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# Acute demyelinating optic neuritis: a review

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## 1. ABSTRACT

Acute demyelinating optic neuritis (ON) is a leading consideration in the differential diagnosis for young adults presenting with sudden onset of painful unilateral visual loss. Multiple sclerosis (MS) is believed to be the most common etiology for ON. Nearly 50% of MS patients will develop ON, and in 15-20% of cases, ON will be the initial manifestation of the illness. Conventional and emerging magnetic resonance imaging (MRI) techniques have provided greater insight into the pathophysiology of ON, and conventional MRI has also allowed clinicians to better estimate the future risk of MS. At 10 years after ON, patients with zero, one, or two or more brain lesions on T2-weighted MRI sequences demonstrated a 22%, 52%, and 56% risk of developing MS, respectively. Treatment with high dose intravenous methylprednisolone may accelerate visual recovery in patients with acute ON, but has little impact on long term visual outcome. Disease modifying therapies in patients with acute demyelinating ON should be considered as a treatment option at the time of initial presentation in those patients whose initial brain MRI shows demyelinating lesions as these therapies have been shown in to be effective at reducing the future risk of MS.

## 2. INTRODUCTION

A 37 year-old woman presented with a 5 day history of right eye pain on eye movement, with visual blurriness that worsened with physical activity. She noticed worsening over the next several days, leading to an inability to read with the right eye. On examination, she had a visual acuity of 20/200 in the right eye and 20/20 in the left eye. She had a central scotoma in the right eye, with full visual fields in the left eye. The pupils were symmetric and equal on inspection, but she had an afferent pupillary defect in the right eye. Magnetic resonance imaging (MRI) of the brain showed three hyperintense lesions on fluid-attenuated inversion-recovery (FLAIR) sequences, with no enhancement on T1-weighted post-gadolinium sequences. MRI of the orbits and optic nerves were normal. Her serum Lyme antibody, antinuclear antibody, rapid plasma regain, glucose, erythrocyte sedimentation rate, angiotensin converting enzyme, thyroid stimulating hormone, and free thyroxine were normal. She was treated with a 3 day course of 1 gram/day IV methylprednisolone, leading to improved visual acuity over the next month. Her acuity returned after 6 weeks to 20/20, with normal visual fields in both eyes, but there remained

an afferent pupillary defect. Despite the improvement, she noted after intense exercising or a warm bath that she would occasionally get visual blurring out of her right eye.

## 3. EPIDEMIOLOGY

The incidence of ON is 5 per 100,000 and the prevalence is 115 per 100,000 (1). Among different causes of ON, MS is felt to be the most common etiology. The close association between MS and ON is demonstrated by the fact that nearly 50% of MS patients will develop ON, and in 15-20% of cases, ON will be the initial manifestation of the illness (2, 3). Much knowledge surrounding the epidemiology of ON has arisen from the Optic Neuritis Treatment Trial (ONTT). The ONTT was a multi-center prospective study at 15 sites where patients between 18 and 46 years of age with acute ON (457 were initially enrolled) were treated with high dose glucocorticoids and followed since 1992. At ten year follow-up after the onset of ON, it was found that nearly 38% of patients had developed MS, with the biggest risk factor being the presence of at least one brain lesion on T2-weighted MRI sequences at baseline (4).

Geography, season, age at onset and human leukocyte antigen (HLA) status have also been shown to influence the epidemiology of ON. ON has a geographic pattern similar to MS, with a higher incidence farther from the equator, both in southern and northern latitudes. For example, Israel has an annual incidence of 1 in 100,000, versus the northern United States, which has an incidence of 3 per 100,000 (5). There is a seasonal influence on the incidence of ON, with more reported cases occurring in the spring and summer than in the other seasons (6). Patients with ON who were HLA DR2 positive have been found to have a higher rate of converting to MS, especially when the initial brain MRI showed evidence of disseminated lesions (7-9). Research has also showed that there is a genetic influence on the incidence of ON, with increased risk linked to the presence of HLA class II antigens (7-9).

Variations in the clinical presentation of ON occur among the different racial groups, notably among African American and Japanese patients. In the ONTT, Caucasians made up 85% of the patients, and 80% of patients were women. African American patients with ON had more impaired visual acuity at onset and after 1 year of follow-up compared with Caucasian study patients (10). In Asian populations, ON has been reported to present bilaterally and with spinal cord involvement more often than in Caucasian patients (this is known as optical-spinal MS or the related neuromyelitis optica syndrome) (11-15).

## 4. PATHOPHYSIOLOGY

In most cases of ON, an unknown trigger causes local inflammation, which may result in demyelination and eventually axonal loss; thus, the condition is idiopathic. In the acute phase before demyelination, lymphocytes and monocytes are believed to infiltrate the blood-brain barrier, which may be seen as perivenular retinal sheathing on a fluorescein angiogram. The white blood cells release cytokines, which are signaling proteins serving to amplify immune responses and communicate with other immune cells. Deckert *et al.* showed that pro-inflammatory cytokine receptors interleukin-2, interleukin-6 and interferon-gamma are increased in the serum and cerebrospinal fluid (CSF) of patients with ON (16). The inflammatory response ultimately leads to demyelination, which causes conduction block or slowed transmission along the optic nerve, resulting in the clinical manifestations of visual loss. Macrophages and plasma cells serving as scavengers will digest the myelin debris surrounding the optic nerve. As the process evolves, astrocytes form scar tissue in the area of myelin loss, and axonal degeneration ensues. Thus, depending on the stage, pathologic specimens demonstrate similar findings to what is seen in MS plaques: early perivenular lymphocytes, macrophage infiltration near the demyelinating lesion, with later stages showing glial scar tissue and axonal loss (17). Petersen *et al.* has demonstrated that other markers of inflammation such as cellular adhesion molecules, specifically intercellular adhesion molecules, are also increased (18).

According to current research, patients in the acute phase of ON also demonstrate increased serum anti-myelin basic protein antibodies and anti-proteolipid antibodies that are believed to target myelin components in the optic nerve - myelin basic protein and proteolipid protein. Berger *et al.* showed that patients with a clinically isolated demyelinating syndrome such as ON who present with anti-myelin basic protein antibodies and anti-myelin oligodendrocytes antibodies (another component of myelin) are associated with a higher risk for conversion to MS compared to patients without such serum antibodies (19). However, further research is being conducted in this area.

## 5. CLINICAL FEATURES

Patients with ON usually present with two main unilateral symptoms: 1) acute to subacute decrease in vision that occurs over hours to days, and 2) orbital pain (20).

The visual acuity in ON ranges from mild (remaining 20/20) to severe (complete blindness with no light perception). Patients often describe the vision as “a blur” or “seeing through a cloud.” Miller has reported that visual acuity may remain normal despite ON, as 20/20 visual acuity requires only 44% of the foveal axons to function (21). The visual symptoms may worsen over hours to days, but usually plateau by 10 to 14 days. The visual loss often affects the central more commonly than the peripheral visual field, in a central scotoma pattern. A visual field deficit that is altitudinal is not typical of ON, and raises the possibility of other diseases, such as anterior ischemic optic neuropathy (22). ON usually presents with a unilateral loss of vision, but the ONTT has shown that the contralateral eye may demonstrate abnormalities on exam in up to 48% of patients (23, 24). Bilateral ON has also been reported most commonly in children (25), as part of a post viral syndrome (26), or associated with Leber's optic neuropathy (27-29), neuromyelitis optica (11-15, 30), toxic exposure (31-33), or vitamin deficiency (31-33).

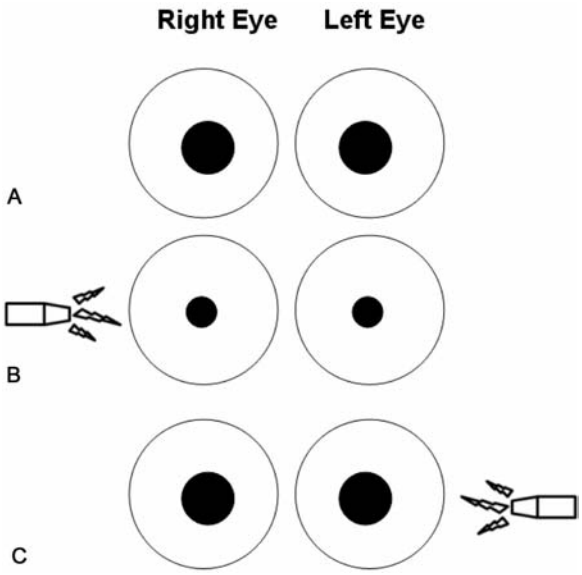


**Figure 1.** A relative afferent pupillary defect in a patient with a left optic neuritis, when tested with a swinging light test. A) When the eyes are examined without any light stimulus, the pupils are symmetric in size. B) When a light is placed in front of the normal right eye, both pupils constrict due to the normal afferent pupillary response. C) Note how when the light goes from the normal right eye to the abnormal left eye, the pupils appear to dilate, as the left eye does not receive the stimulus to the same degree as the right eye.

Close to 90% of patients describe unilateral orbital pain associated with ON, which may precede or accompany the visual symptoms, and may occur at rest or with eye movements. The pain is a dull ache or sinus pain, which may also include tenderness of the globe. It reaches maximum severity in 24-36 hours after the onset of visual symptoms and typically resolves spontaneously in 48-72 hours. Patients may also report the pain of ON as a "headache." The reason for the pain being worse with eye movements is because the optic nerve sheath is innervated with pain receptors, which lead to orbital pain when the extraocular muscles pull the pain sensitive inflamed optic nerve sheath (34, 35).

Patients with ON may also suffer from difficulty with low contrast visual acuity, dyschromatopsia, Uhtoff's phenomena, and loss of depth perception. Patients with ON may have 20/20 acuity but may still have problems with low contrast acuity. A test for low contrast acuity tests the ability to see objects which may not stand out from their background. There are a number of studies recently published that establish this method as the most sensitive in detecting visual symptoms in ON (36-39).

Dyschromatopsia in the form of red desaturation also occurs commonly with optic nerve involvement (40). Uhtoff's phenomenon is deterioration in vision after exercise or exposure to heat, such as a hot bath or shower (41, 42). Increases in body temperature lead to a reversible conduction block in demyelinated optic nerves, ultimately causing a temporary loss of vision (42). Trouble with depth perception, especially with moving objects, arises from unequal feedback to the cortex between the two optic nerves, given that the impaired nerve is transmitting at a slower rate than the unaffected nerve (43).

On examination, patients may present with a relative afferent pupillary defect when tested with a swinging light test (Figure 1). When the light is swung back and forth between the affected and unaffected eyes, one notes a finding that is pathognomonic for optic nerve involvement (anterior to the optic chiasm). In the unaffected eye, the light causes the pupils bilaterally to constrict. When the light is swung back to the eye with ON, both pupils appear to dilate, as the affected optic nerve does not transmit the same quantity of light as the unaffected eye, causing a relatively smaller pupillary constriction or even a dilation described as a Marcus Gunn pupil (44).

On funduscopy, two-thirds of cases of ON show a normal examination. This occurs because ON is often retrobulbar. In the remaining one third of cases, when ON affects the anterior part of the optic nerve, one may see both a swelling of the optic nerve head (papillitis) and peripheral hemorrhages (Figure 2) in the acute stages. Chronically, due to axonal loss, the optic nerve head may appear pale (Figure 3) (45).

The following atypical features should raise red flags concerning the diagnosis of ON, and require further laboratory studies to rule out a mimic such as anterior ischemic or nutritional deficiency optic neuropathy: patients older than 45 years; bilateral presentation; a vertical hemianopic visual field defect; symptoms progressing more than 2 weeks; and recent sinusitis (17). The differential diagnosis of ON is extensive (11-15, 27-33, 46-52), and is summarized in Table 1.

## 6. DIAGNOSTIC EVALUATION

The diagnostic evaluation of ON should include a complete ophthalmologic exam and a complete neurologic exam to look for lesions in the nervous system which would be supportive of another diagnosis. Other investigations to consider include: 1) serologic testing; 2) CSF analysis; 3) visual evoked potentials; 4) MRI of the brain and orbit; and 5) low contrast letter acuity.

Often physicians order specific blood tests when faced with a patient with typical ON, such as antiphosphlipid antibody, antinuclear antibody, angiotensin converting enzyme, fluorescein treponemal antibody and vitamin B12. However, the ONTT has shown that, when faced with a patient having the typical features of ON, these tests are usually negative. Laboratory blood tests are especially indicated when the ON has any atypical features.

The CSF in patients with ON may either be completely normal or show an elevated protein, mild lymphocytosis, elevated IgG index or oligoclonal bands.

**Table 1.** The differential diagnosis of optic neuritis

| Disease | Clinical Features | Investigations |
|---|---|---|
| Ischemic Optic Neuropathy (46)<br>• Arteritic (Giant Cell Arteritis)<br>• Non arteritic (NAION) | • Older age<br>• Painless visual loss<br>• Altitudinal visual field loss<br>• Optic disc swelling or hemorrhages<br>• Relative afferent pupillary defect<br>• In AION, malaise, headache, scalp tenderness and tender temporal arteries, jaw pain on mastication (jaw claudication), generalized muscle aches, and swelling<br>• Poor prognosis for recovery | • Elevated ESR and CRP<br>• Temporal artery biopsy shows characteristic inflammatory infiltrate that has a granulomatous appearance, sometimes with giant cells |
| Leber's Herediatary Optic Neuropathy (27-29) | • Males<br>• Painless blurring of central vision with a large centrocecal scotoma<br>• Contralateral eye follows in 6 months.<br>• Pale disc with telangiecatasic vessels<br>• Prognosis for recovery is poor | • 70% of patients have a point mutation in the mitochondrial DNA mutation G11778A<br>• Two other mitochondrial mutations have been reported also to be associated with this defect |
| Neuroretinitis (47) | • Cat-scratch disease<br>• Fever, regional lymphadenitis and painless visual loss<br>• Papillitis and macular star<br>• Different antibiotic regimes targeted against Bartonella | • Serologic testing for antibodies against Bartonella henselae |
| Vitamin Deficiency (31-33)<br>• B1<br>• B2<br>• B12<br>• B6<br>• Niacin<br>• Folic acid | • Both eyes simultaneously<br>• Central or cecocentral scotomata with preservation of the peripheral field<br>• No afferent pupillary defect as both eyes are involved<br>• Optic discs may appear normal or be slightly hyperemic | • Vitamin levels<br>• Complete blood count<br>• MRI may be normal |
| Susacs's Syndrome (48, 49) | Triad of<br>• Encephalopathy<br>• Branch retinal artery occlusion<br>• Sensorineural hearing loss | • MRI picture similar to MS but with "snowballs" in the corpus callosum |
| Toxic (31-33)<br>• Alcohol<br>• Methanol<br>• Tobacco<br>• Ethambutol<br>• Toluene | • Both eyes simultaneously<br>• Central or cecocentral scotomata with preservation of the peripheral field<br>• No afferent pupillary defect as both eyes are involved.<br>• Optic discs may appear normal or be slightly hyperemic | • Complete blood count<br>• Blood chemistries<br>• Urinalysis<br>• Toxicology screen<br>• MRI may be normal |
| Neuromyelitis Optica (11-15, 30, 50) | • Bilateral optic neuritis and myelitis | • MRI shows increased signal intensity spanning several sections of the spinal cord on T2-weighted images and with gadolinium enhancement<br>• Cerebrospinal fluid shows pleocytosis<br>• Serum neuromyelitis optica antibody in 70% of cases |
| Sarcoid (51) | • Optic disc edema<br>• Optic disc infiltration<br>• Uveitis<br>• May present with systemic/pulmonary symptoms | • Abnormal chest-X-Ray showing lymphadenopathy<br>• Elevated ACE level<br>• Abnormal bone gallium scan |
| Papilledema from elevated intracranial pressure (52)<br>• Tumor<br>• Cerebral venous thrombosis<br>• Meningitis<br>• Pseudotumor cerebri | • Bilateral<br>• Headache<br>• Nausea/vomiting<br>• Transient visual obscurations<br>• Tinnitus<br>• Normal acuity<br>• No afferent papillary defect | • MRI of brain and spine<br>• Lumbar puncture unless contraindicated to measure opening pressure and determine composition |

The ONTT has prospectively followed patients who had initial CSF examination (53). 83 patients with clinically isolated ON had their CSF sampled for cell count, IgG index and oligoclonal bands. At two years, among the 13 patients who converted to Clinically Definite Multiple Sclerosis (CDMS), 11 were found to have CSF oligoclonal bands at baseline. These same 11 patients also had abnormal baseline brain MRIs that were suggestive of dissemination of demyelination in space. There were two patients who went on to develop MS at two years who had initially normal baseline MRI, but with oligoclonal bands present in the CSF. The consensus was that the examination of CSF did not provide any additional information to that provided by neuroimaging. Thus, routine CSF examination on patients with ON was felt to be unnecessary in typical cases (34, 53-55). At 5 years, 76 patients in the ONTT showed an association between the presence of CSF oligoclonal bands at baseline and

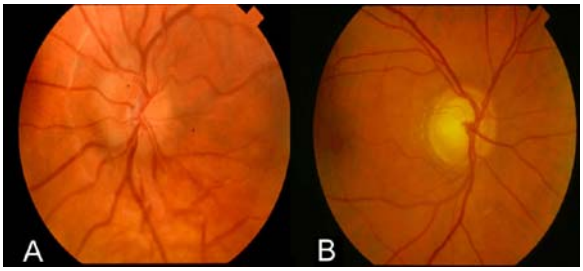


**Figure 2.** A. Optic neuritis involving the anterior part of the optic nerve (left eye) demonstrates swelling with obscuration of the disc margins. B. Note the healthy optic nerve (right eye) with sharp disc margins in the adjacent image from a different patient for comparison.

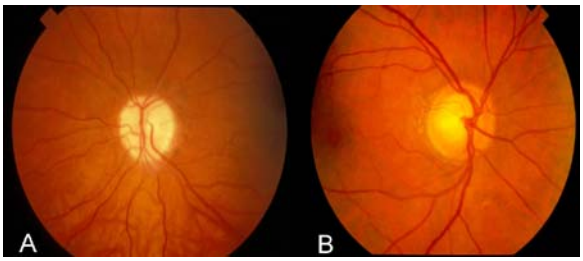


**Figure 3.** A. Chronically, one observes a pale optic disc in patients who had optic neuritis symptoms in the past (right eye). B. Note the healthy right optic nerve in the adjacent image from a different patient for comparison.

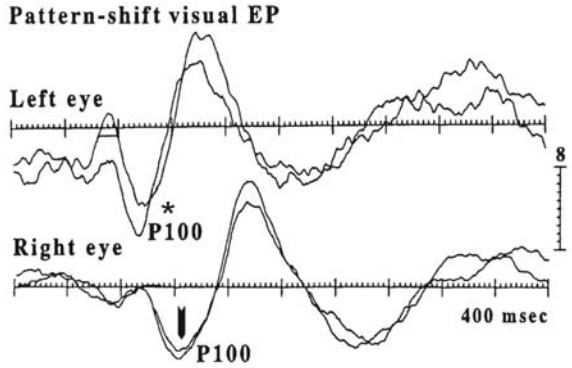


**Figure 4**. Visual evoked potentials use a checkerboard pattern as a visual stimulation to measure the conduction from the retina to the occipital cortex. The x axis is time in milliseconds and the y axis is the amplitude of the response in microvolts. The visual evoked potentials displayed here are from a patient with a 2 month history of cloudy vision in the right eye, with an acuity of 20/40 and a pale disc, who was diagnosed with a unilateral optic neuritis. The left eye was found to have an acuity of 20/20. The visual evoked potential shows the characteristic increase in P100 latency on the affected side. Note in the lower tracings from the right eye, there is an abnormal latency in the P100 peak (arrow) of 125 msec compared to the P100 peak in the left eye of 96 msec (asterix).

conversion to MS (p=0.02) (56). However, many of these patients also had brain MRI which demonstrated baseline dissemination in space, and thus it was felt that CSF examination was helpful for prediction of MS when the initial baseline MRI was negative (56). Ghezzi *et al.* showed that patients with ON and an elevated CSF IgG index and abnormal brain MRI had a 46% increased chance of developing MS in 4 years compared to the 33% risk of patients with ON who had only an abnormal brain MRI (57). In general, CSF analysis is only helpful when considering infectious or other inflammatory diseases that may present with systemic symptoms in the context of ON, and need not be done as part of a routine investigation in a patient with typical ON (57).

After ON has resolved entirely, one may continue to see abnormalities on the visual evoked potentials, as is seen in 65% of patients (Figure 4) (58). Abnormalities on visual evoked potentials are helpful in both localizing and providing the information on the type of process affecting the optic nerve. Unilateral delay and decreased P100 amplitude are suggestive of an abnormality anterior to the chiasm that is demyelinating in origin but is not entirely specific for the underlyling cause. It is important to keep in mind that, when the acuity has been severely affected in the acute phase, it is possible that visual evoked potentials cannot adequately be performed, given that some acuity is required to cooperate with the test. Visual evoked potential abnormalities may also contribute to International Panel Diagnostic Criteria, as paraclinical criteria of dissemination in space in the central nervous system, supporting the diagnosis of MS (59-63).

Brain MRI is helpful to exclude other causes of ON and to assess the risk of converting to MS, which may have an effect on the decision to start disease modifying therapy.

### 6.1. Conventional MRI measures

MRI findings in the optic nerve are non-specific, and cannot reliably distinguish ischemic, infectious or radiation-induced optic neuropathies from ON. An example of MRI findings in acute ON is shown in Figure 5. The most useful conventional sequences to image the optic nerve are: 1) short tau inversion recovery (STIR); 2) fast spin echo (FSE) T2-weighted images; and 3) spin-echo T1 pre and post gadolinium fat suppressed sequences (60, 64-68). Thin sliced (e.g. 3 mm) multiplanar (axial and coronal) (Figure 5) images and higher strength scanner fields (3T) are recommended.

STIR sequences suppress the intraconal fat, and are thus helpful for identifying inflammatory demyelination in the optic nerves. ON manifests on T2-weighted and STIR as hyperintensity within the nerve. Acute inflammatory changes, edema, demyelination, axonal loss and chronic gliosis cannot usually be distinguished by the appearance on T2-weighted or STIR images. Swelling of the nerve may also be seen (Figure 5). Miller *et al.* studied STIR sequences in acute ON, and noted that lesions were detected in 84% of affected optic nerves and in 20% of unaffected nerves. The length of the optic nerve lesions was positively correlated with the time to recovery or long term visual impairment (69).

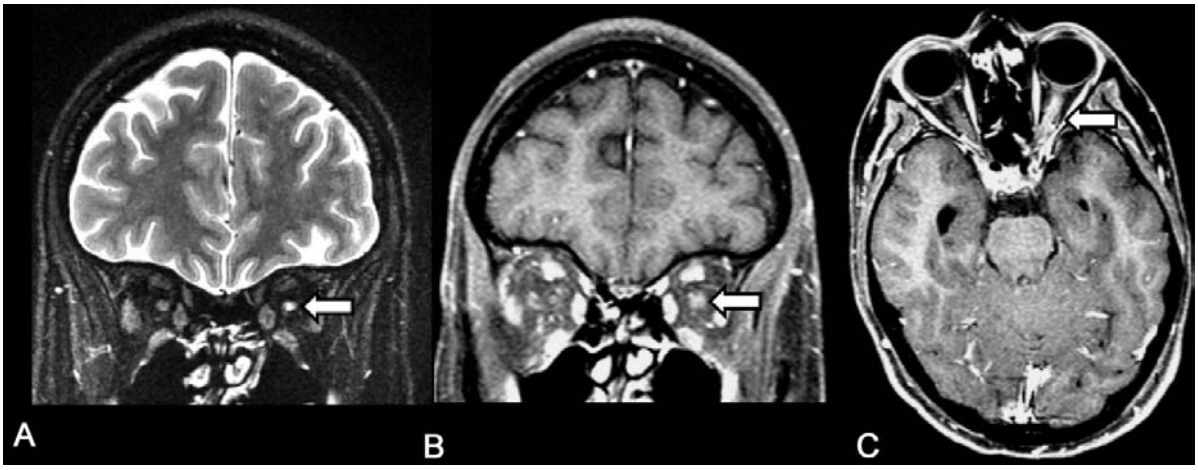


**Figure 5.** MRI findings in acute optic neuritis involving the left optic nerve: A. Coronal short tau inversion recovery sequence shows an increased signal in the left optic nerve (arrow) compared to the fellow right optic nerve. B. Contrast-enhanced spin echo T1-weighted, fat-suppressed coronal MRI through the orbits shows enlargement and contrast enhancement of the left optic nerve (arrow). C. Contrast-enhanced spin echo T1-weighted, fat-suppressed axial MRI through the orbits shows enlargement and contrast enhancement of the left optic (arrow).

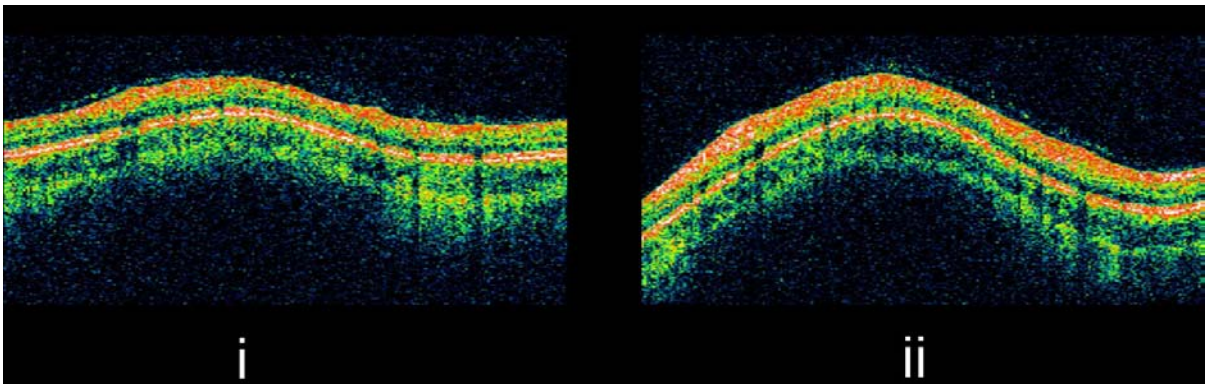


**Figure 6.** Using optical coherence tomography, one notes that the cross-sectional retinal nerve fiber layer thickness in the left eye (i) is reduced after optic neuritis, compared to the normal cross-sectional view of the retinal nerve fiber layer thickness in the healthy right eye (ii).

Gadolinium adds sensitivity to the diagnosis of optic nerve disease, and should be part of the evaluation of suspected ON. Usually, gadolinium-enhancing lesions, reflecting inflammatory infiltration from the systemic circulation, are solitary or multifocal and can be located centrally within the nerve or at its periphery (Figure 5). There is conflicting data regarding the relationship between enhancing baseline optic nerve length and recovery of visual function. Using a single dose gadolinium MRI protocol, a retrospective review of 93 out of a cohort of 107 patients followed for six months after onset of ON did not find an association between acute enhancing lesion length or location of lesion enhancement and visual outcome (70). Using a triple dose gadolinium MRI protocol, 27 out of 28 patients with ON showed lesion enhancement on the MR, although it was not compared to single dose gadolinium. The duration of enhancement did not predict outcome in this study, although there was an association between initial post gadolinium lesion length and poorer visual outcome (70). The investigators concluded that although the cost and safety issues related to triple-dose gadolinium may be prohibitive, measuring the initial lesion length may have prognostic value (70).

### 6.2. Emerging MRI measures

#### 6.2.1. Optic nerve atrophy

The optic nerve diameter in patients who have had ON depends on the stage of the illness. In the acute stage where the optic nerve is edematous, inflammation may lead to an enlargement ("swelling") of the affected optic nerve (Figure 5). As the disease evolves, inflammation decreases, but demyelination may continue and axonal loss ensues, leading to optic nerve atrophy (68). Hickman *et al.* studied the optic nerve diameter using FLAIR MRI in patients with ON at a median time of 19.5 months after the event. There was an association noted between optic nerve atrophy, poor visual recovery and reduced visual evoked potential amplitude (71). In another study of 21 patients, the mean optic nerve diameter for the diseased nerve in the acute phase was 16.1 $mm^2$, compared

to 13.4 $mm^2$ in the contralateral eye and 13.6 $mm^2$ in the healthy control. The optic nerve that was swollen eventually became reduced in diameter (72, 73). Thus, MRI may provide useful information on the phase of the ON and allow a long-term assessment of the overall destruction of the nerve and, in turn, the severity of the insult.

**6.2.2. Magnetization transfer**

Magnetization transfer (MT) MRI allows a quantitative measure of macromolecular density and is thought to have a higher pathologic specificity than conventional T2-weighted imaging for cerebral demyelination in patients with MS (74). A low MT ratio (MTR), as typically seen in both lesions and normal appearing brain tissue in patients with MS, indicates a reduced ability of macromolecules in tissue to exchange magnetization with water molecules, which reflects primarily inflammatory demyelination and axonal loss. Recovery of MTR suggests remyelination or resolution of inflammation/edema (68, 75). Thorpe *et al.* studied MTR of the optic nerves of 20 patients with ON and 6 healthy controls (75). The optic nerve MTR was reduced in patients who had ON, compared to the contralateral healthy eye from the same patients ($p<0.005$), and was also reduced compared to the MTR of healthy controls ($p<0.005$). The increase in the visual evoked latency correlated inversely with the MTR of the optic nerve, suggesting that the reduction in the MTR in ON may be primarily reflective of demyelination and axonal function (68, 75). By providing information about the evolution of ON and by serving as a quantitative tool to assess inflammatory demyelination, MT deserves further study to provide a useful non-invasive surrogate of the underlying disease process. Future studies should address technical challenges and standardization issues related to inter-institutional comparison of MTI data.

**6.2.3. Diffusion-tensor imaging (DTI)**

MRI diffusion-tensor imaging (DTI) measures mean diffusivity (MD) and fractional anisotropy (FA) of water molecules pertinent to the study of the integrity of axonal fibers. Demyelination in the optic nerve and cerebral white matter is associated with MD and decreased FA. Trip *et al.* performed DTI measurements of the optic nerves in 25 patients who had a unilateral ON in the previous year and 15 healthy controls (76). Compared to both the contralateral healthy eye and the healthy controls, the optic nerve affected by ON demonstrated increases in the mean MD ($p<0.001$) and decreases in mean FA ($p<0.001$). DTI measurements did not correlate with visual function, but significant inverse correlations were found between the visual evoked potential amplitude and the MD in the affected eye (68, 76). Thus DTI can potentially provide important information about the integrity of the axons in the optic nerve, which may be useful to follow both in a cross-sectional and in a longitudinal fashion, with an ultimate goal to provide a surrogate for axonal injury related to the disease (77). Much like with MTI, future studies should address technical challenges and standardization issues related to inter-institutional comparison of DTI data. DTI tractography of the ON and related structures is an emerging field (76, 78).

**6.2.4. Functional MRI**

Blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) is an imaging modality that makes use of the magnetic properties of blood oxygen to map out specific areas of the brain related to specific functions (79). In response to neuronal activity, the blood flow to the area of the brain increases, causing an increase in the ratio of oxygenated hemoglobin to deoxygenated hemoglobin compared to the resting state. Deoxyhemoglobin is paramagnetic, thus affecting the magnetic field, causing the MRI signal to decay faster on a T2 or T2* weighted pulse sequence. Therefore, the activated region with increased blood flow will show an intravascular net loss of deoxyhemoglobin, resulting in an overall increase in signal in the activated region on MRI. In an activated area of the brain, an increase in oxygenated hemoglobin causes an increase in the local T2* intensity in the area, which is picked up as a change in BOLD fMRI signal (79-81). In response to a local injury in the brain, neurons may recruit other areas or form new connections to compensate for the injury or to limit disability. This process has been labeled "neuronal plasticity." As fMRI allows one to study alterations in brain activation, it permits researchers to indirectly study neuronal plasticity by inferring patterns of functional changes in the brain activation in response to cerebral insults such as ON and MS, when compared to healthy controls (79-86).

fMRI has been used to study the brain response and brain reorganization in patients with ON. Patients with unilateral ON showed a reduced activation of the occipital cortex, compared to healthy controls, when the ipsilateral eye is stimulated. Decreased occipital activation was seen also in patients when the contralateral eye was stimulated, compared to healthy controls (82-84). The reduced activation of the occipital cortex is thought to be related to demyelination, axonal injury, axonal loss, and tract degeneration along the affected optic nerve and connecting pathways (85).

Werring *et al.* studied the functional brain reorganization in patients who recovered with normal acuity from an isolated episode of unilateral ON (86). Visual stimulation of the affected eye caused a decreased activation in the visual cortex, with an activation in the insula-claustrum, lateral temporal, thalamus and posterior parietal area. This contrasted with the results of stimulation in the contralateral unaffected eye, which produced activation of the visual cortex and right insula-claustrum. Compared to patients with ON, healthy controls who underwent visual stimulation demonstrated visual cortices activation. These results suggest that a functional reorganization of the cerebral cortex occurs after ON, which may be needed as part of the recovery process (68, 80, 81, 86). fMRI may offer a means to predict and track visual recovery in patients with ON and help to design optimal rehabilitation strategies, although further study is required.

**6.2.5. Optical coherence tomography**

Optical coherence tomography (OCT) is an emerging technology used to quantify the thickness of the

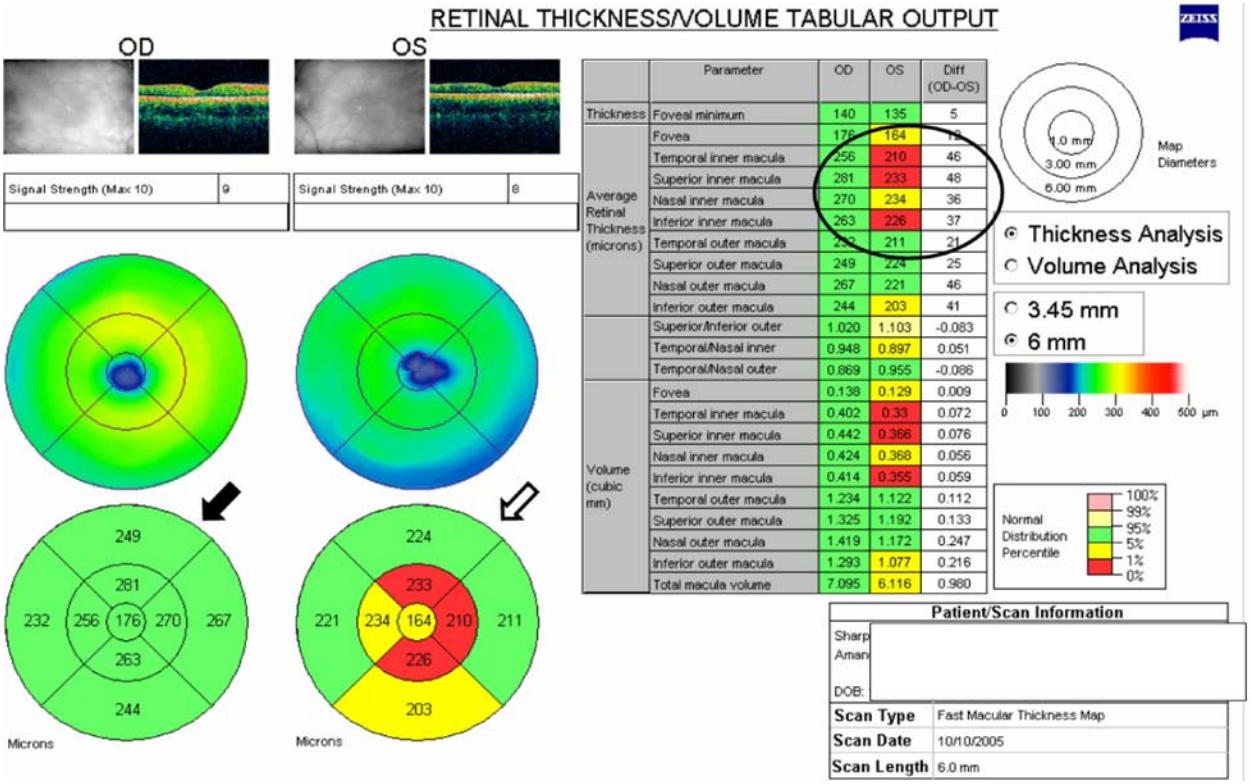


**Figure 7.** Macular centered optical coherence tomography measurements show average retinal nerve fiber layer thickness in both maculas, in a patient with left optic neuritis who has a healthy right optic nerve. Quadrant measurements of the average thickness of the retinal nerve fiber layer thickness for both the right and left eye were categorized on a color diagram based on a normal distribution database of age matched healthy controls. In the right eye (black arrow), the average retinal nerve fiber layer thickness is within the 5th-95th percentile range for all quadrants. The left eye (white arrow) indicates that retinal nerve fiber layer thickness falls into the 0-1$^{st}$ percentile range in three quadrants (superior inner macula, inferior inner macula, temporal inner macula), confirming nerve fiber layer loss. The average thickness measurements of each area are shown in the table (oval) for the right eye (OD), left eye (OS) and the difference between the right and left eye (OD-OS).

retinal nerve fiber layer (RNFL) in the optic nerve in patients with MS. The RNFL axons originate from the retinal ganglion cells (87). As the RNFL passes through the lamina cribosa and becomes myelinated, it forms the optic nerve. The RNFL lacks myelin; therefore, thinning of the RNFL suggests there is axonal loss occurring. In ON, the RNFL may be affected. OCT allows one to measure the thickness of RNFL after an episode of ON to assess the axonal loss in the optic nerve in a non-invasive fashion (Figure 6, 7, 8). OCT measures the thickness of RNFL by measuring the "delay from back scattered infrared light using an interferometer and a low coherence light source" (88). Compared to ultrasound, it has a higher spatial axial resolution of 10 micrometers. In primate models, ON leads to transaction of axons, and eventually to retrograde RNFL loss and loss of the retinal ganglion cells (89). The study of axonal loss is key for studying MS, as it is proposed that axonal loss is a main feature behind the neuropathology associated with MS, which further contributes to the disability associated with the illness (90). Ultimately, OCT serves as a potential model for studying axonal loss in patients with MS via the examination of the RFNL.

Trip *et al.* performed a cross sectional study of the mean RFNL thickness from 25 patients and 15 healthy controls. The patient group was composed of 11 patients with MS by Poser criteria and 14 patients with isolated ON. The mean RNFL widths were reduced in the affected optic nerves compared to both the healthy contralateral eye and the control eye. A decrease in RNFL was also correlated with certain measurements of visual function, including visual field, visual acuity and color vision (91).

Sepulcre *et al.* examined 61 MS patients and healthy controls in a prospective fashion over 2 years, using OCT. Baseline temporal RNFL atrophy was present in MS patients with and without ON. The RNFL atrophy was also associated with future relapses and increases in the Expanded Disability Status Scale, and was correlated with both white and gray matter atrophy (92).

Trip *et al.* studied the optic nerves of 25 patients with monophasic ON and 15 controls over one year, using MRI to measure the cross section and length of the ON and VEP waveform, and using OCT to measure the RNFL thickness. The MRI measures of optic nerve atrophy correlated with RNFL thinning, visual acuity, and VEP

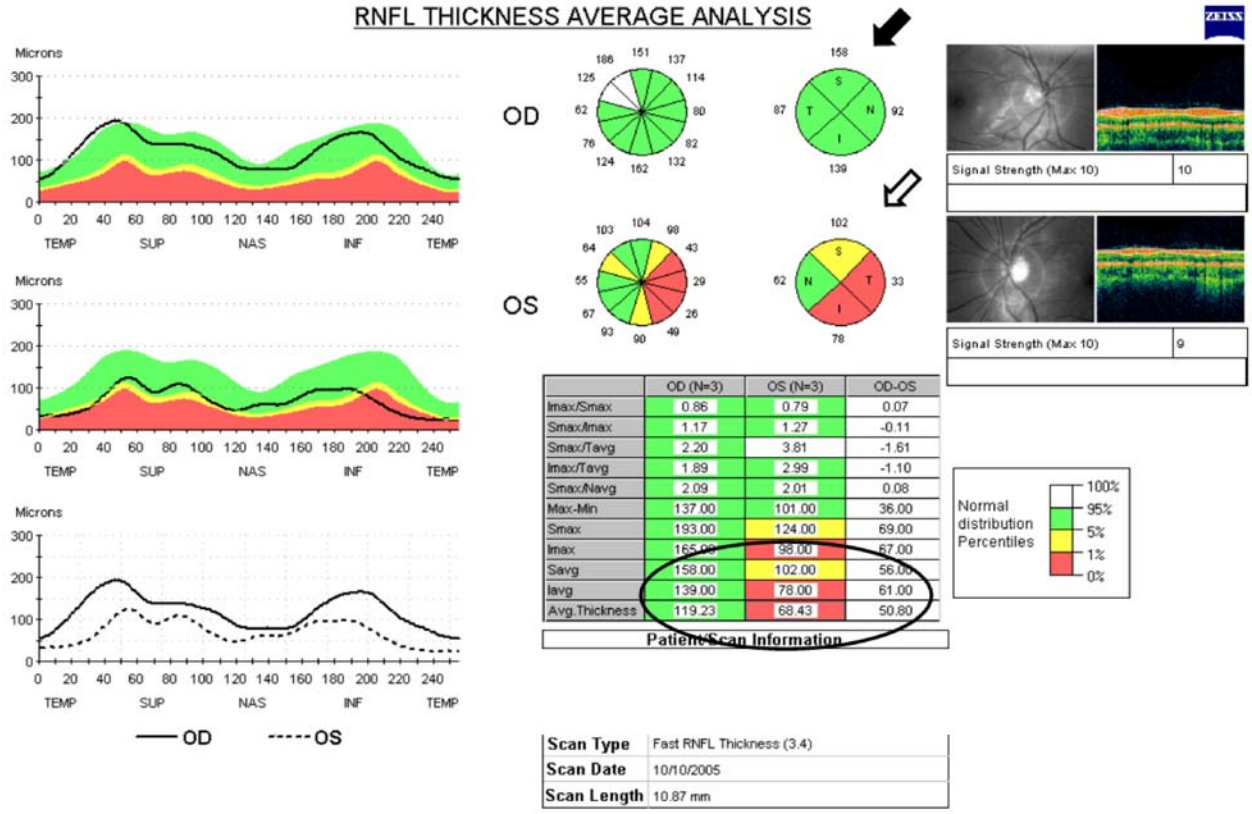


**Figure 8.** Optic nerve centered optical coherence tomography measurements showing average retinal nerve fiber layer thickness in both optic nerves, in a patient with left optic neuritis who has a spared right optic nerve. Quadrant measurements of the average thickness of the retinal nerve fiber layer thickness for both the right and left eye were categorized on a color diagram based on a normal distribution database of age matched healthy controls. In the right eye (black arrow), the average retinal nerve fiber layer thickness is within the 5th-95th percentile range. The left eye (white arrow) demonstrates that the average thickness falls into the 0-1st percentile range in two quadrants (inferior, temporal), confirming nerve fiber layer loss. The average thickness measurements of the retinal nerve fiber layer are shown in the table (oval) for the right eye (OD), left eye (OS) and the difference between the right and left eye measurements (OD-OS).

amplitudes. The authors posited that these correlations suggest that axonal loss as seen in patients with ON was likely responsible for the optic nerve atrophy seen over time in MRI studies (93).

Some of the main challenges of the use of OCT are the lack of guidelines and lack of uniformity across clinical and research centers for patients with ON (88). Further studies are needed to assess a greater longitudinal follow up in patients with ON, and to determine how the thickness of the RNFL correlates with optic nerve functions such as acuity and color saturation over time. Further correlation studies between the RNFL thickness and autopsy studies where axons in the optic nerve may be counted are also needed**.** Moreover, further studies need to be done to determine if OCT can eventually be used in addition to the current laboratory supported criteria to diagnose MS. OCT may become a surrogate marker for axonal loss, and may eventually be used as part of therapeutic trials in ON to assess response to therapy and outcome. Given that OCT is a non invasive tool to study the integrity of the axons, it may also be used as part of clinical and research studies to follow patients with ON.

## 7. TREATMENT

The American Academy of Neurology practice parameter has summarized the views regarding treatment of acute ON. High dose intravenous (IV) methylprednisolone may accelerate visual recovery in patients with acute ON, but is thought to have little impact on long term visual outcome. When taking into account the decision to use this IV methylprednisolone treatment, one must weigh benefits of this treatment with other non evidence based factors such as quality of life, risk, and visual function in the unaffected eye (94). It was emphasized in this practice parameter that oral prednisone in a dose of 1mg/kg should not be used in patients with ON, as oral prednisone was shown to be associated with an increased risk of repeat ON among patients in the first 2 years at follow-up (30 percent in the oral prednisone group compared to 13 percent for patients receiving intravenous methylprednisolone and 16 percent for those receiving placebo) (94).

The recommendation regarding IV methylprednisolone is based on the ONTT, which randomized patients with acute ON into three arms: 1) IV

**Table 2.** FDA-approved drugs for clinically isolated syndromes which included optic neuritis

| Brand Name | Generic Name | Frequency of Injection | Name of Study | Results |
|---|---|---|---|---|
| Avonex | Interferon beta-1a | Once a week | CHAMPS (101) | At three years, risk of MS in treated group lower (35%) compared to the placebo group (50%). |
| Rebif | Interferon beta-1a | Three times a week | ETOMS (102) | At two years, risk of MS in treated group lower (34%) compared to the placebo group (45%) |
| Betaseron | Interferon beta-1b | Every other day | BENEFIT (103) | At two years, risk of MS in treated group lower (38%) compared to the placebo group (45%) |

methylpredisolone at 250 mg every 6 hours for 3 days, followed by 11 days of oral prednisone at 1mg/kg/day, followed by a 4 day taper; (2) oral prednisone at 1mg/kg/day for 14 days, followed by a taper over 4 days; and (3) oral placebo (95). By day 15, patients treated with IV methylprednisolone had a greater improvement in visual recovery compared to the other groups; however, the difference between the groups with respect to visual function was not seen one year later. The oral prednisone group showed no improvement in visual outcome compared to the other arms of the study, and also had a negative impact on the risk of recurrence of ON in the ipsilateral and contralateral eye both at 6 months (95) and at 10 years (96). The ONTT study group postulated that the dose of steroids -- and not the route (oral versus IV) -- had a different immunologic effect on the CD4+ versus CD8+ T-Cells, which accounted for the differences in outcome (97).

Randomized trials have shown that intravenous immunoglobulin is ineffective in the treatment of patients with ON with respect to long term visual outcome (98, 99).

Intravenous methylpredisolone may also delay the diagnosis of MS in the short term. The ONTT showed that 7.5% of patients who received intravenous methylprednisolone for ON had developed MS at 2 years, compared to 16.7% in the placebo group and 14.7% of patients in the oral prednisone group. Among a subgroup of patients who had 2 or more white matter lesions, 16.5% of patients who received intravenous methylprednisolone for ON had developed MS at 2 years, compared to 35.9% in the placebo group and 32.4% of patients in the oral prednisone group; however after two years there was no significant difference in the rate of MS among the groups (100).

To date there are three randomized, double-blind placebo-controlled trials showing that disease modifying therapies in patients with clinically isolated demyelinating syndromes such as ON who have at least 2 or more white matter lesions on brain MRI are clinically effective at reducing the development of MS (Table 2).

Based on CHAMPS (101), ETOMS (102), and the BENEFIT (103) trials, patients are often started on one of the disease modifying drugs after an episode of ON with evidence of dissemination of disease on brain MRI in order to reduce the chance of a second neurologic event and to delay the conversion to MS. However, many patients with ON will not develop MS, even when the brain MRI is abnormal at baseline. Also it should be kept in mind that each of these therapies are only partially effective in preventing the onset of MS and some physicians and patients may choose to delay therapy until the patient manifests a clear second attack of demyelination separated in space and time from the initial ON according to the International Panel and new criteria (61-63). The final decision regarding timing and choice of therapy should be based on a frank and open discussion with a well informed patient weighing risks and benefits.

## 8. PROGNOSIS

Short-term and long-term prognosis for both visual recovery and risk of MS is often guided by the results of the ONTT and its subsequent 10 year follow up.

Based on the ONTT, 93% of patients had recovery of vision by 5 weeks. At 1 year, 91% to 95% of patients had improvement to a visual acuity of 20/40 or more (104). At 10 years, visual acuity was greater or equal to 20/40 in 92% of patients in all three treatment groups (intravenous methylprednisolone, oral prednisone, and placebo) (4, 96). At 10 years, the risk of recurrence of ON in the ipsilateral eye was 14%, 12% in the contralateral eye, 9% in both eyes, and 35% in either eye (4). Celesia *et al.* reported complete recovery of visual function in two thirds of patients followed for a year from the time of onset. Most patients recovered in the first two months, but many went on to show continuing improvement in vision even up to six months from onset (105).

The future risk of MS is based on the time from the initial onset of ON and the baseline MRI of the brain. For all patients with ON, the 5 year risk of MS is 30%, whereas the 10 year risk of MS is 38% (4, 96, 106). The number of lesions appears to correlate with the risk of MS at 5 years, but the same direct correlation is not seen at 10 years. At 5 years, patients with zero, one to two, or three or more lesions demonstrated a risk of MS of 16%, 37%, and 51%, respectively. At 10 years, patients with zero, one lesion, or two or more lesions demonstrated a risk of MS of 22%, 52%, and 56% respectively. When comparing the 10 year risk among the cohorts, the risk of MS at 10 years was statistically significantly higher in patients with 1 or more T2 lesions seen on the initial brain MRI compared to patients with no lesions ($p<0.001$, log rank test). The probability of developing MS in patients with one lesion compared to patients with greater than one brain lesions was not significantly different ($p=0.22$, log rank test) (4). Other than the lack of MRI findings, being male, having papillitis, bilateral ON, no light perception, lack of pain, and peripapillary hemorrhages are associated with a lower risk of developing MS (4, 96, 106). The longest observational study followed a cohort of 86 patients with ON for up to 31 years; Nilsson *et al.* found that 40% of patients progressed to MS. The vast majority of those who

converted to MS did so within three to five years of onset of ON (60% within three years). Only one patient progressed to MS after 15 years of follow-up (107).

## 9. PERSPECTIVE

When approaching a patient with a painful unilateral loss of vision, a careful history and an ophthalmologic and neurologic exam are mandated. Neuroimaging and other laboratory testing may also be indicated to guide diagnosis and therapeutic strategies. Clinicians should keep in mind the mimics of ON and recognize atypical features. Brain MRI allows one to stratify two groups of patients with ON: patients with a normal MRI and those with evidence of multifocal white matter disease, increasing the risk for conversion to MS. Although, in the short-term, intravenous methylprednisolone may accelerate the rate visual recovery, it has no clear long-term effect on the magnitude of visual recovery. Patients with multifocal white matter involvement on MRI in the presence of acute ON should be informed of the future risk of MS. This should open the door for future discussions of the pros and cons of disease modifying therapy and, at minimum, the need for diligent clinical and neuroimaging follow up.

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