Guillain-Barré Syndrome

Mazen M. Dimachkie, M.D.^{1,*}
Richard J. Barohn, M.D.²

Address

^{*1}Department of Neurology,
University of Kansas Medical Center, 3599 Rainbow Blvd.
Mail Stop 2012, Kansas City, KS 66160, USA
Email: mdimachkie@kumc.edu

²Department of Neurology, University of Kansas Medical Center,
3599 Rainbow Blvd. Mail Stop 2012, Kansas City, KS 66160, USA
Email: rbarohn@kumc.edu

Published online: 11 April 2013

© Springer Science+Business Media New York 2013

Keywords Guillain-Barré syndrome • GBS • AMAN • AMSAN • GBS variant • Miller Fisher syndrome • Fisher syndrome • Bickerstaff's brain stem encephalitis • Epidemiology • Clinical manifestations • Nerve conduction studies • Pathogenesis • Treatment • Plasmapheresis • IVIg • Corticosteroids • Prognosis

Opinion statement

Acute Inflammatory polyneuropathies are an important group of neuromuscular disorders and are referred to collectively as Guillain-Barré syndrome (GBS). Our knowledge regarding pathogenesis, diagnosis and management continues to expand, resulting in improved opportunities for identification and treatment. These autoimmune processes cause neuropathy by affecting various structures (myelin or axons), at different locations (nerve root, nerve cell bodies or peripheral nerve) with a variety of patterns. Most clinical neurologists will be involved in the management of patients with these disorders, and there are now a variety of reasonable therapies available for acquired demyelinating neuropathies. In this report, we review the distinctive clinical, laboratory and electro-diagnostic features that aid in their diagnosis, with emphasis on clinical characteristics that are of paramount importance in diagnosing specific conditions and determining the most appropriate therapies, and helpful in determining long-term prognosis.

Introduction

Guillain-Barré syndrome (GBS) is characterized by rapidly evolving weakness, some sensory loss and hyporeflexia, progressing to a nadir over a few days and up to 4 weeks [1, 2]. Acute inflammatory demye-

linating polyneuropathy (AIDP) is the most common form of GBS. In the axonal variant of GBS, the immune attack targets peripheral nerve motor axons. In addition to the Miller-Fisher syndrome (MFS), other

phenotypic variants have been recently described with pure sensory or autonomic manifestations. It is important to recognize GBS and its variants due to the availability of effective therapies.

Epidemiology

GBS is an acute monophasic immune-mediated polyradiculoneuropathy with a worldwide incidence of 0.6 to 2.4/100,000 people [3–7]. Though the mean age of onset is 40 years, all ages are affected with slightly more males than females. A systematic literature review of the epidemiology of GBS found the overall incidence of GBS to be 1.1 to 1.8/100,000, whereas in children it is 0.34 to 1.34/100,000 [8]. In addition, the incidence of GBS increased with age after 50 years from 1.7/100,000 to 3.3/100,000. Whereas only 5 % of GBS in North America and Europe are due to the axonal variant [9], the contribution of axonal GBS is higher in Northern China, Japan and the rest of the Americas [10–13].

Clinical Presentation

Clinical features

The most common initial symptom of GBS is paresthesia consisting of numbness and tingling of the distal extremities [14], with mild or delayed objective sensory loss. Severe radicular back pain or neuropathic pain occurs at some point in the majority of cases. Within days of the onset of paresthesia, weakness begins following a symmetric “ascending pattern”. In addition to marked weakness, patients are hyporeflexic or areflexic within the first few days, although reflex abnormality may be delayed by up to a week. Most patients present initially with proximal and distal leg and arm weakness (32 %) or selective leg weakness that spreads later on to the arms (56 %) [1, 2]. A descending presentation, with onset in the face or arms, is less common, occurring in only 12 % of cases. Facial nerve involvement occurs in up to 70 %, oropharyngeal weakness in 40 %, and 5 % may develop ophthalmoplegia, ptosis, or both [2]. Less frequently patients may have hearing loss, papilledema or vocal cord paralysis.

Over 50 % of cases evolve to their nadir of weakness by 2 weeks, 80 % by 3 weeks, and 90 % by 4 weeks [2]. Symptom progression beyond the one-month mark suggests an alternate diagnosis such as subacute inflammatory demyelinating polyradiculoneuropathy (4–8 weeks) or chronic inflammatory demyelinating polyradiculoneuropathy (> 8 weeks). At nadir, some patients have mild weakness, while others progress to flaccid quadriplegia and respiratory failure within a few days. Overall, up to 30 % will progress to respiratory failure. Dysautonomia affects 65 % of patients [2]. The most common manifestation of autonomic dysfunction is sinus tachycardia, but patients may experience bradycardia, labile blood pressure with hypertension and hypotension, orthostatic hypotension, cardiac arrhythmias, neurogenic pulmonary edema, changes in sweat, and in less than 5 % of cases bladder (urinary retention)

and gastrointestinal (constipation, ileus, gastric distension, diarrhea, fecal incontinence) dysfunction.

The relapse rate is 1 to 5 %, usually occurring within the first 8 weeks. Relapsing-remitting chronic inflammatory demyelinating polyneuropathy (CIDP) should be considered as an alternate diagnosis in relapsing cases [15] when the first relapse is delayed by more than 2 months following an acute attack or the number of relapses exceeds two events. Further clues favoring CIDP in relapsing cases include absence of cranial nerve dysfunction, maintaining the ability to ambulate independently at nadir despite marked demyelination on nerve conductions. Other investigators have identified prominent sensory signs and lack of either autonomic nervous system involvement, facial weakness, preceding infection, or mechanical ventilation, as supportive of acute-onset CIDP rather than GBS [16].

GBS variants

In addition to the classic presentation of GBS, clinical variants are described based on the predominant mode of fiber injury (demyelinating versus axonal), on types of nerve fibers involved (motor, sensory, sensory and motor, cranial or autonomic) and alteration in consciousness. The Miller Fisher Syndrome (MFS) and consists of at least two features of the following: ophthalmoplegia, ataxia, and areflexia without any weakness [17]. In Western countries, MFS represents 5 to 10 % of all GBS cases, while it is more common in Eastern Asia, accounting for 25 % of Japanese cases [18]. Many MFS cases have features overlapping with typical GBS and some cases progress to otherwise classic GBS, while ophthalmoplegia affects 5 % of typical GBS cases. Bickerstaff's brain stem encephalitis (BBE) is a variant affecting 10 % of MFS cases and is characterized by alteration in consciousness, hyperreflexia, ataxia, and ophthalmoplegia [19, 20]. BBE is associated with an antecedent infection (92 %), elevated CSF protein (59 %) anti-GQ1b antibody (66 %) [21, 22] and brain magnetic resonance imaging abnormalities (30 %) [22]. A paraparetic variant affecting the legs predominantly with areflexia and sparing the arms mimics an acute spinal cord lesion and is associated with back pain [23]. Other GBS variants include pharyngeal-cervical-brachial weakness with ptosis that mimics botulism, ptosis without ophthalmoplegia, and facial diplegia or sixth nerve palsies with paresthesias [23, 24]. Pure sensory and pan-autonomic variants are also reported.

Axonal variant of GBS include an axonal motor variant termed acute motor axonal neuropathy (AMAN) [11] and a more severe presentation of acute motor-sensory axonal neuropathy (AMSAN) [25]. AMAN and AMSAN cases were originally described in northern China and are associated with *Campylobacter Jejuni* (*C. Jejuni*) infection, which is a poor prognostic factor [26]. Patients with AMAN have a rapid progression of weakness to an early nadir over a few days resulting in prolonged paralysis and respiratory failure [27]. Acute motor conduction block neuropathy presents with symmetric proximal and distal weakness without sensory abnormalities with normal or even brisk reflexes following *C. Jejuni* enteritis. Elevated IgG antibody titers to GD1a and GM1 have been reported and electrophysiology showed normal sensory conduction

and partial motor conduction block in intermediate and distal nerve segments that resolves within 2 to 5 weeks [28].

Immunopathology

In the acute inflammatory demyelinating polyneuropathy variant of GBS (AIDP), there is lymphocytic mononuclear cell infiltration and intense macrophage-associated segmental demyelination at the nerve roots and proximal nerve segments. Much of the evidence for disease pathogenesis is derived from the animal model of GBS named experimental allergic neuritis, which is caused by a combination of T-cell-mediated immunity to myelin proteins and antibodies to myelin glycolipids. Antibodies to peripheral nerve myelin were identified in sera of some AIDP patients with a decline in titers corresponding to clinical improvement. Antibodies to myelin glycolipids are indicative of humoral autoimmunity in GBS variants. An autopsy study supporting humoral autoimmunity demonstrated an antibody-mediated complement deposition on the Schwann cell abaxonal plasmalemma, but not on the myelin sheath followed by vesicular paranodal myelin degeneration and retraction [29]. Macrophages are then recruited to strip off the myelin lamellae with by-stander axon loss in cases of severe inflammation [2].

Unlike AIDP, AMAN is characterized by the paucity of lymphocytic infiltration and sparing of the dorsal nerve roots, dorsal root ganglia and peripheral sensory nerves. The two early changes are the lengthening of the node of Ranvier followed by complement-mediated recruitment of macrophages to the nodal region [30]. Macrophages distort paranodal axons and myelin sheaths, separate myelin from the axolemma and induce condensation of axoplasm in a reversible fashion. Only a minority of motor axons undergo Wallerian-like degeneration in severe cases, explaining the rapid recovery in some AMAN cases. Another proposed explanation is that axonal degeneration may involve the most distal nerve terminals. Molecular mimicry is suggested as the pathogenetic mechanism of AMAN based on the strong association with *C. jejuni* infection [31]. The lipopolysaccharide capsule of the *C. jejuni* shares epitopes with GM1 and GD1a resulting in cross-reacting antibodies. AMSAN shares many similarities with AMAN, although the attack in AMSAN is more severe or longer lasting resulting in more intense and ultimately diffuse Wallerian-like degeneration of sensory and motor axons. In addition to AMAN and AMSAN, molecular mimicry may also be the most plausible mechanism in the MFS since 90 % of cases have antibodies to GQ1b. These autoantibodies have also been described in 66 % of Bickerstaff's brainstem encephalitis [22].

Antecedent Events

Up to 70 % of cases of GBS are associated with antecedent respiratory or gastrointestinal infections two to four weeks prior to the onset [29]. Most are upper respiratory infections without any specific organism identified, except in 6 % of cases such as the Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, *Mycoplasma pneumonia* and *Borrelia*

burgdorferi infection. In HIV, GBS occurs at seroconversion or early in the disease, a time when the polymerase chain reaction viral load is more diagnostically sensitive than HIV antibodies. Most GBS cases are sporadic, although the axonal variant occurs in summer epidemics of *C. jejuni* infection in northern China. *C. jejuni* enteritis is the most common identifiable antecedent infection and precedes GBS by 9 days in up to 33 % of patients. Although two million cases of *C. jejuni* infection occur each year in the United States, only about one per 1,000 of these patients have the genetic susceptibility to develop GBS [27] in association with specific HLA haplotypes [32]. A comprehensive study showed that 31 % of GBS, and 18 % of MFS, were seropositive for recent *C. jejuni* infection [33]. Other anecdotal antecedent events that have been associated with GBS include surgery, epidural anesthesia, concurrent illnesses such as Hodgkin's disease and immunizations.

There was an increased incidence of GBS after the swine flu vaccine of 1976 in the USA, with an excess risk of ten cases per million vaccinations [34]. The concern about the swine flu vaccine risk resurfaced in the 2009–2010 H1N1 immunization campaign. CDC surveillance data indicated that there was an excess GBS risk of 0.8 cases per million vaccinations [35]. This is similar to the risk associated with the seasonal influenza immunization. The 2009 H1N1 influenza virus has been associated with a hospitalization rate of 222 per million and a death rate of 9.7 per million people. Therefore, the risk of this illness outweighs the risk of the vaccines in non-GBS patients. If a patient's GBS episode was associated with the influenza vaccine there may be a small risk (3.5 %) of a repeat episode on repeat vaccination, with a frequency of serious GBS recurrence requiring admission of 1.2 % [36]. Therefore, patients with a history of GBS who have a serious illness putting them at high risk for severe complications from influenza itself may consider getting vaccinated after at least 3–6 months have elapsed from the original GBS event if the benefits outweigh the risks [35].

Laboratory Evaluation

Electrophysiologic studies

When GBS is suspected, electrophysiologic studies are essential to confirm the diagnosis and exclude mimics. Uncovering multifocal demyelination on early or repeat nerve conduction testing a week later is extremely helpful in confirming the diagnosis of AIDP with a high sensitivity and specificity [37, 38]. Needle electrode examination is nonspecific, as it demonstrates reduced recruitment initially and fibrillations potentials at 3–4 weeks after onset. Clinicians should not expect each AIDP patient to meet strict research criteria for demyelination particularly early in the course. Since treatment is most effective when given earlier, GBS patients should be treated based on clinical suspicion after the exclusion of potential mimics regardless of nerve conduction findings.

In AMAN, CMAP amplitudes are selectively reduced in the first few days and then become absent [39] due to axon loss, conduction block (sodium channel dysfunction) or an immune attack on the nodes of Ranvier. For this reason, fibrillation potentials may occur early on in the course of AMAN and needle electrode examination is helpful. However, in AMSAN the sensory

and motor potentials are reduced in amplitude and often absent [25]. While sensory and motor NCS are often normal, H-reflexes are absent in 75 % of MFS and BBE cases [20].

Cerebrospinal fluid

CSF analysis is critically important in all GBS cases, as it reveals albuminocytologic dissociation; that is an elevated protein up to 1,800 mg/dl [40] with 10 or less white cells/mm in the majority of cases. Half of GBS cases may have a normal CSF protein in the first week but that proportion declines to 10 % if the test is repeated a week later [1, 2]. Most MFS cases and half of BBE cases have albuminocytologic dissociation [20]. If white cells are more than 50/mm³, one should consider early HIV infection, leptomeningeal carcinomatosis, CMV polyradiculitis and sarcoidosis.

Anti-ganglioside antibodies

C. jejuni has GM1-like oligosaccharide epitopes that cross-react with peripheral nerve GM1 gangliosides, explaining why an antibody directed against bacteria may also produce a neuropathy [41]. Antibodies to GM1 gangliosides have been described more frequently in AMAN than in AIDP and some of the reports have correlated GM1 antibodies in AMAN with greater functional disability at 6 months [42]. However, antibodies to GM1 or GD1b are not necessary poor prognostic markers, since three GBS patients with poor recovery and inability to walk at 1 year had no such antibodies but had serological evidence of recent *C. jejuni* infection [43]. IgG antibodies to GD1a are highly associated with AMAN, being detectable in 60 % of AMAN cases and only 4 % of AIDP [31]. While we do not recommend routine antibody testing in GBS, MFS is a notable exception [44, 45]. GQ1b antibodies are highly sensitive and specific to MFS but may be seen in GBS cases with marked ophthalmoparesis and in 66 % of BBE cases [18]. This assay is useful in supporting the clinical diagnosis of MFS or BBE. GT1a antibodies correlate with the presence of bulbar signs and symptoms as in BBE.

Neuroimaging studies

Gadolinium-enhanced magnetic resonance imaging (MRI) of the lumbosacral region can show cauda equina nerve root enhancement in most AIDP cases [46, 47]. While there is no need to obtain this study in routine cases, MRI can be useful in cases of the paraparetic variant of GBS, as it establishes the site of the lesion.

Treatment

General supportive care

Given that up to 30 % of GBS cases progress to respiratory failure, supportive care is the most important element of management. GBS patients are admitted to the neurological intensive care unit or an intermediary care telemetry unit to allow for close monitoring of respiratory, bulbar and autonomic function. A rapid decline of the expiratory forced vital capacities to less than 15 cc/kg of ideal body weight (adjusted for age) or of the negative inspiratory force to below 60 cm H₂O each indicate the need for urgent intubation and mechanical venti-

lation before hypoxemia supervenes [2]. It is important when managing autonomic instability to be conservative and avoid aggressively chasing blood pressure fluctuations, since patients may be sensitive to medications. Treatment with pain modulating drugs is effective including tricyclic antidepressants, gabapentin, pregabalin, carbamazepine, tramadol and mexiletene [48]. Vigilance towards infections is important, as most severe cases develop urinary or pulmonary infections. Treatment with plasmapheresis or IVIg is indicated for patients with weakness impairing function or any respiratory involvement. Patients and their family should be educated about the fact that it takes on average 2–3 months for patients to walk without aids no matter what therapy is used. Physicians, patients, and family members need to have realistic expectations about the extent of the effect of both PE and intravenous gamma globulin. Dramatic improvement within days of beginning treatment is not the rule and if this occurs, it may have happened anyway in that patient without treatment.

Immunotherapy

Plasma exchange

Plasma exchange (PE) directly removes humoral factors such as autoantibodies, immune complexes, complement, cytokines and other nonspecific inflammatory mediators. Two randomized controlled trials established PE as the first effective treatment in GBS [49, 50]. PE performed within 2 weeks from onset consistently demonstrated a statistically significant reduction in the time to weaning from the ventilator by 13 to 14 days and time to walk unaided by 32 to 41 days. The volume of PE is 50 cc/kg administered five times, daily or every other day over 5–10 days, totaling 250 cc/kg. PE beyond the standard amount will not offer additional benefits [51]. The French Cooperative Group on PE in GBS showed that patients with mild GBS on admission (could walk with or without aid but not run, or those who could stand up unaided) would benefit from two PEs [51]. For those who could not stand up unaided (moderate group), four PEs were more beneficial than two for time to walk with assistance and 1-year full muscle-strength recovery rate. Six exchanges were no more beneficial than four in the severe mechanically ventilated GBS cases.

Intravenous immunoglobulin

Though its precise mechanism of action is unknown, IVIg interferes with costimulatory molecules involved in antigen presentation; modulates antibody, cytokines and adhesion molecules production and macrophage Fc receptor; and impedes complement activation leading to membrane attack complex formation [52]. The Dutch GBS Study Group compared IVIg to PE in 147 patients showing that IVIg was as effective as, and possibly more effective than PE [53]. The Plasma Exchange and Sandoglobulin Guillain-Barré Syndrome Trial Group study [54] revealed no difference in outcomes with IVIg or PE.

It was recently reported that sialylated IgG Fc fragments are important for the *in vivo* activity of intravenous immunoglobulin [55•]. Instead of binding with Fc gamma receptors, sialylated Fc fragments initiate an anti-inflammatory cascade through the lectin receptor SIGN-R1 or DC-SIGN. This leads to

upregulated surface expression of the inhibitory Fc receptor, Fc gamma receptor IIb, on inflammatory cells, thereby attenuating autoantibody-initiated inflammation.

PE followed by IVIg?

There is no added benefit in treating with IVIg severe GBS cases that did not improve at 2 weeks after PE [56]. The Plasma Exchange Sandoglobulin GBS (PSGBS) study group compared PE monotherapy, IVIg monotherapy, and PE followed by IVIg [56]. Combined treatment produced no significant difference in patient outcomes compared with either therapy given alone. PE and IVIg treatments were equally effective. An AAN practice parameter [57] concluded that PE be considered for non-ambulatory adult patients with GBS within 4 weeks of the onset of symptoms, and that PE should also be considered for ambulatory patients examined within 2 weeks of the onset of symptoms. IVIg was recommended for non-ambulatory adult patients with GBS within 2 or possibly 4 weeks of the onset. Neither sequential treatment of PE or immunoabsorption followed by IVIg nor corticosteroids were recommended for GBS. PE and IVIg are treatment options for severe childhood GBS.

Prognosis

Most patients with GBS start to recover spontaneously beginning at 28 days with a mean complete recovery time of 200 days in 80 % of cases. However, many (65 %) have minor residual signs or symptoms making recovery less than complete [1, 2]. Major residual neurologic deficits affect 10–15 % of patients. In a study, 8 % had died, 4 % remained bedbound or ventilator dependent, 9 % were unable to walk unaided, 17 % were unable to run, and 62 % had made a complete or almost complete recovery at one year [58].

McKhann et al. [59] identified four factors that indicated a poor prognosis in the North American GBS study: older age (> 50–60), rapid onset over seven days, mechanical ventilation, and severely reduced distal motor amplitudes (to 20 % or less of the lower limit of normal). A preceding diarrheal illness with *C. jejuni* can also be added to this list as CMV infection [60]. Recently, the Erasmus GBS outcome score was derived and consists of three items: age (0 = up to 40 years; 0.5 = 41–60 years; or 1 = for age > 60), preceding diarrhea (0 or 1), and GBS disability score at 2 weeks after entry (1 to 5) [61]. The 2-week score was validated as a predictor of the probability of independent ambulation at 6 months. Twenty-seven percent of patients with a 5 score at 2 weeks were unable to walk independently at 6 months, whereas a score of 5.5–7 raises that proportion to 52 %. More recently, an earlier clinical model in the first week of disease accurately predicted the outcome of GBS at 6 months [62••]. Higher age (> 60), preceding diarrhea, and low Medical Research Council sum score (< 31; range 0–60 scale) at hospital admission and at 1 week were independently associated with being unable to walk at 4 weeks, 3 months, and 6 months. Due to variable pharmacokinetics, slowed recovery and a reduced likelihood of walking unaided at 6 months may be attrib-

utable to a suboptimal increase in IgG levels at 2 weeks following infusion [63]. A prospective is in progress study to test the hypothesis that severe GBS cases with a small increase in serum IgG level at 2 weeks might benefit from second course of IVIg.

Most AMAN patients have more delayed recovery than AIDP [64], while some cases recover quicker due to reversible changes of the sodium channels at nodes of Ranvier or by degeneration followed by regeneration of motor nerve terminals and intramuscular axons [65]. Though IVIg slightly hastened improvement of ophthalmoplegia and ataxia, 96 % of MFS cases were free of all symptoms and signs one year after the onset of neurologic symptoms, regardless of immunotherapy [66]. Most BBE cases given acute immunotherapy showed complete remission at 6 months without any residual symptoms [22].

Conflict of Interest

Mazen M. Dimachkie has served on an advisory board for CSL Behring; has received honoraria from Pfizer, Depomed, and Merck & Co.; and has had travel/accommodations expenses covered/reimbursed by and served on speakers bureaus for Pfizer and Merck & Co.

Richard J. Barohn has served on advisory boards for MedImmune and Novartis and on speaker bureaus for Genzyme and Grifols.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Ropper AH. The Guillain-Barré syndrome. *N Engl J Med*. 1992;326(17):1130–6.
2. Ropper AH, Wijdicks EFM, Truax BT. In: FA Davis Comp (ed.) *Guillain-Barré Syndrome, Contemporary Neurology Series 34*, Philadelphia, PA, 1991.
3. Alter M. The epidemiology of Guillain-Barré syndrome. *Ann Neurol*. 1990;27:S7–12.
4. Hughes RA, Cornblath DR. Guillain-Barré syndrome. *Lancet*. 2005;366(9497):1653–66.
5. Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barré syndrome. *J Infect Dis*. 1997;176 Suppl 2:S92–8.
6. Van Koningsveld R, Van Doorn PA, Schmitz PI, Ang CW, Van der Meché FG. Mild forms of Guillain-Barré syndrome in an epidemiologic survey in The Netherlands. *Neurology*. 2000;54(3):620–5.
7. Govoni V, Granieri E. Epidemiology of the Guillain-Barré syndrome. *Curr Opin Neurol*. 2001;14(5):605–13.
8. McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain-Barré syndrome worldwide. A systematic literature review. *Neuroepidemiology*. 2009;32(2):150–63.
9. Hadden RD, Cornblath DR, Hughes RA, et al. Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. *Ann Neuro*. 1998;44(5):780–8.
10. McKhann GM, Cornblath DR, Ho T, et al. Clinical and electrophysiological aspects of acute paralytic disease of children and young adults in northern China. *Lancet* 1991;7;338(8767):593–597.
11. 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(4):333–42.
12. Ogawara K, Kuwabara S, Mori M, et al. Axonal Guillain-Barré syndrome: relation to anti-ganglioside antibodies and *Campylobacter jejuni* infection in Japan. *Ann Neurol*. 2000;48(4):624–31.

13. Paradiso G, Tripoli J, Galicchio S, Fejerman N. Epidemiological, clinical, and electrodiagnostic findings in childhood Guillain-Barré syndrome: a reappraisal. *Ann Neurol*. 1999;46(5):701–7.
14. Barohn RJ, Saperstein DS. Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. *Semin Neurol*. 1998;18(1):49–61.
15. Ruts L, Drenthen J, Jacobs BC, van Doorn PA, Dutch GBS Study Group. Distinguishing acute-onset CIDP from fluctuating Guillain-Barre syndrome: a prospective study. *Neurology*. 2010;74(21):1680–6.
16. Dionne A, Nicolle MW, Hahn AF. Clinical and electrophysiological parameters distinguishing acute-onset chronic inflammatory demyelinating polyneuropathy from acute inflammatory demyelinating polyneuropathy. *Muscle Nerve*. 2010;41(2):202–7.
17. Fisher CM. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). *N Engl J Med*. 1956;255:57–65.
18. Overell JR, Hsieh ST, Odaka M, Yuki N, Willison HJ. Treatment for Fisher syndrome, Bickerstaff's brainstem encephalitis and related disorders. *Cochrane Database Syst Rev*. 2007;1, CD004761.
19. Bickerstaff E, Cloake P. Mesencephalitis and rhombencephalitis. *Br Med J*. 1951;2:77–81.
20. 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(5):674–82.
21. Yuki N, Sato S, Tsuji S, Hozumi I, Miyatake T. An immunologic abnormality common to Bickerstaff's brain stem encephalitis and Fisher's syndrome. *J Neurol Sci*. 1993;118(1):83–7.
22. Odaka M, Yuki N, Yamada M, et al. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain Barre syndrome. *Brain*. 2003;126:2279–90.
23. Ropper AH. Unusual clinical variants and signs in Guillain-Barré syndrome. *Arch Neurol*. 1986;43:1150–2.
24. 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(7):671–5.
25. Griffin JW, Li CY, Ho TW, et al. Pathology of the motor-sensory axonal Guillain-Barré syndrome. *Ann Neurol*. 1996;39(1):17–28.
26. Ho TW, Mishu B, Li C. Guillain-Barré syndrome in northern China. Relationship to Campylobacter jejuni infection and anti-glycolipid antibodies. *Brain*. 1995;118:597–605.
27. Allos BM. Association between Campylobacter infection and Guillain-Barré syndrome. *J Infect Dis*. 1997;176 suppl 2:S25–S127.
28. Capasso M, Caporale CM, Pomilio F, et al. Acute motor conduction block neuropathy: another Guillain-Barre syndrome variant. *Neurology*. 2003;61:617–22.
29. Hafer-Macko C, Sheikh KA, Li CY, et al. Immune attack on the Schwann cell surface in acute inflammatory demyelinating polyneuropathy. *Ann Neurol*. 1996;39:625–35.
30. 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.
31. Ho TW, Willison HJ, Nachamkin I, et al. Anti-GD1a antibody is associated with axonal but not demyelinating forms of Guillain-Barré syndrome. *Ann Neurol*. 1999;45:168–73.
32. Magira EE, Papaioakim M, Nachamkin I, et al. Differential distribution of HLA-DQ beta/DR beta epitopes in the two forms of Guillain-Barré syndrome, acute motor axonal neuropathy and acute inflammatory demyelinating polyneuropathy (AIDP): identification of DQ beta epitopes associated with susceptibility to and protection from AIDP. *J Immunol*. 2003;170(60):3074–4080.
33. Koga M, Yuki N, Takahashi M, Saito K, Hirata K. Close association of IgA anti-ganglioside antibodies with antecedent Campylobacter jejuni infection in Guillain-Barré and Fisher's syndromes. *J Neuroimmun*. 1998;81(1–2):138–43.
34. 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;110:10523.
35. Centers for Disease Control and Prevention. Preliminary Results: Surveillance for Guillain-Barré Syndrome After Receipt of Influenza A (H1N1) 2009 Monovalent Vaccine—United States, 2009–2010. Morbidity and Mortality Weekly Report (MMWR) June 2, 2010 / 59(Early Release);1–5. Accessed at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm59e0602a1.htm?s_cid=mm59e0602a1_e. Accessed on February 3, 2011.
36. Pritchard J, Mukherjee R, Hughes RA. Risk of relapse of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy following immunization. *J Neurol Neurosurg Psychiatry*. 2002;73(3):348–9.
37. Albers JW, Donofrio PD, McGonagle TK. Sequential electrodiagnostic abnormalities in acute inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve*. 1985;8(6):528–39.

38. Van den Bergh PY, Piéret F. Electrodiagnostic criteria for acute and chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve*. 2004;29(4):565–74.
 39. Tamura N, Kuwabara S, Misawa S, Kanai K, Nakata M, Sawai S, et al. Time course of axonal regeneration in acute motor axonal neuropathy. *Muscle Nerve*. 2007;35(6):793–5.
 40. Wiederholt WC, Mulder DW, Lambert EH. The Landry-Guillain-Barré-Srohl Syndrome or polyradiculoneuropathy. Historical Review, report on 97 cases and present concepts. *Mayo Clin Proc*. 1964;39:427–51.
 41. Oomes PG, Jacobs BC, Hazenberg MP, Bänffer JR, van der Meché FG. Anti-GM1 IgG antibodies and *Campylobacter* bacteria in Guillain-Barré syndrome: evidence of molecular mimicry. *Ann Neurol*. 1995;38(2):170–5.
 42. Kuwabara S, Yuki N, Koga M, et al. IgG anti-GM1 antibody is associated with reversible conduction failure and axonal degeneration in Guillain-Barré syndrome. *Ann Neurol*. 1998;44(2):202–8.
 43. Vriesendorp FJ, Mishu B, Blaser MJ, Koski CL. Serum antibodies to GM1, GD1b, peripheral nerve myelin, and *Campylobacter jejuni* in patients with Guillain-Barré syndrome and controls: correlation and prognosis. *Ann Neurol*. 1993;34(2):130–5.
 44. Willison HJ, Veitch J, Paterson G, Kennedy PGE. Miller Fisher syndrome is associated with serum antibodies to GQ1b ganglioside. *J Neurol Neurosurg Psych*. 1993;56(2):204–6.
 45. Yuki N, Sato S, Tsuji S, Ohsawa T, Miyatake T. Frequent presence of anti-GQ1b antibody in Fisher's syndrome. *Neurology*. 1993;43(2):414–7.
 46. Morgan GW, Barohn RJ, Bazan C, et al. Nerve root enhancement with MRI in inflammatory demyelinating polyradiculoneuropathy. *Neurology*. 1993;43(3 Pt 1):618–20.
 47. Gorson KC, Ropper AH, Muriello MA, Blair R. Prospective evaluation of MRI lumbosacral nerve root enhancement in acute Guillain-Barré syndrome. *Neurology*. 1996;47(3):813–7.
 48. Hughes RA, Wijdicks EF, Benson E, et al. Multidisciplinary Consensus Group. Supportive care for patients with Guillain-Barré syndrome. *Arch Neurol*. 2005;62(8):1194–8.
 49. French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome. Efficiency of plasma exchange in Guillain-Barré syndrome: role of replacement fluids. *Ann Neurol*. 1987;22:753–61.
 50. The Guillain-Barré syndrome Study Group. Plasmapheresis and acute Guillain-Barré syndrome. *Neurology*. 1985;35(8):1096–104.
 51. 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.
 52. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA*. 2004;291(19):2367–75.
 53. van der Meché FG, Schmitz PI, and 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;326:1123–9.
 54. Plasma Exchange and Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomized trial of plasma exchange, intravenous immunoglobulin and combined treatments in Guillain-Barré syndrome. *Lancet*. 1997;349:225–30.
 55. • Anthony RM, Ravetch JV. A novel role for the IgG Fc glycan: the anti-inflammatory activity of sialylated IgG Fcs. *J Clin Immunol*. 2010;30 Suppl 1:S9–14.
- Sialylated IgG Fcs are important for the in vivo activity of intravenous immunoglobulin.*
56. Hughes RA. Plasma exchange versus intravenous immunoglobulin for Guillain-Barré syndrome. *Ther Apher*. 1997;1:129–30.
 57. Hughes RA, Wijdicks EF, Barohn R, Benson E, Cornblath DR, Hahn AF, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: immunotherapy for Guillain-Barré syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2003;61(6):736–40.
 58. Rees JH, Thompson RD, Smeeton NC, Hughes RA. Epidemiological study of Guillain-Barré syndrome in south east England. *J Neurol Neurosurg Psychiatry*. 1998;64(1):74–7.
 59. McKhann GM, Griffin JW, Cornblath DR, et al. Plasmapheresis and Guillain-Barré syndrome: analysis of prognostic factors and the effect of plasmapheresis. *Ann Neurol*. 1988;23(4):347–53.
 60. Dutch Guillain-Barré Study Group. Prognostic factors of Guillain-Barré syndrome after intravenous immunoglobulin or plasma exchange. *Neurology*. 1999;53(3):598–604.
 61. van Koningsveld R, Steyerberg EW, Hughes RA, et al. A clinical prognostic scoring system for Guillain-Barré syndrome. *Lancet*. 2007;6(7):589–94.
 62. •• Walgaard C, Lingsma HF, Ruts L, et al. Early recognition of poor prognosis in Guillain-Barré syndrome. *Neurology*. 2011;76(11):968–75.
- High age, preceding diarrhea, and low Medical Research Council sum score at 1 week were independently associated with being unable to walk at 4 weeks, 3 months, and 6 months.*

63. Kuitwaard K, de Gelder J, Tio-Gillen AP, Hop WC, van Gelder T, van Toorenenbergen AW, et al. Pharmacokinetics of intravenous immunoglobulin and outcome in Guillain-Barré syndrome. *Ann Neuro.* 2009;66(5):597–603.
64. Ho TW, Li CY, Cornblath DR, Gao CY, Asbury AK, Griffin JW, et al. Patterns of recovery in the Guillain-Barre syndromes. *Neurology.* 1997;48(3):695–700.
65. Ho TW, Hsieh ST, Nachamkin I, et al. Motor nerve terminal degeneration provides a potential mechanism for rapid recovery in acute motor axonal neuropathy after *Campylobacter* infection. *Neurology.* 1997;48:717–24.
66. Mori M, Kuwabara S, Fukutake T, Haltori T. Intravenous immunoglobulin therapy for Miller Fisher syndrome. *Neurology.* 2007;68(14):1144–6.