# 29 - 458 Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies

## 458 Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies

Guillain-Barré

Syndrome and Other

Immune-Mediated

Neuropathies Stephen L. Hauser, Anthony A. Amato GUILLAIN-BARRÉ SYNDROME Guillain-Barré syndrome (GBS) is an acute, frequently severe, and fulminant polyradiculoneuropathy that is autoimmune in nature. It occurs year-round at a rate of between 10 and 20 cases per million annually; in the United States, ~5000–6000 cases occur per year. Males are at slightly higher risk for GBS than females, and in Western coun tries, adults are more frequently affected than children. Clinical Manifestations GBS manifests as a rapidly evolving areflexic motor paralysis with or without sensory disturbance. The usual pattern is an ascending paralysis that may be first noticed as rubbery legs. Weakness typically evolves over hours to a few days and is frequently accompanied by tingling dysesthesias in the extremities. The legs are usually more affected than the arms, and facial diparesis is present in 50% of affected individuals. The lower cranial nerves are also frequently involved, causing bulbar weakness with difficulty handling secretions and maintaining an airway; the diagnosis in these patients may initially be mistaken for brainstem ischemia. Pain in the neck, shoulder, back, or diffusely over the spine is also common in the early stages of GBS, occurring in ~50% of patients. Most patients require hospitalization, and in different series, up to 30% require ventilatory assistance at some time during the illness. The need for mechanical ventilation is associated with more severe weakness on admission, a rapid tempo of progression, and the presence of facial and/or bulbar weakness during the first week of symptoms. Fever and constitutional symptoms are absent at the onset and, if present, cast doubt on the diagnosis. Deep

tendon reflexes attenuate or disappear within the first few days of onset. Cutaneous sensory deficits (e.g., loss of pain and temperature sensation) are usually relatively mild, but functions subserved by large sensory fibers, such as deep tendon reflexes and proprioception, are more severely affected. Bladder dysfunction may occur in severe cases but is usually transient. If bladder dysfunction is a prominent feature and comes early in the course or there is a sensory level on examination, diagnostic possibilities other than GBS should be considered, particularly spinal cord disease (Chap. 453). Once clini cal worsening stops and the patient reaches a plateau (almost always within 4 weeks of onset), further progression is unlikely. Autonomic involvement is common and may occur even in patients whose GBS is otherwise mild. The usual manifestations are loss of vasomotor control with wide fluctuations in blood pressure, postural hypotension, and cardiac dysrhythmias. These features require close monitoring and management and can be fatal. Pain is another common TABLE 458-1 Subtypes of Guillain-Barré Syndrome (GBS) SUBTYPE FEATURES ELECTRODIAGNOSIS PATHOLOGY Acute inflammatory demyelinating polyneuropathy (AIDP) Adults affected more than children; 90% of cases in Western world; recovery rapid; anti-GM1 antibodies (<50%) Acute motor axonal neuropathy (AMAN) Children and young adults; prevalent in China and Mexico; may be seasonal; recovery rapid; anti-GD1a antibodies Acute motor sensory axonal neuropathy (AMSAN) Mostly adults; uncommon; recovery slow, often incomplete; closely related to AMAN Miller Fisher syndrome (MFS) Adults and children; ophthalmoplegia, ataxia, and areflexia; anti-GQ1b antibodies (90%)

feature of GBS; in addition to the acute pain described above, a deep aching pain may be present in weakened muscles that patients liken to having overexercised the previous day. Other pains in GBS include dysesthetic pain in the extremities as a manifestation of sensory nerve fiber involvement. These pains are self-limited and often respond to standard analgesics (Chap. 14).

Several subtypes of GBS are recognized, as determined primarily by electrodiagnostic (EDx) and pathologic distinctions (Table 458-1). The most common variant is acute inflammatory demyelinating poly neuropathy (AIDP). Additionally, there are two “axonal” or “nodal/ paranodal” variants, which are often clinically severe: the acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropa thy (AMSAN) subtypes. In addition, a range of limited or regional GBS syndromes are also encountered. Notable among these is the Miller Fisher syndrome (MFS), which presents as rapidly evolving ataxia and areflexia of limbs without weakness, and ophthalmoplegia, often with pupillary paralysis. The MFS variant accounts for ~5% of all cases and is strongly associated with antibodies to the ganglioside GQ1b (see “Immunopathogenesis,” below). Other regional variants of GBS include (1) pure sensory forms; (2) ophthalmoplegia with anti-GQ1b antibodies as part of severe motor-sensory GBS; (3) GBS with severe bulbar and facial paralysis, sometimes associated with antecedent cyto megalovirus (CMV) infection and anti-GM2 antibodies; and (4) acute pandysautonomia (Chap. 451). Antecedent Events Approximately 70% of cases of GBS occur 1–3 weeks after an acute infectious process, usually respiratory or gastroin testinal. Culture and seroepidemiologic techniques show that 20–30% of all cases occurring in North America, Europe, and Australia are pre ceded by infection or reinfection with Campylobacter jejuni. A similar proportion is preceded by a human herpes virus infection, often CMV or Epstein-Barr virus. Other viruses (e.g., HIV, hepatitis E, Zika) and also Mycoplasma pneumoniae have been identified as agents involved in antecedent infections. Cases of GBS have been reported in associa tion with SARS-CoV-2 infection during the COVID-19 pandemic, but a causal relationship has not been established. CHAPTER 458 Guillain-Barré Syndrome and Other Immune-Mediated

C. jejuni has also been implicated in summer outbreaks of AMAN among children and young adults exposed to chickens in rural China, as has infection by Zika virus in the increased incidence of GBS in Brazil and other endemic regions. Recent immunizations have also been implicated in GBS. The swine influenza vaccine, administered widely in the United States in 1976, is the most notable example. Influenza vaccines in use from 1992 to 1994, however, resulted in only one additional case of GBS per million persons vaccinated, and the more recent seasonal influenza vaccines appear to confer a GBS risk of <1 per million. Epidemiologic stud ies looking at H1N1 vaccination demonstrated at most only a slight increased risk of GBS. There appears to be an increased risk of GBS with SARS-CoV-2 vaccines using adenovirus vectors, but not the mes senger RNA vaccines. Meningococcal vaccinations (Menactra) do not appear to carry an increased risk. Older-type rabies vaccine, prepared in nervous system tissue, is implicated as a trigger of GBS in developing countries where it is still used; the mechanism is presumably immuni zation against neural antigens. Demyelinating First attack on Schwann cell surface; widespread myelin damage, macrophage activation, and lymphocytic infiltration; variable secondary axonal damage Axonal First attack at motor nodes of Ranvier; macrophage activation, few lymphocytes, frequent periaxonal macrophages; extent of axonal damage highly variable Axonal Same as AMAN, but also affects sensory nerves and roots; axonal damage usually severe Axonal or demyelinating Few cases examined; resembles AIDP

GBS also occurs more frequently than can be attributed to chance alone in patients with lymphoma (including Hodgkin’s disease), in HIV-seropositive individuals, and in patients with systemic lupus ery thematosus (SLE) and possibly Sjogren’s syndrome. GBS, other inflam matory neuropathies, and myositis can also occur as a complication of immune checkpoint inhibitors used to treat various cancers.

Immunopathogenesis Several lines of evidence support an auto immune basis for AIDP, the most common and best-studied type of GBS; the concept extends to all of the subtypes of GBS (Table 458-1). It is likely that both cellular and humoral immune mechanisms contribute to tissue damage in AIDP. AIDP is also closely analogous to an experimental T cell–mediated immunopathy designated experi mental allergic neuritis (EAN). EAN is induced in laboratory animals by immune sensitization against protein fragments derived from peripheral nerve proteins and, in particular, against the P2 protein. Based on analogy to EAN, it was initially thought that AIDP was also likely to have a T cell–mediated pathogenesis, and consistent with this concept, autoreactive T cells against several peripheral myelin proteins have recently been identified in peripheral blood, cerebrospinal fluid (CSF), and infiltrating nerves from AIDP patients. However, abundant data also indicate that autoantibodies directed against T cell–independent nonprotein determinants may be the central mediators in many cases. Involvement of the humoral arm of the immune system in AIDP is supported by the demonstration of terminal complement complex on Schwann cells in autopsy series and induction of complementdependent demyelination and conduction block following injection of serum from patients with GBS into nerves of animals. In AMAN, there is deposition of IgG and complement activation products on the nodal and internodal axolemma of motor fibers.  Circumstantial evidence suggests that all GBS results from immune responses to nonself antigens (infectious agents, vaccines) that misdirect o t s e i d o b it n a o t u a G g I s t n a ir a v d n a s e p y t b u S Guillain-Barré syndrome Acute inflammatory demyelinating polyneuropathy Facial variant: Facial diplegia and paresthesia Acute motor axonal neuropathy

More and less extensive forms Acute motor-sensory axonal neuropathy Acute motor-conduction-block neuropathy Pharyngeal-cervical-brachial weakness Miller Fisher syndrome Incomplete forms Acute ophthalmoparesis (without ataxia) Acute ataxic neuropathy (without ophthalmoplegia) CNS variant: Bickerstaff's brainstem encephalitis Cer GM1 KEY Galactose Glucose N-Acetylgalactosamine N-Acetylneuraminic acid Ceramide Cer Cer GD1a FIGURE 458-1 Spectrum of disorders in Guillain-Barré syndrome and associated antiganglioside antibodies. IgG autoantibodies against GM1 or GD1a are strongly associated with acute motor axonal neuropathy (AMAN), as well as the more extensive acute motor-sensory axonal neuropathy (AMSAN), and the less extensive acute motor-conduction-block neuropathy. IgG anti-GQ1b antibodies, which cross-react with GT1a, are strongly associated with Miller Fisher syndrome, its incomplete forms (acute ophthalmoparesis [without ataxia] and acute ataxic neuropathy [without ophthalmoplegia]), and its more extensive form, Bickerstaff's brainstem encephalitis. Pharyngeal-cervical-brachial weakness is categorized as a localized form of acute motor axonal neuropathy or an extensive form of 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 Miller Fisher syndrome, acute ophthalmoparesis, acute ataxic neuropathy, Bickerstaff's brainstem encephalitis, and pharyngeal-cervical-brachial weakness. The presence of clinical overlap also indicates that Miller Fisher syndrome is part of a continuous spectrum with these conditions. Patients who have had Guillain-Barré syndrome overlapped with 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 AMAN and anti-GQ1b syndrome. (From N Yuki, H-P Hartung: Guillain-Barré syndrome. N Engl J Med 366:2294, 2012. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

to host nerve tissue through a resemblance-of-epitope (molecular mimicry) mechanism (Fig. 458-1). The neural targets are likely to be glycoconjugates, specifically gangliosides (Table 458-2; Fig. 458-2). Gangliosides are complex glycosphingolipids that contain one or more sialic acid residues; various gangliosides participate in cell-cell interactions (including those between axons and glia), modulation of receptors, and regulation of growth. They are typically exposed on the plasma membrane of cells, rendering them susceptible to an antibodymediated attack. Gangliosides and other glycoconjugates are present in large quantity in human nervous tissues and in key sites, such as nodes of Ranvier. Antiganglioside antibodies, most frequently to GM1, are common in GBS (20–50% of cases), particularly in AMAN and AMSAN, and in those cases, they are preceded by C. jejuni infection. Some AIDP autoantibodies may recognize glycolipid heterocomplexes, rather than single species, present on cell membranes. Furthermore, isolates of C. jejuni from stool cultures of patients with GBS have surface glycolipid structures that antigenically cross react with gan gliosides, including GM1, concentrated in human nerves. Sialic acid residues from pathogenic C. jejuni strains can also trigger activation of dendritic cells via signaling through Toll-like receptor 4 (TLR4), pro moting B-cell differentiation and further amplifying humoral autoim munity. Another line of evidence implicating humoral autoimmunity is derived from cases of GBS that followed intravenous administration of bovine brain gangliosides for treatment of various neuropathies; 5–15 days after injection, some recipients developed AMAN with high titers of anti-GM1 antibodies that recognized epitopes at nodes of Ranvier and motor endplates. Experimentally, anti-GM1 antibodies can trig ger complement-mediated injury at paranodal axon-glial junctions, disrupting the clustering of sodium channels and likely contributing to conduction block (see

“Pathophysiology,” below). Anti-GQ1b IgG antibodies are found in >90% of patients with MFS (Table 458-2; Fig. 458-2), and titers of IgG are highest early in None None GM1, GD1a GM1, GD1a GM1, GD1a GT1a>GQ1b>>GD1a GQ1b, GT1a GQ1b, GT1a GQ1b, GT1a GQ1b, GT1a GT1a Cer GQ1b Cer

TABLE 458-2 Principal Antiglycolipid Antibodies Implicated in Immune Neuropathies CLINICAL PRESENTATION ANTIBODY TARGET USUAL ISOTYPE Acute Immune Neuropathies (Guillain-Barré Syndrome) Acute inflammatory demyelinating polyneuropathy (AIDP) No clear patterns IgG (polyclonal) GM1 most common Acute motor axonal neuropathy (AMAN) GD1a, GM1, GM1b, GalNAc–GD1a (<50% for any) IgG (polyclonal) Miller Fisher syndrome (MFS) GQ1b (>90%) IgG (polyclonal) Acute pharyngeal cervicobrachial neuropathy (APCBN) GT1a (? most) IgG (polyclonal) Chronic Immune Neuropathies Chronic inflammatory demyelinating polyneuropathy (CIDP) (75%) Rarely to P0, myelin P2 protein, or PMP22 IgG, IgA CIDP-M (MGUS associated) (25%) Neural binding sites IgG, IgA (monoclonal) Anti-MAG neuropathy SGPG, SGLPG (on MAG) (50%) IgM (monoclonal) Uncertain (50%) IgM (monoclonal) Nodal/paranodal neuropathies Approximately 10% to CNTN1 or NF155, less often to NF140/186 and Caspr1 IgG4 with CNTN1, NF155, NF140/186, Caspr1 Rare IgM with NF155 Multifocal motor neuropathy (MMN) GM1, GalNAc–GD1a, others (25–50%) IgM (polyclonal, monoclonal) Chronic sensory ataxic neuropathy GD1b, GQ1b, and other b-series gangliosides IgM (monoclonal) Abbreviations: CIDP-M, CIDP with a monoclonal gammopathy; Caspr1, contactin associated protein-1; CNTN1, contactin-1; MAG, myelin-associated glycoprotein; MGUS, monoclonal gammopathy of undetermined significance; NF140/186, neurofascin 140/186; NF155, neurofascin 155; SGPG, sulfoglucuronyl paragloboside; SGLPG, sulfoglucuronyl lactosaminyl paragloboside. Source: Modified with permission from HJ Willison, N Yuki: Peripheral neuropathies and anti-glycolipid antibodies. Brain 125:2591, 2002. the course. Anti-GQ1b antibodies are not found in other forms of GBS unless there is extraocular motor nerve involvement. A pos sible explanation for this association is that extraocular motor nerves are enriched in GQ1b gangliosides in comparison to limb nerves. In addition, a monoclonal anti-GQ1b antibody raised against C. jejuni isolated from a patient with MFS blocked neuromuscular transmission experimentally. Taken together, these observations provide strong but still incon clusive evidence that autoantibodies play an important pathogenic role in GBS. Although antiganglioside antibodies have been studied most intensively, other antigenic targets may also be important. Proof that these antibodies are pathogenic requires that they be capable of mediating disease following direct passive transfer to naïve hosts; this has not yet been demonstrated, although one case of possible maternalfetal transplacental transfer of GBS has been described. In AIDP, an early step in the induction of tissue damage appears to be complement deposition along the outer surface of the Schwann cell. Activation of complement initiates a characteristic vesicular disinte gration of the myelin sheath and also leads to recruitment of activated macrophages, which participate in damage to myelin and axons. In AMAN, the pattern is different in that complement is deposited along with IgG at the nodes of Ranvier along large motor axons. Interest ingly, in cases of AMAN, antibodies against GD1a appear to have a fine specificity that favors binding to motor rather than sensory nerve roots, even though this ganglioside is expressed on both fiber types.

Pathophysiology In the demyelinating forms of GBS (AIDP), the basis for flaccid paralysis and sensory disturbance is conduction block. This finding, demonstrable electrophysiologically, implies that the axonal connections remain intact. Hence, recovery can take place rapidly as remyelination occurs. In severe cases of demyelinating GBS, secondary axonal degeneration usually occurs; its

extent can be estimated electrophysiologically. More secondary axonal degeneration correlates with a slower rate of recovery and a greater degree of residual disability. With AMAN and AMSAN, a primary axonal pattern is encountered electrophysiologically (low-amplitude compound muscle action potentials). The implication has been that axons have degener ated and become disconnected from their targets, specifically the neu romuscular junctions, and must therefore regenerate for recovery to take place. However, the rapid recovery in many cases suggests the low amplitudes are often from reversible conduction block due to binding of antibodies to ion channel proteins in the nodes and paranodes. In severe cases, axonal degeneration can occur, and it is in these cases that recovery is much slower. Laboratory Features CSF findings are distinctive, consisting of an elevated CSF protein level (1–10 g/L [100–1000 mg/dL]) without accompanying pleocytosis. The CSF is often normal when symptoms have been present for ≤48 h; by the end of the first week, the level of protein is usually elevated. A transient increase in the CSF white cell count (10–100/μL) occurs on occasion in otherwise typical GBS; however, a sustained CSF pleocytosis suggests an alternative diagnosis (viral myelitis) or a concurrent diagnosis such as unrecognized HIV infection, leukemia or lymphoma with infiltration of nerves, or neuro sarcoidosis. EDx features are mild or absent in the early stages of GBS and lag behind the clinical evolution. In AIDP, the earliest features are prolonged F-wave latencies, prolonged distal latencies, and reduced amplitudes of compound muscle action potentials (CMAPs), probably owing to the predilection for involvement of nerve roots and distal motor nerve terminals early in the course. Later, slowing of conduction velocity, conduction block, and temporal dispersion may be appre ciated (Table 458-1). Occasionally, sensory nerve action potentials (SNAPs) may be normal in the feet (e.g., sural nerve) when abnormal in the arms. This is also a sign that the patient does not have one of the more typical “length-dependent” polyneuropathies. As mentioned, in AMAN and AMSAN, the principal EDx finding is reduced amplitude of CMAPs (and also SNAPs with AMSAN) without conduction slow ing or prolongation of distal latencies, which early on is caused by conduction block but later can be due to axonal degeneration. Diagnosis GBS is a descriptive entity. The diagnosis of AIDP is made by recognizing the pattern of rapidly evolving paralysis with are flexia, absence of fever or other systemic symptoms, and characteristic antecedent events. In 2011, the Brighton Collaboration developed a new set of case definitions for GBS in response to needs of epidemio logic studies of vaccination and assessing risks of GBS (Table 458-3). These criteria have subsequently been validated. Other disorders that may enter into the differential diagnosis include acute myelopathies (especially with prolonged back pain and sphincter disturbances); diphtheria (early oropharyngeal disturbances); Lyme polyradiculitis and other tick-borne paralyses; porphyria (abdominal pain, seizures, psychosis); vasculitic neuropathy (check erythrocyte sedimentation rate, described below); poliomyelitis and acute flaccid myelitis (wildtype poliovirus, West Nile virus, enterovirus D68, enterovirus A71, Japanese encephalitis virus, and the wild-type poliovirus); CMV polyradiculitis (in immunocompromised patients); critical illness neuropathy or myopathy; neuromuscular junction disorders such as myasthenia gravis and botulism (pupillary reactivity lost early); poi sonings with organophosphates, thallium, or arsenic; paralytic shellfish poisoning; or severe hypophosphatemia (rare). Cases of acute flaccid myelitis may pose particular challenges in distinguishing these from GBS because sphincter disturbances may be absent.


Laboratory tests are helpful primarily to exclude mimics of GBS. CSF pleocytosis is seen with poliomyelitis, acute flaccid myelitis, and Lyme and CMV polyradiculitis. EDx features may be minimal early in GBS, and the CSF protein level may not rise until the end of the first

A Motor neuron Unidentified antigen Axon Myelin Antibody binding Complement activation PART 13 Neurologic Disorders B Axon Myelin Macrophage GM1, GD1a Schwann-cell microvilli Myelin Axon Axon Paranode Node Juxtaparanode KEY KEY IgG anti-GM1 or anti-GD1a antibodies C3 MAC Nav Cytoskeleton Kv Caspr FIGURE 458-2 Possible immune mechanisms in Guillain-Barré syndrome (GBS). Panel A shows the immunopathogenesis of AIDP. Although autoantigens have yet to be unequivocally 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 axonal forms of GBS (acute motor axonal neuropathy [AMAN] and acute motor-sensory axonal neuropathy [AMSAN]). 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. (From N Yuki, H-P Hartung: Guillain-Barré syndrome. N Engl J Med 366:2294, 2012. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.) week. If the diagnosis is strongly suspected, treatment should be initi ated without waiting for evolution of the characteristic EDx and CSF findings to occur. GBS patients with risk factors for HIV or with CSF pleocytosis should have a serologic test for HIV. TREATMENT Guillain-Barré Syndrome In the vast majority of patients with GBS, treatment should be initiated as soon after diagnosis as possible. Each day counts; ~2 weeks after the first motor symptoms, it is not known whether

Macrophage MAC Myelin Axon Macrophage Nerve injury Macrophage scavenging Macrophage MAC Axon immunotherapy is still effective. If the patient has already reached the plateau stage, then treatment probably is no longer indicated, unless the patient has severe motor weakness and one cannot exclude the possibility that an immunologic attack is still ongoing. Either high-dose intravenous immune globulin (IVIg) or plasma pheresis (PLEX) can be initiated, as they are equally effective for typical GBS. A combination of the two therapies is not significantly better than either alone. IVIg is often the initial therapy chosen because of its ease of administration and good safety record. IVIg is usually administered as five daily infusions for a total dose of 2 g/kg body weight. There is some evidence that GBS autoantibod ies are neutralized by anti-idiotypic antibodies present in IVIg

TABLE 458-3 Brighton Criteria for Diagnosis of Guillain-Barré Syndrome (GBS) and Miller Fisher Syndrome Clinical case definitions for diagnosis of GBS Level 1 of diagnostic certainty Bilateral AND flaccid weakness of the limbs AND Decreased or absent deep tendon reflexes in weak limbs AND Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau AND Electrophysiologic findings consistent with GBS AND Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/μL) AND Absence of an identified alternative diagnosis for weakness Level 2 of diagnostic certainty Bilateral AND flaccid weakness of the limbs AND

Decreased or absent deep tendon reflexes in weak limbs AND Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau AND CSF total white cell count <50 cells/µL (with or without CSF protein elevation above laboratory normal value) OR If CSF not collected or results not available, electrophysiologic studies consistent with GBS AND Absence of identified alternative diagnosis for weakness Level 3 of diagnostic certainty Bilateral and flaccid weakness of the limbs AND Decreased or absent deep tendon reflexes in weak limbs AND Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau AND Absence of identified alternative diagnosis for weakness Clinical case definitions for diagnosis of Miller Fisher syndrome Level 1 of diagnostic certainty Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes, and ataxia AND Abbreviation: CSF, cerebrospinal fluid. Source: Reproduced with permission from JJ Sejvar et al: Guillain-Barré syndrome and Fisher syndrome: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 29:599, 2011. preparations, perhaps accounting for the therapeutic effect. A course of PLEX usually consists of ~40–50 mL/kg plasma exchange (PE) 4–6 times over 7–12 days. Meta-analysis of randomized clini cal trials indicates that treatment reduces the need for mechanical ventilation by nearly half (from 27 to 14% with PLEX) and increases the likelihood of full recovery at 1 year (from 55 to 68%). Function ally significant improvement may occur toward the end of the first week of treatment or may be delayed for several weeks. The lack of noticeable improvement following a course of IVIg or PLEX is not an indication to treat with the alternate treatment. However, there are occasional patients who are treated early in the course of GBS and improve, who then relapse within a month. Brief retreatment with the original therapy is usually effective in such cases. Gluco corticoids have not been found to be effective in GBS. Occasional patients with very mild forms of GBS, especially those who appear to have already reached a plateau when initially seen, may be man aged conservatively without IVIg or PLEX.

Absence of limb weakness AND Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau AND Cytoalbuminologic dissociation (i.e., elevation of cerebrospinal protein above the laboratory normal and total CSF white cell count <50 cells/µL) AND Nerve conduction studies are normal, OR indicate involvement of sensory nerves only AND No alterations in consciousness or corticospinal tract signs AND Absence of identified alternative diagnosis Level 2 of diagnostic certainty Bilateral ophthalmoparesis and bilateral reduced or absent tendon CHAPTER 458 reflexes and ataxia AND Absence of limb weakness AND Monophasic illness pattern and interval between onset and nadir of Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies
weakness between 12 h and 28 days and subsequent clinical plateau AND CSF with a total white cell count <50 cells/µL) (with or without CSF protein elevation above laboratory normal value) OR Nerve conduction studies are normal, OR indicate involvement of sensory nerves only AND No alterations in consciousness or corticospinal tract signs AND Absence of identified alternative diagnosis Level 3 of diagnostic certainty Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia AND Absence of limb weakness AND Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau AND No alterations in consciousness or corticospinal tract signs AND Absence of identified alternative diagnosis In the worsening phase of GBS, most patients require monitoring in a critical care setting, with particular attention to vital capac ity, heart rhythm, blood pressure, nutrition, deep-vein thrombo sis prophylaxis, cardiovascular status, early consideration (after

2 weeks of intubation) of tracheotomy, and chest physiotherapy. As noted, ~30% of patients with GBS require ventilatory assistance, sometimes for prolonged periods of time (several weeks or longer). Frequent turning and assiduous skin care are important, as are daily range-of-motion exercises to avoid joint contractures and daily reassurance as to the generally good outlook for recovery. Prognosis and Recovery Approximately 85% of patients with GBS achieve a full functional recovery within several months to a year, although minor findings on examination (such as areflexia) may persist and patients often complain of continued symptoms, including fatigue. The mortality rate is <5% in optimal settings; death usually results from secondary pulmonary complications. The outlook is worst

in patients with severe proximal motor and sensory axonal damage. Such axonal damage may be either primary or secondary in nature (see “Pathophysiology,” above), but in either case, successful regeneration cannot occur. Other factors that worsen the outlook for recovery are advanced age, a fulminant or severe attack, and a delay in the onset of treatment. Elevated serum levels of neurofilament light (Nfl) chains and high titers of serum anti-GM1 antibodies are both associated with more axonal involvement in GBS and poor recovery. Between 5 and 10% of patients with typical GBS have one or more late relapses; many of these cases are then classified as chronic inflammatory demyelinat ing polyneuropathy (CIDP).

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY CIDP is distinguished from GBS by its chronic course. In other respects, this neuropathy shares many features with the common demyelinating form of GBS, including elevated CSF protein levels and the EDx findings of acquired demyelination. Most cases occur in adults, and males are affected slightly more often than females. The incidence of CIDP is lower than that of GBS, but due to the protracted course, the prevalence is greater. As with GBS, CIDP and its variants can be triggered by use of immune checkpoint inhibitors used to treat various cancers. Clinical Manifestations Onset is usually gradual over a few months or longer, but in a few cases, the initial attack is indistinguish able from that of GBS. An acute-onset form of CIDP may mimic GBS but should be considered if it deteriorates >9 weeks after onset or relapses at least three times. Symptoms are both motor and sen sory in most cases. Weakness of the limbs is usually symmetric but can be strikingly asymmetric in multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy variant (Lewis-Sumner syndrome) in which discrete peripheral nerves are involved. There is considerable variability from case to case. Some patients experience a chronic progressive course, whereas others, usually younger patients, have a relapsing and remitting course. A small proportion have cra nial nerve findings, including external ophthalmoplegia. Some have only motor findings, and a small proportion present with a relatively pure syndrome of sensory ataxia. The latter can be seen in the chronic inflammatory sensory polyradiculopathy (CISP) variant of CIDP in which demyelination predominantly occurs at the sensory roots or with the distal acquired demyelinating symmetric (DADS) variant. Some patients with CISP have mild motor involvement, and these cases are termed CISP-plus. New European Academy of Neurology/Periph eral Nerve Society (EAN/PNS) criteria for CIDP considers CISP as a separate entity, but we and others still feel it belongs as a subcategory of CIDP as the histopathology and response to treatment are similar. CIDP tends to ameliorate over time with treatment; the result is that many years after onset, nearly 75% of patients have reasonable func tional status. Death from CIDP is uncommon. Diagnosis The diagnosis rests on characteristic clinical, CSF, and electrophysiologic findings. The CSF is usually acellular with an elevated protein level, sometimes several times normal. As with GBS, a CSF pleocytosis should lead

to the consideration of HIV infection, leukemia or lymphoma, and neurosarcoidosis. EDx findings reveal variable degrees of conduction slowing, prolonged distal latencies, distal and temporal dispersion of CMAPs, and conduction block as the principal features. In particular, the presence of conduction block is a certain sign of an acquired demyelinating process. Evidence of axonal loss, presumably secondary to demyelination, is present in >50% of patients. Serum protein electrophoresis with immunofixation is indi cated to search for monoclonal gammopathy and associated condi tions (see “Monoclonal Gammopathy of Undetermined Significance,” below). Magnetic resonance imaging (MRI) can demonstrate enlarged nerves, clumping of cauda equina, and enhancement. Ultrasound is cheaper and often more readily available and can likewise show enlargement of nerves at the roots or more distally. Studies have shown that imaging complements EDx findings and increases sensitivity. In all patients with presumptive CIDP, it is also reasonable to exclude PART 13 Neurologic Disorders

vasculitis, collagen vascular disease (especially SLE), chronic hepatitis, HIV infection, amyloidosis, and diabetes mellitus. Other associated conditions include inflammatory bowel disease and lymphoma. Pathogenesis Biopsy in typical CIDP reveals little inflammation and onion-bulb changes (imbricated layers of attenuated Schwann cell processes surrounding an axon) that result from recurrent demy elination and remyelination (Fig. 458-1). The response to therapy suggests that CIDP is immune-mediated; CIDP responds to gluco corticoids, whereas GBS does not. Passive transfer of demyelination into experimental animals has been accomplished using IgG purified from the serum of some patients with CIDP, lending support for a humoral autoimmune pathogenesis. A minority of patients have serum antibodies against P0, myelin P2 protein, or PMP22 (proteins whose genes are mutated in certain forms of hereditary Charcot-Marie-Tooth neuropathy). As many as 25% of patients with clinical features of CIDP also have a monoclonal gammopathy of undetermined significance (MGUS), discussed below. Cases associated with monoclonal IgA or IgG kappa usually respond to treatment as favorably as cases without a mono clonal gammopathy. Patients with IgM-kappa monoclonal gammopa thy and antibodies directed against myelin-associated glycoprotein (MAG) have a distinct demyelinating polyneuropathy with more sen sory findings, usually only distal weakness, and a poor response to immunotherapy. TREATMENT Chronic Inflammatory Demyelinating Polyneuropathy Most authorities initiate treatment for CIDP when progression is rapid or walking is compromised. If the disorder is mild, manage ment can be expectant, awaiting spontaneous remission. Controlled studies have shown that high-dose IVIg, subcutaneous Ig (scIg), PLEX, and glucocorticoids are all more effective than placebo. Initial therapy is usually with IVIg, administered as 2.0 g/kg body weight given in divided doses over 2–5 days; three monthly courses are generally recommended before concluding a patient has failed treatment. If the patient responds, the infusion intervals can be gradually increased or the dosage decreased (e.g., starting at 1 g/kg every 3–4 weeks). Patients who require more frequent IVIg, experi ence side effects with IVIg (headaches), have poor venous access, or find it more convenient are treated with scIg (2–3 times a week such that the total dosage per month is the same or slightly higher than the monthly dosage of IVIg). PLEX, which appears to be as effective as IVIg, is initiated at 2–3 treatments per week for 6 weeks; periodic retreatment may also be required. Treatment with glucocorticoids is another option (60–80 mg prednisone PO daily for 1–2 months, followed by a gradual dose reduction of 10 mg per month as tolerated), but long-term adverse effects including bone demin eralization, gastrointestinal bleeding, and cushingoid changes are problematic. As many as one-third of patients with CIDP fail to respond adequately to the initial therapy chosen; a different treat ment should then be tried. Patients who fail therapy with IVIg,

scIg, PLEX, and glucocorticoids may benefit from treatment with immunosuppressive agents such as azathioprine, methotrexate, cyclosporine, and cyclophosphamide, either alone or as adjunctive therapy. Use of these therapies requires periodic reassessment of their risks and benefits. A trial of efgartigimod alfa, a human neonatal Fc antibody fragment approved for myasthenia gravis (Chap. 457), demonstrated effectiveness in preventing relapses in CIDP; however, the medication will need to be compared with other more established options to determine its place in the CIDP treatment algorithm. In patients with a CIDP-like neuropathy who fail to respond to treatment, it is important to evaluate for a nodopathy, paranodopathy, or POEMS syndrome (polyneuropa thy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; see below).

NODOPATHIES AND PARANODOPATHIES Approximately 10% of patients previously considered to have CIDP have autoantibodies targeting antigens residing in nodal and paranodal regions that are responsible for the positioning and anchoring of ion channels and myelin folds in strategic locations along the axolemma. The EAN/PNS criteria now consider these separate from CIDP, and they are called nodopathies and paranodopathies. These neuropathies are associated with IgG4 isotype antibodies directed against nodal or paranodal antibodies including contactin-1 (CNTN1) or neurofas cin 155 (NF155) and, less commonly, IgM anti-NF140/186. Patients typically manifest with progressive symmetric, distally predominant weakness, sensory ataxia, and postural and intention tremor. Renal failure and nephrotic syndrome from membranous glomerulone phritis are associated with CNTN1 neuropathy. Of note, the CNTN1 protein is also present on podocytes on kidneys, and antibodies that deposit along the glomerular basement membrane are visible on renal biopsy. Other antibodies have less clinical specificity. Anti-contactin associated protein-1 (Caspr1) antibodies are associated with severe neuropathic pain. Passive transfer of IgG4 CNTN1 antibodies produces paranodal damage and ataxia in rodents. Electrophysiology is indistin guishable from typical CIDP. Importantly, as these nodopathies and paranodopathies are usually associated with IgG4 antibodies, they are less responsive to IVIg. How ever, they can respond to rituximab.
MULTIFOCAL MOTOR NEUROPATHY Multifocal motor neuropathy (MMN) is a distinctive but uncommon neuropathy that presents with slowly progressive motor weakness and atrophy evolving over years in the distribution of selected nerve trunks, associated with sites of persistent focal motor conduction block in the same nerve trunks. Sensory fibers are relatively spared. The arms are affected more frequently than the legs, and >75% of all patients are male. Some cases have been confused with lower motor neuron forms of amyotrophic lateral sclerosis (Chap. 448). Less than 50% of patients present with high titers of polyclonal IgM antibody to the ganglioside GM1. It is uncertain how this finding relates to the discrete foci of persistent motor conduction block, but high concentrations of GM1 gangliosides are normal constituents of nodes of Ranvier in peripheral nerve fibers. Pathology reveals demyelination and mild inflammatory changes at the sites of conduction block. Most patients with MMN respond to high-dose IVIg or scIg (dos ages as for CIDP, above); periodic retreatment is required (usually at least monthly) to maintain the benefit. Some refractory patients have responded to rituximab or cyclophosphamide. Glucocorticoids and PE are not effective. NEUROPATHIES WITH MONOCLONAL GAMMOPATHY ■ ■MULTIPLE MYELOMA Clinically overt polyneuropathy occurs in ~5% of patients with the commonly encountered type of multiple myeloma, which exhibits either lytic or diffuse osteoporotic bone lesions. These neuropathies are sensorimotor, are usually mild and slowly progressive but may be severe, and generally do not reverse with successful suppression of the myeloma. In most cases, EDx and pathologic features are consistent with a process of axonal degeneration. In contrast, myeloma with osteosclerotic features, although repre senting only 3% of all myelomas, is associated with

polyneuropathy in one-half of cases. These neuropathies, which may also occur with solitary plasmacytoma, are distinct because they (1) are demyelinat ing or mixed axonal and demyelinating by EDx, have elevated CSF protein, and clinically resemble CIDP; (2) often respond to radiation therapy or removal of the primary lesion; (3) are associated with dif ferent monoclonal proteins and light chains (almost always lambda as opposed to primarily kappa in the lytic type of multiple myeloma); (4) are typically refractory to standard treatments of CIDP; and (5) may occur in association with other systemic findings including thicken ing of the skin, hyperpigmentation, hypertrichosis, organomegaly,

endocrinopathy, anasarca, and clubbing of fingers. These are features of POEMS syndrome. Levels of vascular endothelial growth factor (VEGF) are increased in the serum, and this factor is thought to some how play a pathogenic role in this syndrome. Treatment of the neu ropathy is best directed at the osteosclerotic myeloma using surgery, radiotherapy, chemotherapy, or autologous peripheral blood stem cell transplantation.

Neuropathies are also encountered in other systemic conditions with gammopathy, including Waldenström macroglobulinemia, pri mary systemic amyloidosis, and cryoglobulinemic states (mixed essen tial cryoglobulinemia, some cases of hepatitis C). ■ ■MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE Chronic polyneuropathies occurring in association with MGUS are usually associated with the immunoglobulin isotypes IgG, IgA, and IgM. Most patients present with isolated sensory symptoms in their distal extremities and have EDx features of an axonal sensory or senso rimotor polyneuropathy. These patients otherwise resemble idiopathic sensory polyneuropathy, and the MGUS might just be coincidental. They usually do not respond to immunotherapies designed to reduce the concentration of the monoclonal protein. Some patients, however, present with generalized weakness and sensory loss and EDx stud ies indistinguishable from CIDP without monoclonal gammopathy (see “Chronic Inflammatory Demyelinating Polyneuropathy,” above), and their response to immunosuppressive agents is also similar. An exception is the syndrome of IgM-kappa monoclonal gammopathy associated with an indolent, long-standing, sometimes static sensory neuropathy, frequently with tremor and sensory ataxia. Most patients are men and aged >50 years. In the majority, the monoclonal IgM immunoglobulin binds to a normal peripheral nerve constituent, MAG, found in the paranodal regions of Schwann cells. Binding appears to be specific for a polysaccharide epitope that is also found in other normal peripheral nerve myelin glycoproteins, P0 and PMP22, and also in other normal nerve-related glycosphingolipids (Fig. 4581). In the MAG-positive cases, IgM paraprotein is incorporated into the myelin sheaths of affected patients and widens the spacing of the myelin lamellae, thus producing a distinctive ultrastructural pattern. Demyelination and remyelination are the hallmarks of the lesions, but axonal loss develops over time. These anti-MAG polyneuropathies are typical refractory to immunotherapy. In a small proportion of patients (30% at 10 years), MGUS will in time evolve into frankly malignant conditions such as multiple myeloma or lymphoma. CHAPTER 458 Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies
VASCULITIC NEUROPATHY Peripheral nerve involvement is common in polyarteritis nodosa (PAN), appearing in half of all cases clinically and in 100% of cases at postmortem studies (Chap. 375). The most common pattern is multifocal (asymmetric) motor-sensory neuropathy (mononeuropathy multiplex) due to ischemic lesions of nerve trunks and roots; however, some cases of vasculitic neuropathy present as a distal, symmetric sensorimotor polyneuropathy. Symptoms of neuropathy are a common presenting complaint in patients with PAN. The EDx findings are those of an axonal process. Small- to medium-sized arteries of the vasa ner vorum, particularly the epineural vessels,

are affected in PAN, resulting in a widespread ischemic neuropathy. A high frequency of neuropathy occurs in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome [CSS]). Systemic vasculitis should always be considered when a subacute or chronically evolving mononeuropathy multiplex occurs in conjunc tion with constitutional symptoms (fever, anorexia, weight loss, loss of energy, malaise, and nonspecific pains). Diagnosis of suspected vascu litic neuropathy is made by a combined nerve and muscle biopsy, with serial section or skip-serial techniques. Approximately one-third of biopsy-proven cases of vasculitic neu ropathy are “nonsystemic” in that the vasculitis appears to affect only peripheral nerves. Constitutional symptoms are absent, and the course is more indolent than that of PAN. The erythrocyte sedimentation rate may be elevated, but other tests for systemic disease are negative.

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Revision #1
Created 2026-01-06 16:35:53 UTC by Omar Ayman
Updated 2026-01-06 16:35:54 UTC by Omar Ayman