CHAPTER 61

Peripheral Demyelinating and Axonal Disorders

David I. Kaufman

Guillain-Barré syndrome (GBS) until recently had been viewed as a single disorder with variations. It is now clear from electrophysiologic, pathologic, and immunologic evidence that it actually is a group of different syndromes with several distinctive subtypes (1). Some of these have a different tempo of onset and may require different therapeutic strategies; however, almost all have neuro-ophthalmologic manifestations, including disorders of ocular motility, pupil function, and occasionally, optic nerve function.

ACUTE INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Acute inflammatory demyelinating polyneuropathy (AIDP) was formerly known as GBS. Although GBS remains the most popular name, AIDP provides an accurate description of the pathophysiology of this fairly common disease and helps separate it from other peripheral polyneuropathies.

AIDP is the most frequent cause of acute generalized paralysis in the world (2–4). The disease is unique. It can cause a previously healthy patient to deteriorate to the brink of death within weeks, with near complete recovery being the rule. The illness is characterized by rapidly progressive ascending symmetric weakness of the extremities. It usually is preceded in the previous 1–3 weeks by a mild respiratory or gastrointestinal illness. Patients can have significant neuro-ophthalmologic manifestations early in the disease, and recognition of these symptoms and signs by the neuro-ophthalmologist is essential for early diagnosis and treatment, thereby reducing morbidity (2–4).

NOMENCLATURE

The earliest description of AIDP most likely was by Wardrop and Ollivier in 1834. By 1859, Landry had described similar patients with ascending flaccid paralysis of the ex-

tremities, bulbar paralysis, and death within a week. In 1916, Guillain, Barré, and Strohl described two patients with motor disturbances, loss of deep-tendon reflexes, preserved cutaneous reflexes, and increased albumin without pleocytosis in the cerebrospinal fluid (CSF). Authors began to refer to the condition as the Landry-Guillain-Barré-Strohl or Guillain-Barré-Strohl syndrome based on this history. The name was shortened to Guillain-Barré syndrome (GBS) by Draganesco and Claudian in 1927 and remained in use to describe this disease until recently. Pathologic and electrophysiologic findings led to the current designation of the condition as AIDP (5–7), and we will use this term throughout this chapter instead of GBS.

EPIDEMIOLOGY AND ANTECEDENT OR ASSOCIATED EVENTS

The annual incidence of AIDP ranges from 0.4–2 per 100,000 population (3,8,9) with men affected more than women and Caucasians more than African-Americans. The disease becomes more frequent with advancing age, with a range in various series of 8 months to 81 years (mean, 50–74 years). It is the most common cause of acute motor paralysis in both children and in adults (3,8–12,12a). There is no major seasonal difference. There is a significant association with the human leukocyte antigen (HLA) B35 haplotype and also with recent *Campylobacter jejuni* infection (13–21). About 60% of cases of AIDP occur after systemic viral or bacterial infections, after vaccinations to prevent such infections, or in some other specific settings.

AIDP and Systemic Infections

The bacterial species most often associated with AIDP is *Campylobacter jejuni,* with 10 to 66% of cases following both symptomatic and asymptomatic infections by this organism (1,13–27). These cases are caused by an immunologic reaction to *C. jejuni* rather than by direct infection of the peripheral or central nervous system. Clinical symptoms start 1–3 weeks after the initial infection. As noted previously, AIDP is associated with the HLA-B35 haplotype (13–15). Anti-GM1 and anti-GD1a titers are elevated in post-*Campylobacter* AIDP. In addition, there is immunologic evidence that the reaction occurs only in response to infection by specific serotypes of *C. jejuni* (28). Mishandling of raw poultry and consumption of undercooked poultry are the major risk factors for human campylobacteriosis (29).

AIDP occurs in association with infections by bacteria other than *Campylobacter*, including *Brucella*, *Yersinia*, *Salmonella typhi*, *Francisella tularensis*, and *Listeria monocytogenes*. About 5% of patients have evidence of recent infection by *Mycoplasma pneumoniae*, whereas 5–15% demonstrate evidence of cytomegalovirus (CMV) infection, and 2–10% have evidence of Epstein-Barr virus (EBV) infection (30–37). Many have a history of a recent upper respiratory tract infection or pneumonia. Infections by organisms like *Leishmania* and *Chlamydia* also may produce an AIDP-like syndrome, perhaps based on an immune-mediated process (38,39). An association of AIDP with infection by human immune deficiency virus type 1 (HIV-1) and the acquired immunodeficiency syndrome (AIDS) also is well established (40–42). Usually, there is a good prognosis for motor recovery in such patients (40–42). A number of other organisms also have been associated with individual cases of AIDP (3,43–45).

AIDP and Vaccinations

AIDP may occur with increased frequency after vaccinations against certain viruses and bacteria. Cases have been reported after immunization with a conjugate vaccine against *Haemophilus influenzae* type b, as well as after other vaccines including smallpox, diphtheria-pertussis-tetanus (DPT), polyvalent pneumococcal, measles/mumps/rubella (MMR), rabies, hepatitis B, yellow fever, and oral poliovirus (44,46–49).

In 1976, 45 million persons received what was called the Swine flu vaccine to try to prevent what was feared to be a particularly virulent strain of influenza (50). A statistically significant excess rate of AIDP occurred during the first 4–6 weeks after immunization with this vaccine (8,51–55). There was an increased risk of about 1 in 100,000 with a subsequent mortality of 5% and a neurologic morbidity of 5–10%. This was the only fatal complication of this vaccine. Subsequent influenza vaccinations have not been associated with an increased risk of AIDP.

Miscellaneous Associations

AIDP may occur in a variety of other settings (2) including during the latter part of pregnancy (56,57), as a paraneoplastic syndrome (58–61), after spinal or epidural anesthesia (62), after various types of surgical procedures (63–67), after allogeneic bone marrow transplantation (68), and in association with systemic lupus erythematosus (69,70). AIDP also may develop after treatment with various drugs, including lithium (71), intravenous streptokinase (72), exogenous gangliosides (73,74), and intramuscular injections of botulinum toxin A for essential blepharospasm (75).

PATHOLOGY

The pathologic hallmark of AIDP is a variable perivenular mononuclear cell infiltrate with segmental demyelination and relative preservation of axons in the peripheral nervous system (PNS) (3,4,76–85). The pathologic findings are remarkably consistent regardless of whether or not there is an antecedent illness or precipitating event. Perivenular infiltrates composed of lymphocytes and macrophages are seen primarily surrounding endoneural and epineural venules of the PNS (Fig. 61.1). Investigators since 1919 (81) have described virtually all parts of the PNS as a site of involvement (3,4,76–85).

Small- to medium-sized lymphocytes are the earliest cells to exit the venules. They are found immediately outside these vessels in the parenchyma of affected nerves. Larger lymphocytes undergoing transformation and phagocytic macrophages derived from blood monocytes are located farther from the venules. This infiltrate of mononuclear cells is associated with adjacent areas of focal demyelination (76,79,80) (Fig.61.2).

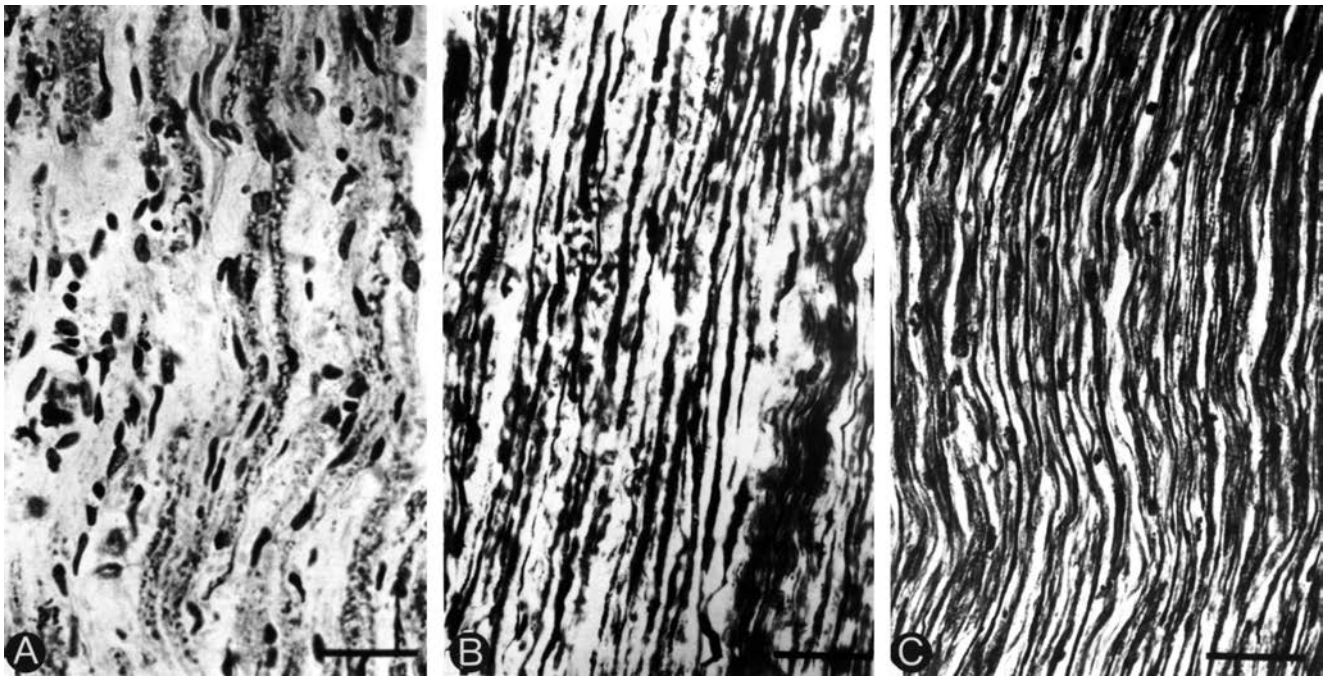

Figure 61.1. Pathology of acute inflammatory demyelinating polyneuropathy (AIDP). *A,* Longitudinal section through the left oculomotor nerve from a patient with ophthalmoparesis associated with AIDP shows focal demyelination. Note scattered lymphocytes. Luxol fast blue/Nissl. *B,* Axis cylinders are relatively well-preserved in area of demyelination. Glees and Marsland. *C,* Another section from the same nerve shows a mild perivenular lymphocytic infiltrate. Luxol fast blue/Nissl. All bars equal 80 μ*m.* (From Honavar M, Tharakan JKJ, Hughes RAC, et al. A clinicopathological study of the Guillain-Barré syndrome: Nine cases and literature review. Brain 1991;114:1245–1269.)

The earliest signs of demyelination generally occur at the node of Ranvier and produce a widened nodal gap. Disintegration of the myelin sheath then proceeds from the nodal region toward the centrally located nucleus of the Schwann cell (84). In less severe cases, there is proliferation of Schwann cells in the areas of demyelination. The demyelinated internodes eventually are replaced by several shorter, lightly myelinated internodes, each with its own Schwann cell (4). Thus, reparative processes seem to proceed despite ongoing inflammation and demyelination. Fiber density of various muscles has been studied in both acute and more chronic cases (85). The deltoid usually is the most abnormal. Fiber density is increased in 58% of cases. Interestingly, there are changes noted even in patients sampled within 3 weeks of onset, strongly suggesting that reinnervation begins soon after the onset of the disease.

Axons may become damaged with significant demyelination representing a ''bystander effect'' secondary to inflammatory infiltration (86). Wallerian degeneration may occur and when severe, causes a central chromatolysis and, in some cases, dissolution of the anterior horn cells. The presence of epiperineurium correlates with a drastic change of pathology with superimposed ischemic lesions and distally accentuated axonal loss, suggesting that endoneurial fluid pressure increase could cause axonal damage in AIDP. Rarely, the axons are specifically attacked. This primary axonal disease represents a different type of condition and is reviewed later (87).

Although some cases of AIDP have clinical features that suggest central nervous system (CNS) damage, there is limited pathologic proof of such damage. In one case of typical AIDP with an early fatal outcome, pathologic examination showed widespread lymphocytic infiltrates throughout the brainstem, even though there were no corresponding neurologic deficits (82).

PATHOGENESIS AND PATHOPHYSIOLOGY

The pathologic findings in AIDP are consistent with an acquired immune-mediated disorder (66,67). Clinical immunologic studies and findings in an almost identical animal model called experimental allergic neuritis (88) indicate that both humoral and cell-mediated systems may participate in production of the disease (2–4,89,90). AIDP may be caused by antibodies to nerve tissue or soluble immune complexes. Macrophages seem to be the chief effector cells mediating damage to myelin, apparently acting as antigen-presenting cells. There also is evidence of activation of T-lymphocytes, but it is unclear if these cells have a primary pathogenic function or simply are involved secondarily in the inflammatory process.

In a series of nine cases examined within 30 days after the onset of the disease, immunohistochemistry using monoclonal antibodies identified more leukocytes (PD7/2B11+) and T-cells (UCHL1+) in the endoneurium than in cases examined later in the course of the disease or in control

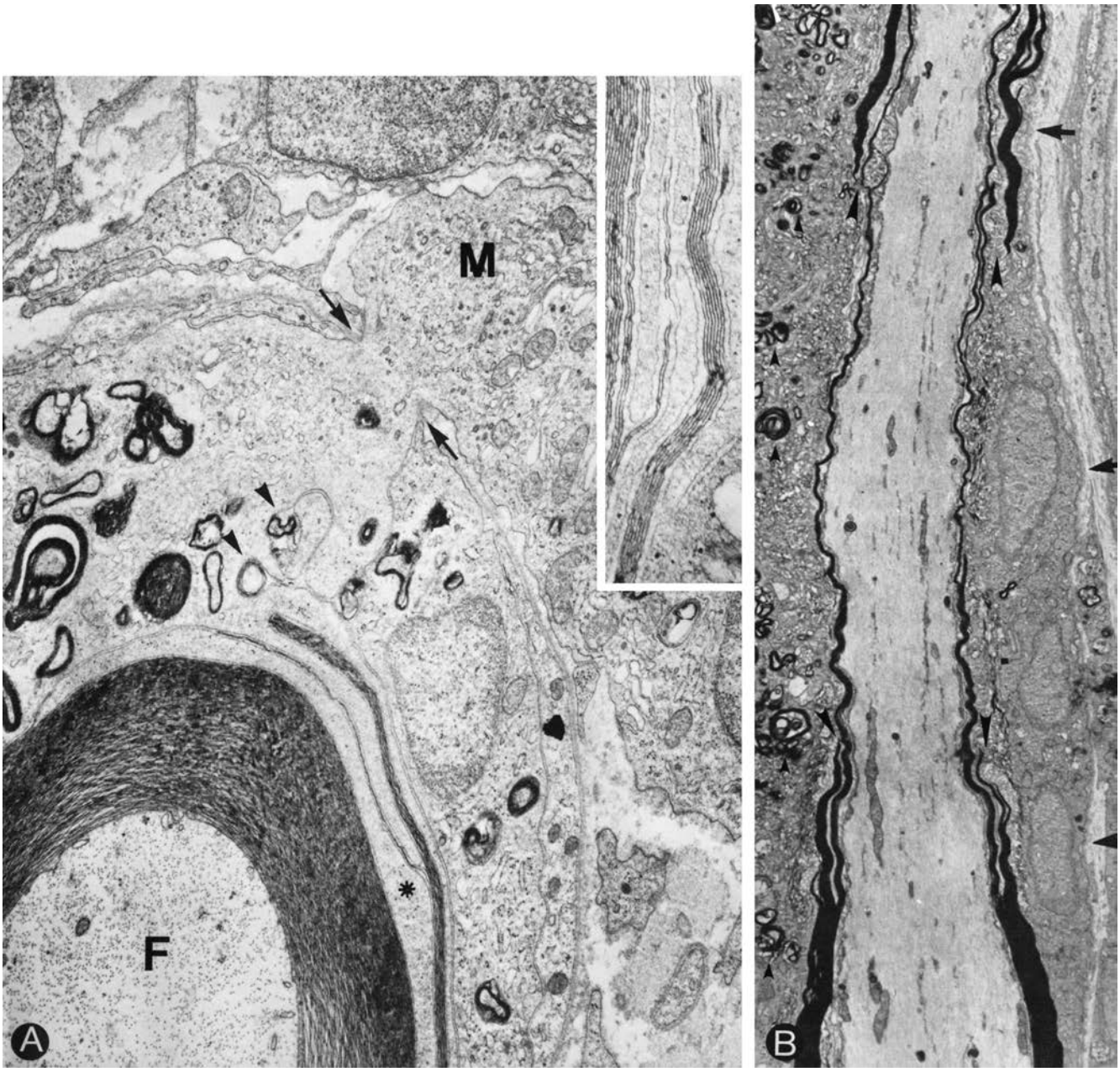

Figure 61.2. Ultrastructural pathology of acute inflammatory demyelinating polyneuropathy. *A,* Electron micrograph shows a macrophage (M) that has extended a cytoplasmic process through a gap (*between arrows*) in the basement membrane of the Schwann cell surrounding a myelinated nerve fiber (F) and is stripping away the outer lamellae of the myelinated sheath (*asterisk*). Phagocytosis of the separated fragments by the macrophage is seen (*arrowheads*). ×18,000. *Inset,* Higher-power view of another myelinated nerve fiber undergoing demyelination by stripping away of its outer lamellae by macrophage processes. ×65,000. *B,* Longitudinal section through a myelinated peripheral nerve shows penetration of the basal lamina of the nerve by lymphocytes and macrophages (*arrows*). The cells are associated with focal demyelination. Note that the outer layers of myelin are being stripped away by the cellular processes (*large arrowheads*). Also note small fragments of myelin being phagocytosed (*small arrowheads*). ×27,000. (From Prineas JW. Acute idiopathic polyneuritis: An electron microscope study. Lab Invest 1972;26:133–146.)

cases. These findings indicate that the pathophysiology of AIDP may be variable. For example, there may be greater cell-mediated immunity in some cases and greater targeted macrophage-mediated demyelination in others (91,92). Tumor necrosis factor-alpha (TNF-α) is one of the immune factors that can induce demyelination of peripheral nerves in AIDP. In one study, 72% showed elevated serum TNF-α levels during the acute disease process. Thus, soluble TNF receptors may have a protective role in AIDP (93,94).

Immunocytochemistry was used to localize complement activation products in the early stages of the disease from three autopsy specimens from three patients with symptoms for 3–9 days at the time of death. Many nerve fibers had a rim of complement activation marker (C3d) and terminal complement complex neoantigen (C5b-9) along the outer surface of the Schwann cells (91). Ultrastructure analysis suggested that at least some forms of AIDP are complement mediated. Complement may be activated by an antibody bound to epitopes on the outer surface of the Schwann cell, and the resulting activation initiates the vesiculation of myelin. More recent studies have shown that Th1/Th2/Th3 cytokines are differently upregulated during various clinical phases of AIDP (95).

CLINICAL MANIFESTATIONS

AIDP usually is characterized by an ascending and symmetrical motor weakness starting in the legs and associated with hypotonia and areflexia (2–4,96,97). The weakness may precede areflexia by 2 or 3 days (2–4,96,97). The trunk, intercostals, neck, and cranial nerves are usually—but not always—affected later. Both proximal and distal muscles usually are involved (2–4).

General Neurologic Manifestations

It is essential to understand the subtlest signs and symptoms of AIDP to allow prompt treatment. Delay in diagnosis can lead to potential life-threatening complications if respiration becomes involved. A number of features support a clinical diagnosis of AIDP (2–4), although there are notable variations (98,99).

Most patients are afebrile at the time neurologic symptoms begin. Rapid progression of motor weakness is typical, with up to 98% of patients reaching maximum weakness by 4 weeks. The weakness is relatively symmetric and develops so rapidly that muscle atrophy does not occur. A persistent monoparesis or hemiparesis is rare. There can be tenderness on deep palpation of the muscles, and more than half the patients complain of pain and an aching discomfort without palpation of the muscles (2–4). Subjective sensory complaints, including occasional burning pain, can occur (100). When objective sensory loss is present, the most common deficits are proprioception and vibration, probably because these fibers are myelinated more heavily than those that conduct temperature, pinprick, and light touch (66,67).

There are important variations in the pattern of muscle involvement. The pharyngeal muscles can be affected first. The upper extremity and respiratory muscles can be involved without lower extremity involvement. Electrocardiographic changes of minor degree can occur, including T-wave variation. Hyponatremia or transient diabetes insipidus from inappropriate secretion of antidiuretic hormone can occasionally develop (2–4).

Autonomic dysfunction occurs in about 20% of cases of AIDP. It usually is mild, producing only minor or brief fluctuations in blood pressure, heart rate, or both; however, in some cases, AIDP produces profound hypotension, occasionally leading to cardiac arrest (101,102). There can be a sinus bradycardia that alternates with a tachycardia. Other manifestations are facial flushing, loss of sweating, or episodic profuse diaphoresis that can last up to 2 weeks. Retention of urine occurs in up to 15% of patients (2–4).

Cranial nerve involvement is common, with the facial nerve affected most often. Indeed, almost 50% of patients develop bilateral facial weakness that is invariably transient. Unilateral or bilateral facial myokymia, a continuous, undulating, involuntary movement of the facial muscles, also may occur (103,104). Bulbar palsy occurs in about one-third of patients, with the glossopharyngeal and vagus nerves being most often affected. The ocular motor nerves are affected in less than 10% of cases (2–4,105) (discussed later).

Neuro-Ophthalmologic Manifestations

Ophthalmoparesis is the most frequent ocular sign in AIDP (Fig. 61.3). It may be complete or incomplete. The abducens nerve is most frequently affected, both in isolation and in association with oculomotor and trochlear nerve paresis or other neurologic deficits (99,105–107). Some of the ocular motor disturbance in patients with AIDP is thought to be caused by internuclear or supranuclear dysfunction (108), but this issue is controversial (discussed later). Ophthalmoplegia may be related to the presence of an antibody to a particular ganglioside in the serum. A close correlation between ophthalmoparesis and an immunoglobuin (Ig) G antibody against ganglioside GQ1b has been identified (109,110). This association is particularly relevant to the Miller Fisher syndrome (MFS) and is described in more detail later.

Disturbances of eyelid function are common in patients with AIDP. Ptosis is the most prominent and common abnormality. It usually is bilateral but may be unilateral. It most often is accompanied by an ophthalmoparesis (2–4) (Fig. 61.3), but early in the course of the disease, some patients develop severe bilateral ptosis without evidence of ocular motor weakness (98). Some patients with typical AIDP develop lid lag (111) (Fig. 61.4). Their appearance thus can mimic that of a patient with dysthyroid orbitopathy, except that the lid lag is unassociated with eyelid retraction in primary gaze, and there are no other signs of dysthyroid orbitopathy.

Disturbances of pupil size and reactivity can occur alone or in combination with ophthalmoparesis (112). Such disturbances include anisocoria and a reduced or absent reaction to light stimulation, near stimulation, or both (113). Pupillary light-near dissociation (see Chapter 16) may occur, producing Argyll Robertson-like pupils (114).

Paralysis or weakness of accommodation occurs in

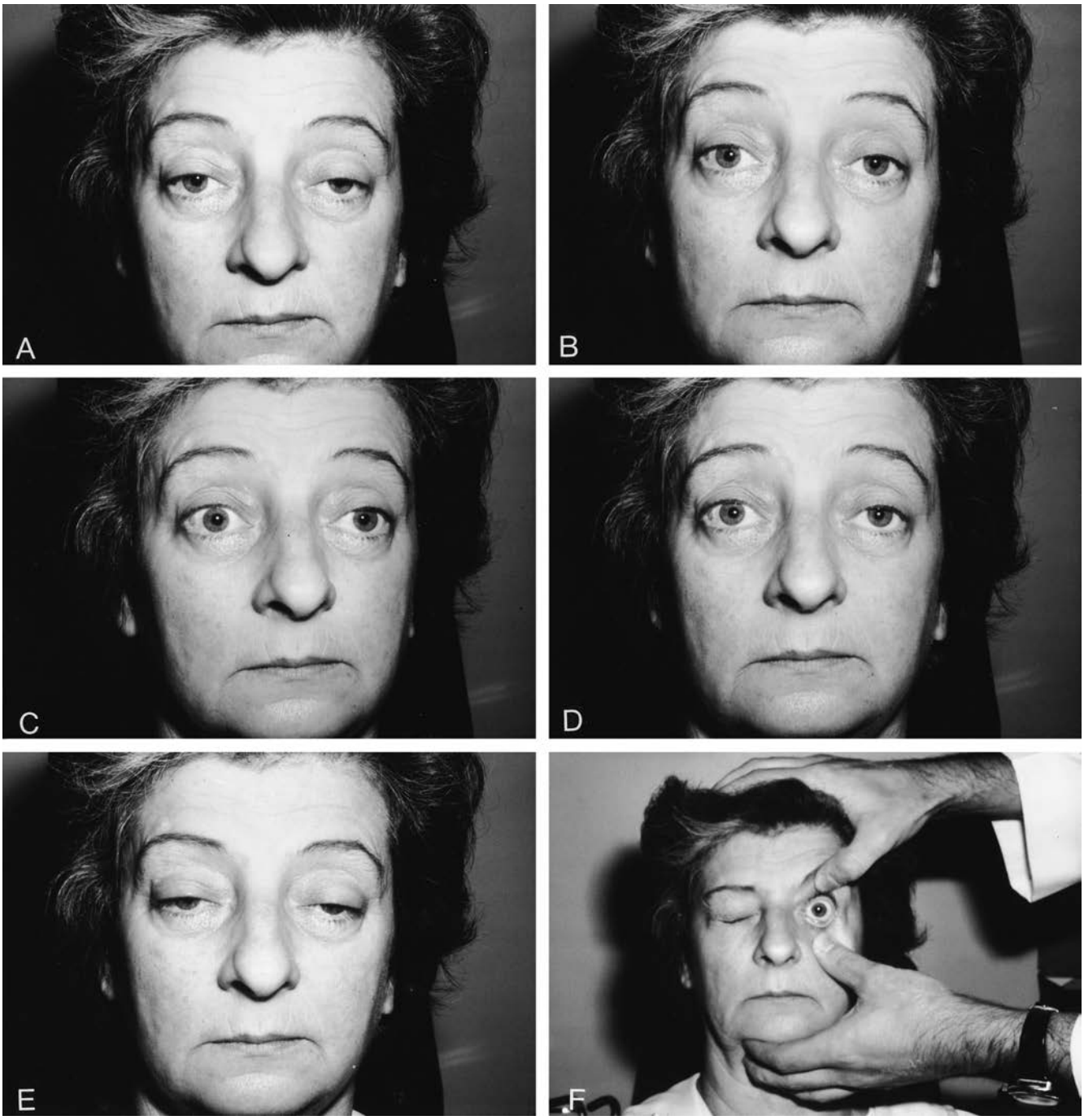

Figure 61.3. Ophthalmoparesis and ptosis in acute inflammatory demyelinating polyneuropathy. The patient was a 53-year-old woman who developed an ascending paralysis 1 week after experiencing a nonspecific febrile gastrointestinal illness. As the paralysis was worsening, she developed bilateral ptosis and diplopia. *A,* External appearance of patient. Note bilateral ptosis, left greater than right. *B,* There is no movement of the eyes during attempted right gaze, although the eyelids elevate slightly during the effort. *C,* There is slight abduction of the left eye during attempted left gaze. *D,* During attempted upward gaze, the eyelids and brows elevate somewhat, but there is no movement of the eyes above the midline. *E,* During attempted downward gaze, the eyelids lower, but the eyes show no significant movement. *F,* The patient has no Bell phenomenon.

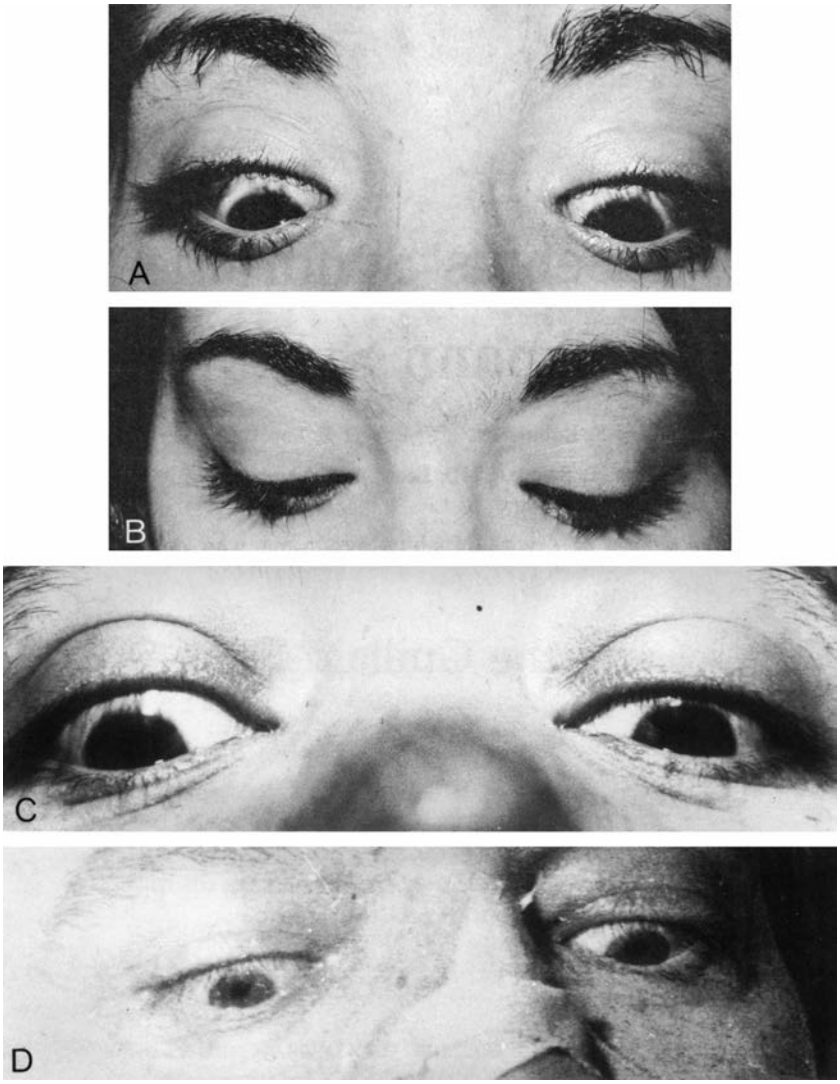

Figure 61.4. Lid lag in acute inflammatory demyelinating polyneuropathy. *A,* Symmetric lid lag on attempted downgaze in a 17-year-old girl. *B,* Three months later, the lid lag has resolved. *C,* Lid lag in a 28-year-old woman. *D,* Lid lag in a 55-year-old man. (*A and B,* From Keane JR. Lid-lag in the Guillain-Barré syndrome. Arch Neurol 1975;32:478–479. *C,* From Tan E, Kansu T, Kirkali P, et al. Lid lag and the Guillain-Barré syndrome. J Clin Neuroophthalmol 1990;10:121–123.)

some patients with AIDP. Accommodation insufficiency usually is part of oculomotor nerve dysfunction or a generalized disturbance of the near reflex, in which case other evidence of oculomotor nerve dysfunction (i.e., ptosis and ophthalmoparesis), reduced or absent convergence, and a reduced or absent pupillary reaction to near stimulation are present; however, paralysis of accommodation also may occur as an isolated phenomenon and may even be the presenting sign of the disorder (115).

Papilledema occurs in some patients with AIDP (Fig. 61.5). Increased intracranial pressure seems to be related to an increased protein concentration in the CSF with resultant reduced CSF absorption through the arachnoid villi (2–4,116,117). In other cases, the protein concentration is at or near normal, suggesting that some other process is responsible for the increased intracranial pressure. Some of these patients fit the criteria for a diagnosis of idiopathic intracranial hypertension (pseudotumor cerebri), especially those who develop signs and symptoms of increased intracranial pressure before they develop the more typical deficits of AIDP (118). Others develop overt hydrocephalus with enlarged ventricles seen on neuroimaging (2–4).

Optic neuritis may occur as the presenting sign or during the course of AIDP (2,36,119). It usually is bilateral and may be retrobulbar or anterior (i.e., a papillitis) (Fig. 61.6). Visual loss may be mild or severe. Most patients with AIDP-associated optic neuritis experience complete or nearly complete return of vision within several weeks, but some have persistent visual difficulties associated with pallor of one or both optic discs. The occurrence of optic neuritis in patients with otherwise typical AIDP is often taken as further evidence that the disease may very rarely affect the CNS (36,119).

LABORATORY TESTS

The two most important confirmatory tests for AIDP are electrophysiologic studies and lumbar puncture. Both should be considered to confirm the disease. Magnetic resonance (MR) imaging can be performed to eliminate other causes

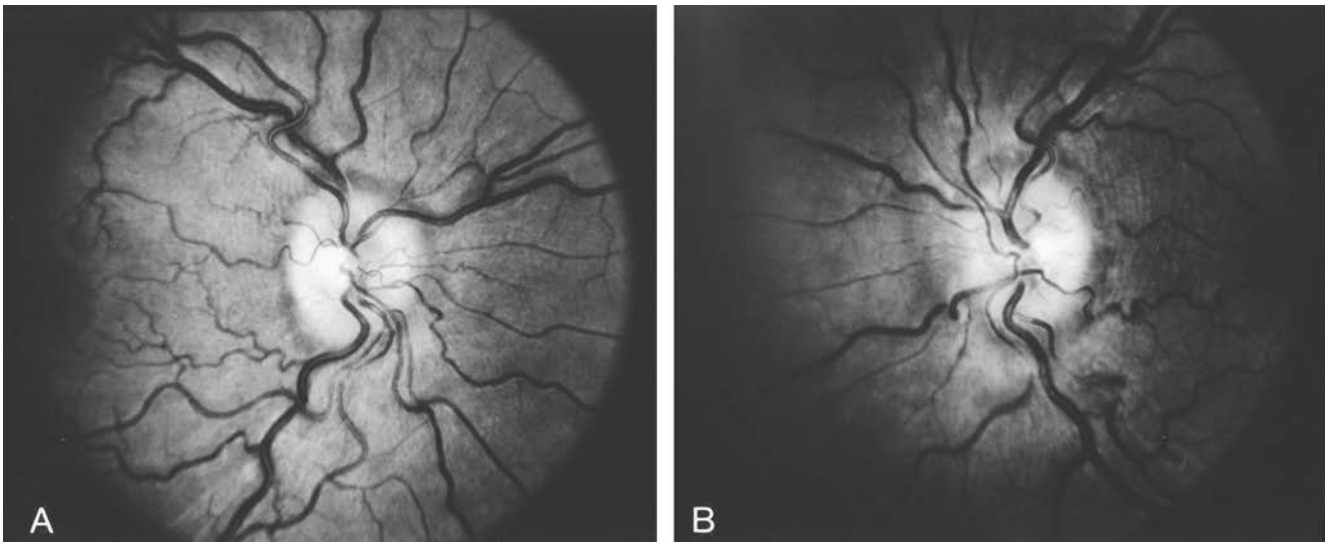

Figure 61.5. Papilledema in acute inflammatory demyelinating polyneuropathy. The patient was a 24-year-old woman who had an ascending paralysis without ptosis or ophthalmoparesis. *A,* The right optic disc shows moderate papilledema. *B,* The left optic disc shows moderate papilledema. Neuroimaging was negative. A lumbar puncture revealed an opening pressure of 350 mm H_2O. The protein concentration of the CSF was only mildly increased (65 mg/dl). The papilledema resolved spontaneously as the patient's neurologic condition improved.

of progressive weakness and may also reveal marked enhancement of nerve roots, cranial nerves, and the cauda equina (120,121), although these findings are not diagnostic of AIDP.

Electrophysiologic Studies

Nerve conduction slowing or block is found in about 80% of patients at some time during the course of AIDP (4). Conduction velocity usually is reduced to 60% of normal or more, and distal latencies may be prolonged to three times normal. The most common abnormality is prolonged distal latency on motor nerve conduction, followed by reduction of compound muscle action potential (CMAP) amplitude, decreased velocity, conduction block, and F-wave abnormality. Sensory conduction abnormalities are detected in over 20% of median, 25% of ulnar, and 33% of sural nerves (122,123). Often the process is patchy, and not all nerves are affected. Thus, the probability of detecting such abnormalities increases with the number of nerves studied.

The F-wave is a late-evoked muscle response. It occurs after the direct motor potential following supramaximal stimulation of a nerve. It probably represents a recurrent antidromic discharge of a motor neuron (124). The H-reflex is another late response that has a slightly longer latency than the F-wave. It has a threshold that usually is lower than that of direct CMAPs (4). The H-reflex study measures the latency over the monosynaptic reflex arc through afferent Ia fibers and efferent alpha motor fibers of the S1 root (125). Importantly, *significant prolongation of the minimal latencies of the F-wave and H-reflex may be demonstrated in patients with AIDP when conventional nerve conduction studies are normal* (126). When these late-response studies are combined with nerve conduction studies, AIDP can be confirmed in almost 100% of cases (127).

Advanced electrophysiologic techniques can also help confirm the diagnosis of AIDP. Low amplitude of the distal CMAP, usually with prolonged distal latency, and temporal dispersion of the distal CMAP are useful early signs of AIDP. Vertebral electric stimulation of nerve roots and motor evoked potentials both have some potential value as a diagnostic and prognostic tool (128). Somatosensory evoked potentials (SEPs) may also be helpful; however, SEP is less sensitive than nerve conduction or late-response studies and are indicated only if both of the latter give normal results (2–4,122,128).

Lumbar Puncture

Analysis of CSF plays an important role in the diagnosis of AIDP (2–4). CSF is under normal pressure in most cases. Rarely, however, patients with AIDP develop increased intracranial pressure, which in most cases appears to be related to increased CSF protein (discussed later); however, cases occur in which increased intracranial pressure develops in the setting of normal CSF protein (2–4,118,129).

The CSF contains no cells or only a few lymphocytes in 90% of cases. In about 10% of cases, however, a mononuclear pleocytosis is present. The pleocytosis usually is quite mild, with 10 or fewer monocytes/mm^3, although rare patients have 10–50 cells/mm^3, and exceptional patients have an even higher number.

An increased concentration of protein occurs in 90% or more of cases of AIDP. The protein content usually is normal (15–45 mg %) during the first few days of the clinical course but then begins to rise, reaching a peak in 4–6 weeks. Ulti-

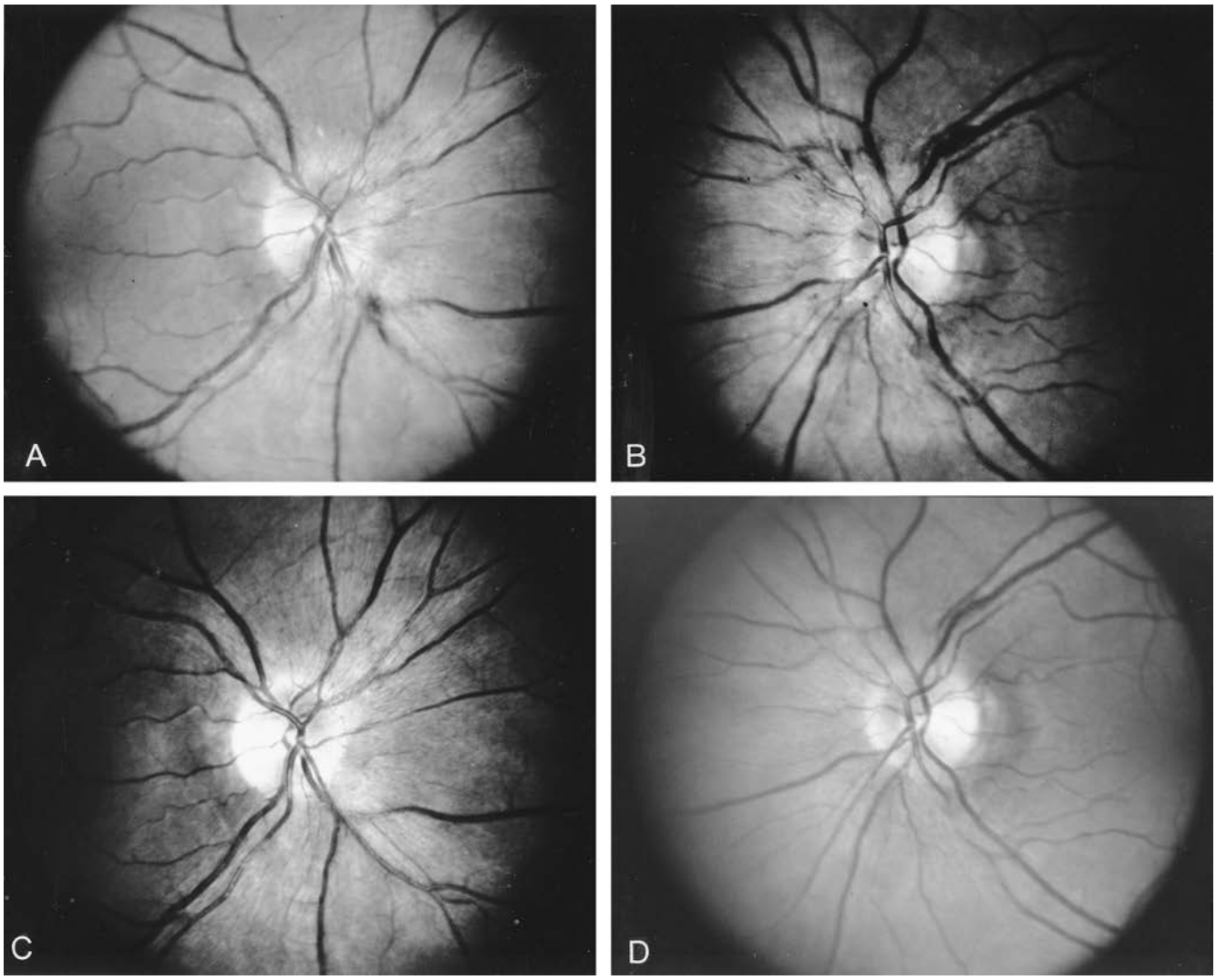

Figure 61.6. Optic neuritis in acute inflammatory demyelinating polyneuropathy (AIDP). The patient was a 53-year-old woman with acute visual loss about 3 days after the onset of typical AIDP. Visual acuity was 20/400 OD and 20/100 OS; color vision was abnormal in both eyes; and visual field testing showed bilateral central scotomas. *A,* The right optic disc is mildly hyperemic and swollen. A few peripapillary hemorrhages are present. *B,* The optic disc OS is mildly hyperemic and swollen, and there are several peripapillary hemorrhages. The patient was treated with systemic corticosteroids and supportive care. Three weeks after the onset of visual loss, visual acuity returned to 20/20 OU; color vision is normal; and visual fields are full. *C,* The right optic disc appears normal. It is no longer hyperemic or swollen. *D,* The left optic disc appears normal.

mately, the protein concentration may be greater than 400 mg/dl, although less dramatic elevations are the rule. The increase in CSF protein in patients with AIDP probably is a reflection of the widespread inflammatory disease of the nerve roots. There is no obvious correlation between the protein concentration in the CSF and the severity, mode of onset, progression, or outcome of the disease (2–4).

DIAGNOSIS

AIDP is the most frequent etiology for an acute polyneuropathy that rapidly evolves to a potentially fatal form; however, other types of acute polyneuopathy and CNS lesions must be eliminated to confirm the diagnosis (2–4). Laboratory features generally inconsistent with AIDP are: (*a*) more than 50 monocytes/mm^3 in the CSF; (*b*) the presence of polymorphonuclear leukocytes in the CSF; and (*c*) normal nerve conduction and late-response studies (2–4).

When clinical findings, the results of lumbar puncture, results of electrophysiologic testing, or clinical course are atypical in a patient with presumed AIDP, other disorders should be considered. Poliomyelitis, although rare, can be distinguished by its epidemic nature, associated fever, meningeal symptoms, pure motor weakness, and asymmetric areflexia. Acute transverse myelitis is typically a complete or near complete sensorimotor paralysis below a certain

level, with hyperreflexia and sphincter paralysis. Rarely, basilar artery aneurysm or thrombosis can be misdiagnosed as AIDP, although both usually present with hyperactive reflexes and extensor toe signs in addition to generalized weakness. Acute myasthenia gravis can mimic AIDP except that sensory abnormalities are absent and reflexes usually can be elicited. In addition, there usually is rapid improvement in myasthenia gravis with rest, after intravenous injection of edrophonium chloride, and after intramuscular injection of neostigmine bromide. Cholinergic crisis (due to the medicines used to treat myasthenia gravis) can mimic AIDP (2–4). Sarcoidosis occasionally mimics AIDP (130), as can tumors within the cauda equina, acute intermittent porphyria, botulism, diphtheria, hexacarbon abuse, nonorganic illness, atypical multiple sclerosis, and toxic polyneuropathy (from a variety of substances like dapsone, lead, nitrofurantoin, and organophosphorus compounds) (2–4).

TREATMENT

Meticulous supportive care and aggressive rehabilitation are essential in the management of patients with AIDP (2–4,101,131–133). Frequent autonomic dysfunction necessitates continuous monitoring of the electrocardiogram and blood pressure. Respiratory dysfunction may lead to respiratory failure or infection. Active respiratory therapy thus is crucial. Elective intubation and assisted ventilation should be performed when necessary (2–4). If this is being considered, it is valuable to remind the patient and family often that AIDP usually is fully reversible. Pulmonary and urinary tract infections are common, and appropriate antibiotics should be used when such infections occur. Frequent repositioning of patients is necessary to avoid nerve pressure palsies and decubitus ulcers. Passive movement of the joints through a full range of motion is beneficial in maintaining flexibility of the limbs and reducing the probability of venous thrombosis. Low-dose heparin and anti-thrombus stockings may be used to prevent deep-vein thrombosis and secondary pulmonary embolism. Active physical therapy improves the speed and degree of recovery (2–4).

Systemic corticosteroids are not advocated in AIDP. They have little or no beneficial effect on the severity or prognosis of the disease whether given orally or intravenously (134–136).

Unlike corticosteroids, **plasma exchange (plasmapheresis)** has a beneficial effect on the severity and course of AIDP that has been well-documented in several controlled clinical trials (3,12,101,132,137–143). In patients treated within 14 days from onset, there is a clear reduction in the length of hospitalization, the time mechanical ventilation is required, and the time to recovery of ambulation. However, if delayed, the procedure often has less value. Predictors of good response are younger age (132,137–143) and preserved CMAPs at the time treatment is begun (143,144). Patients treated with continuous flow plasma exchange may be more likely to experience a relapse of AIDP than patients who are treated with intermittent flow (145). There is a suggestion that patients treated with plasmapheresis very early in the course may suffer a relapse following therapy (145–147). A total of four to six treatments usually are performed on alternate days for most patients with AIDP, but, occasionally, five to nine total exchanges performed daily are necessary for severely affected individuals (2–4,132). The usual replacement fluid is saline mixed with 5% albumin. Potential complications of plasma exchanged are reduced fibrinogen leading to hypoprothrombinemia with bleeding, cardiac arrhythmias, and hypotension. Hepatitis and HIV infection also are potential risks when albumin is used in the exchange fluid (2–4,132).

Intravenous immune globulin (IVIg) is also beneficial in the treatment of patients with AIDP. The effects of IVIg were compared with plasmapheresis in a randomized trial of 150 patients with the condition (148). The IVIg group had fewer complications and less need for artificial ventilation than the group treated with plasmapheresis, and patients in this study who were treated with plasmapheresis did not improve to the degree reported in other studies. Thus, many clinicians now suggest that treatment with IVIg is practical, safe, effective, and possibly superior to plasma exchange in both adults and children with AIDP (138,148–151). The mechanism of action of IVIg is reviewed later in the section concerning chronic inflammatory demyelinating polyneuropathy (CIDP). Rarely, patients treated with IVIg die from complications related to vascular thrombosis; thus, no treatment is without potential risk, and the decision to treat a patient with AIDP with any medication or procedure should be made on an individual basis (137,152–154).

Therapeutic strategies other than those described previously, such as filtration of CSF, have been suggested for patients with AIDP (155). None of these has been used sufficiently to determine if it is truly beneficial.

Not all patients with AIDP require treatment. Many clinicians simply observe the patient as an outpatient if there are only minimal signs and symptoms (2–4,133). Mild AIDP reaches its clinical nadir in a tempo similar to severe disease. Treatment may be unnecessary in patients who can walk during the second week of illness; however careful observation is required to be certain the illness does not progress (2,3). If reduced ambulation, breathing, or swallowing occurs, treatment must be begun immediately.

PROGNOSIS

Although generally considered benign, 3 to 8% of patients with AIDP die. Complications include respiratory failure, pulmonary emboli, and effects of autonomic dysfunction (2,3,101). Disabling weakness, imbalance, or a loss of sensation persists in another 5–10%. About 65% of patients have persistent but minor neurologic disturbances, including distal numbness or foot-drop. In some series, only 15% of patients with AIDP experience complete neurologic, systemic, and visual recovery. In addition, some patients experience recurrent signs and symptoms weeks to months after their disease is thought to have run its course (78,156).

Only a few clinical or laboratory factors can predict outcome in patients with AIDP. There appears to be no correlation between good recovery and gender, prodromal illness,

severity of neurologic deficit, degree of conduction block by nerve conduction studies, or concentration of protein in the CSF (125,157); however, children and young adults have a better prognosis than older adults and the elderly (66,67,142,143). Poor prognostic signs include rapid tempo of disability at onset, early respiratory failure, no respiratory improvement within 3 weeks after reaching peak deficit, and rapid onset of quadriparesis (2,3). In some series, patients with normal electrophysiologic studies had a more rapid recovery. Low mean CMAP amplitudes, positive sharp waves, and spontaneous fibrillations indicative of axon degeneration all imply a slow rate of recovery and a poor prognosis for complete recovery (66,67,143). A high concentration of neuron-specific enolase (NSE) or S-100b protein in the CSF was associated with a longer duration of disease in one study (158).

SITE OF THE LESION

Pathologic studies of patients with AIDP both with and without ophthalmoparesis usually show no lesions in the CNS (76,82,91). Involvement of the CNS thus is considered quite unusual in most patients with AIDP, although apparently it can occur simultaneously on rare occasions (76,82,91,159,160). Immune reactions against target epitopes in Schwann-cell surface membrane or myelin cause AIDP in about 85% of cases (2–4,105). Central chromatolysis affecting the nuclei of the ocular motor and other cranial nerves has been demonstrated (105) (Fig. 61.1).

MILLER FISHER SYNDROME (OPHTHALMOPLEGIA, ATAXIA, AND AREFLEXIA; FISHER'S SYNDROME)

In 1956, C. Miller Fisher described an unusual variant of AIDP (then called GBS) (161). The variant was characterized primarily by external ophthalmoplegia, ataxia, and areflexia. Although similar cases had been described previously (162), the condition became known as the Miller Fisher syndrome (163–165) or simply Fisher's syndrome.

EPIDEMIOLOGY

MFS occurs in the same clinical setting as AIDP, with the majority of cases occurring after a recent viral or bacterial infection (37,166,167). There appears to be a similar association between *C. jejuni* infection and MFS as with AIDP (166). MFS also has been reported after vaccination, and individual cases have occurred in association with systemic lupus erythematosis (168), membranous glomerulonephritis (169), immunosuppressive therapy for rheumatoid arthritis (170), and the use of gold salts as treatment for rheumatoid arthritis (171).

MFS occurs twice as often in men as in women (163–165). Most patients are in the 3rd to 7th decade of life (172), although children and even infants may develop the condition (173–175) (Fig. 61.7). There may be a genetic predisposition to develop MFS. HLA typing for class I antigens on 19 Japanese patients demonstrated an association between the disease and the HLA-B39 haplotype (17).

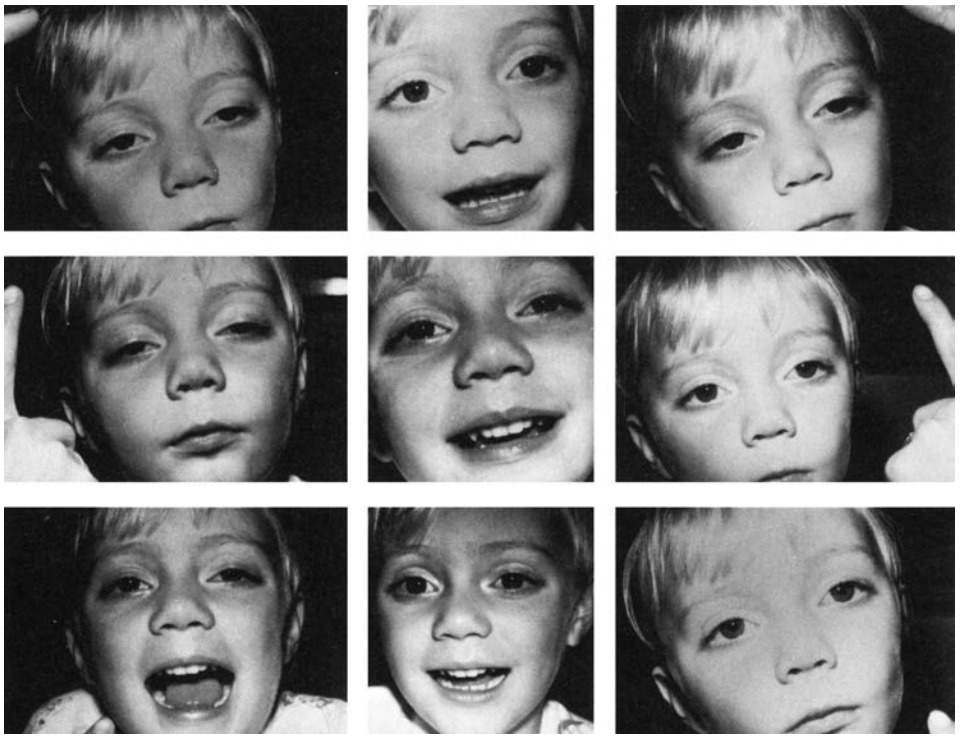

Figure 61.7. Miller Fisher syndrome in childhood. The patient was a 3.5-year-old boy who developed bilateral ophthalmoplegia, ataxia, and areflexia about 8 days after experiencing a flu-like illness characterized by fever, pharyngitis, diarrhea, and vomiting. The center photograph shows mild bilateral ptosis and mild bilateral facial weakness. The other photographs show the patient attempting to look in the nine cardinal positions of gaze. The patient gradually improved. (From Price RL, O'Connor PS, Rothner AD. Acute ophthalmoplegia, ataxia, and areflexia [Fisher's syndrome] in childhood. Cleve Clin Q 1978;45:247–252.)

CLINICAL MANIFESTATIONS

Classic MFS is a clinical triad of bilateral ophthalmoplegia, ataxia, and areflexia; however, many variants occur. Indeed, increasing numbers of cases with only one or two of the components are being reported on a regular basis.

The **ophthalmoplegia** in MFS can be complete (172), although there may be preservation of some movement of one or both eyes. In rare cases, only muscles supplied by one of the ocular motor nerves are affected (176). A variety of other forms of ophthalmoparesis can occur in patients with MFS, including internuclear ophthalmoplegia (Fig. 61.8), the one-and-a-half syndrome, variations of the dorsal mesencephalic (Parinaud) syndrome (Fig. 61.9), spasm of the near reflex, and divergence paralysis. In one series of 243 cases of MFS reported by Al-Din and colleagues (176), the ophthalmoplegia was remarkable in its constant association with a cerebellar type of ataxia and in a bilateral symmetry at all stages from onset through recovery. It usually evolved as a symmetric failure of upward gaze, then horizontal gaze, and, lastly, downward gaze. Recovery occurred in the reverse pattern, with downgaze improving first. It was hypothesized by the authors of this paper that the pattern of development and recovery was related to the fascicle innervating the superior rectus being the most heavily myelinated of all the fascicles of the third cranial nerve and, therefore, the first to be affected and the last to recover.

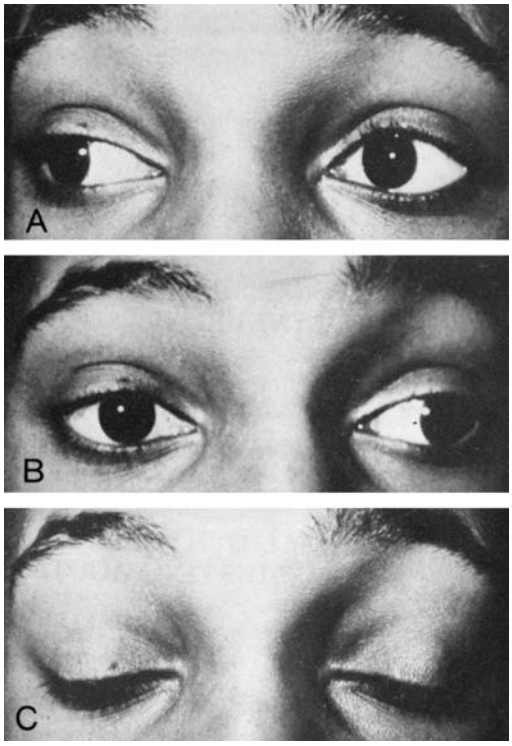

Figure 61.8. Bilateral internuclear ophthalmoplegia in the Miller Fisher syndrome. The patient was a 13-year-old girl with ataxia, areflexia, and ophthalmoparesis. *A,* With attempted gaze right, the patient has fairly normal abduction of the right eye, but the left eye shows limited and slow adduction. *B,* On attempted gaze left, the left eye has full and rapid abduction, but the right eye does not adduct much beyond the midline. *C,* Appearance of the patient attempting tight closure of the eyelids. Note bilateral weakness of the orbicularis oculi muscles. (From Weintraub MI. External ophthalmoplegia, ataxia, and areflexia complicating acute infectious polyneuritis. Am J Ophthalmol 1977;83:355–357.)

Despite the tendency for patients in the series by Al-Din et al. (176) to have a bilateral, symmetric, and complete ophthalmoplegia, 58 of the 243 patients (24%) had at least some sparing of downgaze. There was a Parinaud syndrome in two patients, convergence spasm in six, internuclear ophthalmoplegia in 15, and horizontal dissociated nystagmus in 11. Twenty-three patients had paralysis of abduction progressing to lateral gaze paralysis, whereas five had abduction and contralateral gaze paralysis. Four patients in the series had a defective vestibulo-ocular reflex despite recovery of upgaze, and 10 had central-type nystagmus, including torsional, retraction and rebound nystagmus. Relative preservation of optokinetic nystagmus and preservation of vestibulo-ocular reflexes despite an otherwise complete ophthalmoplegia were reported in six patients and two patients, respectively (176).

Ptosis can occur in patients with MFS. It may be unilateral, bilateral, symmetric or asymmetric, and complete or incomplete (165) (Fig. 61.7). The ptosis may increase when the contralateral eyelid is manually elevated (177) (Fig. 61.10), a phenomenon called ''enhanced ptosis'' and observed most often in patients with myasthenia gravis.

Eyelid retraction occurs in less than 10% of patients with MFS, and about the same percentage show a preserved Bell phenomenon despite paralysis of upgaze (176,177). Upper eyelid jerks are very rarely observed in patients with MFS and may be related to vertical ophthalmoparesis (176,177).

Pupil size and responses were reviewed in a series of 223 patients with MFS and were abnormal in about 50% of them (172) (Fig 61.11). The most common abnormality is unilateral or bilateral pupillary dilation with a poor or no reaction to light stimulation (170,177–180). In most of these cases, some degree of ophthalmoparesis is present, but a case of internal ophthalmoplegia without external ophthalmoplegia has been reported (181). Anisocoria with relatively normal pupillary responses is seen in some cases. In such cases, attempts to define the nature of the anisocoria by pharmacologic testing have produced conflicting or ambiguous results (170,172,177–181).

Ataxia is pronounced in patients with MFS and usually is truncal in nature. It is thought to be caused not by intrinsic damage to the cerebellum but by abnormal conduction through demyelinated peripheral spinocerebellar fibers (182). There usually is no evidence of motor weakness in the extremities, even in patients who are areflexic or have severe, symmetric hyporeflexia. Some of these patients have persistent extensor plantar reflexes, however.

Cranial neuropathies including optic neuritis can occur in patients with MFS. The fact that optic neuritis can rarely occur with MFS provides some evidence that, as in the case of AIDP, the CNS occasionally is involved in this disease. Improvement in the optic neuritis usually occurs, as it does in AIDP (119,183–186). Other than the ocular motor nerve,

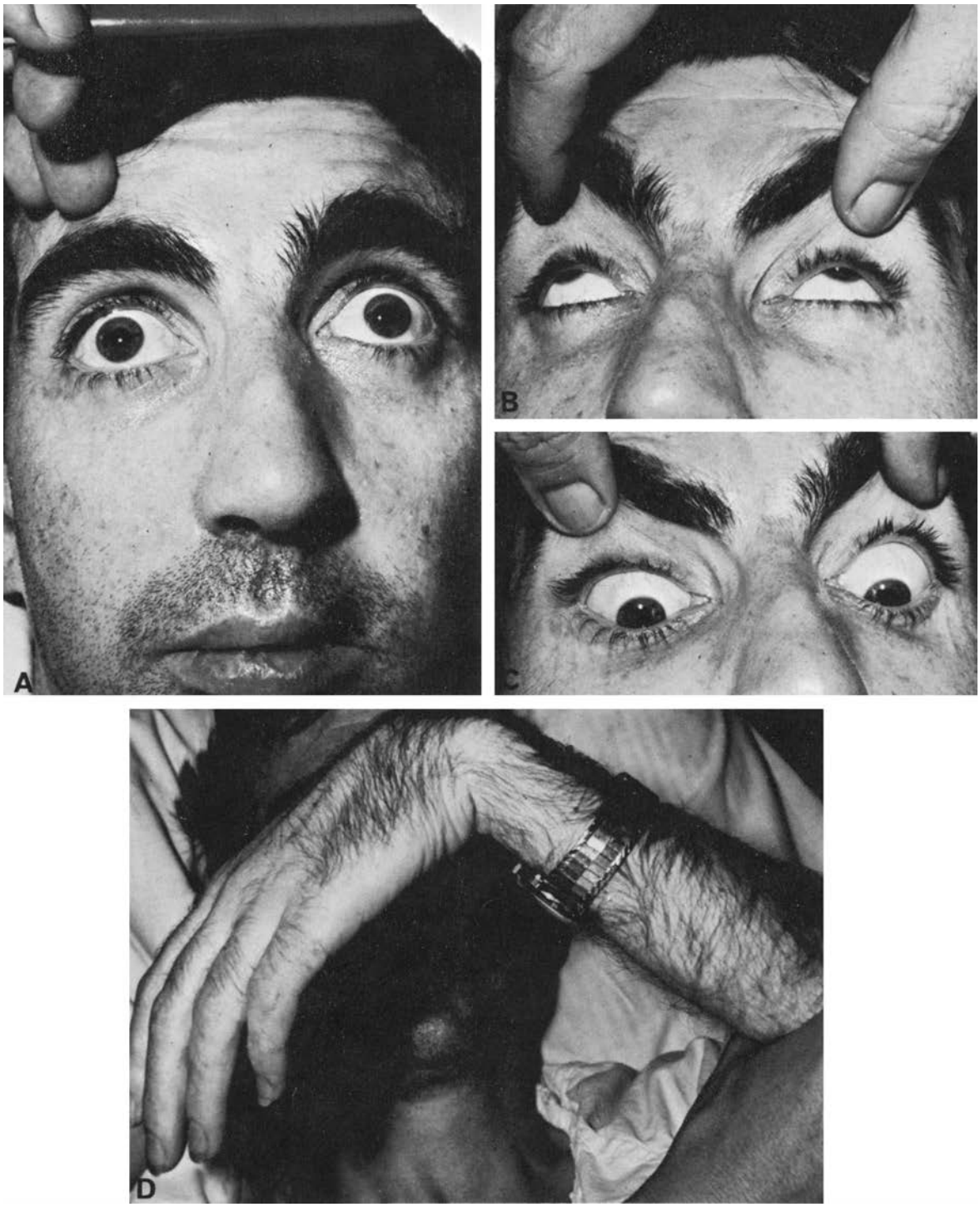

Figure 61.9. Paralysis of upward gaze in the Miller Fisher syndrome. *A,* Appearance of the patient attempting to look upward. Note limited upward gaze. Also note bilateral facial weakness. *B,* The patient has a normal Bell's phenomenon. *C,* The patient has relatively normal downward gaze. *D,* Profound weakness of the left upper extremity, worse distally. The patient experienced complete recovery within 10 weeks.

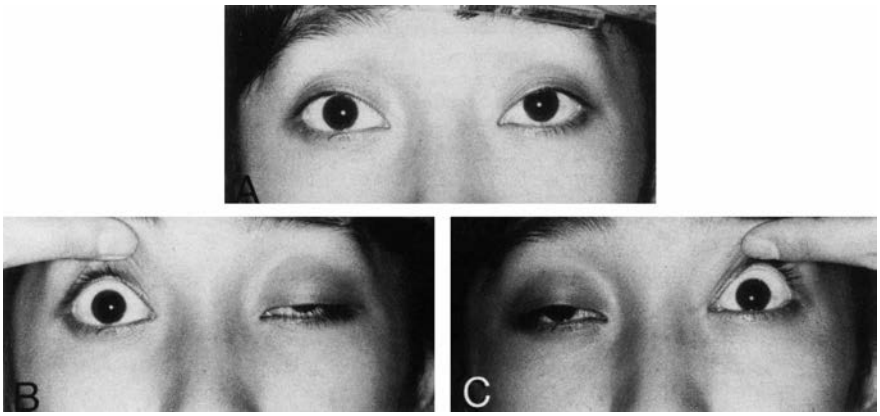

Figure 61.10. Enhancement of ptosis in the Miller Fisher syndrome. The patient was a 20-year-old woman who developed ataxia, areflexia, and ophthalmoplegia about 2 months after experiencing an attack of infectious mononucleosis. *A,* In primary position, the patient has mild left ptosis. *B,* With manual elevation of the right upper eyelid, the left ptosis worsens considerably. *C,* With manual elevation of the left eyelid, the right eyelid becomes severely ptotic. This ''enhancement'' of ptosis while raising the opposite eyelid can mimic myasthenia gravis. (From Ishikawa H, Wakakura M, Ishikawa S. Enhanced ptosis in Fisher's syndrome after Epstein-Barr virus infection. J Clin Neuroophthalmol 1990; 10:197–200.)

the facial nerve is the cranial nerve most often affected (187) (Figs. 61.7 and 61.9). Other cranial nerves may be damaged, however (187). Unusual examples have included trigeminal nerve sensory dysfunction (188), alternating recurrent episodes of peripheral facial palsy (189), and dysfunction of the vestibulo-cochlear nerve (165). Enhancement of affected (and, occasionally, clinically unaffected) cranial nerves may be noted with MR imaging (190–193).

Additional neurologic dysfunction in otherwise typical MFS may include migratory parasthesias and minimal sensory impairment that may progress to a sensory ataxia (194,195). Mental function remains normal throughout the course of MFS, although some patients become extremely agitated in the initial stages of the disease. Most of the neurologic dysfunction that occurs has been ascribed to damage of peripheral nerves on the basis of examination, imaging, and neuropathologic examinations (170–196); however, in rare cases, neurologic findings are consistent with CNS dysfunction (190–196).

LABORATORY TESTS

Patients with MFS can demonstrate changes in the CSF identical with AIDP. There is increased concentration of CSF protein, usually without pleocytosis (165). Electrophysiologic studies tend to be abnormal. Electromyography (EMG) reveals evidence of demyelination, occasionally associated with evidence of axonal degeneration. Detailed EMG and nerve conduction studies usually show abnormal conduction in peripheral sensory fibers from the initial stages of the disease (197,198). Abnormal brainstem auditory evoked potentials (BAEPs) have been reported in some patients (199–200).

Patients with MFS, particularly those with ophthalmoplegia, often have antibodies directed against GQ1b IgG (13,109,110). These antibodies cross react with surface epitopes on MFS-associated *Campylobacter jejuni* strains of bacteria. It is believed that the anti-GQ1b antibodies may be formed during the initial infection. The antigen initiating the immune response in MFS may not actually be GQ1b but rather one or more as yet unidentified glycoprotein antigens. In any event, the presence of cross-reactivity implies that molecular mimicry between bacteria and neural tissue may be part of the pathogenesis of the disease (201). Other potential mechanisms include a relationship to a serum factor (possibly the anti-GQ1b antibody) that leads to the failure of acetylcholine release from nerve terminals or a reversible presynaptic blockade of release caused by antibodies (202,203).

NEUROIMAGING STUDIES

Patients with typical MFS usually have normal imaging. However, in some patients, MR imaging shows abnormal signal, particularly in the brainstem, cerebellum, or both regions (184,186,190–193). As noted previously, MR imaging may also show enhancement of both affected and clinically normal cranial nerves (184,190–193). Occasionally, patients with MFS develop signs and symptoms of multiple sclerosis or a similar demyelinating process after apparent recovery from MFS (204). Whether the two conditions are related in some way is controversial, particularly considering the rarity of such a phenomenon.

DIAGNOSIS

MFS should be considered in any patient who develops the rapidly progressive triad of ophthalmoparesis (with or without pupillary and eyelid involvement), ataxia, and areflexia, and also in patients who develop only a part of the syndrome such as an isolated unilateral or bilateral ophthalmoparesis, ophthalmoparesis and ataxia, ophthalmoplegia and areflexia, or ataxia and areflexia. Diagnoses to exclude in such cases are Wernicke's encephalopathy, vascular brainstem disease, botulism, multiple sclerosis, myasthenia gravis, brainstem neoplasm, and a variety of bacterial or viral brainstem encephalitides (165). EMG and lumbar puncture help confirm the diagnosis, particularly when neuroimaging studies show no evidence of overt CNS involvement.

TREATMENT AND PROGNOSIS

Most patients with MFS improve completely in 8–12 weeks without treatment. Some patients, however, require considerable supportive care that occasionally includes as-

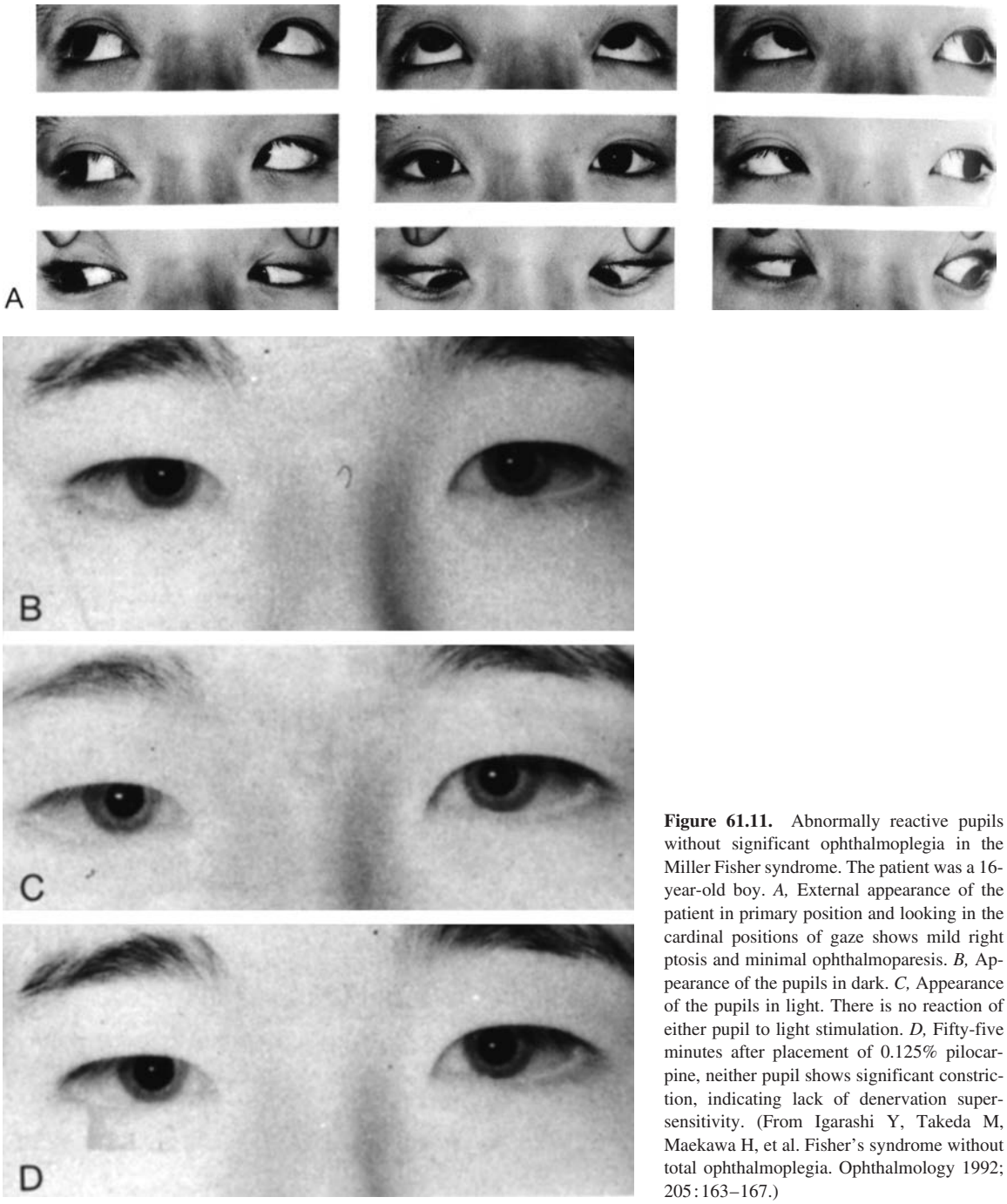

Figure 61.11. Abnormally reactive pupils without significant ophthalmoplegia in the Miller Fisher syndrome. The patient was a 16-year-old boy. *A,* External appearance of the patient in primary position and looking in the cardinal positions of gaze shows mild right ptosis and minimal ophthalmoparesis. *B,* Appearance of the pupils in dark. *C,* Appearance of the pupils in light. There is no reaction of either pupil to light stimulation. *D,* Fifty-five minutes after placement of 0.125% pilocarpine, neither pupil shows significant constriction, indicating lack of denervation supersensitivity. (From Igarashi Y, Takeda M, Maekawa H, et al. Fisher's syndrome without total ophthalmoplegia. Ophthalmology 1992; 205:163–167.)

sisted ventilation (175). Deaths have been reported (205), although this is quite rare. Patients with severe disease may benefit from treatment with plasma exchange or IVIg (170,206–208). Following recovery, most patients do not experience recurrent attacks; however, some patients experience relapses weeks to months after apparent resolution of the condition (194,209,210). Indeed, a relapsing polyneuritis following classic MFS has been reported (211), as has a chronic progressive inflammatory polyradiculopathy associated with a subacute MFS exacerbation (212).

SITE OF THE LESION

As is the case with AIDP, there is considerable controversy as to whether or not MFS is always caused by PNS demyelination or may be caused by lesions in the CNS. As noted previously, optic neuritis has been reported with MFS, implying a CNS process in these rare cases; however, most authors believe that the ocular motor dysfunction is caused by damage to the peripheral ocular motor nerves rather than to any intrinsic brainstem supranuclear or internuclear struc-

tures (159), and this concept is supported by the results of some (but not all) autopsy studies (213); however, clinical and neuroimaging findings challenge this concept (119,214,215). Indeed, both unilateral and bilateral internuclear ophthalmoplegia have been reported (216,217) (Fig. 61.8). On the other hand, one case report described a 60-year-old woman who developed MFS characterized by ataxia, areflexia, and an apparent left internuclear ophthalmoplegia that became bilateral within 24 hours. The patient eventually developed a bilateral, complete ophthalmoplegia, suggesting that the original internuclear ophthalmoplegia may have only been part of an evolving peripheral nerve lesion (216).

Other MFS-related syndromes that imply a brainstem lesion rather than peripheral nerve damage include the one-and-a-half syndrome (217), the dorsal mesencephalic (Parinaud) syndrome (218,219), spasm of the near reflex (220), divergence paralysis (221), and various combinations of vertical (Fig. 61.9) and horizontal gaze pareses (176) with or without nystagmus. Quantitative eye movement recordings in some of these cases reveal changes more consistent with a CNS lesion than a peripheral ocular motor neuropathy (220), and some patients with MFS have corresponding lesions of the brainstem by neuroimaging (192,199,217). Nevertheless, although a few pathologic studies have shown evidence of inflammation or demyelination in the brainstem or cerebellum (199,222), most have not (105,213). In unusual cases, there appear to be inflammatory and demyelinating lesions in a variety of different sites in both the CNS **and** the PNS (165,196,220). It thus may be too simplistic to ascribe all cases of MFS to either PNS or CNS disease.

PRIMARY AXONAL DEGENERATION SYNDROMES

The primary axonal degeneration syndromes include several disorders that mimic typical AIDP and that, like AIDP, appear to have an infectious or postinfectious immune-mediated pathogenesis. Pathologically, however, these conditions cause **degeneration** rather than demyelination of axons (91). Although rare, these disorders also have neuro-ophthalmologic manifestations.

PRIMARY AXONAL DEGENERATION SYNDROME (PADS)

In 1986, several patients were described with an AIDP-like syndrome but with electrophysiologic testing that demonstrated only axonal degeneration with no evidence of primary demyelination (223). Histopathologic examination of nerve roots and peripheral nerves confirmed **isolated axonal degeneration unassociated with demyelination or inflammation** (Fig. 61.12). Lipid-laden macrophages were identified beneath the myelin sheaths adjacent to the axons. This condition was labeled ''an axonal form of Guillain-Barré syndrome'' and subsequently was described in Europe, North America, and Japan (13,91,224–227). It eventually was renamed the **primary axonal degeneration syndrome** (PADS).

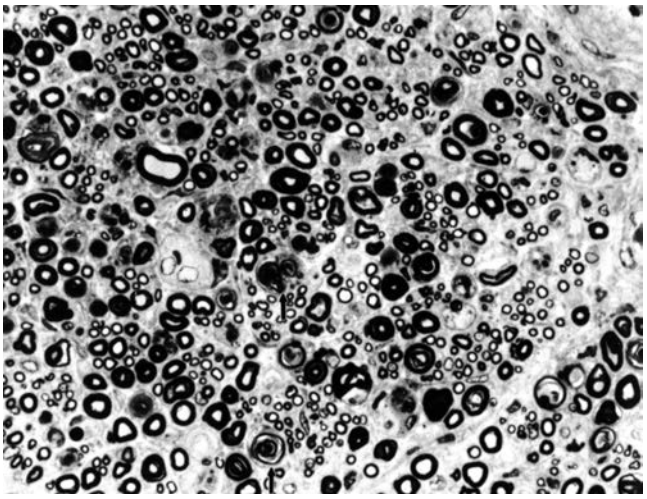

Figure 61.12. Pathology of primary axonal degeneration syndrome. Transverse section through lumbar ventral root shows severe degeneration of axons (*arrows*). Note presence of some macrophages. Toluidine blue. (From Feasby TE, Gilbert JJ, Brown WF, et al. An acute axonal form of Guillain-Barré polyneuropathy. Brain 1986;109:1115–1126.)

Like AIDP, PADS may occur after a viral or bacterial infection, particularly after infection with *Campylobacter jejuni* (13), after ingestion of exogenous gangliosides (228), and after acute respiratory failure (229). It may have a genetic predisposition; in Japan, patients often have the HLA-B35 haplotype (14). In addition, patients with PADS can have IgG antibodies to gangliosides GM_1 and GD1a antibodies in their serum (13,16). Unlike another form of axonal degeneration, acute motor axonal neuropathy (AMAN) (discussed later), PADS seems to have no seasonal or geographic predilection.

PADS produces clinical symptoms and signs similar to those of AIDP (223,225). Areflexia or hyporeflexia is the rule. Ophthalmoparesis, with and without ptosis, pupil disturbances, or both, is common. Affected patients develop an ascending paralysis that may be associated with sensory symptoms. These sensory deficits also help separate this condition clinically from AMAN (144,223,226).

CSF analysis in patients with PADS usually reveals an acellular fluid associated with a mild-to-moderate increase in protein concentration with an occasional mild lymphocytic pleocytosis. Electrophysiologic studies are abnormal, although the findings are different from those present in patients with AIDP. In PADS, both motor and sensory nerves show changes consistent only with axon injury without evidence of conduction block or primary demyelination (227).

Too few cases of PADS have been recognized and reported to determine the optimum treatment for the condition. Some patients can be managed with supportive care only. Others require treatment with plasma exchange or IVIg. The use of systemic corticosteroids in patients with this condition would seem unwarranted, particularly in view of pathologic findings indicating a paucity of inflammation in affected nerve fibers. Regardless of the treatment given, most patients

with this condition seem to recover, although there often is residual weakness.

ACUTE MOTOR AXONAL NEUROPATHY (AMAN)

A condition somewhat similar to PADS occurs mostly in China and initially was called the Chinese Paralytic Syndrome (230–233); however, cases occur in countries other than China, including Mexico (234), Spain (235), and South Korea (236). Accordingly, a more appropriate term is **acute motor axonal neuropathy** (226). AMAN occurs mostly among rural residents of northern China, usually during the summer and primarily in children (237–243). Like AIDP and PADS, AMAN seems to occur most often in patients with serologic evidence of recent *Campylobacter jejuni* infection (226). It appears as though the immune attack is directed against the axolemma and nodes of Ranvier in AMAN (237), sites different from those implicated in AIDP (discussed later).

Clinically, the tempo of progression of AMAN and AIDP differ considerably. AMAN is marked by rapidly progressive ascending tetraparesis, often with respiratory failure, but without fever, systemic illness, or sensory disturbances, whereas AIDP patients frequently have a longer progression after the first examination (240). Lack of sensory signs and symptoms also can be used to differentiate AMAN from AIDP, although this may be an oversimplification (238–240). Lumbar puncture in patients with AMAN usually reveals acellular CSF. If performed in the first week of the illness, the protein concentration of the CSF can be normal; however, protein typically increases during the 2nd or 3rd week of illness. Electrophysiologic studies show normal motor distal latencies and normal limb conduction velocities, although CMAPs are reduced. Sensory nerve action potentials and, when present, F-waves are within normal range (144,226).

Neuro-ophthalmologic manifestations are not unusual in patients with AMAN, although they have not been emphasized in most publications. Bilateral ophthalmoparesis, while not a prominent feature of AMAN, is not uncommon, and is often associated with ptosis. Disturbances of pupillary size and shape are rare.

Therapy for AMAN is not well delineated. Specifically, there are insufficient data to determine if patients with AMAN respond to plasma exchange or IVIg as do patients with AIDP. Even if one considers the electrophysiologic and pathologic findings in AMAN, particularly the lack of evidence of inflammatory demyelination, it would still seem reasonable to assume that patients might improve with such treatment.

The prognosis in most patients with AMAN is good. Many recover without treatment. This often starts within weeks although older patients are more likely to have a slower recovery. The mortality rate in the past was as high as 30% (230–232); however, it subsequently has decreased to less than 5%, presumably because of earlier diagnosis and improved supportive care (2–4,242).

The main pathologic finding in AMAN is Wallerian degeneration of ventral roots and motor fibers within peripheral nerves without evidence of inflammation or primary demyelination (Fig. 61.13). There are macrophages within the perixonal space surrounding or displacing the axon within an intact myelin sheath. Anterior horn cells in the spinal cord

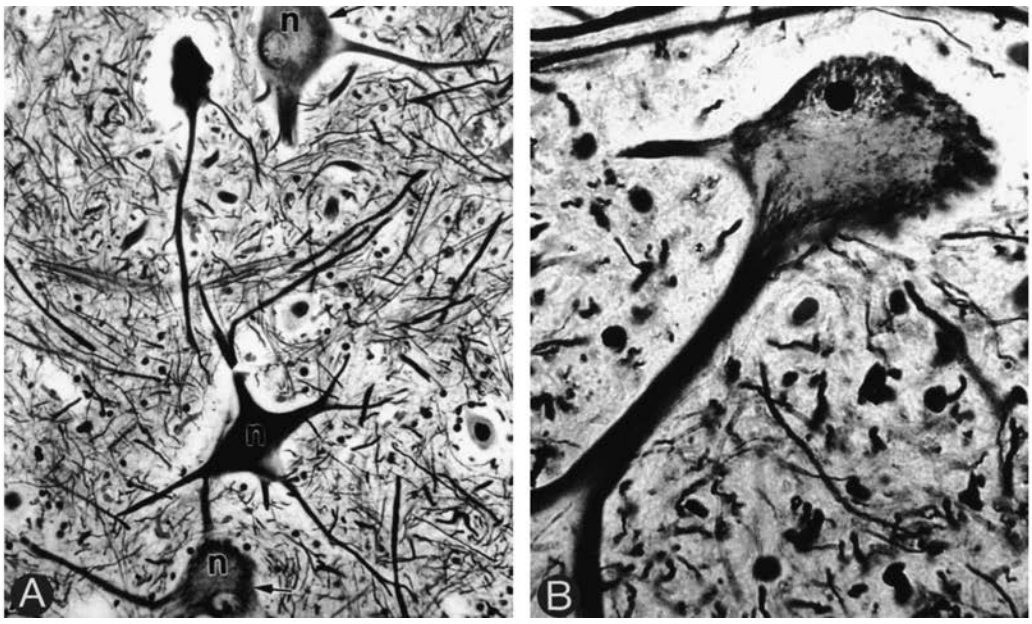

Figure 61.13. Pathology of acute motor axonal neuropathy (AMAN). *A,* Motor neurons (n) in the ventral horn of a patient with AMAN show no evidence of inflammation. Two of the neurons are enlarged and rounded (*arrows*). Both show evidence of chromatolysis. Silver/Luxol fast blue, ×320. *B,* High-power view shows a motor neuron undergoing chromatolysis. Note eccentric nucleus and dispersion of Nissl bodies in the center of the perikaryon. Silver/Luxol fast blue, ×800. *(Figure continues.)*

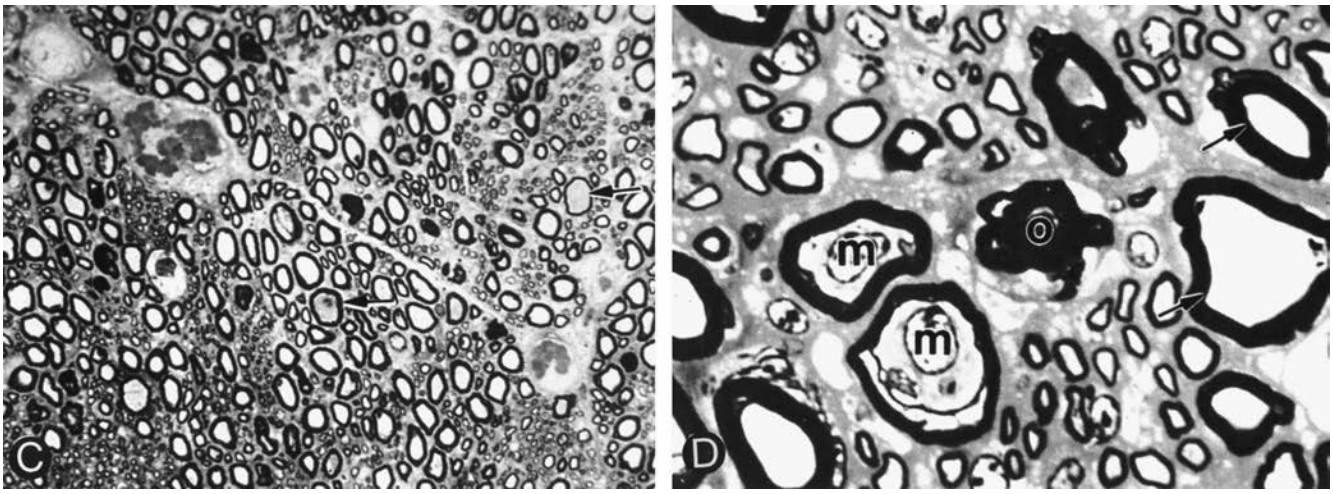

Figure 61.13. Continued. *C,* Midportion of a ventral root in another case of AMAN. Several fibers are undergoing wallerian-like degeneration, and other fibers are swollen (*arrows*). Toluidine blue, ×670. *D,* High-power view of axons in the affected ventral root. The photograph shows two swollen axons undergoing degeneration (*arrows*). Note macrophages (m) beneath their sheaths that, nevertheless, are intact. *o,* myelin ovoid. Toluidine blue, ×1400. (From McKhann GM, Cornblath DR, Griffin JW, et al. Acute motor axonal neuropathy: A frequent cause of acute flaccid paralysis in China. Ann Neurol 1993;33:333–342.)

show extensive chromatolysis. The dorsal columns remain normal, reflecting the lack of degeneration within dorsal roots. Among cranial nerves, degeneration is most prominent in those nerves with a motor component, especially the oculomotor, trochlear, abducens, facial, glossopharyngeal, and hypoglossal (224,226,233,241). This pathology is quite different from that of AIDP (238).

Some patients with apparent AMAN actually have a variant that is characterized by both motor and sensory manifestations as well as pathologic evidence of degeneration of both motor and sensory fibers without evidence of either inflammation or demyelination. This variant, called acute motor-sensory axonal neuropathy (AMSAN), has a strong seasonal occurrence and a geographic predilection for northern China (239).

The pathophysiology of AMAN appears to be similar in some ways to that of AIDP. Immunocytochemistry and reverse transcriptase polymerase chain reaction studies were performed on five patients with pathologically documented AMAN (241). T-lymphocytes in affected spinal nerve roots associated with increased levels of interferon-γ, interleukin-1β, and TNF-α were demonstrated in all cases. These findings are similar to those seen in patients with typical clinical and pathologic findings of AIDP and indicate that despite the very different patterns of the two diseases, both are apparently immune-mediated (241). On the other hand, the frequency of the anti-ganglioside antibodies anti-GM1, anti-GM1b, and anti-GD1a were far higher in patients with AMAN than in AIDP, suggesting a different pathogenesis. Interestingly, the frequency of these autoantibodies in AMSAN is similar to their frequency in AMAN, suggesting that the two conditions share a common immunological profile that is different than AIDP (239).

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

The chronic dysimmune polyneuropathies are a clinically heterogeneous group of disorders united by their presumed immune-mediated etiology. CIDP is the most common of these disorders, but differing subtypes are beginning to emerge. These subtypes include multifocal motor neuropathy (MMN), chronic inflammatory axonal polyneuropathy (CIAP), neuropathies in association with serum paraproteins (paraproteinemic neuropathies) and others (243). In this chapter, we will focus solely on CIDP.

CIDP typically presents as a symmetric sensorimotor polyneuropathy. It becomes chronically worse with gradually progressive (although occasionally exacerbating) motor deficits. There is also a hyporeflexia, classic for lower motor neuron lesions. Although some of the features of CIDP, such as CSF changes and electrophysiologic abnormalities consistent with a demyelinating polyneuropathy, are similar to those of AIDP, there also are important differences that relate to the tempo of disability and the ultimate prognosis. Although CIDP is far less common with fewer associated neuro-ophthalmologic abnormalities than AIDP, there still are many important features for the clinician to recognize.

Austin first emphasized what he described as ''a chronic and relapsing form of GBS'' in 1958, defining it largely by its responsiveness to systemic corticosteroids (244). Others also used the term ''chronic Guillain-Barré syndrome'' to describe these patients (245). Subsequently, it was emphasized that the condition was a different clinical entity from AIDP (246,247), and the disorder eventually was renamed **chronic inflammatory demyelinating polyneuropathy**. The clinical features of CIDP that distinguish it from AIDP

include: (*a*) a longer progression (2–3 months) before plateau; (*b*) a tendency for the illness to be less severe initially; (*c*) fluctuations in the severity of symptoms over many years; (*d*) greater elevations in CSF protein concentration; (*e*) more profoundly slowed motor nerve conduction velocities; and (*f*) a frequent association with systemic diseases such as systemic lupus erythematosus and Hodgkin's disease (2,248).

EPIDEMIOLOGY

Patients with CIDP range in age from 2 to 70 years with somewhat more males than females being affected, at least in some series. Well-defined antecedent events are less common in CIDP than in AIDP (2,249), but CIDP nevertheless develops after acute upper respiratory tract and other presumed viral infections, vaccinations, surgery, or pregnancy in 19–32% of patients (246,250,251). It also has been reported in association with CMV infection (250,251), non-Hodgkin's lymphoma (252), HIV infection (253), malignant melanoma (254), concurrent myasthenia gravis (255), Isaacs' syndrome (256), multiple sclerosis (2,257) and chronic liver disease (258). Among 33 consecutive cases of CIDP, three cases associated with carcinoma (paraneoplastic syndrome) were documented (259). Investigators have found an association between the disease and HLA haplotypes A1, B8, DRw3, and Dw3 (260). In one study, HLA typing was analyzed in 71 patients with CIDP and compared with a control population (261). There was an increased prevalence of HLA-A3, B7, and DR2 in the patients with CIDP compared with the control subjects.

PATHOLOGY

Nerve biopsies show demyelination in 20–40% of cases of CIDP. Onion-bulb formation occurs in 10–40%, indicating repeated episodes of demyelination and remyelination (2) (Fig. 61.14). The material surrounding the nerve fibers is predominantly connective tissue. Mononuclear cell infiltrates occur in 25–50% of biopsy specimens (246). In some pathology studies, there is little or no inflammation in the majority of specimens (247). Immunohistochemistry in 13 cases showed 10 with endoneurial infiltration of CD3+ T-cells (80). Epineural T cells were present in 11 of the 13 cases. Hypesthesia was associated with significantly higher numbers of macrophages. C3d and sometimes IgM have been demonstrated on the myelin sheaths of the sural nerves in CIDP (262). There may be concomitant axonal loss secondary to primary demyelination (263). Axonal loss is the major long-term poor prognostic indicator in CIDP (264).

As CIDP rarely has a fatal outcome, only a few postmortem studies have been performed in patients with the condition (246,265). These have shown clusters of endoneural lymphocytes and monocytes associated with degeneration of myelin in posterior roots and peripheral nerves. Occasional cases show inflammation of the meninges. One autopsy performed on a patient with CIDP who had disturbances of eye movement before death revealed scattered collections of lymphocytes in the brainstem (246).

PATHOGENESIS

The pathogenesis of CIDP remains unclear. Support for a cell-mediated component is based on the observation of a mononuclear cell infiltrate, both diffuse and perivascular, in spinal roots, spinal ganglia, and proximal nerve trunks of postmortem cases (265). The target for the infiltrate is not fully understood (248); however, the expression of endothelial leukocyte adhesion molecule (ELAM) was noted in the epineural vessels of five of 10 cases of CIDP evaluated with sural nerve biopsies (266). Transient expression of ELAM in response to cytokine stimulation has also been documented, suggesting that endothelial cells play a role in the extravasations of infiltrative cells in CIDP; however, the positive response of symptoms to plasma exchange (discussed later) suggests that there also may be a humoral component to the pathogenesis of the disease. IgG and IgM antibodies to the ganglioside GM1 have been found in the serum and CSF of a substantial percentage of patients. A similar finding in the sera of patients has also been found (267). Circulating TNF-α increases during the active phase in a subgroup of CIDP patients and may play a role in the demyelination and breakdown of the blood–nerve barrier (268).

CLINICAL MANIFESTATIONS

CIDP usually begins insidiously and may evolve very slowly. Unlike AIDP, it may take months for it to reach its maximum level of severity. The condition is characterized by symmetric proximal and distal weakness that occurs early in the illness (269). This progressively worsens over 6 weeks or more and is associated with hyporeflexia or areflexia. The weakness may be mild or severe, but assisted ventilation is rarely required (2,3,248). Most patients also develop sensory disturbances, particularly paresthesias in the toes and the tips of the fingers, although painful paresthesias are uncommon. In some patients, these and other sensory symptoms occur early in the course of the disease. In 10 patients with CIDP in whom there was electrophysiologic evidence of demyelination of both sensory and motor nerve fibers, the majority of clinical symptoms were sensory (270). Some patients with CIDP develop a postural tremor that is unrelated to weakness or proprioceptive loss and usually occurs late in the course of the disease (2,3).

Cranial nerve palsies rarely occur in patients with CIDP. Five patients with CIDP in whom cranial nerve involvement accompanied a more generalized neuropathy were reported by Waddy and colleagues (271). Facial and oropharyngeal weakness occurred in less than 15% of the patients in this study, far less than in AIDP. A bilateral vestibulopathy associated with CIDP was reported in one patient with CIDP (272). MR imaging in that patient demonstrated enhancement of the vestibulo-cochlear nerves on both sides. Unilateral or bilateral, nonsimultaneous **optic neuropathies** can occur very rarely in patients with CIDP (218,273,274).

Ophthalmoparesis develops in less than 5% of patients with CIDP (275). It may be bilateral, generalized, and associated with ptosis (276) but most often is associated with unilateral or bilateral abducens nerve paresis (212). In some cases, the abducens nerve paresis seems to be a major and

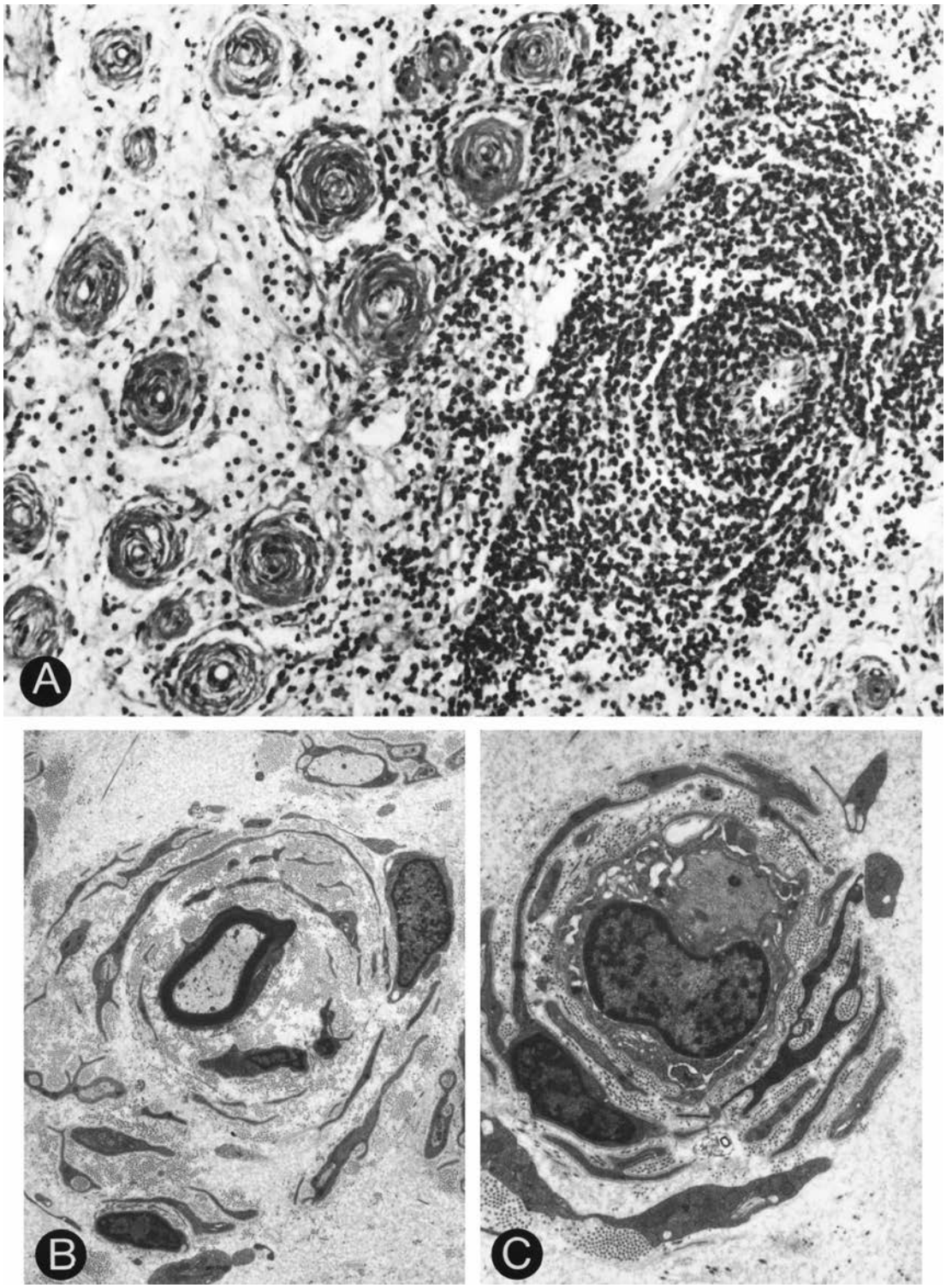

Figure 61.14. Pathology of chronic inflammatory demyelinating polyneuropathy (CIDP). *A,* Nerve biopsy from a patient with CIDP shows an area of generalized demyelination in which there is an area of perivascular demyelination adjacent to several remaining myelinated nerve fibers that show onion bulb formation. Hematoxylin and eosin, ×900. *B,* Structure of an onion bulb in CIDP. This bulb is composed of Schwann cells surrounding a thinly myelinated axon, ×3600. *C,* Structure of an onion bulb in CIDP. This bulb is composed of Schwann cells surrounding a completely demyelinated axon, ×7000. (From Johnson PC. Peripheral nerve. In Davis RL, Robertson RM, eds. Textbook of Neuropathology. Ed 2. Baltimore, Williams & Wilkins, 1991:1004–1088.)

specific manifestation of the disease (277). In others, however, the paresis is not due to the inflammatory process but rather to increased intracranial pressure or some other neurologic process (246). Oculomotor nerve palsy is quite rare in CIDP, occurring in 3–4% of patients (275). Bilateral internuclear ophthalmoplegia has been reported (278). A patient with multiple episodes of diplopia and ptosis who eventually developed CIDP has been described (276). Rarely, patients with CIDP develop mild to moderate unilateral or bilateral ptosis**,** usually in association with ophthalmoparesis (275) or unilateral adduction deficit (279).

Papilledema occurs in about 8% of patients with CIDP (246), a frequency greater than in patients with AIDP. The increased intracranial pressure that occurs in CIDP seems to be caused in most cases by the markedly increased protein concentration, one of the laboratory hallmarks of the condition (246,280); however, papilledema associated with moderately increased intracranial pressure and only a mildly increased concentration of protein in the CSF has been reported (Fig. 61.15), suggesting that, as in AIDP, other mechanisms may play a role. The papilledema of CIDP can spontaneously resolve or progress and cause permanent optic nerve dysfunction (281,282).

Abnormalities of pupil size or shape are extremely rare in patients with CIDP. They were not described in any of the 205 patients reported in the three largest series (246,247,250, 251). There are, however, a few case reports of bilateral parasympathetic denervated pupils (281).

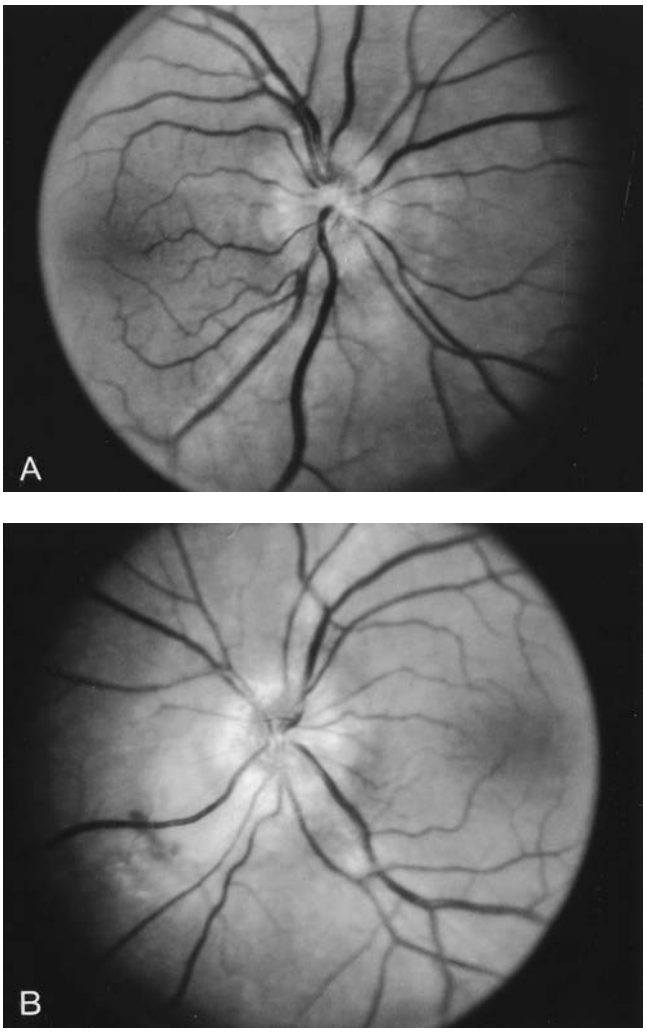

Figure 61.15. Papilledema in chronic inflammatory demyelinating polyneuropathy (CIDP). The patient was a 44-year-old man with well-documented CIDP who was being treated with low-dose systemic corticosteroids when he developed mild headaches but no visual symptoms. Visual acuity was 20/20 in both eyes; color vision was normal; and visual fields were full. *A,* The right optic disc is mildly hyperemic and swollen. *B,* The left optic disc is mildly hyperemic and swollen. Neuroimaging was normal. The intracranial pressure was increased with a moderately increased concentration of protein. No specific treatment was given. The papilledema gradually resolved over about 6 months.

LABORATORY FINDINGS

Electrophysiologic studies in patients with CIDP typically show marked slowing of motor conduction with prolonged distal latencies in at least two limbs (246,247,250,251). Some patients show a multifocal conduction block. F-wave responses are abnormal 95% of the time (283). In a series of eight consecutive patients (284), visual evoked responses were abnormal in six, BAEPs were abnormal in two, and MR imaging showed changes consistent with CNS demyelination in two cases. These laboratory findings suggest that CIDP, like AIDP and MFS, may rarely present as a combined central and peripheral demyelinating syndrome.

CSF analysis performed in patients with CIDP during periods of clinical deterioration reveals that intracranial pressure can be normal or increased and usually is associated with an increased concentration of protein greater than 100 mg/dl (246,247,250,251). There usually is little or no pleocytosis (2,3). In one series, S-100b levels were elevated in nine of 11 patients with clinically progressive CIDP but not in normal controls or in eight other patients studied with various types of axonal neuropathy. During clinical improvement, 10 of 10 patients had normalization of the S-100b levels, although total protein remained high in five of 10 patients. These findings suggest that S-100b levels may be useful in assessing the activity of the disease and in determining the effectiveness of the therapeutic strategy (285).

MR imaging in patients with CIDP occasionally shows enlargement of nerve roots; however, these findings do not correlate with disease activity, severity, or other laboratory features of the disorder (286).

DIAGNOSIS

The diagnosis of CIDP is made by the combination of appropriate clinical, electrophysiologic, and CSF findings (247,248,287). A biopsy, usually of the sural nerve, may be required to confirm the diagnosis and to distinguish the condition from other types of chronic polyneuropathy, such as multifocal motor neuropathy (MMN) (288), chronic idiopathic axonal polyneuropathy (CIAP) (289), POEMS syn-

drome (polyneuropathy, organomegaly, endocrinopathy, M proteins, and skin changes) (290), IgM gammopathy (291), and multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy (292,293). Other disorders to be considered in patients suspected of having CIDP include hereditary polyneuropathies, chronic demyelinating polyneuropathies associated with systemic diseases such as plasma cell dyscrasias and paraproteinemias, and toxic polyneuropathy of diphtheria (2,3). This highlights that even when a diagnosis of CIDP seems clear, a continued search for an underlying etiology may be appropriate.

TREATMENT

Systemic corticosteroids are the primary form of therapy for patients with CIDP (244,247,248,250,294,295), although statistical evidence supporting this treatment is limited to a single randomized controlled study with 35 subjects and several uncontrolled studies that indicate that systemic corticosteroids have a beneficial effect on the course and prognosis of the condition (294).

Unlike steroid therapy, the safety and efficacy of **IVIg** therapy for CIDP have been carefully evaluated in multiple studies (295–304). Two studies showed that a significantly higher proportion of patients with CIDP improved within a month after IVIg therapy compared with placebo. This implies that IVIg is an excellent choice as a first-line therapy (295–304). The predominant mechanism by which IVIg exerts its action appears to be a combined effect on complement inactivation, neutralization of idiotypic antibodies, cytokine inhibition, and saturation of Fc receptors on endoneurial macrophages (303). IVIg also appears to be relatively safe (298), although patients with preexistent disorders such as cardiac disease or renal insufficiency and patients who are immobilized by their illness or from other causes are at higher risk for complication (300,302). Treatment seems to be most helpful in patients whose disease has been present for 1 year or less (298).

Plasma exchange has a beneficial and often rapid effect on patients with CIDP (299,304). In one study, this treatment was shown to be superior to other modalities, including IVIg (304). In another study, IVIg had a similar efficacy to plasma exchange and oral prednisolone (299). In patients that failed any initial therapy, an alternate treatment showed benefit in 35% (304).

Other proposed treatments for CIDP include Etanercept (305), cyclosporin-A (306), interferon-α, interferon-β, and anti-D immunoglobulin (307–309). In the design of therapeutic trials for CIDP, a proper choice of suitable outcome measures is essential to assess effectiveness (305–309). The available evidence is inadequate to decide if these less common strategies are effective. Furthermore, analyses of the outcome measures used in many polyneuropathy treatment studies have revealed flaws in the methodology commonly used (305–309).

NATURAL HISTORY AND PROGNOSIS

There are several clinical profiles of CIDP, although the most common are monophasic with relapse and relapsing-remitting (2,246,247,310). The longer patients are followed, the more likely relapses will be documented. Many relapsing cases resolve after a few years. Patients with a relapsing course tend to have a more favorable prognosis than do those with a chronic progressive course (251). The clinical course may be influenced by the treatments outlined previously. The mortality of CIDP ranges from 5–10%, with death usually resulting from intercurrent infections (2). Most patients treated with systemic corticosteroids, IVIg, plasma exchange, or a combination of these modalities, have a reasonably good prognosis (248). In various larger series, 26 to 30% make a complete recovery, and about 40% recover with minimal impairment of neurologic function (250).

REFERENCES

1. Asbury AK. New concepts of Guillain-Barré syndrome. J Child Neurol 2000; 15:183–191.
2. Ropper AH, Wijdicks EFM, Truax BT. Guillain-Barré Syndrome. Philadelphia, FA Davis, 1991.
3. Ropper AH. The Guillain-Barré syndrome. N Engl J Med 1992;326:1130–1136.
4. Tenorio G, Ashenasi A, Benton JW. Guillain-Barré syndrome. In Scheld WM, Whitley RJ, Durack DT, eds. Infections of the Central Nervous System. New York, Raven Press, 1991:259–279.
5. Guillain G, Barré JA, Strohl A. Sur un syndrome de radiculonevrite avec hyperalbuminose due liquide cephalorachidien sans reaction cellulaire: Remarques sur les caracteres cliniques et graphiques des reflexes tendineux. Bull Soc Med Hop Paris 1916;40:1462–1470.
6. Landry O. Note sur la paralysie ascendante aiguë. Gaz Hebd Med Chirurg 1859; 6:474–488.
7. Draganesco A, Claudian J. Sur un cas de radiculo-névrite curable (syndrome de Guillain-Barré) apparue au cours d'une osteomyelite du bras. Rev Neurol 1927; 2:517–521.
8. Schonberger LB, Hurwitz ES, Katona P, et al. Guillain Barré syndrome: Its epidemiology and associations with influenza vaccination. Ann Neurol 1981; 9(Suppl):S31–S38.
9. Alter M. The epidemiology of Guillain-Barré syndrome. Ann Neurol 1990; 27(Suppl):S7–S12.
10. Briscoe DM, McMenamin JB, O'Donohue NV. Prognosis in Guillain-Barré syndrome. Arch Dis Child 1987;62:733–735.
11. Rantala H, Uhari M, Niemela M. Occurrence, clinical manifestations, and prognosis of Guillain-Barré syndrome. Arch Dis Child 1991;66:706–709.
12. Jansen PW, Perkin RM, Ashwal S. Guillain-Barré syndrome in childhood: Natural course and efficacy of plasmapheresis. Pediatr Neurol 1993;9:16–20.

12a. Sladky JT. Guillain-Barré syndrome in children. J Child Neurol 2004;19: 191–200.

13. Yuki N, Yoshino H, Sato S, et al. Acute axonal polyneuropathy associated with anti-GM_1 antibodies following *Campylobacter* enteritis. Neurology 1990;40: 1900–1902.
14. Yuki N, Sato S, Itoh T, et al. HLA-B35 and acute axonal polyneuropathy following *Campylobacter* infection. Neurology 1991;41:1561–1563.
15. Yuki N, Sato S, Fujimoto S, et al. Serotype of *Campylobacter jejuni,* HLA, and the Guillain-Barré syndrome. Muscle Nerve 1992;15:968–969.
16. Yuki N, Yoshino H, Sato S, et al. Severe acute axonal form of Guillain-Barré syndrome associated with IgG and anti-GD1a antibodies. Muscle Nerve 1992; 15:899–903.
17. Yuki N, Sato S, Tsuji S, et al. Human leukocyte antigens in Fisher's syndrome. Ann Neurol 1993;33:655–657.
18. Rees JH, Soudain SE, Gregson NA, et al. *Campylobacter jejuni* infection and Guillain-Barré Syndrome. N Engl J Med 1995;333:1374–1379.
19. Duret M, Herbaut AG, Flamme F, et al. Another case of atypical acute axonal polyneuropathy following *Campylobacter* enteritis. Neurology 1991;41: 1008–1009.
20. Sheike KA, Nachamkin I, Ho TW, et al. *Campylobacter jejuni* lipopolysaccharides in Guillain-Barré syndrome: Molecular mimicry and host susceptibility. Neurology 1998;51:371–378.
21. Hahn AF. Guillain-Barré Syndrome. Lancet 1998;352:635–641.
22. Molnar GK, Mertsola J, Erkko M. Guillain-Barré syndrome associated with *Campylobacter* infection. Br Med J 1982;285:652.
23. Rhodes KM, Tattersfield AE. Guillain-Barré syndrome associated with *Campylobacter* infection. Br Med J 1982;285:173–174.
24. Ropper AH. Severe acute Guillain-Barré syndrome. Neurology 1986;36: 429–432.
25. Ropper AH. *Campylobacter* diarrhea and Guillain-Barré syndrome. Arch Neurol 1988;45:655–656.

26. Griffin JW, Ho TW-H. The Guillain-Barré syndrome at 75: The *Campylobacter* connection. Ann Neurol 1993;34:125–127.
27. Mishu B, Blaser MJ. Role of infection due to *Campylobacter jejuni* in the initiation of Guillain-Barré syndrome. Clin Infect Dis 1993;17:104–108.
28. Hughes RA, Hadden RD, Gregson NA, et al. Pathogenesis of Guillain-Barré syndrome. J Neuroimmunol 1999;100:74–97.
29. Altekruse SF, Stren NJ, Fields PI, et al. *Campylobacter jejuni:* An emerging foodborne pathogen. Emerg Infect Dis 1999;5:28–35.
30. Schaltenbrand G, Bammer H. La clinique et le traitment des polyneurites inflammatoires ou sereuses aigues. Rev Neurol 1966;115:783–810.
31. Faraq SS, Gelles D. *Yersinia* arthritis and Guillain-Barré syndrome. N Engl J Med 1982;307:755.
32. Samantray SK. Landry-Guillain-Barré-Strohl syndrome in typhoid fever. Aust NZ J Med 1977;7:307–308.
33. Warembourg H, Voisin C, Furon D, et al. Neuropathies peripheriques aigues associées à la brucellose. Lille Med 1969;14:536–539.
34. Steele JC, Gladstone RM, Thanasophon S, et al. *Mycoplasma pneumoniae* as a determinant of the Guillain-Barré syndrome. Lancet 1969;2:710–713.
35. Hankey GJ. Guillain-Barré syndrome in Western Australia, 1980–1985. Med J Aust 1987;146:130–133.
36. Nadkarni N, Lisak RP. Guillain-Barré syndrome (GBS) with bilateral optic neuritis and central white matter disease. Neurology 1993;43:842–843.
37. Slavick HE, Shapiro RA. Fisher's syndrome associated with Epstein-Barr virus. Arch Neurol 1981;38:134–135.
38. Fasanaro AM, Scoleri G, Pizza V, et al. Guillain-Barré syndrome as presenting manifestation of visceral leishmaniasis. Lancet 1991;338:1142.
39. Haidl S, Ivarsson S, Bjerre I, et al. Guillain-Barré syndrome after *Chlamydia pneumoniae* infection. N Engl J Med 1992;326:576–577.
40. Eidelberg D, Sotrel A, Vogel H, et al. Progressive polyradiculopathy in acquired immune deficiency syndrome. Neurology 1986;36:912–916.
41. Cornblath DR, McArthur JC, Kennedy PG, et al. Inflammatory demyelinating peripheral neuropathies associated with human T-cell lymphotropic virus type III infection. Ann Neurol 1987;21:32–40.
42. Leger JM, Bouche P, Bolgert F, et al. The spectrum of polyneuropathies in patients infected with HIV. J Neurol Neurosurg Psychiatry 1989;52:1369–1374.
43. Esselink RAJ, Gerding MN, Brouwers PJAM, et al. Guillain-Barré syndrome associated with hantavirus infection. Lancet 1994;343:180–181.
44. Leneman F. The Guillain-Barré syndrome: Definition, etiology and review of 1100 cases. Arch Intern Med 1966;118:139–144.
45. De Klippel N, Hautekeete ML, De Keyser J, et al. Guillain-Barré syndrome as the presenting manifestation of hepatitis C infection. Neurology 1993;43:2143.
46. Shaw FE Jr, Graham DJ, Guess HA, et al. Post marketing surveillance for neurologic adverse events reported after hepatitis B vaccination: Experience of the first three years. Am J Epidemiol 1988;127:337–352.
47. D'Cruz OF, Shapiro ED, Spiegelman KN, et al. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) after immunization with *Haemophilus influenzae* type b conjugate vaccine. J Pediatr 1989;115:743–746.
48. Samantray SK, Johnson SC, Mathai KV, et al. Landry-Guillain-Barré-Strohl syndrome: A study of 302 cases. Med J Aust 1977;2:84–91.
49. Friedland ML, Wittels EG. An unusual neurologic reaction following polyvalent pneumococcal vaccine in a patient with hairy cell leukemia. Am J Hematol 1983;14:189–191.
50. Betts RF, Douglas RG Jr. Influenza virus. In Mandell GL, Douglas RG Jr, Bennett JE, eds. Principles and Practice of Infectious Disease. Ed 3. New York, Churchill Livingstone, 1990:1306–1326.
51. Centers for Disease Control: Follow-up on Guillain-Barré syndrome—United States. MMWR 1977;26:52–55.
52. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. Am J Epidemiol 1979;110:105–123.
53. Fenichel GM. Neurological complications of immunization. Ann Neurol 1982; 12:119–128.
54. Beghi E, Kurland LT, Mulder DW, et al. Guillain-Barré syndrome. Arch Neurol 1985;42:1053–1057.
55. Kurland LT, Wiederholt WC, Kirkpatrick JW, et al. Swine influenza vaccine and Guillain-Barré syndrome: Epidemic or artifact? Arch Neurol 1985;42: 1089–1090.
56. Novak DJ, Johnson KP. Relapsing idiopathic polyneuritis during pregnancy: Immunological aspects and literature review. Arch Neurol 1973;28:219–223.
57. Sudo N, Weingold AB. Obstetric aspects of the Guillain-Barré syndrome. Obstet Gynecol 1975;45:39–43.
58. Lisak RP, Mitchel M, Zweiman B, et al. Guillain-Barré syndrome and Hodgkin's disease: Three cases with immunological studies. Ann Neurol 1977;1:72–78.
59. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003;349:1543–1554.
60. Rodrigues A, Monteiro A, Viana J, et al. Acute nonlymphoblast leukaemia presenting as a Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 1993;56: 936–938.
61. Rios RJ, Odel JG, Camac A, et al. A 45-year-old female with Guillain-Barré syndrome and optic neuritis. Presented at the 26th Annual Frank B. Walsh Meeting, Chicago, Illinois, April 9–10, 1994.
62. Steiner I, Argov Z, Cahen C, et al. Guillain-Barré syndrome after epidural anesthesia: Direct nerve root damage may trigger disease. Neurology 1985;35: 1473–1475.
63. Wiederholt WC, Mulder DW, Lambert EH. The Landry-Guillain-Barré-Strohl syndrome or polyradiculoneuropathy: Historical review, report on 97 patients and present concepts. Mayo Clin Proc 1964;30:427–451.
64. Arnason BG, Asbury AK. Idiopathic polyneuritis after surgery. Arch Neurol 1968;18:500–507.
65. Kaplan JE, Poduska PJ, McIntosh GC, et al. Guillain-Barré syndrome in Larimer County, CO: A high incidence area. Neurology 1985;35:581–584.
66. Winer JB, Hughes RAC, Osmond C. A prospective study of acute idiopathic neuropathy. II. Antecedent events. J Neurol Neurosurg Psychiatry 1988;51: 613–618.
67. Winer JB, Hughes RAC, Osmond C. A prospective study of acute idiopathic neuropathy. I. Clinical features and their prognostic value. J Neurol Neurosurg Psychiatry 1988;51:605–612.
68. Eliashiv S, Brenner T, Abramsky O, et al. Acute inflammatory demyelinating polyneuropathy following bone marrow transplantation. Bone Marrow Transplant 1991;8:315–317.
69. Millette TJ, Subramony SH, Wee AS, et al. Systemic lupus erythematosus presenting with recurrent acute demyelinating polyneuropathy. Eur Neurol 1986; 251:397–402.
70. Chaudhuri KR, Taylor IK, Niven RM, et al. A case of systemic lupus erythematosus presenting as Guillain-Barré syndrome. Br J Rheumatol 1989;28:440–442.
71. Brust JCM, Hammer JS, Challenor Y, et al. Acute generalized polyneuropathy accompanying lithium poisoning. Ann Neurol 1979;6:360–362.
72. Barnes D, Hughes RAC. Guillain-Barré syndrome after treatment with streptokinase. Br Med J 1992;304:1225.
73. Latov N, Koski CL, Walicke PA. Guillain-Barré syndrome and parenteral gangliosides. Lancet 1991;338:757.
74. Landi G, D'Allesandro R, Dossi BC, et al. Guillain-Barré syndrome after exogenous gangliosides in Italy. Br Med J 1993;307:1463–1464.
75. Haug BA, Dressler D, Prange HW. Polyradiculoneuritis following botulinum toxin therapy. J Neurol 1990;237:62–63.
76. Asbury AK, Arnason BG, Adams RD. The inflammatory lesion in idiopathic polyneuritis: Its role in pathogenesis. Medicine 1969;48:173–215.
77. Prineas JW. Acute idiopathic polyneuritis: An electron microscope study. Lab Invest 1972;26:133–146.
78. Al-Hakim M, Cohen M, Daroff RB. Postmortem examination of relapsing acute Guillain-Barré syndrome. Muscle Nerve 1993;16:173–176.
79. Schmidt RE. Demyelinating diseases. In Nelson JS, Parisi JE, Schochet SS Jr, eds. Principles and Practice of Neuropathology. St Louis, CV Mosby, 1993: 361–397.
80. Schmidt B, Toyka KV, Kiefer R, et al. Inflammatory infiltrates in sural nerve biopsies in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 1996;19:474–487.
81. Casamajor L. Acute ascending paralysis. Arch Neurol Psychiatr 1919;2: 605–620.
82. Haymaker W, Kernohan JW. The Landry-Guillain-Barré syndrome: A clinicopathological report of 50 fatal cases and a critique of the literature. Medicine 1949;28:59–141.
83. Matsuyama H, Haymaker W. Distribution of lesions in the Landry-Guillain-Barré syndrome, with emphasis on involvement of the sympathetic system. Acta Neuropathol 1967;8:230–241.
84. Arnason BG. Acute inflammatory demyelinating polyradiculoneuropathies. In Dyck PJ, Thomas PK, Lambert EH, et al., eds. Peripheral Neuropathy. Vol 1. Philadelphia, WB Saunders, 1984:2050–2100.
85. Gantayat M, Swash M, Schwartz M. Fiber density in acute and chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 1992;15:168–171.
86. Thomas PK. The Guillain-Barré syndrome: No longer a simple concept. J Neurol 1992;239:361–362.
87. Berciano J, Garcia A, Figols J, et al. Perineurium contributes to axonal damage in acute inflammatory demyelinating polyneuropathy. Neurology 2000;55: 552–559.
88. Waksman BH, Adams RD. Allergic neuritis: An experimental disease of rabbits induced by the injection of peripheral nervous tissue and adjuvants. J Exp Med 1955;102:213–236.
89. Rocklin RE, Sheremata WA, Feldman RG, et al. The Guillain-Barré syndrome and multiple sclerosis. In vitro cellular responses to nervous-tissue antigens. N Engl J Med 1971;284:803–808.
90. Simone IL, Annunziata P, Maimone D, et al. Serum and CSF anti-GM1 antibodies in patients with Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. J Neurol Sci 1993;114:49–55.
91. Honavar M, Tharakan JKJ, Hughes RAC, et al. A clinicopathological study of the Guillain-Barré syndrome: Nine cases and literature review. Brain 1991;114: 1245–1269.
92. Hafer-Macko CE, Sheikh KA, Li CY, et al. Immune attack on the Schwann cell surface in acute inflammatory demyelinating polyneuropathy. Ann Neurol 1996; 39:625–635.
93. Putzu GA, Figarella-Branger D, Bouvier-Labit C, et al. Immunohistochemical

localization of cytokines, C5b-9 and ICAM-1 in peripheral nerve of Guillain-Barré syndrome. J Neurol Sci 2000;174:16–21.
94. Radhakrishnan VV, Sumi MG, Reuben S, et al. Circulating tumour necrosis factor alpha and soluble TNF receptors in patients with Guillain-Barré syndrome. Indian J Med Res 2003;117:216–220.
95. Zhu J, Mix E, Link H. Cytokine production and the pathogenesis of experimental autoimmune neuritis and Guillain-Barré syndrome. J Neuroimmunol 1998;84: 40–52.
96. National Institute of Neurological and Communicative Disorders and Stroke Ad Hoc Committee: Criteria for diagnosis of Guillain-Barré syndrome. Ann Neurol 1978;3:565–566.
97. Kennedy RH, Danielson MA, Mulder DW, et al. Guillain-Barré syndrome: A 42 year epidemiological and clinical study. Proc Mayo Clin 1978;53:93–99.
98. Ropper AH. Unusual clinical variants and signs in Guillain-Barré syndrome. Arch Neurol 1986;43:1150–1152.
99. Ropper AH. Four new variants of Guillain-Barré syndrome. Ann Neurol 1993; 34:306.
100. Dyck JB, Dyck PJ. Cutaneous pain in inflammatory neuropathy. Ann Neurol 1993;34:308.
101. Hund EF, Borel CO, Cornblath DR, et al. Intensive management and treatment of severe Guillain-Barré syndrome. Crit Care Med 1993;21:433–446.
102. Santana JC, Garcia PC, Einloft PR, et al. Autonomic dysfunction in Guillain-Barré syndrome: A 13-year experience in pediatric intensive care unit. J Pediatr 1996;72:20–26.
103. Radu EW, Skorpil V, Kaeser HE. Facial myokymia. Eur Neurol 1975;13: 499–512.
104. Wasserstrom WR, Starr A. Facial myokymia in the Guillain-Barré syndrome. Arch Neurol 1977;34:576–577.
105. Grunnet ML, Lubow M. Ascending polyneuritis and ophthalmoplegia. Am J Ophthalmol 1972;74:1155–1160.
106. Goebel W. Über Landrysche Parlyse. Munch Med Wochenschr 1898;45: 956,100,1031.
107. Seifert P. Festschrift zur Feier des 50 jährigen Bestehens des Stadtkrankenhauses. Dresden, 1899:177.
108. Munsat TL, Barnes JE. Relationship of multiple cranial nerve dysfunction to the Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 1965;28:115–120.
109. Chiba A, Kusunoki S, Obata H, et al. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: Clinical and immunohistochemical studies. Neurology 1993;43: 1911–1917.
110. Chiba A, Kusunoki S, Kuwata S, et al. HLA and anti-GQ_{1b} IgG antibody in Miller Fisher syndrome and Guillain-Barré syndrome. J Neuroimmunol 1995; 61:85–88.
111. Tan E, Kansu T, Kirkali P, et al. Lid lag and the Guillain-Barré syndrome. J Clin Neuro-Ophthalmol 1990;10:121–123.
112. Williams D, Brust JCM, Abrams G, et al. Landry-Guillain-Barré syndrome with abnormal pupils and normal eye movements: A case report. Neurology 1979; 29:1033–1036.
113. Tabare E, Bardon P, Leon A, et al. Syndrome de Guillain-Barré révélé par une paralysie oculomotrice unilatérale. Bull Soc Ophtalmol Fr 1992;92:321–323.
114. Pinckney C. Acute infective polyneuritis with a report of 5 cases. Br Med J 1936;2:333–335.
115. DeRespinis PA, Shen JJ, Wagner RS. Guillain-Barré syndrome presenting as paralysis of accommodation. Arch Ophthalmol 1989;107:1282.
116. Ford FR, Walsh FB. Guillain-Barré syndrome (acute infective polyneuritis) with increased intracranial pressure and papilledema: Report of two cases. Bull Johns Hopkins Hosp 1943;73:391–395.
117. Gardner WJ, Spittler DK, Whitten C. Increased intracranial pressure caused by increased protein content in the cerebrospinal fluid; explanation of papilledema in certain cases of small intracranial and intraspinal tumors, and in Guillain-Barré syndrome. N Engl J Med 1954;250:932–936.
118. Weiss GB, Bajwa ZH, Mehler MF. Co-occurrence of pseudotumor cerebri and Guillain-Barré syndrome in an adult. Neurology 1991;41:603–604.
119. Toshniwal P. Demyelinating optic neuropathy with Miller Fisher syndrome: The case for overlap syndromes with central and peripheral demyelination. J Neurol 1987;234:353–358.
120. Matsuki M, Okada N, Matsuo M. MR findings of Guillain-Barré syndrome. Radiat Med 1998;16:133–135.
121. Nagaoka U, Kato T, Kurita K, et al. Cranial nerve enhancement on three dimensional MRI in Miller Fisher syndrome. Neurology 1996;47:1601–1602.
122. Olney RK, Aminoff MJ. Electrodiagnostic features of the Guillain-Barré syndrome: The relative sensitivity of different techniques. Neurology 1990;40: 471–475.
123. Das KB, Taly AB, Gupta SK, et al. Acute inflammatory demyelinating neuropathy: A critical evaluation of diagnostic criteria for demyelination. Electromyogr Clin Neurophysiol 1995;35:451–455.
124. McLeod JG, Wray SH. An experimental study of F wave in the baboon. J Neurol Neurosurg Psychiatry 1966;29:196–200.
125. McLeod JG. Electrophysiological studies in the Guillain-Barré syndrome. Ann Neurol 1981;9(Suppl):S20–S27.
126. Lachman T, Shahani BT, Young RR. Late responses as aids to diagnosis in peripheral neuropathy. J Neurol Neurosurg Psychiatry 1980;43:156–162.
127. Albers JW, Donofrio PD, McGonagle TK. Sequential electrodiagnostic abnormalities in acute inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 1985;8:528–539.
128. Ropper AH, Chiappa KH. Evoked potentials in Guillain-Barré syndrome. Neurology 1986;36:587–590.
129. Ropper AH, Marmarou A. Mechanism of pseudotumor in Guillain-Barré syndrome. Arch Neurol 1984;41:259–261.
130. Shah JR, Lewis RA. Sarcoidosis of the cauda equina mimicking Guillain-Barré syndrome. J Neurol Sci 2003;208:113–117.
131. Shanbag P, Amirtharaj C, Pathak A. Intravenous immunoglobulins in severe Guillain-Barré syndrome in childhood. Indian J Pediatr 2003;70:541–543.
132. Mahalati K, Dawson RD, Collins JO, et al. Characteristic of 73 patients, 1984–1993, treated by plasma exchange for Guillain-Barré syndrome. J Clin Apheresis 1997;12:116–121.
133. Green DM, Ropper AH. Mild Guillain-Barré syndrome. Arch Neurol 2001;58: 1098–1101.
134. Hughes RAC, Newsom-Davis JM, Perkin GD, et al. Controlled trial of prednisolone in acute polyneuropathy. Lancet 1978;2:750–753.
135. Hughes RAC. Ineffectiveness of high-dose intravenous methylprednisolone in Guillain-Barré syndrome. Lancet 1991;338:1142.
136. Guillain-Barré Syndrome Steroid Trial Group: Double-blind trial of intravenous methylprednisolone in Guillain-Barré syndrome. Lancet 1993;341:586–590.
137. Ropper AH. What treatment for the Guillain-Barré syndrome? Arch Neurol 1993;50:687–688.
138. Thornton CA, Griggs RC. Plasma exchange and intravenous immunoglobulin treatment of neuromuscular disease. Ann Neurol 1994;35:260–268.
139. Guillain-Barré Syndrome Study Group: Plasmapheresis and acute Guillain-Barré syndrome. Neurology 1985;35:1096–1104.
140. French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome: Efficacy of plasma exchange in Guillain-Barré syndrome: Role of replacement fluids. Ann Neurol 1987;22:753–761.
141. French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome: Plasma exchange in Guillain-Barré syndrome: One-year follow-up. Ann Neurol 1992;32:94–97.
142. Epstein MA, Sladky JT. The role of plasmapheresis in childhood Guillain-Barré syndrome. Ann Neurol 1990;28:65–69.
143. McKhann GM, Griffin JW, Cornblath DR, et al. The Guillain-Barré Syndrome Study Group: Plasmapheresis and Guillain-Barré syndrome: Analysis of prognostic factors and the effect of plasmapheresis. Ann Neurol 1988;23:347–353.
144. McKhann GM, Cornblath DR, Ho TW, et al. Clinical and electrophysiological aspects of acute paralytic disease of children and young adults in northern China. Lancet 1991;38:593–597.
145. Osterman PO, Fagius J, Säfwenberg J, et al. Early relapse in acute inflammatory polyradiculoneuropathy after successful treatment with plasma exchange. Acta Neurol Scand 1988;77:273–277.
146. Osterman PO, Fagius J, Säfwenberg J, et al. Early relapses after plasma exchange in acute inflammatory polyradiculopathy. Lancet 1986;2:1161.
147. Ropper AH, Albers JW, Addison R. Limited relapse in Guillain-Barré syndrome. Arch Neurol 1988;43:314–315.
148. van der Meché FGA, Schmitz PIM. The Dutch Guillain-Barré Study Group: A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992;326:1123–1129.
149. Cusmai R, Bertini E, Bianchi F, et al. Intravenous immunoglobulin in childhood Guillain-Barré syndrome. Ann Neurol 1993;34:446.
150. Ng KKP, Howard RS, Hirsch NP, et al. Intravenous immunoglobulin versus plasma exchange in Guillain-Barré syndrome. Neurology 1993;43:2729.
151. Al-Qudah AA. Immunoglobulins in the treatment of Guillain-Barré syndrome in early childhood. J Child Neurol 1994;9:178–180.
152. McFarland HR. What treatment for the Guillain-Barré syndrome? Arch Neurol 1993;50:687.
153. Ropper AH, Adelman L. Early Guillain-Barré syndrome without inflammation. Arch Neurol 1992;49:979–981.
154. Silbert PL, Knezevic WV, Bridge DT. Cerebral infarction complicating intravenous immunoglobulin therapy for polyneuritis cranialis. Neurology 1992;42: 257–258.
155. Wolinsky KH, Hulser PJ, Brinkmeier H, et al. Filtration of cerebral spinal fluid in acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome). Ann Med Interne Paris 1994;145:451–458.
156. Davidson DLW, Jellinek EH. Hypertension and papilloedema in the Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 1977;40:144–148.
157. Kleyweg RP, van der Meché FGA, Loonen MCB, et al. The natural history of the Guillain-Barré syndrome in 18 children and 50 adults. J Neurol Neurosurg Psychiatry 1989;52:853–856.
158. Mokuno K, Kiyosawa K, Sugimura K, et al. Prognostic value of cerebrospinal fluid neuron-specific enolase and S-100b protein in Guillain-Barré syndrome. Acta Neurol Scand 1994;89:27–30.
159. Ropper AH. The CNS in Guillain-Barré syndrome. Arch Neurol 1983;40: 397–398.

160. Pareyson D, Ciano C, Fiacchino F, et al. Combined central and peripheral acute demyelination. Ital J Neurol Sci 1993;14:83–86.
161. Fisher CM. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). N Engl J Med 1956;255:57–65.
162. Collier J. Peripheral neuritis. Edinburgh Med J 1932;39:601–618.
163. Smith JL, Walsh FB. Syndrome of external ophthalmoplegia, ataxia, and areflexia (Fisher): Ocular manifestations in acute idiopathic polyneuritis (Guillain-Barré syndrome). Arch Ophthalmol 1957;58:109–114.
164. Goodwin RF, Poser CM. Ophthalmoplegia, ataxia and areflexia (Fisher's syndrome). JAMA 1963;186:258–259.
165. Berlit P, Rakicky J. The Miller Fisher syndrome: Review of the literature. J Clin Neuroophthalmol 1992;12:57–63.
166. Roberts T, Shah A, Graham JG, et al. The Miller Fisher syndrome following *Campylobacter* enteritis: A report of two cases. J Neurol Neurosurg Psychiatry 1987;50:1557–1558.
167. Merkx H, De Keyser J, Ebinger G. Miller Fisher syndrome associated with *Mycoplasma pneumoniae* infection: Report of a case. Clin Neurol Neurosurg 1994;96:96–99.
168. Hass DC, Awad E, Posas H, et al. Miller Fisher syndrome in systemic lupus erythematosus. J Rheumatol 1990;17:1520–1522.
169. Nicholson GD, Prussia PR, Sirarajan S, et al. Membranous glomerulonephritis and the nephrotic syndrome in a patient with Landry-Guillain-Barré-Strohl syndrome. West Indian Med J 1989;38:51–53.
170. Cher LM, Merory JM. Miller Fisher syndrome mimicking stroke in an immunosuppressed patient with rheumatoid arthritis responding to plasma exchange. J Clin Neuroophthalmol 1993;13:138–140.
171. Roquer J, Herraiz J, Maymo J, et al. Miller Fisher syndrome during treatment with gold salts in a patient with rheumatoid arthritis. Arthritis Rheum 1985;28: 838–839.
172. Fötzsch R. Die ophthalmologische Polyneuritis. Ein klinischer Beitrag zum Fisher-Syndrom. Ophthalmol 1978;176:6–11.
173. Bell W, Van Allen M, Blackman J. Fisher syndrome in childhood. Dev Med Child Neurol 1970;12:758–766.
174. Qaqundah BY, Taylor WF. Miller Fisher syndrome in a 22-month-old child. J Pediatr 1970;77:868–870.
175. Eggenberger ER, Coker S, Menezes M. Pediatric Miller Fisher syndrome requiring intubation: A case report. Clin Pediatr 1993;32:372–375.
176. Al-Din AN, Anderson M, Eeg-Olofsson O, et al. Neuroophthalmic manifestations of the syndrome of ophthalmoplegia, ataxia and areflexia: A review. Acta Neurol Scand 1994;89:157–163.
177. Ishikawa H, Wakakura M, Ishikawa S. Enhanced ptosis in Fisher's syndrome after Epstein-Barr virus infection. J Clin Neuroophthalmol 1990;10:197–200.
178. Keane JR. Tonic pupils with acute ophthalmoplegic polyneuritis. Ann Neurol 1977;2:393–396.
179. Okajima T, Imamura S, Kawasaki S, et al. Fisher's syndrome: A pharmacologic study of the pupils. Ann Neurol 1977;2:63–65.
180. Igarashi Y, Takeda M, Maekawa H, et al. Fisher's syndrome without total ophthalmoplegia. Ophthalmol 1992;205:163–167.
181. Mori M, Takeshima T, Yuki N, Nakashima K. A case of anti-GQ1b-positive atypical Fisher syndrome with internal ophthalmoplegia but without external ophthalmoplegia. Rinsho Shinkeigaku 2000;40:887–890.
182. Ropper AH, Shahani BT. Proposed mechanism of ataxia in Fisher's syndrome. Arch Neurol 1983;40:537–538.
183. Williams B, Ghosh TN, Stockley RA. Ophthalmoplegia, amblyopia and diffuse encephalomyelitis associated with pelvic abscess. Br Med J 1979;1:453.
184. Ouhabi H, Bourazza A, Rouimi A, et al. Bilateral optic neuritis and pontomesencephalic involvement shown by MRI in Miller Fisher syndrome. Rev Neurol 1998;154:780–782.
185. Colding-Jorgensen E, Vissing J. Visual impairment in anti-GQ1b positive Miller Fisher syndrome. Acta Neurol Scand 2001;103:259–260.
186. Sasaki Y, Takubo H, Arai T, et al. Atypical Fisher syndrome with optic nerve involvement. No To Shinkei 2001;53:571–573.
187. Shuaib A, Becker WJ. Variants of Guillain-Barré syndrome: Miller Fisher syndrome, facial diplegia and multiple cranial nerve palsies. Can J Neurol Sci 1987; 14:611–616.
188. Farah S, Khuraibet AJ, Montaser MA, et al. Miller Fisher syndrome: Unique involvement of ophthalmic division of trigeminal nerve. Clin Neurol Neurosurg 1995;97:328–331.
189. Sangla I, Ceccaldi M, Poncet M. Recurrent idiopathic facial paralysis and other cranial nerve involvement in 2 members of a family. Rev Neurol Paris 1996; 152:291–293.
190. Garcia-Riveria CA, Rozen TD, Zhou D, et al. Miller Fisher Syndrome: MRI findings. Neurology 2001;57:1755.
191. Hosoya T, Adachi M, Yamaguchi K, et al. Abducens nerve enhancement demonstrated by multiplanar reconstruction of contract-enhanced three-dimensional MRI. Neuroradiology 2001;43:295–301.
192. Val Ferreira C, Glaser JS, Schatz NJ. Magnetic resonance imaging enhancement of cranial nerves in inflammatory bulbar polyneuropathy. J Neuroophthalmol 2000;20:45–47.
193. Tanaka H, Yuki N, Hirata K. Trochlear nerve enhancement of three-dimensional magnetic resonance imaging in Fisher syndrome. Am J Ophthalmol 1998;126: 322–324.
194. Elizan TS, Spire JP, Andiman RM, et al. Syndrome of acute idiopathic ophthalmoplegia with ataxia and areflexia. Neurology 1971;21:281–292.
195. Weiss JA, White JC. Correlation of 1A afferent conduction with the ataxia of Fisher syndrome. Muscle Nerve 1986;9:327–332.
196. Ropper AH. Three patients with Fisher's syndrome and normal MRI. Neurology 1988;38:1630–1631.
197. Guiloff RJ. Peripheral nerve conduction in Miller Fisher syndrome. J Neurol Neurosurg Psychiatry 1977;40:801–809.
198. Jamal GA, Ballantyne JP. The localization of the lesion in patients with acute ophthalmoplegia, ataxia, and areflexia (Miller Fisher syndrome). A serial multimodal neurophysiological study. Brain 1988;111:95–114.
199. Al-Din AN, Anderson M, Bickerstaff ER, et al. Brainstem encephalitis and the syndrome of Miller Fisher. Brain 1982;105:481–495.
200. Vincent FM, Vincent T. Relapsing Fisher's syndrome. J Neurol Neurosurg Psychiatry 1986;49:604–606.
201. Jacobs BC, Endtz H, van der Meche FG, et al. Serum anti-GQ1b IgG antibodies recognize surface epitopes on *Campylobacter jejuni* from patients with Miller Fisher syndrome. Ann Neurol 1995;37:260–264.
202. Willison HJ, Veitch J. Immunoglobulin subclass distribution and binding characteristics of anti-GQ1b antibodies in Miller Fisher syndrome. J Neuroimmunol 1994;50:159–165.
203. Buchwald B, Weishaupt A, Toyka KV, et al. Immunoglobulin G from a patient with Miller Fisher syndrome rapidly and reversibly depresses evoked quantal release at the neuromuscular junction of mice. Neurosci Lett 1995;201:163–166.
204. Ferrer X, Ellie E, Larreniare M, et al. Late central demyelination after Fisher's syndrome: MRI studies. J Neurol Neurosurg Psychiatry 1993;56:698–699.
205. Phillips MS, Stewart S, Anderson JR. Neuropathological findings in Miller Fisher syndrome. J Neurol Neurosurg Psychiatry 1984;47:492–495.
206. Maisey DN, Olczak SA. Successful plasmapheresis in the Miller Fisher syndrome. Br Med J Clin Res Ed 1981;282:1159.
207. Yuki N, Sato S, Tsuji S, et al. Frequent presence of anti-GQ1b antibody in Fisher's syndrome. Neurology 1993;43:414–417.
208. Sternman D, Braun C. Fisher's syndrome. Neurology 1994;44:360.
209. Van Allen MW, MacQueen JC. Ophthalmoplegia, ataxia and the syndrome of Landry-Guillain-Barré. Trans Am Neurol Assoc 1964;89:98–103.
210. Kaplan JC, Schaumburg HH, Summer A. Relapsing ophthalmoplegia-sensory neuropathy syndrome. Neurology 1985;35:595–596.
211. Kaiser-Smith, Barone. Relapsing polyneuritis following classic Miller Fisher syndrome. J Neurol Neurosurg Psychiatry 1989;52:802–803.
212. Chalmers AC, Miller RG. Chronic inflammatory polyradiculoneuropathy with ophthalmoplegia. J Clin Neuroophthalmol 1986;6:166–168.
213. Dehaene I, Martin JJ, Geens K, et al. Guillain-Barré syndrome with ophthalmoplegia: Clinicopathologic study of the central and peripheral nervous systems, including the oculomotor nerves. Neurology 1986;36:851–854.
214. Al-Din AN. The nosological position of the ophthalmoplegia, ataxia and areflexia syndrome: ''The spectrum hypothesis.'' Acta Neurol Scand 1987;75: 287–294.
215. Goldberg-Stern H, Melamed E, Gadoth N. Abnormal evoked potentials in Miller Fisher syndrome: Further evidence of combined peripheral and central demyelination. J Neurol Neurosurg Psychiatry 1994;57:506.
216. Swick HM. Pseudointernuclear ophthalmoplegia in acute idiopathic polyneuritis (Fisher's syndrome). Am J Ophthalmol 1974;77:725–728.
217. Sauron B, Bouche P, Cathala HP, et al. Miller Fisher syndrome: Clinical and electrophysiologic evidence of peripheral origin in 10 cases. Neurology 1984; 34:953–956.
218. Walsh FB, Hoyt WF. Clinical Neuroophthalmology. Vol 2. Baltimore, Williams & Wilkins, 1969:1159–1164.
219. Keane JR, Finstead BA. Upward gaze paralysis as the initial sign of Fisher's syndrome. Arch Neurol 1982;39:781–782.
220. Meienberg O, Ryffel E. Supranuclear eye movement disorders in Fisher's syndrome of ophthalmoplegia, ataxia, and areflexia: Report of a case and literature review. Arch Neurol 1983;40:402–405.
221. Pinchoff BS, Slavin ML, Rosenstein D, et al. Divergence paralysis as the initial sign in the Miller Fisher syndrome. Am J Ophthalmol 1986;101:741–742.
222. Bignami A, Servi M. Acute internal and external ophthalmoplegia with muscle weakness. Lancet 1963;1:1110.
223. Feasby TE, Gilbert JJ, Brown WF, et al. An acute axonal form of Guillain-Barré polyneuropathy. Brain 1986;109:1115–1126.
224. Yuki N. Pathogenesis of axonal Guillain-Barré syndrome: Hypothesis. Muscle Nerve 1994;17:680–682.
225. Yuki N, Miyatake T. Axonal Guillain-Barré syndrome. Neurology 1993;43: 1443–1444.
226. McKhann GM, Cornblath DR, Griffin JW, et al. Acute motor axonal neuropathy: A frequent cause of acute flaccid paralysis in China. Ann Neurol 1993;33: 333–342.
227. Berciano J, Coria F, Montoén F, et al. Axonal form of Guillain-Barré syndrome: Evidence for macrophage-associated demyelination. Muscle Nerve 1993;16: 744–751.

228. Figueras A, Morales-Olivas FJ, Cappelà D, et al. Bovine gangliosides and acute motor polyneuropathy. Br Med J 1992;305:1330–1331.
229. Gorson KC, Ropper AH. Acute respiratory failure neuropathy: A variant of critical illness polyneuropathy. Crit Care Med 1993;21:267–271.
230. Chiae CK, Su SH, Su CE. Pediatric acute infective polyradiculitis: Clinical features and analysis. Chin J Neurol Psychiatr 1979;19:149–151.
231. Zhang ZL, Li TN. Acute polyradiculoneuritis: clinical analysis of 514 cases. Chin J Neurol Psychiatry 1979;12:17–21.
232. Zhao B, Yang T, Huang H, et al., Acute polyradiculitis (Guillain-Barré syndrome): An epidemiological study of 156 cases observed in Beijing. Ann Neurol 1981;9(Suppl):S146–S148.
233. Griffin JW, Li CY, Ho TW, et al. Guillain-Barré syndrome in northern China. The spectrum of neuropathologic changes in clinically defined cases. Brain 1995; 118:577–595.
234. Ramos-Alvarez M, Bessudo L, Sabin A. Paralytic syndromes associated with noninflammatory cytoplasmic or nuclear neuronopathy: Acute paralytic disease in Mexican children, neuropathologically distinguishable from Landry-Guillain-Barré syndrome. JAMA 1969;207:1481–1492.
235. Valenciano L, Naéjera E, Gallardo FP, et al. Outbreak of paralytic illness of unknown etiology in Albecete, Spain. Am J Epidemiol 1971;94:450–456.
236. Coe CJ. Guillain-Barré syndrome in Korean children. Yonsei Med J 1989;30: 81–87.
237. Kuwabara S, Ogawara K, Sung JY, et al. Differences in membrane properties of axonal and demyelinating Guillain-Barré syndromes. Ann Neurol 2002;52: 180–187.
238. Ho TW, Mishu B, Gao CY, et al. Guillain-Barré syndrome in northern China. Relationship to *Campylobacter jejuni* infection and anti-glycolipid antibodies. Brain 1995;597–605.
239. Yuki N, Kuwabara S, Koga M, et al. Acute motor axonal neuropathy and acute motor-sensory axonal neuropathy share a common immunological profile. J Neurol Sci 1999;168:121–126.
240. Hiraga A, Mori M, Ogawara K, et al. Differences in patterns of progression in demyelinating and axonal Guillain-Barré syndromes. Neurology 2003;61: 471–474.
241. Ho T, Li CY, Wesselingh S, et al. Spectrum of immunopathology in acute motor neuropathies. Ann Neurol 1993;34:310–311.
242. Zhang X, Zhang Z, Tang X. Guillain-Barré syndrome in six cities and provinces of northern China: Is it a new entity? Clin Med J English 1995;3:734–738.
243. Busby M, Donaghy M. Chronic dysimmune neuropathy. A subclassification based upon the clinical features of 102 patients. J Neurol 2003;250:714–724.
244. Austin JH. Recurrent polyneuropathies and their corticosteroid treatment: With five-year observations of placebo-controlled case treated with corticotrophin, cortisone, and prednisone. Brain 1958;81:157–192.
245. Thomas PK, Lasacelles RG, Hallpike JF, et al. Recurrent and chronic relapsing Guillain-Barré polyneuritis. Brain 1969;92:589–606.
246. Dyck PJ, Lais AC, Ohta M, et al. Chronic inflammatory polyradiculoneuropathy. Mayo Clin Proc 1975;50:621–637.
247. Barohn RJ, Kissel JT, Warmolts JR, et al. Chronic inflammatory demyelinating neuropathy. Arch Neurol 1989;46:878–884.
248. Mendell JR. Chronic inflammatory demyelinating polyradiculoneuropathy. Annu Rev Med 1993;44:211–219.
249. Sladky JT, Brown MJ, Berman PH. Chronic inflammatory demyelinating polyneuropathy of infancy: A corticosteroid-responsive disorder. Ann Neurol 1986; 20:76–81.
250. McCombe PA, Pollard JD, McLeod JG. Chronic inflammatory demyelinating polyradiculoneuropathy: A clinical and electrophysiological study of 92 cases. Brain 1987;110:1617–1630.
251. McCombe PA, McManis PG, Frith JA, et al. Chronic inflammatory demyelinating polyneuropathy associated with pregnancy. Ann Neurol 1987;21:102–104.
252. Vallat JM, De-Mascarel HA, Bordessoule D, et al. Non-Hodgkin's malignant lymphomas and peripheral neuropathies. Brain 1995;118:1233–1245.
253. Cruz-Martinez A, Rabano J, Villoslada C, et al. Chronic inflammatory demyelinating polyneuropathy as first manifestation of human immunodeficiency virus infection. Electromyogr Clin Neurophysiol 1990;30:379–383.
254. Bird SJ, Brown MJ, Shy ME, et al. Chronic inflammatory demyelinating polyneuropathy associated with malignant melanoma. Neurology 1996;46:822–824.
255. Patawa HS, Fecko JF, Goldstein JM. Concurrent myasthenia gravis and chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 1996;19:1059–1060.
256. Odabasi Z, Joy JL, Claussen GC, et al. Isaac's syndrome associated with chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 1996;19:210–215.
257. Capello E, Roccatagliata L, Schenone A, et al. Acute axonal form of Guillain-Barré syndrome in a multiple sclerosis patient: Chance association of linked disorders? Eur J Neurol 2000;7:223–225.
258. Ohyama T, Okiyama R, Yamada M, et al. Chronic inflammatory demyelinating polyneuropathy associated with chronic liver disease due to type B and type C hepatitis virus. No To Shinkei 1995;47:161–165.
259. Antoine JC, Mosnier JF, Lapras J, et al. Chronic inflammatory demyelinating polyneuropathy associated with carcinoma. J Neurol Neurosurg Psychiatry 1996; 60:188–190.
260. Adams D, Festenstein H, Gibson JP, et al. HLA antigens in chronic relapsing idiopathic inflammatory polyneuropathy. J Neurol Neurosurg Psychiatry 1979; 42:184–186.
261. Feeney DJ, Pollard JD, McLeod JG, et al. HLA antigens in chronic inflammatory demyelinating polyneuropathy. J Neurol Neurosurg Psychiatry 1990;53: 170–172.
262. Hays AP, Lee SS, Latov N. Immune reactive C3d on the surface of myelin sheaths in neuropathy: J Neuroimmunol 1988;18:231–244.
263. Kieseier BC, Dalakas MC, Hartung HP. Immune mechanisms in chronic inflammatory demyelinating neuropathy. Neurology 2002;59(12 Suppl 6):S7–S12.
264. Bouchard C, Lacroix C, Plante V, et al. Clinicopathologic findings and prognosis of chronic inflammatory demyelinating polyneuropathy. Neurology 1999;52: 498–503.
265. Lisak RP, Brown MJ. Acquired demyelinating polyneuropathies. Semin Neurol 1987;7:40–48.
266. Oka N, Akiguchi I, Kawasaki T, et al. Expression of endothelial leukocyte adhesion molecule-1 (ELAM-1) in chronic inflammatory demyelinating polyneuropathy. Neurology 1994;44:946–950.
267. Van-Schaik IN, Vermeulen M, van Doorn PA, et al. Anti-GM1 antibodies in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) treated with intravenous immunoglobulin (IVIg). J Neuroimmunol 1994;54: 109–115.
268. Misawa S, Kuwabara S, Mori M, et al. Serum levels of tumor necrosis factor-alpha in chronic inflammatory demyelinating polyneuropathy. Neurology 2001; 56:666–669.
269. Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: Clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. Neurology 1997;48: 321–328.
270. Oh SJ, Joy JL, Kuruoglu R. ''Chronic sensory demyelinating neuropathy'': Chronic inflammatory demyelinating polyneuropathy presenting as a pure sensory neuropathy. J Neurol Neurosurg Psychiatry 1992;55:677–680.
271. Waddy HM, Misra VP, King RHM, et al. Focal cranial nerve involvement in chronic inflammatory demyelinating polyneuropathy: Clinical and MRI evidence of peripheral and central lesions. J Neurol 1989;236:400–405.
272. Frohman EM, Tusa R, Mark AS, et al. Vestibular dysfunction in chronic inflammatory demyelinating polyneuropathy. Ann Neurol 1996;39:529–535.
273. Lee AG, Galetta SL, Lepore FE, et al. Optic atrophy and chronic acquired polyneuropathy. J Neuroophthalmol 1999;19:67–69.
274. Stojkovic T, de Seze J, Hurtevent JF, et al. Visual evoked potentials study in chronic idiopathic inflammatory demyelinating polyneuropathy. Clin Neurophysiol 2000;111:2285–2291.
275. Arroyo JG, Horton JC. Acute painful, pupil-involving third nerve palsy in chronic inflammatory demyelinating polyneuropathy. Neurology 1995;45: 846–847.
276. Fleet WS, Valenstein E. Ocular palsy preceding chronic relapsing polyneuropathy. Ann Neurol 1986;19:413–414.
277. Wokke JH, van den Berg LH, van Schaik JP. Sixth nerve palsy from a CNS lesion in chronic inflammatory demyelinating polyneuropathy. J Neurol Neurosurg Psychiatry 1996;60:695–696.
278. Korkmaz A, Topaloglu H, Kansu T. Wall-eyed bilateral internuclear ophthalmoplegia in chronic inflammatory demyelinating polyneuropathy. Eur J Neurol 2002;9:691.
279. Pieh C, Rossillion B, Heritier-Barras AC, et al. Isolated unilateral adduction deficit and ptosis as the presenting features of chronic inflammatory demyelinating polyradiculoneuropathy. J Neuroophthalmol 2002;22:92–94.
280. Fantin A, Feist RM, Reddy CV. Intracranial hypertension and papilloedema in chronic inflammatory demyelinating polyneuropathy. Br J Ophthalmol 1993; 77:193.
281. Midroni G, Dyck PJ. Chronic inflammatory demyelinating polyneuropathy: Unusual clinical features and therapeutic responses. Neurology 1996;46: 1206–1212.
282. Buchsbaum HW, Gallo AE Jr. Polyneuritis, papilledema, and lumboperitoneal shunt. Arch Neurol 1969;21:253–257.
283. Kiers L, Clouston P, Zuniga G, et al. Quantitative studies of F responses in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. Electroencephalogr Clin Neurophysiol 1994;93:255–264.
284. Uncini A, Gallucci M, Lugaresi A, et al. CNS involvement in chronic inflammatory demyelinating polyneuropathy: An electrophysiology and MRI study. Electromyogr Clin Neurophysiol 1991;31:365–371.
285. Nagamatsu M, Mokuno K, Sugimura K, et al. Cerebrospinal fluid levels of S-100b protein and neuron-specific enolase in chronic inflammatory demyelinating polyneuropathy. Acta Neurol Scand 1995;91:483–487.
286. Midroni G, de Tilly LN, Gray B, et al. MRI of the cauda equina in CIDP: Clinical correlations. J Neurol Sci 1999;170:36–44.
287. Latov N. Diagnosis of CIDP. Neurology 2002;59(Suppl 6):S2–S6.
288. Lefaucheur JP, Gregson NA, Gray I, et al. A variant of multifocal motor neuropathy with acute, generalized presentation and persistent conduction blocks. J Neurol Neurosurg Psychiatry 2003;74:1555–1561.
289. Bosboom VM, van den Berg LH, Franssen H, et al. Diagnostic value of sural nerve demyelination in chronic inflammatory demyelinating polyneuropathy. Brain 2001;124(Pt 12):2427–2428.

290. Vital C, Vital A, Ferrer X, et al. Crow-Fukase (POEMS) syndrome: A study of peripheral nerve biopsy in five new cases. J Peripher Nerv Syst 2003;8:136–144.
291. Cocito D, Durelli L, Isoardo G. Different clinical, electrophysiological and immunological features of CIDP associated with paraproteinaemia. Acta Neurol Scand 2003;108:274–280.
292. Saperstein DS, Amato AA, Wolfe GI, et al. Multifocal acquired demyelinating sensory and motor neuropathy: The Lewis-Sumner syndrome. Muscle Nerve 1999;22:560–566.
293. Koski CL. Therapy of CIDP and related immune-mediated neuropathies. Neurology 2002;59(Suppl 6):S22–S27.
294. Mehndiratta MM, Hughes RA. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2002:CD002062.
295. Hughes R, Bensa S, Willison H, et al. Randomized controlled trial of intravenous immunoglobulin versus oral prednisone in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol 2001;50:195–201.
296. Mendell JR, Barohn RJ, Freimer ML, et.al. Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. Neurology 2001;57:938.
297. Dalakas MC. Mechanisms of action of IVIg and therapeutic considerations in the treatment of acute and chronic demyelinating neuropathies. Neurology 2002; 59(Suppl 6):S13–S21.
298. Hahn AF, Bolton CF, Zochodne D, et al. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: A double-blind, placebo-controlled, cross-over study. Brain 1996;119(Pt 4):107–177.
299. van Schaik IN, Winer JB, de Haan R, et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy: A systemic review. Lancet Neurol 2002;1:491–498.
300. Wittstock M, Benecke R, Zettl UK. Therapy with intravenous immunoglobulin: Complications and side-effects. Eur Neurol 2003;50:172–175.
301. Kissel JT. The treatment of chronic inflammatory demyelinating polyradiculoneuropathy. Semin Neurol 2003;23:169–180.
302. Comi G, Quattrini A, Fazio R, et al. Immunoglobulins in chronic inflammatory demyelinating polyneuropathy. Neurol Sci 2003;24(Suppl 4):S246–S250.
303. Dalakas MC. Mechanisms of action of IVIg and therapeutic considerations in the treatment of acute and chronic demyelinating neuropathies. Neurology 2002; 59(Suppl 6):S13–S21.
304. Gorson KC, Allan G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: Clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. Neurology 1997;48:321–328.
305. Chin RL, Sherman WH, Sander HW, et al. Etanercept (Enbrel) therapy for chronic inflammatory demyelinating polyneuropathy. J Neurol Sci 2003;210: 19–21.
306. Brannagan TH III, Pradhan A, Heiman-Patterson T, et al. High-dose cyclophosphamide without stem-cell rescue for refractory CIDP. Neurology 2002;58: 1856–1858.
307. Hughes RA, Swan AV, van Doorn PA. Cytotoxic drugs and interferons for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2003:CD003280.
308. Highes RA. Management of chronic inflammatory demyelinating polyradiculoneuropathy. Drugs 2003;63:275–287.
309. Creange A, Sharshar T, Raphael JC, et al. Cellular aspects of neuroinflammation in Guillain-Barré syndrome: a key to a new therapeutic option? Rev Neurol 2002;158:15–27.
310. Matthews WB, Howell DA, Hughes RC. Relapsing corticosteroid-dependent polyneuritis. J Neurol Neurosurg Psychiatry 1970;33:330–337.