gadolinium contrast and a lumbar puncture (LP) were performed. MRI findings

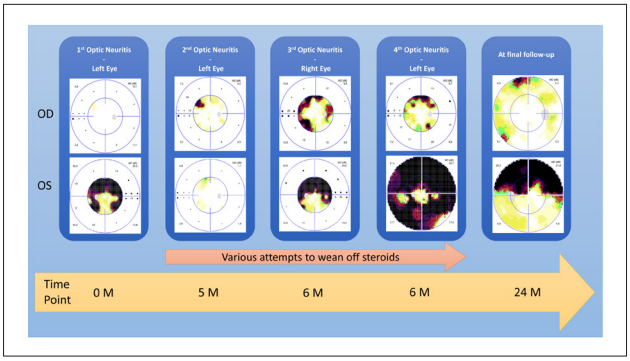

Figure 1. Initial macular OCT with ganglion cell layer.

were remarkable for left optic nerve contrast enhancement, no signs of demyelination in the remaining central nervous system were found. LP findings were unremarkable. Due to this, the diagnosis of multiple sclerosis (MS) or neuromyelitis optica (NMO) were placed aside. Blood work showed increased angiotensin converting enzyme (ACE) levels (100 nmol/mL/min), alanine transaminase (ALT) (84 U/L) and aspartate transaminase (AST) (52 U/L), while interferon-gamma release assays, human immunodeficiency virus (HIV) and syphilis serology were negative. Based on these findings, a suspicion of systemic sarcoidosis was raised. Chest and abdominal computerized tomography were performed; they were unremarkable. A diagnosis of sarcoidosis was assumed and treated accordingly with weekly 12.5 mg methotrexate followed by a slow steroid taper.

Despite receiving treatment, over the following six months, the patient developed another three episodes of optic neuritis affecting both eyes sequentially. The lowest visual acuity recorded during episodes of ON was +0.4 LogMAR. Progression and ON relapses were documented on SAP and show the clinical course timeline (Fig. 2). Fig. 2 demonstrates multiple new and resolving scotomas of the superior and inferior hemifields of both eyes. Repeat ON episodes impeded steroid tapering. Increasingly greater immunosuppression was necessary to obtain adequate disease control; the diagnosis of sarcoidosis was called into question. MRI of the neuroaxis, repeat blood work with expanded serology, and Leber hereditary optic neuropathy

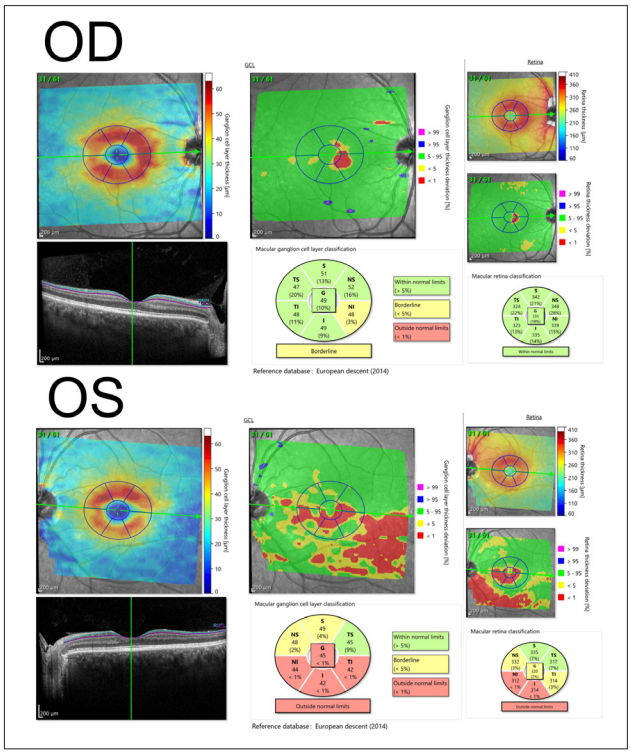

Figure 2. Visual field clinical course timeline.

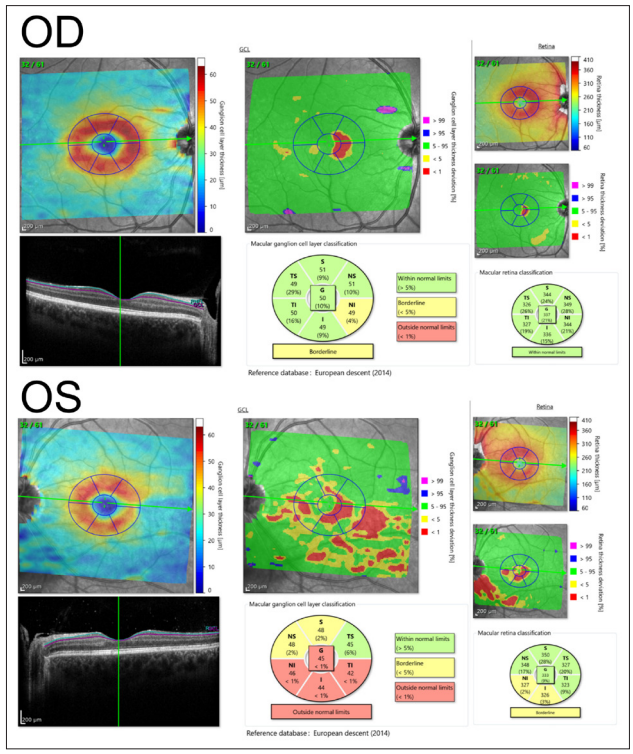

Figure 3. Final macular OCT with ganglion cell layer.

genetic testing were performed. MRI findings remained nonsuggestive of a central nervous system demyelinating disease. ACE levels and well as hepatic enzymes were now within normal values. Aquaporin-4 (AQ4), anti-MOG antibodies and genetic testing were negative. Thus, based on current diagnostic guidelines1 the diagnosis of CRION was established.

The final OCT of the macula is shown in Fig. 3. Although similar to the presenting OCT, there is a decrease in total retinal thickness of the inferior retina of the left eye. At the final follow-up, Fig. 2 demonstrates a concordant superior scotoma of the left eye. After two years and further relapses, visual acuities were 0 and +0.1 LogMAR of the right and left eye, respectively. Bilateral optic disk atrophy was evident on fundoscopic evaluation. Currently, to wean off steroid treatment, the patient is attempting to start rituximab.

DISCUSSION

CRION is a disease whose pathophysiology remains elusive, recent studies suggest that it is encompassed into the group of diseases related to the presence of anti-MOG antibodies.[4–6] MOG is a glycoprotein present on the surface of oligodendrocytes and its function is thought to relate to intercellular adhesion, microtubule stability and complement activation.[6] Other diseases share the same inciting antibody, such as acute disseminated encephalomyelitis, isolated myelitis, isolated ON and AQ4 IgG negative neuromyelitis optica (NMO), and are thought to have similar pathophysiology.[4,6] Recent OCT studies show that CRION optic-nerve atrophy, unlike that in MS, involves marked loss of total macular volume, ganglion-cell and inner plexiform layers,[7] these changes are consistent with this disease's high risk of blindness.[1]

As CRION is a diagnosis of exclusion, and as suggested by Petzold *et al*, other clinical entities need to be excluded.[1] The differential diagnosis includes other autoimmune causes of ON, such as multiple sclerosis ON (MSON), NMO and relapsing isolated ON (RION). MSON was excluded through negative neuroaxis MRI and LP findings, while NMO was excluded by both negative MRI and AQ4 antibodies. RION does not present with the steroid dependence, high number of relapses and bilaterality exhibited in this case. Infectious etiologies (such as HIV, syphilis, and tuberculosis) were excluded through serologic testing, Lyme disease was not entertained as the region is not considered endemic. LHON was excluded through genetic testing.

This clinical case demonstrates the classic clinical picture of CRION as described by Kidd *et al*.[3] It features imaging-confirmed relapsing bilateral ON that is steroid dependent. Petzold *et al* in 2013 published a systematic review of 122 case reports of CRION and put forth the currently accepted diagnostic criteria (Table 1). He found that most patients present with bilateral sequential visual loss, having at least one episode, followed by multiple relapses. Petzold et al reported that visual acuity during optic neuritis episodes was inconsistent, yet typically poor: 68 % of patients recorded +1.0 LogMAR or worse. At final follow-up, vision was still reduced, with a mean acuity of +0.48 LogMAR.[1]

Table 1. CRION suggested diagnostic criteria. Petzold *et al*[1].	
History	ON and at least one relapse
Clinical	Objective evidence for loss of visual function
Labor	NMO-IgG seronegative
Imaging	Contrast enhancement of the acutely inflamed optic nerves
Treatment	Response to immunosuppressive treatment and relapse on withdrawal or dose reduction of immunosuppressive treatment

In the clinical case presented, visual acuity during episodes was higher than expected by Petzold's description, this could be attributed to timely immunosuppressive treatment of ON episodes. Although the clinical presentation and course strongly suggested a specific disorder, a definitive diagnosis was complicated by elevated ACE, AST, and ALT levels that suggested sarcoidosis.[8] Although lacking a target for histopathological confirmation, clinical suspicion was deemed high enough to motivate treating for sarcoidosis. Raised ACE levels have been historically linked to sarcoidosis and used in patients with a high degree of suspicion for sarcoidosis. Recent population-based studies have demonstrated a low sensitivity (41.4%) and moderate specificity (89.9%) in patients with systemic sarcoidosis and raised ACE levels.9 These findings may suggest that, in this patient, an earlier repeat ACE analysis could have been warranted owing to a low pretest probability. OCT findings demonstrated in Figures 2 and 3 appear to agree with recent publications, as substantial macular and ganglion cell layer thinning is shown, particularly on the left eye.[7] This structural loss matches the scotomas seen on SAP.

Despite the current understanding of the pathophysiology of CRION and recent association with anti-MOG antibodies, around a third of CRION cases are seronegative,[10] this being the case with our patient. As suggested by Liu *et al*, anti-MOG positivity may be related to worse prognosis as relapses are more frequent,[10] this may explain the surprisingly high visual acuity of the patient at final follow-up.

CRION should become the leading diagnosis when patients show steroid-dependent, relapsing bilateral optic neuritis after mimics such as MS, NMO, sarcoidosis, and infection have been ruled out. Rapid treatment with corticosteroids or other immunosuppressants, guided by OCT and perimetry, can preserve useful vision. This case highlights that clinical vigilance, and timely therapy can protect long-term visual function.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

ALC, SRD, and VML: Writing, design, and revision.
JTF: Writing and revision.
All authors approved the final version to be published.

ALC, SRD e VML: Escrita, desenho e revisão.
JTF: Escrita e revisão.
Todos os autores aprovaram a versão final a ser publicada.

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