CAUSES OF OPTIC NEURITIS OTHER THAN PRIMARY DEMYELINATION

In a few cases, a primary demyelinating process in the optic nerve or the CNS is not the cause of unilateral or bilateral anterior or retrobulbar optic neuritis. Instead, the condition develops in the setting of, or as the presenting manifestation of, an underlying systemic infection.

OPTIC NEURITIS FROM VIRAL AND BACTERIAL DISEASES

Parainfectious optic neuritis typically follows the onset of a viral or, less often, a bacterial infection by 1 to 3 weeks (37,434,435). It is more common in children than in adults and is thought to occur on an immunologic basis, producing demyelination of the optic nerve. The optic neuritis may be unilateral, but it is often bilateral. The optic discs may appear normal or swollen. Swelling of the peripapillary retina may be observed in patients with anterior optic neuritis. If a star figure composed of lipid exudates develops in the macula of the affected eye, the condition is called “neuroretinitis” (discussed later). If there is evidence of optic disc swelling but no evidence of optic nerve dysfunction, and the intracranial pressure is normal, the inflammation is assumed to be affecting the periphery of the nerve and is called “perioptic neuritis” or “optic perineuritis” (discussed later).

Parainfectious optic neuritis, whether viral or bacterial, may occur in patients with no evidence of neurologic dysfunction or in association with a meningitis, meningoencephalitis, or encephalomyelitis. When neurologic manifestations are present, patients have typical abnormalities in the CSF. Patients with encephalitis usually have disturbances on electroencephalography and also may have changes in the brain seen by neuroimaging, whereas patients with encephalomyelitis may show such changes in both the brain and the spinal cord.

Visual recovery following parainfectious optic neuritis is usually excellent without treatment. Whether corticosteroids hasten recovery in patients with postviral optic neuritis is unknown, but this treatment is reasonable to consider, particularly if visual loss is bilateral and severe.

Optic neuritis may occur in association with infections by a large number of both DNA and RNA viruses, including adenovirus (436,437), Coxsackie virus (438,439), cytomegalovirus (440), hepatitis A (441), hepatitis B (442,443), human herpesvirus type 4 (Epstein-Barr virus) (444–448), human immunodeficiency virus (HIV) type 1 (449,450), measles (451–455), mumps (456–458), rubella, rubella (459), and varicella zoster (in chicken pox [460,461] and in herpes zoster [462,463]). The neuro-ophthalmologic significance of these and other viruses is discussed in detail in Chapters 57 and 58.

Bacterial infections can produce optic neuritis. Some bacterial infections in which anterior or retrobulbar optic neuritis may occur include anthrax (464), β-hemolytic streptococcal infection (465), brucellosis (466,467), cat scratch disease (39,468,469,470), meningococcal infection (471), pertussis (472), tuberculosis (473–477), typhoid fever (478,479), and Whipple’s disease (480). The neuro-ophthalmologic significance of these and other bacteria is discussed in detail in Chapter 49.

OPTIC NEURITIS AFTER VACCINATION

Although there is extensive anecdotal evidence of optic neuritis occurring following vaccinations, the actual evidence of a demyelinating event following vaccination is limited. In this section we first review the anecdotal information regarding optic neuritis and vaccinations; we then will explore the evidence-based medicine surrounding the relationship of vaccinations to demyelinating events in general.

Optic neuritis has been reported to occur after vaccinations against both bacterial and viral infections (38). Most cases are bilateral, and both anterior and retrobulbar forms of optic neuritis may occur. Optic neuritis may develop after vaccinations with bacillus Calmette Guérin (BCG) (481), hepatitis B virus (482,483), rabies virus (484–486), tetanus toxoid (487), and varicella virus (488). The use of a combined smallpox, tetanus, and diphtheria vaccine was associated with a bilateral anterior optic neuritis in a 7-year-old child who eventually recovered completely (489), and a similar case was reported in association with combined measles, mumps, and rubella vaccination (490). Influenza vaccine is commonly associated with the development of optic neuritis. Perry et al. (491) reported a patient with bilateral anterior optic neuritis that occurred 6 days following vaccination with bivalent influenza vaccine. Ray and Dreizen (492) described a similar case. Cangemi and Bergen (493) reported a previously healthy man who developed a unilateral optic neuritis with disc swelling, 3 weeks after inoculation with 200 units of A-New Jersey swine influenza and 200 units of A-Victoria influenza whole-virus vaccine. Although most cases of postvaccination optic neuritis appear to be of the anterior variety, unilateral retrobulbar neuritis has been reported 3 weeks following a swine influenza vaccination (494).

Despite the previous anecdotal reports, the evidence-based medicine that vaccination may precipitate the onset of MS or lead to relapses is simply not present. Confavreux et al. (495) conducted a case-crossover study to assess whether vaccinations increase the risk of relapse in MS. The subjects included 643 patients included in the European Database for Multiple Sclerosis who had a relapse between 1993 and 1997. The index relapse was the first relapse confirmed by a visit to a neurologist and preceded by a relapse-free period of at least 12 months. Information on vaccinations was obtained in a standardized telephone interview and confirmed by medical records. Exposure to vaccination in the 2-month risk period immediately preceding the relapse was compared with that in the four previous 2-month control periods for the calculation of relative risks, which were estimated with the use of conditional logistic regression. Of these patients with relapses of MS, 15% reported having been vaccinated during the preceding 12 months. The reports of 94% of these vaccinations were confirmed. Of all the patients, 2.3% had been vaccinated during the preceding 2-month risk period, compared with 2.8–4.0% who were vac-
cinated during one or more of the four control periods. The relative risk of relapse associated with exposure to any vaccination during the previous 2 months was 0.71 (95% CI, 0.40–1.26). There was no increase in the specific risk of relapse associated with tetanus, hepatitis B, or influenza vaccination (range of relative risks, 0.22–1.08). Analyses based on risk periods of 1 and 3 months yielded similar results. These authors concluded that vaccination does not appear to increase the short-term risk of relapse in MS.

To further evaluate the association between vaccination and onset of MS or optic neuritis, DeStefano et al. (496) looked at a case-control study involving cases of MS or optic neuritis among adults 18–49 years of age. Data on vaccinations and other risk factors were obtained from computerized and paper medical records and from telephone interviews in three health maintenance organizations. Four hundred forty case subjects and 950 control subjects matched on health maintenance organization, sex, and date of birth were assessed. They noted the onset of first symptoms of demyelinating disease at any time after vaccination and during specified intervals after vaccination (less than year, 1–5 years, and more than 5 years). Cases and controls had similar vaccination histories. The odds ratios (95% CI), adjusted for potential confounding variables, of the associations between ever having been vaccinated and risk of demyelinating disease (MS and optic neuritis combined) were 0.9 (0.6–1.5) for hepatitis B vaccine; 0.6 (0.4–0.8) for tetanus vaccination; 0.8 (0.6–1.2) for influenza vaccine; 0.8 (0.5–1.5) for measles, mumps, rubella vaccine; 0.9 (0.5–1.4) for measles vaccine; and 0.7 (0.4–1.0) for rubella vaccine. The results were similar when MS and optic neuritis were analyzed separately. There was no increased risk according to timing of vaccination. It was the conclusion in this case-control study that vaccination against hepatitis B, influenza, tetanus, measles, or rubella is not associated with an increased risk of MS or optic neuritis.

It would appear that there are two primary issues regarding the relationship between vaccinations and MS: Does the vaccination precipitate the first attack of MS? Does it increase the short- or long-term risk in patients with known disease? It would appear from the preceding studies that vaccinations do not precipitate the seminal event in MS. The second question is more difficult to answer. Acute disseminated encephalomyelitis (ADEM), a monophasic and multifocal illness of the white and gray matter, has been observed following various viral or bacterial infections as well as vaccine injections for diseases such as pertussis, tetanus, and yellow fever. The similarities between ADEM and EAE are suggestive of an immunologic process. In addition to the dramatic presentation of ADEM, more limited white matter involvement, such as optic neuritis or myelitis, has been reported following vaccine injections and has occasionally been counted as the first attack of MS. In France, 25 million inhabitants, almost half of the population, were vaccinated against hepatitis B (HB) between 1991 and 1999 (497). Several hundred cases of an acute central demyelinating event following HB vaccination were reported to the pharmacovigilance unit, leading to a modification of vaccination policy in the schools and the initiation of several studies designed to examine the possible relationship between the vaccine and the central demyelinating events. The results of these studies failed to establish the causality of the HB vaccine. Nevertheless, molecular mimicry between HB antigen(s) and one or more myelin proteins, or a nonspecific activation of autoreactive lymphocytes, could constitute possible pathogenetic mechanisms for these adverse neurologic events.

Although demyelinating events might in fact be precipitated by vaccinations, the chance of this occurring is low, and the risk to the patient with MS is minimal compared with the potential risk to the MS patient of disease state worsening due to an infectious disease.

### OPTIC NEURITIS IN SARCOIDOSIS

Granulomatous inflammation of the optic nerve may occur in sarcoidosis, producing a typical anterior or retrobulbar optic neuritis (498–502). In some cases, the optic neuritis occurs during the disease; in others, it is the presenting manifestation. Clinical findings may be indistinguishable from those of demyelinating optic neuritis. However, the optic disc may have a characteristic lumpy, white appearance, which suggests a granulomatous etiology, and there may be an inflammatory reaction in the vitreous. Pain, common in a demyelinating optic neuritis, is often absent in the optic neuropathy of sarcoidosis.

Unlike primary demyelinating optic neuritis, which does not respond dramatically to systemic corticosteroids (discussed previously), the optic neuritis associated with sarcoidosis is usually extremely sensitive to steroids. In most cases, recovery of vision is rapid after treatment is instituted, although vision may decline again once steroids are tapered or stopped. Indeed, it must be emphasized that rapid recovery of vision with corticosteroid treatment and subsequent worsening when the steroids are tapered is atypical for demyelinating optic neuritis and suggests an infiltrative or nondemyelinating inflammatory process, such as sarcoidosis.

Patients with possible sarcoid optic neuritis should undergo an evaluation that includes a careful history and physical examination, a chest radiograph, serum chemistries, an assay for angiotensin converting enzyme (ACE) in the serum and CSF, a gallium scan, and in some cases bronchoscopic lavage or biopsy of skin, conjunctiva, lung, liver, or other organs looking for noncaseating granulomas. Sarcoidosis and related conditions are discussed in detail in Chapter 59.

### SYPHILIS

Optic neuritis from syphilis is not rare (503–505), but it is particularly common in patients also infected with HIV (506–509) (see Chapters 56 and 58). The optic neuritis of syphilis can be unilateral or bilateral and anterior or retrobulbar. When the condition is anterior, there is usually some cellular reaction in the vitreous, which serves to distinguish it (and other systemic inflammatory diseases that cause anterior optic neuritis) from demyelinating optic neuritis, in which the vitreous usually is clear (discussed previously).

The diagnosis of syphilis is established using a variety of serologic and CSF assays. Treatment with intravenous