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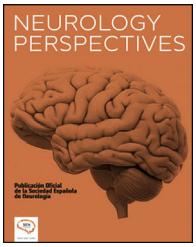

REVIEW

Autoimmune eye diseases in multiple sclerosis

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KEYWORDS
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Treatment

Abstract
Introduction: The eye is a complex organ that can present complications related to autoimmune diseases, including multiple sclerosis (MS). Ocular manifestations may act as early indicators of autoimmune diseases, and their early diagnosis and treatment are essential to guaranteeing patients' quality of life. This review analyses the main autoimmune eye diseases associated with MS, focusing on intermediate uveitis and its personalised management.
Development: MS-associated uveitis includes various forms of intraocular inflammation affecting different areas of the eye. The relationship between MS and uveitis is complex and involves shared immunological mechanisms and diagnostic and therapeutic challenges. The clinical presentation of uveitis varies from asymptomatic forms to severe vision-threatening complications. The treatment of uveitis involves careful assessment and the consideration of immunomodulatory or immunosuppressive treatment with a view to controlling inflammation and preventing visual sequelae.
Conclusions: Treatment of MS-related uveitis is complex and requires a multidisciplinary approach. Advances in immunomodulatory therapy offer new treatment options, as well as challenges related to adverse reactions and disease management. Further research is needed to better understand the relationship between MS and eye diseases, and to optimise therapeutic strategies and improve patients' visual and neurological outcomes.

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PALABRAS CLAVE
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Tratamiento

Enfermedades oculares autoinmunes en esclerosis múltiple

Resumen
Introducción: El ojo es un órgano complejo que puede reflejar complicaciones relacionadas con enfermedades autoinmunes, incluida la esclerosis múltiple (EM). Las manifestaciones oculares pueden actuar como indicadores tempranos de enfermedades autoinmunitarias y su diagnóstico y tratamiento oportunos son cruciales para la calidad de vida del paciente. En esta revisión, se analizan las principales enfermedades autoinmunes oculares asociadas con la EM, centrándose en las uveítis intermedias y su manejo personalizado.
Desarrollo: Las uveítis asociadas con la EM incluyen diversas formas de inflamación intraocular que afectan diferentes áreas del ojo. Existe una relación compleja entre la EM y las uveítis, involucrando mecanismos inmunológicos compartidos y desafíos diagnósticos y terapéuticos. La presentación clínica de las uveítis varía, desde formas asintomáticas hasta complicaciones graves que amenazan la visión. El tratamiento de estas uveítis implica una evaluación cuidadosa y la consideración de terapias inmunomoduladoras o inmunosupresoras, con el objetivo de controlar la inflamación y prevenir daños visuales.
Conclusiones: El tratamiento de las uveítis asociadas a la EM es complejo y requiere un enfoque multidisciplinar. Los avances en terapias inmunomoduladoras ofrecen nuevas opciones, aunque también presentan desafíos en términos de efectos secundarios y manejo de la enfermedad. Se necesita más investigación para comprender mejor la relación entre la EM y las enfermedades oculares, así como para optimizar las estrategias terapéuticas y mejorar los resultados visuales y neurológicos de los pacientes.

Introduction

The eye is a complex organ whose microenvironment is sensitive to systemic changes in the body; each section of the eye may be a potential target for autoimmune complications. Eye disorders may be the initial indicator of underlying autoimmune disease. Ocular manifestations may appear before or during active disease, or years after diagnosis; delayed diagnosis and treatment directly affect patients' quality of life, and there is a significant risk of vision loss or damage. Ideally, periodic ophthalmological examination would be included in the routine management of autoimmune disease, enabling early diagnosis, research, and treatment of potential ophthalmic alterations, even in asymptomatic patients.

This review addresses the main autoimmune eye diseases associated with multiple sclerosis (MS), focusing on the most frequent, uveitis (specifically, intermediate uveitis [IU]), as well as the personalised management of the condition.

Eye disease in multiple sclerosis

MS-associated ocular inflammation may manifest as optic neuritis, granulomatous or non-granulomatous anterior uveitis (AU), IU, periphlebitis, posterior uveitis (retinitis and/or choroiditis), panuveitis, or a combination of any of the above.[1]

Patients with MS present a greater risk of developing uveitis, potentially due to common target antigens, genetic susceptibility, or similar immunological effector pathways.[2] It is not completely clear whether uveitis is a manifestation of MS or a concomitant disorder; however, the pathogenesis of both diseases involves similar immune cell populations (CD4+ Th1 and Th17 cells, CD8+ cytotoxic T cells, regulatory T cells, B cells, macrophages, and natural killer cells) and common cytokines (TNF, IFN-γ, IL-2, IL-6, IL-10, IL-12, IL-17, and IL-21/23), and several potential trigger antigens have been detected.[2] This uncertainty gives rise to challenges both in the diagnosis and in the treatment of these patients, such as the importance of recognising visual symptoms derived from demyelination and intraocular inflammation, or visual complications of disease-modifying therapies for MS, such as fingolimod. Similarly, treatment decisions in patients with uveitis are influenced by the risk of triggering or exacerbating episodes of demyelination, for instance after biological treatment against tumour necrosis factor, and other neurological complications of immunosuppressive treatments for uveitis.[2]

Uveitis is classified anatomically, according to the main foci of inflammation: AU involves the iris and ciliary body; IU primarily affects the vitreous body; posterior uveitis involves the retina and/or choroid; and panuveitis is defined as a combination of all 3.[3] There is a certain controversy in the literature regarding the incidence of uveitis, the most frequent clinical form, the timing of onset with respect to MS, and the visual prognosis of each form of uveitis. As a general rule, uveitis in patients with MS is classified as IU or pars planitis with retinal periphlebitis in 60%–80% of cases, acute and/or chronic AU in 15%, posterior uveitis (retinitis or choroiditis) in 3%, and panuveitis in 2%.[1,4]

The general incidence of uveitis in patients with MS is estimated at approximately 1%,[4,5] and up to 1% of cases of uveitis are associated with MS, a rate 10 times higher than that observed in the general population.[2,5] However, in the specific case of IU, up to 16% of cases are associated with demyelinating disease, most frequently MS (78%).[1,5,6] Nonetheless, up to 20%–44% of these patients are estimated to present subclinical periphlebitis, which is only detectable with fluorescein angiography; this disorder typically affects white women aged 20–50 years (mean: 36.6 years), who account for up to 74% of cases. Uveitis may occur before neurological symptoms of MS in 25%–46% of cases, concomitantly with MS symptoms in 18%–19%, and after established diagnosis of MS (mean of 5 years) in 36%; in these cases, MS diagnosis is often delayed due to the subtlety and low frequency of this form of presentation.[1,4,7] MRI of the central nervous system (CNS) is not routinely performed in the work-up of uveitis and is mainly restricted to cases of strong clinical suspicion. To date, no recommendations have been issued regarding the indication of MRI in patients with uveitis; however, it would be advisable in patients displaying neurological signs or symptoms suggestive of MS, patients with IU showing neurological signs, and patients under evaluation for certain biological therapies.[8]

Uveitis in these patients may affect one or both eyes, with bilateral involvement being more frequent (50%–94% of cases, in different series), and is often chronic, granulomatous, and presents a relapsing course. Another noteworthy detail is the fact that up to 2% of patients with chronic AU may present MS; therefore, MS should be considered during differential diagnosis.[4,7] As mentioned previously, pars planitis or IU is the most frequent form of presentation, developing with intraocular inflammation that primarily involves the anterior vitreous body and pars plana, although this inflammation may extend to the iris and ciliary body, resulting in associated chronic iridocyclitis.[6] Symptom onset in IU may be insidious, or be delayed for several years. The most frequent symptoms are floaters, blurred vision, pain, photophobia, and red eye; these symptoms may be mistaken for optic neuritis, although uveitis does not present with relative afferent pupillary defect, unless optic disc oedema presents as a complication.[2] Patients with IU present an 8%–16% risk of developing MS, even years later,[1,5,6] with the majority of patients carrying the HLA-DR15 serotype.[7] Furthermore, MS and IU share an association with the rs2104286 polymorphism of the *IL2RA* gene, although this variation is not pathognomonic for the disease, as it is also detected in other autoimmune diseases.[4] IU in patients with MS tends to be bilateral and is often associated with vasculitis that is only detectable by angiography, or displaying whitish inflammatory perivascular cuffing.[4]

Between 10% and 39% of patients with MS present retinal vasculitis characterised by perivascular exudates, haemorrhage, and even retinal vein occlusion.[7] The presence of uveitis with periphlebitis has been regarded as a marker of MS severity, due to its association with greater disability and risk of relapse.[4,7] An association has also been described between asymptomatic periphlebitis affecting the peripheral retina and optic neuritis and its predictive value for subsequent diagnosis of MS.[9]

Ocular complications associated with IU are rare, but may have severe repercussions for vision; the most relevant are cataracts, anterior or posterior synechiae, glaucoma, cystoid macular oedema, neovascularisation, vitreous/retinal haemorrhages, or retinal detachment.[6,10,11] The visual prognosis of these patients is generally favourable with appropriate medical or surgical treatment; however, up to 47% of affected eyes lose visual acuity at 5 years of follow-up, with up to 12% of these losing 3 or more lines of acuity.[1,12]

Treatment of uveitis in patients with multiple sclerosis

The available treatments for MS and uveitis aim to relieve symptoms and reduce visual and neurological disability, but they may also have bidirectional undesired effects. Care must be taken to differentiate these adverse reactions from MS relapses or progression, which require a different therapeutic approach[13]; therefore, a multidisciplinary approach involving both the neurology and the ophthalmology departments is essential. Treatment for uveitis includes several therapeutic lines; different treatments will be selected according to the specific type of uveitis. This review focuses on the treatment of IU in patients with MS (Fig. 1).

Few articles have addressed the treatment of MS-associated IU. Generally speaking, the gradual treatment approach followed in non-infectious IU can be extrapolated to MS-associated uveitis. Although bilateral involvement is rare in IU, long-term visual prognosis is usually good, even in untreated or locally treated cases; therefore, it is important to ensure that the remedy is not worse than the disease.[12,14] The Multicenter Uveitis Steroid Treatment trial reported that patients with IU presented relatively good outcomes, except in cases displaying macular thickening or oedema in optical coherence tomography studies, combined with active inflammation.[15] Furthermore, according to a retrospective review of cases at a tertiary-level centre, 22.5% of patients with IU did not require treatment, with 60% of patients presenting relatively well-preserved visual acuity at 10 years of follow-up.[16] This suggests that immunomodulatory or immunosuppressive drugs are not needed in the majority of these cases of uveitis, if they are prescribed to treat only the ocular and not the neurological disorder.[13,17] Additionally, since immunosuppressive therapy is associated with a slight increase in the risk of infections and cancer, alternative treatment options may be considered. Treatments should ideally be simple to use, safe, present few systemic or local secondary effects, and delay or even prevent greater demyelination, in addition to suppressing ocular inflammation.[14]

Prior to starting anti-inflammatory and/or immunosuppressive treatment, it is essential to rule out the presence of other types of uveitis that may not be associated with MS, but do present concomitantly with it, such as infectious uveitis or uveitis masquerade syndromes, which may be traumatic or post-surgical, drug-induced, or related with other autoimmune diseases. We must also seek to identify the cause of reduced visual acuity: as noted above, ocular inflammation may give rise to more or less insidious onset of a series of complications, which are treated in different ways. Regular ophthalmological follow-up is needed to prevent and promptly treat these complications.[2]

Corticosteroids, which are immediately and highly efficacious, are the first line of treatment for any uveitis and can be administered via different routes (topical,

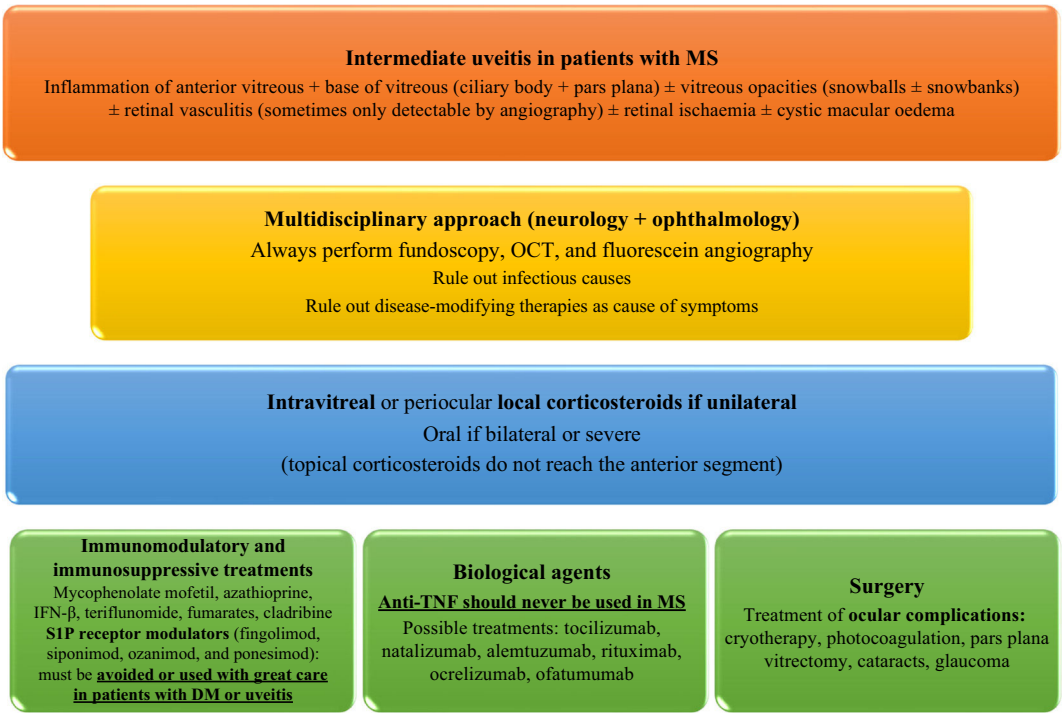

Figure 1 Therapeutic algorithm.

periocular, intraocular, or systemic).[4] In the acute context, treatment of IU should begin with local administration, with systemic therapy being reserved for severe or bilateral uveitis. Unlike topical corticotherapy, corticosteroids administered via periocular injections or sustained-release intravitreal implants are able to reach the posterior segment of the eye; furthermore, these treatments are sustained and long-lasting, avoiding the secondary effects of systemic administration.[2,4]

Classical immunosuppressants and immunomodulatory agents are used for corticosteroid-sparing therapy in the chronic phase of uveitis in patients with frequent relapses, vision-threatening complications, or corticosteroid resistance.[2,4] Few studies have specifically addressed the impact of established treatments for IU on MS, and vice versa; however, immunomodulatory treatments for both diseases target the same effector cells and/or the trafficking of leukocytes from the blood to the CNS; therefore, there is great potential for these agents to be efficacious when both diseases coexist.[2] A small, retrospective case series concluded that interferon beta (IFN-β) and glatiramer acetate may be efficacious in reducing uveitis episodes in patients with MS-associated uveitis; the majority of patients showed good clinical tolerance.[18] Two small studies reported favourable results with IFN-β treatment of MS-associated uveitis, especially in patients presenting cystoid macular oedema. Administration of IFN-β1a in 13 patients with corticosteroid-resistant MS-associated uveitis had beneficial effects on visual acuity, vitreous cell count, and presence of cystoid macular oedema.[19] Furthermore, IFN-β has been demonstrated to be superior to methotrexate in improving visual acuity, reducing cystoid macular oedema, and inducing long-term remission in patients with corticosteroid-resistant uveitic cystoid macular oedema secondary to MS or IU.[20] On the contrary, another study found that IFN-β treatment was associated with greater severity and chronicity of MS-associated uveitis.[17] Due to the small sample sizes and retrospective design of these studies, it is difficult to draw reliable conclusions. As their action is based on immunomodulation, rather than immunosuppression, IFNs rarely cause infectious complications and may therefore be particularly beneficial in patients with partial resistance to systemic corticosteroids or immunosuppressants.[21] Therefore, there is a clear need for larger prospective studies to determine the exact role of IFN-β in the treatment of MS-associated uveitis.

Jouve et al.[17] concluded that corticosteroids could be reduced or withdrawn in 50% of patients treated with azathioprine, without uveitis relapses during the follow-up period. In another study, Hedayatfar et al.[22] examined the use of mycophenolate mofetil (500–1000 mg, twice daily) for the prevention of relapses and for corticosteroid sparing in 15 patients with MS-associated IU, observing good tolerance and efficacy. Therefore, conventional immunosuppressants (eg, azathioprine and mycophenolate mofetil) appear to be more effective than immunomodulatory therapy (eg, IFN-β) in controlling intraocular inflammation. Insufficient evidence is available to support the efficacy and safety of intravitreal injection of immunomodulatory drugs in the treatment of uveitis; no studies have addressed this treatment in patients with MS. Research is underway into the treatment of other forms of uveitis with intravitreal administration of methotrexate (400 mg/0.10 mL) or rituximab (1 mg/0.10 mL) with or without methotrexate, although no clinical study has been published to date.[4]

The use of biological therapy is increasingly widespread in the treatment of uveitis. Currently, evidence is available on the treatment of non-infectious uveitis with drugs targeting

TNF (infliximab, adalimumab, etanercept, golimumab) and IL-6 (tocilizumab), IFN-α and -β, and B-cell inhibitors and anti-CD20 therapies (rituximab); however, other inflammatory mediators or immune cells may also be identified as new therapeutic targets.[4] In the specific case of MS, it is important to bear in mind that drugs targeting TNF-α may exacerbate symptoms and would therefore be contraindicated.[4,7] Tocilizumab is efficacious in treating uveitis,[4] and has been shown to reduce inflammation in other diseases, such as neuromyelitis optica spectrum disorder and some cases of fulminant MS[23]; therefore, it may be a good treatment option for co-presence of both diseases, although no studies have evaluated the use of the drug in patients with MS and IU. We also lack clinical studies assessing the efficacy of anti-CD20 therapies, such as rituximab, in patients with concomitant MS and uveitis. Despite this, these drugs have been shown to be effective in treating each disease independently.[4] Furthermore, no study has specifically addressed the effect of natalizumab on uveitis; the only available information is from a case report of a patient with MS and IU who was treated with the drug, who presented near-complete symptom resolution.[24] In a study by Jouve et al.,[17] natalizumab was efficacious for controlling intraocular inflammation in a single patient treated with the drug, and corticosteroid treatment was gradually reduced without subsequent relapses. Although this progression seems promising, a single case is insufficient to draw conclusions about the effect of natalizumab on MS-associated uveitis. Despite this, these results are consistent with those reported by Havrdova et al.[25], who found that 37% of patients treated with natalizumab were free of any MS activity at 2 years, compared to just 7% of those treated with placebo. Alemtuzumab has also been reported to improve refractory IU.[26]

Finally, uveitis may require laser therapy, cryotherapy, or even surgical treatment in the event of ocular complications, including procedures to treat the cornea or iris, cataracts, glaucoma, or vitreoretinal surgery; all of these treatments must be performed by an ophthalmologist.[4]

MS treatments with ophthalmological secondary effects

Immunomodulatory and immunosuppressive therapies for MS have made spectacular advances over the last 2 decades, creating interesting pathways for the management of neurological and ophthalmological diseases. In the light of the potentially shared aetiopathogenesis, it may be interesting to extrapolate MS treatments to MS-associated uveitis. With the exception of IFNs, disease-modifying treatments for MS have not yet been studied in this context, despite their potential usefulness.[8,14] However, some of these treatments may cause visual problems (Table 1); it is important to be aware of these in order to distinguish them from symptoms of the disease and to avoid exacerbating or triggering other eye diseases.

- **Glucocorticoids**. Chronic, prolonged administration of these drugs may cause the development of cataracts and/or chronic open-angle glaucoma. Susceptible individuals may also present onset or exacerbation of central serous

Table 1 Disease-modifying treatments for MS and their visual adverse effects. Adapted from Abraham et al.[2]

Treatment	Indication in MS	Visual adverse effects
Interferon beta	CIS, RRMS, and SPMS	Interferon-related retinopathy. Greater risk in patients with diabetes or hypertension
Glatiramer acetate	RRMS	No significant visual adverse effects
Teriflunomide	RRMS	No visual adverse effects
Cladribine	RMS (RRMS and SPMS)	No significant visual adverse effects
Natalizumab	RRMS	PML may present with visual symptoms.
Dimethyl fumarate	RRMS	PML has been linked to dimethyl fumarate.
Diroximel fumarate	RRMS	
Fingolimod	RRMS	Macular oedema in <0.5%
Ozanimod	RRMS	Macular oedema in 0.3%–0.4%
Ponesimod	RMS (RRMS and SPMS)	Macular oedema in 0.7% Possible risk of PML
Siponimod	SPMS	Macular oedema in 0.7%. Possible risk of PML
Alemtuzumab	RRMS	Autoimmune diseases, particularly thyroid disease
Anti-CD20 drugs:		
Ocrelizumab	RMS (RRMS and SPMS) and PPMS	No significant visual adverse effects
Ofatumumab	RMS (RRMS and SPMS)	
Rituximab	RMS (RRMS and SPMS)	
Mitoxantrone	RMS (RRMS and SPMS) and PPMS	Acute promyelocytic leukaemia may present with visual symptoms.
Bone marrow transplant	RMS (RRMS and SPMS) and PPMS	Cataract formation

Abbreviations: RMS: relapsing multiple sclerosis; RRMS: relapsing–remitting multiple sclerosis; PML: progressive multifocal leukoencephalopathy; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; CIS: clinically isolated syndrome.

chorioretinopathy, characterised by serous detachment of the neurosensory retina. Visual prognosis is generally good, with some patients presenting spontaneous recovery within 1–4 months.[13]

- **Disease-modifying treatments**
  - Interferons (IFN). Cases have been reported of such retinal ischaemic signs as cotton wool spots and venous or arterial occlusions, generally in patients with cardiovascular risk factors (eg, diabetes mellitus or systemic arterial hypertension) or of advanced age, associated with IFN-α (generally used to treat viral hepatitis) or IFN-β treatment; however, these signs are far less frequent in association with the latter drug, which is the one used to treat MS.[27]
  - Glatiramer acetate (GA). The summary of product characteristics lists diplopia as a frequent adverse effect; less frequent effects include cataracts, corneal lesions, dry eyes, haemorrhage, ptosis, and even optic nerve atrophy.[28]
  - S1P receptor modulators (fingolimod, siponimod, ponesimod, and ozanimod). Macular oedema may develop in patients treated with fingolimod (0.5% of patients), siponimod (1.8%), ponesimod (0.7%), or ozanimod (0.3–0.4%). It is usually unilateral and associated with vision loss, appearing 3–4 months after treatment onset, although it may also appear during the first year of treatment; oedema typically resolves after withdrawal of the drug, although cases have also been reported of improvement occurring spontaneously or with topical anti-inflammatory treatment. Therefore, it is advisable to perform an ophthalmological evaluation at 3–4 months after treatment onset, or at any other time in patients reporting visual alterations. Fingolimod-associated macular oedema is thought to result from an alteration to the blood-retinal barrier; therefore, this drug should be avoided in diabetic patients, who present pre-existing changes to the retinal blood vessels, increasing susceptibility to macular oedema when they are exposed to the drug. However, the use of fingolimod in patients with uveitis is controversial, as experiments with mice have shown it to be efficacious in improving autoimmune uveitis and restoring vascular permeability.[13,29]
  - Natalizumab. Patients receiving natalizumab may present progressive multifocal leukoencephalopathy (PML), a potentially fatal disease caused by opportunistic JC virus infection, with an incidence rate of 1/1000. Cortical blindness, which is bilateral and may be acute or subacute, may appear as one of the first symptoms of PML. It is typically associated with confusion, which differentiates this type of visual dysfunction from optic neuritis or other forms of vision loss attributed to MS itself. Therefore, any patient presenting bilateral vision loss during treatment with natalizumab should undergo complete physical and ophthalmological examination, including a neuroimaging study. Cases have also been reported of acute necrotising retinitis due to varicella zoster virus in patients treated with natalizumab, with poor visual prognosis and reactivation of ocular toxoplasmosis.[13,30]
  - Alemtuzumab. This drug can trigger an autoimmune reaction that can cause thyroid disease, affecting 36.8% of patients with MS treated with alemtuzumab. This can result in Graves orbitopathy of variable characteristics, ranging from mild eyelid retraction and superficial symptoms to severe restrictive myopathy and compression neuropathies. It may appear months or years after treatment onset and is managed in the same way as thyroid-associated orbitopathy not induced by the drug.[13] Conjunctivitis and ophthalmic herpes zoster infection have also been described.[30]
  - Mitoxantrone. A case was reported of bilateral optic nerve involvement secondary to acute promyelocytic leukaemia in a patient receiving mitoxantrone for MS.
  - Amantadine. Two published studies describe cases of corneal oedema, which improved after topical administration of prednisolone, although one patient required penetrating keratoplasty.[30]

Conclusions

It is essential to recognise and treat MS-associated eye diseases, and it is the responsibility of the treating physician to consider causes of ophthalmological involvement other than optic neuritis in patients with MS who complain of vision loss. It is also necessary to be aware of ophthalmological adverse events associated with MS treatment; while rare, these can be highly disabling. Therefore, in any patient presenting vision loss while receiving disease-modifying therapy for MS, we must consider the possibility of a treatment-related cause, rather than simply attributing the symptom to an MS relapse. As the majority of treatments for MS are immunosuppressive, we must always consider the possibility of an acquired infection in patients presenting atypical retinopathy associated with MS.

Furthermore, a multidisciplinary approach is fundamental in managing these patients, with active communication and collaboration between specialists enabling early management of the concomitant eye disease, prevention of unnecessary treatment, and greater patient well-being.

Finally, but no less importantly, there is a need for further research to establish the efficacy of new MS drugs in treating associated eye diseases.

Patient informed consent

No patient data are reported.

Ethical considerations

Not applicable.

Funding

None.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2025.100195.

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