CONTINUING MEDICAL EDUCATION

The Diagnosis and Treatment of Optic Neuritis

Helmut Wilhelm, Martin Schabet

SUMMARY

Background: Typical optic neuritis is often the presenting manifestation of multiple sclerosis (MS). Its incidence in central Europe is 5 cases per 100 000 persons per year.

Methods: This review is based on articles retrieved by a selective search of the PubMed database, on the pertinent guidelines, and on the authors' clinical experience.

Results: The diagnosis of optic neuritis is based on a constellation of symptoms and signs. The onset is usually with pain on eye movement in one eye and subacute visual loss. In unilateral optic neuritis, the direct pupillary light reflex is weaker in the affected eye. One-third of patients with optic neuritis have a mildly edematous optic disc. The visual disturbance resolves in 95% of cases. A less favorable course may be evidence of neuromyelitis optica, and macular involvement may be evidence of neuroretinitis. High-dosed intravenous methylprednisolone therapy speeds recovery but does not improve the final outcome. The risk that a patient with optic neuritis will later develop multiple sclerosis can be assessed with an MRI scan of the brain.

Conclusion: Optic neuritis is easy to distinguish from other diseases affecting the optic nerve. Atypical forms of this disease and other optic nerve diseases require special treatment. For patients judged to be at high risk of developing multiple sclerosis, immune prophylaxis with beta-interferon or glatiramer acetate is recommended.

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University Eye Hospital, University Hospital Tübingen: Prof. Dr. med. Wilhelm

Department of Neurology, Klinikum Ludwigsburg: Prof. Dr. med. Schabet

Typical optic neuritis is an acute, severe visual disturbance without any clear diagnostic findings on ocular examination. It generally affects young, otherwise healthy individuals. It is caused by an autoimmune reaction directed against the optic nerve. Optic neuritis may be the first manifestation of multiple sclerosis. It is increasingly used in clinical trials as a model for multiple sclerosis relapses, because visual function is relatively easy to measure and, in particular, because changes in the retinal nerve fiber layer can be visualized in detail with optical coherence tomography. The optic nerve, in this situation, can be used as a window to the brain.

Learning goals

This article is intended to acquaint the reader with

- the signs and symptoms of optic neuritis,
- the necessary diagnostic evaluation,
- the course of the disease, and
- the options for treatment.

The reader will also acquire knowledge of the main atypical forms of optic neuritis and its relation to multiple sclerosis.

Epidemiology

The incidence of optic neuritis in central Europe is 5 cases per 100 000 persons per year. The mean age at onset is 36 years; it is rare in persons under 18 or over 50 (1, 2). More than 70% of patients are women (1, 2). According to a current study, optic neuritis accounts for 43% of the cases of clinically isolated neurological syndromes that are considered potential precursors of multiple sclerosis (2). The ophthalmologist is thus often confronted with an otherwise healthy young woman whom he must tell that she might one day develop multiple sclerosis, or might already have the disease.

Occurrence

Typical optic neuritis is a young person's disease. It may be the first manifestation of multiple sclerosis.

We think it is right to inform the patient of this openly from the beginning.

Symptoms and signs

Typically, optic neuritis first manifests itself with pain on movement of the eyes, followed by a worsening of vision. Only 0.4% of patients develop symptoms in both eyes simultaneously (3). Nearly all patients can date the onset of symptoms precisely to a specific day; in contrast, patients with optic nerve tumors usually cannot do this.

Patients report seeing things darkly, unclearly, and with poor contrast; colors look dirty and pale *(Figure 1)*. After a subacute onset, the patient's visual acuity continues to deteriorate for a few more days; in the untreated course of the disease, it generally reaches its nadir in one to two weeks and then improves again (1). Some patients perceive positive optic phenomena (4).

The pain and worsening of vision are so disturbing that hardly any affected person waits to see whether they will improve spontaneously; patients tend to find their way to an ophthalmologist very early in the course of the disease. Pain on eye movement is absent in the 8% of patients whose inflammatory focus lies in the intracranial portion of the optic nerve and thus proximal to its mobile portion (1).

Two classic phenomena are associated with optic neuritis. In the Pulfrich phenomenon, an object swinging back and forth in the plane of vision is perceived as moving in a circle. This phenomenon also arises in persons with normal vision when one eye is covered with a gray filter; it is thus nonspecific. In the Uhthoff phenomenon, vision worsens when the body temperature rises as a result of athletic activity, other sustained physical exertion, or a hot bath or shower. This tends to occur mainly when the optic neuritis is already wearing off, or when it takes a chronic course (5). The Uhthoff phenomenon is MS specific but arises in only half of all patients (6).

Ophthalmological examination

The task of the ophthalmologist is to provide objective evidence for the diagnosis. In unilateral optic neuritis, the direct pupillary light reaction and the accompanying consensual reaction of the opposite pupil are weaker on illumination of the affected eye than on illumination of the unaffected eye *(Figure 2)*. This finding, known as a relative afferent pupillary defect (RAPD), is best seen with the aid of the swinging flashlight test. Pain on movement of the eyes should be elicited with appropriate movements, in case the patient does not spontaneously report having it. Any unusual sensation is of diagnostic relevance, because eye movements are normally not felt at all.

Figure 1: An illustration of the visual disturbance in a patient with optic neuritis, visual acuity 0.1. The photograph of a puffin was manipulated with Photoshop until the patient said that the altered image at left, seen with the normal eye, looked roughly the same as the original image at right, seen with the affected eye

Visual acuity in optic neuritis can range from 0, i.e., no light perception, to 1.5; in two-thirds of patients, it is below 0.5 (1). The affected eye is blind in 3% of cases but has an acuity of 1.0 or better in 11% of cases (1). Most patients have central and centrocecal scotomata. One-third have mild deficits on the opposite side as well, which one might be tempted to attribute to inattentiveness during perimetry; the Optic Neuritis Treatment Trial showed, however, that the "solidary" deficit in the opposite optic nerve is real and quite typical (7). Documenting visual acuity and visual field is important to enable comparison at follow-up..

The optic disc usually appears normal but is mildly edematous in one-third of cases *(Figure 3a)* (1). Impaired color perception is best tested by having the patient look at a colored object first with the right eye, then with the left (or vice versa). The object's color should seem equally saturated and bright in the two eyes; if one eye is affected by optic neuritis, that eye perceives a darker, desaturated color *(Figure 1)*.

The clinical constellation of pain on eye movement, a relative afferent pupillary defect, and a

The clinical history

Nearly all patients can date the onset of symptoms precisely to a specific day. Patients with optic nerve tumors usually cannot do this.

Symptoms and signs

Pain on eye movement, the subacute onset of worsening of vision, a relative afferent pupillary defect, and normal-appearing fundus (with at most mild papilledema) are the typical symptoms and signs of optic neuritis.

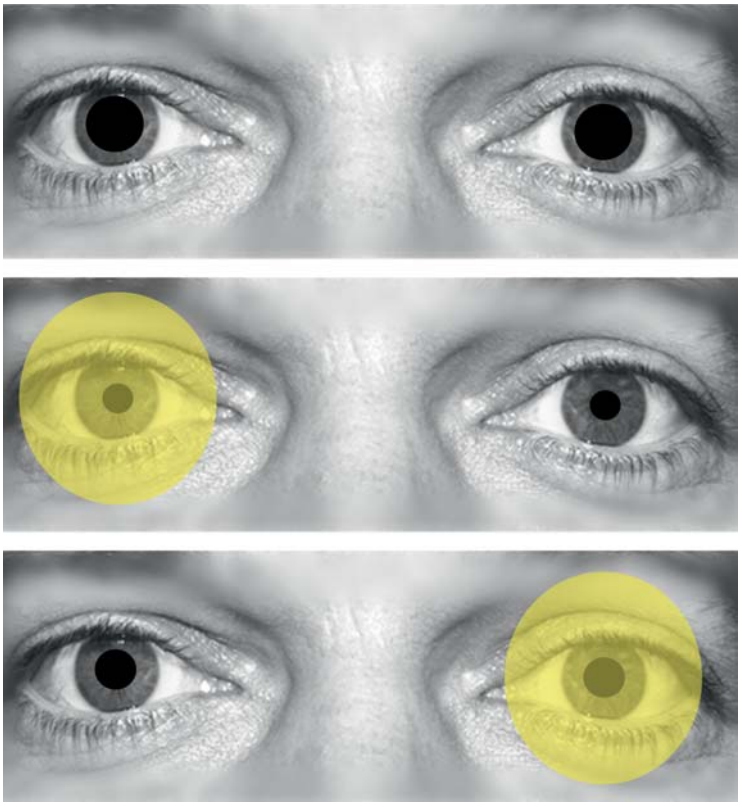

Figure 2: Swinging flashlight test in a patient with left optic neuritis (schematic figure). The pupils react more rapidly, and to a greater extent, with illumination of the healthy right eye, compared to the affected left eye

normal or mildly edematous optic disc *(Figure 3a)* is pathognomonic for optic neuritis and suffices to establish the diagnosis (8). Macular inspection is important for the exclusion of neuroretinitis.

Course and differential diagnosis in relation to other diseases of the optic nerve

Usually, the patient's visual acuity improves. About 60% of patients regain normal acuity within two months; in the Optic Neuritis Treatment Trial, only 6% of patients still had an acuity of less than 0.5 six months after onset (1). Visual contrast, visual fields, and color perception all improved as well.

Nonetheless, although the visual acuity, fields, and color perception generally revert to normal, visual contrast often remains markedly impaired and is thus the best functional parameter to use for the assessment of permanent dysfunction due to optic neuritis. This fact is important for clinical trials. In routine practice, however, it would seem psychologically ill-advised to demonstrate to a patient who has regained normal visual acuity that she or he actually still has an impairment of visual contrast.

As 92% of patients have pain on eye movement (1), optic neuritis is nearly ruled out if this is not the case and vision fails to improve. Conversely, if all three elements of the typical diagnostic triad—pain on eye movement, acute loss of visual acuity, and improvement in the further course of the disease—are present, then other diagnoses need hardly even be considered. In a Danish cohort, the most common differential diagnoses were tumor and anterior ischemic optic neuropathy (AION) (8). These conditions are generally easy to distinguish from optic neuritis *(Table 1)*. The distinction is more difficult in the case of Leber's hereditary optic neuropathy (LHON), a condition that begins acutely, like optic neuritis, but without pain. The second eye is usually affected as well within a few weeks of onset. LHON tends to affect young men. The impairment of visual acuity is severe and, in nearly all cases, irreversible. 95% of patients have a typical mutation in the mitochondrial genome (9).

Disc pallor implies longstanding disease of the optic nerve. If papilledema is seen, together with hemorrhages lying outside the immediate surroundings of the disc, central venous thrombosis should be considered; this condition does not cause pain on eye movement. Soft exudates and narrow arteries are seen in hypertensive retinopathy. Edema in or adjacent to the disc, with hypercellularity in the vitreous body, suggests juxtapapillary chorioretinitis.

Special types of optic neuritis

Typical optic neuritis is characterized by:

- age 18–50
- unilaterality
- pain on eye movement
- subsequent improvement
- no evidence of any systemic disease other than multiple sclerosis.

The fewer of these criteria are met, the higher the likelihood that the patient is suffering from an atypical form of optic neuritis, or from another disease *(Box 1, Table 2)*. Even in atypical cases of optic neuritis, however, multiple sclerosis is usually the underlying cause. Conversely, typical optical neuritis also sometimes has unusual causes other than multiple sclerosis.

Criteria of exclusion

Unclear time of onset, lack of pain on eye movement, and lack of improvement of the visual deficit over time largely rule out optic neuritis.

Atypical forms

The fewer of the diagnostic criteria for optic neuritis are met, the higher the likelihood that the patient is suffering from an atypical form of optic neuritis, or from another disease.

Neuroretinitis, neuromyelitis optica, chronic recurrent immune optic neuropathy, and optic nerve involvement in other autoimmune diseases are the most common atypical type of optic neuritis. These are generally hard to diagnose on presentation from the clinical findings alone. Only neuroretinitis can be diagnosed early on the basis of the macular findings.

The frequencies of these atypical types of optic neuritis varies from one institution to the next. To understand this better, we evaluated data from the past 12 months of patient care in our neuro-ophthalmological outpatient clinic. Atypical types of optic neuritis accounted for about one-fourth of the total caseload, with neuroretinitis as the most common type *(Box 1)*.

In neuroretinitis, inflammation spreads from the optic nerve to the retina (10). The disc is markedly swollen, and, when the symptoms are most severe, a stellate figure composed of hard exudates is seen in the macula. The inflammation often leaves marked damage behind, with cumulative damage after each recurrence. Many case reports have pointed to a bacterially triggered immune response as the cause of this disease, most often with *Bartonella* as the pathogen. The true percentage of cases of neuroretinitis that are due to this organism remains unknown (10). We treat patients with neuroretinitis with antibiotics and, in parallel, steroids in a dose of 1 mg/kg of body weight. If the disease recurs, immune suppression should be given for a longer time, e.g., with azathioprine. Patients with neuroretinitis are not at elevated risk for multiple sclerosis.

Neuromyelitis optica (NMO, also called Devic syndrome) accounts for 1–3% of cases of optic neuritis (3). It is conceivable, however, that this diagnosis is missed in some patients whose cerebral MRI findings are normal. In a classic case of NMO, the patient has both optic neuritis and transverse myelitis extending over at least 2–3 segments of the spinal cord, with little or no abnormality in the brain. Antibodies against the water channel protein aquaporin-4 are pathognomonic and are present in 80% of cases (11). If this antibody is not found, the case is said to represent an NMO spectrum disorder (NMOSD), which is diagnosed on the basis of the clinical and MRI findings (12). Optic neuritis is more often bilateral in neuromyelitis optica than in multiple sclerosis, and leaves worse damage behind (11).

If optic neuritis takes an unfavorable course, is bilateral, or is accompanied by MRI findings that are atypical for multiple sclerosis, the diagnosis of neuromyelitis optica or an NMO spectrum disorder should be considered.

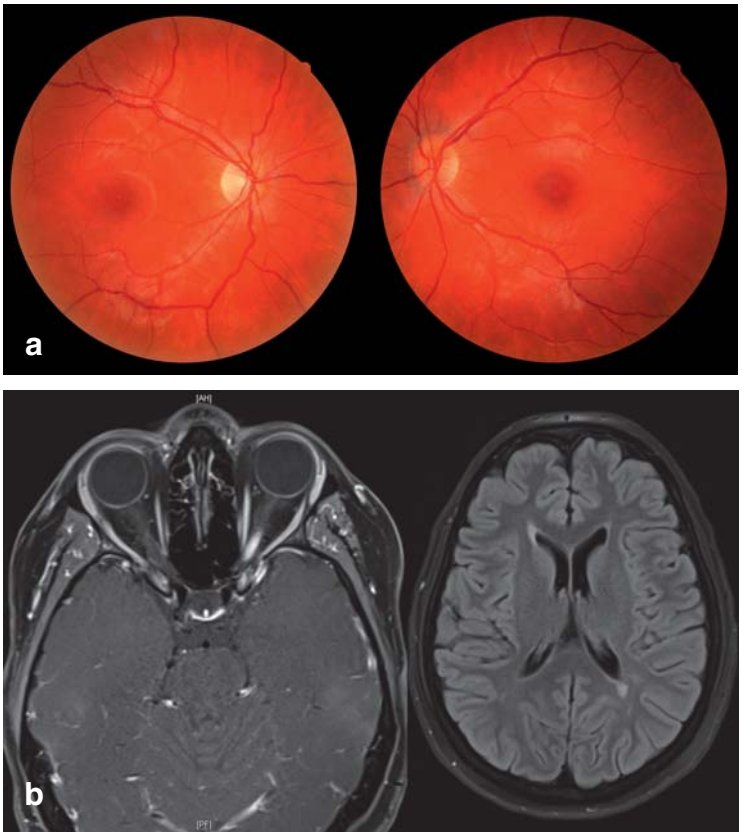

Figure 3: a) Left optic neuritis in a 23-year-old woman with mild papilledema.
b) MRI of the same patient, revealing contrast enhancement of the inflamed optic nerve, as well as two periventricular foci of demyelination on the T2-FLAIR sequence

Chronic recurrent immune optic neuropathy begins like typical optic neuritis and improves rapidly under steroid treatment, but recurs when the steroid dose is lowered. Recurrence is common, and the disease often affects first one eye, then the other. If untreated, it leaves marked damage behind: in one-third of all affected eyes, visual acuity remains less than 0.1 (13). We give prednisolone for at least three months at a dose below the threshold for producing Cushing syndrome (7.5 mg/day), or at the lowest dose that prevents recurrences. If this proves insufficient, then azathioprine or methotrexate can be considered as the next line of treatment.

Neuroretinitis

In neuroretinitis, inflammation spreads from the optic nerve to the retina. The disc is very swollen, and, when the symptoms are most severe, a stellate figure composed of hard exudates is seen in the macula.

Neuromyelitis optica

Patients with NMO have both optic neuritis and transverse myelitis extending over at least 2–3 segments of the spinal cord, with little or no abnormality in the brain. Antibodies against the water channel protein aquaporin-4 are pathognomonic.

TABLE 1

The differential diagnosis of optic neuritis and other diseases of the optic nerve

Disease	Acute onset?	Pain on eye movement?	Papiledema?	Spontaneous recovery?
Optic neuritis	Always	92%	In about 30% of cases (mild)	Marked improvement of visual acuity in 95%
Tumor of the anterior visual pathway	Almost never	Never	Possible	Very rare
Anterior ischemic optic neuropathy	Always	Never (there may be diffuse ocular pain)	In the acute stage: always*	Usually only slight improvement

*Posterior ischemic optic neuropathy (PION),which can cause optic nerve infarction without papilledema, is very rare; nearly all cases are due to giant-cell arteritis

The rarer atypical types of optic neuritis also include optic neuritis in the setting of autoimmune diseases other than multiple sclerosis, such as sarcoidosis, systemic lupus erythematosus (SLE), and Wegener's granulomatosis. In our experience, these diseases confer a worse prognosis for visual acuity than multiple sclerosis does, probably because they also cause ischemia of the optic nerve. Neurosyphilis causes bilateral papilledema with moderate worsening of visual acuity and a more favorable prognosis. We have never seen a case of neuroborreliosis (Lyme disease) presenting as isolated optic neuritis.

Ancillary diagnostic tests

Blood tests

Extensive laboratory testing is recommended in the neurologic guidelines if multiple sclerosis is suspected *(Box 2)*. The ophthalmologic guidelines, in contrast, restrict extensive testing to atypical cases (14).

In the Optic Neuritis Treatment Trial, testing for antinuclear antibodies, syphilis serology, and chest x-rays was found to have no therapeutic consequence whatsoever in any of the 457 cases included in the trial (1). The authors recommended meticulous history-taking followed by targeted laboratory testing. Excessive testing can also generate false-positive results leading to unnecessary further tests and much anxiety. Moreover, the atypical types of optic neuritis and further diseases in the differential diagnosis that extensive testing is meant to detect are, in fact, quite rare (8).

Magnetic resonance imaging

Magnetic resonance imaging is certainly the most important ancillary test; it can directly reveal inflammation of the optic nerve, typically as contrast uptake in a contrast-enhanced T1 sequence *(Figure 3b)*. It cannot, however, be used as a substitute for clinical diagnosis. An optic nerve sheath meningioma can look

BOX 1

Optic neuritis in the outpatient neuro-opthalmology clinic of the University Eye Hospital in Tübingen over 12 months, from 1 July 2014 to July 2015

- Optic neuritis with typical course 73
  - No other findings on brain MRI 22
  - Inactive foci of demylination 28
  - Definite multiple sclerosis 23
- Neuroretinitis 15
- Chronic recurrent immune optic neuropathy 4
- Neuromyelitis optica 3
- Sarcoidosis 2
- Due to sinusitis 1
- Uninterpretable findings on brain MRI 2

Magnetic resonance imaging

Magnetic resonance imaging is the most important ancillary test in optic neuritis.

MRI diagnostic criteria for multiple sclerosis

Multiple sclerosis can be diagnosed when the MRI in a patient with optic neuritis reveals two or more typical lesions of multiple sclerosis, at least one of which is contrast-enhancing.

TABLE 2

Atypical types of optic neuritis

Disease	Features	Course	Treatment
Neuroretinitis	Macular involvement, bacterial infection	Longer-lasting and more severe than typical optic neuritis	Antibiotics and steroids, immune prophylaxis
Chronic recurrent immune optic neuropathy	Recurrence as soon as the steroid dose is lowered	Many recurrences	Long-term steroid therapy
Neuromyelitis optica	Foci of demyelination in the spinal cord, antibodies against aquaporin-4	Often bilateral; incomplete recovery	High-dose steroid therapy, plasmapheresis, immune prophylaxis
Optic neuritis due to an autoimmune disease other than multiple sclerosis	Other clinical evidence of the underlying disease	Rare; course often unfavorable	High-dose steroid therapy, treatment of the underlying disease

exactly like optic neuritis on MRI and should be suspected if the contrast enhancement does not subside within 3 months. Contrast enhancement involving more than half of the length of the optic nerve or continuing into the optic chiasm should arouse the suspicion of neuro-myelitis optica (12).

It is important to determine whether there are any foci of demyelination in the brain; these most commonly appear in the corpus callosum and periventricular white matter *(Figure 3b)* and are best seen on T2-FLAIR images. Active foci of multiple sclerosis take up contrast medium. The number of inactive typical white-matter lesions is the most important criterion for estimating the risk that the patient will develop multiple sclerosis (15). Optic neuritis with two or more non-contrast enhancing lesions typical of multiple sclerosis on MRI is called a "clinically isolated syndrome" and is associated with a high risk of multiple sclerosis. Multiple sclerosis arises in only 25% of patients whose MRI reveals no foci of demyelination in the brain. If one or two such foci are initially present, the risk is 65%; if three or more are present, it is 78% (16). If a clinically asymptomatic lesion takes up contrast medium, then the definition of multiple sclerosis has already been met (17).

Cerebrospinal fluid examination

Cerebrospinal fluid (CSF) examination is generally performed in Germany as part of the clinical evaluation of optic neuritis, but this is not currently an international standard (15). According to the German neurologic guidelines, the CSF tests that should be performed include cytology; measurement of albumin, IgG, IgA, and IgM concentrations according to the quotient scheme (Reiber–Felgenhauer diagram); isoelectric focusing for the demonstration of oligoclonal IgG bands; and measurement of antibodies against neurotropic viruses (measles, rubella, varicella-zoster). CSF examination is important if the MRI findings are unclear, the clinical findings are atypical, the blood tests reveal an abnormality, or the patient is atypically young or old for the development of optic neuritis.

In our opinion, the measurement of IgA and IgM in the CSF can generally be dispensed with; the measurement of antibodies against neurotropic viruses does not usually yield any useful additional information either.

Visual evoked potentials

Optic neuritis delays the latency of visual evoked potentials. The latency can only be measured, however, if the potential is sharply demarcated, which often is not the case in the acute phase of the disease. In a recent retrospective study, the sensitivity of visual evoked potentials was only 37% (8). This test is not necessary for the establishment of the diagnosis.

The relation between optic neuritis and multiple sclerosis

The Optic Neuritis Treatment Trial yielded precise figures on the risk of developing multiple sclerosis. Half of all patients with typical optic neuritis will develop multiple sclerosis within 15 years (16).

The diagnosis of multiple sclerosis requires the demonstration of inflammatory lesions in the central nervous system that are disseminated in both space and time (16). Recurrent optic neuritis on the same side does not, therefore, establish the diagnosis.

The relation between optic neuritis and multiple sclerosis

Half of all patients with typical optic neuritis will develop multiple sclerosis within 15 years.

Elevated risk of multiple sclerosis

Even if the MRI is free of typical lesions of multiple sclerosis (MS), 25% of the patients with optic neuritis will later develop MS.

BOX 2

Diagnostic recommendations of the neurologic guidelines

- **Recommended laboratory tests**
  - C-reactive protein
  - Complete blood count
  - Serum chemistry
  - Blood sugar
  - Vitamin B_{12}
  - Rheumatoid factor
  - Antinuclear antibodies
  - Anti-phospholipid antibodies
  - Anti-ds-DNA antibodies
  - Lupus anticoagulant
  - Serum angiotensin-converting enzyme test
  - *Borrelia* serology
  - Urinalysis

- **Additional tests in case of "clinically possible differential diagnosis"**
  - Anti-neutrophilic cytoplasmic antibodies (ANCA)
  - Extractable nuclear antibody (ENA) profile
  - Autoantibodies against aquaporin-4
  - HIV serology
  - Human T-lymphotropic virus type 1 (HTLV-1) serology
  - *Treponema pallidum* hemagglutination assay (TPHA), long-chained fatty acids
  - *Mycoplasma* serology
  - Urinary methylmalonate excretion

According to the revised McDonald criteria (2011), multiple sclerosis can be diagnosed when the MRI in a patient with optic neuritis reveals two or more typical lesions of multiple sclerosis, at least one of which is contrast-enhancing (17).

25% of patients with optic neuritis who do not have any typical lesions of multiple sclerosis on an MRI scan of the brain will go on to develop the disease, most of them within 5 years. The risk is higher if visual acuity does not return to a level above 0.5, or if oligoclonal bands are found in the cerebrospinal fluid (18).

The role of optical coherence tomography

Optical coherence tomography (OCT) is now an increasingly used tool in research on the pathogenesis and treatment of multiple sclerosis. Thinning of the peripapillary retinal nerve fiber layer is correlated with other parameters for assessing the course of multiple sclerosis (19). OCT thus reflects the severity of damage in optic neuritis and in related conditions such as neuromyelitis optica (20). It is easy to perform and yields objectively measured values; it has thus come into widespread use in clinical trials. The best parameter is probably the peripapillary nerve fiber layer thickness in the ring-scan that is centered on the optic disc.

The utility of OCT in routine clinical practice is limited, because the thickness of the retinal nerve fiber layer varies widely among normal persons and can also be influenced by other diseases, such as glaucoma.

Acute treatment

A number of randomized, controlled, double-blind trials of cortisone for the treatment of optic neuritis were evaluated in a meta-analysis in 2012 (21). One randomized and controlled trial (RCT), the Optic Neuritis Treatment Trial, had a major effect on the current standard of treatment (21). In this trial, oral prednisone treatment at a dose of 1 mg/kg body weight [BW]/day for 14 days was compared with intravenous methylprednisolone treatment at 1000 mg/day for 3 days followed by oral prednisolone (1 mg/kg BW) for 11 days, and with placebo treatment. Treatment with intravenous methylprednisolone, which was not blinded, led to more rapid recovery of vision, but the final outcome with respect to visual acuity, fields, and perception of contrast and color was no better than with oral prednisone alone, or indeed with placebo (1, 21, 22). Similar results were found in earlier and later studies as well; thus, it was concluded in the meta-analysis of 2012 that faster recovery is the sole benefit of steroid treatment (21). Among the patients in the Optic Neuritis Treatment Trial who were treated only with low-dose oral prednisolone, early recurrences within 6 months were twice as common as in the placebo group. Since the publication of these findings, low-dose oral prednisolone alone has been considered to be contraindicated for patients with typical optic neuritis.

In experimental allergic encephalomyelitis, an animal model of multiple sclerosis, treatment with methylprednisolone was found to cause a loss of retinal ganglion cells (23, 24). In the view of most experts, however, this finding—without any counterpart in clinical studies to date—does not contraindicate the use of high-dose methylprednisolone in patients with optic neuritis.

Clinically isolated syndrome

Optic neuritis with two or more non-contrast enhancing lesions typical of multiple sclerosis on MRI is called a "clinically isolated syndrome" and is associated with a high risk of multiple sclerosis.

Acute treatment

3–5 days of treatment with methylprednisolone (500–1000 mg/day) leads to more rapid recovery of vision in optic neuritis but does not improve the final outcome with respect to visual acuity.

TABLE 3

Clinical trials on the prevention of conversion of a clinically isolated syndrome to clinically definite multiple sclerosis

Trial	Year	Drug	Number of patients	Follow-up (years)	Conversion to clinically definite multiple sclerosis		
					Active drug (%)	Placebo (%)	Relative risk reduction (%)
CHAMPS (40)	2000	IFN-β-1a	383	3	35	50	30
CHAMPS (e1)	2012	IFN-β-1a		5	38	53	28
CHAMPS (e1)	2012	IFN-β-1a		10	76	84	10
ETOMS (e2)	2001	IFN-β-1a	309	2	34	45	24
BENEFIT (e3)	2007	IFN-β-1b	468	3	34	48	29
BENEFIT (e4)	2014	IFN-β-1b		8	56	66	15
PreCISe4 (e5)	2009	Glatiramer acetate	481	3	25	43	42

Patients in the Optic Neuritis Treatment Trial who received high-dose intravenous methylprednisolone had fewer multiple sclerosis relapses in the ensuing two years than those who received either low-dose oral prednisone or placebo, but there was no further difference in the third year (25). This finding led researchers to ask whether the favorable effect could be prolonged by a second steroid infusion. Although some evidence indicates this may be the case (26), the matter has not yet been studied any further. The patients in the Optic Neuritis Treatment Trial who received intravenous methylprednisolone for 3 days all also received oral prednisolone over the ensuing 11 days. It is unclear whether this is necessary, and the guidelines leave the question open. We generally do not give oral prednisolone after intravenous methylprednisolone.

It is stated in the neurological and ophthalmological guidelines that optic neuritis should be treated with methylprednisolone at a dose of 500–1000 mg/day for 3–5 days (14, 15). During steroid treatment, a proton-pump inhibitor is also given to prevent peptic ulcers. Osteoporosis prophylaxis, in contrast, is not necessary, because steroids are only given for a short time. The complete blood count, serum glucose, and electrolyte levels are checked before the first intravenous dose of methylprednisolone and on the third and (sometimes) fifth day of treatment. Although methylprednisolone can be given orally in higher doses (27, 28), this is not standard practice.

The adverse effects of corticosteroids must be weighed against their modest benefit in the treatment of optic neuritis. Steroid treatment is a valid therapeutic option, but it is not mandatory.

At least the first intravenous steroid treatment should be given in the inpatient setting (in our opinion). This will enable the rapid recognition of adverse effects and the efficient performance of ancillary tests. It is also psychologically beneficial for the patient to have doctors and nurses nearby at the moment when she or he must emotionally contend with a new diagnosis of multiple sclerosis.

No controlled trials have yet addressed the question what to do next if visual acuity fails to improve. The treatment options in such cases are documented by nothing more than individual case studies and small case series. In most cases of persistently poor visual acuity, the treatment that was given initially is given a second time, sometimes in a double dose and/or for a longer duration. The last option for acute treatment is plasmapheresis, which is sometimes very effective (29). It should be performed within six weeks of the onset of the disease. The decision for or against plasmapheresis is a difficult one, as spontaneous improvement is possible as late as two months after disease onset. If there is evidence of neuromyelitis optica, rather than typical optic neuritis, methylprednisolone is generally given in a higher dose and for a longer time; if no improvement ensues, early plasmapheresis is performed (30, 31).

The special case of neuromyelitis optica

Optic neuritis as a component of neuromyelitis optica generally requires longer and more intense treatment than optic neuritis as a manifestation of multiple sclerosis.

Beta-interferon and glatiramer acetate

Immune prophylaxis with a beta-interferon or glatiramer acetate lowers the risk of clinically definite multiple sclerosis.

However, this treatment approach is currently not supported by randomized and blinded trials.

Immune prophylaxis of multiple sclerosis

Beta-interferons and glatiramer acetate have been used for two decades to lessen the number of new and active multiple sclerosis lesions on MRI and the number of clinical relapses, and, in the long term, to slow the progression of neurologic impairment. These drugs have also been used in several clinical trials to treat clinically isolated syndromes (35–40). In about one-third of the patients in these trials, the isolated clinical syndrome was optic neuritis. In all trials, the patients who received the active drug developed a second neurologic manifestation (and thus a clinically diagnosable case of multiple sclerosis) less frequently, and (if at all) at a later time, than those given placebo. Even after a second episode, treated patients had a significantly lower annual rate of relapse for the duration of follow-up. Neurologic impairment was relatively mild and not significantly different in the two groups. These findings are summarized in *Table 3*.

In the light of these findings, the interferons and glatiramer acetate have been approved for the treatment of clinically isolated syndromes as well, including optic neuritis with two or more inactive typical lesions of multiple sclerosis on MRI. Newer drugs for multiple sclerosis—in particular, oral drugs such as teriflunomide (32, 33) and dimethyl fumarate (34)—are not approved for this indication.

The early treatment of clinically isolated syndromes is not favored by all experts and remains a matter of judgment for the experienced neurologist (35, 36). In neuromyelitis optica and NMO-spectrum disorders, immune prophylaxis with a beta-interferon or glatiramer acetate is not indicated. Rather, azathioprine or rituximab is given to prevent recurrences.

Drug treatment to promote optic nerve regeneration

No current treatment can restore the function of a damaged optic nerve. In a phase 2 trial, an antibody against LINGO (leucine-rich repeat and Ig domain containing 1, a protein inhibitor of axonal growth) was found to shorten the latency of visual evoked potentials; this may reflect optic nerve regeneration (37). The results of another phase 2 trial of anti-LINGO-1 are expected in 2016 (the SYNERGY trial, NCT 01864148). Pilot trials have shown benefit from erythropoietin (38) and simvastatin (39). A prospective controlled trial of erythropoietin is in progress (NCT01962571, www.tone-studie.de).

Conflict of interest statement

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Corresponding address
Prof. Dr. med. Helmut Wilhelm
Universitätsklinikum Tübingen
Augenklinik, Neuroophthalmologie
Schleichstr. 12–16
72076 Tübingen, Germany
helmut.wilhelm@med.uni-tuebingen.de

Supplementary material:
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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What is the incidence of optic neuritis in central Europe?

a) 1 per 100 000 per year
b) 3 per 100 000 per year
c) 5 per 100 000 per year
d) 7 per 100 000 per year
e) 9 per 100 000 per year

Question 2

What diagnostic test is indispensable for the objective diagnosis of unilateral optic neuritis?

a) Visual acuity measurement
b) Perimetry
c) Visual evoked potentials (VEP)
d) Swinging flashlight test
e) Optical coherence tomography

Question 3

For what type of optic neuritis are antibodies to aquaporin-4 pathognomonic?

a) Typical optic neuritis as a presentation of multiple sclerosis
b) Neuromyelitis optica (NMO)
c) Chronic recurrent immune optic neuritis (CRION)
d) Neuroretinitis
e) Infection-associated optic neuritis

Question 4

Which of the following is more compatible with a tumor compressing the optic nerve than with optic neuritis?

a) The patient cannot date the onset of the problem precisely.
b) The opposite eye also has mild visual field defects.
c) Visual field examination reveals a central scotoma.
d) The optic disc is swollen.
e) The visual acuity is 1.0.

Question 5

According to the guidelines, how should optic neuritis be treated?

a) Methylprednisolone 500–1000 mg IV qd × 3–5 d
b) Plasmapheresis
c) Prednisolone 75 mg po qd × 7 d, taper to off over 2 weeks
d) Immediate administration of IFN- -1a
e) ASA 100 mg po qd × 8 weeks

Question 6

If a brain MRI in a patient with optic neuritis reveals two non-contrast enhancing lesions in the periventricular white matter, then:

a) The patient has multiple sclerosis (MS)
b) The patient will certainly develop MS
c) The risk of developing MS is high (ca. 65%)
d) The risk of developing MS is low (ca. 25%)
e) Neuromyelitis optica is ruled out

Question 7

What test is most suitable for measuring permanent functional damage due to optic neuritis in clinical trials?

a) Visual acuity measurement
b) Perimetry
c) Testing of color perception
d) Visual evoked potentials (VEP)
e) Testing of visual contrast perception

Question 8

The MRI findings in what disease are most likely to be misdiagnosed as showing optic neuritis?

a) Anterior ischemic optic neuropathy
b) Optic sheath meningioma
c) Leber's hereditary optic neuropathy
d) Toxic optic neuropathy of alcoholism
e) Optic neuropathy due to vitamin B_{12} deficiency

Question 9

If the brain MRI of a patient with optic neuritis reveals no other abnormality, what is the patient's approximate long-term risk of developing multiple sclerosis?

a) less than 1%
b) 5%
c) 10%
d) 25%
e) 50%

Question 10

What benefit is achieved by the acute treatment of optic neuritis?

a) Faster recovery of vision
b) Less permanent damage to vision
c) A disability score that is 1.5 points lower at 5 years
d) A 30–40% lower risk of an MS episode within 5 years
e) Regression of more than 50% of foci of demyelination

Supplementary material to:

The Diagnosis and Treatment of Optic Neuritis

by Helmut Wilhelm and Martin Schabet

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