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REVIEW

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An update on the developments and challenges with the diagnosis and classification of autoimmune optic neuritis

Murat Delikaya[a,b], Roua Hamdi[a,b], Charlotte Bereuter[a,b], Jan Schroeter[c] and Frederike C. Oertel [a,b,d,e]

[a]Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [b]Neuroscience Clinical Research Center, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [c]Institute of Transfusion Medicine and University Tissue Bank, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [d]Department of Neurology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [e]Einstein Center Digital Future, Berlin, Germany

ABSTRACT

Introduction: Autoimmune optic neuritis (ON) is a heterogeneous spectrum that includes multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), myelin oligodendrocytes glycoprotein antibody-associated disease (MOGAD), and other etiologies. Early and accurate attribution at the first attack is clinically decisive as treatment pathways diverge.

Areas covered: This review synthesizes current knowledge on clinical signs and red flags as well as structured neuro-ophthalmic assessment with data on paraclinical tools including imaging, electrophysiology and fluid biomarkers. This issue is based on literature curated from PubMed/MEDLINE search (January 2000–June 2025; emphasis on 2022–2025) complemented by reference screening of key consensus criteria and landmark studies. Diagnostic gray zones are addressed, including seronegative and unclassified ON, along with practical implementation barriers such as protocol variability, assay access, optical coherence tomography (OCT) interoperability, and reimbursement. Artificial Intelligence (AI) applications for imaging data and mutli-parameter integration are outlined.

Expert opinion: Real-world improvements will depend on standardized diagnostic pathways integrating orbital magnetic resonance imaging (MRI), high-quality antibody assays, OCT, and visual evoked potentials (VEP). Fluid biomarkers such as serum neurofilament light chain (sNfL) and serum glial fibrillary acidic protein (sGFAP), together with AI-supported analytics, may refine risk estimates, especially in seronegative cases.

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1. Introduction

Autoimmune optic neuritis (ON) is an inflammatory disorder of the optic nerve at the crossroads of ophthalmology and neuroimmunology. ON represents a shared clinical manifestation across several inflammatory demyelinating disorders of the central nervous system such as multiple sclerosis (MS), aquaporin-4 immunglobuline G-positive neuromyelitis optica spectrum disorders (AQP4-IgG + NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) [1,2]. This review summarizes current concepts, diagnostic approaches, and ongoing challenges in defining and classifying autoimmune ON.

We conducted a targeted literature search in PubMed/MEDLINE from January 2000 to June 2025, with particular emphasis on publications from 2022–2025 to capture recent developments. Search terms combined 'optic neuritis' with disease entities (MS, NMOSD/AQP4, MOG/MOGAD) and diagnostic modalities (OCT, orbital MRI, VEP, serum/CSF biomarkers including NfL and GFAP). We prioritized clinical studies, systematic reviews, meta-analyses and consensus criteria with direct diagnostic relevance. In addition, foundational and landmark publications (e.g. diagnostic criteria, key mechanistic studies, and seminal imaging/OCT/VEP work) were included through reference screening to provide essential context for current practice.

1.1. Overview and definition of autoimmune ON

Autoimmune ON is an inflammatory disorder of the optic nerve that presents among other symptoms with subacute visual loss, peri-orbital pain, dyschromatopsia and characteristic neuro-ophthalmological findings [1,2]. Once regarded primarily as a manifestation of MS, ON is now recognized as a shared clinical phenotype across several distinct autoimmune and neuroinflammatory diseases of the central nervous system (CNS). These include MS, AQP4-IgG+ NMOSD, MOGAD, and other conditions – each characterized by different immunopathological mechanisms, relapse patterns and long-term visual outcomes [1,2].

The discovery of aquaporin-4 immunglobulin G (AQP4-IgG) in 2004 and the subsequent identification of pathogenic myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) fundamentally reshaped the concept of ON, expanding

CONTACT Frederike C. Oertel frederike-cosima.oertel@charite.de Experimental and Clinical Research Center (ECRC), Charité – Universitätsmedizin Berlin & Max Delbrück Center for Molecular Medicine, Lindenberger Weg 80, Berlin 13125, Germany

Article highlights

- Optic neuritis requires phenotype-first reasoning to rapidly separate typical demyelinating ON from antibody-mediated and mimicking optic neuropathies.
- Red flags and structured neuro-ophthalmic assessment provide a practical triage framework to identify mimics and prioritize urgent investigations.
- AQP4-IgG and MOG-IgG testing (cell-based assays preferred) is central for classification, but seronegativity does not exclude autoimmune ON.
- Standardized orbital MRI acquisition and structured interpretation improve discrimination between MS-ON, NMOSD-ON, and MOGAD-ON in atypical or severe presentations.
- OCT (pRNFL/GCIPL patterns and quality-controlled segmentation) and VEP (P100 latency and amplitude) provide complementary structural and functional markers for diagnosis and longitudinal monitoring.
- Fluid biomarkers (sNfL, sGFAP) and AI-supported multi-parameter integration can refine risk estimates and support reclassification, particularly in seronegative and unclassified optic neuritis.

it from a single, uniform entity into a heterogeneous syndrome with astrocytopathic, oligodendrocytopathic, and demyelinating subtypes [3,4]. This shift emphasized that accurate attribution of ON to its underlying disease is critical, as treatment strategies and prognoses differ substantially across conditions.

Today, autoimmune ON is best understood within an integrated diagnostic framework combining clinical evaluation with magnetic resonance imaging (MRI), optical coherence tomography (OCT), visual evoked potentials (VEP) and disease-specific serology. These tools help differentiate typical MS-ON from NMOSD-ON, MOGAD-ON, and rarer autoimmune causes – including paraneoplastic, sarcoid-related, and glial fibrillary acidic protein immunoglobulin G (GFAP-IgG) associated ON. Nevertheless, overlap between phenotypes persists, and a proportion of people remain seronegative or unclassified despite thorough evaluation, highlighting the need for improved biomarkers and refined diagnostic criteria.

2. Pathophysiology

Autoimmune ON shares a common final pathway leading to immune-mediated inflammation of the optic nerve in all these conditions. The upstream mechanisms differ substantially across MS, NMOSD and MOGAD- associated ON and are extensively reviewed elsewhere [1–3,5,6].

In short, in MS, ON reflects a *T*- and B-cell-mediated demyelinating process of the optic nerve: breakdown of the blood–brain barrier allows inflammatory cell infiltration, activation of microglia and macrophages, and formation of focal demyelinating plaques, leading to segmental myelin loss and secondary retinal ganglion cell and axonal degeneration that parallels white-matter pathology elsewhere in the CNS [5,7].

In AQP4-IgG+ NMOSD, ON represents an astrocytopathy in which circulating AQP4-IgG enters the CNS, binds perivascular astrocytic endfeet in the optic nerve, and triggers complement activation and Fc-mediated effector mechanisms, causing astrocyte loss with secondary oligodendrocyte damage and often severe axonal injury. Seronegative NMOSD (SN-NMOSD) probably comprises a heterogeneous group with similar clinical attacks but no detectable AQP4- or MOG-IgG; its immunopathology is less well defined, and no single pathogenic antibody has been consistently identified to date [5,6].

In MOGAD, ON is associated with antibodies against surface-exposed myelin oligodendrocyte glycoprotein (MOG) on oligodendrocytes and myelin, which are thought to induce inflammatory demyelination via complement activation and antibody-dependent cellular cytotoxicity, while astrocytes are relatively preserved and lesions show a predominantly perivenous demyelinating pattern.

Some autoimmune ON presentations occur outside the spectrum of MS, NMOSD, and MOGAD [1,8]. This group includes paraneoplastic disorders, autoimmune astrocytopathies, systemic autoimmune diseases, and post-infectious or post-vaccination syndromes, with a residual fraction remaining idiopathic or seronegative [1].

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is characterized by antibodies against an intermediate filament protein highly expressed in astrocytes, including those in the optic nerve [9,10]. Collapsin response mediator protein 5 (CRMP5) autoimmunity, mediated by CRMP5-immunglobulin G (CRMP5-IgG), represents a paraneoplastic response directed against intracellular neuronal proteins [8,11,12]. The strong association with underlying malignancy, most commonly small-cell lung cancer or thymoma, supports the concept of a tumor-driven break in immune tolerance that secondarily involves the optic nerve [8,11,12]. In systemic autoimmune diseases such as sarcoidosis, systemic lupus erythematosus (SLE) and Behçet's disease, optic nerve involvement equally reflect the underlying tissue-specific pathology.

Post-infectious and post-vaccination ON are thought to arise from transient dysregulation of adaptive immunity, involving mechanisms such as molecular mimicry, epitope spreading, or bystander activation [13–15]. While many cases follow a monophasic course, some people later fulfil criteria for defined neuroinflammatory diseases such as MOGAD or NMOSD, suggesting that, in a subset, such events unmask a preexisting tendency to CNS-directed autoimmunity.

Finally, a subgroup of people remains idiopathic or seronegative [1]. In these cases, several mechanisms are considered: autoantibodies against yet-unidentified antigens, low-titer or compartmentalized antibodies below assay detection thresholds, or non–antibody-mediated processes [16,17]. Serological testing and careful longitudinal reassessment are therefore crucial to detect delayed seroconversion or reclassify people into emerging autoimmune ON entities mentioned above [18].

3. Diagnostic approaches

Diagnostic evaluation of autoimmune ON begins with a careful analysis of the clinical presentation (Figure 1), as patterns of onset, pain, fundus findings, and recovery trajectories provide important clues to the underlying etiology. To translate these features into a practical, pretest probability – guided and resource-aware decision framework, we additionally provide a guideline-aligned diagnostic pathway (Figure 2). The following overview highlights distinguishing features and red flags to

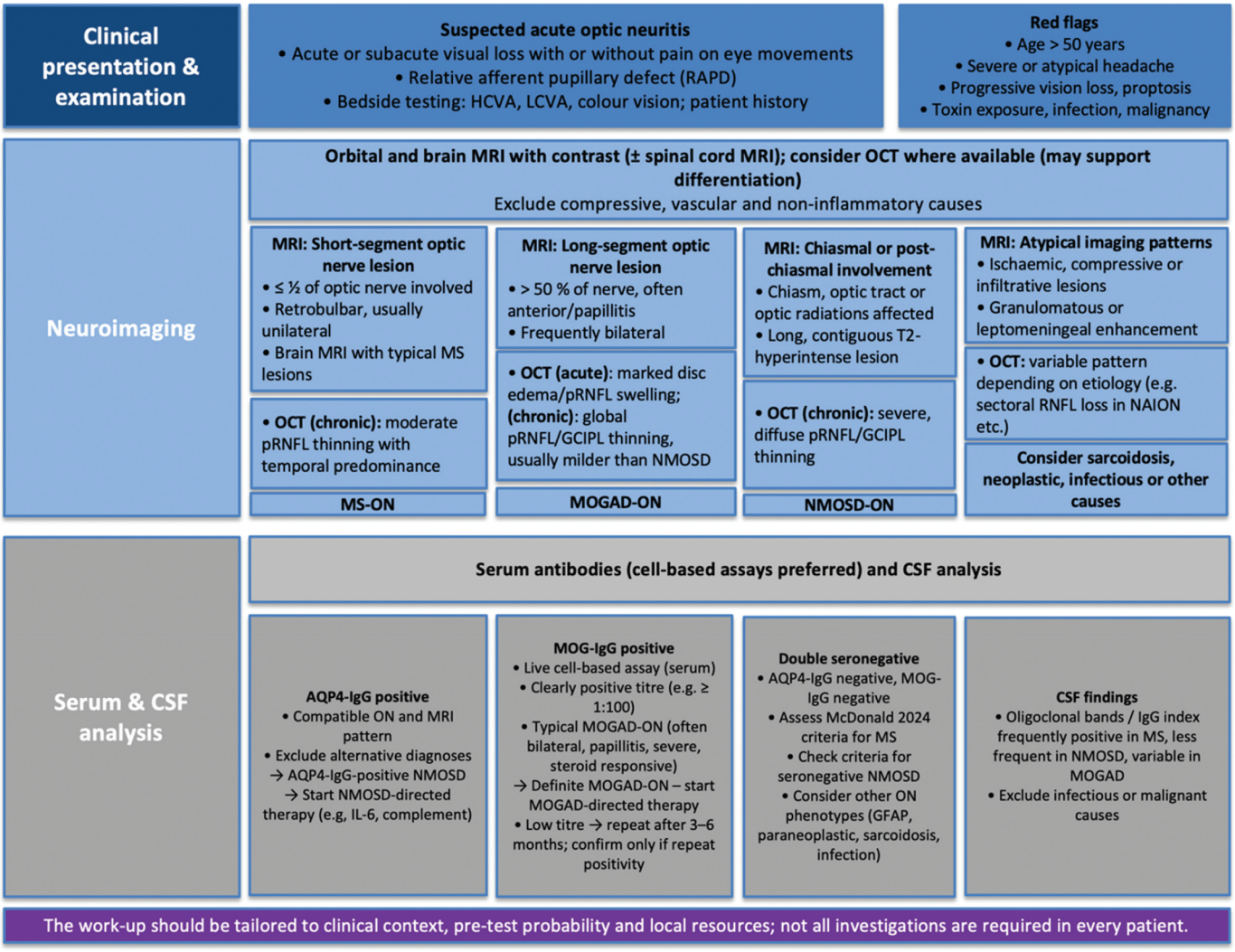

Figure 1. Diagnostic algorithm for optic neuritis (ON).

Flowchart illustrating the diagnostic pathway from clinical presentation and imaging findings to antibody testing and etiologic categorization into multiple sclerosis (MS), aquaporin-4 immunoglobulin G – positive neuromyelitis optica spectrum disorder (AQP4-IgG+ NMOSD), myelin oligodendrocyte glycoprotein antibody – associated disease (MOGAD), and other causes. Abbreviations: HCVA = high-contrast visual acuity; LCVA = low-contrast visual acuity; RAPD = relative afferent pupillary defect; OCT = optical coherence tomography; MRI = magnetic resonance imaging; pRNFL = peripapillary retinal nerve fiber layer; GCIPL = ganglion cell – inner plexiform layer; MME = microcystic macular edema; CSF = cerebrospinal fluid.

differentiate MS-associated ON from NMOSD, MOGAD, and less common autoimmune causes (Table 1).

3.1. Clinical features of autoimmune ON

Autoimmune ON is associated with several different autoimmune diseases. The table below reflects some of the different entities including the onset and laterality of ON as well as distinguishing clinical cues.

3.1.1. Clinical neuro-ophthalmological assessment

A systematic and quantitative clinical assessment forms the cornerstone of the diagnostic evaluation in autoimmune ON, providing critical data to guide subsequent paraclinical testing and initial therapeutic decisions. Because ON is a shared phenotype of MS, AQP4-IgG+ NMOSD, MOGAD, and several rarer autoimmune entities, the clinical examination should not only document deficit severity but also seek patterns that favor one diagnosis over another [1,19].

3.1.1.1. Patient history.

History taking should capture the speed of symptom onset, time to visual nadir, and presence and character of periocular pain, particularly pain with eye movements. At this stage, it is also essential to consider non-inflammatory optic neuropathies – most importantly non-arteritic anterior ischemic optic neuropathy (NAION) as well as hereditary (e.g., Leber Hereditary Optic Neuropathy) and toxic optic neuropathies (e.g. amiodarone- or linezolid-associated) – which may clinically mimic autoimmune ON but follow a different pathophysiology and require distinct management. Painful, unilateral, subacute visual loss is typical of MS-associated ON, whereas NMOSD-ON more often presents with profound visual loss that may be bilateral or sequential and sometimes minimal or absent pain on eye movement [20–22]. Bilateral simultaneous or rapidly sequential attacks, very poor visual acuity at nadir, or incomplete recovery after appropriate corticosteroid therapy should prompt consideration of AQP4-IgG+ NMOSD, MOGAD, or paraneoplastic and systemic autoimmune causes rather than

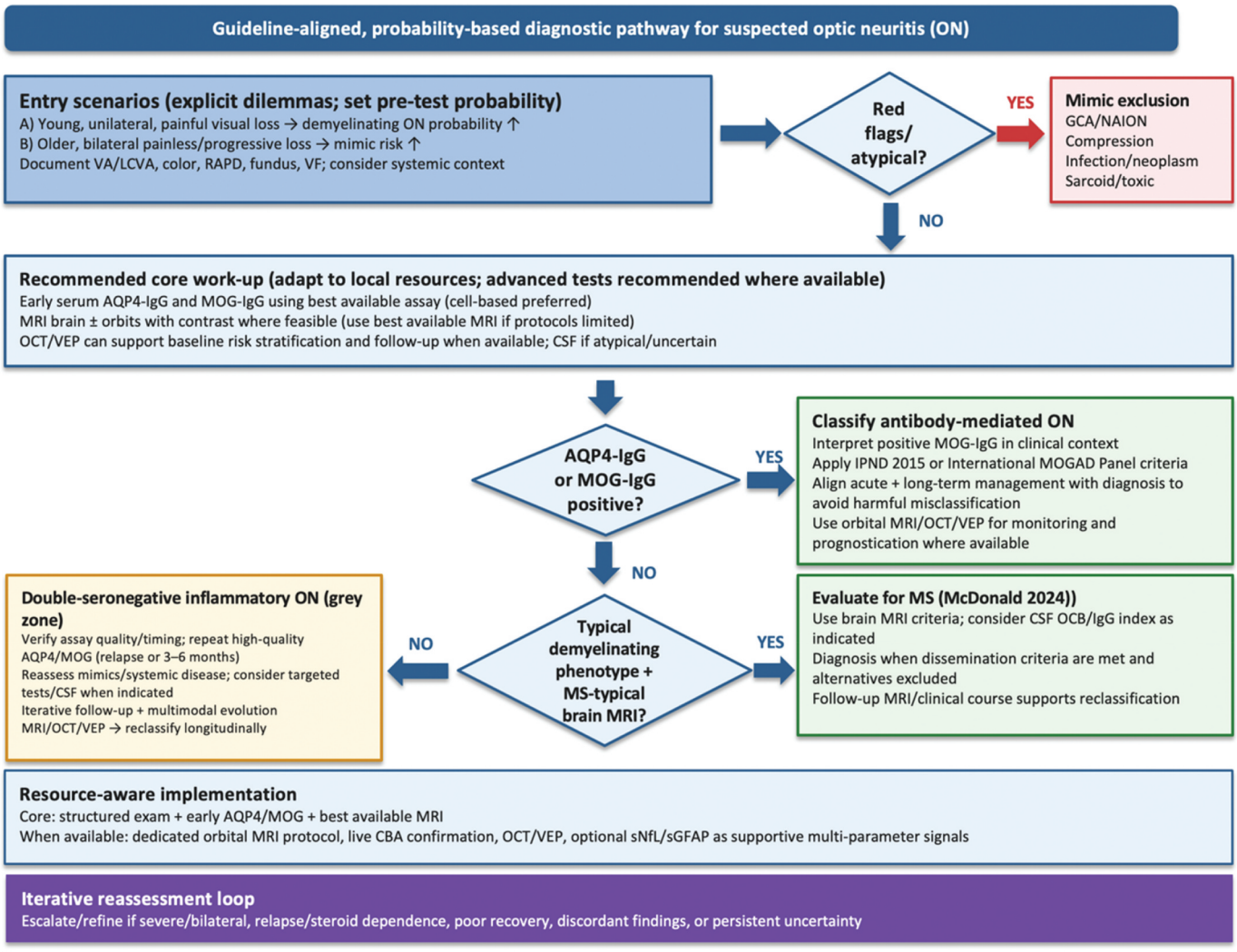

Figure 2. Guideline-aligned, probability-based diagnostic pathway for suspected optic neuritis (ON).

Flowchart illustrating a pre-test probability–guided and resource-aware diagnostic approach for suspected acute optic neuritis, integrating clinical entry scenarios, red flags/mimic exclusion, recommended core investigations, and iterative reassessment. The pathway emphasizes early serum AQP4-IgG and MOG-IgG testing (cell-based assays preferred where available), MRI brain and orbits with contrast where feasible, and supportive use of OCT/VEP and CSF analysis in atypical or uncertain cases. Subsequent steps guide etiologic categorization into antibody-mediated ON (NMOSD/MOGAD; aligned with IPND 2015 and MOGAD diagnostic criteria), MS evaluation (aligned with McDonald 2024), and a structured strategy for the double-seronegative grey zone with repeat testing and longitudinal reclassification.

Abbreviations: ON = optic neuritis; VA = visual acuity; LCVA = low-contrast visual acuity; RAPD = relative afferent pupillary defect; VF = visual field; AQP4-IgG = aquaporin-4 immunoglobulin G; MOG-IgG = myelin oligodendrocyte glycoprotein immunoglobulin G; NMOSD = neuromyelitis optica spectrum disorder; MOGAD = myelin oligodendrocyte glycoprotein antibody-associated disease; IPND = International Panel for NMO Diagnosis; MRI = magnetic resonance imaging; OCT = optical coherence tomography; VEP = visual evoked potentials; CSF = cerebrospinal fluid; MS = multiple sclerosis; OCB = oligoclonal bands; sNfL = serum neurofilament light chain; sGFAP = serum glial fibrillary acidic protein; GCA = giant cell arteritis; NAION = non-arteritic anterior ischemic optic neuropathy; CBA = cell-based assay.

isolated MS-ON [20,22,23]. A detailed review of previous attacks of ON, myelitis, brainstem or encephalopathic episodes, and systemic symptoms (e.g. constitutional 'B symptoms,' rash, arthralgia, sicca symptoms, uveitis, or pulmonary complaints) is essential to uncover NMOSD, GFAP astrocytopathy, sarcoidosis, Behçet's disease, or connective-tissue disease – associated ON [9,23–28]. Nausea, hiccups, or vomiting suggesting area postrema involvement. Longitudinally extensive myelitis, or fluctuating encephalopathic symptoms strongly argue against pure MS-ON and increase the pretest probability of NMOSD or GFAP astrocytopathy [9,10,23].

3.1.1.2. Quantitative visual function testing. Best-corrected visual acuity (BCVA) should be measured with standardized high-contrast charts (e.g. Snellen or Early Treatment Diabetic Retinopathy Study (ETDRS) charts). However, low-contrast visual acuity (LCVA) provides a more sensitive measure of visual dysfunction in demyelinating disease and often remains abnormal even when high-contrast visual acuity (HCVA) has recovered, making it a valuable outcome measure in both MS and ON trials [29,30].

Color vision testing with pseudoisochromatic plates (e.g. Ishihara) and quantitative contrast sensitivity measurement (e.g. Pelli – Robson chart) can reveal subtle optic nerve dysfunction, as inflammatory ON typically causes a disproportionate loss of color discrimination (particularly red desaturation) and contrast sensitivity, even when HCVA is relatively preserved [29–31]. These tests therefore help differentiate optic neuropathies from macular or media abnormalities, in which contrast and color deficits usually

Table 1. Clinical characteristics across ON associated autoimmune diseases.

Entity	Typical onset & laterality	Pain	Fundus findings	Recovery & relapse pattern	Distinguishing clinical cues
MS-associated	Subacute onset, usually unilateral	Pain on eye movement common	Normal or mildly swollen disc (retrobulbar in many)	Usually good recovery; relapses possible but less frequent than in NMOSD/MOGAD	Dyschromatopsia(especially red color) and contrast loss may exceed HCVA loss; 'typical ON' phenotype with good steroid response
AQP4-IgG+ NMOSD	Often severe at nadir; uni- or bilateral/ sequential; chiasmal involvement possible	Variable or mild	Often normal or mild disc edema in the acute phase	Poorer visual recovery; high relapse propensity	Profound vision loss, bilateral or sequential ON, bitemporal field defects from chiasmal involvement; association with myelitis/area postrema syndrome
MOGAD	Acute severe vision loss, frequently bilateral or rapidly sequential	Pain frequent	Marked disc edema in the acute phase	Often substantial HCVA recovery; residual contrast/field deficits common; relapses common	Younger age; recurrent isolated ON common
CRMP5-associated (paraneoplastic)	Subacute, often bilateral	Variable	Disc edema; may coexist with vitritis/ retinitis	Course depends on tumor control; relapses possible	Paraneoplastic context (esp. SCLC or thymoma); consider systemic 'B-symptoms'
GFAP astrocytopathy	Often bilateral; part of a meningo-encephalomyelitic syndrome	Variable	Disc edema; clinical course may precede imaging changes	Steroid-responsive; relapses possible without maintenance therapy	Headache, meningism, encephalitic features
Sarcoidosis-associated	Variable; uni- or bilateral	Usually painless	Disc edema; may coexist with uveitis; peripapillary granulomas uncommon	May improve with corticosteroids; relapses if systemic disease uncontrolled	Systemic clues (uveitis, hilar lymphadenopathy, ↑sIL-2 R/ACE); biopsy with non-caseating granulomas when feasible
SLE-associated	Subacute, often unilateral	Variable	Edema ± hemorrhages; may show ischemic features	Variable; ischemic phenotypes carry worse prognosis	Occurs during systemic activity; inflammatory or ischemic optic neuropathy; ANA/dsDNA positivity supports context
Behçet's disease – associated	Variable; uncommon but reported; can be bilateral	Variable	Disc edema with signs of retinal vasculitis	Relapsing course paralleling systemic activity	Oral/genital ulcers and vasculitis uveitis are suggestive; optic nerve involvement typically accompanies vasculitis
Post-infectious /post-vaccination/ para-infectious	Monophasic, temporally linked to infection or immunization	Common	Variable	Often corticosteroid-responsive; usually non-recurrent	Typically antibody-seronegative; reevaluate if course becomes atypical/relapsing
Idiopathic/ seronegative £	Isolated ON, usually unilateral at onset	Common	Variable	Monophasic or later reclassified	Follow-up essential; plan repeat live-CBA AQP4/MOG testing at relapse; exclude mimics

AQP4: aquaporin-4; ANA: antinuclear antibodies; dsDNA: double-stranded DNA; ED: edema; GCIPL: ganglion cell – inner plexiform layer; GFAP: glial fibrillary acidic protein; HCVA: high-contrast visual acuity; MOG: myelin oligodendrocyte glycoprotein; MOGAD: MOG-antibody – associated disease; MRI: magnetic resonance imaging; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; OCT: optical coherence tomography; ON: optic neuritis; pRNFL: peripapillary retinal nerve fiber layer; sGFAP: serum glial fibrillary acidic protein; sIL-2R: soluble interleukin-2 receptor; ACE: angiotensin-converting enzyme SLE: systemic lupus erythematosus; SCLC: small-cell lung carcinoma; VEP: visual evoked potentials.

Note: 'Typical onset & laterality,' 'Pain,' and 'Fundus findings' refer to the acute phase of ON. 'Recovery & relapse pattern' reflects the subacute and long-term clinical course, while 'Distinguishing clinical cues' summarize features that can help differentiate etiologies across both acute and follow-up stages.

follow more characteristic patterns or progress more slowly [30,31]. In MOGAD-ON, marked dyschromatopsia and contrast loss commonly accompany severe disc edema [20,32], whereas in AQP4-IgG+ NMOSD-ON, profound visual acuity reduction is often associated with similarly pronounced color and contrast deficits despite only mild optic disc changes [33–35].

3.1.1.3. Pupillary responses and ocular alignment. The presence of a relative afferent pupillary defect (RAPD) remains an objective hallmark of unilateral or asymmetric optic nerve dysfunction. When subtle, the defect can be quantified using neutral-density filters. In the acute phase of ON, RAPD magnitude correlates primarily with functional impairment – such as visual field loss or contrast deficits – rather than with structural OCT metrics, which may be confounded by optic disc swelling [18,36,37]. In the subacute and chronic phases, once edema has resolved, RAPD strength correlates more closely with underlying axonal loss on OCT (e.g. pRNFL or GCIPL thinning), but it is not a reliable predictor of the degree of future degeneration. Careful assessment of ocular alignment and motility is also essential, as associated cranial nerve palsies or internuclear ophthalmoplegia may suggest brainstem involvement in MS, NMOSD, or neurosarcoidosis rather than isolated ON [19,38].

3.1.1.4. Funduscopic examination. Dilated funduscopy should document optic disc appearance, peripapillary hemorrhages, cotton-wool spots, and signs of retinal vasculitis. In MS-ON, the disc is often normal or only mildly swollen, especially when inflammation is retrobulbar [2,25]. MOGAD-ON frequently shows disc edema, sometimes with peripapillary hemorrhages and macular exudation, whereas NMOSD-ON may exhibit relatively modest swelling despite severe visual loss [20,32–34]. Granulomatous lesions at the disc or peripapillary region favor sarcoidosis [24,25], while retinal vasculitis and

hemorrhages suggest Behçet's disease, systemic lupus erythematosus, or other forms of vasculitis, including anti-neutrophil cytoplasmic antibody (ANCA) – associated and immune-complex – mediated vasculitides [26–28,39]. These patterns complement OCT-based structural assessment discussed in later sections.

3.1.1.5. Visual field assessment. Automated perimetry is essential to characterize the pattern and extent of visual field loss. Central and centrocaecal scotomas are common across autoimmune ON subtypes and reflect papillomacular bundle involvement [40–42]. Altitudinal defects, particularly inferior altitudinal losses, should raise suspicion for NAION or giant-cell arteritis rather than demyelinating ON [39,40,43]. Bitemporal hemianopic or 'chiasmal' defects are more frequently associated with AQP4-IgG+ NMOSD, in which lesions may extend through the optic chiasm, and should prompt careful MRI evaluation of the optic pathways [21,44–46]. The evolution of visual fields over time also carries diagnostic and prognostic information: Good recovery with restoration of central sensitivity is typical of MS-ON, whereas persistent dense defects are more common after NMOSD-ON, especially in the context of delayed or inadequate attack treatment [32,46]. Recurrent attacks in the same eye or alternating eyes, often with incomplete field recovery, are particularly suggestive of MOGAD or AQP4-IgG+ NMOSD rather than MS [47,48].

3.2. Paraclinical features of autoimmune ON

Paraclinical testing is essential for etiologic attribution of optic neuritis, especially when phenotypes overlap. In the following sections, we summarize how MRI, OCT, electrophysiology, and fluid biomarkers contribute complementary information across acute and post-acute stages.

3.2.1. Optic nerve/Orbit MRI

MRI provides critical paraclinical insights for the differential diagnosis of autoimmune ON, with distinct radiographic patterns observed across differential diagnoses [46]. The MRI protocol should include orbital MRI sequences such as fat-suppressed T2-weighted or Short Tau Inversion Recovery (STIR) images and post-contrast fat-suppressed T1-weighted images to visualize optic nerve inflammation and enhancement. Diffusion-weighted imaging (DWI) sequences can offer supportive evidence in cases of acute inflammation [49]. Its greatest strength lies in the acute phase and in identifying chiasmal or perineural involvement, which strongly support NMOSD and MOGAD, respectively. Acute MRI abnormalities in MOGAD usually resolve more quickly than in NMOSD, with chronic scans potentially normal or showing optic nerve atrophy [47]. However, its diagnostic yield decreases outside the acute window, and normal imaging does not exclude ON, particularly in rarer disorders [46].

In MS-ON, imaging typically reveals unilateral, short-segment T2 hyperintensity and contrast enhancement localized to the intra-orbital retrobulbar portion of the optic nerve, with more rare optic chiasm involvement compared to AQP4-IgG+ NMOSD (15% vs. 64%). In chronic stages, residual optic nerve atrophy may be present without ongoing enhancement or involvement of the optic chiasm or sheath [21,50]. A study showed that in people diagnosed with MS without prior history of ON, MRI was able to detect demyelinating plaques in 73% of cases [51].

In contrast, AQP4-IgG+ NMOSD and MOGAD more frequently exhibit bilateral and longitudinally extensive optic nerve involvement (>50% of the nerve length) [52], ranging between 50–79% in NMOSD and 23–88% in MOGAD, as a multi study analysis reported [53].

Regarding NMOSD, the most characteristic orbital MRI findings include the optic chiasm lesion with involvement varying from 20% to 64% of cases, and thereby considered as a key imaging discriminator from MOGAD-ON and MS-ON [44,46].

MOGAD can often be distinguished employing features such as the presence of perineural enhancement, commonly referred to as the 'tram-track' sign, indicating inflammation of the optic nerve sheath and surrounding orbital tissue [48,54]. This finding, reported in approximately 33–50% of MOGAD-ON cases, is rarely observed in MS or AQP4-IgG+ NMOSD [55,56]. Additionally, the enhancement in MOGAD is often located anteriorly and involves the intra-orbital segment of the nerve (93%) [47] correlating with a higher incidence of optic disc edema (85%).In many CRMP5 cases, orbital MRI is normal, as the ON is typically prelaminar and does not extend into the retrobulbar segment [57]. However, when abnormalities are present, they most commonly include mild optic nerve enhancement or optic nerve sheath (perineural) enhancement is common as it occurred in four of five people reported in a recent study, sometimes with associated peribulbar fat enhancement seen in one patient [57].

In some people with GFAP astrocytopathy (15%) optic nerve involvement can also be seen; MRI often demonstrates optic nerve sheath edema (71%) and enhancement (up to 100%), particularly affecting the anterior part of the optic nerve with hyperintensity on T2 weighted-imaging (T2WI) (25%) reported among four individuals who underwent orbital MRI and had optic nerve sheath enhancement [58]. However, in many cases, the optic nerves may appear normal despite clinical symptoms: In a cohort of 88 people, only twelve (19%) demonstrated abnormal optic nerve MRI, all characterized by unilateral T2-hyperintense lesions [59].

3.2.2. Optical coherence tomography (OCT)

OCT is increasingly recognized as a noninvasive biomarker for ON as it provides critical insights into retinal neuroaxonal damage across autoimmune demyelinating diseases [33,60]. The most relevant OCT-derived layers for ON evaluation are the pRNFL, which reflects optic nerve axonal integrity, the GCIPL, indicative of retinal ganglion cell body and dendrite state, and the inner nuclear layer (INL), where inflammatory changes such as microcystic macular edema (MME) may occur. Acute ON can be associated with normal or even increased pRNFL due to optic disc edema, and normal GCIPL thickness [34,61]. In the acute stage, swelling may obscure axonal loss. Over 3–6 months, ON results in pRNFL and GCIPL thinning as a consequence of neuroaxonal loss [33,34,61]. INL alterations may vary from swelling during acute inflammation to thinning

in chronic stages [34,62]. OCT is most informative in the subacute and chronic phase, when resolution of swelling reveals the extent of retinal axonal and neuronal loss, making it ideal for chronic assessment and longitudinal monitoring, since thinning predicts poorer long-term vision.

A recent meta-analysis by El-Ayoubi et al. demonstrated that eyes with a history of MS-associated ON have, on average, a 16.4 µm reduction in pRNFL thickness and a 14.8 µm reduction in GCIPL thickness, whereas MS eyes without prior ON still exhibit smaller but significant thinning of about 7.0 µm pRNFL and 6.4 µm GCIPL compared with healthy controls (HC) [63]. People with MS generally show more pronounced thinning in the temporal pRNFL sector, reflecting preferential involvement of the papillomacular bundle, compared to people with NMOSD and MOGAD [60,64]. This pattern is thought to reflect vulnerability of the papillomacular bundle composed of thin parvocellular axons that transmit signals from central vision and are responsible for visual acuity (Figure 3(A,G)). NMOSD affected eyes had an evenly distributed pRNFL loss across quadrants [64,65] (Figure 3(I)).

In NMOSD, pRNFL thinning is more pronounced than in MS, with a mean difference of −16.78 µm, and GCIPL thickness decreases by about 22.7 µm after the first ON episode – an absolute loss that is greater than after subsequent attacks [61,66] (Figure 3(C,D)). In MOGAD, a multicenter study demonstrated that during the acute phase of ON, the median pRNFL thickness is often higher than in MS because of more pronounced optic disc edema [33]. Importantly, a pRNFL cutoff of 118 µm was identified to discriminate MOGAD from MS with 74% sensitivity and 82% specificity [64]. Building on these findings, Pakeerathan et al. developed a composite diagnostic score combining bilaterality of ON with temporal superior and nasal pRNFL thickness to differentiate MOGAD-ON from MS-ON [64]. This score achieved 75% sensitivity and close to 90% specificity. In the chronic stage, however, MOGAD eyes can show substantial pRNFL thinning after ON, as illustrated in Figure 2(B).

OCT-derived inter-eye difference (IED) of the macular GCIPL (mGCIPL) have a high diagnostic accuracy for people with MS (area under the receiver operating characteristic curve (AUC) of 0.88–0.94), distinguishing them from HC [37]. Pathological IED values are typically defined as ≥4 µm (or ≥4%) for mGCIPL and ≥6 µm (or ≥6%) for pRNFL [36,37,67]. In line with these data, the 2024 revision of the McDonald criteria now accepts OCT-derived IED as paraclinical evidence of optic nerve involvement to fulfil dissemination in space, provided alternative causes are excluded and scan quality meets recommended standards [68,69]. Recent multicenter data have further validated the diagnostic utility of IED metrics in AQP4-IgG+ NMOSD that distinguished people with a prior unilateral ON episode when compared to both healthy individuals and people with NMOSD without ON history [36,67]. IED metrics have also demonstrated high diagnostic accuracy for detecting previous ON in MOGAD, with a sensitivity higher than 99% [67]. For rarer entities (CRMP5-ON and GFAP-ON), findings include markedly increased pRNFL thickness, macular edema, and optic disc swelling in the acute stage [57,59,70].

Studies using OCT have identified INL as a prominent location of ongoing inflammation and marked microglial activation, presumed to contribute to the development of microcystic macular edema (MME) in people with MS [71]. In NMOSD, INL was also shown to be thicker compared to HC and a proportion of 13% of ON eyes displayed MME [61]. Previous multicenter study found that INL volume is higher in MOGAD eyes with a history of ON compared to both MOGAD eyes without ON and HCs demonstrating that INL swelling or edema is a prominent feature during the acute phase of MOGAD-associated ON [34].

Beyond traditional OCT measurements of retinal changes, several other markers are described: Peripapillary hyperreflective ovoid mass-like structures (PHOMS) are a newly identified OCT modalities that occur more frequently in people with MS, AQP4-IgG+ NMOSD and MOGAD compared to HC, in cohorts including eyes with and without a history of ON [72,73]. Similarly, central serous chorioretinopathy (CSCR) is a retinal disorder featuring serous detachment and subretinal fluid accumulation due to leakage at the level of the retinal pigment epithelium. Recent evidence indicates a higher frequency of CSCR (about 21%) in people with NMOSD, MOGAD, and SN-NMOSD. The occurrence of CSCR in these people was not directly linked to disease diagnosis, ON history, or retinal neuroaxonal loss [74].

3.2.3. Visual evoked potentials (VEP)

VEPs are objective, noninvasive electrophysiological tests that assess the functional integrity of the visual pathways and are widely used as biomarkers of ON [75]. They are commonly performed using full-field monocular stimulation with pattern-reversal black-and-white checkerboards, a standard method to record responses from the visual cortex [75]. VEP is particularly useful in the acute and subacute phases, as it detects latency prolongation even when structural damage is not yet apparent. Pathophysiologically, prolongation of the P100 latency mainly reflects demyelination and slowed conduction along the anterior visual pathway, whereas a reduction in P100 amplitude is more closely related to axonal loss and a reduced number of functioning retinal ganglion cell axons. In chronic ON, persistent amplitude loss can reflect axonal damage, but distinguishing new from old lesions becomes more difficult.

The main measurable outcome is the P100 wave, a positive peak occurring approximately 100 ms after stimulus. Delays in the P100 latency indicate slowed or impaired conduction along the optic nerves, typically due to demyelination, whereas a predominant reduction in amplitude with relatively preserved latency suggests mainly axonal damage (Figure 4). According to a retrospective study of patients with a first demyelinating event, VEP abnormalities detected MS-ON with a sensitivity of 93% and specificity of 85%, whereas for NMOSD-ON the sensitivity was much lower at 17%, but specifitiy was higher at 93% [76]. Another study showed that NMOSD- ON is characterized by more severe amplitude reduction of the P100 wave compared to MS, indicating greater axonal loss – although

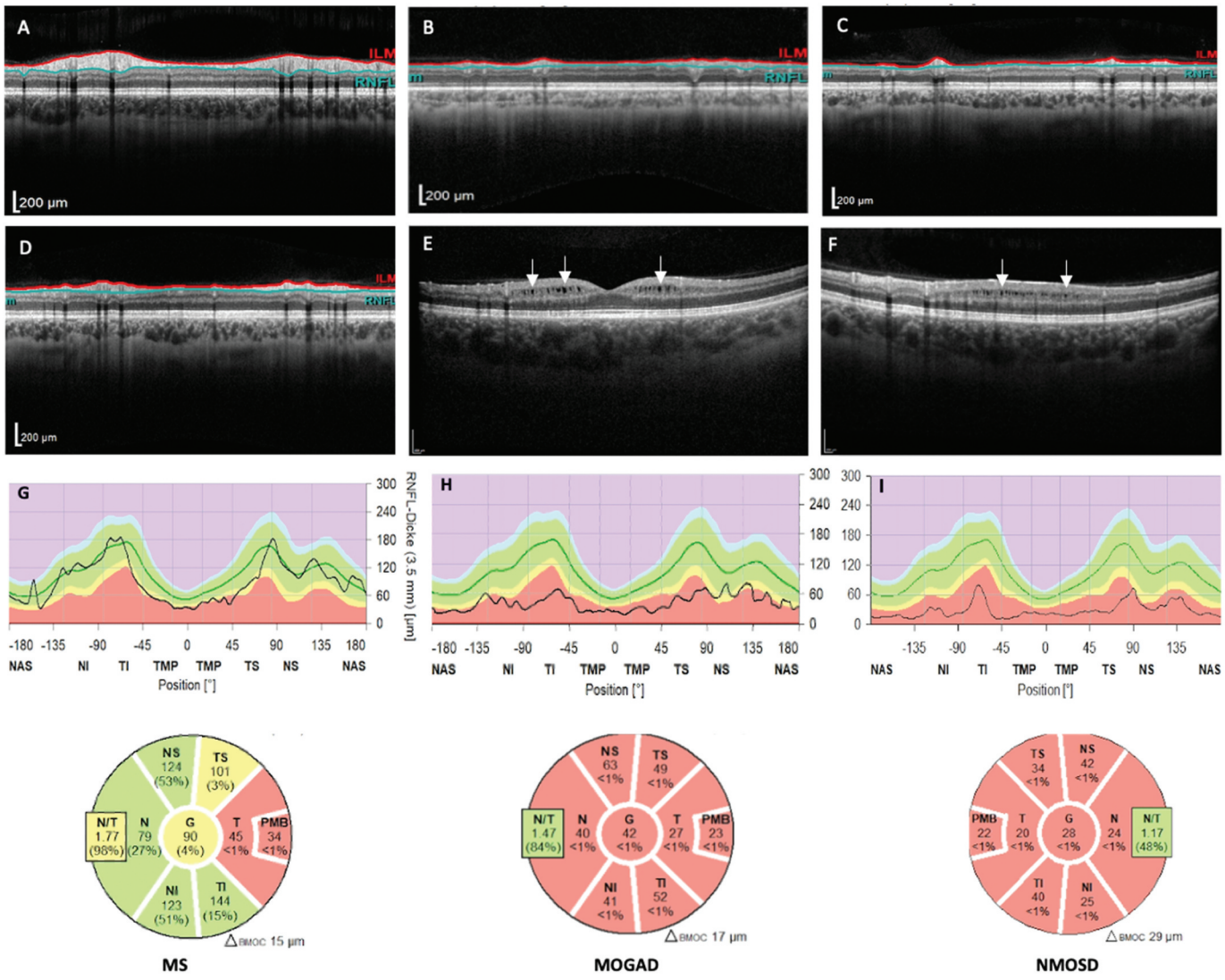

Figure 3. OCT images illustrating peripapillary RNFL (pRNFL) changes across autoimmune ON entities; all illustrated eyes had at least one documented episode of optic neuritis (ON) in the respective disease. Left column: multiple sclerosis (MS); middle column: MOGAD; right column: AQP4-IgG-positive NMOSD.

(A) Peripapillary B-scan OCT (right eye) in MS showing moderate, segmental pRNFL thinning. (B) Peripapillary B-scan OCT (right eye) in MOGAD showing more widespread but still patchy pRNFL thinning. (C) Peripapillary B-scan OCT (right eye) in NMOSD showing severe, diffuse pRNFL thinning. (D) Corresponding macular scan from the same MS eye. (E) Corresponding macular scan from the same MOGAD eye. (F) Corresponding macular scan from the same NMOSD eye; microcystic macular edema (MME) is visible as hyporeflective cystic spaces within the inner nuclear layer (white arrows). (G) pRNFL thickness profile (µm) around the optic disc (3.5-mm ring) for the MS example; thinning is most pronounced in temporal sectors corresponding to the papillomacular bundle. (H) pRNFL thickness profile for the MOGAD example; thinning is more widespread but less extreme than in NMOSD, with several sectors falling below the borderline low range. (I) pRNFL thickness profile for the NMOSD example; nearly all sectors show values in the red band, indicating severe, diffuse pRNFL loss consistent with profound optic nerve axonal injury after ON. The circular plots beneath each column summarize sectoral pRNFL values. Coloured bands indicate normative reference ranges (purple = above the 99th percentile, blue = borderline high, green = within normal limits, yellow = borderline low, red = below normal). Sector labels: NAS (nasal superior), NI (nasal inferior), TI (temporal inferior), TMP (temporal), TS (temporal superior) and NS (nasal superior). Images are intended to illustrate qualitative patterns rather than diagnostic thresholds; OCT interpretation should consider timing after the attack, relapse history, image quality and segmentation errors, and coexisting ocular disease.

Abbreviations: OCT, optical coherence tomography; pRNFL, peripapillary retinal nerve fiber layer; GCIPL, ganglion cell–inner plexiform layer; INL, inner nuclear layer; MME, microcystic macular edema; ON, optic neuritis; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease.

the sample size was limited [77]. MOGAD-ON often presents with severe VEP abnormalities during acute attacks, including both prolonged latency and reduced amplitude, although long-term visual recovery and partial normalization of VEPs tend to be better than in NMOSD [78]. Long-term visual recovery in MS tends to be better than in NMOSD, and VEPs may normalize or improve over time [78]. In rarer cases, VEP has been showed to be delayed bilaterally in a patient representing NMO-like symptoms who tested positive for CRMP5-IgG [79]. In autoimmune GFAP astrocytopathy, abnormal W-shaped VEPs have been reported [80]. W-shaped waveforms have classically been described in MS and in other demyelinating conditions and are generally not interpreted as a disease-specific pattern.

In MS, several studies have also shown that prolonged VEP latency in non-ON eyes is associated with retinal ganglion cell loss and anterior visual pathway neurodegeneration and may have prognostic value for subsequent neuroaxonal damage [78,81]. Altogether, VEPs are highly valuable for assessing the functional integrity of the visual pathways but have several limitations to consider: Firstly, VEPs are not site-specific: latency delays can result from demyelination anywhere along the entire anterior and posterior visual pathway and can be influenced by

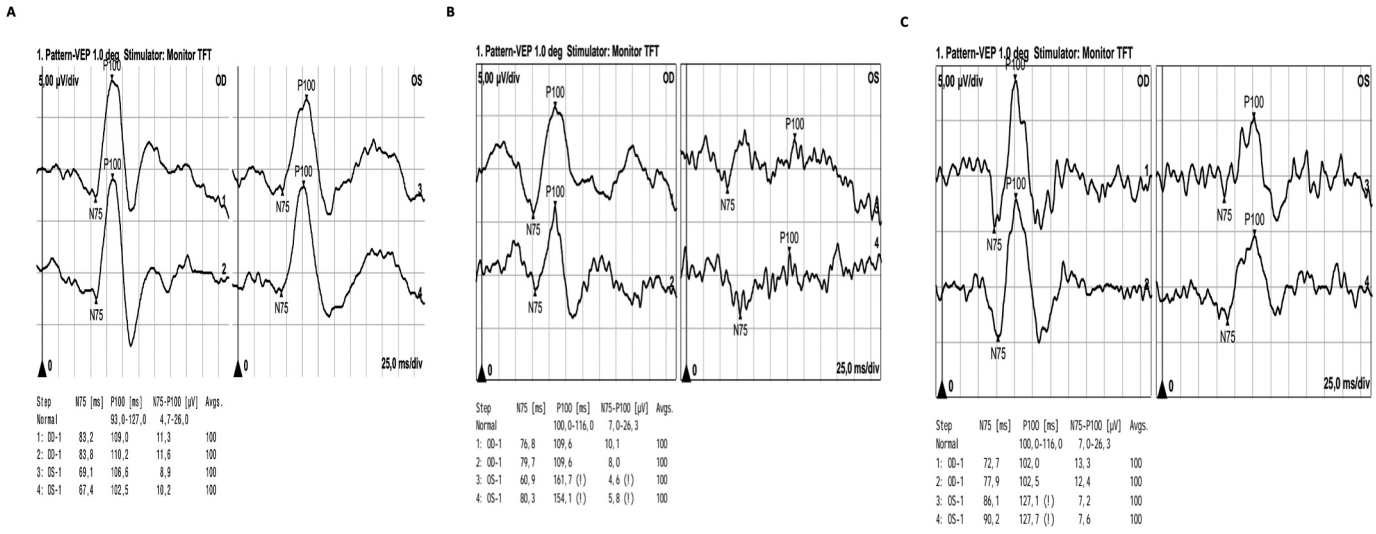

Figure 4. Pattern-reversal visual evoked potentials (VEPs) illustrating typical findings across autoimmune optic neuritis entities.

(A) MS example: P100 latencies are within normal limits and amplitudes are preserved in both eyes, with only a mildly lower amplitude in the left eye (OS) still within the normal range, consistent with good functional recovery after previous unilateral ON. (B) MOGAD example: the right eye (OD) shows an almost normal P100 response, whereas the left eye (OS) demonstrates a severely abnormal, poorly formed waveform with markedly delayed P100 latency (>150 ms) and very low, almost extinguished amplitude, indicating severe unilateral optic nerve dysfunction after ON. (C) NMOSD example: both eyes show pronounced P100 prolongation and marked amplitude reduction, consistent with bilateral chronic optic nerve damage. In all panels, waveform morphology (e.g. broad, low-amplitude or W-shaped P100 complexes) should be considered alongside latency and amplitude, and interpretation should be made relative to laboratory-specific normative values and the clinical context.

Abbreviations: VEP, visual evoked potentials; PR-VEP, pattern-reversal VEP; ON, optic neuritis; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease.

the size and topographic distribution of visual field defects [82]. Secondly, recordings are susceptible to reduced visual acuity, refractive errors, media opacities, macular pathology, and poor fixation or attention, all of which may reduce amplitudes and increase variability [75,82]. Multifocal VEP (mfVEP) technique might offer advantages over conventional VEP by simultaneously recording responses from multiple regions of the visual field, including peripheral areas, while reducing the cancellation effects caused by differently oriented dipoles. By employing orthogonal recording channels and stimulating numerous visual field locations at once, mfVEP achieves higher spatial resolution, enabling independent assessment of distinct visual field regions. However, mfVEP is more time-consuming than conventional full-field VEP, requires stable fixation and at least moderate visual acuity, and is therefore mainly used in specialized centers and research settings [82].

3.2.4. Visual field

Visual field (VF) testing, usually via automated perimetry, non-invasively evaluates central and peripheral vision by detecting areas of loss or deficits resulting from ON. The mean deviation (MD) score is the most commonly reported global index and summarizes how much the entire field deviates from age-matched normal values. It is primarily sensitive to diffuse sensitivity loss, whereas the distinction between localized and widespread defects requires inspection of threshold values and probability or pattern-deviation plots. VF testing can therefore reveal paracentral and peripheral scotomata that may be missed by standard HCVA charts, which mainly assess foveal central vision. In MS, eyes with a history of MS-ON most frequently show central or centrocecal VF defects, consistent with predominant involvement of the papillomacular bundle [83]. In longitudinal cohorts of eyes after ON, NMOSD has been associated with a more rapid decline in both HCVA and VF MD than MOGAD, suggesting greater vulnerability to functional visual loss in NMOSD [42]. In contrast, MOGAD-ON often results in relatively good HCVA outcomes, even as VF deficits persist. For instance, studies show that 40% of analyzed eyes with MOGAD-ON had abnormal MD values, and among those with normal or near-normal final high-contrast visual acuity (≥1.0), 31% still demonstrated mild to moderate VF impairment [41].

3.2.5. Electroretinogram (ERG)

The ERG measures retinal electrical responses to light stimulation and can detect subtle retinal dysfunction in people with visual complaints both with and without a history of ON, but in routine neuro-ophthalmic practice it is most often used when atypical findings raise concern for an alternative retinal diagnosis (e.g. maculopathies) rather than for the assessment of inflammatory ON itself. Although ERG abnormalities are frequently observed in MS [84], their diagnostic specificity and prognostic value remain limited, reducing their utility for tracking disease progression or predicting long-term outcomes. Nevertheless, ERG may reveal subtle or subclinical retinal dysfunction, especially with advanced disease or using specialized protocols in MS as well as NMOSD such as photopic negative response (PhNR) and multifocal ERG (mfERG) [85,86]. Small cohort studies suggest that PhNR amplitudes may differ between NMOSD and MOGAD and may help to characterize patterns of inner retinal dysfunction beyond what can be explained by ON-related damage alone [85]. mfERG has been demonstrated to detect early outer retinal abnormalities

in people with MS, highlighting dysfunction in specific retinal regions prior to major structural damage [85]. Despite these advances, ERG techniques are largely confined to research, or to selected clinical situations where exclusion of non-inflammatory retinal disease is important, with limited incorporation into routine clinical practice due to their technical complexity, relatively long examination time and associated patient burden, and the still unclear impact of ERG results on everyday management decisions [86].

3.2.6. Fluid biomarkers

Established and clinically relevant fluid biomarkers include antibodies against AQP4-IgG and MOG-IgG, as well as serum neurofilament light chain (sNfL) and serum glial fibrillary acidic protein (sGFAP), which are suggested to reflect neuroaxonal and astrocytic injury, respectively. Recent advances have highlighted various fluid biomarkers for diagnosis, disease stratification, and prognosis in autoimmune ON [87]. In clinical routine, only AQP4-IgG and MOG-IgG testing represent established serological assays for the diagnostic work-up of autoimmune ON. Other antibody tests such as CRMP5-IgG or GFAP-IgG are reserved for selected clinical scenarios (e.g. suspected paraneoplastic or autoimmune astrocytopathies) and are not part of standard diagnostic workflows.

Cell-based assays (CBAs) are the gold standard for detecting AQP4-IgG and MOG-IgG, offering high sensitivity ranging between 76% and 94%, and specificity of nearly 100% [88]. Measuring AQP4-IgG in clinical practice serves primarily diagnostic purposes as its presence confirms diagnosis and differentiates NMOSD from both MS and MOGAD [23,88]. Beyond its diagnostic value, serial measurements of AQP4-IgG titers have not reliably predicted relapses, relapse severity, or long-term disability [89]. Similarly, the recognition of MOG-IgG antibodies revolutionized the field once again [90]. This led to the definition of MOGAD recognized as a separate nosological entity [91,92].

In people with ON, elevated sNfL levels in serum correlate with active optic nerve damage and/or concomitant damage elsewhere in the CNS. Neurofilament light chain (NfL) measurement in cerebrospinal fluid (CSF) is typically performed using standard enzyme-linked immunosorbent assays (ELISA). However, due to the much lower concentrations of NfL in blood compared to CSF, ultrasensitive methods are required for blood measurements, notably single-molecule array (SIMOA)-based assays with 25 times higher sensitivity than ELISA [93]. Studies indicate that higher sNfL concentrations during acute ON attacks are associated with more severe neuroaxonal injury and poorer visual outcomes after the attack [87]. Although sNfL is not disease-specific, it is valuable for capturing ongoing neuroaxonal injury across MS, NMOSD, and MOGAD [94–96].

In MS, sNfL levels increase during relapses and reflect greater MRI lesion activity, including T2 and gadolinium-enhancing lesions [97]. Moreover, a recent study suggested that age-adjusted NfL ratio may serve as a reliable biomarker for identifying MS and potentially detecting active inflammatory lesions [98].

In AQP4-IgG+ NMOSD, research has demonstrated that serum sNfL with a cutoff value of 32 pg/mL can differentiate ON related to AQP4-IgG from non-inflammatory optic neuropathies, notably NAION with moderate accuracy [99], indicating that sNfL alone is not ideal as a standalone clinical test for definitive diagnosis. Nevertheless, elevated sNfL levels measured during ON attacks in AQP4-IgG+ NMOSD have been shown to correlate with long-term visual impairment, underscoring their potential prognostic value [99]. It may also help evaluate treatment efficacy in people with AQP4-IgG+ NMOSD. For example, reduced sNfL levels in people treated with inebilizumab in the N-MOmentum trial indicate decreased axonal damage [100].

sGFAP serves as a biomarker of astrocyte damage and has gained particular relevance in AQP4-IgG+ NMOSD. In serum studies using ultrasensitive SIMOA assays, sGFAP levels are defined as elevated when they reach or exceed two standard deviations above the mean concentration observed in HC [101]. In people with AQP4-IgG+ NMOSD, sGFAP levels often exceed 200 pg/mL at baseline and can rise sharply, sometimes above 500 pg/mL during acute relapses, including ON [96]. Because absolute sGFAP concentrations vary between assay platforms and sample matrices, these values represent approximate ranges rather than universally applicable cutoffs. Importantly, sGFAP may aid in distinguishing AQP4-IgG+ NMOSD-ON from other optic neuropathies, and its integration into multimodal monitoring frameworks is a promising strategy for personalized disease management in AQP4-IgG+ NMOSD [96]. Overall, incorporating sGFAP measurements into clinical practice offers a promising avenue for improving diagnosis, prognosis, and treatment monitoring in AQP4-IgG+ NMOSD.

?tlb 2Interleukin-6 (IL-6) elevated levels in serum and CSF were reported in people with NMOSD. Thus, IL-6 was identified to be highly involved NMOSD pathophysiology as it was originally described as B cell stimulatory factor-2, enhancing plasmablasts survival and promoting their differentiation into AQP4-IgG producers [102].

?tlb 3Several additional biomarkers are under investigation but are not yet established for clinical use. CSF cytokines, such as Interleukin-17A (IL-17A), Interleukin-21 (IL-21), and C-X-C motif chemokine ligand 13 (CXCL13), may reflect inflammatory activity and B-cell recruitment during acute ON in MS [103], though specificity remains limited. Complement components (C3a, C4a, sC5b-9) have been linked to relapse activity in NMOSD, particularly relevant for people receiving complement inhibitors [104]. Kim et al., have described elevated levels of serum Tau protein as a potential axonal damage biomarker for MOGAD, possibly reflecting oligodendrocyte injury [105].

3.2.7. Visual quality of life (QoL)

?tlb 2Autoimmune ON significantly impacts vision-related quality of life (QoL), affecting daily functioning and well-being even after apparent clinical recovery. The National Eye Institute Visual Function Questionnaire (NEI VFQ) is widely used to quantify this impact [106]. A German single-center study showed that vision-related QoL, measured with the NEI VFQ, was significantly lower in patients with NMOSD than in age- and sex-matched MS patients, with the most pronounced QoL loss in those with bilateral ON; lower NEI VFQ scores were closely associated with more severe retinal thinning and

reduced HCVA and LCVA [107]. In a recent multicenter Canadian cohort study, people with AQP4+ NMOSD and MOGAD reported similarly impaired vision-related QoL in the overall cohort, as well as in subgroups with a history of unilateral or bilateral ON. Predictors of reduced QoL included a history of bilateral ON and higher visual Functional System Scores (FSS). The frequency and bilaterality of ON in MOGAD may partly explain the observed similarities [108]. Supporting these findings, the German Neuromyelitis optica study group (NEMOS) showed that, despite notable age differences, people with NMOSD, MOGAD, and MS reported similarly poor vision-related QoL, all lower than that of healthy controls [109].

4. Diagnostic challenges in special populations

The diagnosis and management of autoimmune ON present unique challenges in specific populations, where atypical presentations, comorbidities, and epidemiological differences can confound standard diagnostic algorithms.

4.1. Pediatric population

ON in children exhibits distinct differences compared to adults. Bilateral simultaneous onset is more common, occurring in up to 50% of pediatric cases, which can lead to initial misdiagnosis as other causes of bilateral optic neuropathy [110]. The differential diagnosis is broader than in adults, encompassing post-infectious and post-vaccination syndromes, with Acute disseminated encephalomyelitis (ADEM)-related ON being particularly frequent and often associated with MOGAD in this age group [111]. Clinical evaluation is complicated by potentially unreliable history-taking, and young children may struggle to articulate visual symptoms or perform sophisticated visual testing. Serological interpretation requires special consideration; transient MOG-IgG positivity can occur following infections, and the long-term prognostic significance of antibody status in pediatric-onset disease continues to be elucidated [92]. Emerging evidence suggests that attack-independent optic nerve injury, detected through OCT parameters such as retinal layer thinning in children with MOGAD, occurs more frequently than previously recognized, adding complexity to monitoring and treatment decisions [112].

4.2. Elderly population

In older adults, the diagnosis of autoimmune ON is typically one of exclusion. The high prevalence of ischemic in this demographic, particularly NAION, necessitates a comprehensive differential diagnosis [39]. giant cell arteritis (GCA) represents a critical vision-threatening mimicker that requires urgent exclusion [43]. Atypical features that may suggest non-autoimmune etiologies in the elderly include absence of pain, altitudinal visual field defects, and the presence of pallid rather than hyperemic disc edema [39]. Comorbid conditions such as hypertension and diabetes can modify the clinical presentation and confound OCT interpretation due to preexisting retinal vascular changes [113]. Serum biomarkers including sNfL, while elevated in acute ON, demonstrate reduced specificity in elderly populations due to age-related axonal degeneration and a higher burden of comorbid neurological conditions [98,114].

4.3. People with preexisting autoimmune comorbidities

Diagnosing ON in people with established systemic autoimmune diseases (e.g. SLE, Sjögren's syndrome, sarcoidosis) presents particular challenges. Determining whether ON represents a direct manifestation of the known systemic disease, a coincidental occurrence, or indicates a new overlapping CNS-specific autoimmune disorder can be difficult. AQP4-IgG seropositivity has been documented in people with SLE and other systemic autoimmune conditions, suggesting either shared immunological predisposition or genuine overlap syndromes [115]. A comprehensive diagnostic evaluation incorporating MRI, OCT, and targeted antibody testing is essential for establishing etiology and guiding therapeutic decisions, particularly as treatment strategies for systemic autoimmune disease-associated ON versus NMOSD-ON may differ, notably with the use of B-cell depletion therapies for NMOSD [116].

5. Current challenges

The diagnosis of autoimmune ON remains complex and often uncertain. The following sections outline key limitations of existing criteria and their implications for diagnostic accuracy and treatment safety.

5.1. Current challenges with the diagnosis and classification

The current diagnostic challenge in autoimmune ON lies mainly in the precise and early differentiation between MS, NMOSD, MOGAD, and other rare causes. Although specific features – such as simultaneous bilateral involvement, severe optic disc edema, or poor recovery after corticosteroids – can suggest a specific etiology, their sensitivity and specificity are imperfect [1]. For instance, while bilateral ON is a strong indicator of MOGAD or NMOSD, a significant proportion of these people still present with unilateral attacks [20]. Paraclinical investigations, while essential, each present specific limitations. MRI patterns provide valuable clues, such as longitudinally extensive optic nerve lesions being highly suggestive of NMOSD, and perineural enhancement of MOGAD. However, these findings are not absolute, and a normal MRI does not exclude ON, particularly in chronic phases or in seronegative cases [46]. OCT is a powerful tool for quantifying neuroaxonal damage, but its utility in the hyperacute phase is limited by disc edema, which can mask underlying atrophy and confound retinal layer segmentation – as well as by delay of the retinal neurodegeneration itself [19]. Serum antibody testing remains the diagnostic cornerstone, yet it introduces its own challenges. The existence of SN-NMOSD suggests either undiscovered autoantibodies or different pathophysiologies [23,117]. Furthermore, MOG-IgG titers can fluctuate, and low-positive results require careful clinical correlation [117,118]. Crucially, antibody titers have not consistently proven reliable

for predicting relapses or monitoring treatment efficacy [118,119]. These collective challenges highlight the critical need for a multimodal diagnostic approach and underscore the importance of developing novel biomarkers with improved prognostic value.

5.2. Diagnostic criteria

The recent 2024 revisions to the McDonald criteria have intensified this diagnostic complexity by formally incorporating the optic nerve as a fifth anatomical region to demonstrate DIS [68]. While this change facilitates an earlier diagnosis of MS, it concurrently increases the risk of misclassification if applied without rigorously excluding alternative causes of ON [120]. This is critical, as clinical phenotypes such as the bilateral or severe optic disc edema often seen in MOGAD-ON or the longitudinally extensive involvement in NMOSD-ON are not pathognomonic and show considerable overlap. Therefore, the accurate application of the McDonald criteria now mandates prior exclusion of these mimics through highly specific antibody testing to prevent therapeutic missteps, as several MS disease-modifying therapies can exacerbate NMOSD [121,122].

This necessity brings the international consensus diagnostic criteria for NMOSD, developed by the International Panel for NMO Diagnosis (IPND), to the forefront of the diagnostic workflow [23]. The strength of these criteria lies in their foundation on disease-specific antibodies, particularly AQP4-IgG. However, their application in clinical practice faces limitations, most notably the diagnostic ambiguity of seronegative NMOSD, a heterogeneous group that may include cases of MOGAD or other, as yet unidentified, disorders. Updated IPND criteria for NMOSD have recently been proposed and are expected to refine the definition of AQP4-IgG – positive and double-seronegative phenotypes, but the 2015 criteria currently remain the clinical standard. The International MOGAD Panel proposed diagnostic criteria likewise build on disease-specific MOG-IgG, but must account for the dynamic nature of MOG-IgG serology, in which low-positive titers can be non-specific and antibody status may be transient, complicating interpretation in atypical cases [105].

5.3. Seronegative and unclassified ON cases – diagnostic gray zones

Despite modern diagnostics, a meaningful subset of people with ON remains in a diagnostic gray zone – either meeting criteria for SN-NMOSD under the stringent 2015 IPND consensus or being labeled unclassified ON [23,79]. These groups pose major practical challenges. SN-NMOSD is unlikely to be a single entity: it probably includes people with antibody levels below current assay detection, people with antibodies to yet-unknown targets, and cases driven by T-cell – mediated mechanisms distinct from classical antibody-mediated disease [79]. Recent data show that SN-NMOSD still carries substantial retinal neuroaxonal loss comparable to AQP4-IgG+ NMOSD, supporting a severe, non-MS disease process even when the target is elusive [35,61]. A proportion of SN-NMOSD people prove MOG-IgG positive, whereas others remain persistently double-seronegative and clinically heterogeneous [117].

Management is controversial: There are no evidence-based treatment guidelines specifically for seronegative or unclassified ON [116]. Clinicians must balance the risk of untreated relapses against the potential harms of empiric immunosuppression. Repeated, high-specificity antibody testing – preferably CBA – at relapse or before committing to long-term therapy is advisable, given assay variability, low-positive pitfalls, and serostatus dynamics (particularly with MOG-IgG) [22,105,119,123]. Overall, an iterative, multimodal approach that integrates careful clinical and radiologic phenotyping (including orbital MRI and OCT) with serial serology remains the most reliable strategy to minimize misclassification and to guide durable treatment planning [1,19]

6. Future directions and new potential diagnostic biomarkers for autoimmune ON

Over the past decades, multiple neuroimaging and AI-based biomarkers have been identified and evaluated for their utility in monitoring disease activity in ON-related demyelinating diseases. Thus, advancements in prognostic and diagnostic technology are opening new frontiers in the classification and monitoring of autoimmune ON [1,31]. Those can include algorithm-supported diagnostic framework that integrates imaging, fluid biomarkers, and clinical features to improve diagnostic certainty and inform individualized treatment strategies. Schindler et al., conducted the first systematic evaluation of sGFAP, sNfL, and advanced MRI measures in people with AQP4-IgG+ NMOSD, confirming sGFAP as a pathophysiology-based biomarker of astrocytic injury and supporting the concept of subclinical disease activity in this cohort [124]. While this study robustly demonstrated the complementary value of integrating fluid biomarkers with brain MRI lesion profiles, it did not specifically include orbital MRI sequences to assess optic nerve involvement in ON. Therefore, further research incorporating dedicated orbital imaging could enhance biomarker-based disease monitoring tailored to ON manifestations in NMOSD.

Accurate differentiation of ON subtypes remains a critical yet underexplored area in AI research. Nevertheless, recent research by us and others has demonstrated that deep learning-based analysis of pRNFL ring OCT scans can effectively distinguish eyes with a prior history of MS derived acute ON from healthy control eyes, outperforming conventional thickness-based classification methods. This multicenter study demonstrated that a dilated residual convolutional neural network achieved an accuracy of 85% and AUC of 0.86 in the primary cohort, compared with an AUC of 0.77 using pRNFL thickness alone [125]. Another recent retrospective study developed a deep learning algorithm using fundus photographs to differentiate MS ON from non-MS ON subtypes. The model demonstrated good diagnostic performance on a holdout test set, achieving an area under the receiver operating characteristic (ROC) curve of 0.83 and an accuracy of 76.2%, with balanced sensitivity and specificity, supporting AI's potential to aid early subtype differentiation and guide treatment decisions in ON [126].

AI-based postprocessing techniques are increasingly applied to OCT to enhance diagnostic accuracy and disease monitoring. Recent studies demonstrate that AI-driven segmentation improves delineation of the thin and complex optic nerve fibers, overcoming challenges posed by partial volume effects and low image resolution. Additionally, recent advances in automated fovea detection using OCT have introduced the PRE U-Net, a deep learning model that uses pixel-wise regression combined with spatial location priors and a novel target map design to improve accuracy and robustness [127]. Beyond simple detection, AI-based analysis of foveal contour and shape, as proposed by Yadav et al., may capture subtle macular changes related to ON and could further refine structure – function correlations in future studies [128]. AI-based, device-agnostic post-processing of optic nerve head (ONH) OCT scans using convolutional neural network was shown to improve reliability of key biomarkers, including circumpapillary retinal nerve fiber layer (cpRNFL), which measures optic nerve axon thickness around ONH, and minimum rim width (MRW), which reflects neuroretinal rim integrity. This approach reduces dependence on manufacturer-specific algorithms and supports more consistent patient monitoring and collaborative research in ON.

7. Expert opinion

Autoimmune ON is best understood as a spectrum of diseases with distinct immunopathology, risks and treatment responses rather than as a single entity. In clinical practice, however, the first diagnostic label is still often 'MS-related ON' by default. This creates a tension between the reality of overlapping phenotypes and the need for simple, actionable decisions in the emergency room. In our view, the central task for the next decade is not to discover an ever longer list of tests, but to design coherent diagnostic pathways that minimize misclassification while remaining feasible across different healthcare settings.

Conceptually, an ideal approach to autoimmune ON would align three layers of information.

First, clinical pattern recognition: Onset pattern, bilaterality, recovery, associated systemic features and demographic context should immediately stratify the likelihood of MS, AQP4-IgG+ NMOSD, MOGAD and other autoimmune or vascular causes. Second, structured paraclinical assessment using MRI, OCT, VEP and high-quality antibody assays should refine this pretest probability rather than being ordered in an ad hoc fashion. Third, longitudinal follow-up with clinical and visual outcomes would feed back into the initial label, allowing re-classification if new attacks or seroconversion occur.

Translating this ideal into real-world care is challenging. Adoption is currently concentrated in specialist centers, while many hospitals still rely on heterogeneous MRI protocols, non-standardized OCT outputs and serological testing that varies in sensitivity and availability. The consequence is that people with atypical presentations may receive labels – and therefore therapies – that do not fully reflect their underlying disease. From a systems perspective, the main bottlenecks are not a lack of technology but variability in protocols, reimbursement structures that reward single tests instead of coordinated care, and limited awareness of NMOSD and MOGAD outside neuroimmunology circles.

Addressing these gaps will require action at several levels. At the clinical level, expert groups could move from high-level recommendations to pragmatic pathway descriptions: which investigations should be considered at first ON attack, how to prioritize tests in resource-limited settings, and how to interpret low-positive or discordant results. At the organizational level, hospitals and payers can experiment with bundled 'ON work-ups' that incentivize coherent diagnostic packages rather than piecemeal testing. At the educational level, continued professional development for neurologists, ophthalmologists and emergency physicians should emphasize that ON can be the first manifestation of several treatable but very different diseases, and that exclusion of NMOSD and MOGAD is a prerequisite before applying McDonald criteria to isolated ON.

Looking ahead, the most important advances are likely to come from standardization and evidence generation rather than from single breakthrough tests. Harmonized MRI protocols with explicit coverage of the optic pathways, shared OCT acquisition and reporting standards, and agreed minimal datasets for ON registries would allow data from different centers to be pooled. This, in turn, would support external validation of diagnostic algorithms and provide more reliable estimates of misclassification rates, treatment responses and long-term visual outcomes across ON subtypes.

Research priorities naturally extend beyond diagnosis. The next frontier is prognosis and monitoring. Biomarkers such as sNfL and sGFAP, together with quantitative OCT measures, have the potential to provide dynamic estimates of tissue injury and future risk, but they currently lack universally accepted cutoffs, age-adjusted reference ranges and clear management algorithms. Prospective cohort studies embedded in routine care, with pre-specified sampling schedules and patient-reported outcomes, are needed to define how changes in these biomarkers should inform treatment escalation or de-escalation in MS-ON, NMOSD-ON and MOGAD-ON.

In parallel, data-driven methods will likely play an increasing role. Machine-learning models that integrate raw OCT scans, orbital MRI and clinical features could assist clinicians in estimating the probability of each ON subtype and in detecting subclinical damage over time. For these tools to be trustworthy, they must be device-agnostic, trained on ethnically and geographically diverse populations, and accompanied by transparent performance metrics and calibration plots that clinicians can understand. Regulatory and ethical frameworks will need to keep pace, ensuring that algorithmic assistance enhances rather than replaces clinical judgment.

Seronegative and unclassified ON cases will remain a diagnostic gray zone even in the best-resourced systems. Here, the emphasis should be on process rather than on a definitive label at first presentation. Iterative reassessment, repeated high-quality serology when clinically indicated, and openness to re-classifying people as new criteria and

biomarkers emerge are preferable to prematurely forcing atypical cases into existing categories. Future research into novel antigenic targets, cell-mediated immune mechanisms and longitudinal imaging changes in seronegative cohorts will be essential to shrink this gray zone.

In five to ten years, we expect the field to have moved toward integrated health-care pathways for autoimmune ON. Initial assessment will more consistently combine clinical features, standardized imaging and antibody testing; fluid biomarkers and OCT-based metrics will be incorporated into risk scores rather than interpreted in isolation, and decision support tools will offer calibrated probabilities and management suggestions while leaving ultimate responsibility with the clinician. The hoped-for result is not only fewer misclassified people and better visual outcomes, but also a more rational allocation of high-cost diagnostics and immunotherapies to those, who stand to benefit most.

Overall, the opportunity in autoimmune ON lies less in discovering a single new marker than in aligning what we already know into coherent, scalable practice. If clinical leaders, societies and payers work together on standardized pathways and data infrastructure, the considerable progress made in understanding MS, NMOSD and MOGAD can be translated into reliably better care for people experiencing their first episode of ON.

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ORCID

Frederike C. Oertel http://orcid.org/0000-0003-4906-5983

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