

The investigation of optic neuritis: a review and proposed protocol

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Abstract

Optic neuritis (ON) affects most patients with multiple sclerosis (MS) at some point during their disease. It is not always straightforward to differentiate episodes of MSON from other autoimmune and inflammatory optic neuropathies. Recognition of other optic neuropathies is relevant for treatment choice and further patient management. Over the past decade a number of new imaging, laboratory and electrophysiological techniques have entered the clinical arena. There are to date no consensus guidelines how and when to apply these techniques most rational for the diagnostic work-up of patients with ON. This paper reviews the literature and formulates a consensus for the investigation of patients with ON in standard care and research as relevant to clinical treatment trials.

Keywords:. inflammatory optic neuropathies, optic neuritis, multiple sclerosis, investigation, diagnosis.

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Key points:

- Optic neuritis (ON) is frequently but not always associated with multiple sclerosis (MS) and patients will want to know about their risk to develop MS.
- Early recognition of patients with forms of ON other than MSON is important to prevent severe visual loss as typical MS targeted treatments fail and mimics of MSON need to be excluded.
- There is no international consensus on the nosology of ON, the aetiology remains idiopathic in many cases and attempts for classification fall short, in part because the lack of a uniform investigation protocol.
- This review on established and emerging diagnostic tools proposes a consensus on the investigation of patients with suspected ON in standard care and research to have a base for follow-up.
- The aim is to help recognising patients at risk for severe visual loss (standard care), to contribute to future attempts on the classification of ON and to provide endpoints for clinical studies (research).

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1. Introduction

Optic neuritis (ON) is frequently but not always associated with multiple sclerosis (MS) [34]. Once a patient is diagnosed with MS, visual symptoms may be summarily attributed to a MS relapse, potentially missing other treatable aetiologies for visual loss. Transient problems such as conduction block may be mistaken as relapses of optic neuritis [18, 23, 76] and problems related to impaired eye movements may be overlooked [32, 94, 95].

It is important to recognise patients with forms of ON other than MSON including neuromyelitis optica (NMO) spectrum disorder and chronic relapsing inflammatory optic neuropathy (CRION) as early as possible because they are at risk for severe visual loss [83, 116].

This review reveals a striking contrast between what is known about MSON in Caucasian patients and other inflammatory/autoimmune optic neuropathies embracing the full human ethnic range (Table 2). This review also emphasizes that ON represents a pragmatic model for testing structural–functional relationships [25, 45]. The visual system is the best known part of the human brain. In each eye 100 million rod photoreceptors capture light which is then converted by 12 types of bipolar cells into a digital signal [61] making its way through the 1,158,000 axons of the optic nerve [46], decussate in the chiasm, synapse in the lateral geniculate nucleus (LGN) and finally project through the optic radiations into the well defined cyto–architecture of the visual cortex [39] in with plastic capabilities continuously shape our subjective visual experience [29]. There is a real chance and need to make use of this detailed knowledge in an increasingly complex diagnostic and therapeutic landscape.

2. Definitions

Table 1 summarises the published criteria for a single episode of isolated optic neuritis (ION) [75], relapsing episodes of isolated optic neuritis (RION) [75], CRION [83], optic neuritis in multiple sclerosis (MSON) [86] and optic neuritis as observed in the NMO spectrum disorder [116].

There is no consensus how to investigate these patients. The present review of optic neuritis and related diagnostic tests aims to contribute to developing such a consensus. Standard care and research protocols should take associated costs and resources into account (Figure 1).

3. History taking

A structured history taking should search for warning signs which may suggest an alternative diagnosis to MSON (synopsis 1) that must lead to further investigations (Figure 1).

The classical clinical presentation of ON consists of (peri-)ocular pain, preceding loss of vision and dyschromatopsia. Pain which gets worse on eye movement suggests inflammation of the optic nerve adjacent to the ocular muscles [59]. Ocular pain or headache, not worsened on eye movement, may indicate inflammation within the optic canal or intracranial space. In addition, positive phenomena such as phosphenes and scintillations may be present.

Following recovery of ON, patients may also experience glare disability, reduced vision in bright light, visual fading, Uhthoff and Pulfrich phenomenon.

Uhthoff phenomenon. Symptoms and signs of optic neuritis may get worse with rise of body temperature either due to exercise, taking a bath, fever due to infection, warm meals, cognitive/emotional stress or high ambient temperatures. This is caused by transient conduction block and are typically observed during the recovery phase [18, 23].

Pulfrich phenomenon. Perception of movement in depth may be difficult following optic neuritis [63, 76]. Patients may report problems with judging the course of vehicles/bicycles in moving traffic, problems pouring liquid into jars, or judging the trajectory of a tennis/squash ball. We specifically ask if these problems also occur if the patient is not moving, with best corrected visual acuity (BCVA) under binocular viewing conditions. The Pulfrich phenomenon is usually found in patients with recovered optic neuritis and good acuity rather than in the acute situation.

4. Clinical, bed-side assessment

4.1. Standard care

The standard of care includes measuring 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 3.

Retinal examination should be performed in each patient by direct and indirect ophthalmoscopy. A normal and a pale optic disc are shown in Figure 2 (A).

Monocular visual fields can be assessed clinically by confrontation using either finger movements or differentially sized and coloured objects [34]. We use a 4 mm red pin and also ask for red desaturation as a hint for impaired colour vision. Testing for red desaturation can be performed either by comparing central vision 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 not be well tolerated by all patients.

A relative afferent pupillary deficit (RAPD, Marcus Gunn pupil) should always be searched for using the swinging light test. The RAPD can be enhanced by holding a 0.3 log unit neutral density filter in front of the affected eye [49]. The RAPD should be present with unilateral ON, but can be absent in binocular simultaneous or sequential ON. If there is no RAPD a diagnosis can only be made with extreme caution.

If present, pain on eye movements is one of the strongest indicators of ON and the few other conditions who do (myositis, orbital inflammation, subtarsal foreign body) can generally be excluded at the bedside by testing eye-lid 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 examining horizontal saccades as evidence of a sub-clinical internuclear ophthalmoplegia (INO) which is highly suggestive of demyelination elsewhere in the CNS [58]. Cross-over testing helps to look for transient visual problems which may be due to a phoria.

4.2. Research

Low contrast visual acuity should be tested with best correction using Sloan charts [3]. In addition, Pelli-Robson charts are useful for testing contrast sensitivity. A colour vision test should be used such as either the Ishihara, the Hardy Hand Ritter (HRR) pseudoisochromatic plates, the Lanthony desaturated D-15 test or, if time does not matter, even 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. Computerised testing of colour vision provides quantitative data [88]. Importantly, this also considers relevant

age adjusted normal limits of colour vision, required for reliable recognition of acquired problems [88].

Patients with the Pulfrich phenomenon, can be assessed using a classical pendulum [63, 76]. A horizontal swinging pendulum is perceived as following an ellipsoid trajectory by the patient [2]. This phenomenon is best assessed if the pendulum swings in front of a high contrast pattern background which enhances disparity.

5. Optical coherence tomography

5.1. Review

Retinal OCT permits accurate documentation of changes in thickness of retinal layers [21, 64]. The full spectrum of retinal pathology unravelled by using OCT in MS is not yet known. New differential diagnoses are actually being added as OCT data improves. At present there are two types of pathology in favour of making recommendations for standard care and research:

1. Thinning or atrophy of the inner retinal layers: the retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL, Figures 2 & 3).
2. Thickening or swelling of the peripapillary RNFL can be seen in cases with optic disc swelling. There is also localised thickening of the INL which can be associated microcystic macular oedema (MMO, Figure 4).

Thinning. Loss of the non-myelinated axons in the retina can readily be quantified by OCT and is understood to represent [80]: (1) pathology in the retinal layers resulting in anterograde (Wallerian) degeneration leading to thinning of the RNFL; (2) pathology of the optic nerve such as an acute ON attack causing axonal transection and loss (direct retrograde degeneration); (3) posterior visual pathways lesions which lead to thinning of the RNFL by trans-synaptic

(via the LGN) retrograde axonal degeneration [4, 25, 85]. One should allow a three month interval after acute ON before attempting to quantify peripapillary atrophy of the RNFL [15, 103]. Strictly sectoral thinning should prompt investigation for vascular pathology such as AION or SUSAC [12] (see Table 2). Occasionally, this may require additional fluorescein angiography (FAG) [69]. Likewise, RNFL and GCL atrophy is more severe in NMO and CRION compared to MSON [8, 10, 17, 48, 71, 111]. Caution will be 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 ON is well recognised [34, 103]. There is recent evidence that a thickened INL and MMO are more frequent in NMO compared to MSON [27, 92]. Because of the association between MMO and NMO we advise to test for presence of anti-AQP4 antibodies in patients with MMO who experience relapsing ON or in presence of red flags (synopsis 1).

MMO is not specific for MS and also seen in NMO, RION, CRION and a range of acute and chronic ophthalmological conditions (Figure 4) [5, 13, 26, 53, 83, 92, 96]. Because of the transient nature of MMO in over 80% of cases in a large study (1,370 patients, 6,551 OCT scans) we suggest to follow these patients up [13]. It has been suggested that the preferred terminology should be “microcystic macular changes” [53]. In neuroretinitis macular deposits are seen very well in OCT [109].

5.2. *Standard care protocol*

The reviewed evidence suggests that the incorporation of OCT findings will likely become routine. Protocols still have to be validated and stand the test of time in clinical practise. As a minimalistic protocol for standard care, we suggest obtaining two scans using a spectral domain retinal OCT system. The

acquisition time for the proposed scans takes 2-5 minutes per eye in patients who can maintain visual fixation:

1. a peripapillary ring scan (Figure 3 A)
2. a macular volume scan (Figure 3 B)

Asymmetry of RNFL of more than 20% may suggest “subclinical” ON.

Macular scans should be carefully reviewed for presence of MMO [13].

5.3. Research protocol

All scans should fulfil rigorous established quality control criteria [102]. A sharp image and high contrast between retinal layers is a pre-requisite for image-post processing and layer segmentation (Figure 3 C).

In all cases it is advised to have a baseline scan registered to allow for long term follow-up of the macular ganglion cell complex analysis and the peripapillary RNFL as sensitive measures for progressive neurodegeneration affecting the eye.

There is a range of additional research techniques such as en-face OCT, polarisation sensitive OCT, adaptive optics, fluorescence labelling and doppler OCT [80].

6. Laboratory investigations

6.1. Review

It is important to note that in most patients with typical MSON there is no evidence to suggest need for routine blood tests or cerebrospinal fluid (CSF) examination [34].

6.2. Standard care protocol

In patients with an atypical presentation, particularly painless or severe visual loss (<6/60), bilateral visual loss, severe disk swelling with haemorrhages, a relevant past medical or family history will require additional blood investigation (Synopsis 2).

Metabolic pathology. In suspected metabolic conditions (bilateral and symmetrical visual loss) test for vitamin B12, red blood cell folate and methylmalonic acid (MMA) [97]. Note low vitamin B12 levels may co-exist with NMO [41].

Systemic pathology. For suspected systemic disease (see table 2 systemic and ischaemic conditions) test for haematology, electrolytes, liver function, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum angiotensin converting enzyme (ACE) levels.

Inflammatory pathology. Serological studies should be guided by clinical history. Consideration should be given to syphilis, Lyme and Bartonella Henselae (see table 2 nutritional and toxic conditions).

Immunological pathology. A resource saving screening approach to immunological blood tests is to start with anti-nuclear antibodies (ANA) following international guidelines [1]. In cases where the ANA are positive, particularly in young patients, this test may be followed by a more targeted approach with extractable nuclear antigens (ENA), perinuclear anti-neutrophil cytoplasmic antibodies (ANCA), anti-cardiolipin and beta 2 glycoprotein IgG because there is an about 5% autoimmune disease overlap spectrum [43, 68]. One patient with ON was seropositive for anti-GQ1b and GT1a IgG [9].

If there is a suspicion of orbital disease causing a compressive optic neuropathy, thyroid function and anti-thyroid antibodies should be requested. Likewise,

anti-CRMP5 (also called anti-CV2) and recoverin auto-antibodies should be requested in cases with a history of cancer or suspected para-neoplastic disease in order to identify patients with melanoma associated retinopathy (MAR) and cancer associated retinopathy (CAR).

In suspected NMO, testing for anti-aquaporin 4 antibodies (AQP4-IgG) is recommended using state-of-the-art assays because of their high diagnostic specificity (>95%) and sensitivity (77%) [24, 44, 113]. Testing for AQP4-IgG is advised in all cases with features atypical for MSON, particularly severe relapsing or bilateral loss of vision for diagnostic and prognostic implications [42, 62]. Because of the heterogeneity of assays [113] and the possible harmful and ethical consequences of false negative or false positive diagnosis of NMO-ON, we recommend to perform AQP4-IgG detection in laboratories using validated assays of high sensitivity and specificity. There is evidence for a subgroup of NMO patients who are AQP4-IgG seronegative and myelin oligodendrocyte glycoprotein (MOG)-IgG positive [54, 90].

CSF. examination will only very occasionally be necessary. The CSF examination should include cytology, total protein, glucose and oligoclonal bands [98]. Of note, CSF oligoclonal bands (OCB) are not specific for MS and might also be found in over 30 other conditions [79]. In NMO, CSF OCB (type 2 pattern which reveals oligoclonal bands in CSF but not in the serum and is indicative of isolated intrathecal oligoclonal IgG synthesis) are only found in about 10% of patients [40, 70].

If acute NMO is suspected CSF glial fibrillary acidic protein (GFAP) levels are sensitive (85%–100%) and specific (77%-100%) [67, 74, 100, 108].

6.3. Research protocol

Testing for Vitamin D may become interesting as there is an emerging body of literature on the role of Vitamin D for demyelination [16, 110]. Blood neuro-

filament levels may be of prognostic value in optic neuritis [78, 84, 101].

Sample processing and storage recommendations

Standardised sample collection, processing, storage and analyses are mandatory for ensuring high quality biomarker research, enabling multi-centre analyses, making use of historical cohorts and safeguard against bias [81].

The collection of both, plasma and serum is recommended. Samples should be well mixed prior to transport to the laboratory. Samples should be centrifugation at 2,000 g for 10 minutes within 1 hour of sampling at room temperature. In situations in which 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 which makes multiple aliquots necessary. We advise to have at least 4 aliquots of 500 μ L which are stored in 1.5 mL Eppendorf tubes with a polypropylene surface, to be stored at -80°C.

We anticipate that the (retrospective) discovery of new auto-antibodies will be relevant for the differential diagnosis of ON.

7. Magnetic resonance imaging

7.1. Review

This section is focused on MRI of the optic nerves which is complementary to the well established literature on brain MRI [6]. MRI of the optic nerve(s) help to:

1. Rule out alternative diagnoses
2. Demonstrate optic nerve inflammation
3. Research assessment of optic nerve damage and atrophy

Classic MRI findings in acute ON are high signal intensity lesions in the optic nerve (occasionally extending to the chiasm) and the optic tracts on T2-weighted MR images (preferably with fat suppression). Poor clinical outcome such as slow and incomplete recovery were associated with large optic nerve lesions [55, 66].

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, but not necessarily in areas which have been affected previously. The sensitivity in the detection of contrast-enhancing lesions in the optic nerve can be further increased by using a higher contrast dosage (e.g., triple dose), but this is in our view not cost-effective [33, 56].

Patients with NMO have a higher propensity to affect the anterior visual pathways more extensively and to involve the intracranial as opposed to intraorbital segments including chiasmitis and simultaneous bilateral disease [52, 99].

7.2. Standard care protocol

There are no consensus guidelines on how and when to perform optic nerve MRI in ON. The assessment of the optic nerve the MRI protocol has to include fat suppressed T2-weighted images (e.g. short-tau inversion recovery (STIR) or frequency specific selective partial inversion recovery (SPIR) [55]) and contrast-enhanced (fat suppressed) T1-weighted images (Synopsis 3). It is most cost-effective to use a standard dosage of gadolinium-based contrast media.

In addition, T1- and T2-weighted sequences for the assessment of the whole orbit and brain are useful to simultaneously detect possible demyelinating brain lesions. For best spatial resolution, images should be acquired without any interslice gap. The spatial resolution should be 3 mm slice thickness, in plane 1 x 1 mm (measured voxel size 3 x 1 x 1 mm). Additional, sagittal PD/T2-

weighted and T1-weighted postcontrast images of the spinal cord are useful for detecting demyelinating spinal cord lesions and for differential diagnosis purposes (see Synopsis 3, and flowchart). Further radiological tests to exclude vascular malformations or vasculitis may be indicated as summarised in Table [t'dd'on].

7.3. Research protocol

Although MRI at higher magnetic field strengths (3T) do not necessarily lead to an earlier diagnosis of MS, they result in a higher image quality [114, 115]. In general, a head coil is sufficient for the assessment of the orbit and the optic nerves. Surface coils further improve the spatial resolution [47].

Important MRI methods for research purposes are measures of optic nerve atrophy using high resolution 3D T2-weighted sequences [106] and quantitative MR techniques [105] and diffusion tensor imaging [107]. These advanced techniques can assist in the early detection of clinical impairment and estimate quantitatively the presence and extent of damage of the optic nerve [30, 117]. All these measures have been proposed as markers of irreversible tissue damage and disease progression, and predictors of clinical recovery.

8. Electrodiagnostic tests

8.1. Review

Electrodiagnostic tests have a role in the investigation of atypical presentations of ON [37]. This should not be limited to visual evoked potentials (VEP) alone, as any retinal abnormality will impact on the VEP signal [35, 37]. Indeed, the International Society for Clinical Electrophysiology of Vision (ISCEV) standards recommends that in cases of unexplained visual loss, the VEP results be interpreted with both a standard electroretinogram (ERG) and a pattern electroretinogram (PERG) [73].

8.2. Standard care protocol

The ISCEV standards (www.iscev.org/standards/proceduresguide.html , accessed 14 March 2014) state that electrophysiological tests are of little diagnostic value in acute retrobulbar optic neuritis, but that they may be of value in studies evaluating therapy. However, if the diagnosis is uncertain, the full electrophysiology series of tests should be performed, as outlined below.

VEP. The VEP represent a specific change in on-going electroencephalographic recording due to response of the visual pathway to either a pattern or flash stimulus.

The VEP has shown to be a highly sensitive but less specific test for optic neuritis. A unilateral substantially delayed VEP with minimal amplitude reduction is highly suggestive of a demyelinating optic neuropathy in either recovered MSON or subclinical involvement of the optic nerve in MS. VEP abnormalities will also be seen in patients with refractive errors, purely retinal dysfunction, compressive lesions of the optic nerve, Parkinson disease [72] and migraine [11]. A normal ERG and VEP support the differential diagnosis of non-organic aetiology if performed after other investigations did not yield a diagnosis (Figure 1).

ERG. gives diagnostic information about the rod and cone photoreceptors, and the 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 VEP alone is used.

8.3. Research protocol

Multifocal VEP (mfVEP). allow for fine mapping of the electrophysiological abnormalities in the visual pathway. This mapping allows to detect abnormalities restricted to specific topographies and may be more sensitive than VEP.

Pattern electroretinogram (PERG). 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 retinal location stimulated is primarily the macula [35]. The PERG is a surrogate test of macular function, and can therefore be used to differentiate macula from optic nerve causes of central vision loss. The two main components of the PERG are the N95 and P50 [19, 20, 35]. In ON the N95 component and N95:P50 ratio were found to be useful [19, 20, 36, 89].

Multifocal ERG (mfERG). The optic nerve head component responses of mfERG may also emerge as a useful tool in assessing optic neuritis [22].

9. Perimetry

9.1. Review

The classical visual field defect (VFD) described in MSON is a centro-caecal scotoma with a sloping border of the isopters [28]. Of note, a classical centro-caecal scotoma only been reported in 2% of cases [50]. It becomes even rarer later in the disease course (0.5%). Most patients suffer from a more generalised reduction in their VF sensitivity (66%) [50]. In contrast altitudinal VF defects suggest a vascular differential diagnosis [82].

Automated perimetry should be performed using threshold estimation strategies [77, 91]. An important limitation, particularly in neurological conditions, children or elderly patients is that the test takes long and the test failure rate may be up to 46% [31, 93, 104]. One needs to consider operator instruction effects, “natural variation in test results” and learning effects [57, 60]. It may not be possible to detect a VFD until about 25–35% of retinal ganglion cells have been lost [51, 65, 87]. Therefore, as a consensus we hesitate to recommend

perimetry as a mandatory part of a standard care protocol, but rather advocate selective use of perimetry in cases where test results may guide with the differential diagnosis (Table 2) or in presence of red flags (Synopsis 1).

9.2. Research protocol

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

10. Further perspectives

The clinical spectrum of optic neuritis has broadened over the past two decades. This development was driven by (1) the cumulative experience from trials on treatment of optic neuritis, (2) the clinical recognition of a divergent semiology, (3) the discovery of new auto-antibodies and biomarkers and (4) the availability of new high-resolution imaging techniques of the optic nerve and retina.

There is a need to make use of this knowledge and techniques to better investigate and define the clinical spectrum of optic neuritis with the aim to guide future patient management. Importantly, some forms of optic neuritis (NMO, CRION) will require rigorous immunosuppression to protect patients from blindness. Such patients must be recognised to prevent contamination of MSON treatment trials.

We anticipate that the consensus investigation protocol reviewed here will help to come to an agreement on the classification of optic neuritis and how to optimise treatment. We also propose that the consensus should be pursued

internationally so that different approaches can be validated in those parts of the world where MS is less common.

List of abbreviations

ACE = angiotensin converting enzyme,
ANA = anti-nuclear antibodies,
ANCA = anti-neutrophil cytoplasmic antibodies,
ADEM = acute demyelinating encephalomyelitis,
AION = anterior ischaemic optic neuropathy,
AQP4 = aquaporin-4,
AZOOR = acute zonal occult outer retinopathy,
CAR = cancer associated retinopathy,
CNS = central nervous system,
CRION = chronic relapsing inflammatory optic neuropathy,
CRP = C-reactive protein,
CSF = cerebrospinal fluid,
ENA = extractable nuclear antigens,
ESR = erythrocyte sedimentation rate,
FAG = fluorescein angiography,
GBS = Guillain Barr/e Syndrome,
GFAP = glial fibrillary acidic protein,
GCC = ganglion complex,
GCL = ganglion cell layer,
HRR = Hardy Hand Ritter,
IgG = immunoglobulin G,
INL = inner nuclear layer,
ION = isolated optic neuritis,

IPL = inner plexiform layer,
INL = inner nuclear layer,
INO = internuclear ophthalmoplegia,
LETM = longitudinal extensive transverse myelitis,
LGN = lateral geniculate nucleus,
LHON = Leber's hereditary optic atrophy,
MAR = melanoma associated retinopathy,
MMA = methylmalonic acid,
MME = microcystic macular edema,
MMO = microcystic macular oedema,
MOG = myelin oligodendrocyte glycoprotein,
MRI = magnetic resonance imaging,
MS = multiple sclerosis,
MSON = Multiple Sclerosis associated optic neuritis,
NMO = neuromyelitis optica,
OCB = oligoclonal bands,
OCT = optical coherence tomography,
ON = optic neuritis,
OPL = outer plexiform layer,
PION = posterior ischaemic optic neuropathy,
PPMS = primary progressive multiple sclerosis,
RAPD = relative afferent pupillary deficit,
RION = relapsing isolated optic neuritis,
RNFL = retinal nerve fibre layer,
RRMS = relapsing remitting multiple sclerosis,
SPMS = secondary progressive multiple sclerosis,
UCON = Unclassified Optic Neuritis.

Competing interests

None declared.

Author contributions

AP had the idea for this protocol, reviewed the literature, provided figures, wrote the first draft and finalised the manuscript. CS, FC, FP, KF and SS revised the manuscript. MW performed an independent literature review and wrote the MRI section. CF performed an independent literature and wrote the VEP/ERG section. GP and BW contributed to the conception and design of the protocol. All authors revised the final version of the manuscript.

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SYNOPSIS 1 — Red flags suggestive of an alternative diagnosis but MSON

- atypical clinical presentation:
 1. pain or loss of vision presenting for more than 2 weeks
 2. absence of pain
 3. retinal abnormalities
 4. unexplained optic atrophy
 5. severe loss of vision in patients with a non-Caucasian ethnic background
 6. severe loss of vision without early recovery

- atypical course:
 1. progressive loss of vision
 2. absence of recovery for more than 3 months
 3. worsening of visual function after reducing or stopping steroids or immunosuppression

- bilateral ON^a

- past medical history of cancer

^a Simultaneous binocular visual loss needs to be distinguished from sequential bilateral visual loss. Both VA and VF need to be documented. Sole assessment of VA may miss a peripheral VF defect.

SYNOPSIS 2 — Laboratory tests

- haematology, electrolytes, GT, ASAT, ALAT, ESR or CRP
- Vitamin B12, MMA, folate, thyroid function
- appropriate serology^a
- ACE
- ANA, AQP4-IgG

^a Of note, optic neuritis has been observed following almost any type of infection and a rational choice of serological testing needs to be guided by the history and clinical picture. Amongst the more frequent agents are Bartonella (did patient have contact with cats?), borrelia (tick bite, endemic region?), syphilis and HIV (exposure?), tuberculosis (been to risk area? Family members?).

SYNOPSIS 3 — MRI protocol

- Optic nerve (≈ 10 minutes):
 1. Coronal T2-weighted images with fat suppression (e.g., STIR, SPIR)
 2. Coronal T1-weighted images before and after contrast administration
- Brain (≈ 20 minutes)^a:
 1. Axial PD/T2-weighted
 2. Sagittal FLAIR (preferably 3D)
 3. Axial T1-weighted after contrast administration
- Spinal cord (≈ 15 minutes)^b:
 1. Sagittal PD/T2-weighted
 2. Sagittal T1-weighted after contrast administration
- Research
 1. High resolution 3D T2-weighted (CISS) images for the visualisation and volume measurements of the optic nerve
 2. Diffusion tensor imaging (DTI)

^a for suspected demyelination in the brain (e.g. MS).

^b for suspected demyelination of the spinal cord (e.g. NMO).

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 English-language, full-text papers. 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.

Table 1: *Definitions of optic neuritis (ON) incorporating the disease course. In order to show demonstrate an isolated episode of ON relevant pathology elsewhere in the CNS will need to be excluded. DIS = dissemination in space, DIT = dissemination in time.*

Nosology	Definition	Reference
ION	a single and isolated episode of ON. The MRI of the optic nerve shows signs of inflammation with brain and spinal cord imaging being essentially ¹ normal.	[75]
RION	a spontaneously relapsing and isolated episode of ON, MRI as for ION	[75]
CRION	relapses of isolated episodes of ON on steroid withdrawal , MRI as for ION	[83]
NMO-ON	spontaneously relapsing episodes of ON, AQP4+, MRI not typical for MS	[116]
MSON	an episode of ON with radiological evidence for DIS & DIT	[86]

¹ One will need to be pragmatic and permit for occasional unspecific MRI lesions, which tend to become more and more frequent as magnetic field strength and resolution increase.

Table 2: *The differential diagnosis of optic neuritis (ON) and ON mimics.*

Differential diagnosis	Clinical features	Paraclinical tests ¹
MSON	good recovery within 2 months	MRI typical for MS
ION	red flags	MRI: only ON inflammation
RION	spontaneous relapses, red flags	MRI: only ON inflammation
CRION	relapses on steroid withdrawal	AQP4-IgG negative, MRI: only ON inflammation
NMO ON	relapses, poor recovery	AQP4-IgG positive
Infectious		
HIV	subacute or progressive visual loss following	Serology
Syphilis	exposure to infectious agent	PCR
Tuberculosis	frequently with broader cellular	CSF, Chest radiography
Lyme disease	reaction in the eye	

¹ ACE = angiotensin converting enzyme, ADEM = acute disseminated encephalomyelitis, AION = anterior ischaemic optic neuropathy, ANA = anti-nuclear antibodies, AVM = arteriovenous malformation, AZOOR = acute zonal occult outer retinopathy, CCF = carotid cavernous sinus fistula, CRP = c-reactive protein, CSF = cerebrospinal fluid, CTA = computed tomography angiography, DSA = digital subtraction angiography, ECG = electrocardiogram, ERG = electroretinogram, GCA = Giant cell arteritis, HIV = human immunodeficiency virus, LHON = Leber's hereditary optic neuropathy, MMA = methylmalonic acid, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, OCT = optical coherence tomography, OPO = mutations present in patients with autosomal dominant optic atrophy, PCR = polymerase chain reaction, PION = posterior ischaemic optic neuropathy, SLE = systemic lupus erythematosus, VEP = visual evoked potentials, VF = visual fields.

Viral		
Sinusitis ¹	sinus pain	MRI
Reactive		
Post-infectious	Bilateral and simultaneous	Serology, CSF
Post-vaccination	often in childhood,	OCT, ERG
ADEM		MRI
Neuroretinitis	mostly good prognosis	macular star ²
Vascular		
AION	Sudden onset visual loss,	ESR, CRP, glucose
PION	mostly painless (except GCA)	coagulation,
GCA	acutely swollen optic disc (except PION)	biopsy (GCA)
	cardio-vascular risk factors	ECG, doppler
Retinal vasospasm	frequent episodes, migraine	ECG, doppler
SUSAC	hearing loss, encephalitis	audiogram
Diabetic papillopathy		OCT, VF

¹ Sinusitis had been high up in the differential diagnosis in the past but almost disappeared over the past decades [14].

² A macular star is suggestive for neuroretinitis and can be associated with peripheral retinal haemorrhages and spickeled appearance of the pigment epithelium.

CCF	proptosis, chemosis, orbital venous congestion, diplopia	orbital bruit, CTA/MRA
Vascular malformations	(intermittent) proptosis, seizures, neurological signs	CTA/MRA, DSA, CSF

Nutritional & toxic

Vitamins B ₁₂ deficiency	Bilateral, painless,	Vitamin B ₁₂ , MMA
Tobacco-alcohol	progressive,	full blood cobalt levels
Endemic ¹	implant ² ,	OCT, VF
Methanol	pale discs,	
Ethambutol	poor prognosis.	

Compressive

Primary tumours	Painless, progressive,	CT or MRI, orbits and brain
Metastases	pale disc at presentation,	with contrast, MRA
Tuberculoma	cilioretinal shunt vessels, history of cancer	OCT, biopsy
Grave disease	history of thyroid disease	proptosis, lid lag, diplopia, anti-thyroid antibodies
Sinus mucoceles		

¹ Endemic optic neuropathies have been described in Cuba and Tanzania.

² There is emerging data that cobalt toxicity [7] may also be relevant to (hip) joint implants containing cobalt.

Systemic disease

Sarcoidosis	Painful, progressive and often bilateral	ACE, CSF, biopsy (sarcoid)
Behçet disease	more frequent in non-Caucasians	OCT, chest radiography, MRI
SLE		coagulation, if ANA positive search for specific antibodies
Cancer	subacute visual loss	paraneoplastic antibodies brain and orbits with contrast
Persistent visual aura	history of migraine	

Ocular

Posterior scleritis	Pain	OCT, ultrasound, ANCA [112]
Maculopathies	painless, metamorphosia	OCT, ERG
Retinopathies	preserved colour vision	Fluoroscein angiogram
Big blind spot syndromes	VF loss, photopsias	VF, OCT
AZOOR	preserved colour vision	ERG

Hereditary

LHON	Family history	Genetic testing
OPA1&3	bilateral painless	

12. Supplementary material

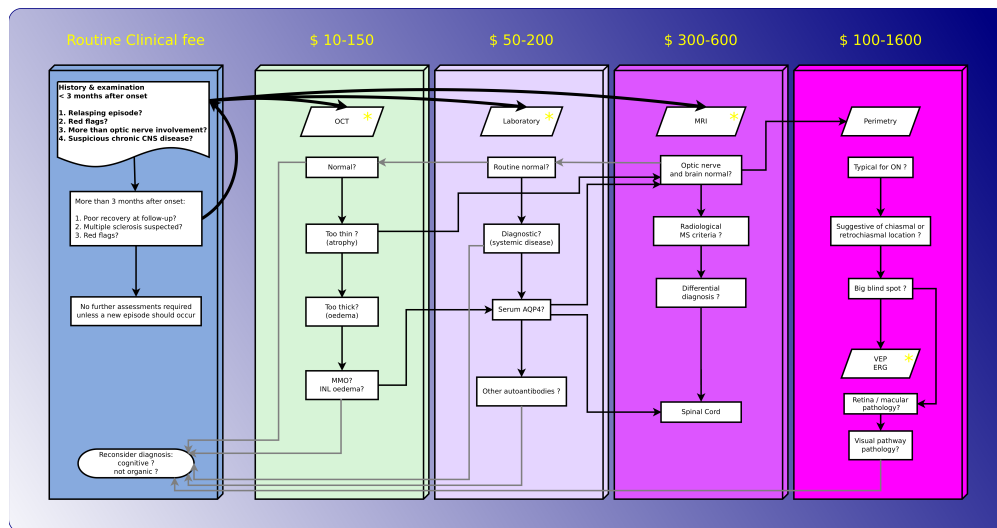


Figure 1: **Investigation protocol for patients presenting with suspected optic neuritis.** The clinical decision on whether or not a patient requires further investigations depends on key points from the history and clinical examination. The approximate costs (USD = \$) related to escalation of investigations are highlighted against the colour-coded background from left to right (grey-green \$ 10-150, light purple \$ 50-200, light magenta \$ 300-600, magenta \$ 100-1600).

The clinical decision tree emphasises pertinent questions, pointing horizontally for “yes” and vertically for “no” answers.

A research protocol should include all investigations marked with a yellow star (*).

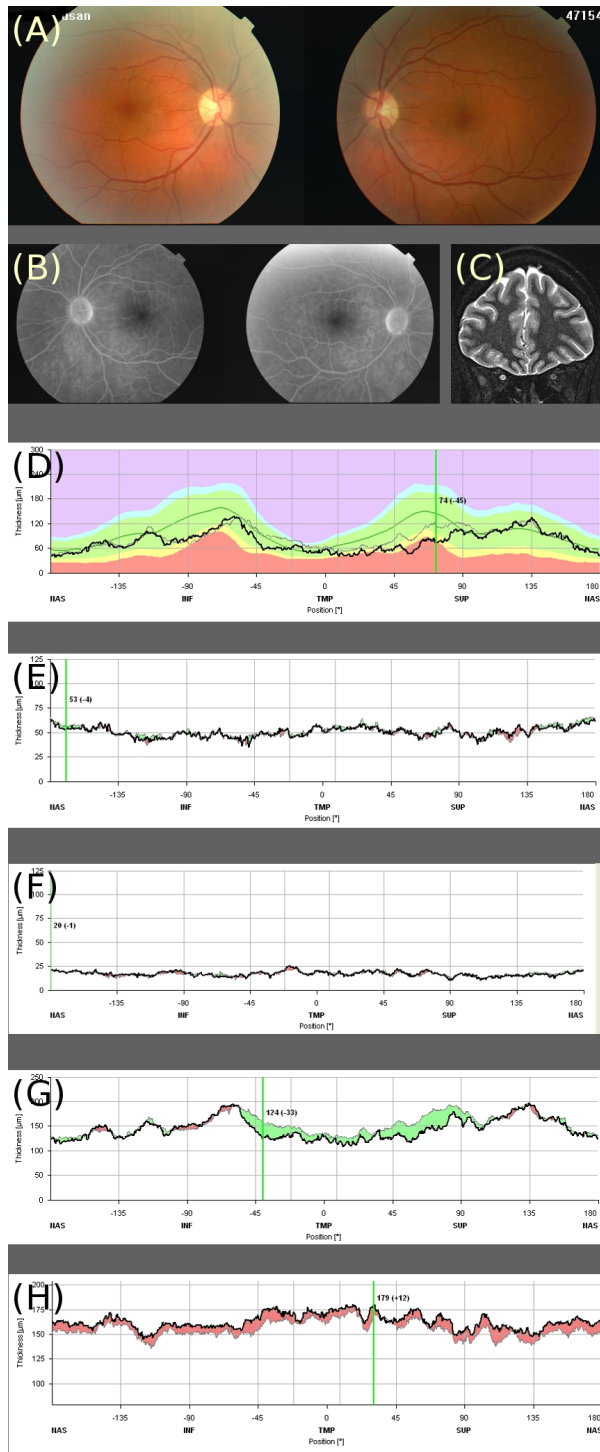


Figure 2: **A** Photographs of the optic discs from a 35-year old woman presented with the second of two episodes of blurred vision OD within the last three months. The right optic disc is pale temporally, the left optic disc is normal. Visual loss was preceded by several days with photopsias, but without pain on eye movements. She had never required refraction and her uncorrected VA OD was 0.03 with a central scotoma. There were oligoclonal bands in the CSF and additional identical oligoclonal bands in CSF and serum (“type 3” or mirror plus pattern [79]). The CSF white cell count was elevated at 25 leucocytes/ $3\mu\text{L}$, with a normal total protein of 194 mg/L. The test for AQP4-IgG was normal as were the remainder of the autoimmune, infectious and metabolic laboratory investigations. **B** Fluorescein angiography (FAG) was normal. **(C)** The coronal section of the fat-suppressed MRI FLAIR sequence of the orbit demonstrates an increased signal of the right optic nerve. She received intravenous steroids according to the optic neuritis treatment trial protocol, but her vision failed to improve over the following nine months. Serial OCT measurements demonstrated the development of further peripapillary retinal layer atrophy. **D** Consistent with the photograph of the right optic disc, there is some pRNFL atrophy of the temporal nerve fibres (thin black line). Atrophy of the pRNFL progressed over the following nine months and mainly affected the temporal fibres. **E** Automated layer segmentation demonstrated only a very small degree of atrophy (green shaded areas) in the inner plexiform layer (IPL) and **F** inner nuclear layer (INL). **G** Extend and location of atrophy can best be appreciated by summation of the inner retinal layers (pRNFL, IPL, INL). **G** In contrast, more global thickening developed in the outer retinal layers (red shade area in the summation graph from the outer plexiform layer to basal membrane).

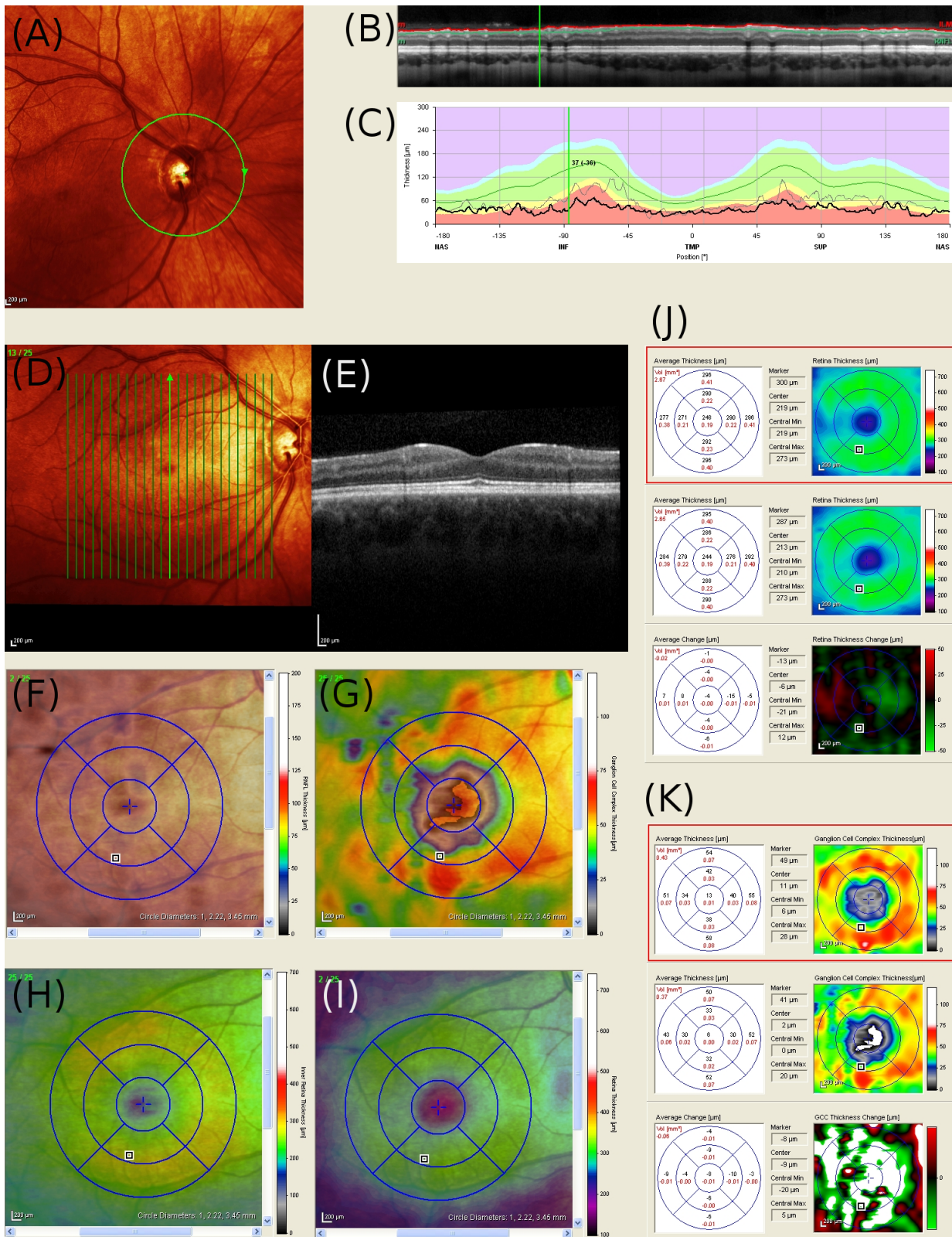


Figure 3: Minimal retinal OCT protocol consisting of a peripapillary ring scan and a macular volume scan. All images are from a 27-year old woman with who experienced two episodes of NMO-ON OS (AQP4-IgG seropositive). VA OS was no perception light (NPL) after the first episode of NMO-ON. The second episode of NMO-ON started with pain on eye-movements, but VA was not helpful for clinical monitoring. (A) The infrared image (IR) of the The peripapillary ring scan, with the corresponding (B) OCT B-scan. The inner limiting membrane (ILM) is indicated by the red line and the retinal nerve fibre layer (RNFL) by the green line. The distance between the two lines calculates to the RNFL thickness shown in (C) with the thin black line indicating the reference RNFL thickness after the first episode of NMO-ON and the thick black line the additional RNFL loss manifesting 3-months after the second episode of NMO-ON. The macular volume scan is shown in (D) and (E) shows the OCT B-scan through the foveola. Thickness maps (note layer thickness specific colour maps) are presented for (F) the RNFL, (G) the ganglion cell complex (GCC), (H) all inner retinal layers combined and (I) the total retinal thickness. (J) Atrophy of the macular region following the second episode of NMO-ON is hardly visible for the total retinal thickness (reference scan to the top, next scan 3-months after the second episode of NMO-ON and difference between the two scans to the bottom (red areas indicating increased thickness and green areas indicating further atrophy). In contrast, (K) illustrates better the loss of the GCC.

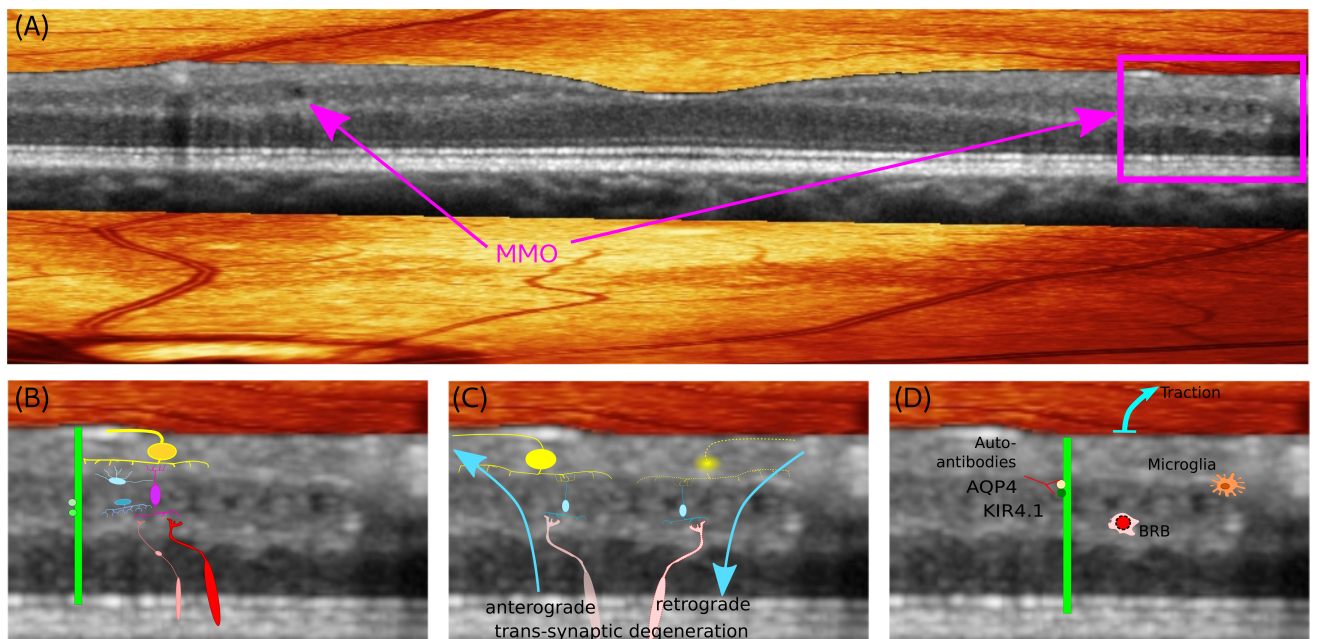


Figure 4: (A) Microcystic macular oedema (MMO, magenta arrows) in the perimacular rim of the left eye (OS) of a 44-year old man with Harding's disease (combination of MS and Leber's mutation). Fifteen years earlier there was an episode of ON OS (RAPD OS, BCVA OD 0.9, OS 0.1). The left optic disc is now pale with severe atrophy of the peripapillary RNFL (global average $42\mu\text{m}$). The inset (magenta box) is shown magnified in (C) in relationship to the retinal layer cytoarchitecture. The retinal ganglion cell (RGC) is shown in yellow, the inner nuclear layer (INL) where MMO resides, contains bipolar cells (magenta), horizontal cells (light blue) and amacrine cells (dark blue). Bipolar cells synapse with the rods (pink) and cones (red) located in the outer retina. The only cell transverse all retinal layers are the Müller cells (green). Presence of MMO may be due to (C) persistent microcystic changes of the INL, likely following bi-directional trans-synaptic axonal degeneration (anterograde \Rightarrow from the outer retina to the brain, retrograde \Rightarrow from the brain to the eye). The transient nature of MMO has been related to (D) traction at the retino-vitreous interface (blue arrow) and proposed to reflect signs of inflammation either by breakdown of the blood-retina barrier (BRB), microglial activation or presence of auto-antibodies against AQP4 or KIR4.1 or Müller cell pathology. For an animated video demonstrating the extend of MMO through the macular see supplementary material on the Journal's website.

Table 3: Conversion of visual acuities. Table adapted from [38]. CF = count fingers at 2 feet (0.6 meter) distance, HM = hand movements at 2 feet (0.6 meter) distance, NPL = no perception light.

Snellen Equivalent (meters) (feet)	Decimal (minutes)	Chart not possible	LogMAR Equivalent	
6/3	20/10	2.00	.	-0.3
6/3.75	20/12.5	1.60	.	-0.2
6/4.8	20/16	1.25	.	-0.1
6/6	20/20	1.00	.	0.0
6/7.5	20/25	0.80	.	+0.1
6/6.4	20/32	0.63	.	+0.2
6/12	20/40	0.50	.	+0.3
6/15	20/50	0.40	.	+0.4
6/18.9	20/63	0.32	.	+0.5
6/24	20/80	0.25	.	+0.6
6/30	20/100	0.20	.	+0.7
6/37.5	20/125	0.16	.	+0.8
6/48	20/160	0.13	.	+0.9
6/60	20/200	0.10	.	+1.0
6/75	20/250	0.08	.	+1.1
6/96	20/320	0.06	.	+1.2
6/120	20/400	0.05	.	+1.3
.
6/600	20/2000	0.01	CF	+2.0
6/6000	20/20000	0.001	HM	+3.0
.	.	.	NPL	.