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The investigation of acute optic neuritis: a review and proposed protocol

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ABSTRACT | Optic neuritis is an inflammatory optic neuropathy that affects many patients with multiple sclerosis (MS) at some point during their disease course. Differentiation of acute episodes of MS-associated optic neuritis from other autoimmune and inflammatory optic neuropathies is vital for treatment choice and further patient management, but is not always straightforward. Over the past decade, a number of new imaging, laboratory and electrophysiological techniques have entered the clinical arena. To date, however, no consensus guidelines have been devised to specify how and when these techniques can be most rationally applied for the diagnostic work-up of patients with acute optic neuritis. In this article, we review the literature and attempt to formulate a consensus for the investigation of patients with acute optic neuritis, both in standard care and in research with relevance to clinical treatment trials.

Introduction

Optic neuritis is characterized by inflammation of the optic nerve, and is frequently but not always associated with multiple sclerosis (MS).[1] Once a patient is diagnosed with MS, visual symptoms may be summarily attributed to a MS relapse, potentially missing other treatable aetiologies of visual loss. Transient problems such as conduction block might be mistaken for relapses of optic neuritis,[2,3] and problems related to impaired eye movements may be overlooked.[4–6] Patients with forms of optic neuritis other than MS-associated optic neuritis (MSON)—including neuromyelitis optica (NMO) spectrum disorder and chronic relapsing inflammatory optic neuropathy (CRION)—must be recognized as early as possible, because these individuals are at risk of severe visual loss.[7,8]

In this Review, we emphasize that optic neuritis represents a pragmatic model for testing structural–functional relationships.[9,10] The visual system is the best-understood and most accessible part of the human CNS. In each eye, 100 million rod photoreceptors capture light, which is then converted by 12 types of bipolar cell into a digitally coded electrical signal,[11] which passes through the 1,158,000 axons of the optic nerve.[12] The nerve fibres decussate partially at the optic chiasm, synapse in the lateral geniculate nucleus, and finally project through the optic radiations into the well-defined cytoarchitecture of the visual cortex,[13] wherein plastic capabilities continuously shape our subjective visual experience.[14] A real opportunity exists to make use of this detailed knowledge in an increasingly complex diagnostic and therapeutic landscape.

Table 1 summarizes the published criteria for a single episode of isolated optic neuritis (ION),[15] relapsing episodes of isolated optic neuritis (RION),[15] CRION,[7] MSON,[16] and optic neuritis as observed in NMO spectrum disorder.[8] No consensus has been reached on how to investigate patients who present with acute optic neuritis, and this Review aims to contribute to the development of such a consensus. Protocols for standard care and research (Supplementary Figure 1 online) should take associated costs and resources into account.

History taking

A structured history-taking process should search for warning signs (‘red flags’) that suggest an alternative diagnosis to MSON (Box 1), thereby prompting further investigations.

The classic clinical presentation of optic neuritis consists of (peri)ocular pain, often retrobulbar, which frequently precedes loss of vision and is typically associated with dyschromatopsia. Pain that is exacerbated by eye movement suggests inflammation of the optic nerve adjacent to the ocular muscles.[17] Ocular pain or headache not worsened on eye movement, or painless optic neuritis, may indicate inflammation within the optic canal or intracranial space. In addition, positive phenomena such as phosphenes and scintillations can be present.

Following recovery from optic neuritis, patients might experience glare disability, reduced vision in bright light, visual fading, and/or the Uhthoff or Pulfrich phenomenon.

Uhthoff phenomenon

The symptoms and signs of optic neuritis can be aggravated by a rise in body temperature due to exercise, taking a bath, fever due to infection, warm meals, cognitive and/ or emotional stress, or high ambient temperatures. This so-called ‘Uhthoff phenomenon’ is caused by transient conduction block, and is typically observed during the recovery phase of optic neuritis.[2,3]

Pulfrich phenomenon

Perception of movement in depth may be difficult following optic neuritis - a condition termed the Pulfrich phenom enon.[18,19] Patients might report problems with judging the course of vehicles or bicycles in moving traffic, pouring liquid into jars, or judging the trajectory of a tennis or squash ball. We specifically ask whether these problems also occur if the patient is not moving, with best corrected visual acuity under binocular viewing conditions. The Pulfrich phenomenon is usually found in patients who have recovered from optic neuritis and exhibit good visual acuity, rather than in the acute-situation.

Clinical and bedside assessment
Standard care protocol

An example of the diagnostic work-up for a patient with Key points optic neuritis is presented in Supplementary Figure1 online and Box 2.

The standard of care for optic neuritis includes measurement of best corrected high-contrast visual acuity, preferably with a LogMAR retroilluminated chart. For conversion of the various acuity tests used around the world to a LogMAR value, see Supplementary Table 1 online.

In each patient, retinal examination should be performed by direct and indirect ophthalmoscopy. A pale optic disc, as shown in Figure 1a, is indicative of optic atrophy.

Monocular visual fields can be assessed clinically by confrontation using either finger movements or differentially sized and coloured objects.[1] We use a 4 mm red pin and also test for red desaturation as an indicator of impaired colour vision. Testing for red desaturation can be performed by comparing central vision either between the two eyes (affected and unaffected) or regionally within different areas of the visual field of one affected eye.

We acknowledge that formal perimetry such as the SITA 24-2 protocol would be considered standard care in a well-equipped neuro-ophthalmological service, but might not readily be available in a routine neurological outpatient department, and may not be well tolerated by all patients.

The swinging light test should be used to search for a relative afferent pupillary defect (RAPD, also known as Marcus Gunn pupil). The RAPD can be amplified by holding a 0.3 log unit neutral density filter in front of the affected eye.[20] An RAPD should be present in cases of unilateral optic neuritis, but can be absent in binocular simultaneous or sequential optic neuritis. If no RAPD is detected, a diagnosis can only be made with extreme caution. The test cannot be used if the optic neuropathy is bilateral and symmetrical.

Pain on eye movements is one of the strongest indicators of optic neuritis, and the few other conditions that manifest with this symptom—for example, myositis, orbital inflammation or subtarsal foreign body—can generally be excluded at the bedside by testing eyelid function and eye movements. Eye movements are best tested if the patient has sufficient visual acuity to focus on an appropriately moving target. We examine smooth pursuit, saccades and vergence movements binocularly. We are looking particularly for evidence of slow adduction of one or both eyes on examination of horizontal saccades as evidence of subclinical internuclear ophthalmoplegia, which is highly suggestive of demyelination elsewhere in the CNS.[21] The cover–uncover test helps us to identify transient visual problems that might be attributable to a phoria.

Research protocol

Additional tests that are not routinely used because of time and financial constraints can be incorporated into research protocols for optic neuritis. Low-contrast visual acuity can be tested with best correction using Sloan charts.[22] In addition, Pelli–Robson charts are useful for testing contrast sensitivity. Colour vision tests include, among others, the Ishihara Test, the Hardy–Rand–Ritter Pseudoisochromatic Plates, the Lanthony Desaturated D-15 Test or, if time permits, the Farnsworth–Munsell 100 Hue Test. Both low-contrast acuity and colour vision tests are sensitive for subtle impairment of visual function even years after the episode. Computerized testing of colour vision provides quantitative data.[23] Importantly, this approach also considers relevant age-adjusted normal limits of colour vision, which are required for reliable recognition of acquired problems.[23]

Patients with the Pulfrich phenomenon can be assessed using a classic pendulum.[18,19] A horizontal swinging pendulum is perceived as following an ellipsoid trajectory by patients who exhibit this symptom.[24] The Pulfrich phenomenon is best assessed if the pendulum swings in front of a high-contrast patterned background, which enhances binocular disparity (stereoscopic vision).

Optical coherence tomography
Overview

Retinal optical coherence tomography (OCT) permits accurate documentation of changes in thickness of retinal layers.[25,26] The full spectrum of retinal pathology that might be unravelled through the use of OCT in MS is not yet known, and new differential diagnoses are being added as the quality of OCT data improves. At present, recommendations for standard care and research protocols for optic neuritis are based largely on two types of pathology. First, thinning or atrophy of the inner retinal layers—that is, the retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL, Figures 1, 2 and 3)—is commonly observed. Second, thicke ning or swelling of the peripapillary RNFL can be seen in cases with optic disc swelling. There might also be localized thickening of the inner nuclear layer (INL), which can be associated with microcystic macular oedema (MMO, also known as microcystic macular changes or retrograde maculopathy;[27–29] Figure 4 and Supplementary Video 1 online).

Thinning

Loss of the unmyelinated axons in the retina can readily be quantified by OCT, and is understood to represent several processes:[30] first, pathology in the retinal layers resulting in anterograde (Wallerian) degeneration, leading to thinning of the RNFL; second, pathology of the optic nerve, such as an acute optic neuritis attack, causing axonal transection and loss (direct retrograde degeneration); and third, posterior visual pathway lesions that lead to thinning of the RNFL by trans- synaptic (via the lateral geniculate nucleus) retrograde axonal degeneration. [9,31,32] In reality, axonotemesis in the hard-wired visual pathways will always lead to bidirectional transsynaptic axonal degeneration.[33] One should allow a 3-month interval after an acute attack of optic neuritis before attempting to quantify peripapillary atrophy of the RNFL.[34,35] Wedge-like thinning should prompt investigation for vascular pathology, such as AION or Susac syndrome (Table 2).[36] Occasionally, fluor escein angio graphy (FAG; Figure 1b) may be required to further assess retinal blood flow and leakage.[37] RNFL and GCL atrophy is more severe in NMO and CRION than in MSON.[38–43] Caution is required when interpreting data from patients with recurrent episodes, as more-severe thinning may be the result of cumulative damage.

Thickening

Disk swelling in the acute phase of optic neuritis is well recognized.[1,35] Recent evidence indicates that MMO and thickening of the INL are more frequent in NMO than in MSON.[44,45] Because of the association between MMO and NMO, we advocate testing for the presence of anti-aquaporin 4 antibodies (AQP4-IgG) in patients with MMO who experience relapsing optic neuritis, or in the presence of red flags (Box 1, Supplementary Figure 1 online). MMO is not specific for either MS or NMO, and is also seen in RION, CRION and a range of other acute and chronic ophthalmological conditions (Figure 4).[7,27,45–49] A large study involving 6,551 OCT scans from 1,370 patients indicated that MMO is transient in over 80% of cases, so we suggest longitudinal follow-up of patients who exhibit this sign.47 In neuroretinitis, acute subretinal fluid and chronic exudates can be effectively visualized by OCT.[50]

Standard care protocol

The reviewed evidence suggests that incorporation of OCT findings into the standard care protocol for optic neuritis is likely to become routine. However, protocols still have to be validated and to stand the test of time in clinical practice. As a minimalistic protocol for standard care, we suggest obtaining two scans using a spectral domain retinal OCT system. The proposed scans—a peripapillary ring scan (Figure 2a) and a macular volume scan (Figure 2b)—take 2–5 min per eye in patients who can maintain visual fixation. A difference of RNFL values of more than 20% between the two eyes may suggest a previous ‘subclinical’ episode. Macular scans should be carefully reviewed for the presence of MMO.[47]

Research protocol

All scans should fulfil rigorous established quality control criteria.[51,52] A sharp image and high contrast between retinal layers is a prerequisite for image post-processing and layer segmentation (Figure 2c). In all cases, we advise acquisition of each scan with reference to a stored reference scan taken at baseline, so as to allow long-term follow-up of the macular ganglion cell complex analysis and the peripapillary RNFL as sensitive measures for progressive neurodegeneration affecting the eye. A range of additional research techniques are available, such as en face OCT, polarization-sensitive OCT, adaptive optics, fluorescence labelling, and Doppler OCT.[30]

Laboratory investigations
Overview

It is importan t to note that in most patients with typical MSON, there is no evidence to suggest a need for routine blood tests or cerebrospinal fluid (CSF) examination.[1]

Standard care protocol

Additional blood investigation is warranted in patients with an atypical presentation, such as lack of pain or severe visual loss (<6/60), bilateral visual loss, or severe disc swelling with haemorrhages, and/or with a relevant medical or family history. Blood tests can aid identification of conditions such as paraneoplastic optic neuropathy and cancer-associated-retinopathy.

Metabolic pathology

In s uspected metabolic conditions, which can be characterized by bilateral and symmetrical visual loss, tests for vitamin B12, red blood cell folate and methylmalonic acid levels are recommended.[53] Note that low vitamin B12 levels can coexist with NMO.[54]

Systemic pathology

For suspected systemic disease (see systemic and ischaemic aetiologies in Table 2), tests for haematology, electrolytes, liver function, erythrocyte sedimentation rate, C-reactive protein and serum angiotensin-converting enzyme levels are advised.

Inflammatory pathology

Serological studies should be guided by the clinical history. Consideration should be given to syphilis, Lyme disease and Bartonella henselae (see infectious aetiologies in Table 2).

Immunological pathology

A resource-saving screening approach to immunological blood tests is to start with antinuclear antibodies (ANA), following the international guidelines.[55] In cases of ANA seropositivity, particularly in young patients, this test may be followed by a more targeted approach that includes assays for autoantibodies against extractable nuclear antigens, perinuclear antineutrophil cytoplasmic antibodies, cardiolipin and β2 glycoprotein 1. This approach facilitates the detection of autoimmune overlap syndromes, which occur in around 5% of patients with autoimmune disease.[56,57] In one case, a patient with optic neuritis was found to be seropositive for anti-GQ1b and anti-GT1a IgG.[58]

If orbital disease causing a compressive optic neuropathy is suspected, thyroid function and anti-thyroid antibody tests should be requested. Tests for anti-CRMP5 (also called anti-CV2) and recoverin autoantibodies should be requested in patients with a history of cancer or suspected paraneoplastic disease, in order to identify conditions such as cancer-associated retinopathy. In suspected NMO, state-of-the-art assays for AQP4- IgG are recommended because of their high diagnostic specificity (>95%) and sensitivity (77%).[59–61] Testing for AQP4-IgG is advised in all cases with features atypical for MSON—in particular, severe relapsing or bilateral loss of vision—as AQP4-IgG seropositivity has specific diagnostic and prognostic implications.[62,63] Because of the heterogeneity of assays[61] and the possible harmful and ethical consequences of a false-negative or false-positive diagnosis of NMO–optic neuritis, we recommend that AQP4-IgG detection should be performed in laboratories that use validated assays with high sensitivity and specificity. Evidence exists, however, for a subgroup of patients with NMO who are AQP4-IgG seronegative but myelin oligodendrocyte glycoprotein IgG seropositive, so AQP4-IgG seronegativity does not necessarily preclude a diagnosis of NMO.[64,65]

Cerebrospinal fluid

CSF exa mination will occasionally be necessary in patients presenting with symptoms of optic neuritis, principally when there is doubt as to the aetiology. CSF examination is rarely contributory in cases deemed to be MSON on other criteria.[16] The CSF examination should include cytology, total protein, glucose and oligo clonal bands.[66] Of note, CSF OCBs are not specific for MS, and might also be found in over 30 other conditions. [67] The type 2 OCB pattern, in which OCBs are found in the CSF but not in the serum, indicating isolated intrathecal oligoclonal IgG synthesis, is only found in about 10% of patients with NMO.[68,69] However, CSF glial fibrillary acidic protein (GFAP) levels have a high sensitivity (85–100%) but low specificity (77–100%) for acute NMO.[70–73]

Research protocol

In view of the emerging body of literature on the role of vitamin D deficiency as a risk factor for demyelination, testing of vitamin D levels is becoming increasingly relevant for optic neuritis research.[74,75] In addition, blood neurofilament levels might be of prognostic value in optic neuritis.[76–78]

Standardized sample collection, processing, storage and analyses are mandatory to ensure high-quality biomarker research, enable multicentre analyses, make use of historical cohorts, and safeguard against bias.[79] Collection of both plasma and serum is recommended. Samples should be well mixed prior to transport to the laboratory, and should be centrifuged at room temperature (2,000 g for 10 min) within 1 h of sampling. In situations where a longer interval between sampling and processing can be expected, transport and storage at 4 °C is advised. Some biomarkers are sensitive to repeated freeze–thaw cycling, so we advise that each sample should be stored in at least four 500 l aliquots at –80 °C.

We anticipate that the discovery of new autoantibodies, in part through retrospective analysis of stored CSF, serum and plasma samples, will be relevant for the differential diagnosis of optic neuritis.

MRI Overview

This section focuses on MRI of the optic nerves, which is complementary to the well-established literature on brain MRI.[80] MRI of the optic nerves helps us to rule out alternative diagnoses, demonstrate optic nerve inflammation, and con duct research into the assessment of optic nerve damage and atrophy.

Classic MRI findings in acute optic neuritis are highsignal- intensity lesions in the optic nerve (occasionally extending to the chiasm and the optic tracts) on T2-weighted MRI (preferably with fat suppression; Figure 1c). There is usually also swelling of the affected segment of the optic nerve. More-extensive optic nerve lesions are associated with poor clinical outcomes such as slow and incomplete recovery.[81,82]

Depending on the severity of inflammation, contrast enhancement can be observed on (fat-suppressed) T1-weighted images in about 94% of patients with acute optic neuritis. In established optic atrophy from previous damage, T2 high signal changes will also be seen, but these changes are associated with thinning of the nerve and do not change over time. Sensitivity of detection of contrast-enhancing lesions in the optic nerve can be further increased by using a higher dosage of contrast medium (for example, a triple dose), but in our view this approach is not cost-effective.[83,84]

Patients with NMO have a propensity towards extensive involvement of the anterior visual pathways, and of the intracranial as opposed to the intraorbital segments, making these individuals particularly prone to chiasmitis and simultaneous bilateral disease.[85,86]

Standard care protocol

No consensus guidelines have been formulated on how and when to perform optic nerve MRI in cases of optic neuritis. For assessment of the optic nerve, the MRI protocol must include fat-suppressed T2-weighted images (for example, short tau inversion recovery or frequency-specific selective partial inversion recovery)[81] and contrast- enhanced (fat-suppressed) T1-weighted images (Box 3). The most cost-effective approach is to use a standard dosage of gadolinium-based contrast medium.

T1-weighted and T2-weighted sequences for the assessment of the whole orbit and brain are useful to simultaneously detect possible demyelinating brain lesions. For the best spatial resolution, images should be acquired without any interslice gap. The spatial resolution should be 3 mm slice thickness, in plane 1 × 1 mm (measured voxel size 3 × 1 × 1 mm). Additional sagittal proton density-weighted/T2-weighted (preferably spin echo) and T1-weighted post-contrast images of the spinal cord are useful for detecting demyelinating spinal cord lesions and for differential diagnostic purposes (Box3). Further radiological tests to exclude vascular malformations or vasculitis may be indicated, as summarized in Table 2.

Research protocol

Although MRI at higher magnetic field strengths (for example, 3 T) does not necessarily lead to an earlier diagnosis of MS, it does result in a higher image quality.[87,88] In general, a standard head coil is sufficient for the assessment of the orbit and the optic nerves. However, surface coils focusing on the orbit may further improve the image quality.[89]

Important MRI methods for research purposes include measures of optic nerve atrophy obtained using highresolution 3D T2-weighted sequences,[90] quantitative MRI techniques91 and diffusion tensor imaging.[92] These advanced techniques can assist in the early detection of clinical impairment, and enable quantitative estimation of the presence and extent of damage to the optic nerve.[93,94] These measures have all been proposed as markers of irreversible tissue damage and disease progression, and as predictors of clinical recovery.

Electrodiagnostic tests
Overview

Electrodiagnostic tests have a role in the investigation of atypical presentations of optic neuritis.[95] The tests should not be limited to visual evoked potentials (VEPs), as any retinal abnormality will affect the VEP signal.[95,96] Indeed, the International Society for Clinical Electrophysiology of Vision (ISCEV) standards[97] recommend that in cases of unexplained visual loss, the VEP results should be interpreted in conjunction with both a standard electroretinogram (ERG) and a pattern electroretinogram(PERG).[98]

Standard care protocol

The ISCEV standards[97] state that electrophysiological tests are of little diagnostic value in acute retrobulbar optic neuritis, but may be useful in studies evaluating therapy. If the diagnosis is uncertain, however, a full series of electrophysiological tests should be performed, as outlined below.

Visual evoked potentials

The VEP represents a specific change in an ongoing EEG recording due to the response of the visual pathway to either a pattern or a flash stimulus. VEPs have been shown to be a highly sensitive but not especially specific test for optic neuritis. A unilateral substantially delayed VEP with minimal amplitude reduction is highly suggestive of a demyelinating optic neuropathy, for example, recovered MSON or subclinical involvement of the optic nerve in MS. VEP abnormalities will also be seen in patients with refractive errors, pure retinal dysfunction, compressive lesions of the optic nerve, Parkinson disease[99] or migraine.[100] Normality of both the ERG and VEP supports the differential diagnosis of non-organic aetiology if performed after other investigations failed to yield a diagnosis.

Electroretinography

An ERG provides diagnostic information about the rod and cone photoreceptors, and inner retinal function across the entire retina. The differential diagnosis of a pale optic disc with reduced central vision includes cone dystrophies and maculopathies, which will be incorrectly diagnosed if VEPs are used alone.

Research protocol

Multifocal VEPs allow fine mapping of the electrophysiological abnormalities in the visual pathway. This mapping enables detection of abnormalities restricted to specific topographies, and may be more sensitive than standard VEPs.

As the macula comprises less than 5% of the retina, a maculopathy will generally not affect the full-field ERG. The PERG stimulus parameters mean that the macula is the retinal location that is primarily stimulated.[96] The PERG is a surrogate test of macular function, and can, therefore, be used to differentiate macular from optic nerve causes of central vision loss. The two main components of the PERG are N95 and P50,[96,101,102] and the N95 component and N95:P50 ratio were found to be useful in optic neuritis.[101–104] The optic nerve head component responses of multifocal ERG may also emerge as a useful tool in the assessment of optic neuritis.[105]

Perimetry Overview

The classic visual field defect described in MSON is a central scotoma with a sloping border of the isopters.[106] Of note, however, this feature has only been reported in 2% of cases,[107] and becomes even rarer (0.5%) later in the disease course. Most patients experience a more generalized reduction in their visual field sensitivity (66%).[107] By contrast, altitudinal visual field defects suggest a vascular differential diagnosis,[108] and sparing of central vision suggests an optic perineuritis,[109] but neither pattern will rule out optic neuritis.

Automated perimetry should be performed using threshold estimation strategies.[110,111] An important limitation, particularly in neurological conditions, children or elderly patients, is that the test is time-consuming and the failure rate may be up to 46%.[112–114] One needs to consider operator instruction effects, ‘natural variation’ in test results, and learning effects.[115,116] It may not be possible to detect a visual field defect until about 25–35% of retinal ganglion cells have been lost.[117–119] Therefore, as a consensus, we hesitate to recommend perimetry as a mandatory part of a standard care protocol but, rather, advocate selective use in cases where the test results may guide the differential diagnosis (Table 2), or in the presence of red flags (Box 1).

Research protocol

Given that production of the Goldmann perimeter has stopped and experience is vanishing, we recommend use of standard threshold automated perimetry. The stimulus size should be Goldmann No. III (0.481°). A visual field of 20–30° should suffice (24-2 or 30-2 protocols on the Humphrey Zeiss perimeter; full threshold 32 or static white-on-white fields on the Octopus 900 series).

Conclusions and further perspectives

The clinical spectrum of optic neuritis has broadened over the past two decades. This development was driven by several factors: cumulative experience from trials on treatment of optic neuritis; clinical recognition of a divergent semiology; discovery of new autoantibodies and biomarkers; and availability of new high-resolution imaging techniques for the optic nerve and retina.

A need exists to make use of this knowledge and these techniques to better investigate and define the clinical spectrum of optic neuritis with the aim of guiding future patient management. Importantly, some forms of optic neuritis (for example, NMO and CRION) will require rigorous immunosuppression to protect patients from blindness. It is also essential that patients with these conditions are not included in MSON treatment trials. We anticipate that the investigation protocol presented here will help us to reach a consensus on the classification of optic neuritis and how to optimize treatment. This consensus should, in turn, be pursued internationally so that different approaches can be validated in those parts of the world where MS is less common.

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Author contributions

A.P. had the idea for this protocol, reviewed the literature, provided figures, wrote the first draft and finalized the manuscript. F.C., K.F., F.P., S.S. and C.S. revised the manuscript. M.P.W. performed an independent literature review and wrote the MRI section. C.L.F. performed an independent literature review and wrote the VEP/ERG section. B.W. and G.T.P. contributed to the conception and design of the protocol. All authors revised the final version of the manuscript.

Supplementary information is linked to the online version of the paper at www.nature.com/nrneurol.

Competing interests

The authors declare no competing interests.

Review criteria

A search for original articles published between 1970 and 2014, focusing on optic neuritis, was performed in Google Scholar, MEDLINE and PubMed. The search terms used were “optic neuritis”, “imaging”, “MRI”, “OCT”, “cerebrospinal fluid”, “CSF”, “biomarker”, “immune”, “VEP”, “ERG”, “visual field”, “perimetry”, “vision”, “visual system”, “retina” and “optic nerve”, alone and in combination. All articles identified were full-text papers in the English language. We also searched the reference lists of identified articles for further relevant papers. Furthermore, specific papers from the literature archives of the authors were included.

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Key points

- Optic neuritis is frequently but not always associated with multiple sclerosis (MS), and patients who present with optic neuritis will want to know about their risk of developing MS
- Early recognition of optic neuritis not caused by MS is important to prevent severe visual loss, and to avoid inappropriate use of MS-targeted treatments
- No international consensus exists on the nosology of optic neuritis: the aetiology remains idiopathic in many cases, and attempts at classification fall short, in part because we lack a uniform investigation protocol
- This Review on established and emerging diagnostic tools proposes a consensus on the investigation of patients with suspected optic neuritis in both standard care and research
- The aims are to aid recognition of patients at risk of severe visual loss, to contribute to future attempts at classification of optic neuritis, and to provide end points for clinical studies

Box 1 | Red flags implying diagnosis other than MSON

A typical clinical presentation
- Pain or loss of vision presenting for more than 2 weeks
- Absence of pain
- Retinal abnormalities
- Unexplained optic atrophy
- Severe loss of vision in patients with a non-white ethnic background
- Severe loss of vision without early recovery

Atypical course
- Progressive loss of vision
- Absence of recovery for more than 3 months
- Worsening of visual function after reducing or stopping steroids or immunosuppression

Bilateral optic neuritis*
Past medical history of cancer

*Simultaneous binocular visual loss must be distinguished from sequential bilateral visual loss. Both visual acuity and visual field need to be documented; sole assessment of visual acuity may miss a peripheral visual field defect.
Abbreviation: MSON, multiple sclerosis-associated optic neuritis.

Box 2 | A case of relapsing isolated optic neuritis

A 35-year-old woman presented with blurred vision in her right eye for the second time in 3 months. Visual loss was preceded by several days with photopsia, but no pain on eye movements was reported. Uncorrected visual acuity in the right eye was 0.03 with a central scotoma. Oligoclonal bands were detected in the cerebrospinal fluid (CSF), and additional identical oligoclonal bands (OCBs) were found in CSF and serum (‘type 3’ or mirror plus pattern67). CSF white cell count was elevated (25 per mm3), with a normal total protein level (19 mg/l). The test for anti-aquaporin 4 antibodies was negative, as were the remaining autoimmune, infectious and metabolic laboratory investigations.

Fundus photography (Figure 1a) showed that the right optic disc was pale temporally, indicating optic atrophy, whereas the left optic disc was normal. Fluorescein angiography (Figure 1b) indicated normal retinal blood flow and absence of leakage. Short tau inversion recovery MRI (Figure 1c) demonstrated an increased signal in the right optic nerve, indicating inflammation.

The patient received intravenous steroids according to the optic neuritis treatment trial protocol, but her vision failed to improve over the subsequent 9 months. Serial optical coherence tomography measurements demonstrated the development of further peripapillary retinal nerve fibre layer (pRNFL) atrophy. Consistent with the photograph of the right optic disc, some pRNFL atrophy of the temporal nerve fibres was observed (thin black line in Figure 1d). Atrophy of the pRNFL progressed over the subsequent 9 months and mainly affected the temporal fibres. Automated layer segmentation (Figure 1e - h) demonstrated only a very small degree of atrophy in the inner plexiform layer and inner nuclear layer. By contrast, more-global thickening developed in the outer retinal layers (Figure 1h). This is a consistent finding in the literature, but its significance is unknown.

Box 3 | MRI protocol

Optic nerve (~10 min)
- Coronal T2-weighted images with fat suppression (for example, short tau inversion recovery or frequency-specific selective partial inversion recovery)
- Coronal T1-weighted images before and after contrast administration

Brain (~20 min)*
- Axial proton density-weighted/T2-weighted

Sagittal fluid-attenuated inversion recovery (preferably 3D)
- Axial T1-weighted after contrast administration

Spinal cord (~15 min)‡
- Sagittal proton density-weighted/T2-weighted
- Sagittal T1-weighted after contrast administration

Research
- High-resolution 3D T2-weighted (CISS) images for visualization and volume measurements of the optic nerve
- Diffusion tensor imaging

*For suspected demyelination in the brain (for example, multiple sclerosis). ‡For suspected demyelination of the spinal cord (for example, neuromyelitis optica).

Tables and figures

Table 1 | Definitions and diagnosis of optic neuritis

Nosology	Definition	Clinical features	Paraclinical tests	Reference
Isolated optic neuritis (ION)*	A single and isolated episode of optic neuritis	Red flags (Box 1)	MRI of the optic nerve shows signs of inflammation, but brain and spinal cord imaging results are essentially ‡ normal	Petzold *et al.* (2010) [15]
Relapsing isolated optic neuritis (RION)	A spontaneously relapsing and isolated episode of optic neuritis	Spontaneous relapses, red flags (Box 1)	MRI findings as for ION	Petzold *et al.* (2010) [15]
Chronic relapsing inflammatory optic neuropathy (CRION)	Relapses of isolated episodes of optic neuritis on steroid withdrawal	Relapses on steroid withdrawal	Seronegative for AQP4-IgG; MRI findings as for ION	Petzold & Plant (2013) [7]
Neuromyelitis optica–optic neuritis (NMO-ON)	Spontaneously relapsing episodes of optic neuritis	Relapses, poor recovery	Seropositive for AQP4-IgG; MRI findings not typical for multiple sclerosis	Wingerchuk *et al.* (2006) [8]
Multiple sclerosis-associated optic neuritis (MSON)	An episode of optic neuritis in association with radiological evidence for dissemination in space and dissemination in time	Good recovery within ~2 months in most cases.	MRI findings typical for multiple sclerosis	Polman *et al.* (2005) [16]

*To demonstrate an isolated episode of optic neuritis, relevant pathology elsewhere in the CNS must be excluded. ‡The assessor should be pragmatic and allow for occasional nonspecific MRI lesions, which tend to become increasingly frequent as magnetic field strength and resolution increase. Abbreviation: AQP4-IgG, anti-aquaporin 4 antibodies.

Table 2 | Differential diagnoses and mimics of optic neuritis

Aetiology	Features	Differential diagnoses	Paraclinical tests
Infectious	Subacute or progressive visual loss following exposure to infectious agent; frequently with broader cellular reaction in the eye	Spirochaetes (syphilis, Lyme)	Serology, PCR, CSF, MRI
		HIV	MRI, serology
		Bartonella henselae , neurocysticercosis, tuberculosis	Chest radiography, serology, CSF, MRI
	Sinus pain	Viral sinusitis*	MRI
Reactive	Bilateral and simultaneous; often in childhood and then mostly good prognosis. In contrast, in adults the outcome is more frequently poor	Post-infectious ‡	Serology, CSF
		Post-vaccination	OCT, ERG
		Acute disseminated encephalomyelitis (ADEM)	MRI
		Neuroretinitis	Macular star §
Vascular	Sudden-onset visual loss, mostly painless (except GCA); acutely swollen optic disc (except PION); cardiovascular risk factors	AION	ESR, CRP, glucose
		PION	Coagulation
		GCA	Biopsy
		Diabetic papillopathy	ECG, Doppler ultrasound
	Frequent episodes, migraine	Retinal vasospasm	ECG, Doppler ultrasound
	Hearing loss, encephalitis	Susac syndrome	Audiogram, OCT, visual fields
	Proptosis, chemosis, orbital venous congestion, diplopia (intermittent)	CCF	Orbital bruit, CTA/MRA
	Seizures, neurological signs	Vascular malformations	CTA/MRA, DSA, CSF
Nutritional and toxic	Bilateral, painless, progressive; evidence is emerging that cobalt toxicity[120] may also be relevant to (hip) joint implants containing cobalt. Pale discs, poor prognosis	Vitamin B_{12} deficiency	Vitamin B_{12}, MMA
		Tobacco–alcohol, toxic	Full blood, cobalt levels
		Endemic‖	OCT, visual fields
		Methanol, ethambutol, ethylene glycol	Plasma osmolar gap, ethylene glycol, glycolic acid, formate
Compressive	Painless, progressive, pale disc at presentation, cilioretinal shunt vessels, history of cancer; proptosis, lid lag, diplopia, history of thyroid disease	Primary tumours, metastases, tuberculoma, sinus mucoceles, Graves disease	CT or MRI, orbits and brain with contrast, MRA, OCT, biopsy, anti-thyroid antibodies (Graves disease only)
Systemic disease	Painful, progressive and often bilateral, more frequent in non-whites, subacute visual loss, history of migraine	All diagnoses	Brain and orbits with contrast
		Sarcoidosis	ACE, CSF, biopsy (sarcoid)
		Behçet disease	OCT, chest radiography, MRI
		SLE	Coagulation, if ANA-positive search for specific antibodies
		Cancer	Paraneoplastic antibodies
		Persistent migrainous visual aura	Further tests not part of routine work-up
Ocular	Pain	Posterior scleritis	OCT, ultrasound, ANCA [121]
	Painless, metamorphosia	Maculopathies	OCT, ERG
	Preserved colour vision	Retinopathies	Fluoroscein angiogram
	Visual field loss, photopsias	Big blind spot syndromes	Visual fields, OCT
	Preserved colour vision	AZOOR	ERG
Hereditary	Family history. Bilateral, painless	LHON; OPA1 and OPA3 mutations	Genetic testing

*Sinusitis was high up in the differential diagnosis in the past but has almost disappeared over the past few decades.[122] It is absolutely mandatory to obtain a good history including recent travels to high-risk areas for certain infections (malaria, dengue virus, West Nile virus, cysticercosis) or other forms of exposure. §A macular star is suggestive of neuroretinitis and can be associated with peripheral retinal haemorrhages and speckled appearance of the pigment epithelium. ‖Endemic optic neuropathies have been described in Cuba and Tanzania. Abbreviations: ACE, angiotensin-converting enzyme; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; AZOOR, acute zonal occult outer retinopathy; CCF, carotid cavernous sinus fistula; CRP,c-reactive protein; CSF, cerebrospinal fluid; CTA, CT angiography; DSA, digital subtraction angiography; ECG, electrocardiogram; ERG, electroretinogram; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; LHON, Leber hereditary optic neuropathy; MMA, methylmalonic acid; MRA, magnetic resonance angiography; OCT, optical coherence tomography; PION, posterior ischaemic optic neuropathy; SLE, systemic lupus erythematosus; VEP, visual evoked potentials.

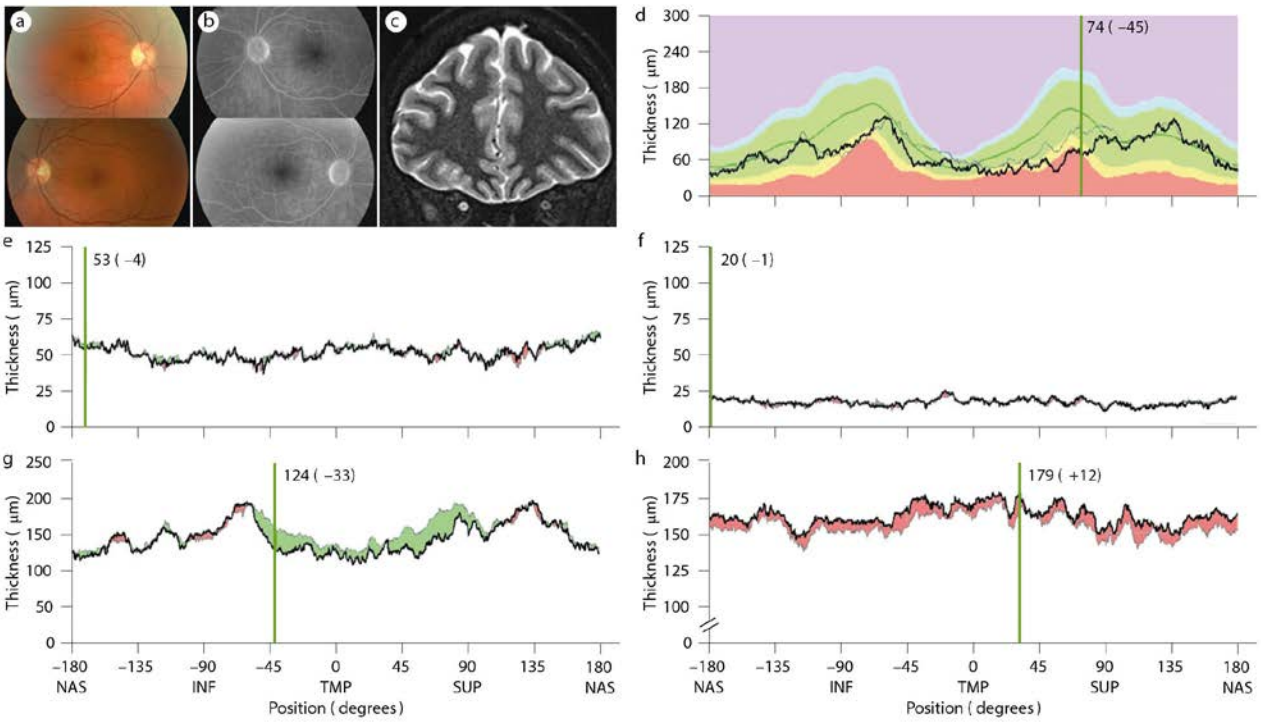

Figure 1 | Ophthalmological and MRI investigations in a 35-year-old woman with blurred vision in the right eye. **a** | On fundus photographs, the right optic disc (top image) was pale temporally, whereas the left optic disc (bottom image) was normal. **b** | Fluorescein angiography was normal. **c** | Coronal section of a fat-suppressed MRI STIR sequence of the orbit demonstrates an increased signal in the right optic nerve. **d** | Optical coherence tomography shows pRNFL atrophy of the temporal nerve fibres (thin black line at baseline, thick black line at 9-month follow-up). Yellow and red areas indicate atrophy; green area describes the normal thickness profile around the optic disc; blue and purple areas indicate pRNFL thickening. Vertical green line shows the reference position in the corresponding confocal scanning laser ophthalmoscopy image (not shown). **e** | Automated layer segmentation demonstrated a small degree of atrophy (green areas) in the IPL and **f** | INL. **g** | Extent and location of atrophy is best appreciated by summation of the inner retinal layers (pRNFL, IPL and INL). **h** | More-global thickening developed in the outer retinal layers (outer plexiform layer to basal membrane; red area in summation graph). Abbreviations: INF, inferior; INL, inner nuclear layer; IPL, inner plexiform layer; NAS, nasal; pRNFL, peripapillary retinal nerve fibre layer; SUP, superior; TMP, temporal.

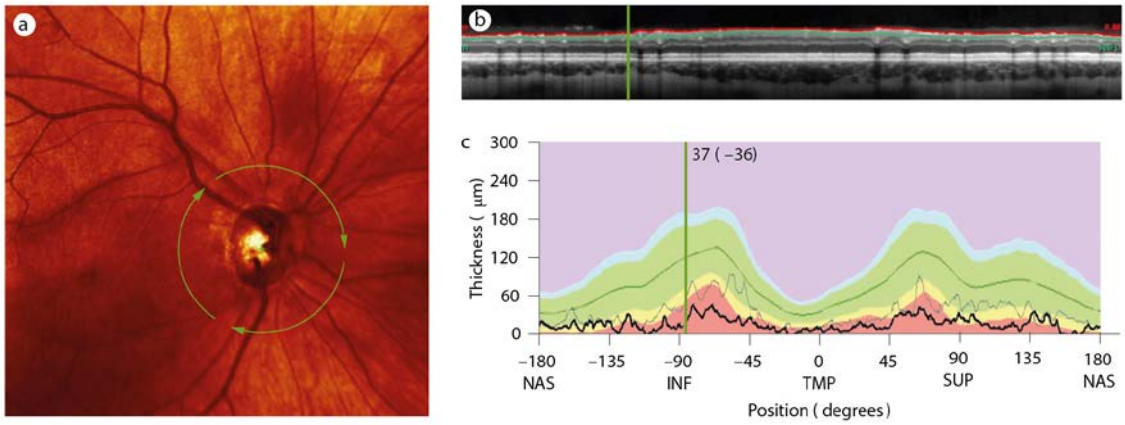

Figure 2 | Minimal retinal OCT protocol—part I: peripapillary ring scan. A 27-year-old woman experienced two episodes of NMO-ON in her left eye. Visual acuity in the left eye was 'no light perception' after the first episode of NMO-ON. The second episode started with pain on eye movements, but visual acuity was not helpful for clinical monitoring. a | Peripapillary ring scan (green circle in SLO image). b | Corresponding OCT B-scan. Distance between the red line (inner limiting membrane) and the horizontal green line indicates RNFL thickness. Vertical green line indicates the corresponding anatomical position in the SLO image. c | Thin black line indicates reference RNFL thickness after the first episode of NMO-ON and thick black line indicates additional RNFL loss manifesting 3 months after the second episode of NMO-ON. Abbreviations: INF, inferior; NAS, nasal; NMO-ON, neuromyelitis optica–optic neuritis; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer; SLO, confocal scanning laser ophthalmoscopy; SUP, superior; TMP, temporal.

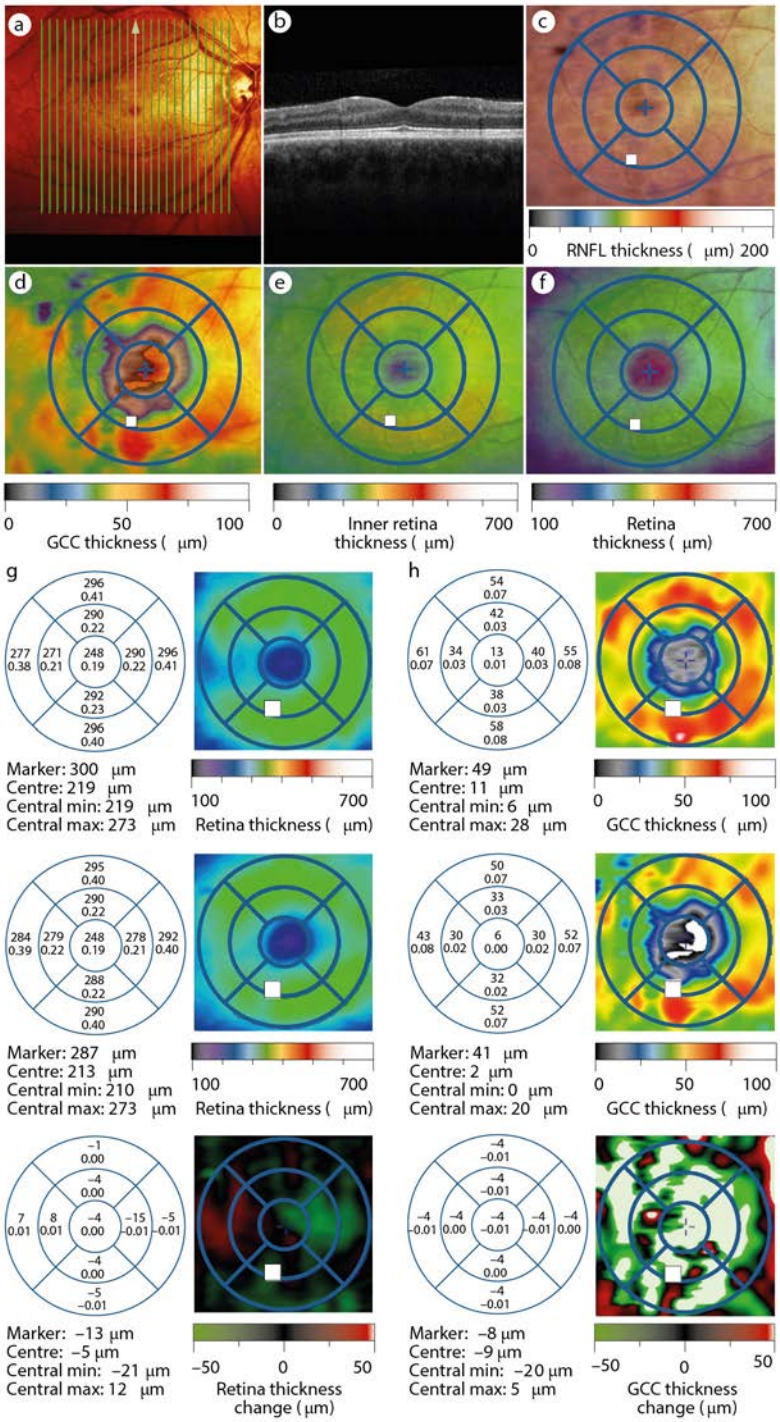

Figure 3 | Minimal retinal OCT protocol—part II: macular volume scan. Scans are from a 27-year-old woman who experienced two episodes of NMO-ON in her left eye (same patient as in Figure 2). **a,b** | Macular volume scan showing the confocal scanning laser ophthalmoscopy image. Thin green lines indicate the entire volume scan and bold green line indicates the OCT B-scan through the foveola. Thickness maps for c | retinal nerve fibre layer, **d** | GCC, **e** | all inner retinal layers combined and **f** | total retinal thickness. **g,h** | Atrophy of the macular region following the second episode of NMO-ON. Each panel shows reference scan (top), scan 3 months after the second episode of NMO-ON (middle), and difference between the two scans (bottom; red areas indicate increased thickness and green areas indicate further atrophy). Atrophy is less visible in the total retinal thickness scans (part g), but is pronounced in the GCC scans (part h). Abbreviations: GCC, ganglion cell complex; NMO-ON, neuromyelitis optica–optic neuritis; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer.

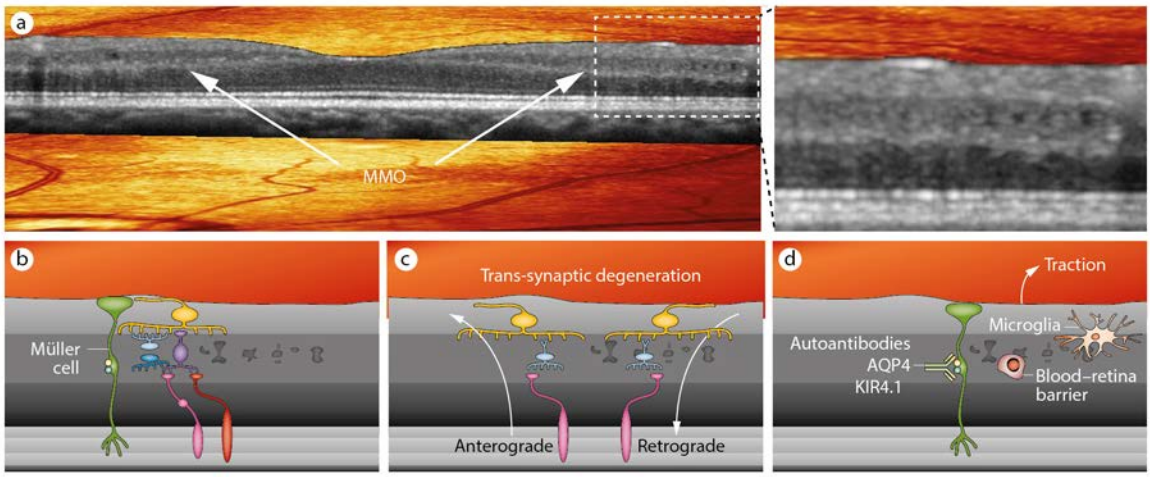

Figure 4 | MMO in a 44-year-old man with Harding disease (multiple sclerosis plus Leber hereditary optic neuropathy). 15 years earlier, he experienced an episode of optic neuritis in his left eye. Left optic disc was pale with severe atrophy of the peripapillary retinal nerve fibre layer (global average 42 μm). **a** | MMO in the perimacular rim of the left eye (see also Supplementary Video 1 online). **b** | Inset magnified to show retinal layer cytoarchitecture. A retinal ganglion cell is drawn in yellow; the INL, where MMO resides, contains bipolar cells (magenta), horizontal cells (light blue) and amacrine cells (dark blue). Bipolar cells synapse with rods (pink) and cones (red) located in the outer retina. Müller cells (green) traverse all retinal layers. **c** | MMO may be attributable to persistent microcystic changes of the INL, probably following bidirectional trans-synaptic axonal degeneration (anterograde: from outer retina to brain; retrograde: from brain to eye). **d** | The transient nature of MMO has been related to traction at the vitreoretinal interface (arrow), and is proposed to reflect signs of inflammation from breakdown of the blood–retina barrier, microglial activation, presence of autoantibodies against AQP4 or KIR4.1, and/or Müller cell pathology. Abbreviations: AQP4, aquaporin 4; INL, inner nuclear layer; MMO, microcystic macular oedema.