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Systematic Review

Comparative Analysis of Biomarkers for Treatments of Optic Neuritis: A Systematic Review of Diagnostic Accuracy

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Abstract:

Background: Optic neuritis (ON) is an inflammation of the optic nerve, presenting with acute or sub-acute vision loss, pain in eye movements, and potentially altered colour vision. This systematic review aims to analyse the diagnostic accuracy of various biomarkers for optic neuritis.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed while conducting this systematic review. The literature search encompassed various databases such as PubMed, Science Direct and Cochrane library. Studies published from 2014-2024 were included in the analysis. The quality of the included studies was meticulously evaluated using the proper tools suited to the study design. The synthesis and analysis of data included a summary of study characteristics, aims and objectives, biomarkers, and main study results/conclusions.

Results: Sample sizes range from 16 to 246 participants. Common biomarkers include serum levels of AQP4-IgG and MOG-IgG, MRI characteristics, Optical Coherence Tomography (OCT) and Neurofilament light chain (NfL), GFAP, and BDNF. MOG-associated ON tends to present with more bilateral involvement and is often linked to better visual outcomes than AQP4-associated ON. The studies consistently show significant differences in MRI lesions profiles between NMO and MS, aiding clinical differentiation. Furthermore, various studies report that serum biomarkers, particularly GFAP and BDNF, correlate with visual outcomes and disease severity, shedding light on potential new diagnostic tools.

Conclusion: This systematic review underlines the critical role of specific biomarkers and imaging techniques in diagnosing, prognosticating, and managing optic neuritis.

Keywords: Optic Neuritis, Biomarkers, Myelin Oligodendrocyte Glycoprotein, Neurofilament Light Chain, Multiple Sclerosis, Neuromyelitis Optica, Advanced Imaging.

Introduction

Optic neuritis (ON) is an inflammatory process affecting the optic nerve, presenting with acute or sub-acute vision loss, pain in eye movements, and potentially altered colour vision [1]. It is a clinically relevant condition because MS and NMOSD are demyelinating diseases. Optic neuritis is commonly the first presentation of these diseases; therefore, accurate diagnosis at this stage determines the global management of the condition. In the past decades, enormous advances have been made in the pathophysiology of ON [2]. It has now become possible scientifically to accept that the immunological press has its way in the instance of demyelination and axonal damage. Nonetheless, existing clinical diagnostic capabilities remain limited since the clinical and imaging manifestations of ON are similar to those of other optic neuropathies [3]. Biomarkers have come out as useful in enhancing diagnostic precision, following the progression of the disease, and even the prognosis of ON response to treatment. Biomarkers are substances that can be objectively measured and reported to indicate normal biological processes, pathological processes, or pharmacologic responses to a specific intervention [4]. With regards to ON, biomarkers have an essential function in many clinical circumstances, thereby improving knowledge and therapy of these diseases. In many cases, optic neuritis is described as the inflammation of the optic nerve and results in vision loss, which can be incapacitating [5]. By identifying biomarkers that are unique and essential for disease diagnosis, severity assessment, or monitoring of treatment efficacy, it becomes possible to diagnose diseases at an early stage, classify major types of diseases,

assess possible outcomes, and overall enhance patients' outcomes [6]. Biomarkers can be used uniquely, making one of the biggest strengths of utilizing biomarkers in the context of optic neuritis – early diagnosis. ON can manifest identical symptoms to a number of other diseases that affect the optic nerve, such as ischemic optic neuropathy, toxic optic neuropathy, and hereditary optic neuropathies [7]. These must be distinguished from other causes of ON that vary from this description; biomarkers make this possible, hence enabling timely diagnosis. For example, normal or slightly elevated inflammatory markers or the detection of certain antibodies in blood might point to an autoimmune process; that way, clinicians will know what directions to follow in terms of further diagnostics and make sure that the patient will receive appropriate treatment on time [8].

The other important use of biomarkers in ON is disease staging. Various types of ON, which include multiple sclerosis (MS), Neuromyelitis optica spectrum disorders (NMOSD), or other demyelinating disorders like myelin oligodendrocyte glycoprotein (MOG), can have varied clinical patterns and overall outcomes of the neurological condition [9]. There may be specific biomarkers differentiating between these conditions, and frequent treatments reflect this fact. Of these, aquaporin-4 antibodies are highly specific for NMOSD, and antibodies against MOG are related to other conditions [10]. By diagnosing these biomarkers, clinicians are then in a position to better plan for the individual needs of each patient in a way that enhances general treatment plans and overall therapeutic success.

Biomarkers are also important in prognostication; for instance, doctors use them to forecast the degree of visual rehabilitation and the likelihood of the disease relapse in patients with optic neuritis [11]. Some of these biomarkers have been found to predict chances of being able to see better after an ON episode. For example, the concentrations of certain inflammatory cytokines or the presence of certain autoantibodies indicate how the disease's progression is likely to proceed[12]. This knowledge on Optic Hypoplasia (OH) is so helpful for clinicians because it helps give patients information and insight into what the future holds for them so they can make competent decisions regarding treatments and modifications to their routines [12].

Biomarkers provide an accurate way of assessing the effectiveness of various therapeutic approaches as a sensitive and specific assessment tool [13]. Biomarkers also allow the clinician to see the effect a specific treatment is having on a patient, and from this, alterations in care can be made if necessary [14]. For example, if a patient is not improving in a certain way by showing poor inflammatory marks, then there is a need to review the current treatment strategy. This dynamic approach to evaluating the effectiveness of the treatment makes sure that the approach used to address this problem will suit the response of the individual patient to the highest level of effectiveness [15].

ON has an inflammatory and demyelinating neuropathy as its pathogenesis, the optic nerve being its target. This is followed by axon damage and neurons that are lost, and in situations where the damage is very severe, the individual is at risk of developing permanent vision complications that would require immediate treatment [16]. This knowledge at the molecular and cellular level of ON has facilitated the search for biomarkers, and based on their assay, they can be classified as imaging biomarkers, fluid biomarkers, and electrophysiological biomarkers [17]. Magnetic resonance imaging (MRI) is the gold standard in diagnosing ONs and is highly valuable because it gives structural as well as functional information on the optic nerves and the brain [18]. Current state-of-the-art MRIs, like Diffusion Tensor Imaging (DTI) and Magnetization Transfer Imaging (MTI), can act as biomarkers to identify minor alterations in the local structure of the optic nerve and perineural tissues [19]. Other retinal imaging modalities like optical coherence tomography (OCT) and its advanced versions, optical coherence tomography angiography (OCTA), have also been increasingly used in quantifying RNFL thinning and microvascular alterations [20].

Optic neuritis (ON) is an inflammation of the optic nerve commonly linked with multiple sclerosis, for instance, and other autoimmune diseases. The management of ON depends mainly on high-dose corticosteroids given with the objective of enhancing the rate of visual improvement [21]. In this case, corticosteroids are also used to speed up the recovery process. However, they do not affect the prognosis for most patients to any great extent. This highlights a critical aspect of ON management: focusing on early outcomes is even critical, but the outcomes remain a concern for most patients [22].

Where ON is repeated or very severe, it may be necessary to look at immunomodulatory treatments. In the following therapies, the immune system either increases or decreases. Such treatments are plasma exchange, IVIG, and certain DMTs that are applicable to the treatment of multiple sclerosis [21]. These modalities themselves have different mechanisms of action, and their biomarkers are also different; thus, they are useful in understanding the effectiveness of the management and ON pathophysiology. The first-line therapy in ON remains corticosteroids. The therapeutic value of both AAV and ON-target effects can be assessed through multiple biomarkers, such as

Neurofilament light chains (NfL) and OCT [22]. It is known that NfL is released in serum and CSF when there is axonal inflammation or damage, and increased levels of this protein may mean that the optic nerve is continuing to be damaged [23]. In addition, effective for the assessment of corticosteroids-treated structural alteration of the optic nerve, OCT reveals detailed images of the retinal nerve fibre layer [23]. Combined, these biomarkers assist in determining how useful corticosteroids are for intervention in inflammation and healing. In patients with AQP4-IgG-positive NMOSD or refractory ON, plasma exchange, as well as IVIG, might be used. In such cases, subtle markers like AQP4-IgG titer and CSF cytokine will help diagnose the disease. NMO is characterized by AQP4-IgG, which is crucial in treatment strategies and therapy outcomes [24]. Further, the cytokine profile in the CSF may help to understand the inflammatory conditions that occur during the ON episode and guide the treatment.

In the case of patients with MS-related ON, several biomarkers are used in the assessment of disease-modifying medications. These include oligoclonal bands (OCBs), neurofilament light chains (NfLs), and magnetic resonance imaging lesion loads. OCBs are associated with intrathecal antibody synthesis and may point to ongoing CNS inflammation [25]. Likewise, abnormal increments in the protein NfL refer to the disease's activity associated with the neuronal lesion [25]. MRI lesion load represents the impact of demyelination and inflammation on the brain and spinal cord [24]. Altogether, those biomarkers will allow clinicians to determine the effectiveness of DMTs and decide whether changes in therapy should be made [26].

While significant progress has begun to be made in using biomarkers to assess treatment outcomes in ON, it continues to be unclear what their diagnostic yield might be regarding distinct aetiologies of ON or different treatment conditions. Such uncertainty highlights the need for meta-analyses of the existing evidence from studies documenting the performance of biomarkers in ON. Such reviews could help develop standard guidelines for biomarkers, which would, in turn, improve patient care delivery and, therefore, patient results. The systematic review aims to achieve the following objectives:

1. To evaluate and compare the diagnostic accuracy of various biomarkers for optic neuritis.
2. To assess the clinical utility of biomarkers in guiding treatment decisions for optic neuritis.
3. To identify and analyse sources of heterogeneity in biomarker studies related to optic neuritis.
4. To explore the relationship between biomarker levels and clinical outcomes in patients with optic neuritis.

Materials and Methods:

Literature search: Our investigation encompasses databases such as PubMed, Science Direct and Cochrane library. Our goal of literature search is to mitigate the potential influence of publication bias and encompass a wide spectrum of pertinent studies.

Keyword Selection and Search Terms: Crafting a precise search strategy involved the utilization of a blend of controlled vocabulary terms (e.g., MeSH terms) and free-text keywords. The primary search terms included "optic neuritis" "biomarkers" and "diagnostic accuracy". Other keywords included aquaporin-4 antibodies, myelin oligodendrocyte glycoprotein antibodies, Neurofilament light chain, and advanced imaging studies in optic neuritis. These terms were interconnected using Boolean operators and refined through the incorporation of synonyms and related expressions.

Criteria for Study Inclusion: The inclusion criteria mandated the consideration of studies published post the year 2013. To uphold the dependability and credibility of the literature selection process, a preliminary screening, or pilot literature review, was meticulously conducted. This preliminary screening involved two independent researchers, with any disparities resolved by a third reviewer. Each study's title and abstract underwent thorough scrutiny to ascertain its relevance to the research objectives. Subsequently, the full text of identified articles was obtained and meticulously examined to extract the pertinent outcome estimates reported in each study. This rigorous approach aimed to maintain a methodologically sound and accurate foundation throughout the data collection process, ensuring a robust basis for the subsequent analysis and synthesis of findings.

Inclusion Criteria: The systematic review adhered to explicit inclusion and exclusion criteria to govern the selection of studies. Included studies met specific criteria: they were original research studies, encompassing randomized controlled trials (RCTs), observational, prospective and retrospective studies, and were published in English.

Exclusion Criteria: Studies failing to meet these criteria or exhibiting low methodological quality were excluded. Additionally, systematic reviews/meta-analyses, review articles, case reports, case series, editorials, letters, and animal studies were excluded from consideration.

Study Screening and Selection Procedure: The study selection process followed a two-stage screening protocol. Initially, two independent

reviewers evaluated titles and abstracts of retrieved articles against predefined inclusion and exclusion criteria. Subsequently, the full-text articles of potentially suitable studies underwent a thorough assessment by the same reviewers. Any disparities or disagreements between the reviewers were resolved through discussion or consultation with a third reviewer if needed.

Extraction of Data: A standardized form for data extraction was devised to systematically gather pertinent information from the selected studies. The extracted data covered various aspects:

1. Study particulars: Title, authors, publication year.
2. Patient attributes: Age, sample size, and inclusion/exclusion criteria.
3. Outcome measures: Biomarkers for diagnosis of optic neuritis.

Assessment Tools for Quality: The quality of the included studies underwent evaluation using specific tools tailored to their respective designs. The Cochrane Risk of Bias tool [27] was applied to assess biases in various domains for randomized controlled trials (RCTs), including random sequence generation, allocation concealment, blinding, and attrition. Non-randomized studies were evaluated using tools such as the Newcastle-Ottawa Scale for cohort and case-control studies [28]. Systematic reviews and meta-analyses underwent quality assessment through the AMSTAR-2 tool [29]. The studies included for analysis are illustrated in Figure 1.

Data Integration: The data synthesis involved creating a narrative summary encompassing study characteristics, outcomes, and findings which aims to provide an analysis of biomarkers for treatments of optic neuritis.

Reporting Guidelines: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for conducting this systematic review to ensure transparent and comprehensive reporting [30].

Result: Initial search identified 889 studies from the databases and other sources. 875 records were screened after initial exclusion of the studies. Following an assessment of the titles and abstracts, 32 articles were selected for further consideration. Following that, 13 articles were eliminated based on the inclusion criteria. We screened 19 studies based on the inclusion and exclusion criteria. Finally, we selected 11 studies because of non-availability of some data in the other studies. The process of selection of the studies is depicted in the PRISMA study selection diagram (Figure 1).

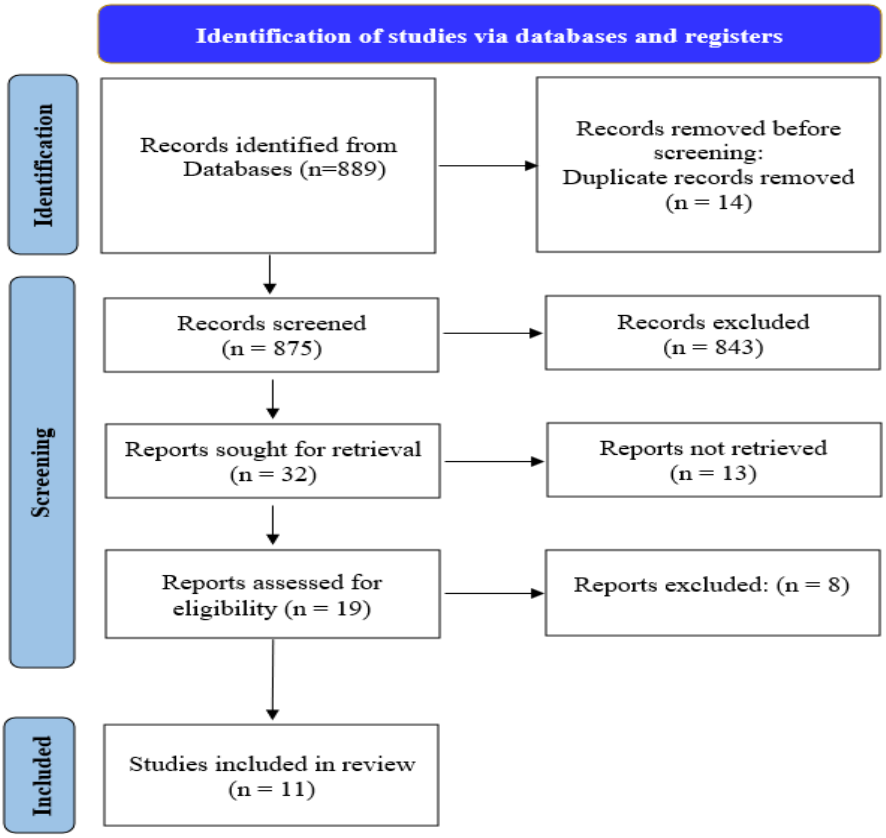

Figure 1: PRISMA study selection flow-chart

Table 1: Characteristics of the included studies

Author	Country	Design of the study	Sample size	Biomarkers tested/ Outcome	Result	Conclusion
Mealy MA et al. 2015[31]	USA	Retrospective study	52	Magnetic resonance imaging (MRI)	Differences in MRI characteristics between NMO- and RRMS-associated optic neuritis.	Optic neuritis in NMO has a distinct pattern on MRI as compared with RRMS.
Ramanathan S et al. 2016 [32]	Australia	Comparative study	50	Magnetic resonance imaging (MRI)	Bilateral involvement was more common in MOG-ON and AQP4-ON than MS-ON.	MOG-ON and AQP4-ON are more commonly bilateral and longitudinally extensive. MOG-ON tends to involve the anterior optic pathway, whereas AQP4-ON the posterior optic pathway.
Stiebel-Kalish H et al. 2017[33]	Israel	Retrospective study	16	Serum MOG-IgG and AQ-4 IgG	Final average RNFL was significantly better in eyes following MOG-IgG-ON (75.33µm), compared to 63.63µm in AQP4-IgG-ON.	Following ON, RNFL is better preserved in eyes of patients with MOG-IgG antibodies compared to those with AQP4-IgG antibodies, correlating with better visual outcomes.
Chen JJ et al. 2018 [34]	USA	Randomized Clinical Trial	177	Aquaporin-4-IgG and MOG-IgG serostatus	1.7% patients were positive for MOG-IgG and none were positive for AQP4-IgG.	Frequency of MOG-IgG was rare in the ONTT, and AQP4-IgG was not found in patients in the ONTT.
Jitprapaikulsan J et al. 2018 [35]	USA	Cross-sectional cohort study	246	Aquaporin-4 IgG and MOG IgG1 serostatus	Glial autoantibodies were detected in 32% (aquaporin-4 IgG, 19%; MOG IgG1, 13%); 186 patients had rON only and 60 patients had rON with subsequent additional inflammatory demyelinating attacks (rON-plus group).	Glial autoantibodies (MOG IgG1 or aquaporin-4 IgG) are found in one third of all patients with rON. Aquaporin-4 IgG seropositivity predicts a worse visual outcome than MOG IgG1 seropositivity, double seronegativity, or MS diagnosis.

						Myelin oligodendrocyte glycoprotein IgG1 is associated with a greater relapse rate but better visual outcomes.
Hassan MB et al. 2020 [36]	USA	Retrospective study	110	AQP4-IgG and MOG-IgG	final diagnosis was MS in 57%, idiopathic in 29%, MOG-IgG-associated disorder in 5%, AQP4-IgG-seropositive neuromyelitis optic spectrum disorder (NMOSD) in 3%, infectious type in 2%, sarcoidosis in 2%, seronegative NMOSD in 1%, and medication-related in 1%.	AQP4-IgG and MOG-IgG account for 9% of optic neuritis and are associated with recurrent attacks, but MOG-IgG optic neuritis has a better visual outcome than AQP4-IgG optic neuritis.
Tavazzi E et al. 2020 [37]	USA	Prospective study	110	serum neurofilament light chain (sNfL) and multiple optical coherence tomography (OCT)	Multiple sclerosis (MS) showed significantly lower pRNFLT, mGCIP, and TMV both in MS-associated optic neuritis (MSON) and n-MSON eyes.	This study confirms the ability of sNfL to detect neurodegeneration in MS and advocates for the inclusion of sNfL and OCT measures in clinical trials.
Pujari SS et al. 2021 [38]	India	Retrospective study	30	Serum MOG-IgG and AQ-4 IgG	This study found 60% optic neuritis, 20% longitudinally extensive transverse myelitis (LETM), 13.4% acute disseminated encephalomyelitis (ADEM), 3.3% simultaneous ON with myelitis and diencephalic Syndrome.	MOG-IgG related manifestations in were monophasic/ recurrent/ simultaneous ON, myelitis, recurrent ADEM, brainstem encephalitis and diencephalic Syndrome. MRI features suggestive of MOG-IgG disease were confluent ADEM-like lesions, middle cerebellar peduncle fluffy lesions, LETM, LEON and non-

						LEON.
Ambika S et al. 2022 [39]	India	Retrospective study	203	serum myelin oligodendrocyte glycoprotein (MOG) and neuromyelitis optica (NMO).	28.08% patients were positive for MOG-antibody and 9.85% patients were positive for NMO antibody.	The prevalence of MOG-ON was higher than NMO-ON. MOG-ON had a better visual outcome than NMO-ON.
Kim HJ et al. 2023 [19]	South Korea	Prospective study	60	Serum neurofilament light chain and glial fibrillary acidic protein (GFAP), and brain-derived neurotrophic factor (BDNF).	No correlation of Serum NfL levels with the degree of visual symptoms. Serum GFAP levels were significantly correlated with severe visual impairment during the attack state in the AQP4-ON group. Serum BDNF levels were positively associated with improved future visual outcome in the AQP4-ON group.	Serum GFAP reflected disease status and severity, while serum BDNF was identified as a prognostic biomarker in AQP4-ON. Serum biomarkers are potentially helpful for patients with ON, particularly those with AQP4-ON. Serum NfL may not be a useful biomarker in patients with ON.
Pakeerathan T et al. 2024 [40]	Germany	Retrospective study	162	optical coherence tomography (OCT)	OCT-based composite score distinguished between multiple sclerosis (MS) and myelin-oligodendrocyte-glycoprotein IgG-associated disease (MOGAD) and confirmed its diagnostic accuracy in the independent validation cohort.	This study emphasizes the potential relevance of OCT as an accurate additional method in the diagnostic of MOGAD.

Table 1 summarizes various studies focused on optic neuritis (ON), particularly differentiating between different types associated with specific biomarkers (e.g., aquaporin-4 [AQP4-IgG] and myelin oligodendrocyte glycoprotein [MOG-IgG]) and their implications on clinical outcomes.

The studies span from 2015 to 2024 and have been conducted by various authors across different countries, including the USA, Australia, Israel, India, South Korea, and Germany. This showcases a global commitment to understanding optic neuritis. The methodologies vary, with designs including retrospective studies, comparative studies, randomized clinical trials, and cross-sectional cohort studies. This variety helps cover different aspects of ON, from clinical characteristics to diagnostic methods.

Sample sizes range from 16 to 246 participants. Smaller studies (like Stiebel-Kalish H et al. with 16 participants) might have limitations in generalizability, while larger populations (like Jitprapaikulsan J et al. with 246) provide more

robust data, potentially leading to more reliable conclusions. Several studies aim to differentiate the MRI characteristics and clinical features of ON based on the presence of specific antibodies (MOG and AQP4). Studies also aim to evaluate the visual outcomes in relation to serostatus, the radiological features, and the implications of biomarkers on disease prognosis.

The primary biomarkers examined include:

MRI characteristics: Identified distinct patterns in lesion morphology and location between conditions associated with MOG and AQP4 compared to RRMS.

Serum antibodies: Multiple studies tested for AQP4-IgG and MOG-IgG to assess their prevalence and correlation with clinical features and visual outcomes.

Serum proteins: Neurofilament light chain (NfL), GFAP, and BDNF: These serum proteins were studied for their potential as prognostic indicators of disease outcome.

Mealy MA et al. [31] found significant differences in MRI characteristics between optic neuritis associated with neuromyelitis optica (NMO) and relapsing remitting multiple sclerosis (RRMS). NMO lesions usually spanned at least three segments of the optic nerve and were longitudinally extensive (≥17.6 mm in length). The study found that lesion length was a reliable metric for diagnosing NMO, with a specificity of 76.9% and a sensitivity of 80.8% at the designated cutoff. In contrast, RRMS lesions were predominantly focal and localized within a single optic nerve segment.

Ramanathan S et al. [32] found that bilateral involvement was more frequent in MOG-ON (84%) and AQP4-ON (82%) compared to MS-ON (23%). MOG-ON was more likely to have certain characteristics including optic nerve head edema (53%), but AQP4-ON had more noticeable chiasmal involvement (64%). MOG-ON and AQP4-ON are presented with longer lesion lengths than MS-ON. The presence of MRI brain abnormalities was shown to effectively distinguish between autoantibody-associated ON and MS.

Stiebel-Kalish H et al. [33] investigated that the patients with MOG-IgG-associated optic neuritis had a significantly better average retinal nerve fiber layer (RNFL) thickness (75.33 μm) compared to those with AQP4-IgG (63.63 μm), indicating better preservation of retinal integrity and thus better visual outcomes after ON.

The study of Chen JJ et al. [34] indicated that only 1.7% of the patients were positive for MOG-IgG, with none positive for AQP4-IgG. All MOG-IgG positive patients demonstrated disc edema at presentation, and despite some developing recurrent optic neuritis, all had complete recovery of visual acuity over 15 years, with no signs of demyelinating lesions on subsequent MRI.

According to the study of Jitprapaikulsan J et al., [35] glial autoantibodies were found in 32% of patients with recurrent optic neuritis, with AQP4-IgG associated with worse visual outcomes compared to MOG-IgG. MOG-IgG was associated with a higher rate of relapses but better visual outcomes, highlighting the nuanced clinical differences associated with each antibody.

In the study of Hassan MB et al., [36] the final diagnoses included 57% multiple sclerosis, 29% idiopathic cases, with 9% being MOG-IgG-associated and 3% AQP4-IgG-seropositive NMOSD. MOG-IgG optic neuritis showed better visual outcomes compared to AQP4-IgG optic neuritis, reinforcing the prognostic differences between these conditions. The study of Tavazzi E et al. [37] demonstrated that MS patients had significantly reduced measures on optical coherence tomography (OCT), indicative of neurodegeneration, compared to healthy controls. Serum neurofilament light chains (sNfL) were linked to retinal measures, suggesting their utility in assessing neurodegeneration.

In the study of Pujari SS et al. [38] 2021, among MOG-IgG positive patients, 60% experienced optic neuritis, while 20% had longitudinally extensive transverse myelitis, confirming a diverse clinical presentation. MRI findings included distinct lesions indicative of ADEM-like patterns and longitudinally extensive lesions, highlighting the complex manifestations associated with MOG-IgG. The study of Ambika S et al. [39] found 28.08% of patients tested positive for MOG antibodies, whereas 9.85% were positive for NMO antibodies. The study highlighted the greater prevalence of MOG-ON compared to NMO-ON, with MOG-ON patients showing better visual outcomes.

The results of Kim HJ et al. [19] indicated that serum GFAP levels correlated with severe visual impairment in AQP4-ON, while BDNF was positively associated with visual improvement in follow-up, indicating these biomarkers' potential relevance in prognosis. The optical coherence tomography (OCT) findings of Pakeerathan T et al. [40] distinguished between MS and MOG-associated diseases, emphasizing pronounced pRNFL atrophy in MOGAD cases and a correlation with poorer visual acuity post-ON.

Discussion

The present systematic review found that MOG-IgG is associated with better visual outcomes compared to AQP4-IgG. Stiebel-Kalish et al. [33] Found significantly better Retinal Nerve Fiber Layer (RNFL) preservation in MOG-IgG optic

neuritis (75.33µm) compared to AQP4-IgG (63.63µm) Hassan et al.[36] confirmed that MOG-IgG optic neuritis has better visual outcomes than AQP4-IgG. Jitprapaikulsan et al. [35] noted that AQP4-IgG seropositivity predicts worse visual outcomes compared to MOG-IgG.

Multiple studies have consistently demonstrated that MOG-IgG is associated with better visual outcomes compared to AQP4-IgG. MOG-IgG associated ON demonstrated better visual recovery compared to AQP4-IgG positive cases [41,42]. The mean logarithm of the minimum angle of resolution (logMAR) showed significantly better outcomes in MOG-ON compared to AQP4-ON [41]. Despite similar severity of inner retinal layer thinning, visual outcomes differed between MOG-IgG and AQP4-IgG patients [41,42]. Peripapillary retinal nerve fiber layer (pRNFL) and macular ganglion cell + inner plexiform layer (GCIPL) thicknesses were comparable between MOG-ON and AQP4-ON [41].

Interestingly, the seroprevalence of MOG-IgG varies across populations. MOG-IgG seroprevalence in adults with isolated ON was 20% in Asian populations and 8% in non-Asian cultures. In children, MOG-IgG seroprevalence was 47% in non-Asian and 31% in Asian populations [41]. MOG-ON also presents with distinctive clinical features: higher frequency of bilateral involvement [42], more common optic disc edema, higher prevalence of eye pain (73-92% of cases) [43].

Visual outcomes in MOG-ON are substantially better than in AQP4-ON patients as found in the present systematic study are consistent with several other studies [35,41,44]. After five years, the long-term visual prognosis reveals that MOG-ON patients fare better than AQP4-ON patients and have outcomes comparable to those of multiple sclerosis patients [44]. When compared to MOG IgG seropositivity, AQP4 IgG seropositivity predicts inferior visual results [35]. Despite recurrent attacks, most MOG-ON patients retain functional vision [45]. AQP4-ON is associated with markedly worse visual outcomes compared to MOG-ON, even with similar initial retinal nerve fiber layer thickness [41]. Most MOG-ON patients (22 out of 23) experienced almost full visual recovery spontaneously or after acute treatment [44]. Early steroid treatment can further facilitate visual acuity recovery in MOG-ON patients [44]. Importantly, while MOG-ON generally has better outcomes, a small fraction of patients (around 5.6%) may still experience poor visual outcomes despite immediate treatment [46].

These findings suggest that while the underlying pathological mechanisms might be similar, the clinical manifestation and recovery potential differ significantly between MOG-IgG and AQP4-IgG associated optic neuritis. Tavazzi E et al. [37] found that serum neurofilament light chains (sNfL) were linked to retinal measures, suggesting their utility in assessing neurodegeneration. The findings of Kim HJ et al. indicate that GFAP levels reflect disease severity and may serve as prognostic biomarkers, while NfL may not be reliable in this context. Serum neurofilament light chain (sNfL) plays a significant role in understanding and monitoring optic neuritis (ON), with several key insights from previous published studies. Neurofilament light chain is a promising biomarker for axonal damage in neurological disorders, particularly in optic neuritis. It is a neuronal cytoskeletal protein that increases proportionally to the degree of axonal damage [47].

sNfL levels are associated with neurodegeneration in multiple sclerosis (MS), particularly in measuring retinal nerve fiber layer changes [37]. At baseline and follow-up, sNfL was significantly associated with peripapillary retinal nerve fiber layer thickness (pRNFLT) and macular ganglion cell layer thickness [37]. Elevated baseline sNfL is linked to accelerated rates of retinal neuroaxonal loss in relapsing-remitting MS, even independent of overt optic neuritis [48].

New immunoassays can detect sNfL at ultra-low levels, enabling easy and repeated disease monitoring. sNfL shows potential as a diagnostic, prognostic, and monitoring biomarker in neurological diseases. The biomarker could help improve diagnostic accuracy and prognostic assessment in optic neuritis and related neurological conditions [47]. Researchers consider sNfL one of the most promising biomarkers for clinical and research applications in neurological disorders, with increasing evidence supporting its utility in tracking disease progression and neuronal damage [47].

The study identifies Optical Coherence Tomography (OCT) as a valuable diagnostic tool for differentiating between MS and MOGAD, emphasizing the potential for OCT to provide additional insights into disease mechanisms and visual outcomes. This supports the idea that OCT should be considered in standard assessments for patients suspected of having MOGAD. Tavazzi E et al. [37] and Pakeerathan T et al [40].

OCT captures retinal manifestations of neuroaxonal injury along the visual pathway [49]. It provides quantitative measurement of retinal nerve fiber layer (RNFL) and ganglion cell inner plexiform layer (GCIPL) thickness [50]. It can identify previous unilateral optic neuritis with excellent sensitivity. GCIPL analysis showed 96% sensitivity in identifying optic neuritis eyes compared to unaffected eyes [50]. OCT can detect RNFL thickness changes as early as 2-4 months after ON

onset [51]. OCT is used to diagnose ON associated with Multiple Sclerosis, Neuromyelitis Optica Spectrum Disorder, Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease [49]. OCT serves as a surrogate endpoint for central nervous system neuroaxonal injury. It provides micron-scale resolution in visualizing optic nerve head topography and non-invasive, reproducible, and easy to obtain imaging techniques [51]. OCT has emerged as an indispensable tool in neuroophthalmology, offering objective and quantitative insights into optic neuritis progression and neuronal damage.

The distinct MRI patterns between optic neuritis in NMO and RRMS can aid in differentiating these neuroinflammatory diseases at presentation. This highlights the importance of MRI imaging in clinical practice for accurate diagnosis and management, suggesting that MRI characteristics should be routinely evaluated in patients with suspected optic neuritis [31]. Distinctive MRI features that help differentiate NMOSD from MS include; NMOSD-specific lesions: longitudinally extensive optic nerve lesions (>half nerve length), area postrema lesions, hypothalamic involvement, periaqueductal grey matter lesions, linear periventricular and brainstem periependymal lesions [52, 53].

MRI also helps to detect lesion morphology in different conditions. In NMOSD, 'Cloud-like' gadolinium-enhancing white matter lesions, 'Bright spotty' spinal cord lesions, Heterogeneous corpus callosum lesions [53] and in MS, typically ovoid/round shaped lesions, periventricular lesions, corpus callosum and temporal lobe lesions [52]. Recent studies have developed advanced diagnostic approaches; Machine learning algorithms can accurately predict NMOSD or MS with over 85% accuracy using MRI features alone [52], Important differences were found in 7T MRI investigations, especially in cortical lesions, which are absent in NMOSD and common in MS [54]. These findings underscore the importance of detailed MRI analysis in distinguishing between NMOSD and MS, potentially expediting appropriate investigation and targeted therapy.

These nuanced MRI differences can aid early and accurate diagnosis of MOGAD versus AQP4-NMOSD [55, 56].

Clinical implications

This systematic review highlights several clinical implications for healthcare professionals. Clinicians may benefit from integrating serum biomarker evaluations, especially GFAP and BDNF, into patient monitoring strategies for AQP4-ON. The study supports the use of serum neurofilament light chains as indicators of neurodegeneration in MS. By assessing sNfL alongside OCT measurements, clinicians can better track disease progression and potentially evaluate treatment responses, indicating that these biomarkers should be incorporated into clinical trials and regular practice. The distinct MRI patterns between optic neuritis in NMO and RRMS can aid in differentiating these neuroinflammatory diseases at presentation. This highlights the importance of MRI imaging in clinical practice for accurate diagnosis and management, suggesting that MRI characteristics should be routinely evaluated in patients with suspected optic neuritis. The study suggests that specific patterns of involvement, such as anterior versus posterior optic pathway engagement, can be utilized in distinguishing between these conditions, underscoring the need for detailed imaging assessments in diagnosing first-episode demyelinating ON. When compared to individuals with AQP4-IgG, patients with MOG-IgG have much greater RNFL preservation, which is associated with superior visual results. This suggests that anti-MOG-IgG-associated ON may have a more favorable prognosis than AQP4-IgG-associated ON, influencing treatment approaches and patient counseling regarding recovery expectations.

Conclusion

The collective conclusions from these studies underline the critical role of specific biomarkers and imaging techniques in diagnosing, prognosticating, and managing optic neuritis. There is a clear trend towards personalized medicine, where distinguishing between different antibody-associated conditions influences treatment decisions and patient outcomes. The emphasis on combining imaging and serological tests can enhance the accuracy of diagnoses and inform individualized management strategies, ultimately leading to improved care for patients with these complex neurological conditions.

Differentiating between MOG and AQP4-associated ON is crucial for treatment strategies and predicting visual recovery. The varying patterns observed in imaging studies can assist clinicians in making informed decisions. The presence of glial autoantibodies significantly influences visual outcomes, emphasizing the need for routine testing for these markers in clinical practice. Advancements in techniques such as optical coherence tomography (OCT) may further enhance the accuracy of ON diagnosis and improve shared decision-making in treatment protocols.

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