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Optic neuritis: a narrative review on biomarkers and imaging in differential diagnosis

Neurite óptica: uma revisão narrativa sobre biomarcadores e imagem no diagnóstico diferencial

Neuritis óptica: una revición narrative sobre biomarcadores e imágenes en el diagnóstico diferencial

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João Pedro Gambetta Polay
ORCID: https://orcid.org/0000-0003-0170-1469
Universidade Estadual de Ponta Grossa, Brazil
E-mail: polayjp@gmail.com
Renata Nadal Bayer
ORCID: https://orcid.org/0009-0007-5492-8727
Universidade Estadual de Ponta Grossa, Brazil
E-mail: renatabayer4@ggmail.com
João Matheus Schirlo
ORCID: https://orcid.org/0009-0005-2886-7700
Universidade Estadual de Ponta Grossa, Brazil
E-mail: schirlo.joaomatheus@gmail.com
Juliane Tramontin
ORCID: https://orcid.org/0009-0008-2925-0712
Universidade Estadual de Ponta Grossa, Brazil
E-mail: juhtramontim@gmail.com
Nathan Nabozny
ORCID: https://orcid.org/0000-0003-0647-2087
Universidade Estadual de Ponta Grossa, Brazil
E-mail: naboznynathan@gmail.com

Abstract
Optic neuritis (ON), an acute inflammation of the optic nerve, is the most common optic neuropathy in young adults and constitutes a neuro-ophthalmologic emergency. For years, ON was viewed primarily as a sentinel event for Multiple Sclerosis (MS). However, recent discoveries, particularly serum antibodies against aquaporin-4 (AQP4-IgG) and myelin oligodendrocyte glycoprotein (MOG-IgG), have redefined the diagnostic landscape. This narrative review aims to synthesize the most recent scientific evidence (2020-2024) on the ON approach, focusing on the clinical, serological, and imaging findings that differentiate these etiologies. Methods: A narrative review was conducted, searching PubMed, SciELO, and LILACS for publications from 2020 to 2024 using relevant descriptors. Results: The synthesized literature indicates that atypical presentations (such as bilaterality, severe vision loss, pronounced papillitis, poor recovery) mandate immediate serological investigation. MOGAD-ON often presents with significant disc edema but a strong steroid response, whereas NMOSD-ON (AQP4+) is linked to a poor visual prognosis and high relapse risk. Tools like Optical Coherence Tomography (OCT) are essential for quantifying axonal damage (retinal nerve fiber layer), which is demonstrably more severe in NMOSD. Therapeutic management differs drastically; MS therapies can be ineffective or harmful in NMOSD. Conclusion: The approach to optic neuritis is no longer monolithic. The ophthalmologist plays a central role in the initial suspicion and must use biomarkers and imaging (OCT, MRI) for precise etiological classification, which dictates acute therapy and the need for chronic immunosuppression.
Keywords: Optic neuritis; Differential diagnosis; Optical Coherence tomography; Neurology, Ophthalmology.

Resumo
A Neurite Óptica (NO), uma inflamação aguda do nervo óptico, é a neuropatia óptica mais comum em adultos jovens e constitui uma emergência neuro-oftalmológica. Durante anos, a NO foi vista principalmente como um evento sentinela para a Esclerose Múltipla (EM). No entanto, descobertas recentes, particularmente os anticorpos séricos contra a aquaporina-4 (AQP4-IgG) e a glicoproteína da mielina de oligodendrócitos (MOG-IgG), redefiniram o panorama diagnóstico. Esta revisão narrativa tem como objetivo sintetizar as evidências científicas mais recentes (2020-2024) sobre a abordagem da NO, focando nos achados clínicos, sorológicos e de imagem que diferenciam essas etiologias. Métodos: Foi realizada uma revisão narrativa, com busca no PubMed, SciELO e LILACS por publicações de 2020 a 2024 usando descritores relevantes. Resultados: A literatura sintetizada indica que apresentações atípicas

(como bilateralidade, perda visual grave, papilite pronunciada, má recuperação) exigem investigação sorológica imediata. A NO associada ao MOGAD (MOGAD-ON) frequentemente se apresenta com edema de disco significativo, mas com uma forte resposta a esteroides, enquanto a NO associada ao NMOSD (NMOSD-ON, AQP4+) está ligada a um prognóstico visual ruim e alto risco de recidiva. Ferramentas como a Tomografia de Coerência Óptica (OCT) são essenciais para quantificar o dano axonal (camada de fibras nervosas da retina), que é demonstravelmente mais grave na NMOSD. O manejo terapêutico difere drasticamente; terapias para EM podem ser ineficazes ou prejudiciais na NMOSD. Conclusão: A abordagem da neurite óptica não é mais monolítica. O oftalmologista desempenha um papel central na suspeita inicial e deve usar biomarcadores e exames de imagem (OCT, RM) para uma classificação etiológica precisa, que dita a terapia aguda e a necessidade de imunossupressão crônica.
Palavras-chave: Neurite óptica; Diagnóstico diferencial; Tomografia de coerência óptica; Neurologia, Oftalmologia.

Resumen

La neuritis Óptica (NO), una inflamación aguda del nervio óptico, es la neuropatía óptica más común en adultos jóvenes y constituye una emergencia neuro-oftalmológica. Durante años, la NO se consideró principalmente como un evento centinela de la Esclerosis Múltiple (EM). Sin embargo, descubrimientos recientes, en particular los anticuerpos séricos contra la acuaporina-4 (AQP4-IgG) y la glicoproteína de la mielina de oligodendrocitos (MOG-IgG), han redefinido el panorama diagnóstico. Esta revisión narrativa tiene como objetivo sintetizar la evidencia científica más reciente (2020-2024) sobre el abordaje de la NO, centrándose en los hallazgos clínicos, serológicos y de imagen que diferencian estas etiologías. Métodos: Se realizó una revisión narrativa, buscando en PubMed, SciELO y LILACS publicaciones de 2020 a 2024 utilizando descriptores relevantes. Resultados: La literatura sintetizada indica que las presentaciones atípicas (como bilateralidad, pérdida visual grave, papilitis pronunciada, mala recuperación) exigen una investigación serológica inmediata. La NO asociada a MOGAD (MOGAD-ON) a menudo se presenta con un edema de disco significativo pero con una fuerte respuesta a los esteroides, mientras que la NO asociada a NMOSD (NMOSD-ON, AQP4+) se relaciona con un mal pronóstico visual y un alto riesgo de recaída. Herramientas como la Tomografía de Coherencia Óptica (OCT) son esenciales para cuantificar el daño axonal (capa de fibras nerviosas de la retina), que es demostrablemente más grave en la NMOSD. El manejo terapéutico difiere drásticamente; las terapias para la EM pueden ser ineficaces o perjudiciales en la NMOSD. Conclusión: El abordaje de la neuritis óptica ya no es monolítico. El oftalmólogo juega un papel central en la sospecha inicial y debe usar biomarcadores e imágenes (OCT, RM) para una clasificación etiológica precisa, que dicta la terapia aguda y la necesidad de inmunosupresión crónica.
Palabras clave: Neuritis óptica; Diagnóstico diferencial; Tomografía de coherencia óptica; Neurología, Oftalmología.

1. Introduction

Optic Neuritis (ON) is defined by the inflammation of the optic nerve, classically presenting with subacute vision loss, periocular pain on movement, and dyschromatopsia. Historically, the Optic Neuritis Treatment Trial (ONTT) (Optic neuritis study group, 1997) served as the paradigmatic foundation for understanding the disease, establishing its strong association with Multiple Sclerosis (MS). The ONTT defined that while pulse methylprednisolone accelerated recovery, the long-term visual prognosis was generally good, and the risk of conversion to MS was dictated by brain lesions on Magnetic Resonance Imaging (MRI) (Optic neuritis study group, 1997).

This landscape, however, has been drastically altered. The last decade has witnessed a neuro-immunological reconfiguration with the discovery of specific autoantibodies that cause ON but belong to distinct pathological spectra.

The first watershed was the discovery of anti-aquaporin-4 (AQP4-IgG) antibodies, the biomarker for Neuromyelitis Optica Spectrum Disorder (NMOSD) (Kim et al., 2023; Zakrzewska-pniewska et al., 2024). NMOSD-ON proved to be more severe, often bilateral, and with poor recovery (Kim et al., 2023). Shortly after, a second antibody, against myelin oligodendrocyte glycoprotein (MOG-IgG), was characterized in AQP4-seronegative patients, defining MOG Antibody-Associated Disease (MOGAD) (Chen; Pittock; Flanagan, 2020; Bennett et al., 2023).

This new etiological triad (MS-ON, NMOSD-ON, and MOGAD-ON) imposes an immediate challenge for the ophthalmologist, who is often the patient's first point of contact (Stiebel-kalish et al., 2023). Misdiagnosis is not trivial: using certain MS disease-modifying therapies (DMTs) can, for example, exacerbate NMOSD (Pisani et al., 2023), leading to severe visual and neurological consequences. The modern management of atypical ON now relies on this precise classification (Spillers et al., 2024).

Given this new diagnostic reality, this narrative review aims to synthesize the most recent scientific evidence (2020-2024) on the ON approach, focusing on the clinical, serological, and imaging findings that differentiate these etiologies.

2. Methodology

A narrative review of the literature (Rother, 2007) of qualitative nature (Pereira et al., 2018) was performed. The guiding research question was: "What is the current evidence for the differential diagnosis and management of optic neuritis, distinguishing between MS, NMOSD, and MOGAD etiologies?"

The search was conducted in the PubMed/MEDLINE, SciELO, and LILACS electronic databases. Combined descriptors (DeCS/MeSH) were used: "Optic Neuritis" AND "Ophthalmology"; "Atypical Optic Neuritis"; "MOGAD" OR "MOG antibody disease"; "NMOSD" OR "Neuromyelitis Optica Spectrum Disorders"; "Aquaporin-4"; "Optical Coherence Tomography".

Inclusion criteria were: original articles (clinical trials, cohorts), systematic reviews, and meta-analyses published between January 2020 and October 2024; languages of English, Portuguese, or Spanish; and a focus on the diagnosis, prognosis, or treatment of ON in humans. Articles focused purely on infectious, ischemic, or compressive etiologies, as well as editorials or letters without original data, were excluded.

The selected articles were critically analyzed, and relevant data were extracted and categorized for the synthesis presented in the results and discussion.

3. Results and Discussion

The analyzed literature allowed the findings to be grouped into three main axes: (1) The clinical features that define atypical ON ("red flags"); (2) The diagnostic role of serum biomarkers; and (3) The use of ophthalmic tools (OCT) and neuroimaging (MRI) in differentiation.

A consensus is observed in the recent literature regarding the need to classify ON beyond the "typical" (MS-associated) presentation described in the ONTT: a young woman, mild-to-moderate unilateral vision loss, prominent periocular pain, and a normal fundus exam (retrobulbar neuritis) (Optic neuritis study group, 1997).

The presence of "red flags" should direct the investigation toward atypical etiologies (Chen; Pittock; Flanagan, 2020). The most cited in the literature are: severe vision loss, bilaterality, absence of pain, severe papillitis (pronounced disc edema, sometimes with peripapillary hemorrhages), poor steroid response, and extremes of age (Bichuetti, 2021; Sá, 2021; Žorić; Silva, 2023; Čolak, 2024).

The most significant change identified in recent years is the mandatory serological testing in atypical cases (Dubuy et al., 2023). NMOSD-ON (AQP4-IgG Positive) is consistently reported as the most severe form of ON (Pisani et al., 2023). The attack on astrocytes (via AQP4) results in extensive secondary neuronal damage. Clinically, attacks are severe, often bilateral, and visual recovery is incomplete (Kim et al., 2023). MRI may show long, extensive enhancement of the optic nerve, sometimes extending to the chiasm (Zakrzewska-pniewska et al., 2024). The visual prognosis is guarded, with cumulative damage at each relapse, as demonstrated in cohort studies (Garcia-gutierrez et al., 2023; Vieira, 2020).

MOGAD-ON (MOG-IgG Positive), is a distinct entity, where the target is myelin (Bennett et al., 2023). MOGAD-ON presents with striking ophthalmologic features: a high frequency of bilaterality (especially in children), ocular pain, and, notably, a strong association with severe papillitis (Pisani et al., 2023; Bennett et al., 2023). Although the acute attack can be severe, the response to steroids is typically excellent, with good recovery. However, the disease is highly recurrent, potentially requiring chronic treatment (Bennett et al., 2023; Spillers et al., 2024).

Ophthalmic tools and imaging in differential diagnosis involve Optical Coherence Tomography (OCT), which has established itself as the primary tool for quantifying axonal damage (loss of ganglion cells and nerve fibers) after the acute edema resolves (Stiebel-kalish et al., 2023). Comparative studies demonstrate that Retinal Nerve Fiber Layer (RNFL) thinning is significantly more pronounced in NMOSD-ON (AQP4+) compared to MS-ON and MOGAD-ON (Chen; Pittock; Flanagan, 2020; Garcia-gutierrez et al., 2023). MOGAD-ON, despite intense initial edema, tends to preserve the RNFL structure better long-term (Bennett et al., 2023). Newer studies using OCT-Angiography (OCTA) are also helping differentiate the microvascular changes between these conditions (Chen et al., 2023; Nasr, 2024).

Magnetic Resonance Imaging (MRI) of the orbits and brain is indispensable. In MS-ON, enhancement is commonly short and intra-orbital. In NMOSD-ON, enhancement is typically long (longitudinally extensive), potentially affecting the chiasm (Pisani et al., 2023). In MOGAD-ON, enhancement of the perineural sheath (the "tram-track sign") and the anterior portion of the nerve is common (Stiebel-kalish et al., 2023).

The etiology determines the treatment of this disease (Zakrzewska-pniewska et al., 2024). In the acute phase, pulse intravenous methylprednisolone is the first line for all forms. However, in severe cases of NMOSD or MOGAD, or in steroid failure, Plasma Exchange (PLEX) or Intravenous Immunoglobulin (IVIG) are recommended early (Kim et al., 2023; Spillers et al., 2024).

Long-term maintenance, however, is where the critical differences lie. MS utilizes specific disease-modifying therapies (DMTs). In NMOSD (AQP4+), these DMTs can be ineffective or worsen the disease (Pisani et al., 2023); treatment requires chronic immunosuppression (e.g., Rituximab, Azathioprine, Mycophenolate) or approved biologics (Eculizumab, Inebilizumab, Satralizumab) (Kim et al., 2023; Zakrzewska-pniewska et al., 2024). In MOGAD, recurrent cases also require immunosuppression, as outlined in recent consensus criteria (Bennett et al., 2023; Žorić; Čolak, 2024).

The data from this review confirm that optic neuritis can no longer be treated as a single diagnosis, but rather as a clinical syndrome with distinct etiologies (Sá, 2021). The "pre-antibody" era, dominated by the ONTT and focused on MS risk (Optic neuritis study group, 1997), has been replaced by the "post-antibody" era, focused on the immediate identification of MS mimetics like NMOSD and MOGAD (Chen; Pittock; Flanagan, 2020; Kale, 2023; Paplińska, 2024).

The ophthalmologist's role in this context has expanded. They are not just the diagnostician of the acute event, but the professional who must initiate the correct investigation (Stiebel-kalish et al., 2023). This distinction is not merely academic; it is clinically vital. The visual prognosis, as demonstrated, differs substantially: MOGAD-ON tends to recover well (Bennett et al., 2023), whereas NMOSD-ON (AQP4+) carries the worst prognosis, with severe, cumulative axonal damage (Kim et al., 2023; Garcia-gutierrez et al., 2023).

OCT, in particular, has solidified its role as an "optical biopsy" (Sá, 2021). The quantification of RNFL and ganglion cell complex thinning provides a direct structural correlate of the damage. The recent literature is clear that severe post-attack thinning is highly suggestive of NMOSD (Stiebel-kalish et al., 2023). The addition of OCTA further refines this by showing microvascular differences (Chen et al., 2023).

Perhaps the most pressing practical implication of this review is the need for a low threshold for serological testing. Authors such as Chen, Pittock, and Flanagan (2020) and Dubuy et al. (2023) suggest that AQP4-IgG and MOG-IgG testing should be considered in nearly all first episodes of ON, not just "atypical" ones. The reason is that the cost of misdiagnosis—such as starting an MS therapy in an AQP4+ patient—is catastrophic (Pisani et al., 2023).

A limitation inherent to any review in this rapidly evolving field is its currency. However, the 2023 international consensus on MOGAD provides a solid foundation for current management (Bennett et al., 2023).

4. Conclusion

The contemporary diagnosis of optic neuritis demands a multifaceted approach, integrating clinical findings (typical vs. atypical), multimodal imaging data (OCT and MRI), and, indispensably, serum biomarkers (AQP4-IgG and MOG-IgG).

The correct etiological identification (MS, MOGAD, or NMOSD) emerges as the critical factor determining visual prognosis, the choice of acute therapy (steroids vs. PLEX), and the selection of maintenance immunosuppression. Failure in this initial differentiation can result in irreversible vision loss.

References

Bennett, J. L., et al. (2023). Diagnosis and classification of MOGAD. *The Lancet Neurology*, *22*(4), 348-362.

Bichuetti, D. B., et al. (2021). Neuromyelitis optica spectrum disorders: a review with a focus on children and adolescents. *Arquivos de Neuro-Psiquiatria*, *79*(6), 535-546.

Chen, J. J., Pittock, S. J., & Flanagan, E. P. (2020). Optic neuritis in the era of aquaporin-4 and MOG antibodies. *Journal of Neuro-Ophthalmology*, *40*(1), 89-97.

Chen, X., et al. (2023). Retinal structural and microvascular changes in myelin oligodendrocyte glycoprotein antibody disease and neuromyelitis optica spectrum disorder: An OCT/OCTA study. *Frontiers in Immunology*, *14*, 1029124.

Dubuy, A., et al. (2023). Beyond myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies: Alternative causes of optic neuritis. *International Journal of Molecular Sciences*, *24*(21), 15986.

Garcia-Gutierrez, G., et al. (2023). Clinical outcomes and prognostic factors in patients with optic neuritis related to NMOSD and MOGAD in distinct ethnic groups from Latin America. *Multiple Sclerosis and Related Disorders*, *73*, 104648.

Kale, N. (2023). The neuro-ophthalmological manifestations of NMOSD and MOGAD—a comprehensive review. *Eye*, *37*(11), 2237-2248.

Kim, H. J., et al. (2023). Diagnosis and treatment of neuromyelitis optica spectrum disorder (NMOSD). *Experimental & Molecular Medicine*, *55*, 1167-1178.

Mendanha, D. B. A., et al. (2024). Neuropatia óptica isquêmica e envelhecimento: revisão sistemática e metanálise. *Revista Brasileira de Oftalmologia*, *83*, e0054.

Nasr, J., et al. (2024). Optical coherence tomography angiography measurements in neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein antibody disease: A systematic review and meta-analysis. *European Journal of Ophthalmology*, *34*(5), 2003-2016.

Optic Neuritis Study Group. (1997). The 5-year risk of MS after optic neuritis. Experience of the Optic Neuritis treatment trial. *Neurology*, *49*(6), 1404-1413.

Paplińska, M., et al. (2024). Visual outcome measures in pediatric myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). *Frontiers in Neurology*, *14*, 1314986.

Pereira, A. S. et al. (2018). Metodologia da pesquisa científica. [free ebook]. Santa Maria: Editora da UFSM.

Pisani, L., et al. (2023). Updates in NMOSD and MOGAD diagnosis and treatment: A tale of two CNS autoimmune inflammatory disorders. *Cells*, *12*(22), 2650.

Rother, E. T. (2007). Revisão sistemática x revisão integrativa. Acta Paulista de Enfermagem. 20(2), 5-6.

Sá, M. J. (2021). Neurite óptica: um desafio diagnóstico e terapêutico. *Arquivos de Neuro-Psiquiatria*, *79*(9), 848-857.

Silva, D. B., et al. (2023). Neuromielite Óptica: Abordagens Diagnósticas. In R. M. C. Pereira (Org.), *Tópicos em Ciências da Saúde 28* (cap. 14, pp. 187-194). Atena Editora.

Spillers, N. J., et al. (2024). A comparative review of typical and atypical optic neuritis: Advancements in treatments, diagnostics, and prognosis. *Cureus*, *16*(3), e56178.

Stiebel-Kalish, H., et al. (2023). The ophthalmologist's role in diagnosing MOGAD and NMOSD. *Eye*, *37*, 2249-2259.

Vieira, G. R., Diniz, D. S., & Monteiro, M. L. R. (2020). Myelin oligodendrocyte glycoprotein antibody-associated optic neuritis: an update. *Arquivos Brasileiros de Oftalmologia*, *83*(2), 160-168.

Zakrzewska-Pniewska, B., et al. (2024). Update on diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) — recommendations of Section of Multiple Sclerosis and Neuroimmunology of Polish Neurological Society. *Neurologia i Neurochirurgia Polska*, *58*(1), 1-13.

Žorić, L., & Čolak, E. (2024). Review of atypical optic neuritis. *Neurological Sciences*, *45*(1), 81-91.