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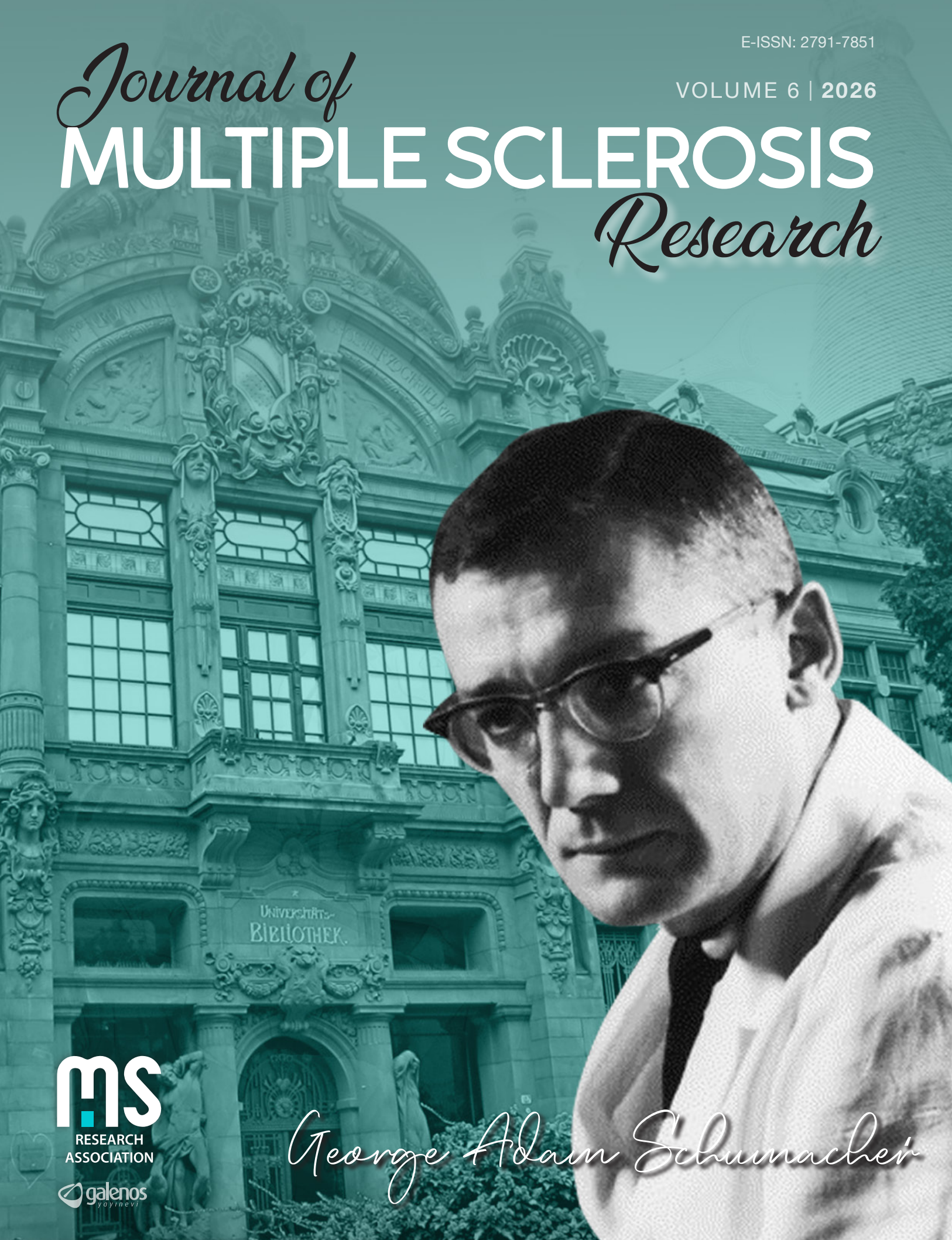

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REVIEW

Management of Infusion-related Reactions (IRRs) in Patients Receiving Ocrelizumab for Multiple Sclerosis (MS) Treatment: A Systematic Review

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Abstract

Ocrelizumab demonstrates positive outcomes in patients with multiple sclerosis. However, approximately 40% of patients experience infusion-related reactions (IRRs), which can reduce adherence despite premedications. This review examines the safety of shortened infusion protocols in reducing IRRs and improving the patient experience. Additionally, other strategies for minimizing IRRs are discussed. Scopus, PubMed, and the Cochrane Library were searched up to November 30, 2024, for cohort studies, as well as randomized and non-randomized clinical trials. Seven studies were included following two stages of screening. The primary outcome was a documented reduction in the incidence rate of IRRs. The seven included studies comprised a total of 1,834 patients. Overall, shorter infusion protocols were found to be safe as conventional protocols, with only a slight increase in IRR incidence. Patients receiving shorter infusions at-home reported higher satisfaction, comfort, and confidence. Splitting the first dose appears to be safer than administering a full dose at once, although a single full dose is also relatively safe. Shorter infusion rates and a single full dose of ocrelizumab are generally preferred to save time and effort. Premedication has been shown to reduce IRRs, and patients report greater comfort with at-home infusions. Further clinical trials are needed to evaluate all proposed procedures and to establish a comprehensive understanding of the optimal management strategies for ocrelizumab-related IRRs.

Keywords: Systemic review, multiple sclerosis, ocrelizumab, infusion-related reactions, shorter infusion, management

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system characterized by inflammation, demyelination, and axonal damage (1). This debilitating disease presents with a wide range of symptoms, including sensory disturbances, motor impairments, and cognitive dysfunction. MS disproportionately affects younger adults aged 20-44 years. Globally, it accounted for over 973,300 disability-adjusted life years and 16,300 deaths in 2021, underscoring its substantial impact on health and productivity (2,3).

The advent of disease-modifying therapies has transformed MS management, providing options to reduce relapse rates, slow disease progression, and enhance quality of life. Among these, ocrelizumab—a humanized monoclonal antibody (mAb) targeting CD20-positive B-cells—has demonstrated efficacy in both relapsing and primary progressive forms of MS (4,5). By modulating immune activity, ocrelizumab targets the inflammatory mechanisms driving the disease. Despite its therapeutic benefits, its use can be complicated by infusion-related reactions (IRRs), ranging from mild symptoms, such as itching and flushing, to severe issues like shortness of breath and hypotension (6).

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IRRs, often triggered by cytokine release during infusion, represent a significant barrier to treatment adherence and optimal outcomes. These reactions are commonly observed with mAb treatments and can occur via multiple pathogenic mechanisms, including cytokine release syndrome and hypersensitivity reactions mediated by immunoglobulins E and G (7,8). IRRs may delay therapy, lead to treatment discontinuation, or diminish the therapeutic benefits of ocrelizumab (9). Effective management of IRRs is essential and includes premedication with antihistamines, corticosteroids, and antipyretics, along with close monitoring during and after infusions (10). Despite these premedication strategies, IRRs still occur in 34-40% of patients receiving ocrelizumab, with the highest incidence observed during the first infusion (11). To address these challenges, recent efforts have explored shortening infusion durations as an alternative strategy to reduce IRR incidence and severity while improving overall patient experience.

While existing research has examined IRRs with monoclonal antibodies, there remains a need for more focused investigation of ocrelizumab-specific IRRs. A deeper understanding of their frequency, underlying mechanisms, and risk factors could refine clinical protocols and enhance safety. Clarifying these mechanisms may also improve risk prediction and inform targeted strategies to mitigate adverse reactions.

The absence of well-defined criteria for stratifying patients' IRR risk presents a challenge to personalizing ocrelizumab therapy. In addition, the long-term impact of IRRs on treatment adherence remains understudied; such reactions may lead to therapy discontinuation or hesitation to continue, ultimately compromising effective disease management. By systematically evaluating shortened versus conventional infusion protocols, this review aims to assess whether reduced administration times can lower IRR rates while maintaining treatment efficacy. The findings may inform more patient-centered treatment approaches, optimizing adherence and improving quality of care for individuals with MS.

Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (12).

Search Strategy, PICO, and Study Eligibility Criteria

Databases, including PubMed, Cochrane Library, and Scopus, were searched till November 30, 2024. The search strategy used was: ("IRR*" or "Infusion-Related Reaction*" or "Infusion Reaction*" or "Infusion Event*" or "Infusion Syndrome*") and ("Multiple Sclerosis" or "MS" or "Disseminated Sclerosis" or "Cerebrospinal Sclerosis" or "Autoimmune Demyelinating Disorder" or "Encephalomyelitis Disseminata") and ("Ocrelizumab" or "Ocrevus").

Additionally, we made subtle modifications to the search strategy for each database to ensure the most comprehensive results.

The study population included adult patients aged 18-65 years with MS receiving ocrelizumab as the primary treatment. Interventions included any procedures and/or medications used to reduce the incidence or severity of IRRs. As a control, we used data from patients who were not exposed to the interventions described above. The primary outcome of interest was the reduction in IRRs, measured using the Common Terminology Criteria for Adverse Events. Secondary outcomes included treatment satisfaction (Treatment Satisfaction Questionnaire for Medication), sleepiness (Stanford Sleepiness Scale), fatigue (Visual Analog Scale-Fatigue; Modified Fatigue Impact Scale), and disease impact (Multiple Sclerosis Impact Scale) scores.

We included prospective and retrospective studies, randomized and non-randomized trials, and sub-studies that assessed ocrelizumab IRR incidence as a primary outcome. Studies evaluating IRR incidence as a secondary outcome were included only if they reported sufficient data. Case reports and case series were excluded, as none provided detailed data or management procedures. We also excluded studies lacking essential data, animal or *in vitro* studies, book chapters, conference abstracts, and publications presented solely as commentaries.

Study Screening, Quality Assessment, and Data Extraction

Initially, one researcher identified and eliminated duplicate studies based on title, author, publication year, and DOI. Screening was then conducted in two stages: in stage 1, studies were evaluated based on titles and abstracts; in stage 2, full-text screening was performed using the aforementioned eligibility criteria. Both stages were performed by three independent authors, with a fourth author resolving any conflict.

Quality assessment was performed using the Cochrane's risk of bias tool (ROB) for randomized trials. Non-randomized trials were evaluated using the Newcastle-Ottawa Scale (NOS). Assessments were conducted independently by two authors, with a third author resolving any disagreements. Data from eligible studies were extracted using a standardized Excel form, including publication characteristics (authors, national clinical trial numbers, year, study duration) and study design (intervention details, control and treatment groups, total number of participants). Patient demographics (age and gender), as well as study outcomes and conclusions, were also recorded.

Search Results

The literature search identified a total of 745 studies using a pre-formatted search strategy: 59 from PubMed, 645 from Scopus, and 41 from Cochrane. Using EndNote, 76 duplicate studies were removed before the first stage of screening. A total of 699 studies underwent title and abstract screening, of

which 635 were excluded. Following full-text review, seven of the remaining 41 studies met the inclusion criteria and were included in this systematic review.

See PRISMA flow diagram (Figure 1).

Study Characteristics

The seven included studies comprised a total of 1,834 patients. Five studies (9,13-16) were clinical trials: four of which were randomized and one non-randomized. Two (17,18) were cohort studies: one was a single-center cohort (comparative analysis), and the other was an open-label, single-arm, non-randomized study. Study durations ranged from 2 to 252 weeks. All studies reported comparable mean ages, ranging from 34.2 to 48.2 years, and Expanded Disability Status Scale scores ranging from 0 to 6.5. Sample sizes varied from 19 to 745 participants. Regarding gender distribution, 586 patients were male and 1,248 were female, representing 68% female participants. An analysis of 4,495 MS patients found that 3,030 were female (67.4%), confirming that our study population aligns with the gender-based prevalence of MS (19) (Tables 1 and 2).

Four studies (13-15,18) evaluated the safety of rapid ocrelizumab infusion and its effect on IRRs. One study assessed IRRs and

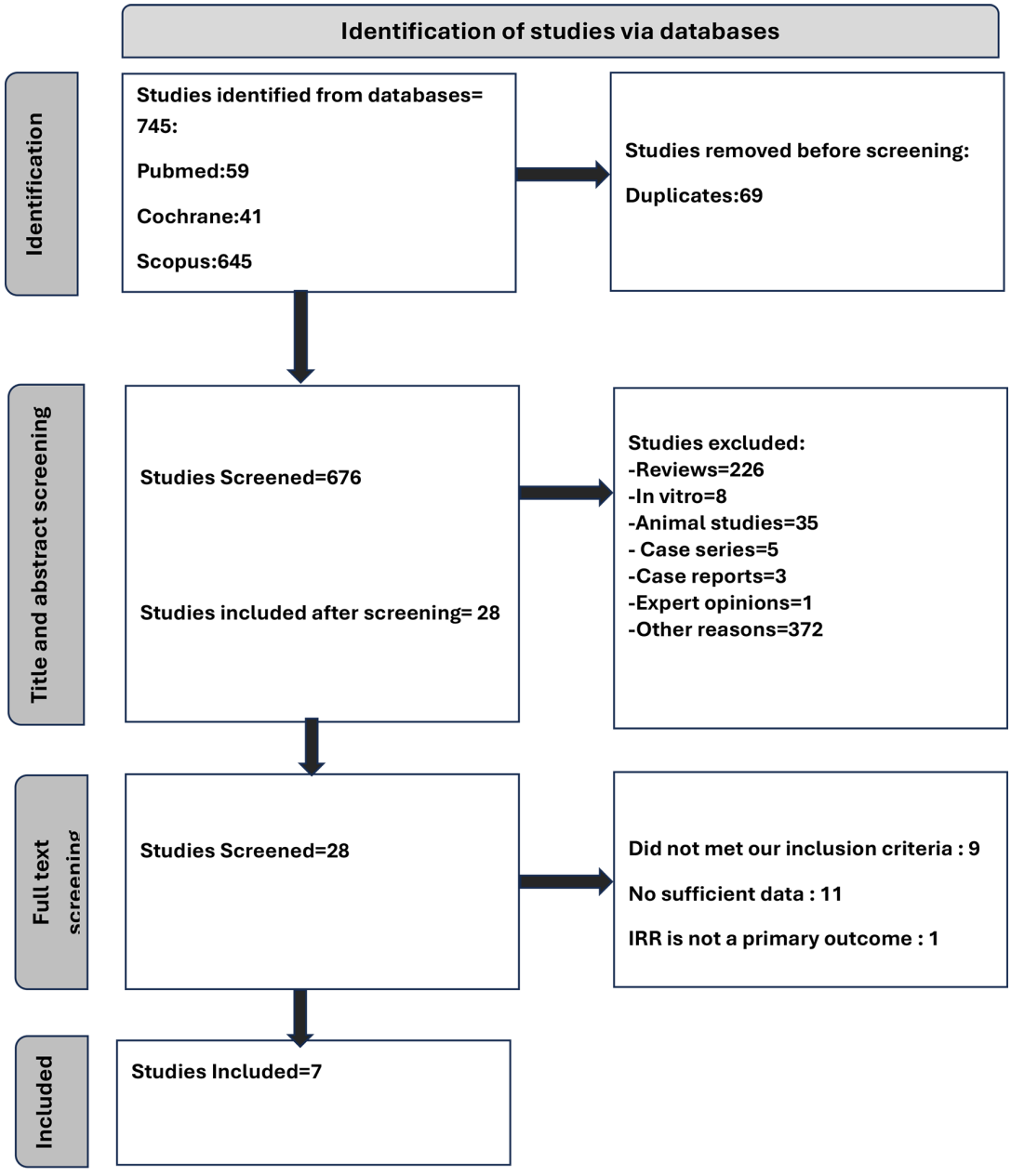

Figure 1. PRISMA flow diagram of study selection. Flow diagram summarizing the identification, screening, eligibility, and inclusion process of studies in the systematic review

PRISMA: Preferred reporting items for systematic reviews and meta-analyses, IRR: Infusion-related reaction

Table 1. Demographic and clinical characteristics of included studies. Overview of patient demographics and clinical characteristics across the included studies, including treatment regimens, age, gender distribution, and MS subtypes

Study	Treatment regime (n)	Gender male/female	Age, year (mean ± SD)	Type of phenotype (n)	EDSS score (mean ± SD)
1. Zanetta et al. (18)	**OCR-RI, OCR-SI**	**154/215**	**39.9 (10.5)**	**PPMS =75 RRMS =274 SPMS =20**	**3 (3.33)**
2. Abbasi Kasbi et al. (16)	**Ocrelizumab**	**82/250**	**38 (9.9)**	**PPMS RRMS Total: 332**	**3 (2.22)**
3. Vollmer et al. (13)	**OCR-SI**	**Cohort 1: 36/59 Cohort 2: 12/34 Total: 48/93**	**Cohort 1: 41.7 (8.8) Cohort 2: 41.1 (8.7) Total: 41.5(8.8)**	**PPMS =12 RMS =129**	**2.64 (1.67)**
4. Smoot et al. (9)	**Ocrelizumab pretreated with cetirizine, ocrelizumab pretreated with diphenhydramine**	**Cetirizine: 1/6 Diphenhydramine: 3/9 Total: 4/15**	**Cetirizine: 48.2 (4) Diphenhydramine: 46.3 (3.1) Total: 47.5 (3.6)**	**PPMS =1 RRMS =16 SPMS =2**	**Not mentioned**
5. Hartung et al. (14)	**OCR-RI, OCR-SI**	**271/474**	**34.2(8.8)**	**PPMS RRMS**	**Not mentioned**
6. Bermel et al. (15) NCT0237856	OCR-SI	**Not mentioned**	**36.7 (8.1)**	**PPMS RMS**	**Not mentioned**
7. Barrera et al. (17) NCT04650321	Home-based ocrelizumab	27/72	42.3 (7.7)	PPMS =13 RMS =178	2 (1.11)

MS: Multiple sclerosis, SD: Standard deviation, EDSS: Expanded Disability Status Scale, OCR-RI: Ocrelizumab rapid infusion, OCR-SI: Ocrelizumab standard infusion, PPMS: Primary progressive multiple sclerosis, RRMS: Relapsing remitting multiple sclerosis, SPMS : Secondary progressive multiple sclerosis, RMS : Relapsing multiple sclerosis

Table 2. Summary of study characteristics. Overview of study designs, participant numbers, treatment arms, and study durations for the seven studies included in the review

Study	Type of ocrelizumab	Treatment group (number of participants)	Total number of participants (n)	Study period (weeks)
1. Zanetta et al. (18)	**OCR-RI OCR-SI**	**OCR-RI: 283 OCR-SI: 86**	**369**	**291**
2. Abbasi Kasbi et al. (16)	**Two 300 mg ocrelizumab doses/ One 600 mg ocrelizumab dose**	**Two 300 mg ocrelizumab doses: 150 One 600 mg ocrelizumab dose: 182**	**332**	**Not mentioned**
3. Vollmer et al. (13)	**OCR-SI**	**Cohort 1: 95 Cohort 2: 46**	**141**	**48**
4. Smoot et al. (9)	**Ocrelizumab pretreated with cetirizine/ Ocrelizumab pretreated with diphenhydramine**	**Ocrelizumab pretreated with cetirizine: 10/ Ocrelizumab pretreated with diphenhydramine: 9**	**19**	**24**
5. Hartung et al. (14)	**OCR-RI OCR-SI**	**OCR-RI: 373 OCR-SI: 372**	**745**	**120**
6. Bermel et al. (15) NCT0237856	**OCR-SI**	**OCR-SI: 129**	**129**	**96**
7. Barrera et al. (17) NCT04650321	**Home-based ocrelizumab**	**Home-based ocrelizumab: 99**	**99**	**2**

OCR-RI: Ocrelizumab rapid infusion, OCR-SI: Ocrelizumab standard infusion

patient satisfaction using patient-reported outcomes during at-home ocrelizumab administration (17). Another study examined the effects of administering 600 mg of ocrelizumab and compared it with the current standard protocol in terms of IRR frequency during the first infusion (16). The final study focused on optimizing treatment safety by investigating diphenhydramine as a premedication and its impact on reaction severity and patient satisfaction (9). All studies included both types of MS, except for two that enrolled only patients with relapsing-remitting MS (14,17).

Risk of Bias

Due to the heterogeneity of study designs, the risk of bias for included studies was assessed using two tools: the NOS (20) for four non-randomized studies (13,15,17,18), and the ROB (21) for three randomized studies (9,14,16). All studies evaluated with NOS scored between 7-8 (Figure 2), indicating a low ROB. Using ROB, one study was assessed (9) as having a high risk of bias due to concerns about outcome measurement and selective reporting. Another study was rated as having some concerns regarding the randomization process and a high ROB for outcome measurement (16). The final study was judged to have a low ROB score (Figure 3) (14).

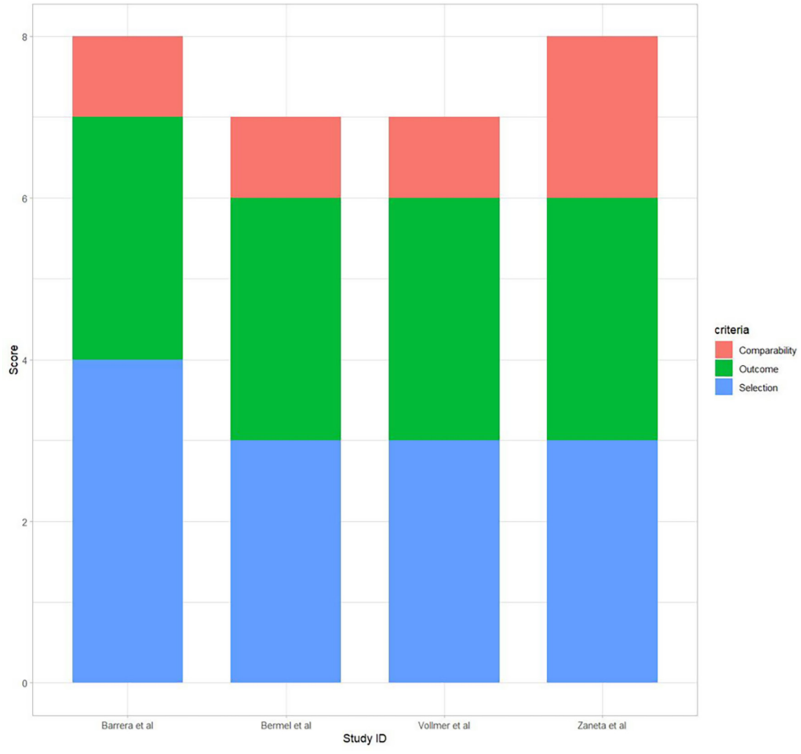

Figure 2. Newcastle-Ottawa Scale (NOS) assessment for non-randomized studies. Quality assessment scores of the included non-randomized studies based on the NOS criteria

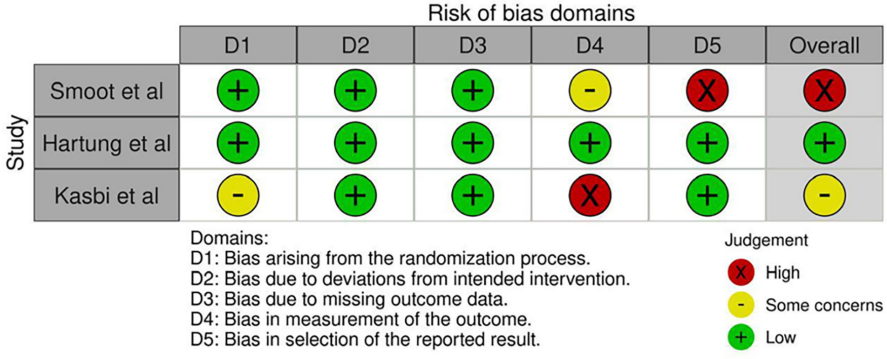

Figure 3. Risk of bias by domain for randomized studies. Domain-specific risk of bias assessments for randomized trials, evaluated using the ROB2 tool and categorized by level of concern

ROB2: Cochrane's Risk of Bias Tool

Outcomes

Conventional vs. Shorter Infusion

One sub-study, comparing conventional and shorter infusion groups in patients receiving six doses of ocrelizumab 600 mg, found a similar number of patients experiencing IRRs after the first dose (101/373 vs. 107/372 patients, respectively) (14). Across all six doses in the sub-study, the proportion of patients experiencing IRRs was similar between groups (41.6% vs. 46.2%). Most IRRs were mild or moderate (Grade 1-2), occurring in 99.4% of patients in the conventional infusion group and 97.7% in the shorter infusion group. Only five reactions were severe (Grade 3): one in the conventional infusion group and four in the shorter infusion group.

No Grade 3 or higher IRRs were reported after the second dose, and no patients discontinued treatment due to IRRs. The most common IRRs during the first infusion were throat irritation (18.8% vs. 29.9%) and dysphagia (6.9% vs. 7.5%) in the conventional and shorter infusion groups, respectively. Within 24 hours post-infusion, headache (25.7% vs. 17.8%) and fatigue (22.8% vs. 18.7%) were the most frequently reported adverse events.

In another sub-study (15), patients receiving a single dose of ocrelizumab (600 mg) via shorter infusion experienced no severe or life-threatening IRRs. Grade 1-2 IRRs were reported in 12.4% of patients, consistent with findings from the main study, particularly at dose 3. Infusion rate reduction or treatment interruption was required for nine patients, as observed at dose 3, and all IRRs resolved without further medical intervention.

In study, patients receiving a single dose of home-based ocrelizumab (600 mg) infusion over 2 h were assessed, with 25.3% (95% confidence interval: 16.7-33.8%) experiencing an IRR of any grade (17). Of these, 18.2% were Grade 1 and 7.1% were Grade 2, with no IRRs ≥ Grade 3 reported.

Another study evaluated patients receiving varying numbers of ocrelizumab 600 mg doses with an infusion time reduced from 3.5 to 2 h (18). Overall, 25 patients (8.8%) in the rapid infusion group and 13 patients (15.1%) in the conventional group experienced IRRs. The frequency of IRRs did not differ significantly between the two groups. Most IRRs were mild (Grade 1, 81.6%) or moderate (Grade 2, 18.4%).

Full First Dose (600 mg) vs. Split Dose (300 mg)

One study compared IRRs of the first dose 600 mg vs. two 300 mg showed that most of the IRRs were mild in both (two 300 mg doses and one 600 mg dose) groups (16).

Shorter Full Dose vs. Shorter Split Dose

In sub-study, patients were divided into two cohorts: cohort 1 (n=95) received 600 mg of ocrelizumab over 2 hours, while cohort 2 (n=46) received a split dose of 300 mg over 1.5 hours (13). The results were as follows:

In cohort 1, 35 patients experienced IRRs during the first dose and 30 during the second dose, whereas only 7 patients in cohort 2 experienced IRRs. No observed Grade 3 or 4 IRRs were reported in either cohort.

In cohort 1, 14% of patients experienced IRRs that required interruption or slowing of the infusion, while no such interruptions occurred in cohort 2.

Premedication

IRRs were compared between groups that received different premedications in the study (9): one group received oral cetirizine (10 mg), and the other received diphenhydramine (25 mg). Following the first infusion of the initial dose, each group reported six IRRs (corresponding to 60% of the cetirizine group and 67% of the diphenhydramine group). At the end of the study (after two doses), 80% of patients in the cetirizine group and 89% in the diphenhydramine group experienced at least one IRR. The incidence of IRRs was similar between groups, with no increase in severity and no Grade 3 events reported (Table 3).

Patient Satisfaction

After blinding in the study, most patients in the conventional group chose to switch to short-infusion (79.7% (n=279/350), whereas most patients in the short-infusion group opted to continue with short-infusions (94.6%; n=331/350) (14). Among patients who preferred conventional infusions (n=90), 57.7% (n=51/90) had experienced IRRs, compared to 42.0% (n=256/610) of those who preferred shorter infusions.

A significant improvement in the overall infusion experience was reported by patients receiving at-home infusions (17). They described feeling more comfortable, safer, and respected. They also noted that nurses provided clearer explanations compared with the hospitals.

Discussion

This systematic review provides the most recent data about the procedural interventions to reduce IRRs in patients receiving ocrelizumab for MS. Management of IRRs is rarely discussed in general, and specifically for ocrelizumab. In patients with MS, experiencing IRRs is critical as it may lead to treatment delays or discontinuation; therefore, preventing these reactions is essential for successful treatment.

"Do no harm" is a fundamental principle in medical practice. Despite this, fewer than 10% of systematically published reviews each year assessed harm associated with medical interventions as their primary objective (22).

Short vs. Conventional

Shorter infusions did not significantly increase the incidence or severity of IRRs in any of the studies (2-6). However, in one study, only 0.53% of patients could not tolerate the short infusion and

Table 3. Summary of interventions and IRR outcomes. Comparative overview of intervention strategies, infusion-related reaction (IRR) rates, and key findings across the included studies evaluating ocrelizumab administration in patients with multiple sclerosis

Study	Design	Intervention	Comparator	IRR rate	IRR severity	Key finding
Zanetta et al. (18)	Cohort	600 mg over 2 h (Shortened)	600 mg over 3.5 h (Conventional)	8.8% vs. 15.1%	Mild-moderate	Shortened infusion showed fewer IRRs
Abbasi Kasbi et al. (16)	RCT	One 600 mg dose	Two 300 mg doses	Similar	Mostly mild	Both dosing strategies are safe
Vollmer et al. (13)	Open-label phase IIIb	600 mg (2 h) or 300 mg (1.5 h)	None	Cohort 2 had fewer IRRs	No Grade ≥3	Shorter infusions well-tolerated
Smoot et al. (9)	RCT	Cetirizine premedication	Diphenhydramine premedication	80% vs. 89%	No Grade 3	Both premedications are similarly effective
Hartung et al. (14)	RCT	600 mg over 2 h	600 mg over 3.5 h	41.6% vs. 46.2%	Mild-moderate	No significant difference in IRRs
Bermel et al. (15)	Single-arm phase IIIb	600 mg over 2 h	None	12.4%	Grade 1-2 only	No severe IRRs, consistent with prior data
Barrera et al. (17)	Open-label phase IIIb	600 mg at home (2 h)	Historical control	25.3%	Grade 1-2 only	At-home infusion is safe and well-tolerated

IRR: Infusion-related reaction, RCT: Randomized controlled trial

continued ocrelizumab treatment, representing a very small percentage (14).

Short infusion is a feasible and patient-preferred option, with 80% of patients opting to switch to shorter infusions (14). Reducing infusion time also helps optimize clinic scheduling and reduce staff workload. Additionally, at-home short infusions demonstrated positive outcomes and increased patient comfort, providing an alternative for stable MS patients (17).

This is primarily because peak ocrelizumab concentrations were similar between shorter and conventional infusions, suggesting no increase in drug exposure-related toxicity (14). Additionally, premeditation reduced cytokine release and hypersensitivity reactions.

The incidence of IRRs varies widely across studies due to multiple factors. Higher IRR rates in open-label studies suggest ascertainment bias, where clinicians and patients may over-report mild symptoms due to heightened awareness (13). Some studies included treatment-naïve patients (9), who typically experience higher IRR rates compared with pre-exposed patients (18). Additionally, some studies captured IRRs only during infusion (13), while others included events occurring within 24 hours post-infusion (14). Non-standardized IRR definitions across all studies further contribute to variability in reported rates.

Premedication

Methylprednisolone and antihistamines were administered universally (9). Cetirizine was non-inferiority to diphenhydramine in preventing IRRs and was associated with fewer sedative side effects. Some studies allowed on-demand dose adjustments, which may also contribute to variability in reported IRR severity (9).

The First Dose

As per the standard protocol, the first dose is administered in two infusions to reduce IRR rates. However, a single 600 mg dose may be considered, as there is no difference in 24-hour post-infusion or life-threatening reactions. Slightly higher IRR rates can be managed by increasing premedication or reducing the infusion rate (16).

Study Limitations

The included studies were highly heterogeneous, which influenced the reported incidence of IRRs and prevented a meta-analysis. Additionally, long-term safety data were lacking, limiting the generalizability of our findings for long-term management and hindering the detection of complications that may develop over time, such as malignancies and infections. The primary progressive MS cohorts were small compared to the relapsing-remitting MS cohorts. Additionally, only a few studies reported details on premedication administered before infusion.

Future Directions

Further studies are needed to investigate different strategies for reducing IRRs and to establish a safer infusion protocol for ocrelizumab. In particular, additional trials on premedication strategies would significantly contribute to the literature. Long-

term observational studies are also warranted to provide a deeper understanding of ocrelizumab adverse events. Finally, standardizing the definition of IRRs would allow for more consistent and comparable results across studies.

Conclusion

Short and at-home infusions demonstrated safety comparable to conventional infusions, while offering a more comfortable, patient-preferred option. The single 600 mg first infusion was associated with slightly higher IRR rates, which can be easily managed. Both cetirizine and diphenhydramine were effective as premedications, showing similar reductions in IRR incidence.

Footnotes

Authorship Contributions

Concept: M.N.B., H.I.M., Design: M.N.B., B.N.B., A.S.A., Data Collection or Processing: M.N.B., B.N.B., A.S.A., A.A.A.R., A.N.A., A.I.A., Analysis or Interpretation: M.N.B., H.I.M., Literature Search: M.N.B., H.I.M., B.N.B., Writing: M.N.B., H.I.M., B.N.B., A.S.A., A.A.A.R., A.N.A., A.I.A.

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REVIEW

Visual Impairment in Multiple Sclerosis: A Comprehensive Review of Clinical Impact and Pathogenesis

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Abstract

Multiple sclerosis (MS), a chronic immune-mediated disease of the central nervous system with frequent visual involvement and frequently causes visual dysfunction through demyelination, neurodegeneration, and vascular impairment. Among the earliest and most disabling manifestations are optic neuritis, ocular motor dysfunction, and reduced contrast sensitivity, and for optometrists early recognition and consistent monitoring of these deficits are essential for timely referral, rehabilitation, and quality-of-life support. This review discusses the implications for optometric practice by synthesizing recent evidence on visual pathway alterations in MS. A narrative review of literature published between 2018 and 2025 was conducted using PubMed, Scopus, and Web of Science, and keywords included "multiple sclerosis,""optic neuritis,""visual function,""optical coherence tomography," and "optometry." Articles focusing on visual dysfunction, assessment tools, and management strategies relevant to optometry were prioritized. Emerging evidence highlights the utility of optical coherence tomography (OCT) and visual evoked potentials for detecting subclinical optic nerve damage, while functional deficits such as impaired contrast sensitivity, reduced stereoacuity, and visual field loss significantly impact daily activities. Through comprehensive eye examinations, monitoring of visual performance, and identification of red flags requiring neurological referral, optometrists play a central role in early detection. Recent studies also emphasize low-vision rehabilitation, prisms, and tailored visual aids as effective strategies to improve quality of life in affected patients. Visual dysfunction is a common and often under-recognized component of MS, and optometrists are well positioned to provide functional support, detect early signs, and collaborate in multidisciplinary management. Integrating advanced imaging, functional testing, and low-vision strategies into routine optometric care may improve both visual outcomes and patient quality of life. The present review summarizes pathophysiological mechanisms, clinical manifestations, diagnostic tools, and rehabilitation approaches, while new advances in OCT, OCT-angiography, and artificial intelligence-based analytics are discussed.

Keywords: Multiple sclerosis, optic neuritis, visual function, optical coherence tomography, optometry, low vision

Introduction

Multiple sclerosis (MS), a chronic immunemediated demyelinating disorder of the central nervous system that primarily affects young adults with peak onset between 20 and 40 years, is characterized by multifocal lesions, inflammation, demyelination, and neurodegeneration in brain, spinal cord, and optic nerves, and often leads to progressive neurological dysfunction (1). As of 2023, MS affected ~2.9 million individuals globally, with females more commonly affected than males (2), and visual disturbance is often an early sign reflecting the disease's predilection for the optic nerves and visual pathways (3).

Visual impairment in MS encompasses a broad spectrum, ranging from acute optic neuritis (ON) to chronic, subclinical dysfunction. ON presents as the initial symptom in about one fifth of MS cases, and up to half of patients experience at least one episode during the disease course (4,5). Persistent visual deficits, including reduced contrast sensitivity, color desaturation, visual field defects, diplopia, or ocular motility disorders, are also common often impairing daily functioning even when high contrast visual acuity (HCVA) remains relatively preserved (6,7).

Beyond acute inflammation, MS produces chronic retinal neurodegeneration even in eyes without clinical ON. Optical

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coherence tomography (OCT) demonstrates thinning of the retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer (GCIPL), correlating with both visual dysfunction and global central nervous system changes (8,9). These findings reinforce the value of visual system biomarkers for assessing disease activity and monitoring progression.

This review aims to integrate recent findings (2018-2025) on visual impairment in MS and to outline the clinical implications for both optometric and neurological practice.

Methodology

Search Strategy and Selection Criteria

A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar for publications between January 2018 and September 2025, using the keywords "multiple sclerosis," "optic neuritis," "visual dysfunction," "low contrast acuity," "retinal nerve fiber layer," "OCT," "OCT-angiography (OCT-A)," "visual rehabilitation," and "artificial intelligence (AI) in MS," with Boolean operators ("and," "or") applied to combine terms. Studies were included if they comprised (a) peer-reviewed original research articles, systematic reviews, or meta-analyses, (b) English-language publications, and (c) work focusing on visual or ocular manifestations of MS. Exclusion criteria consisted of (a) case reports, conference abstracts, or commentaries lacking primary data; (b) non-English articles, and (c) studies unrelated to visual outcomes. Reference lists of included papers were also screened to identify additional relevant studies. From a total of 136 publications, 92 met the inclusion criteria and were used to inform this review.

Epidemiology and Clinical Context

Visual disturbances are a hallmark of MS and commonly constitute one of its earliest clinical manifestations. ON represents the most frequent acute visual event, functioning as presenting symptom in ~20% of patients and occurring in nearly half during the disease course (4,10), while subclinical optic nerve damage is even more widespread (11,12).

The global burden of MSrelated visual impairment is substantial: more than 60% of patients report visual symptoms—including acute ON, persistent low contrast loss, blurred vision, or diplopia—at some stage (13). These impairments occur across both relapsing and progressive forms, including secondary progressive MS and primary progressive MS (14).

Demographically, onset usually falls between ages 20 and 40 with a marked female predominance (~3:1), and visual symptoms follow similar distributions (2,15). When ON presents after age 50, alternative etiologies such as ischemic or inflammatory non-MS causes are more likely (16).

ON and Risk of Multiple Sclerosis

Prognostic Significance

The ON treatment trial demonstrated that about 50% of individuals with isolated ON develop clinically definite MS over ~15 years (5,17), and risk rises markedly when white matter lesions are present on brain magnetic resonance imaging (MRI) at presentation. Patients with at least one demyelinating lesion have ~72% chance of conversion (5,18). Under the 2017 McDonald criteria, ON is incorporated as diagnostic evidence when MRI or cerebrospinal fluid findings are supportive, enabling earlier diagnosis and earlier initiation of disease-modifying therapies (DMTs) (19).

Clinical Course and Recovery

Recovery after ON is variable: highdose IV corticosteroids accelerate restoration of vision, particularly contrast sensitivity and visual fields, but they do not improve long term HCVA outcomes (5,17,20). Oral prednisone alone is contraindicated because of elevated risk of recurrence (17). Even after apparent recovery occurs, persistent deficits in contrast sensitivity, color perception, and visual fields are common, reflecting incomplete remyelination or axonal injury (21).

Neuroimaging Correlates

MRI is central in evaluating ON, with acute ON typically showing optic nerve T2 hyperintensity and frequently gadolinium enhancement during active inflammation (17). Brain white matter lesions not only support the diagnosis but predict both conversion and future disability. Advanced techniques such as diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI) detect microstructural changes in optic nerve and retrochiasmal pathways even in eyes without clinical ON (22).

Chronic Visual Dysfunction Beyond ON

Persistent visual deficits are experienced by many MS patients even without a history of ON, and up to ~40% exhibit low contrast letter acuity (LCLA) deficits that are missed by highcontrast tests (7,20). These chronic impairments include reduced contrast sensitivity, color desaturation, visual field irregularities, motion perception anomalies, and reading fatigue (6,21).

Structural retinal changes account for much of this dysfunction: OCT demonstrates RNFL and GCIPL thinning in both ON affected and unaffected eyes, and these correlate with quality-of-life measures such as the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ25) (22). RNFL thinning in eyes without ON is also associated with greater disability (as per Expanded Disability Status Scale) and brain atrophy (8,9,23,24), reinforcing the value of routine visual function monitoring as a component of MS assessment.

Pathophysiology of Visual Dysfunction in MS

ON and Demyelination

ON involves perivascular inflammation with disruption of the blood-brain barrier, immune cell infiltration, and demyelination of optic nerve axons. Clinically, patients typically present with subacute unilateral vision loss accompanied by pain with eye movement, color desaturation, reduced contrast sensitivity, and a relative afferent pupillary defect (25,26). In demyelination, visual evoked potentials (VEPs) (pattern and multifocal) demonstrate prolonged latency together with reduced amplitude (27-29).

Axonal Injury and Retinal Neurodegeneration

Significant axonal loss begins early, and ON may result in loss of up to ~40% of optic nerve axons within weeks (30,31). Even when eyes appear clinically unaffected, OCT reveals progressive thinning of the RNFL and GCIPL, correlating with visual deficits, brain atrophy, and disability scores (8,9,12,25,32).

Subclinical Visual Pathway Damage

Eyes without clinical ON frequently demonstrate deficits in lowcontrast acuity, motion perception, and binocular vision (20,33,34), and multifocal VEPs show delayed responses or reduced amplitudes in these unaffected eyes (27,35). Lesions in optic radiations or visual cortex contribute to visual field defects, slowed processing, and interactions with cognitive impairment (36).

Mechanisms of Retinal Injury

Retinal damage can occur independently of optic nerve inflammation: histopathology demonstrates microglial activation, retinal ganglion cell loss, and retinal atrophy even without clinical ON (8,37). A subset of patients develops microcystic macular edema (MME), which is associated with worse visual function and inflammatory disease activity. Proposed mechanisms include Muller cell dysfunction, disruptions of bloodretina barrier and retrograde degeneration (38,39).

Inflammation and Neurodegeneration: A Dual Framework

Inflammation and demyelination account for acute events such as ON, whereas chronic retinal thinning and visual pathway damage reflect ongoing neurodegeneration. This dual framework has therapeutic implications: immunomodulatory therapies reduce relapses and ON frequency but do not prevent longterm axonal loss or retinal thinning (33,40).

Clinical Features and Diagnostic Evaluation

Clinical Features of ON

• ON typically presents with subacute unilateral vision loss evolving over hours to days and is frequently accompanied by pain on eye movement (41).

• Color desaturation, particularly of red hues, and contrast sensitivity deficits are common (42,43).

• Visual field defects are often central or centrocecal. Optic disc swelling is seen in ~35% of cases, whereas the optic disc remain normal in retrobulbar ON (44,45).

Other Ocular Manifestations

• Diplopia from internuclear ophthalmoplegia (medial longitudinal fasciculus involvement), nystagmus or gazeevoked oscillations to brainstem or cerebellar lesions (46,47).

• Homonymous visual field defects arise from optic radiation or occipital lesions.

• More subtle deficits: motion perception, reading fatigue, or binocular dysfunction (34).

Diagnostic Tools

A wide range of diagnostic tools is available to assess visual function in MS, each offering distinct clinical insights. These methods allow detection of both structural and functional abnormalities, from subtle visual deficits to significant neurodegenerative change, and Table 1 presents a comparative overview of the most commonly used techniques, highlighting their utility in diagnosis, monitoring, and prognosis.

- **High Contrast Visual Acuity (HCVA)**

Measures central vision clarity and remains the standard clinical test, although it is less sensitive to subtle visual deficits in MS patients (7,20).

- **Low Contrast Letter Acuity (LCLA)**

Measures contrast sensitivity deficits and detects impairments even when HCVA is preserved; LCLA correlates with RNFL and GCIPL thinning, and is a sensitive functional measure in MS (22,33,48).

- **Color Vision Testing**

Assesses color desaturation, particularly relevant during or after episodes of ON (44).

- **Visual Field Testing**

Detects scotomas and central or peripheral visual field defects, providing lesion localization within the visual pathways (45,36).

- **Optical Coherence Tomography (OCT)**

Measures structural parameters including RNFL and GCIPL thickness and detects MME; OCT is a sensitive biomarker for both acute inflammatory and chronic neurodegenerative damage in MS (8,12,39,40).

- **VEPs and multifocal VEPs**

Evaluate latency and amplitude of visual signal transmission and reveal demyelination and conduction delays even in subclinical cases (27,35,49,50).

Table 1. Comparative summary of major diagnostic tools

Diagnostic tool	Primary parameter assessed	Clinical advantages	Limitations	Relevance in MS-related visual dysfunction
OCT	RNFL and ganglion cell complex thickness	Non-invasive, quantitative, sensitive to axonal loss	Limited correlation with cortical demyelination	Standard tool for detecting retinal neurodegeneration
OCT-A	Retinal microvasculature and perfusion	Visualizes microvascular impairment; complements structural OCT	Motion artifacts; limited field of view	Emerging biomarker for neurovascular coupling and disease activity
VEP	Electrical response of visual cortex to stimuli	Detects subclinical demyelination, functional measure	Influenced by fatigue, non-specific to lesion site	Essential for early detection and monitoring of optic pathway damage
MRI	Demyelinating plaques and optic pathway lesions	Whole-brain visualization, correlates with disease burden	Expensive, less sensitive to subtle retinal changes	Gold standard for diagnosing and staging MS
AI-based image analysis	Multimodal pattern recognition (OCT, MRI)	Automated detection, predictive analytics	Requires validation, potential for algorithmic bias	Promising adjunct for precision diagnosis and prognosis

OCT: Optical coherence tomography, OCT-A: OCT-angiography, VEP: Visual evoked potentials, MRI: Magnetic resonance imaging, AI: Artificial intelligence, RNFL: Retinal nerve fiber layer, MS: Multiple sclerosis

- **Magnetic Resonance Imaging (MRI)**

Detects lesions, active inflammation, and optic radiation involvement; advanced techniques such as DTI and MTI provide microstructural information. MRI remains the gold standard for diagnosis and prognosis in MS (17,22,36).

- **Patient Reported Outcomes (e.g., NEI VFQ-25)**

Capture quality of life and real-world visual impact, providing an essential complement to objective clinical testing (22).

Treatment of Visual Dysfunction in MS

Acute Management of ON

High dose intravenous corticosteroids (e.g., methylprednisolone 1 g/day for 3-5 days with taper) shorten time to visual recovery, particularly contrast, fields, and color perception, although they do not improve long term HCVA (5,17,20). For severe or steroid non-responsive cases, plasma exchange is reserved.

Disease-Modifying Therapies (DMTs)

DMTs (interferon beta, glatiramer acetate, fingolimod, ocrelizumab, cladribine) reduce ON recurrence and suppress MRI inflammatory activity, yet their effect on slowing retinal thinning and neurodegeneration remains modest (46,47,51).

Neuroprotective and Remyelinating Strategies

Strategies under investigation include:

- Phenytoin, which has been shown to reduce RNFL loss in acute ON cohorts (44,45).

- Clemastine fumarate, anti-LINGO1 antibodies, neurotrophic and antioxidant therapies all of which remain in study phases (45).

Symptomatic and Supportive Therapies

- Lowvision aids, magnifiers, electronic reading devices to assist reading and mobility.

- Prism therapy for diplopia and oculomotor exercises with vision therapy for improving gaze stability.

- Vision rehabilitation and occupational therapy further support and maximize independence (46).

Digital Monitoring and AI Integration

Smartphonebased tests for visual acuity and contrast sensitivity correlate with OCT metrics and may enable remote follow-up (46). AI/machine learning models that combine OCT, VEP, MRI, and biomarkers (serum neurofilament light chain) show growing promise for prediction of disease progression and for personalized treatment planning (33).

Rehabilitation of Visual Dysfunction in MS

Visual rehabilitation plays a central role in improving functional outcomes and quality of life in MS-related visual impairment. Conventional strategies such as contrast sensitivity and reading training are now complemented by contrast enhancement filters, digital magnification, and adaptive lighting systems to optimize residual vision, while occupational therapy emphasizes mobility and orientation training for safe navigation and spatial awareness. Adaptive software solutions, including screen-reading programs, speech-to-text converters, and AI-assisted visual scene interpreters, significantly enhance patient independence. Multidisciplinary rehabilitation models integrating neurologists, optometrists, and low-vision specialists are increasingly recommended to deliver holistic, goal-oriented care.

Illustrative Case Example: A 34-year-old woman with relapsing-remitting MS reported fluctuating vision and difficulty with contrast discrimination. OCT revealed thinning of the RNFL, while OCT-A demonstrated reduced vessel density in the superficial plexus. A customized rehabilitation plan involving contrast filters, adaptive magnification, and mobility training resulting in a 25% improvement in LCLA and increased

subjective quality-of-life scores on the NEI VFQ-25 scale after 12 weeks, illustrating the functional impact of integrating structural assessment with rehabilitative care (52).

Emerging Research and Future Directions

Growing evidence supports OCT-A as a sensitive biomarker in MS, detecting reduced retinal vessel density—particularly in macular and peripapillary regions—which may precede structural damage and help distinguish ON-affected eyes.

Parallel research has accelerated development of AI and machine learning models capable of predicting MS progression using OCT, VEP, MRI, and clinical data, with increasing emphasis on model explainability for clinical adoption (12).

An expanding literature also highlights sex differences and lifestyle influences: although MS is more common in women, men may experience greater visual decline, and modifiable factors such as smoking, vitamin D, diet, and physical activity are under investigation for their effects disease progression and visual outcomes.

Explainable Artificial Intelligence in MS-Related Vision Research

Artificial intelligence has substantial potential for early detection and monitoring of optic nerve and retinal changes in MS, but translation to clinical use depends on transparency and interpretability. Explainable AI frameworks aim to demonstrate which image features or biomarkers drive predictions, increasing diagnostic confidence, reducing bias, and supporting ethical integration of AI systems into multidisciplinary MS care. Ongoing research should prioritize clinician-interpretable AI models for OCT and MRI analysis to ensure real-world applicability.

Conclusion

Visual dysfunction in MS is multifactorial, involving acute inflammatory injury (ON), chronic neurodegeneration, and subclinical visual pathway damage. Diagnostic tools—OCT, VEP, MRI—permit early detection and longitudinal monitoring. Current DMTs lessen ON recurrence and reduces relapses but provide limited protection against long term axonal loss and retinal thinning. Emerging strategies, including neuroprotective and remyelinating therapies, AI-based predictive tools, OCTA vascular metrics, and structured rehabilitation, are increasingly important for preserving vision and quality of life. Personalized multimodal monitoring together with early intervention holds the greatest promise for improving outcomes.

Footnotes

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REVIEW

Impact of Acquired Brain Injury on Vision: Patterns, Assessment, and Rehabilitation

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Abstract

Acquired brain injury (ABI), including stroke and traumatic brain injury, is frequently associated with visual system impairments that range from basic sensory deficits to complex perceptual dysfunctions, substantially affecting patient independence, safety, and quality-of-life. This narrative review synthesizes current evidence on the patterns, underlying mechanisms, assessment strategies, and management of vision impairments following ABI, while also highlighting gaps in clinical care and research. A comprehensive literature search was conducted using PubMed, Scopus, and Google Scholar to identify studies addressing post-ABI visual deficits, their pathophysiology, rehabilitation approaches, and outcomes in both adult and pediatric populations. Visual impairments after ABI include visual field defects (e.g., homonymous hemianopia), oculomotor dysfunction, cortical visual impairment, and higher-order visual perceptual disorders such as visual neglect and visual agnosia. Accurate assessment requires interdisciplinary collaboration and the use of tools such as perimetry, visual evoked potentials, neuroimaging, and neurocognitive testing. Rehabilitation strategies encompass compensatory training, prism adaptation, vision therapy, and assistive technologies; however, the strength of evidence supporting these interventions remains variable, and standardized care pathways are lacking. Early screening, coordinated interdisciplinary management, and individualized rehabilitation programs are essential to optimize visual recovery. Further research is needed to establish robust evidence-based interventions and to integrate visual assessment and rehabilitation into comprehensive neurorehabilitation services.

Keywords: Acquired brain injury, visual impairment, cortical visual impairment, visual field loss, traumatic brain injury, stroke rehabilitation, neuro-ophthalmology

Introduction

Acquired brain injury (ABI), encompassing traumatic brain injury (TBI) as well as non-traumatic etiologies such as stroke, hypoxia, infection, and tumors, represents a leading cause of long-term neurological disability worldwide. In addition to cognitive and motor impairments, visual dysfunction is among the most common yet underrecognized sequelae of ABI. The visual system occupies nearly one-third of the human cerebral cortex, rendering it particularly susceptible to both focal and diffuse neural damage. As a result, even localized lesions may disrupt multiple visual pathways, producing a broad spectrum of deficits that substantially affect independence, mobility, and quality-of-life (1).

Epidemiological studies suggest that approximately 50-80% of individuals with ABI experience some degree of visual impairment, ranging from basic sensory deficits, such as visual field loss, to higher-order perceptual disturbances, including visual neglect, visual agnosia, and cortical visual impairment (CVI) (2). These abnormalities frequently coexist with oculomotor dysfunctions—such as strabismus, convergence insufficiency, and saccadic dysmetria—which further compromise binocular vision and reading efficiency. Despite their high prevalence, visual impairments are often overlooked during acute management and rehabilitation, where attention is typically directed toward more apparent motor or language deficits. This underrecognition may delay appropriate intervention and adversely affect functional recovery (3).

Growing recognition within neuro-ophthalmology and vision rehabilitation has underscored the importance of

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integrating systematic visual assessment into multidisciplinary ABI care. Early identification through standardized screening tools, including perimetry, ocular motility assessment, and evaluation of visual perceptual function, allows for timely and targeted interventions that may meaningfully improve patient outcomes. Rehabilitation approaches—such as compensatory scanning training, prism adaptation, vision therapy, and assistive technologies—have demonstrated increasing potential benefit; however, their implementation remains inconsistent across clinical settings (4).

Given the heterogeneity of ABI and the complexity of visual processing, a comprehensive understanding of post-ABI visual dysfunction is essential for the development of effective diagnostic and therapeutic frameworks. Accordingly, this narrative review aims to synthesize current evidence on the mechanisms, clinical manifestations, assessment strategies, and management of visual impairments following ABI, while identifying key gaps in research and clinical practice that must be addressed to optimize patient care.

Epidemiology of Visual Impairments After ABI

Visual dysfunction is among the most prevalent yet frequently underestimated sequelae of ABI. Epidemiological studies consistently report that approximately 50-80% of individuals with ABI experience some form of visual impairment during the acute or chronic phases of recovery (5). However, the true prevalence is likely higher, as subtle sensory deficits and higher-order visual perceptual disturbances may remain undetected in the absence of specialized assessment. Moreover, heterogeneity in study design, visual assessment methods, and patient populations contributes substantially to the wide variability observed in reported prevalence rates.

Global and Regional Prevalence

Globally, the World Health Organization estimates that more than 60 million people live with long-term neurological disability resulting from stroke and TBI combined, a substantial proportion of whom experience visual impairment (6). Among individuals with stroke, visual field defects—such as homonymous hemianopia and quadrantanopia—are reported in approximately 30-50% of cases. Oculomotor abnormalities, including gaze palsy, diplopia, and nystagmus, affect nearly 40% of stroke survivors, while visual neglect occurs in up to 30%, particularly following right hemispheric lesions (7).

TBI, another major contributor to ABI, is associated with an even higher burden of visual sequelae. Recent studies indicate that 60-70% of individuals with moderate-to-severe TBI experience one or more visual dysfunctions, ranging from accommodative and vergence abnormalities to deficits in visual processing (8). Although often considered less severe, mild TBI—commonly related to sports injuries or blast exposure—can also result in subtle yet functionally significant visual symptoms, including photophobia, blurred vision, and impairments in reading and visual attention.

Determinants and Outcomes

The likelihood and severity of visual dysfunction following ABI are influenced by several factors, including lesion location, the extent of diffuse axonal injury, patient age, and the presence of concomitant cognitive deficits. Early identification of visual impairments is frequently impeded by the limited integration of comprehensive vision assessment into routine neurological evaluation and rehabilitation protocols. Consequently, unrecognized visual deficits may contribute to delayed functional recovery, impaired mobility, increased risk of falls, and reduced reintegration into activities of daily living and employment.

Although the epidemiological burden of post-ABI visual impairment has been relatively well characterized in high-income Western countries, data from low- and middle-income regions remain limited. In the context of the rising global incidence of cerebrovascular disease and traumatic injury, enhanced epidemiological surveillance and the implementation of standardized visual screening protocols are essential to accurately define the scope of vision loss secondary to ABI.

Types and Mechanisms of Visual Impairments After ABI

The human visual system relies on the integrated functioning of ocular, cortical, and subcortical structures. ABI—whether caused by ischemic stroke, TBI, or hypoxic insult—can disrupt these networks at multiple levels, resulting in a broad spectrum of visual impairments. The type and severity of deficits depend on lesion location, extent of neural damage, and individual neuroplastic potential.

1. Visual Field Defects

Visual field loss is among the most prevalent visual consequences of ABI, particularly following occipital lobe lesions or posterior cerebral artery strokes. Disorders such as homonymous hemianopia, quadrantanopia, and scotomas arise from injury along the geniculocalcarine pathway, extending from the optic tract to the primary visual cortex. These deficits can significantly impair navigation, reading, and spatial orientation. Although spontaneous partial recovery may occur, persistent field loss often necessitates compensatory strategies, including visual scanning training or prism adaptation. Functional neuroimaging studies suggest that perilesional cortical reorganization may contribute to recovery in selected cases (9).

2. Oculomotor Dysfunction

Oculomotor abnormalities—including impaired saccades, smooth pursuit deficits, nystagmus, and convergence insufficiency—are

common following ABI, particularly in TBI. These deficits result from disruption of cortical-subcortical control circuits involving the frontal eye fields, cerebellum, and brainstem. Affected individuals frequently report diplopia, eye strain, or difficulty with reading. Quantitative assessment tools, such as eye movement recordings and infrared oculography, support accurate diagnosis and guide rehabilitation strategies, including vergence and pursuit training. Persistent oculomotor dysfunction may exacerbate dizziness and postural instability (10).

3. Cortical Visual Impairment

CVI arises from damage to the visual cortex or its associated white matter tracts, leading to deficits in visual perception despite normal ocular health. Although traditionally recognized in pediatric populations, CVI is increasingly identified in adults with ABI. Clinical manifestations include reduced visual acuity, impaired visual attention, and difficulty recognizing faces or objects. Neuroimaging studies indicate functional disconnection among occipital, temporal, and parietal regions. Rehabilitation emphasizes structured visual stimulation, environmental modifications, and targeted perceptual retraining (11).

4. Visual Neglect and Spatial Attention Deficits

Damage to the parietal or temporo-parietal junction can lead to visual neglect, characterized by the failure to attend to one side of space despite intact visual fields. This condition is particularly common after right-hemisphere stroke and is associated with severe disability and safety risks. Visual neglect arises from disrupted attentional control and interhemispheric imbalance rather than primary sensory loss. Interventions such as prism adaptation, scanning therapy, and non-invasive brain stimulation have demonstrated promising, albeit variable, benefits. Early detection using standardized assessments, such as the behavioral inattention test, improves rehabilitation outcomes (12).

5. Higher-order Visual Perceptual Disorders

In addition to primary visual deficits, ABI can result in complex perceptual disorders, including visual agnosia, prosopagnosia, and alexia, typically due to damage in the ventral visual stream connecting the occipital and inferotemporal cortices. These disorders often cooccur with cognitive or language deficits, which can complicate recognition and recovery. Management strategies primarily include cognitive-perceptual training and compensatory cueing, although large-scale trials assessing their efficacy remain limited.

Mechanistic Insights and Clinical Implications

Contemporary neuroimaging suggests that visual dysfunction following ABI arises not only from focal damage but also from network-level disconnection and maladaptive neuroplasticity. Injury to white matter tracts and trans-synaptic degeneration contributes to persistent deficits. Rehabilitation strategies that leverage visual neuroplasticity—such as repetitive stimulation and adaptive visual tasks—may facilitate recovery in selected patients. However, variability in injury patterns and the absence of standardized diagnostic criteria continue to limit widespread application.

A clear understanding of the mechanisms underlying visual dysfunction after ABI is essential for developing personalized interventions. The integration of neuro-optometric assessment, neuropsychology, and occupational therapy remains critical for achieving functional improvement and enhancing quality-of-life.

Types and Mechanisms of Visual Impairment in ABI

Visual dysfunction following ABI is diverse and reflects the complexity of the visual system, which involves multiple cortical and subcortical pathways. These impairments may result from direct structural damage to the visual cortex, optic radiations, or visual association areas, as well as secondary factors such as cerebral edema, ischemia, or diffuse axonal injury. The most commonly observed visual sequelae after ABI include visual field loss, oculomotor dysfunction, CVI, and higher-order perceptual disorders.

Visual field defects occur in approximately one-third of patients with stroke or TBI and typically present as homonymous hemianopia or quadrantanopia. These defects generally arise from lesions in the retrochiasmal visual pathways, particularly the optic radiations and occipital cortex. Patients with visual field loss often experience spatial disorientation, difficulty reading, and impaired mobility. Although partial recovery may occur within the first six months, persistent visual field loss requires compensatory strategies, such as visual scanning training or prism adaptation therapy (13).

Oculomotor dysfunction, including convergence insufficiency, saccadic dysmetria, strabismus, and impaired smooth pursuit, is also common after ABI. Lesions in the brainstem, cerebellum, or cortical eye movement centers disrupt binocular coordination, leading to symptoms such as diplopia, blurred vision, and eye strain. These dysfunctions are often underdiagnosed despite their significant impact on balance, mobility, and reading efficiency (14).

CVI represents a distinct form of visual loss resulting from cortical or subcortical injury, despite anatomically normal eyes. Individuals with CVI frequently exhibit fluctuating visual responses, difficulty recognizing complex scenes, and challenges with visual crowding. Functional magnetic resonance imaging (MRI) studies suggest that these symptoms are associated with altered connectivity and compensatory neuroplasticity in occipito-temporal pathways (15).

Higher-order perceptual disorders, including visual neglect, simultanagnosia, prosopagnosia, and visual agnosias, result from lesions affecting the parietal and temporal cortices. Visual neglect, particularly when associated with right parietal lobe damage, reduces awareness of the contralesional visual field and severely impacts daily functioning and spatial attention (16).

Mechanistically, ABI-induced visual deficits arise from both focal and diffuse neural injury. Hypoperfusion, excitotoxicity, inflammation, and axonal shearing contribute to secondary degeneration of interconnected visual networks. Advanced neuroimaging has revealed disrupted connectivity between fronto-parietal and occipito-temporal regions, which underlies persistent dysfunction. Understanding these mechanisms facilitates accurate diagnosis and informs targeted rehabilitation strategies (17).

Assessment of Visual Dysfunction After ABI

Evaluation of visual dysfunction following ABI requires a comprehensive, multidisciplinary approach that integrates neurological, ophthalmological, and optometric perspectives. Because visual deficits can range from basic sensory loss to complex perceptual disorders, no single test can capture the full spectrum of impairments. Early, structured visual assessment is essential to identify functional limitations, guide rehabilitation, and improve quality-of-life.

Clinical screening typically begins with a standard ophthalmic assessment, including visual acuity, refraction, and ocular health evaluation, to exclude preexisting ocular pathology. Visual field testing—performed using automated or manual perimetry—remains the cornerstone for detecting hemianopia, quadrantanopia, or scotomas. Goldmann and Humphrey perimetry can precisely delineate the extent and pattern of field loss, providing critical information for both diagnosis and rehabilitation planning (18). In acute settings where formal perimetry is impractical, bedside confrontation tests may serve as an initial screening tool.

Oculomotor assessment is equally important, as dysfunctions in vergence, saccades, and pursuit movements are common after ABI. Objective techniques, such as eye-tracking or video-oculography, can detect subtle abnormalities that routine clinical examination might miss. Specific assessments, including the developmental eye movement test and the King-Devick test, are useful for evaluating reading-related eye movements and can indicate underlying oculomotor inefficiencies (19). Additionally, pupillary responses and near point of convergence testing provide further insight into cranial nerve and brainstem function.

Assessment of visual attention, neglect, and higher-order perceptual deficits often requires neuropsychological evaluation. Standardized tests, such as the behavioral inattention test and the Bells test, are commonly used to detect unilateral neglect, whereas object and face recognition tasks can identify agnosias or prosopagnosia (20). Functional visual assessment, including observation of reading, navigation, and visually guided reaching, provides ecological validity to formal test results.

Neuroimaging techniques, particularly MRI and diffusion tensor imaging (DTI), are invaluable for identifying lesions within visual pathways and associated networks. These modalities can correlate structural damage with clinical symptoms and monitor recovery over time (21). Electrophysiological assessments, including visual evoked potentials, offer objective evidence of postchiasmal dysfunction and are particularly useful when behavioral responses are unreliable, such as in pediatric or severely impaired patients (22).

Given the complex interplay between visual, cognitive, and motor domains, interdisciplinary collaboration is essential. Optometrists, ophthalmologists, neurologists, and neuropsychologists should work together to ensure comprehensive evaluation and integrated management. The implementation of standardized vision screening protocols in neurorehabilitation programs has been shown to improve detection rates and facilitate timely intervention (23). Emerging digital technologies, including virtual reality (VR)-based visual field mapping and mobile vision assessment platforms, further enhance accessibility and accuracy in post-ABI visual evaluation (24).

Rehabilitation and Management Approaches in Visual Dysfunction After ABI

Rehabilitation of visual dysfunction following ABI aims to restore visual performance, enhance compensatory mechanisms, and improve functional independence. The complexity of visual processing and the heterogeneity of impairments necessitate a multimodal, interdisciplinary approach that integrates optometric, neurological, and occupational rehabilitation strategies.

Management begins with a comprehensive assessment of the type and severity of visual impairment, followed by individualized therapy plans. For patients with visual field deficits, compensatory techniques such as visual scanning training, systematic eye movement exercises, and reading retraining are commonly employed. Scanning therapy promotes systematic exploration of the blind hemifield, facilitating adaptation and improving detection of peripheral stimuli. Prism adaptation therapy, using yoked or sectoral prisms, has demonstrated efficacy in shifting the visual field and enhancing awareness of the impaired field (25,26). Recently, VR-based rehabilitation platforms have emerged as effective adjuncts, providing immersive environments for repetitive, feedback-based training (27).

Restorative approaches aim to enhance neural plasticity and residual visual field function through visual restitution therapy (VRT) and perceptual learning. These interventions involve repetitive visual stimulation near the border of the visual field defect to strengthen synaptic activity and cortical representation. Although the evidence remains mixed, some studies report measurable improvements in detection sensitivity and functional outcomes following sustained training (28,29).

Oculomotor rehabilitation targets common deficits after traumatic or ischemic brain injury, including convergence insufficiency, saccadic dysmetria, and pursuit impairments. Techniques such as vergence exercises, accommodative therapy, and dynamic saccadic training can restore binocular control and improve reading fluency. Computer-assisted oculomotor training and neuro-optometric rehabilitation have demonstrated promising results in enhancing fixation stability and visual endurance (30). Furthermore, integrating vestibular and balance training can further support overall recovery, particularly in patients experiencing postural instability or dizziness.

Management of CVI and higher-order perceptual disorders primarily emphasizes compensatory strategies and environmental modifications. Simplifying visual scenes, enhancing contrast, and providing structured routines can reduce visual crowding and cognitive load. For patients with visual neglect, interventions such as prism adaptation, optokinetic stimulation, and non-invasive brain stimulation techniques—including transcranial direct current stimulation—are under investigation for their potential to improve spatial awareness (31,32).

Assistive technologies are playing an increasingly important role in vision rehabilitation. Electronic magnifiers, head-mounted display systems, and augmented reality (AR) devices facilitate reading and mobility. Mobile applications offering gaze-tracking, text-to-speech, and scene interpretation have enhanced accessibility for individuals with visual-perceptual deficits (33). Emerging evidence also supports the integration of artificial intelligence-based adaptive vision aids, which can adjust display and contrast parameters in real time according to user needs (34).

Ultimately, successful rehabilitation depends on individualized goal setting, patient engagement, and early initiation of therapy. Interdisciplinary coordination among ophthalmologists, optometrists, neuropsychologists, and occupational therapists ensures comprehensive care. Despite advances, gaps remain in the standardization of rehabilitation protocols and the measurement of long-term outcomes, highlighting the need for high-quality, controlled trials to establish evidence-based best practices (35).

Discussion and Future Directions

Despite growing recognition of visual dysfunction following ABI, significant gaps remain in understanding its mechanisms, diagnosis, and management. The heterogeneity of ABI—including stroke, TBI, hypoxic injury, and intracranial hemorrhage—contributes to variability in visual outcomes and complicates the development of standardized rehabilitation approaches. Recent advances in neuroimaging, digital technologies, and neurorehabilitation have opened promising avenues for personalized interventions; however, integrating these approaches into routine clinical practice remains challenging (36,37).

Current evidence highlights the critical role of neuroplasticity in postinjury visual recovery. Functional MRI and DTI studies have demonstrated cortical reorganization within the occipital and parietal regions following targeted rehabilitation, particularly through VRT and perceptual learning paradigms (38). The extent of cortical plasticity, however, appears to depend on lesion location, size, and chronicity. This variability underscores the potential benefit of tailoring rehabilitation strategies to individual neural profiles, using imaging biomarkers as predictive tools to optimize outcomes (39).

Technological innovations—particularly VR, AR, and telerehabilitation—offer unprecedented opportunities for visual training. These tools create immersive, adaptive, and feedback-rich environments that can enhance patient engagement and facilitate home-based rehabilitation (40). Artificial intelligence powered gaze-tracking systems and machine-learning algorithms can further personalize therapy intensity and objectively monitor progress. Nevertheless, accessibility, cost, and the need for rigorous clinical validation remain significant barriers, especially in low-resource settings (41).

Multidisciplinary collaboration is another key determinant of successful outcomes. Integrated care models involving neuro-ophthalmologists, optometrists, occupational therapists, and neuropsychologists ensure that visual, cognitive, and perceptual deficits are addressed holistically (42). Despite this, vision rehabilitation remains underrepresented in many neurorehabilitation programs, often overshadowed by motor and language therapies. Incorporating vision screening protocols into early post-stroke and post-TBI care pathways can substantially improve detection rates and recovery potential (43).

Future research should prioritize three key areas. First, large-scale randomized controlled trials are necessary to establish evidence-based protocols for specific interventions, including prism adaptation, visual scanning, and non-invasive brain stimulation. Second, long-term follow-up studies should assess sustained functional gains and quality-of-life outcomes rather than focusing solely on short-term visual metrics. Third,

interdisciplinary and patient-centered research frameworks should incorporate patient-reported outcomes to address the psychosocial and occupational impacts of visual dysfunction (44).

In conclusion, although substantial progress has been made in understanding and managing visual impairments following ABI, the field remains in an evolving state. Bridging the gap between neuroscience, technology, and rehabilitation practice will be critical to achieving meaningful visual recovery and enhancing life participation among affected individuals (45).

Conclusion

Visual dysfunction following ABI remains a significant yet frequently underrecognized contributor to long-term disability. Early screening and targeted rehabilitation can substantially enhance functional recovery and quality-of-life. Incorporating visual assessment into standard neurorehabilitation programs is essential for comprehensive care. A coordinated, multidisciplinary approach—augmented by advancing technologies such as VR and telerehabilitation—offers promising opportunities for improving visual outcomes. Ongoing research and the standardization of evidence-based practices will be critical to ensuring that vision rehabilitation becomes an integral component of brain injury recovery globally.

Footnotes

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