

ial motor polyneuropathy and myopathy in CIP is often difficult. Often, clinical testing of the sensory functions is neither reliable nor helpful in the determination. Theoretically, predominant proximal weakness, neck flexor weakness, and facial weakness occur more often in patients with myopathy. On needle electromyography, low amplitudes and short duration of the motor unit potentials suggest myopathy. Normal sensory nerve action potential amplitudes and decreased compound motor action potential (CMAP) amplitudes are usually present in the conduction study. However, absent or decreased sensory nerve action potential amplitudes do not exclude a myopathy. Because of tissue edema, sensory nerve action potential amplitudes may be spuriously low. If serious edema is absent, serial examinations may reveal a significant fall in sensory nerve action potential amplitudes in CIP. Reliable examination of the motor unit potentials on voluntary activation is also difficult in patients with severe muscle weakness. Rich and associates (1997) described in neuropathy or endplate dysfunction that the excitability of the muscle remains normal, which appeared not to be the case in acute quadriplegic myopathy. We postulate that direct muscle stimulation can be helpful in the distinction of polyneuropathy and myopathy in the spectrum of CIP. Determination of the creatinine phosphokinase serum concentration is also helpful in revealing myopathic changes. Elevated levels of creatine phosphokinase suggest a necrotizing myopathy; furthermore, severe myopathy is associated with myoglobinuria. The best method to differentiate between underlying polyneuropathy or myopathy is a muscle biopsy using standard light microscopic examination of the muscle tissue. As mentioned in the introductory paragraphs, we prefer to consider critical illness myopathy as part of CIPNM.

Guillain-Barré Syndrome

Guillain-Barré syndrome is a (sub)acute, immune-mediated polyneuropathy. Clinical features that are required for diagnosis are (1) progressive motor weakness of more than one limb (degree ranges from minimal ataxia, to total paralysis of the legs, to total paralysis of the muscles of all four extremities and the trunk, to bulbar *and facial paralysis*, and to external ophthalmoplegia) and (2) areflexia (universal areflexia is the rule, although distal areflexia with definite hyporeflexia of the biceps and knee jerks [viii suffice if other features are consistent]).

The diagnostic criteria are based on clinical, laboratory, and electrodiagnostic criteria and are defined by Asbury and Cornblath (1990).

The clinical spectrum of Guillain-Barré syndrome consists of acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, acute motor sensory axonal neuropathy, and Miller-Fisher syndrome. These heterogeneous groups of pathological entities most likely have their own

pathogenesis. In about two thirds of all patients, Guillain-Barré syndrome is preceded by infections. We pointed out that motor Guillain-Barré syndrome without sensory loss is characterized by rapid onset of weakness, early nadir, distal-dominant weakness, *sparing of the* cranial nerves, and a preceding gastrointestinal infection, often subsequent to *Cam pylobacter jejuni* infection (Visser et al., 1995). The electrodiagnostic findings of the axonal types of Guillain-Barré syndrome show little evidence of demyelination; low distal CMAP amplitudes usually characterize signs of axonal damage. The presence of spontaneous activity in the remainder of the muscle fibers on needle electromyography also confirms this. The clinical picture may show many similarities with CIP. Many patients with acute motor neuropathy have high IgG anti-GM1 titers or IgG antibodies to anti-GM1ac-GD1a (Kaida et al., 2000). These antibodies are not found in CIP (De Letter et al., 2000b).

A *C. jejuni* infection has been postulated to induce both acute motor neuropathy and acute motor sensory neuropathy, as well as Miller-Fisher syndrome. An acute motor neuropathy in the Dutch Guillain-Barré syndrome study population was never caused by a cytomegalovirus infection. Cytomegalovirus-related Guillain-Barré syndrome patients have a different clinical pattern. They are significantly younger, have a severe initial course, indicated by a high frequency of artificial respiration; and often develop cranial nerve involvement and severe sensory loss (Visser et al., 1996). It is possible that anti-GM2 antibodies are important in cytomegalovirus-associated Guillain-Barré syndrome.

ELECTROPHYSIOLOGICAL EVALUATION AND FINDINGS

The electrophysiological characteristics of Guillain-Barré syndrome point to a demyelinating polyneuropathy with an occasional and variable axonal component. Disturbance of the Schwann cells causes segmental demyelination, which results in significant reduction in conduction velocity. Conduction block clinically results in weakness and sensory loss. Increased desynchronization and temporal dispersion cause loss of reflexes. A prolonged refractory period with blocking at high frequency possibly accounts for reduced strength despite maximal voluntary effort.

Sensory Conduction Studies

This study should include multiple sensory nerves in both the upper and lower limbs, such as the sural, superficial peroneal, median, and ulnar nerves. The more distal nerves are affected earlier in the course of the disease than are the proximal nerves. This can be explained by the less protective myelin coating of this part of the nervous system, predisposing it to damage. Nerves that traverse entrapment sites are even more prone to involvement.

In axonal-type Guillain-Barré syndrome, the sensory nerve action potential amplitudes become sig-

nificantly lowered after about 4 to 6 weeks. The sensory nerve action potential amplitude drops to 20% or less of normal values and commonly disappears between 3 to 4 weeks after onset of the disease. The conduction velocity and latency do not drop below 80% to 90% of the normal mean value. Conduction block or axonal loss is suspected when the alteration in sensory nerve action potential amplitude is larger than in conduction velocity.

Somatosensory Evoked Potential Conduction Studies

To study the proximal aspects of the sensory conduction system in Guillain-Barré syndrome, somatosensory evoked potential techniques are useful. Segmental conduction times, using Erb's point (N9) and cervical (Ni 1) potentials (upper extremity), lumbar (N20) potential, and the central conduction, can be calculated. Central conduction times are essentially normal.

In Guillain-Barré syndrome, there seems to be a predisposition toward the proximal or nerve root regions. These features explain why patients have complaints of sensation and clinical abnormalities and only a few distal electrophysiological sensory nerve action potential abnormalities. Somatosensory evoked potential studies of both the upper and lower limbs should be performed, but because the neural pathway of the lower limbs is considerably longer, it is more beneficial to study them first.

Motor Conduction Studies

To establish the diagnosis and monitoring of Guillain-Barré syndrome, distal motor latencies, conduction velocities, F waves, H reflexes, and CMAP amplitudes; duration, and morphology are used. In 80% to 90% of the patients, at least one of these motor nerve parameters is disturbed. The distal motor latency and CMAP conduction velocity measurements reach a peak reduction of 60% to 80% of the normal mean values about 3 weeks after the onset of the clinical symptoms. After 4 weeks, the values begin to increase to normal over several weeks to months, although 1 year or longer can be required. In general, there is little correlation between the clinical presentation and nerve conduction velocity or distal motor latency.

To perform an examination of the F waves in Guillain-Barré syndrome, high amplifier gains (100 to 200 μ V/cm), prolonged pulse duration, and increased current intensities should be used to conclude that F waves are reduced in number. Some type of abnormality can be expected in 80% to 90% of the patients, and the absence of F waves should be considered a definite abnormality. H reflexes should also be tested in the lower limbs to assess possible disturbed proximal neural conduction.

The most frequently encountered abnormality early in Guillain-Barré syndrome is conduction block. Such a block is present if there is a reduction

in the peak-to-peak CMAP amplitude of more than 20% (a drop in proximal compared with distal CMAP), as defined by Asbury and Cornblath (1990), in the following nerves: (1) median (proximal arm compared with wrist, recording from thenar muscles), (2) ulnar (Erb's point compared with wrist, recording from hypothenar muscles), and (3) peroneal (popliteal fossa to ankle, recording from extensor digitorum brevis). Due to the lack of unanimity on the percentage of amplitude reduction; a range of 20% to 40% is used. In pseudo-conduction block, a reduction in amplitude is a result of excessive temporal dispersion, which may increase the duration of the potential, with a concomitant and compensatory reduction in amplitude. To distinguish between conduction block and temporal dispersive effects, small-segment stimulation can be used to localize focal reduction in amplitude. The conduction block is pathophysiologically caused by the loss of myelin, leading to conduction failure and symptoms of weakness and sensory loss. Permanent reduction of function is secondary to axonal loss.

Abnormalities with regard to the phrenic nerve are frequently noted, although reduced ventilatory capacity is not due to reduced conduction velocity in the phrenic nerve. If present, axonal damage of this nerve can be diagnosed with needle electromyography of the diaphragm.

In addition, abnormalities of the facial nerve can be tested in Guillain-Barré syndrome, as well as those of the supraorbital nerve. Direct facial nerve stimulation and the blink reflex reveal abnormalities in either or both pathways.

Needle Electromyography Examination

Positive sharp waves and fibrillation potentials at rest appear between 2 to 4 weeks, peaking about 6 to 15 weeks (earlier in the proximal than in the distal muscles). Within the first 3 weeks, myokymia (complex bursts of repetitive discharges that cause vermicular movements of the skin) are detected, especially in the facial muscles.

This examination is mainly adjunctive to explore other disease entities.

In Guillain-Barré syndrome, a reduced recruitment for motor unit potentials is one of the earliest findings. After about 6 to 16 weeks, voluntary motor unit potential amplitude, duration, and number of phases increase. These findings imply (1) axonal loss with motor unit remodeling and (2) reverse motor unit remodeling during axonal regrowth.

Single-fiber electromyography shows mild-to-moderate increase in fiber density later in the course of Guillain-Barré syndrome, substantiating the initial phases of motor unit remodeling in patients with axonal loss.

ELECTRODIAGNOSTIC CRITERIA of GUILLAIN-BARRE SYNDROME AND THEIR VALIDATION

Most electrodiagnostic criteria have been defined on the basis of demyelination. Alam (1998) studied

the six different sets of criteria that have been used in previous studies and applied them to 43 patients with the clinical diagnosis of Guillain-Barré syndrome. This resulted in 21% to 72% of the patients giving the diagnosis of acute inflammatory demyelinating polyradiculoneuropathy. The sets were defined by Albers and colleagues (1985), Albers and Ally (1989), Cornblath (1990), Ho and associates (1997), and Meulstee and van der Meché (1995). Although the criteria of Albers (Albers et al., 1985; Albers and Kelly, 1989) identified most cases as acute inflammatory demyelinating polyradiculoneuropathy, the importance of performing analyses on the criteria to achieve consensus and to reduce the variability in diagnosing the acute inflammatory demyelinating polyradiculoneuropathy variant of Guillain-Barré syndrome was emphasized.

In acute inflammatory demyelinating polyradiculoneuropathy, most distal sites, roots, and physiological entrapment sites are fragile, and early demyelination and secondary axonal degeneration occur here. Axonal degeneration easily masks demyelinating conduction changes. However, with careful follow-up, the presence of delayed F waves or increased distal motor latencies definitely mitigates against primary axonal pathology, as in acute motor axonal neuropathy or acute motor sensory axonal neuropathy.

Electrodiagnostic primary axonal Guillain-Barré syndrome was defined by Hadden and associates (1998) and Ho and colleagues (1997) as (1) no evidence of demyelination and (2) CMAP amplitude less than 80% of the lower limit of normal.

TREATMENT AND PROGNOSIS

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The treatment of Guillain-Barré syndrome with intravenous immunoglobulin or plasma exchange results in earlier recovery, but morbidity rates remain considerable. Trials may lead to other methods of improving outcome.

The time of recovery depends on the extent of demyelination and axonal degeneration. Patients with severe axonal loss may not regain motor function for 1 to 2 years, implying a poor prognosis. Axonal regeneration takes considerably longer than demyelination. The Dutch multicenter study on prognostic factors that influence Guillain-Barré syndrome revealed that a preceding gastrointestinal illness, older age (>50 years), severe weakness (a Medical Research Council sum score of <40 at the start of the treatment), and rapid progression of weakness within 4 days of onset of weakness were important independent, significant prognostic factors at 6 months of follow-up (Visser, 1999). Others found that the electrodiagnostic finding of a low CMAP amplitude (<4 mV) is an important prognostic factor.

To distinguish CIP from the acute motor axonal variant of Guillain-Barré syndrome, the following characteristics may be useful (De Letter et al., 1993).

- Guillain-Barré syndrome is the primary neurological reason for admission to the intensive care unit. On the other hand, CIP develops during a patient's stay in the intensive care unit for another reason.
- Infectious symptoms like fever and diarrhea usually subside before the clinical features of Guillain-Barré syndrome appear.
- The characteristic alterations in the cerebrospinal fluid of Guillain-Barré syndrome patients include a raised protein level and a normal to slightly elevated cell count.
- There is a possibility of detecting IgG antibodies against GM 1, GM 1 b, GD 1 a, and GalNac-GD1a in the serum of axonal Guillain-Barré syndrome patients.
- Electrodiagnostic changes in Guillain-Barré syndrome occur in both sensory and motor nerves in about 80% of the patients in the Western world. In CIP, there is clinically a predominantly motor dysfunction. Both CIP and axonal-type Guillain-Barré syndrome show sensorimotor or pure motor axonal features. Critical illness polyneuropathy and myopathy can sometimes be distinguished from Guillain-Barré syndrome by the presence of myopathic motor unit potentials on voluntary activation.
- During the progression of Guillain-Barré syndrome, the demyelinating features of the nerve conduction study may change into a secondary axonal pattern. In the latter, slow nerve conduction velocity remains in some patients and the initial needle electromyography study lacks spontaneous activity (Chen, 1998). In CIP, spontaneous activity of the muscle fibers is an early feature. Further phrenic nerve conduction studies usually show no significantly prolonged latencies in CIP (Bolton et al., 1986).
- Severe autonomic disturbances are more common in the patient with Guillain-Barré syndrome after the polyneuropathy has developed than in patients with CIP (Bolton et al., 1986).
- Septic encephalopathy may be present before the onset of CIP. Patients with Guillain-Barré syndrome do not have a disturbed consciousness.

Porphyrie Neuropathy

Porphyrie neuropathy is an acute or subacute, predominantly motor neuropathy. Disturbances of porphyrie metabolism are associated with acute attacks of neurological disease in cases of hepatic porphyries. These porphyries, consisting of acute intermittent porphyrie, hereditary coproporphyria, and variegate porphyrie, are caused by enzyme defects (uroporphyrinogen-1-synthetase, coproporphyrinogen oxidase, or protoporphyrinogen oxidase, respectively). Acute intermittent porphyrie (Stein and Tschudy, 1970; Kappas et al., 1993), hereditary coproporphyria (Magnussen et al., 1975), and variegate porphyrie (Eales et al., 1980) all occur on a genetic basis. The attacks of acute hepatic porphyries may be precipitated by drugs (must often be bi-