REVIEW ARTICLE

MEDICAL PROGRESS

Guillain–Barré Syndrome

Nobuhiro Yuki, M.D., Ph.D., and Hans-Peter Hartung, M.D.

From the Department of Medicine, National University of Singapore, Singapore (N.Y.); and the Department of Neurology, Heinrich Heine University, Düsseldorf, Germany (H.-P.H.). Address reprint requests to Dr. Yuki at the Department of Medicine, National University of Singapore, Unit 09-01, Centre for Translational Medicine, 14 Medical Dr., Singapore 117599, Singapore, or at yuki.research@gmail.com.

THE GUILLAIN–BARRÉ SYNDROME, WHICH IS CHARACTERIZED BY ACUTE areflexic paralysis with albuminocytologic dissociation (i.e., high levels of protein in the cerebrospinal fluid and normal cell counts), was described in 1916.[1] Since poliomyelitis has nearly been eliminated, the Guillain–Barré syndrome is currently the most frequent cause of acute flaccid paralysis worldwide and constitutes one of the serious emergencies in neurology. A common misconception is that the Guillain–Barré syndrome has a good prognosis — but up to 20% of patients remain severely disabled and approximately 5% die, despite immunotherapy.[2] The Miller Fisher syndrome, which is characterized by ophthalmoplegia, ataxia, and areflexia, was reported in 1956 as a likely variant of the Guillain–Barré syndrome, because the cerebrospinal fluid of affected patients showed albuminocytologic dissociation.[3] Furthermore, frank Guillain–Barré syndrome has developed in some patients with the Miller Fisher syndrome.[4]

Various studies of the immunopathogenesis of the Guillain–Barré syndrome suggest that the disease actually encompasses a group of peripheral-nerve disorders, each distinguished by the distribution of weakness in the limbs or cranial-nerve–innervated muscles and underlying pathophysiology (Fig. 1).[5-7] There is substantial evidence to support an autoimmune cause of this syndrome, and the autoantibody profile has been helpful in confirming the clinical and electrophysiological relationship of the typical Guillain–Barré syndrome to certain other peripheral-nerve conditions. This review considers the current understanding, diagnosis, and management of the Guillain–Barré syndrome.

CLINICAL FEATURES

EPIDEMIOLOGY

The reported incidence of the Guillain–Barré syndrome in Western countries ranges from 0.89 to 1.89 cases (median, 1.11) per 100,000 person-years, although an increase of 20% is seen with every 10-year rise in age after the first decade of life.[8] The ratio of men to women with the syndrome is 1.78 (95% confidence interval, 1.36 to 2.33).

Two thirds of cases are preceded by symptoms of upper respiratory tract infection or diarrhea. The most frequently identified infectious agent associated with subsequent development of the Guillain–Barré syndrome is *Campylobacter jejuni*, and 30% of infections were attributed to *C. jejuni* in one meta-analysis,[9] whereas cytomegalovirus has been identified in up to 10%.[10,11] The incidence of the Guillain–Barré syndrome is estimated to be 0.25 to 0.65 per 1000 cases of *C. jejuni* infection, and 0.6 to 2.2 per 1000 cases of primary cytomegalovirus infection.[12] Other infectious agents with a well-defined relationship to the Guillain–Barré syndrome are Epstein–Barr virus, varicella–zoster virus, and *Mycoplasma pneumoniae*.[10,11,13]

During a 1976 mass immunization against A/New Jersey/1976/H1N1 "swine flu"

Subtypes and variants	IgG autoantibodies to
Guillain–Barré syndrome	
Acute inflammatory demyelinating polyneuropathy	None
Facial variant: Facial diplegia and paresthesia	None
Acute motor axonal neuropathy	GM1, GD1a
More and less extensive forms	
Acute motor–sensory axonal neuropathy	GM1, GD1a
Acute motor-conduction-block neuropathy	GM1, GD1a
Pharyngeal–cervical–brachial weakness	GT1a > GQ1b >> GD1a
Miller Fisher syndrome	GQ1b, GT1a
Incomplete forms	
Acute ophthalmoparesis (without ataxia)	GQ1b, GT1a
Acute ataxic neuropathy (without ophthalmoplegia)	GQ1b, GT1a
CNS variant: Bickerstaff's brain-stem encephalitis	GQ1b, GT1a

Figure 1. Spectrum of Disorders in the Guillain–Barré Syndrome and Associated Antiganglioside Antibodies.

IgG autoantibodies against GM1 or GD1a are strongly associated with acute motor axonal neuropathy, as well as the more extensive acute motor–sensory axonal neuropathy and the less extensive acute motor-conduction-block neuropathy. IgG anti-GQ1b antibodies, which cross-react with GT1a, are strongly associated with the Miller Fisher syndrome, its incomplete forms (acute ophthalmoparesis [without ataxia] and acute ataxic neuropathy [without ophthalmoplegia]), and its more extensive form, Bickerstaff's brain-stem encephalitis. Pharyngeal–cervical–brachial weakness is categorized as a localized form of acute motor axonal neuropathy or an extensive form of the Miller Fisher syndrome. Half of patients with pharyngeal–cervical–brachial weakness have IgG anti-GT1a antibodies, which often cross-react with GQ1b. IgG anti-GD1a antibodies have also been detected in a small percentage of patients. The anti-GQ1b antibody syndrome includes the Miller Fisher syndrome, acute ophthalmoparesis, acute ataxic neuropathy, Bickerstaff's brain-stem encephalitis, and pharyngeal–cervical–brachial weakness. The presence of clinical overlap also indicates that the Miller Fisher syndrome is part of a continuous spectrum with these conditions. Patients who have had the Guillain–Barré syndrome overlapped with the Miller Fisher syndrome or with its related conditions have IgG antibodies against GM1 or GD1a as well as against GQ1b or GT1a, supporting a link between acute motor axonal neuropathy and the anti-GQ1b antibody syndrome. CNS denotes central nervous system.

in the United States, people who received the vaccine were at increased risk for the development of the Guillain–Barré syndrome.[14] Other seasonal influenza vaccines have not been associated with the same increase in risk. With the pandemic influenza A (H1N1) outbreak in 2009, there was great concern that vaccination against H1N1 might also trigger the Guillain–Barré syndrome, but that did not occur.[15]

DIAGNOSIS

The first symptoms of the Guillain–Barré syndrome are numbness, paresthesia, weakness, pain in the limbs, or some combination of these symptoms. The main feature is progressive bilateral and relatively symmetric weakness of the limbs, and the weakness progresses over a period of 12 hours to 28 days before a plateau is reached.[16] Patients typically have generalized hyporeflexia or areflexia.

A history of upper respiratory infectious symptoms or diarrhea 3 days to 6 weeks before the onset is not uncommon.

The differential diagnosis is wide, and detailed neurologic assessment localizes the disease to the peripheral nerves rather than to the brain stem, spinal cord, cauda equina, neuromuscular junction, or muscles. The presence of distal paresthesia increases the likelihood that the correct diagnosis is the Guillain–Barré syndrome. If sensory involvement is absent, disorders such as poliomyelitis, myasthenia gravis, electrolyte disturbance, botulism, or acute myopathy should be considered. Hypokalemia shares some features with the Guillain–Barré syndrome but is commonly overlooked in the differential diagnosis. In patients with acute myopathy, tendon jerks are preserved and serum creatine kinase levels are increased. If paralysis develops abruptly and urinary retention is prominent, magnetic resonance imaging of the spine should be considered, to rule out a compressive lesion.

Nerve-conduction studies help to confirm the presence, pattern, and severity of neuropathy. These studies are essential for research, given specific criteria for categorizing the diagnosis,[17] but nerve-conduction studies are not obligatory for the recently proposed Brighton criteria for diagnosis, which were developed for use in resource-poor environments.[16] Once the diagnosis of an acute peripheral neuropathy is clear, the Guillain–Barré syndrome is the likely diagnosis in the majority of patients. However, clinicians should consider alternative causes, such as vasculitis, beriberi, porphyria, toxic neuropathy, Lyme disease, and diphtheria.

A lumbar puncture is usually performed in patients with suspected Guillain–Barré syndrome, primarily to rule out infectious diseases, such as Lyme disease, or malignant conditions, such as lymphoma. A common misconception holds that there should always be albuminocytologic dissociation. However, albuminocytologic dissociation is present in no more than 50% of patients with the Guillain–Barré syndrome during the first week of illness, although this percentage increases to 75% in the third week.[18] Some patients with human immunodeficiency virus infection and the Guillain–Barré syndrome have pleocytosis.

The Guillain–Barré syndrome generally follows a monophasic course and typically does not recur, but two or more episodes have been reported in 7% of patients.[19] The mean interval between recurrences in these patients was 7 years. Although hyporeflexia or areflexia is a hallmark of the Guillain–Barré syndrome, 10% of patients have normal or brisk reflexes during the course of the illness. Thus, the possibility of the Guillain–Barré syndrome should not be excluded in a patient with normal or brisk reflexes if all other features are supportive of the diagnosis.[20] Clinical deterioration after initial improvement or stabilization with immunotherapy suggests that the treatment had a transient effect or that chronic inflammatory demyelinating polyneuropathy is present.[21]

NATURAL HISTORY AND PROGNOSTIC MODELS

In the majority of patients, the Guillain–Barré syndrome continues to progress for up to 1 to 3 weeks after the onset of symptoms.[22] Two thirds of patients are unable to walk independently when maximum weakness is reached.[2] Respiratory insufficiency occurs in 25% of patients, and major complications, including pneumonia, sepsis, pulmonary embolism, and gastrointestinal bleeding, develop in 60% of intubated patients.[23] Among severely affected patients, 20% remain unable to walk 6 months after the onset of symptoms. The variations in the rate and extent of recovery in the Guillain–Barré syndrome make prognostication difficult.

One clinical scoring system that has been developed uses the patient's age, the presence or absence of antecedent diarrhea, and disease severity to predict whether a patient will be able to walk independently at 1, 3, or 6 months (see the table in the Supplementary Appendix, available with the full text of this article at NEJM.org).[24,25] Another prognostic scale uses the number of days between the onset of weakness and hospital admission, the presence or absence of facial or bulbar weakness, and the severity of the limb weakness to predict the likelihood that respiratory insufficiency will develop.[26] Both scales, validated in their respective patient populations, can be useful in the care of patients with the Guillain–Barré syndrome.

DEMYELINATING AND AXONAL SUBTYPES

The histologic features of the Guillain–Barré syndrome support a classification that includes demyelinating and axonal subtypes — acute inflammatory demyelinating polyneuropathy and

acute motor axonal neuropathy.[27,28] The classification is based on nerve-conduction studies (Fig. 1 in the Supplementary Appendix),[29,30] and there is a notable difference in the geographic distribution of subtypes of the syndrome. In Europe and North America, the demyelinating Guillain–Barré syndrome accounts for up to 90% of cases,[29] whereas in China, Japan, Bangladesh, and Mexico, the frequency of the axonal Guillain–Barré syndrome ranges from 30% to 65% and the frequency of the demyelinating Guillain–Barré syndrome ranges from 22% to 46%.[22,30-32] In an Italian cohort, nerve-conduction studies overestimated the incidence of the demyelinating Guillain–Barré syndrome when the studies were performed early in the course of the disease, and subsequent nerve-conduction studies in the same patients indicated a need for reclassification: the proportion of cases that were classified as the demyelinating subtype decreased from 67% to 58%, and the proportion classified as the axonal subtype increased from 18% to 38%.[33] It is generally thought that test results obtained early in the course of illness may lead to misclassification of the subtype and that serial nerve-conduction studies are therefore important for accurate subtype classification (see the Supplementary Appendix).

In acute motor–sensory axonal neuropathy, there is clear involvement of the sensory fibers, but detailed studies have suggested that mild changes occur in the sensory nerves of some patients with acute motor axonal neuropathy.[34] Acute motor-conduction-block neuropathy is a mild form of acute motor axonal neuropathy but does not progress to axonal degeneration.[35]

There are localized forms of the Guillain–Barré syndrome that are distinguished by involvement of certain muscle groups or nerves. Facial diplegia with paresthesia is a localized form of the demyelinating Guillain–Barré syndrome,[36] whereas pharyngeal–cervical–brachial weakness, which is characterized by acute weakness of the oropharyngeal, neck, and shoulder muscles, represents a localized form of the axonal Guillain–Barré syndrome.[37,38]

THE MILLER FISHER SYNDROME

The Miller Fisher syndrome appears to be more common among patients with the Guillain–Barré syndrome who live in eastern Asia than among those who live in other parts of the world, occurring in up to 20% of patients in Taiwan and 25% of patients in Japan.[4,39] Most patients with the Miller Fisher syndrome have evidence of infection 1 to 3 weeks before the development of ophthalmoplegia or ataxia; in one study, 20% of patients had *C. jejuni* infection and 8% had *Haemophilus influenzae* infection.[40]

The presence of distal paresthesia is associated with the Miller Fisher syndrome. Careful clinical assessment and focused investigations such as brain imaging and electrophysiological examinations can rule out other conditions, such as brain-stem stroke, Wernicke's encephalopathy, myasthenia gravis, and botulism. The disease peaks at a median of 1 week, and improvement often starts at a median of 2 weeks.[4] Recovery from ataxia and recovery from ophthalmoplegia take a median of 1 and 3 months, respectively. By 6 months after the onset of neurologic symptoms, most patients have recovered from ataxia and ophthalmoplegia.

PATHOGENESIS

POSTMORTEM STUDIES AND CLINICOPATHOLOGICAL CORRELATION

The classic pathological findings in acute inflammatory demyelinating polyneuropathy are inflammatory infiltrates (consisting mainly of T cells and macrophages) and areas of segmental demyelination, often associated with signs of secondary axonal degeneration, which can be detected in the spinal roots, as well as in the large and small motor and sensory nerves.[27] There is evidence of early complement activation, which is based on antibody binding to the outer surface of the Schwann cell and deposition of activated complement components; such complement activation appears to initiate the vesiculation of myelin (Fig. 2).[41] Macrophage invasion is observed within 1 week after complement-mediated myelin damage occurs.

In acute motor axonal neuropathy, IgG and activated complement bind to the axolemma of motor fibers at the nodes of Ranvier, followed by formation of the membrane-attack complex.[42] The resultant nodal lengthening is followed by axonal degeneration of motor fibers with neither lymphocytic inflammation nor demyelination.[28,43] There are autopsy reports indicating that the neurologic signs of the Miller Fisher syndrome overlap with those of the Guillain–Barré syndrome (oph-
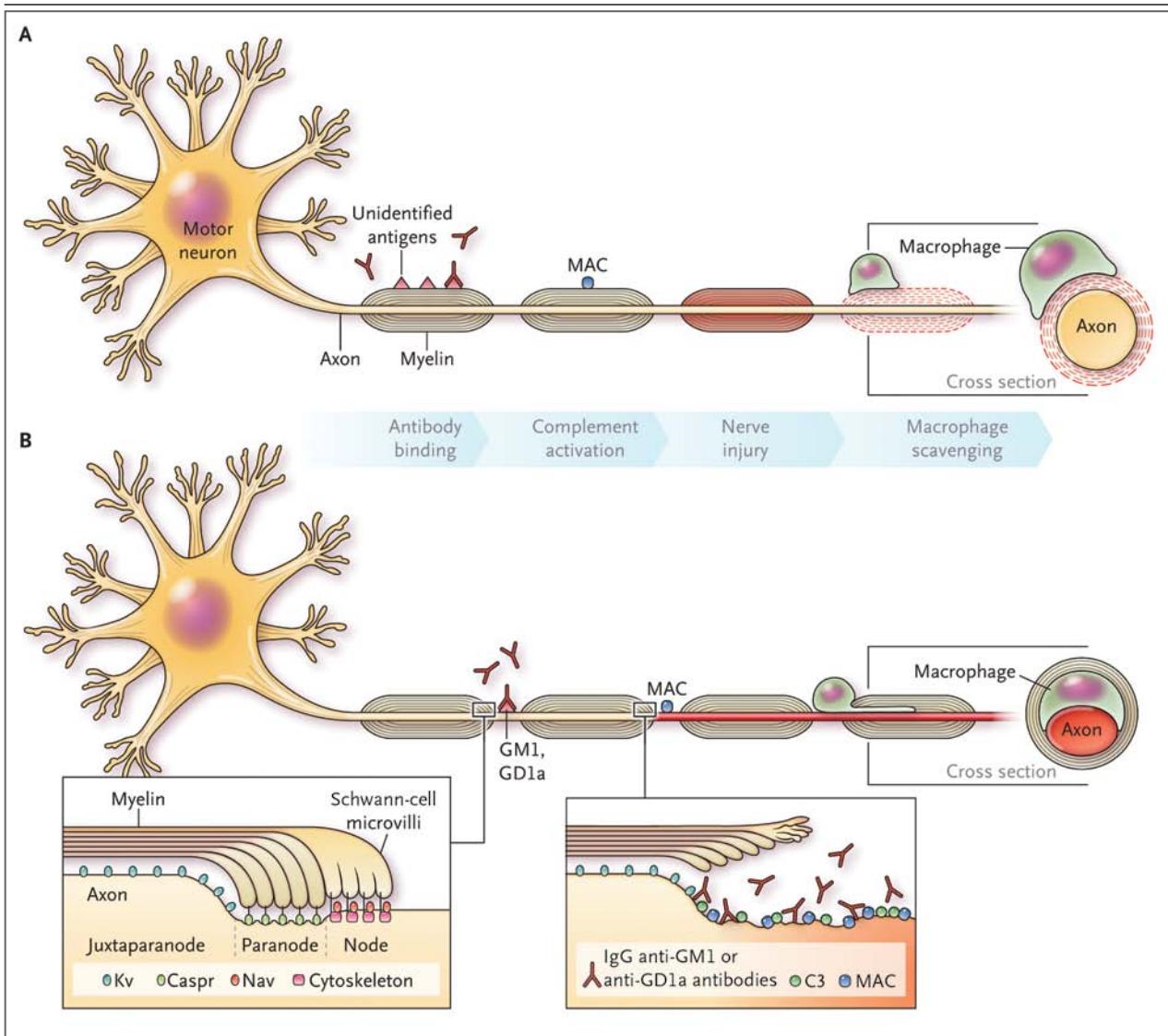
Figure 2. Possible Immunopathogenesis of the Guillain–Barré Syndrome.

Panel A shows the immunopathogenesis of acute inflammatory demyelinating polyneuropathy. Although autoantigens have yet to be un-equivocally identified, autoantibodies may bind to myelin antigens and activate complement. This is followed by the formation of membrane-attack complex (MAC) on the outer surface of Schwann cells and the initiation of vesicular degeneration. Macrophages subsequently invade myelin and act as scavengers to remove myelin debris. Panel B shows the immunopathogenesis of acute motor axonal neuropathy. Myelinated axons are divided into four functional regions: the nodes of Ranvier, paranodes, juxtaparanodes, and internodes. Gangliosides GM1 and GD1a are strongly expressed at the nodes of Ranvier, where the voltage-gated sodium (Nav) channels are localized. Contactin-associated protein (Caspr) and voltage-gated potassium (Kv) channels are respectively present at the paranodes and juxtaparanodes. IgG anti-GM1 or anti-GD1a autoantibodies bind to the nodal axolemma, leading to MAC formation. This results in the disappearance of Nav clusters and the detachment of paranodal myelin, which can lead to nerve-conduction failure and muscle weakness. Axonal degeneration may follow at a later stage. Macrophages subsequently invade from the nodes into the periaxonal space, scavenging the injured axons.

thalmoplegia and ataxia in the former and sub-stantial limb weakness in the latter),[44] which suggests that the available immunohistochemi-cal and electron-microscopical studies do not accurately differentiate the demyelinating sub-type from the axonal subtype of the Guillain–Barré syndrome.[41,42] The pathological features of the "pure" Miller Fisher syndrome remain un-certain because almost all patients eventually have a complete recovery and fatal cases are very rare.

ANTIGANGLIOSIDE ANTIBODIES

Gangliosides, which are composed of a ceramide attached to one or more sugars (hexoses) and contain sialic acid (*N*-acetylneuraminic acid) linked to an oligosaccharide core, are important components of the peripheral nerves. Four gangliosides — GM1, GD1a, GT1a, and GQ1b — differ with regard to the number and position of their sialic acids, where M, D, T, and Q represent mono-, di-, tri-, and quadri-sialosyl groups (Fig. 1). IgG autoantibodies to GM1 and GD1a are associated with acute motor axonal neuropathy and its more extensive and less extensive subtypes, acute motor–sensory axonal neuropathy and acute motor-conduction-block neuropathy, respectively, but not with acute inflammatory demyelinating polyneuropathy.[5,34,35] Motor and sensory nerves express similar quantities of GM1 and GD1a, but their expression within various tissues may differ.[45] This could explain the preferential motor-axon injury seen in acute motor axonal neuropathy.

IgG autoantibodies to GQ1b, which cross-react with GT1a, are strongly associated with the Miller Fisher syndrome, its incomplete forms (acute ophthalmoparesis and acute ataxic neuropathy), and its central nervous system variant, Bickerstaff's brain-stem encephalitis, which includes acute ophthalmoplegia, ataxia, and impaired consciousness after an infectious episode.[6,7,46] Patients with pharyngeal–cervical–brachial weakness are more likely to have IgG anti-GT1a antibodies, which may cross-react with GQ1b; they are also less likely to have IgG anti-GD1a antibodies, which suggests a link to the axonal Guillain–Barré syndrome.[37]

The localization of these target ganglioside antigens has been associated with distinct clinical patterns of ophthalmoplegia, ataxia, and bulbar palsy. GQ1b is strongly expressed in the oculomotor, trochlear, and abducens nerves, as well as muscle spindles in the limbs.[46,47] The glossopharyngeal and vagus nerves strongly express GT1a and GQ1b, possibly accounting for dysphagia.[48]

In some situations, antibodies against complexes consisting of two different gangliosides, rather than antibodies against a single ganglioside, develop in patients with the Guillain–Barré syndrome, suggesting specific recognition of a new conformational epitope formed by these glycolipids (see the Supplementary Appendix).[49]

MOLECULAR MIMICRY

Some evidence supports the presence of molecular mimicry between gangliosides and antecedent infectious agents in patients with the Guillain–Barré syndrome and those with the Miller Fisher syndrome. Lipooligosaccharide is a major component of the outer membrane of *C. jejuni*. Studies have shown that bacterial isolates from patients with the Guillain–Barré syndrome bear GM1-like or GD1a-like lipooligosaccharide, and those from patients with the Miller Fisher syndrome have lipooligosaccharides mimicking GQ1b (Fig. 2 in the Supplementary Appendix).[40,50] In another study, an *H. influenzae* isolate from a patient with the Miller Fisher syndrome also carried a GQ1b-mimicking lipooligosaccharide.[51]

ANIMAL MODELS

Experimental autoimmune neuritis, which can be induced by immunization with peripheral-nerve proteins or transferred to animals by T cells sensitized to these proteins, resembles the demyelinating Guillain–Barré syndrome clinically and pathologically.[52] However, evidence in support of the concept that such autoreactive T-cell or autoantibody responses occur in a sizable proportion of patients is lacking, suggesting that experimental autoimmune neuritis is not a valid model of the Guillain–Barré syndrome.

A rabbit model of the axonal Guillain–Barré syndrome produced by sensitization with GM1 or GM1-like lipooligosaccharides of *C. jejuni* from patients with the disorder supports the role of molecular mimicry in the pathogenesis of this disease.[53,54] In the rabbit model, anti-GM1 antibodies bound to nodes and activated complement, resulting in the formation of a membrane-attack complex at the anterior roots of the spinal nerve, which was followed by the disappearance of the sodium-channel cluster (Fig. 3 in the Supplementary Appendix). Such a constellation of abnormalities might induce nerve-conduction failure and muscle weakness. Axonal degeneration occurred at a later stage in this model.

In a murine model, the passive transfer of anti-GM1 or anti-GD1a antibodies produced a replica of the axonal Guillain–Barré syndrome in the presence of human complement, providing supportive evidence of the pathogenic roles of antiganglioside antibodies and complement in the development of the axonal Guillain–Barré syndrome.[55,56] Eculizumab, a human monoclo-

nal antibody that binds to and blocks cleavage of the complement component C5, prevented dysfunction and structural nerve damage in the murine model.[57]

The presence of anti-GM1 or anti-GD1a antibodies impeded axonal regeneration after peripheral-nerve injury in a murine model,[45] and erythropoietin, which is used to treat anemia in chronic kidney disease, enhanced nerve regeneration.[58] The activation of RhoA and Rho kinase appears to prevent neurite outgrowth induced by anti-GM1 or anti-GD1a antibodies.[59] An inhibitor of Rho kinase, fasudil, which has been used in the prevention of cerebral vasospasm in patients with subarachnoid hemorrhage, has shown therapeutic effects in experimental autoimmune neuritis.[60]

ASSOCIATED INFECTIOUS DISEASES

Infection with cytomegalovirus or Epstein–Barr virus is associated with the demyelinating Guillain–Barré syndrome, whereas *C. jejuni* infection is associated with the axonal Guillain–Barré syndrome and with the Miller Fisher syndrome.[10,40,61,62] The pathogenesis of the demyelinating Guillain–Barré syndrome has yet to be clarified, despite the documentation of characteristic histologic changes.[27,41] In contrast, our understanding of the underlying pathogenesis of the axonal Guillain–Barré syndrome and the Miller Fisher syndrome has been, in part, elucidated.

Infection by *C. jejuni* carrying GM1-like or GD1a-like lipooligosaccharide induces anti-GM1 or anti-GD1a antibodies in some patients. These autoantibodies bind to GM1 or GD1a expressed on the motor nerves of the limbs, resulting in the axonal Guillain–Barré syndrome (Fig. 2 in the Supplementary Appendix). In contrast, infection by *C. jejuni* bearing GQ1b-mimicking lipooligosaccharide elicits the generation of anti-GQ1b antibodies. The autoantibodies, on binding to GQ1b expressed in the oculomotor nerves and muscle spindles, may cause the Miller Fisher syndrome.

TREATMENT

GENERAL CARE

Even in developed countries, 5% of patients with the Guillain–Barré syndrome die from medical complications such as sepsis, pulmonary emboli, or unexplained cardiac arrest, perhaps related to dysautonomia.[23] Thus, management requires measures for the early detection of such complications (Table 1).[63] Ideally, all patients should remain under hospital observation until it has been established that there is no evidence of clinical progression.[65] Whenever feasible, patients should be treated in a critical care unit, where adequate resources are available to allow continuous cardiac and respiratory monitoring. Patients with very mild weakness and the ability to walk independently are unlikely to require any treatment beyond supportive care.

Even in the absence of clinical respiratory distress, mechanical ventilation may be required in patients with at least one major criterion or two minor criteria. The major criteria are hypercarbia (partial pressure of arterial carbon dioxide, >6.4 kPa [48 mm Hg]), hypoxemia (partial pressure of arterial oxygen while the patient is breathing ambient air, <7.5 kPa [56 mm Hg]), and a vital capacity less than 15 ml per kilogram of body weight, and the minor criteria are inefficient cough, impaired swallowing, and atelectasis.[66] An early assessment of swallowing will identify patients at risk for aspiration, necessitating the placement of a nasogastric tube.[23] Selective decontamination of the digestive tract decreases the time that patients remain on a ventilator.[67]

Table 1. Management of the Guillain–Barré Syndrome.

Monitoring of cardiac and pulmonary dysfunction

Electrocardiography, blood pressure, pulse oximetry for oxyhemoglobin saturation, vital capacity, and swallowing should be regularly monitored in patients who have severe disease, with checks every 2–4 hr if the disease is progressing and every 6–12 hr if it is stable.[63]

Insertion of a temporary cardiac pacemaker, use of a mechanical ventilator, and placement of a nasogastric tube should be performed on the basis of the monitoring results.

Prevention of pulmonary embolism

Prophylactic use of subcutaneous heparin and compression stockings is recommended for adult patients who cannot walk.

Immunotherapy

Intravenous immune globulin or plasma exchange should be administered in patients who are not able to walk unaided.

In patients whose status deteriorates after initial improvement or stabilization, retreatment with either form of immunotherapy can be considered. However, plasma exchange should not be performed in patients already treated with immune globulin because it would wash out the immune globulin still present in the blood. Also, immune globulin should not be used in patients already treated with plasma exchange because this sequence of treatments is not significantly better than plasma exchange alone.[64]

Serious and potentially fatal autonomic dysfunction, such as arrhythmia and extreme hypertension or hypotension, occurs in 20% of patients with the Guillain–Barré syndrome.[23] Severe bradycardia may be preceded by wide swings (exceeding 85 mm Hg) in systolic blood pressure from day to day. Bradycardia may be so marked that it causes asystole, warranting the use of a temporary cardiac pacemaker.

When patients with the Guillain–Barré syndrome are not ambulatory, prophylaxis against deep-vein thrombosis, consisting of subcutaneous heparin and the use of compression stockings, is important.[23] Other possible complications include urinary retention and constipation, which may be addressed by bladder catheterization and the use of laxatives, respectively. The implementation of early and active individualized rehabilitation programs will maximize the chances of a favorable outcome.[68]

Pain, in the form of dysesthesia or muscular, radicular, arthralgic, and meningitic pain, has been reported to precede weakness in one third of patients with the Guillain–Barré syndrome: two thirds of all patients have pain during the acute phase and one third a year later.[69] Early recognition and treatment are important, and opioids, gabapentin, and carbamazepine may be effective, whereas glucocorticoids are not.[70] Severe fatigue has been reported in 60% of patients[71] and, when persistent, may respond to a program of strengthening, aerobic, and functional exercise.[72]

The Guillain–Barré syndrome can affect the central nervous system. In one study, vivid dreams, hallucinations, or psychosis affected one third of patients.[73] These changes occurred during the progression or plateau phase of the syndrome and disappeared as the patients recovered.

IMMUNOTHERAPY

Plasma exchange was the first treatment that was found to be effective in hastening recovery in patients with the Guillain–Barré syndrome,[74] and it appeared to be most effective when it was started within the first 2 weeks after disease onset in patients who were unable to walk. An electrophysiological examination is not always required for the initiation of immunotherapy. Plasma exchange nonspecifically removes antibodies and complement and appears to be associated with reduced nerve damage and faster clinical improvement, as compared with supportive therapy

alone.[74] The usual empirical regimen is five exchanges over a period of 2 weeks, with a total exchange of 5 plasma volumes. One trial showed that patients who could walk with or without aid but could not run benefited from two exchanges of 1.5 plasma volumes, but more severely affected patients required at least four exchanges.[75]

Treatment with intravenous immune globulin, initiated within 2 weeks after disease onset, is reported to be about as effective as plasma exchange in patients with the Guillain–Barré syndrome who cannot walk independently.[64,76] It is thought that immune globulin may act by neutralizing pathogenic antibodies and inhibiting autoantibody-mediated complement activation, resulting in reduced nerve injury and faster clinical improvement, as compared with no treatment,[77,78] although no comparative studies have been performed. In general, intravenous immune globulin has replaced plasma exchange as the treatment of choice in many medical centers because of its greater convenience and availability. According to the standard treatment regimen, immune globulin is given at a total dose of 2 g per kilogram of body weight over a period of 5 days.[64,76] The pharmacokinetics of immune globulin varies among patients, and some patients have a smaller rise in serum IgG after the administration of immune globulin.[79] These patients are likely to have a poorer outcome, with fewer able to walk unaided at 6 months. A second course of immune globulin in severely unresponsive patients was reported to be beneficial in one study.[80] Whether this observation holds will be assessed in an international study by the Inflammatory Neuropathy Consortium.

The combination of plasma exchange followed by a course of intravenous immune globulin is not significantly better than plasma exchange or immune globulin alone.[64] Neither prednisolone nor methylprednisolone can significantly accelerate recovery or affect the long-term outcome in patients with the Guillain–Barré syndrome.[81,82] One study showed that combined administration of immune globulin and methylprednisolone was not more effective than immune globulin alone, although an analysis corrected for known prognostic factors suggested a short-term effect.[83]

There have been no randomized trials of treatment for patients with the Miller Fisher syndrome. In retrospective analyses, intravenous immune globulin, but not plasmapheresis, re-

sulted in a slight hastening of recovery from ophthalmoplegia or ataxia in patients with the Miller Fisher syndrome, although the time to complete recovery remained unchanged.[4,84]

SUMMARY

The Guillain–Barré syndrome, an acute immune-mediated neuropathy, still carries a grave prognosis. The syndrome is manifested as a spectrum of peripheral-nerve disorders with several clinical variants that are characterized by the distribution of weakness of the limbs or cranial-nerve–innervated muscles, underlying pathological abnormalities, and associated autoantibodies.[5-7,34,35,37,85]

The most frequent antecedent infection is *C. jejuni* infection, which is associated with 30% of cases of the Guillain–Barré syndrome and 20% of cases of the Miller Fisher syndrome.[9,40] Molecular mimicry between the bacterial and peripheral-nerve components appears to elicit autoantibodies and induce the development of the axonal subtype of the Guillain–Barré syndrome or the Miller Fisher syndrome after enteritis with *C. jejuni*.[40,50,53,54] Eculizumab, erythropoietin, and fasudil, which have been used in the treatment of other, unrelated medical conditions, have shown promise in animal models of the Guillain–Barré syndrome,[57,58,60] but clinical studies are lacking.

REFERENCES

1. Guillain G, Barré JA, Strohl A. Sur un syndrome de radiculonévrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire: remarques sur les caractères cliniques et graphiques des réflexes tendineux. Bulletins et mémoires de la Société des Médecins des Hôpitaux de Paris 1916;40:1462-70.

2. Hughes RAC, Swan AV, Raphaël JC, Annane D, van Koningsveld R, van Doorn PA. Immunotherapy for Guillain-Barré syndrome: a systematic review. Brain 2007; 130:2245-57.

3. Fisher M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). N Engl J Med 1956;255:57-65.

4. Mori M, Kuwabara S, Fukutake T, Yuki N, Hattori T. Clinical features and prognosis of Miller Fisher syndrome. Neurology 2001;56:1104-6.

5. Sekiguchi Y, Uncini A, Yuki N, et al. Antiganglioside antibodies are associated with axonal Guillain-Barré syndrome: a Japanese-Italian collaborative study. J Neurol Neurosurg Psychiatry 2012;83: 23-8.

6. Ito M, Kuwabara S, Odaka M, et al. Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum: clinical analysis of 581 cases. J Neurol 2008;255:674-82.

7. Ito M, Matsuno K, Sakumoto Y, Hirata K, Yuki N. Ataxic Guillain-Barré syndrome and acute sensory ataxic neuropathy form a continuous spectrum. J Neurol Neurosurg Psychiatry 2011;82:294-9.

8. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology 2011;36:123-33.

9. Poropatich KO, Walker CL, Black RE. Quantifying the association between Campylobacter infection and Guillain-Barré syndrome: a systematic review. J Health Popul Nutr 2010;28:545-52.

10. Hadden RDM, Karch H, Hartung HP, et al. Preceding infections, immune factors, and outcome in Guillain-Barré syndrome. Neurology 2001;56:758-65.

11. Jacobs BC, Rothbarth PH, van der Meché FGA, et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology 1998;51:1110-5.

12. Orlikowski D, Porcher R, Sivadon-Tardy V, et al. Guillain-Barré syndrome following primary cytomegalovirus infection: a prospective cohort study. Clin Infect Dis 2011;52:837-44.

13. Kang JH, Sheu JJ, Lin HC. Increased risk of Guillain-Barré syndrome following recent herpes zoster: a population-based study across Taiwan. Clin Infect Dis 2010;51:525-30.

14. Lehmann HC, Hartung HP, Kieseier BC, Hughes RAC. Guillain-Barré syndrome after exposure to influenza virus. Lancet Infect Dis 2010;10:643-51.

15. Dieleman J, Romio S, Johansen K, Weibel D, Bonhoeffer J, Sturkenboom M. Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. BMJ 2011;343:d3908.

16. Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2011; 29:599-612.

17. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990;27:Suppl:S21-S24.

18. Nishimoto Y, Odaka M, Hirata K, Yuki N. Usefulness of anti-GQ1b IgG antibody testing in Fisher syndrome compared with cerebrospinal fluid examination. J Neuroimmunol 2004;148:200-5.

19. Kuitwaard K, van Koningsveld R, Ruts L, Jacobs BC, van Doorn PA. Recurrent Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 2009;80:56-9.

20. Yuki N, Kokubun N, Kuwabara S, et al. Guillain-Barré syndrome associated with normal or exaggerated tendon reflexes. J Neurol 2011 December 6 (Epub ahead of print).

21. Ruts L, Drenthen J, Jacobs BC, van Doorn PA. Distinguishing acute-onset

CIDP from fluctuating Guillain-Barré syndrome: a prospective study. Neurology 2010;74:1680-6.

22. Hiraga A, Mori M, Ogawara K, Hattori T, Kuwabara S. Differences in patterns of progression in demyelinating and axonal Guillain-Barré syndromes. Neurology 2003;61:471-4.

23. Hughes RAC, Wijdicks EF, Benson E, et al. Supportive care for patients with Guillain-Barré syndrome. Arch Neurol 2005;62:1194-8.

24. van Koningsveld R, Steyerberg EW, Hughes RAC, Swan AV, van Doorn PA, Jacobs BC. A clinical prognostic scoring system for Guillain-Barré syndrome. Lancet Neurol 2007;6:589-94.

25. Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain-Barré syndrome. Neurology 2011; 76:968-75.

26. Walgaard C, Lingsma HF, Ruts L, et al. Prediction of respiratory insufficiency in Guillain-Barré syndrome. Ann Neurol 2010;67:781-7.

27. Asbury AK, Arnason BG, Adams RD. The inflammatory lesion in idiopathic polyneuritis: its role in pathogenesis. Medicine (Baltimore) 1969;48:173-215.

28. McKhann GM, Cornblath DR, Griffin JW, et al. Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. Ann Neurol 1993;33:333-42.

29. Hadden RDM, Cornblath DR, Hughes RAC, et al. Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome. Ann Neurol 1998;44:780-8.

30. Ho TW, Mishu B, Li CY, et al. Guillain-Barré syndrome in northern China: relationship to *Campylobacter jejuni* infection and anti-glycolipid antibodies. Brain 1995;118:597-605.

31. Islam Z, Jacobs BC, van Belkum A, et al. Axonal variant of Guillain-Barré syndrome associated with Campylobacter infection in Bangladesh. Neurology 2010;74: 581-7.

32. Nachamkin I, Arzarte Barbosa P, Ung H, et al. Patterns of Guillain-Barré syndrome in children: results from a Mexican population. Neurology 2007;69:1665-71.

33. Uncini A, Manzoli C, Notturno F, Capasso M. Pitfalls in electrodiagnosis of Guillain-Barré syndrome subtypes. J Neurol Neurosurg Psychiatry 2010;81:1157-63.

34. Capasso M, Notturno F, Mazoli C, Uncini A. Involvement of sensory fibers in axonal subtypes of Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 2011;82:664-70.

35. Capasso M, Caporale CM, Pomilio F, Gandolfi P, Lugaresi A, Uncini A. Acute motor conduction block neuropathy: another Guillain-Barré syndrome variant. Neurology 2003;61:617-22.

36. Ropper AH. Further regional variants of acute immune polyneuropathy: bifacial weakness or sixth nerve paresis with paresthesias, lumbar polyradiculopathy, and ataxia with pharyngeal-cervical-brachial weakness. Arch Neurol 1994;51:671-5.

37. Nagashima T, Koga M, Odaka M, Hirata K, Yuki N. Continuous spectrum of pharyngeal-cervical-brachial variant of Guillain-Barré syndrome. Arch Neurol 2007;64:1519-23.

38. Ropper AH. Unusual clinical variants and signs in Guillain-Barré syndrome. Arch Neurol 1986;43:1150-2.

39. Lyu RK, Tang LM, Cheng SY, Hsu WC, Chen ST. Guillain-Barré syndrome in Taiwan: a clinical study of 167 patients. J Neurol Neurosurg Psychiatry 1997;63:494-500.

40. Koga M, Gilbert M, Li J, et al. Antecedent infections in Fisher syndrome: a common pathogenesis of molecular mimicry. Neurology 2005;64:1605-11.

41. Hafer-Macko CE, Sheikh KA, Li CY, et al. Immune attack on the Schwann cell surface in acute inflammatory demyelinating polyneuropathy. Ann Neurol 1996; 39:625-35.

42. Hafer-Macko C, Hsieh S-T, Li CY, et al. Acute motor axonal neuropathy: an antibody-mediated attack on axolemma. Ann Neurol 1996;40:635-44.

43. Griffin JW, Li CY, Macko C, et al. Early nodal changes in the acute motor axonal neuropathy pattern of the Guillain-Barré syndrome. J Neurocytol 1996; 25:33-51.

44. Dehaene I, Martin JJ, Geens K, Cras P. Guillain-Barré syndrome with ophthalmoplegia: clinicopathologic study of the central and peripheral nervous systems, including the oculomotor nerves. Neurology 1986;36:851-4.

45. Lopez PH, Zhang G, Zhang J, et al. Passive transfer of IgG anti-GM1 antibodies impairs peripheral nerve repair. J Neurosci 2010;30:9533-41.

46. Chiba A, Kusunoki S, Obata H, Machinami R, Kanazawa I. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. Neurology 1993;43:1911-7.

47. Liu JX, Willison HJ, Pedrosa-Domellof F. Immunolocalization of GQ1b and related gangliosides in human extraocular neuromuscular junctions and muscle spindles. Invest Ophthalmol Vis Sci 2009; 50:3226-32.

48. Koga M, Yoshino H, Morimatsu M, Yuki N. Anti-GT1a IgG in Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 2002;72:767-71.

49. Kusunoki S, Kaida K. Antibodies against ganglioside complexes in Guillain-Barré syndrome and related disorders. J Neurochem 2011;116:828-32.

50. Yuki N, Taki T, Inagaki F, et al. A bacterium lipopolysaccharide that elicits Guillain-Barré syndrome has a GM1 ganglioside-like structure. J Exp Med 1993; 178:1771-5.

51. Houliston RS, Koga M, Li J, et al. A *Haemophilus influenzae* strain associated with Fisher syndrome expresses a novel disialylated ganglioside mimic. Biochemistry 2007;46:8164-71.

52. Willison HJ. Biomarkers in experimental models of antibody-mediated neuropathies. J Peripher Nerv Syst 2011;16: Suppl 1:60-2.

53. Susuki K, Rasband MN, Tohyama K, et al. Anti-GM1 antibodies cause complement-mediated disruption of sodium channel clusters in peripheral motor nerve fibers. J Neurosci 2007;27:3956-67.

54. Yuki N, Susuki K, Koga M, et al. Carbohydrate mimicry between human ganglioside GM1 and *Campylobacter jejuni* lipooligosaccharide causes Guillain-Barré syndrome. Proc Natl Acad Sci U S A 2004; 101:11404-9.

55. Greenshields KN, Halstead SK, Zitman FM, et al. The neuropathic potential of anti-GM1 autoantibodies is regulated by the local glycolipid environment in mice. J Clin Invest 2009;119:595-610.

56. Goodfellow JA, Bowes T, Sheikh K, et al. Overexpression of GD1a ganglioside sensitizes motor nerve terminals to anti-GD1a antibody-mediated injury in a model of acute motor axonal neuropathy. J Neurosci 2005;25:1620-8.

57. Halstead SK, Zitman FM, Humphreys PD, et al. Eculizumab prevents anti-ganglioside antibody-mediated neuropathy in a murine model. Brain 2008;131:1197-208.

58. Zhang G, Lehmann HC, Bogdanova N, Gao T, Zhang J, Sheikh KA. Erythropoietin enhances nerve repair in anti-ganglioside antibody-mediated models of immune neuropathy. PLoS One 2011; 6(10):e27067.

59. Zhang G, Lehmann HC, Manoharan S, et al. Anti-ganglioside antibody-mediated activation of RhoA induces inhibition of neurite outgrowth. J Neurosci 2011;31:1664-75.

60. Pineda AA, Minohara M, Kawamura N, et al. Preventive and therapeutic effects of the selective Rho-kinase inhibitor fasudil on experimental autoimmune neuritis. J Neurol Sci 2011;306:115-20.

61. Drenthen J, Yuki N, Meulstee J, et al. Guillain-Barré syndrome subtypes related to Campylobacter infection. J Neurol Neurosurg Psychiatry 2011;82:300-5.

62. Kuwabara S, Ogawara K, Misawa S, et al. Does *Campylobacter jejuni* infection elicit "demyelinating" Guillain-Barré syndrome? Neurology 2004;63:529-33.

63. van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. Lancet Neurol 2008;7:939-50.

64. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. Lancet 1997;349:225-30.

65. Ropper AH. The Guillain-Barré syndrome. N Engl J Med 1992;326:1130-6.

66. Burakgazi AZ, Höke A. Respiratory muscle weakness in peripheral neuropathies. J Peripher Nerv Syst 2010;15:307-13.

67. Bos Eyssen ME, van Doorn PA, Jacobs BC, et al. Selective digestive tract decontamination decreases time on ventilator in Guillain-Barré syndrome. Neurocrit Care 2011;15:128-33.

68. Khan F, Ng L, Amatya B, Brand C, Turner-Stokes L. Multidisciplinary care for Guillain-Barré syndrome. Eur J Phys Rehabil Med 2011;47:607-12.

69. Ruts L, Drenthen J, Jongen JL, et al. Pain in Guillain-Barré syndrome: a long-term follow-up study. Neurology 2010;75:1439-47.

70. Ruts L, van Koningsveld R, Jacobs BC, van Doorn PA. Determination of pain and response to methylprednisolone in Guillain-Barré syndrome. J Neurol 2007;254:1318-22.

71. Garssen MP, van Koningsveld R, van Doorn PA. Residual fatigue is independent of antecedent events and disease severity in Guillain-Barré syndrome. J Neurol 2006;253:1143-6.

72. Graham RC, Hughes RAC, White CM. A prospective study of physiotherapist prescribed community based exercise in inflammatory peripheral neuropathy. J Neurol 2007;254:228-35.

73. Cochen V, Arnulf I, Demeret S, et al. Vivid dreams, hallucinations, psychosis and REM sleep in Guillain-Barré syndrome. Brain 2005;128:2535-45.

74. The Guillain-Barré Syndrome Study Group. Plasmapheresis and acute Guillain-Barré syndrome. Neurology 1985;35:1096-104.

75. The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Appropriate number of plasma exchanges in Guillain-Barré syndrome. Ann Neurol 1997;41:298-306.

76. van der Meché FGA, Schmitz PIM, Dutch Guillain–Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain–Barré syndrome. N Engl J Med 1992;326:1123-9.

77. Jacobs BC, O'Hanlon GM, Bullens RW, Veitch J, Plomp JJ, Willison HJ. Immunoglobulins inhibit pathophysiological effects of anti-GQ1b-positive sera at motor nerve terminals through inhibition of antibody binding. Brain 2003;126:2220-34.

78. Zhang G, Lopez PH, Li CY, et al. Antiganglioside antibody-mediated neuronal cytotoxicity and its protection by intravenous immunoglobulin: implications for immune neuropathies. Brain 2004;127:1085-100.

79. Kuitwaard K, de Gelder J, Tio-Gillen AP, et al. Pharmacokinetics of intravenous immunoglobulin and outcome in Guillain-Barré syndrome. Ann Neurol 2009;66:597-603.

80. Farcas P, Avnun L, Frisher S, Herishanu YO, Wirguin I. Efficacy of repeated intravenous immunoglobulin in severe unresponsive Guillain-Barré syndrome. Lancet 1997;350:1747.

81. Guillain-Barré Syndrome Steroid Trial Group. Double-blind trial of intravenous methylprednisolone in Guillain-Barré syndrome. Lancet 1993;341:586-90.

82. Hughes RAC, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial prednisolone in acute polyneuropathy. Lancet 1978;2:750-3.

83. van Koningsveld R, Schmitz PIM, van der Meché FGA, et al. Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barré syndrome: randomised trial. Lancet 2004;363:192-6.

84. Mori M, Kuwabara S, Fukutake T, Hattori T. Intravenous immunoglobulin therapy for Miller Fisher syndrome. Neurology 2007;68:1144-6.

85. Susuki K, Koga M, Hirata K, Isogai E, Yuki N. A Guillain–Barré syndrome variant with prominent facial diplegia. J Neurol 2009;256:1899-905.

Copyright © 2012 Massachusetts Medical Society.

IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal*'s website at NEJM.org. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.