Optic Nerve Disorders
Optic Nerve Disorders

Diagnosis and Management

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This book is dedicated to my parents, Tom and Rosalie Chan—especially to my mother for her unconditional love and support. I also appreciate my mentors, Drs. William F. Hoyt, John L. Keltner, and David P. Richman, who have given me guidance in my career.
Preface

This book presents the salient features of optic nerve disorders, encompassing optic neuritis, papilledema, ischemic optic neuropathies, compressive and infiltrative optic neuropathies, traumatic optic neuropathies, nutritional and toxic optic neuropathies, hereditary optic neuropathies, and optic disc tumors. Chapters 1 to 9 outline key clinical aspects of each of these disorders. Chapter 10 illustrates some newer applications of optical coherence tomography (OCT) in monitoring optic nerve-related processes causing retinal nerve fiber layer loss and in ruling out retinal disorders. Chapter 11 discusses the adjunctive role of visual evoked potential (VEP), multifocal VEP, electroretinogram (ERG), and multifocal ERG in the diagnosis of more challenging visual problems, especially in distinguishing them from macular disorders and psychogenic etiologies.

Although there are excellent textbooks covering various aspects of neuro-ophthalmology, this book is intended for any physician, including ophthalmologists, neurologists, and neurosurgeons. Fellows, residents, and medical students can acquire an up-to-date knowledge base to better help their patients with optic nerve disorders. It is a unique reference that combines the applications of some newer diagnostic techniques with the symptoms and signs approach to visual loss in a useful and practical format.

Jane W. Chan, MD
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Optic Neuritis

Jane W. Chan

Introduction

Although neurologists usually diagnose and treat multiple sclerosis, the visual loss that often accompanies this disease often presents to an ophthalmologist or neuro-ophthalmologist for evaluation. It is an inflammation of one or both optic nerves resulting in (usually) temporary visual loss. It affects young to middle-aged adults between 16 and 55 years of age. The female-to-male ratio is 2:1. Children often are affected bilaterally, whereas adults are affected unilaterally. The annual incidence of acute optic neuritis has been estimated in population-based studies to be between 1 and 5 per 100,000. Clinically definite multiple sclerosis (CDMS) is apparent at the onset of optic neuritis in 15% to 20% of patients with optic neuritis; another 40% will later experience a multiple sclerosis attack. The clinical diagnosis and advances of understanding the pathogenesis and current recommended treatment of this disorder are outlined here.

Clinical Presentation of Optic Neuritis

Symptoms

The loss of central vision is the major symptom reported in more than 90% of patients who have acute optic neuritis. Others who have normal visual acuity may complain of loss of peripheral vision to one side in the superior or inferior fields. The patient usually experiences mild orbital pain above or behind the eye, but the pain is mild even with severe visual loss. This dull retrobulbar pain may precede or occur concurrently with the visual loss. It also may be aggravated by upward eye movement and may occasionally last for as long as several weeks. The optic nerve inflammation may stimulate the trigeminal innervation of the optic nerve sheath to cause this orbital pain. As visual acuity decreases over the next several days, the pain usually subsides when visual loss is maximal. Loss of color vision or dullness in the vision is also more commonly noticed by patients than photophobia. Other less common symptoms are perception of phosphenes (flashing lights with noise or eye movement) and decreased depth perception.

Signs

Visual Acuity

Visual acuity worsens over several hours, days, or even minutes and ranges in severity from 20/20 to no light perception. The degree of visual loss does not correlate with the final visual outcome. Visual loss usually peaks at several days to a week. Maximal improvement in visual function typically occurs within 2 to 3 weeks and at most within 6 months or more.

Visual Field

Patients who have acute optic neuritis can present with a wide variety of visual field
defects, most commonly a central scotoma. Less frequent defects may include an arcuate scotoma, a superior or inferior altitudinal scotoma, peripheral constriction, a cecocentral scotoma, and bitemporal or a left or right hemi-anopic defect. In the Optic Neuritis Treatment Trial (ONTT), this wide variety of baseline patterns of visual field loss had limited usefulness in differentiating optic neuritis from other optic nerve disorders. During the recovery phase, the central scotoma reduces to a small, dim, central or paracentral defect. Occasionally, an arcuate scotoma may persist. Less severe optic neuritis may cause only “blurry vision” and a relative scotoma that eventually resolves. Because of the Uhthoff phenomenon, as is discussed later, patients whose optic neuritis have resolved can have large variations in visual field results on different days and at different times on the same day.

**Contrast Sensitivity and Color Vision**

Contrast sensitivity and color vision are both reduced in acute optic neuritis. The loss of contrast sensitivity is often proportionate to or sometimes worse than the loss of visual acuity. The color dysfunction is also usually more severe than the visual acuity level. Although Ishihara color plates are most commonly used in the clinic, the Farnsworth–Munsell 100-hue test has been shown to be more sensitive and specific. The shortened version with caps 22 to 42 has a similar sensitivity for serial monitoring of dyschromatopsia after optic neuritis. The dyschromatopsia is related to the time course of the disease. More blue-yellow defects occur in the acute stage of optic neuritis, whereas more red-green defects occur after 6 months. In the ONTT, no particular type of color vision defect was consistently associated with optic neuritis. The type of defect appeared to be inconsistent in individual patients as they recovered. The kind of color defect did seem to correlate with spatial vision at the time of testing, but the type of color defect at 6 months did not correlate with the severity of initial visual loss. Patients also have decreased sensation of brightness in the affected eye.

**Pupillary Abnormality**

The relative afferent pupillary defect is almost always present in anterior (swollen disc) or retrobulbar neuritis. If it is not present, then one should seriously consider other ophthalmic problems, such as a coexisting optic neuropathy in the fellow eye or other causes of visual loss unrelated to an optic neuropathy. Subclinical optic neuritis in the fellow eye is not uncommon. In the Optic Neuritis Study Group, 48% of patients who had unilateral optic neuritis and no prior optic neuritis in the fellow eye had an abnormal visual field in the asymptomatic eye. Approximately 68% of the asymptomatic fellow eyes had baseline visual field defects that mostly affected the peripheral rim or were diffuse; 62% of these visual field defects were classified as minimal. Most patients recovered normal visual field with varying pattern and location of sensitivity loss. Between 10% and 20% of these patients believed that their vision was normal, despite having abnormal visual acuity, color vision, or contrast sensitivity. These clinical abnormalities are consistent with the pathological evidence of demyelination and atrophy found in the optic nerves of patients who have subclinical optic neuritis.

**Fundus Findings**

Fundus findings also help to localize the site of the optic nerve lesion. Lesions that are adjacent to the optic nerve head cause papillitis (anterior optic neuritis) with minimal blood vessel enlargement and rarely peripapillary hemorrhages (Figure 1.1). Vitritis is present in anterior optic neuritis caused by infections or inflammations (sarcoidosis, syphilis, tuberculosis, Lyme disease) and may be associated with multiple sclerosis (MS) as part of an intermediate uveitis. More posterior lesions (retrobulbar optic neuritis) do not produce papillitis. Unilateral retrobulbar optic neuritis and papillitis both are part of the multiple sclerosis spectrum of presentation. In retrobulbar optic neuritis, the optic disc is normal. Irrespective of the location of the lesion, 75% of patients who have MS, including those who have had a previous subclinical attack, eventually develop diffuse or
temporal optic disc pallor and nerve fiber layer atrophy.\textsuperscript{5} The optic disc swelling and the disc pallor both are nonspecific findings in optic neuritis. Peripheral retinal venous sheathing may also be seen in MS, but this finding is not specific for MS as it may also be found in sarcoidosis, pars planitis, intermediate uveitis, lymphoma, and other localized ocular conditions. This sheathing represents the visible clinical sign of perivascular lymphocytic infiltration and edema of MS lesions. The vascular inflammation occurs in a region that lacks myelin and oligodendrocytes, suggesting that the vascular endothelium may be the initial site for the formation of new lesions. The presence of peripheral retinal venous sheathing has been shown to be correlated with the development of MS.\textsuperscript{15}

**Differential Diagnosis of Optic Neuritis**

The acute monocular visual loss suggestive of optic neuritis should alert the ophthalmologist and neurologist to consider vascular optic nerve disorders.\textsuperscript{16} Acute ischemic optic neuropathy (AION) is an infarction of the prelaminar anterior optic nerve as a result of an occlusion of the two main posterior ciliary arteries that supply the optic nerve and choroid. The orbital pain of MS-related optic neuritis, when it is severe and when it occurs or worsens during eye movement, is often a useful feature in differentiating acute optic neuritis from anterior ischemic optic neuropathy.\textsuperscript{17} A course that is painless and does not progress to significantly improved visual function (at least two lines of visual acuity improvement) after several weeks does not suggest optic neuritis.\textsuperscript{4} Furthermore, altitudinal rather than generalized disc swelling, disc pallor, arterial attenuation, and peripapillary hemorrhages are features much more commonly seen in AION than in optic neuritis.\textsuperscript{18} AION is much more common in patients who are older than 50 years and who have symptoms of giant cell arteritis and an elevated sedimentation rate.\textsuperscript{5} It may also occur independently of giant cell arteritis.

Another neuro-ophthalmic disorder to consider in the differential diagnosis of optic neuritis is Leber’s hereditary optic neuropathy (LHON). Males between 15 and 35 years of age are more commonly affected than females. Impairment of ganglion cell function results in visual loss that typically begins painlessly and

*Figure 1.1. The left optic disc (right) is normal, but the right optic disc (left) is mildly swollen, as seen in anterior optic neuritis. (Reprinted from Spalton et al.,\textsuperscript{14} with permission from Elsevier.)*
centrally in one eye followed by the second eye over days or months. Circumpapillary telangiectatic microangiopathy, swelling of the nerve fiber layer around the disc (pseudoedema), and absence of leakage from the disc or papillary region on fluorescein angiography are the key features distinguishing LHON from other causes of optic disc edema. Genetic testing for the mitochondrial DNA mutations 11778, 3460, and 14484 can also help confirm the diagnosis of LHON.

Other systemic infections, granulomatous inflammations, and autoimmune diseases besides MS may present with optic disc edema as part of a neuroretinitis, posterior uveitis, or posterior scleritis. Para-infection optic neuritis usually develops 1 to 3 weeks after the onset of a viral or bacterial infection. It is more common in children than in adults and may be unilateral, but it is more often bilateral. It is usually caused by demyelination associated with swollen optic discs. It may occur with no evidence of neurological dysfunction or with a meningitis, meningoencephalitis, or encephalomyelitis. Cerebrospinal fluid is usually abnormal when neurological manifestations are present. Visual recovery after para-infectious optic neuritis is often excellent. Postviral optic neuritis may be caused by underlying adenovirus, coxsackievirus, hepatitis A, and B, cytomegalovirus, Epstein–Barr virus (EBV), human immunodeficiency virus type 1 (HIV-1), measles, mumps, rubella, varicella zoster, and herpes zoster. Optic neuritis may also be seen in bacterial infections including anthrax, beta-hemolytic streptococcal infections, brucellosis, cat scratch disease, meningococcal infection, pertussis, tuberculosis, typhoid fever, and Whipple’s disease. Postvaccination optic neuritis is more often anterior and bilateral. It may develop after vaccination with Bacillus Calmette–Guerin (BCG), hepatitis B, rabies virus, tetanus toxoid, variola virus, and influenza virus. However, in a recent matched case-control study of 1131 patients in the U.S. military with optic neuritis, no statistically significant associations between optic neuritis and anthrax, smallpox, hepatitis B, or influenza vaccines were observed between 1998 and 2003.

In sarcoidosis, the optic neuritis may be anterior or retrobulbar; it can be the presenting feature or may occur during the course of the disease. In contrast to demyelinating optic neuritis, in sarcoidosis the optic disc may have a lumpy, white appearance that suggests a granulomatous reaction and may be associated with vitritis. Unlike the course of recovery in primary demyelinating optic neuritis, which is not steroid dependent, vision may decrease again in sarcoid once steroids are tapered or stopped. This steroid-dependent course of recovery is atypical for demyelinating optic neuritis and suggests an infiltrative or nondemyelinating inflammatory process, such as sarcoidosis.

Both anterior and retrobulbar optic neuritis may occur in HIV-infected patients with cryptococcal meningitis, cytomegalovirus (CMV) infection, herpesvirus infection, syphilis, tuberculous meningitis, and various fungal infections. HIV is capable of invading the optic nerve itself. Opportunistic infections usually occur with a low CD 4 count. CMV papillitis is necrotizing, and CMV inclusion bodies have been isolated in the optic nerve. Herpes zoster papillitis can precede outer retinal necrosis. Retrobulbar optic neuritis from herpes zoster can either precede or follow acute retinal necrosis, based upon a study of six patients with central nervous system (CNS) imaging abnormalities associated with retrobulbar optic neuritis that were temporally related to acute retinal necrosis. Optic neuritis related to Cryptococcus and toxoplasmosis usually presents concurrently with CNS infection.

Optic neuritis can be seen in patients with West Nile virus. It appears to be self-limited, and vision improves with or without corticosteroids over the course of several months. Diagnosis is based upon abnormal serum West Nile virus titers. Rarely, patients with toxoplasmosis may also develop optic neuritis. Optic neuritis in patients with autoimmunodeficiency syndrome (AIDS) may also represent infection of the optic nerve by HIV itself. Regarding spirochetal infections, both anterior and retrobulbar optic neuritis may be seen in patients with Lyme disease.
1. Optic Neuritis

In severe acute sphenoid sinusitis, the infection may spread posteriorly to the optic nerve in the orbital apex or within the optic canal, causing retrobulbar optic neuritis and acute visual loss.69

In neuroretinitis, intraocular inflammation itself may cause optic disc edema. Unlike the visual loss from damage to the optic nerve in demyelinating optic neuritis, the visual acuity is limited by the degree of vitreous inflammation or by secondary changes in the macula, such as cystoid macular edema, associated with optic disc edema after cataract extraction. Swelling of the peripapillary retina may be observed in patients with anterior optic neuritis. Lipid exudates in a star configuration may also develop in the macula of the affected eye. Neuroretinitis may be seen in infections involving *Borrelia burgdorferi* (cat scratch disease),70 toxoplasmosis,71 hepatitis B,72 and influenza.73 Syphilis can cause both neuroretinitis and optic perineuritis, which are seen more frequently as part of syphilitic meningitis.74 Coxackievirus infection may also cause an optic neuritis or neuroretinitis.75

In posterior uveitis, optic disc edema and profound visual loss may occur with inflammation of the retina and choroid. Posterior uveitis may be associated with some form of systemic disease. The bacterial infections include *Treponema pallidum*,76 *Borrelia burgdorferi*,77 *Leptospira interrogans*,78 *Brucella*,79 *Nocardia asteroides*,80 *Mycobacterium tuberculosis*,81 and *Neisseria meningitides*.82 Viruses causing posterior uveitis include cytomegalovirus,83 herpes simplex,84 herpes zoster,85 rubella,86,87 rubeola,88 and HIV.89 Parasites, such as *Toxoplasma*,90 *Toxocara canis*,91 and *Onchocerca volvulus*,92 and fungi, such as *Candida*,93 *Histoplasma capsulatum*,94 *Cryptococcus neoformans*,95 *Aspergillus*,96 *Coccidioides immitis*,97 and *Blastomyces dermatitides*,98 may also cause optic disc edema in the clinical setting of posterior uveitis.

In the setting of autoimmune-related posterior uveitis, vasculitis of the optic nerve in Wegener’s granulomatosis may cause optic disc edema.99,100 Papillitis occurs in the acute phase of the posterior uveitis in at least 25% of cases of Behcet’s disease and is related to microvasculitis of the arterioles feeding the optic nerve.101 Retinopathy more often than choroidopathy is seen in systemic lupus erythematosus; the optic neuritis may occur with or without posterior uveitis.102 Hyperemia of the optic disc and optic neuritis, in addition to uveitis, choroiditis, and exudative retinal detachments, can be seen in Vogt–Koyanagi–Harada disease.103

Various malignancies may also invade the uvea and optic nerve. Up to 18% of acute leukemias and 16% of chronic leukemias have some leukemic infiltration of the optic nerve, causing optic disc edema and hemorrhage.104 Intraocular lymphoma, malignant melanoma, and metastatic lesions may also spread to the optic nerve.105-107

Regarding posterior uveitis in primary ocular disorders, severe disc edema and cystoid macular edema can be commonly seen in birdshot retinochoroiditis.108 Papillitis occasionally may be present in acute posterior multifocal placoid pigment epitheliopathy (APMPPE)109 and multiple evanescent white dot syndrome (MEWDS).110 The optic nerve is usually not affected in serpiginous choroiditis, but optic neuritis has been reported so far in one patient with recurrent disease.111

Optic disc edema may be seen in about 20% of patients with posterior scleritis, which usually presents with unilateral periorcular pain and decreased vision with little or no redness. Patients more than 50 years of age usually have an associated systemic disease and are more likely to experience visual loss, mostly from macular changes or optic atrophy related to the posterior scleritis. The more common associated systemic diseases are rheumatoid arthritis, Wegener’s granulomatosis, systemic vasculitis, relapsing polychondritis, and other autoimmune diseases similar to those seen in anterior scleritis, and, rarely, systemic lymphoma and multiple myeloma.112

Less commonly, optic neuritis may be the only initial manifestation of an underlying autoimmune disease not associated with MS. Young females present with unilateral or bilateral decreased vision and usually do not have overt signs or symptoms of a preexisting collagen-vascular disease, such as systemic lupus erythematosus. Laboratory tests for antinuclear
antibody (ANA) and double-stranded DNA are most useful in confirming the diagnosis of lupus. Patients who have occult symptoms of rheumatic disease or who have positive family histories for collagen-vascular diseases may initially present with optic neuritis and/or transverse myelitis. The diagnosis of antiphospholipid antibody syndrome in these patients is confirmed by the presence of elevated serum immunoglobulin M (IgM) anticardiolipin antibody. Another form of optic-spinal MS more commonly seen in Asians is associated with significantly high levels of antithyroid autoantibodies. It is thought that this MS variant could represent a pathogenic link between antithyroid autoimmunity and a subgroup of optic-spinal MS in Japanese that is not related to human T-cell lymphotropic virus (HTLV)-1 disease.

Rarely, optic nerve inflammation can be part of a paraneoplastic syndrome. Optic neuritis has been documented in cases involving bronchial carcinoma, oat cell carcinoma, and lymphoma. Pathological data have shown that inflammation and demyelination, not the carcinomatous or lymphomatous invasion of the optic nerve, cause the decreased vision (see following section on paraneoplastic optic neuropathies).

Pathogenesis of Optic Neuritis

Demyelination

Fifty percent of MS patients have clinical evidence of having had optic neuritis (at autopsy, almost 100% have optic neuritis), and 20% of them have it as their presenting sign. The initial event before demyelination is the breakdown of the blood-brain barrier through the inflammation of the vascular endothelium. With the lack of oligodendrocytes in the retina, perivascular retinal sheathing represents this vascular inflammation without demyelination. The venous sheathing occurs as a clinically silent retinal disease before the development of optic neuritis. This feature may not be visible on funduscopic examination but may be demonstrable on fluorescein angiography. The basic defect in optic neuritis/MS involves demyelination of the optic nerve, which blocks or slows the conduction of axonal transmission or decreases the amplitude of the nerve action potential. Various degrees of visual loss result from this process. The perivenular demyelinating plaques from optic nerves of patients who have acute MS reveal similar pathology to the periventricular plaques found elsewhere in the brain. These plaques show a perivascular cuffing of T and B cells, edema in the myelin nerve sheaths, and subsequent myelin breakdown. In optic neuritis the axons of the optic nerve are usually spared, resulting in good clinical recovery. More advanced lesions elsewhere in the CNS white matter often involve axonal degeneration, resulting in physical or mental disability. On histopathology, macrophages engulf the degraded myelin products and glial cells proliferate to cause permanent conduction block with no clinical recovery.

Cell-Mediated Damage

The neuroimmunological factors that mediate demyelination of the optic nerve involve cell-mediated cytotoxicity. In one study, 76% of the patients who had optic neuritis were found to have encephalitogenic, myelin basic protein (MBP), cerebroside, and ganglioside antibodies. Patients who had optic neuritis/MS and patients who had isolated optic neuritis and cerebrospinal fluid (CSF) oligoclonal bands both had encephalitogenic antibodies. Elevated T-cell-mediated cytotoxicity against the encephalitogenic peptide is a highly specific marker for demyelination in MS. Optic neuritis patients who test positive for this antigen have a greater risk of developing clinically definite MS. The increased CSF MBP- and MBP-reactive B cells in patients who had optic neuritis could correlate with the process of early myelin breakdown or restoration. Although magnetic resonance imaging (MRI) generally has been accepted as the marker of disease activity in patients who have MS, the concentration of MBP in CSF also has been useful as a marker during acute exacerbations of MS. It is significantly correlated with the visual acuity in patients who have optic neuritis, the Kurtzke
1. Optic Neuritis

expanded disability status scale score in patients who have MS, the cerebrospinal leukocyte count, intrathecal immunoglobulin G synthesis, and the cerebrospinal albumin concentration quotient.\textsuperscript{126} Furthermore, the activated T cells recognizing these MBP peptides secreted interferon-gamma (IFN-\(\gamma\)).\textsuperscript{127} The cytokine profile of IFN-\(\gamma\), interleukin-4, and tumor growth factor-\(\beta\) in patients who had optic neuritis was the same as that found in patients who had CDMS.\textsuperscript{127} The production of these cytokines is much greater in the CSF than systemically, which underscores the autonomy of the immune responses in the CSF. The upregulation of these cytokines has been demonstrated in very early MS, as manifested by acute optic neuritis associated with more than two MS lesions on MRI of the brain and oligoclonal IgG bands in CSF.\textsuperscript{127} The activated IFN-\(\gamma\)-producing T cells in the inflammatory foci of optic nerve sections in rats with acute experimental allergic encephalomyelitis showed elevated levels of calpain expression.\textsuperscript{128} Calpain has been shown to degrade axonal and myelin proteins, including MBP, neurofilament proteins, and myelin-associated glycoprotein, and may, therefore, play a role in the pathogenesis of optic neuritis in MS.\textsuperscript{129} Furthermore, the proinflammatory cytokines tumor necrosis factor and lymphotoxin in the CSF were found to be elevated in patients who had optic neuritis to the same degree as patients who had CDMS.\textsuperscript{130}

Anti-MBP and antimyelin phospholipid protein (PLP) antibodies may significantly contribute to the pathophysiology of optic nerve damage.\textsuperscript{131} Patients who had isolated optic neuritis were found to have significantly more anti-PLP-secreting B cells in the blood than patients who had other neurological diseases; anti-PLP antibody is more specific for demyelinating disease than is anti-MBP antibody.\textsuperscript{132} It is also associated with the subtype of MS that has less frequent inflammation in the CSF and CNS parenchyma, whereas anti-MBP antibody is associated with the more common form of MS, which has more frequent prominent inflammatory CSF and CNS features.\textsuperscript{133} The increased CNS synthesis of both anti-MBP and anti-PLP antibodies is found in patients who have optic neuritis, whether idiopathic or MS related. The synthesis of these antibodies is also not associated with the presence of the human leukocyte antigen (HLA)-DRB1*1501 gene.\textsuperscript{134}

Genetic Factors

Based on studies in Canada\textsuperscript{135} and Finland,\textsuperscript{136} first-degree relatives have a 25 to 50 times greater risk of being affected than the general population. Overall, the risk is highest in monozygotic twins, with a concordance rate of about 30\% in dizygotic twins and in other siblings less than 10\%, providing strong evidence for genetic factors in MS.\textsuperscript{137-140} In siblings, the earliest symptoms of the disease tend to cluster by age rather than by year, suggesting that genetic factors influence the onset of the disease.\textsuperscript{141-143}

Based on association studies using the case-control design testing specific candidate genes and studying sporadic and familial cases, the only consistently replicated finding has been an association with the HLA-DR2 allele within the major histocompatibility complex (MHC) on chromosome 6. Data from the study by Haines et al. in 1998\textsuperscript{143} strongly indicate that sporadic and familial MS share a common genetic susceptibility. These data also support the hypothesis that a genetically determined immune response plays a primary role in the pathogenesis of MS. Furthermore, the MHC locus probably represents less than half of the entire genetic etiology of MS. Families not segregating the HLA-DR2 allele appear to have no linkage to the MHC and therefore must be influenced by other genes.\textsuperscript{143}

Based on the study by The Multiple Sclerosis Genetics Group in 2002,\textsuperscript{144} the association of DR2 in families with diverse clinical presentations suggests there exists a common genetic basis to various clinical phenotypes of MS. The MHC genes appear to primarily influence penetrance, whereas other loci modulate specific phenotypes, such as location in the brain or spinal cord, demyelination, and severity of inflammation.\textsuperscript{145} Epigenetic factors, such as the selection of different disease-inducing antigens, also influence the location and severity of experimental allergic encephalitis phenotypes induced with different encephalitogenic
peptides. It is likely that a similar interplay of genetic and epigenetic factors operate in human MS. The HLA region at 6p21 and several other suggestive loci have been proposed. Therefore, non-HLA genes or other epigenetic factors must modulate disease expression. Locus heterogeneity at the HLA region suggests a distinct immunopathogenesis in DR2 negative patients. Different classes of HLA may have different roles in susceptibility to MS. The DR2, A23, and B21 allele is associated with the evolution of optic neuritis to CDMS. The high prevalence of A23 and DR2 alleles in CDMS patients compared with the normal population may suggest an important role for these alleles in the development of MS. The B51 allele may be a protective factor against the development of optic neuritis in the normal population.

Mitochondrial DNA mutations may also contribute to the cause of MS. Pathogenic mitochondrial DNA point mutations usually are not associated with typical optic neuritis/MS. Only certain secondary LHON mutations have been associated with MS and optic neuritis. This partial overlap between the two diseases may be related to the association of MS with a mitochondrial DNA haplotype (a set of mitochondrial DNA polymorphisms) within which LHON mutations preferentially occur.

**Epidemiological Factors**

Age, sex, and race all play some role as risk factors for the development of MS. The onset of optic neuritis at a young age is a predictive factor in the development of MS. One study found that the relative risk for MS increases by a factor of 1.7 for each decade less than 54 years of age in adults. There is also a tendency for females to develop MS after optic neuritis, such that 69% of 47 females and 33% of 20 males developed MS after approximately 15 years since their initial attack of optic neuritis. Based on the 2-year data from the ONTT, Caucasians were found to be at higher risk than African Americans to develop MS, even after 4 years of follow-up.

The place of residence in relationship to the distance from the equator during the first 15 years of life is a major risk factor for the development of MS after optic neuritis. People who are younger than 15 years will acquire the risk of the country to which they migrate. It is still not certain whether people who migrate later in adulthood retain the risk of their original country or the risk of their new residence.

The fall and winter months also are risk factors. One study showed that 43% of 42 patients developed MS with an onset of optic neuritis between October and March; only 29% of 44 patients whose onset of optic neuritis occurred between April and September developed MS.

**Diagnostic and Prognostic Tests**

**Typical Optic Neuritis**

According to the conclusions of the ONTT, MRI of the brain is a good predictor of MS and should be considered to assess the risk of future neurological events of MS and for treatment decision making. Forty percent to 70% of patients who have isolated optic neuritis have been reported to have periventricular white matter signal abnormalities on T2-weighted MRI scans (Figure 1.2). In the ONTT, the 2-year risk for developing CDMS was 3% if the patient initially had a normal brain MRI scan and 36% if the patient initially had two or more lesions within the central white matter. The 4-year risk for having CDMS was 13% if the MRI scan of the brain initially was normal, 35% if the MRI scan showed one to two abnormalities, and 50% if the MRI scan showed three or more abnormalities in the white matter. According to the Optic Neuritis Study Group, the 5-year cumulative probability of developing CDMS after optic neuritis was 30% for all treatment groups. Neurological impairment was slight. At 5 years, 16% of 202 patients who had no brain MRI lesions developed CDMS, whereas 51% of 89 patients who had three or more MRI lesions did. Presence of previous nonspecific symptoms also was predictive of CDMS. Low-risk factors for CDMS included optic disc swelling, lack of pain, and mild visual acuity loss. The number of MRI lesions highly
1. Optic Neuritis

Figure 1.2. Most MS activity in the CNS is clinically silent. This proton density-weighted image demonstrates multiple T2-hyperintense lesions in both hemispheres. In the setting of acute optic neuritis, the multiple white matter lesions in a number and pattern atypical for patient age are considered supportive of the diagnosis of multiple sclerosis.

correlated with the 5-year risk for CDMS, but a normal brain MRI scan did not preclude the development of CDMS. After 10 years of follow-up in the ONTT, patients with optic neuritis with greater than or equal to one brain MS lesion had a 56% chance of developing CDMS. Those with no brain MS lesions had a 22% chance of developing CDMS. Factors that conferred a low risk of developing CDMS among patients with optic neuritis without lesions on brain MRI included the following: male gender and the atypical features of optic neuritis, such as no light perception, absence of pain, optic disc edema, peripapillary hemorrhages, and retinal exudates. In a recent study by Brex et al. of patients who first presented with optic neuritis or other isolated syndromes clinically suggestive of MS, CDMS developed in 88% of patients with abnormal MRI findings at presentation and in 19% with normal initial MRI results. After the 8-year follow-up of 26 patients who had acute monosymptomatic optic neuritis, 54% of them developed CDMS. Furthermore, patients who presented with optic neuritis actually developed much milder MS. Overall, it is believed that most patients who have a history of optic neuritis and who are destined to develop MS do so within 7 years of the onset of visual symptoms.

The signs of optic nerve inflammation may be visualized on neuroimaging. In some cases of typical optic neuritis, diffuse enlargement of the optic nerve can be seen on fat-suppressed MRI scans with and without contrast enhancement on coronal orbital sections. Gadolinium enhancement and T2-signal abnormalities correlated with ultrastructural studies showing inflammatory infiltrate and expansion of the extracellular space. Demyelinative lesions seemed to progress from the optic nerve insertion at the globe to the orbital apex. MRI can also detect foci of enhancement along the nerve, which represent demyelinative lesions. It is important to note that similar MRI enhancements along the optic nerve can also be seen in patients who have ischemic, infectious, or radiation-induced optic neuropathies, but they are not pathognomonic for a demyelinative process.

Based on the ONTT, ancillary laboratory testing in patients who have typical optic neuritis does not yield any clinically useful information: these results included routine blood tests, ANA, fluorescein treponemal antibodies (FTA-ABS), chest X-ray, and CSF analysis (as detailed later). Based on the experience of the ONTT, it was concluded that CSF analysis was not necessary in the routine evaluation of patients who present with a typical profile of acute optic neuritis. Most CSF tests added little additional information to MRI results for predicting the 2-year development of CDMS. However, a more recent study showed some predictive value in the assessment of CSF of patients who have MS: those who had both abnormal MRI and elevated intrathecal IgG synthesis had a 46% increased risk for developing MS after 4 years, compared with 33% if they had only an abnormal MRI.
Furthermore, a positive ANA did not have any effect on the patient’s course or response to any treatment given.\(^4\) Therefore, besides neuroimaging, no further laboratory testing is required for typical optic neuritis.

The visual evoked potential (VEP), a measure of afferent visual function, is not useful when optic neuritis is suspected. The poor visual acuity during acute disease precludes adequate measurement of the P100 latency. On the other hand, the VEP is useful later in determining whether the episode of visual loss involved demyelination.\(^165,166\) Recently, the multifocal VEP latency delay has been shown to help in predicting progression to future MS. In a study of 22 patients with optic neuritis, 36.4% with prolonged latencies on multifocal VEP progressed to CDMS compared with 0% of those with normal latencies.\(^167\)

Optical coherence tomography (OCT) is a noninvasive procedure that can accurately and reproducibly measure the thickness of the peripapillary retinal nerve fiber layer (RNFL). It is now being used in clinical investigations to assess axonal preservation and degree of neuroprotection.\(^168\)

**Atypical Optic Neuritis**

MRI of the orbits with fat suppression is indicated for patients who have the following characteristics of atypical optic neuritis: (1) older than 45 years, (2) bilateral presentation, (3) a vertical hemianopic visual field defect, (4) progression of the optic neuritis for more than 2 weeks, and (5) recent sinusitis. It is imperative to rule out compressive lesions, such as aneurysms and tumors in the intraorbital, intracanalicular, and intracranial areas.\(^152\) Serological and CSF studies should be performed on any patient who presents signs or symptoms and course of disease that are unlike typical optic neuritis and who are suspected of having an underlying systemic or local infection or inflammation. Laboratory tests should include erythrocyte sedimentation rate (ESR) and ANA for connective tissue disease, rapid plasma reagin and FTA-ABS for syphilis, and serum angiotensin-converting enzyme for sarcoidosis.

In the ONTT, CSF analysis did not detect any additional, unsuspected diagnoses other than MS. A normal initial CSF after optic neuritis did not exclude development of MS in the future. Certain serological and CSF findings in isolated optic neuritis are associated with MS: (1) MS CSF oligoclonal bands, (2) CSF anti-MBP antibody, (3) CSF anti-PLP antibody, and (4) a cytokine profile of activated T cells (interferon-\(\gamma\), interleukin-4, and tumor growth factor-\(\beta\)) similar to that found in patients who have CDMS. These CSF and serological factors all were detected in patients who had isolated optic neuritis and who eventually developed CDMS.\(^124,127,169\) Based on the Optic Neuritis Study Group assessment, the presence of CSF oligoclonal bands was useful as a predictive factor for developing MS 5 years after optic neuritis only when the brain MRI scan was normal.\(^170\) It is generally accepted that an abnormal MRI scan at the time of optic neuritis is significantly related to later MS development. Further studies on the exact role of oligoclonal bands in the development of MS after optic neuritis are in progress.\(^163\)

**Visual Prognosis**

Young to middle-aged adults, predominately females, who present with optic neuritis as the initial manifestation of MS have a better prognosis of nondisabling MS than those who present initially with other MS features.\(^169\) After 1 year of follow-up in the ONTT, 69% of patients had visual acuity of 20/20 or better, 93% had 20/40 or better, and 3% had 20/200. These results were similar in each treatment group.\(^171\)

Other factors besides age may also affect visual prognosis. Longer lesions of the optic nerve and involvement of the intracanalicular segment are related to slightly less complete visual recovery.\(^172\) The presence of Uthohff’s phenomenon, transient visual blurring associated with an elevation of body temperature following optic neuritis, is most common in patients with other evidence of MS.\(^173-176\) Scholl et al.\(^176\) reported that these patients were more likely to have an abnormal MRI of the brain and that
they were more likely to develop MS. Uthohff's symptom was present in about 10% of patients in the ONTT 6 months after the onset of optic neuritis. It is important to note that Uhtohff's phenomenon may also occur in healthy patients after optic neuritis, in patients with Leber's optic neuropathy, and in patients with optic neuropathies from other causes. Uthohff's symptom results from a reversible conduction block in impulse transmission by demyelinated nerve fibers.

**Visual Residual Deficits**

**Optic Disc Pallor and Relative Afferent Pupillary Defect**

Specific residual eye signs serve as indicators of previous optic nerve damage. Despite good recovery of vision, the afferent pupillary defect does not always persist after resolution of unilateral acute optic neuritis. It serves as a marker for earlier optic nerve dysfunction. The optic disc pallor, located diffusely or temporally, persists irrespective of the degree of visual recovery. Retinal nerve fiber layer defects also can be seen.

**Color Vision Defect**

One of the most common residual visual deficits in patients whose optic neuritis resolved was defective color vision as tested with the Farnsworth–Munsell 100-hue color test. Despite the return of visual acuity to 20/20 or better, 32% of cases had residual visual field defects after 6 months using a Humphrey Field Analyzer. Patients often continue to complain of visual difficulties months after their attack of acute optic neuritis. In the ONTT, 215 patients perceived their vision to be worse than it was before their optic neuritis, even though 66% had normal visual acuity, 30% had normal contrast sensitivity, 55% had normal color vision, and 58% had no significant visual field defects. These patients may have subtle visual fields defects not detected by conventional perimetry. They complain of disappearing “holes” in their field of vision and the reappear-

**Contrast Sensitivity Abnormality**

No matter how good the Snellen visual acuity recovery, contrast sensitivity usually remains abnormal in resolved cases of optic neuritis and in subclinical cases. Brightness sensitivity is also reduced in most patients whose unilateral optic neuritis has resolved.

**Other Risk Factors for the Development of Multiple Sclerosis**

**Recurrent Optic Neuritis**

Some features of optic neuritis can increase the risk of developing subsequent MS. Many studies suggest that nonspecific symptoms associated with the initial attack and previous optic neuritis are risk factors for later MS. Recurrent optic neuritis increases the incidence of MS, but bilateral optic neuritis in adults has not been confirmed as a risk factor. The probability that visual acuity will return to normal decreases with each recurrence. The visual acuity after recovery from optic neuritis does not influence the later development of MS.

**Optic Neuritis in Children**

Pediatric optic neuritis usually presents bilaterally associated with headache. Periorbital pain that worsens with eye movements supports a diagnosis of optic neuritis. It is not often related
to MS, but is often associated with a postinfectious or postimmunization etiology. It is often preceded by a febrile prodromal illness, such as a bacterial or viral infection.

Optic neuritis in children usually presents with visual loss, relative afferent papillary defect, abnormal optic disc appearance, visual field defects, and color vision abnormalities. Papillitis is seen in 60% to 70% of children and in only 35% of adults. Both clinical and VEP parameters improve until vision recovers. In a recent 1-year follow-up study of 12 children with optic neuritis (6 with bilateral and 6 with unilateral optic neuritis), 14% of all eyes had residual visual loss and 85% had abnormal optic disc appearance; relative afferent pupillary defects (67% at onset), visual field defects (58.5% at onset), and color vision defects (56% at onset) resolved 1 year later. VEP were abnormal in 83% of eyes initially and in 56% at the end of 1 year. Complete clinical and VEP recovery occurred in 3 children. Visual recovery in the other children was attained within 1 year.

Children who present unilaterally have a greater tendency to develop MS. The incidence of MS following unilateral and bilateral childhood optic neuritis has ranged from 5.2% to 55.5% in different studies. Kriss et al. found that MS developed in 3 of 29 (10.3%) children with bilateral optic neuritis and 3 of 10 (30%) children with unilateral optic neuritis over a mean follow-up of 4.6 years. Although children with bilateral optic neuritis have a lower incidence of MS than those with unilateral optic neuritis, the risk in those with bilateral optic neuritis is not negligible. In 8 of the 30 patients from the Kennedy and Carroll series that developed MS over a mean follow-up of 8 years, 4 had simultaneous bilateral disc swelling. According to Riihonen, MS developed in 7 of 8 (87.5%) patients with unilateral optic neuritis and in only 2 of 15 (15.4%) patients with bilateral optic neuritis over a mean follow-up of 7 years. This study showed that all patients who later developed MS had a second attack of optic neuritis within 1 year of the first attack. Morales et al. found that children who developed MS were, on average, older at presentation with optic neuritis than those who did not develop MS (Table 1.1).

### Treatment of Optic Neuritis

#### Corticosteroids

Visual recovery is accelerated with the use of intravenous (IV) methylprednisolone within the first 2 to 3 weeks of onset of visual symptoms. In the ONTT, visual acuity improved to 20/25 after only 4 days of IV methylprednisolone, compared with 15 days of no therapy or oral steroids. After 1 month, the recovery rate was similar in treated and placebo-oral steroid groups. Most visual recovery is completed by 1 month. Some further improvement may occur 6 months to 1 year later.

The major conclusions of the ONTT related to treatment consist of guidelines in the use of corticosteroids. Treatment with high-dose IV methylprednisolone followed by 2 weeks of oral prednisone accelerated visual recovery but did not give any long-term benefit to ultimate visual outcome. At 6 months, the IV corticosteroid group had better contrast sensitivity and visual color function. One year later, all the groups had similar recovery of the foregoing functions. Conversely, treatment with oral prednisone alone did not improve the ultimate visual outcome. In fact, it increased the risk of a new attack of optic neuritis in either eye. Within the first 2 years of follow-up in the ONTT, a new attack of optic neuritis occurred in 30% of the oral prednisone group, 16% of the placebo group, and 13% of the IV methylprednisolone group.
Treatment with IV methylprednisolone followed by 14 days of oral prednisone decreased the 2-year rate of development of MS, especially in patients who had magnetic resonance signal abnormalities. Fewer patients developed neurological signs and symptoms of MS during that period, and fewer of them met criteria for CDMS.\textsuperscript{200} Of the 150 patients who were treated with corticosteroids and who had two or more lesions on MRI scans, 36\% developed CDMS within 2 years, whereas only 5\% of 202 patients who had normal or minimal abnormalities on MRI scans did so. The patients in the ONTT had a brain MRI scan within 9 days of the onset of visual loss. The side effects of corticosteroid therapy as used in the ONTT were minimal.\textsuperscript{198,201}

Despite some criticisms about the ONTT, it is considered a hallmark for a well-controlled prospective clinical trial on the evaluation and treatment of optic neuritis.\textsuperscript{201} Table 1.2 summarizes the treatment recommendations of the ONTT. The treatment outcome was not related to the effect of steroids and more likely reflected the natural history of MS. In contrast to the immunomodulatory agents that delay the progression of MS, steroids promote more rapid recovery from the demyelinating attack. It has been shown that patients with abnormal brain MRI results at presentation are more likely to progress to CDMS within 2 years of onset than those who present with normal brain MRI results.\textsuperscript{158} Increases in volume of brain MRI lesions in patients with isolated syndromes, such as optic neuritis, in the first 5 years correlate only moderately with the degree of long-term disability; therefore, the volume of lesions should not be used alone as a basis for decisions about the use of disease-modifying treatment.\textsuperscript{156}

**Intravenous Immunoglobulin**

Other treatments, such as intravenous immunoglobulin (IVIG) and retrobulbar steroids, were reported to improve visual acuity in patients who had CDMS with optic neuritis, but no definite conclusions for treatment guidelines could be reached from these small, uncontrolled studies.\textsuperscript{202–204} Although IVIG had been demonstrated to have some therapeutic benefit for other demyelinating diseases, such as chronic inflammatory demyelinating polyneuropathy,\textsuperscript{202,203} Noseworthy et al. recently found that IVIG did not reverse the chronic visual loss in patients with optic neuritis.\textsuperscript{204}

**Plasmapheresis**

Plasmapheresis is not commonly used for the treatment of optic neuritis. In a recent study of 10 patients treated with plasma exchange for acute, severe optic neuritis unresponsive to previous high-dose IV glucocorticoids,\textsuperscript{205} 7 patients experienced visual improvement. On follow-up, 3 patients continued to improve, 2 were stable, and 2 experienced worsening of vision. Plasmapheresis may have a role as “rescue therapy” for patients with a severe attack of optic neuritis.

**Interferon Beta-1a**

Based upon recent results of the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS),\textsuperscript{206} patients who received interferon beta-1a at the time of a first

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**TABLE 1.2. Treatment recommendations of the Optic Neuritis Treatment Trial**

- Corticosteroid treatment should be considered when the brain MRI scan reveals multiple abnormalities consistent with MS.
- Methylprednisolone 250mg IV should be administered to patients with optic neuritis over a 30-min period every 6h for a total of 12 doses, or 1g IV methylprednisolone in one dose over 1h each day for 3 consecutive days, followed by a prednisone taper at 1mg/kg/day orally for 11 days. Prednisone should be tapered to 20mg on day 15 and to 10mg on days 16 and 18. There are no current studies to demonstrate a clinically significant difference between administering IV methylprednisolone four times a day and giving it all in one dose.
- IV methylprednisolone decreases the incidence of more neurological deficits within the 2 years after treatment, especially in patients who had initial abnormal brain MRI scans.
- IV methylprednisolone does not improve the ultimate visual outcome.

*Source: Optic Neuritis Treatment Trial.\textsuperscript{198–200}*
demyelinating event, such as optic neuritis, had a relative reduction in the volume of brain lesions, fewer new or enlarging lesions, and fewer gadolinium-enhancing lesions at 18 months. These patients also had a significantly lower cumulative probability of developing CDMS over the 3-year period of follow-up. The study strongly suggests that long-term clinical benefits with this treatment can be achieved by preventing or delaying a second attack of MS and reducing the progression of CNS demyelination as demonstrated on MRI scans of the brain.\textsuperscript{207} Based on the results of the CHAMPS trial, some neuro-ophthalmologists in the United States recommend initiating interferon beta-1a (-\(\beta\)-1a) in patients who present with a first demyelinating event, such as optic neuritis. These patients must also have two or more clinically silent lesions in the brain that are at least 3 mm in diameter on MRI scans and that are characteristic of MS, such that at least one lesion must be periventricular or ovoid.\textsuperscript{207,208}

In the extension of the CHAMPS study, CHAMPIONS,\textsuperscript{208} patients initially randomized to interferon-\(\beta\)-1a had a 35\% less chance of conversion to CDMS over a 5-year period. The placebo group who then started interferon-\(\beta\)-1a at 2.5 years still had twice the relapse rate when compared to the treated arm in years 2.5 and 5.

In the BENEFIT (Betaseron in Newly Emerging MS for Initial Treatment) study,\textsuperscript{209} interferon-\(\beta\)-1b reduced the risk of progression to CDMS by 69\% compared to 85\% (46\% reduction by proportional hazards regression) in placebo after 2 years. Treated optic neuritis patients were less likely to develop newly active brain MS lesions at 12 and 24 months compared to placebo.

After following patients in the ONTT for the past 10 years, those who developed CDMS following an initial episode of optic neuritis had a relatively benign course. Fifty-six percent of patients with greater than or equal to one MS lesion converted to CDMS (the second lesion not including the fellow eye developing optic neuritis). Only 22\% with a normal MRI converted.\textsuperscript{157} Neurological disability was mild in that two-thirds of the patients with CDMS had an Expanded Disability Status Scale (EDSS) score lower than 3.0, whereas severe disability with EDSS score of greater than 6.0 was present in less than 20\% of patients.\textsuperscript{210} In contrast to the results of Brex et al.,\textsuperscript{211} in which the number of lesions shown on baseline MR imaging was significantly correlated with the degree of disability after 10 years, the ONTT data revealed moderate or severe disability in 29\% of patients with no lesions on baseline brain MRI and in 38\% of patients with one or more lesions. Therefore, the results of the baseline brain MRI were not useful in predicting later disability in patients who presented with optic neuritis.\textsuperscript{212}

After more than 10 years of follow-up, the ONTT cohort also revealed that a subset of patients with monosymptomatic optic neuritis manifested neither clinical signs nor MRI evidence of demyelination. Not all patients with optic neuritis develop MS. MRI signal abnormalities may also accumulate without causing any clinical manifestations of MS even after more than a decade.\textsuperscript{212}

Although some may consider the initiation of immunomodulatory agents in patients at risk of developing MS presenting with optic neuritis expensive and controversial at this time, the weight of the evidence from recent clinical trials support their use early and aggressively to delay the progression of disability.\textsuperscript{213} Patients who present initially with optic neuritis in association with other MS symptoms are at greater risk of progressing to CDMS.\textsuperscript{212} Although patients with optic neuritis recover their vision, various degrees of cognitive, motor, and sensory deficits accumulate with each exacerbation of MS, leading to permanent neurological disability. The cost of interferon-\(\beta\)-1a must be weighed against the cost of long-term disability. The most frequently reported adverse reactions resulting in discontinuation or dosage adjustment of the drug are injection site disorders, influenza-like symptoms, depression, and elevation of liver enzymes.\textsuperscript{214} Data analyzed by Patten and Metz in the SPECTRIMS Trial\textsuperscript{215} showed no significant difference in depression ratings before and after administration of interferon-\(\beta\)-1a at 22- and 44-\(\mu\)m three times a week in patients with secondary progressive MS. According to the study by Feinstein et al.,\textsuperscript{216}
antidepressant medication given to the 21% of relapsing-remitting MS patients (n = 40) diagnosed with depression before treatment with interferon-β-1b had experienced an overall decrease in depression to 6% at 12 months. Because the lifetime prevalence of depression in MS itself is approximately 40% to 60%, psychiatric complications of MS should be treated aggressively with medications and/or mental health counseling. The decision on whether to start immunomodulatory agents after the first attack of optic neuritis in patients at risk for progressing to CDMS should be based upon consideration of the risks and benefits of the medication and the cost of treatment.

**Neuromyelitis Optica**

Optic neuritis is an inflammatory demyelinating syndrome of the CNS. It may occur in isolation or as part of multiple sclerosis or neuromyelitis optica (NMO) or Devic’s disease. Neurinomyelitis Optica

**Epidemiology**

NMO predominately affects women in 80% to 90% of cases with a median age of onset in the late forties, which is about 10 years later than for MS. Most NMO patients are Caucasians living in North America, but in other parts of the world NMO may be more prevalent in Asians and Africans. Although familial cases have been reported, NMO is usually a sporadic disease. In contrast to MS, NMO is not associated with the HLA-DPB1*0501 allele.

**Diagnosis**

The diagnosis of NMO comprises unilateral or bilateral optic neuritis and myelitis without clinical evidence of demyelination in the cerebral white matter. The course of NMO is relapsing-remitting. Although very severe attacks suggest NMO, there is substantial overlap in clinical severity between NMO and MS. Diagnostic evidence that distinguishes NMO from MS includes lack of CSF oligoclonal banding and immunoglobulin abnormalities and lack of autoimmune markers such as ANA, extractable nuclear antigen (ENA), and thyroid autoantibodies. In a study of CSF, oligoclonal bands were detected in 97% (399 of 411) of MS patients and did not disappear. Oligoclonal bands were detected in 27% (3 of 11) of patients and disappeared in all cases. The absence of CSF IgG-1 responses in patients with relapsing NMO may suggest less Th1 immunity and may also explain the low frequency of oligoclonal IgG bands in NMO patients. During a relapse of NMO, CSF pleocytosis and increased CSF protein may be observed. The CSF may have polymorphonuclear lymphocytosis of more than 50 leukocytes/mm³. Between relapses, the CSF is usually normal. Overall, MRI of the brain and spinal cord is most useful in differentiating NMO from MS. The brain MRI is usually normal (except for possible findings of optic neuritis) or may have a few punctuate nonspecific abnormalities that do not fulfill the radiologic criteria for MS. The spinal cord MRI often reveals a contiguous, longitudinally extensive, gadolinium-enhancing cord lesion that extends over three or more vertebral segments, unlike the shorter cord lesions in MS. The criteria are now being revised to require NMO-IgG seropositivity. The exact specificity of these revised criteria for discrimination of NMO from MS is unclear at this time. The criterion of a negative brain MRI is also being questioned, as asymptomatic and symptomatic lesions develop in patients with a well-established diagnosis of NMO. In another study of 60 NMO patients who fulfilled the 1999 NMO criteria by Wingerchuck et al., 10% MS-like lesions and 8% had brainstem lesions atypical for MS. Although most lesions were asymptomatic, some were mildly symptomatic. Magnetization transfer (MT) ratio also reveals early abnormalities in normal-appearing brain of NMO patients. Reduced and mean diffusivity is increased in the normal-appearing white and gray matter of patients with NMO.

An indirect immunofluorescence assay that is specific for NMO is the anti-MOG antibody. This IgG marker of NMO binds to the aquaporin-4 water channel, a component of the
dystroglycan protein complex located in astrocytic foot processes at the blood–brain barrier. NMO may represent a novel autoimmune channelopathy. This marker has an approximate 75% sensitivity and greater than 90% specificity for NMO. Approximately 60% of patients with Japanese opticospinal MS, relapsing transverse myelitis, and relapsing optic neuritis with negative brain MRI are seropositive for NMO-IgG. These data suggest that these disorders represent the same disease or a forme fruste of NMO.

Clinical Course

In a retrospective study of 1274 patients with optic neuritis by Pirko et al., the 10-year conversion rate to MS was 29.8% and to NMO 12.5%. Based upon data from several studies, the cumulative conversion rate tends to increase most rapidly in the first 10 years, after which it continues to rise, albeit more slowly. More severe visual loss occurred in those who converted to NMO than to MS. In NMO converters, subsequent relapses also tended to occur earlier than in MS converters or nonconverters.

The course of NMO involves stepwise accumulation of disability because of poor recovery with each relapse. Within 5 years, greater than 50% of relapsing NMO patients have visual acuity of worse than 20/200 or require at least some ambulatory assistance.

Although NMO is a monophasic disorder, the relapsing form is more common and occurs in about 90% of cases. Predictive factors that may increase the risk of developing relapsing NMO include the following: (1) first interattack interval is several weeks or more in length; (2) female gender; and (3) better motor recovery after the first myelitis event. Therefore, patients who meet the criteria for NMO and who have a longer interval between the first and second attacks will likely develop relapsing disease. These patients require preventive therapy to decrease disability.

Pathophysiology

NMO is associated with a major humoral immune response (particularly anti-MOG IgM production) and eosinophil activation present exclusively in CSF. Evidence that supports a humoral immune mechanism in NMO includes the following: (1) coexisting systemic autoimmune disorders or autoimmune seropositivity; (2) IgG deposition and activated complement in spinal cord lesions; (3) excellent response to plasma exchange; (4) discovery of NMO-specific IgG autoantibody; and (5) analogy with myelin oligodendrocyte glycoprotein-associated experimental allergic encephalomyelitis.

Treatment

For acute relapses of NMO, IV methylprednisolone 1000 mg/day for 5 consecutive days followed by oral prednisone taper is recommended. Corticosteroids help stabilize or improve function within 1 to 5 days in most patients.

For the prevention of relapses, the combination of azathioprine and prednisone can be used for relapsing NMO patients who do not need immediate induction therapy because they have not had recent clusters of severe attacks or have been free of relapses for several months. These patients often present with severe MS and have not had any improvement with conventional MS therapies. As onset of action of azathioprine can be delayed up to 6 months, prednisone can serve as more immediate immunosuppression. There have been no controlled, double-blind studies on the efficacy of the combination of azathioprine and prednisone, but an uncontrolled, open-label series of seven patients has shown that this combination stabilized relapsing NMO and neurological function improved, as measured by the EDSS. Azathioprine is started at 50 mg/day and increased by 50-mg increments weekly up to a maximal dose of 2.5 to 3 mg/kg/day. Dosage changes are needed if the leukocyte count falls below 3,000/mm³ or the platelet count decreases below 100,000/mm³. Prednisone is also started at 1 mg/kg/day, usually up to 60 mg/day to 80 mg/day with the azathioprine. Prednisone can be tapered off when azathioprine reaches its target dose and when clinical symptoms are stable. Some patients may become steroid dependent.
and require prednisone 5 mg/day to 15 mg/day to prevent relapses. Some contraindications to this drug are hypersensitivity to the drug itself, pregnancy, and prior exposure to alkylating agents (increased risk of lymphoma). Some side effects include gastrointestinal problems, rash, drug fever, hepatotoxicity, infection leukopenia, anemia, thrombocytopenia, pancreatitis, and alopecia.

For patients who cannot tolerate azathioprine and who do not require immediate-onset therapy, mycophenolate mofetil is another option. It suppresses B- and T-cell proliferation but does not affect hemopoiesis and neutrophil count and activity. It also does not cause gastrointestinal side effects as does azathioprine. For patients with thiopurine methyltransferase deficiency, mycophenolate mofetil may be a better treatment choice. The onset of action is not faster than azathioprine. Mycophenolate mofetil is started at 500 mg twice daily; after 1 week, it is increased to 1000 mg twice daily. Some contraindications to this drug are pregnancy, hypersensitivity to the drug itself, concurrent use of live attenuated vaccines, bone marrow suppression, and hypoxanthine-guanine phosphoribosyl-transferase deficiency.

Rituximab is an anti-CD20 monoclonal antibody that destroys B cells. Because NMO is a B-cell-mediated disorder, this drug has the potential to be beneficial. In a case series of eight patients with worsening NMO, rituximab stabilized the disease for at least several months after its administration. Six of the eight patients were relapse free, and the median attack rate decreased from 2.6 to 0 attacks/patient/year. Seven of the eight patients experienced substantial recovery of neurological function over 1 year of follow-up. The median EDSS score increased from 7.5 to 5.5. Rituximab can be started in patients who have relapsing NMO despite treatment with other immunosuppressive therapies or in patients who need fast-onset induction therapy because of a recent severe relapse. Rituximab is started at 1000 mg intravenously and is again given 2 weeks later. If symptoms continue, rituximab is repeated 1 year later. Contraindications to this drug include type 1 hypersensitivity reactions and hepatitis B infection (may cause reactivation). Some side effects include infusion reactions, such as fever, chills, rigors, nausea, urticaria, angioedema, bronchospasm, and hypotension; and also headache, dizziness, asthenia, rash, and cardiac arrhythmias.

Intravenous immunoglobulin (IVIG) is another treatment option for preventing relapses of NMO, as IVIG is reserved for the treatment of antibody-mediated disorders. No randomized, controlled trials have been done yet on the efficacy of IVIG for NMO. In a report of two relapsing NMO patients who underwent monthly IVIG, they attained complete remission for up to 5.5 years in one patient and for 1 year in the other. IVIG may be effective in preventing relapses in NMO.

Although mitoxantrone has been approved by the U.S. Food and Drug Administration for the treatment of worsening relapsing-remitting or secondary progressive MS, it has been used to treat relapsing NMO in some instances. Mitoxantrone inhibits B-cell, T-cell, and macrophage proliferation and impairs antigen presentation. In a report of five patients, four of them with relapsing NMO underwent mitoxantrone treatment that resulted in stabilized disease and improvement on MRI. Mitoxantrone is given at 12 mg/m² intravenously every 3 months for up to 2 years for a total of 96 mg/m² for relapsing MS. In the small case series, mitoxantrone was started at 12 mg/m² and was administered monthly for 6 months followed by three additional treatments at 3-month intervals. Some contraindications to this drug include hypersensitivity to mitoxantrone, hepatic failure, and left ventricular ejection fraction less than 50%. Some side effects are alopecia, diarrhea, nausea, vomiting, headache, myelosuppression, menstrual irregularities, decreased fertility, and urinary tract infections.

Although interferon-β-1b has been used as an immunomodulatory drug for relapsing-remitting MS, a recent randomized, controlled study showed that interferon-β-1b at 250 µg every other day subcutaneously significantly reduced relapse rates [relative reduction of 28.6% (P = 0.047)] of relapsing remitting MS and optico-spinal MS. The optico-spinal MS in Japanese patients could be the same disorder as NMO.
Plasmapheresis or plasma exchange (PE) can be used in acute, severe attacks of NMO as "rescue therapy." In a retrospective study of 59 patients with severe attacks of CNS demyelinating disorders, 16.9% had NMO. Sixty percent of the NMO patients had marked functional improvement. These patients improved rapidly following PE, and improvement was sustained.²⁴ Plasmapheresis is given in exchanges of 55 ml/kg every other day for a total of seven treatments. Some contraindications to this drug include hemodynamic instability, coagulopathy, recent myocardial infarction, severe cardiac disease, thrombocytopenia, and sepsis. Some complications related to insertion of the catheter include thrombotic occlusion of the catheters, hemothorax, pneumothorax, hemorrhage, infection, and venous thrombosis.²³⁹

Paraneoplastic Optic Neuropathy Syndromes

Paraneoplastic ophthalmologic syndromes are usually retinopathies and rarely optic neuropathies. Only 18 cases of paraneoplastic optic neuropathies have been reported in the literature so far (Table 1.3). Paraneoplastic optic neuropathy is a subacute, progressive, usually bilateral visual loss not associated with pain. The optic disc is normal or edematous and can involve the optic chiasm. Direct compression or infiltration of the optic nerve and acute ischemic optic neuropathy should be ruled out.²⁴⁸

Optic neuropathy, as part of a paraneoplastic brainstem or cerebellar syndrome, has been reported in patients with small cell lung carcinoma,²⁴⁹⁻²⁵⁴ Hodgkin’s and non-Hodgkin’s lymphoma,²⁵⁵,²⁵⁶ neuroblastoma,²⁵⁷ pancreatic glucagonoma,²⁵⁸ nasopharyngeal carcinoma,²⁵⁹ bronchial carcinoma,²⁶⁰ and, most recently, thymoma²⁶¹ (Table 1.3). Most cases present with bilateral optic disc edema and improve with treatment of the cancer (see Table 1.4).²⁴⁹,²⁵¹⁻²⁵⁵,²⁵⁷,²⁵⁸,²⁶¹

Neuropathological findings have shown either nonspecific perivascular inflammation,²⁵⁰,²⁵⁸,²⁶⁰,²⁶¹ axonal loss, or demyelination of the optic nerve.²⁵⁰,²⁵³,²⁵⁶,²⁶¹ Pillay et al.²⁶¹ reported a case of bilateral visual loss in a 56-year-old man who had bronchial carcinoma; he had bilateral optic disc edema and internuclear ophthalmoplegia. Neuropathological findings revealed that he had secondary demyelination of the medial longitudinal fasciculus with non-specific lymphocytic infiltration and adhesive arachnoiditis of the optic nerve without any evidence of central nervous system metastasis.²⁶⁰ In contrast, other cases of paraneoplastic brainstem or cerebellar syndromes showed specific demyelination of the optic nerve, in addition to brainstem gliosis and glial nodule formation and perivascular lymphocytic infiltration without vasculitis affecting small arterioles in the cranial nerve nuclei, the inferior olivary nuclei, the vestibular nuclei, the basis pontis, or the substantia nigra.²⁵²,²⁵⁶,²⁶¹ De la Sayette et al.²⁵¹ in 1998 identified a novel autoantibody in a paraneoplastic cerebellar syndrome with optic neuropathy that was associated with small cell lung

Table 1.3. Frequency of malignancies associated with paraneoplastic optic neuropathies

<table>
<thead>
<tr>
<th>Types of malignancies associated with paraneoplastic optic neuropathies</th>
<th>Number of reported cases in the current literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung²⁵³,²⁵⁵-²⁵⁸,²⁶⁸</td>
<td>6</td>
</tr>
<tr>
<td>Bronchial²⁶⁴</td>
<td>1</td>
</tr>
<tr>
<td>Nasopharyngeal²⁶³</td>
<td>1</td>
</tr>
<tr>
<td>Neuroblastoma²⁶¹</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma²⁵⁹</td>
<td>1</td>
</tr>
<tr>
<td>__*</td>
<td>8/116 patients with lung cancer, thymoma, or other malignancies who tested positive for CRMP-5 developed optic neuropathies⁴</td>
</tr>
</tbody>
</table>

*Specific data for individual patients were not available in the study done by Yu et al. 2001.²⁶⁴
<table>
<thead>
<tr>
<th>Authors and year of reference</th>
<th>Pt. age in years/sex</th>
<th>Type of cancer</th>
<th>Initial VA and/or eye findings</th>
<th>Type of treatment</th>
<th>Effect of treatment on VA and VF</th>
<th>Length of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pillay et al. 1984&lt;sup&gt;30&lt;/sup&gt;</td>
<td>56/M</td>
<td>Mixed cell bronchial carcinoma</td>
<td>VA&lt;sup&gt;a&lt;/sup&gt; VF&lt;sup&gt;a&lt;/sup&gt; Internuclear ophthalmoplegia OU and optic neuritis OS</td>
<td>None</td>
<td>—&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Died 9 months later of sepsis; no autopsy done</td>
</tr>
<tr>
<td>Waterston and Gilligan 1986&lt;sup&gt;34&lt;/sup&gt;</td>
<td>58/M</td>
<td>Small cell lung carcinoma</td>
<td>6/24 OD 6/6 OS Optic neuritis and external ophthalmoplegia OU VF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Prednisolone</td>
<td>6/8 OD 6/6 OS VF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Died 9 months later without clinical evidence of metastases; no autopsy done</td>
</tr>
<tr>
<td>Kennedy et al. 1987&lt;sup&gt;25&lt;/sup&gt;</td>
<td>21/M</td>
<td>Neuroblastoma</td>
<td>Poor VA OU Disc edema OU Slight enlargement of blind spots OU</td>
<td>Dexamethasone, cyclophosphamide, doxorubicin, VP16-213, alternating with cisplatin, vinblastin, and bleomycin for a total of six courses</td>
<td>Normal vision</td>
<td>5 months</td>
</tr>
<tr>
<td>Coppeto et al. 1988&lt;sup&gt;36&lt;/sup&gt;</td>
<td>52/M</td>
<td>Chronic lymphomatous meningitis secondary to paranasal sinus lymphoma</td>
<td>CF at 2 feet OD 20/30 OS Optic disc edema OU Generalized constriction of VF</td>
<td>Prednisone and chemotherapy</td>
<td>20/20 OU</td>
<td>Died 14 months later of pneumonia and pleural effusion; no autopsy done</td>
</tr>
<tr>
<td>Hoh et al. 1991&lt;sup&gt;29&lt;/sup&gt;</td>
<td>31/M</td>
<td>Nasopharyngeal carcinoma</td>
<td>Poor VA OU Optic neuritis OS Sectorial VF defect OS</td>
<td>ACTH 80 U/day tapered to 10 U/day</td>
<td>6/6 OU Inferior arcuate defect OS Improved VF</td>
<td>20 months</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Pt. age in years/sex</th>
<th>Type of cancer</th>
<th>Initial VA and/or eye findings</th>
<th>Type of treatment</th>
<th>Effect of treatment on VA and VF</th>
<th>Length of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malik et al. 1992&lt;sup&gt;253&lt;/sup&gt;</td>
<td>63/M</td>
<td>Undifferentiated small cell lung carcinoma with subacute cerebellar degeneration</td>
<td>20/200 OU Cecocentral scotomas and generalized peripheral constriction OU</td>
<td>XRT to mediastinum then chemotherapy</td>
<td>Resolved scotoma OS</td>
<td>Died 20 months later of metastases; confirmed on autopsy</td>
</tr>
<tr>
<td>Blumenthal et al. 1998&lt;sup&gt;49&lt;/sup&gt;</td>
<td>72/F</td>
<td>Small cell lung carcinoma</td>
<td>Poor VA OU Disc edema OU Severe peripheral constriction OU</td>
<td>Four cycles of chemotherapy</td>
<td>Normal vision</td>
<td>16 months</td>
</tr>
<tr>
<td>De la Sayette et al. 1998&lt;sup&gt;51&lt;/sup&gt;</td>
<td>62/M</td>
<td>Small cell lung carcinoma</td>
<td>20/25 OD 20/400 OS Central scotomas OU</td>
<td>Cisplatin, etoposide, mediastinal and subclavicular XRT</td>
<td>20/20 OU OD and central scotoma OS</td>
<td>23 months</td>
</tr>
<tr>
<td>Luiz et al. 1998&lt;sup&gt;52&lt;/sup&gt;</td>
<td>59/F</td>
<td>Small cell lung carcinoma</td>
<td>20/30 OD 20/40 OS Disc edema OU Severe peripheral constriction OU</td>
<td>Solumedrol</td>
<td>Improved vision</td>
<td>9 months</td>
</tr>
<tr>
<td>Yu et al. 2001&lt;sup&gt;261&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Pt., patient; F, female; M, male; VA, visual acuity; VF, visual fields; OD, right; OS, left; OU, both; CF, count fingers; ERG, electroretinogram; XRT, radiation therapy.  
<sup>a</sup>Information not available.  
<sup>b</sup>Data for individual patients were not available in the study by Yu et al. 2001<sup>261</sup>; 8 of 116 patients with lung cancer, thymoma, or other malignancies who tested positive for CRMP-5 developed optic neuropathies.
carcinoma. This optic neuropathy was identified in only 1 of 12 patients with anti-CV2 antibody-related paraneoplastic syndromes. Anti-CV2, a 66-kDa protein, is the only paraneoplastic autoantibody reported to bind exclusively to oligodendrocytes. The patient was a 62-year-old man who had simultaneously developed a severe cerebellar syndrome and bilateral painless visual loss greater in the left eye than in the right. Funduscopic examination revealed bilateral disc edema, and fluorescein angiography showed marked leakage in the area of the optic discs, also greater in the left eye than in the right. The CV2 antigen was found to be expressed by oligodendrocytes of the cerebellum, brainstem, spinal cord, and optic chiasm. Although a pathological examination was not performed, an immune-mediated secretion or a toxic secretion of cytokines, rather than demyelination, was thought to explain the clinical findings. Nonspecific inflammatory changes and diffuse loss of cerebellar Purkinje cells were seen in previously reported cases involving anti-CV2 antibodies.

CRMP-5 is another recently characterized autoantibody associated with paraneoplastic optic neuropathy in small cell lung carcinomas and, rarely, thymomas. This IgG is directed against a 62-kDa neuronal cytoplasmic protein of the collapsin response-mediator family. CRMP-5 is expressed in adult central and peripheral neurons, including synapses, and in small cell lung carcinomas, and rarely in thymomas. The CRMP family of proteins is believed to mediate growth guidance cues during neurogenesis. The CRMP-5 antibody is as frequent as anti-Yo antibody and second in frequency to anti-Hu antibody. The neurological deficits include chorea, cranial neuropathies, peripheral neuropathy, autonomic neuropathy, cerebellar ataxia, subacute dementia, and neuromuscular junction disorders. It is not associated with any specific neurological syndrome. Although 8 of 116 CRMP-5 seropositive patients had optic neuropathy, only 3 of the 8 presented with optic neuropathy at the onset of the illness.

Treatment of the specific cancer in paraneoplastic optic neuropathy patients with chemotherapy and/or radiation therapy resulted in significant visual improvement (see Table 1.3). Vision recovered to normal or near normal with improvement of visual fields in 8 of 11 patients (see Table 1.4). Hoh et al. showed that treatment with steroids alone also improved vision in a patient with paraneoplastic optic neuropathy and nasopharyngeal cancer. The visual defects improved with an increase in prednisolone and worsened with its decrease (see Table 1.4).

References
10. Nichols BE, Thompson HS, Stone EM. Evaluation of a significantly shorter version of the


