Guillain-Barré syndrome and related disorders

Amato AA

RESUMEN

En 1859, Landry describió una neuropatía caracterizada por parálisis severa ascendente. Posteriormente, Guillain, Barré y Strohl observaron la disociación arreflexia y la albuminocitológica en el fluido cerebro espinal asociado con esta neuropatología. Las contribuciones de Landry y Strohl no han sido tomadas en cuenta y la neuropatía ha sido referida comúnmente como síndrome de Guillain-Barré (SGB). En 1949, Haymaker y Kernohan reportaron características histopatológicas de 50 casos fatales de SGB.

Palabras clave: *síndrome de Guillain-Barré, neuropatías.*

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ABSTRACT

In 1859, Landry described a neuropathy characterized by acute ascending paralysis. Subsequently, Guillain, Barré, and Strohl noted the areflexia and the albuminocytological dissociation in the cerebral spinal fluid (CSF) associated with this neuropathy. The contributions of Landry and Strohl have been neglected and the neuropathy has been most commonly referred to as Guillain-Barré syndrome (GBS). In 1949, Haymaker and Kernohan reported the histopathological features of 50 fatal cases of GBS.

Key words: *Guillain-Barré syndrome's, neuropaties.*

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In 1859, Landry described a neuropathy characterized by acute ascending paralysis. Subsequently, Guillain, Barré, and Strohl noted the areflexia and the albuminocytological dissociation in the cerebral spinal fluid (CSF) associated with this neuropathy. The contributions of Landry and Strohl have been neglected and the neuropathy has been most commonly referred to as Guillain-Barré syndrome (GBS). In 1949, Haymaker and Kernohan reported the histopathological features of 50 fatal cases of GBS. The earliest features were edema of the proximal nerves followed by degeneration of the myelin sheaths within the first week of the illness. They did not appreciate inflammatory cells infiltrate until later in the course of the illness. However, Asbury and colleagues found prominent perivascular inflammation in the spinal root's dorsal root ganglia, cranial nerves, and randomly along the whole length of peripheral nerves along with segmental demyelination adjacent to the areas of inflammation in all 19 autopsy cases of GBS. Thus, the term acute inflammatory demyelinating polyradiculoneuropathy (AIDP), which is quite descriptive of the disease process, has been used synonymously with GBS. Subsequently, diagnostic criteria have been developed to assist in the diagnosis of patients suspected of AIDP.

The underlying pathophysiology/neurophysiology of GBS was not uncovered until one century following the original clinical descriptions of the neuropathy by Landry, Guillain, Barré, and Strohl. It is now appreciated that GBS is not a single disorder but again a syndrome of several types of acute immune-mediated polyneuropathies. In addition, to AIDP, there are two axonal forms of GBS: acute motor-sensory axonal neuropathy (AMSAN) and acute motor axonal neuropathy (AMAN). Further, some disorders which appear clinically different from AIDP (e.g., the Miller-Fisher syndrome, acute autonomic neuropathy) may share similar pathogenesis and can be considered a variant of GBS.

ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Epidemiology and antecedent illness

AIDP is the most common cause of acute generalized weakness with an annual incidence ranging from 1-4/100,000 population. The

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neuropathy can occur at any age, with a peak age of onset of approximating 38-40 years. There may be a slight male predominance.

Approximately 60-70% of patients with AIDP have a history of a recent infection a few weeks prior to the onset of the neuropathy. A control study of 154 patients with GBS revealed serological evidence of recent infections with *Campylobacter jejun* (32%), cytomegalovirus (13%), Epstein-Barr virus (10%), and *Mycoplasma pneumoniae* (5%). These were more frequent than that seen in the control population. Other studies have also reported 15- 45% of patients with AIDP have serologic evidence of recent *Campylobacter*enteritis. The relationship between *Campylobacter jejuni* infection and the different variants of GBS (AIDP, AMSAN, and AMAN) has been the subject of many reports and is discussed in detail in the pathogenesis sections of these disorders. Besides cytomegalovirus (CMV) and Epstein-Barr virus (EBV), other virus infections have been described in AIDP including influenza, hepatitis A, hepatitis B, hepatitis C, and human immunodeficiency virus (HIV). In HIV infection, AIDP usually occurs at the time of seroconversion or early in the course of the disease. Vaccinations, most notably to swine flu, have been associated with GBS. Further, other disorders have been linked to GBS, including other autoimmune disorders (i.e., systemic lupus erythematosus), lymphoma, organ rejection or graft-versus host disease following solid organ and bone marrow transplantation, and perhaps recent surgery.

Clinical features

AIDP usually presents with numbness and tingling in the feet that gradually progresses up the legs and then into the arms. Numbness and paresthesia can also involve the face. Severe, aching, prickly, or burning neuritic pain sensations in the back and limbs are present in at least half of patients. Large fiber modalities (touch, vibration, and position sense) are more severely affected than small fiber functions (pain and temperature perception).

Progressive weakness typically accompanies the sensory disturbance. The severity can range from mild distal weakness to complete quadriplegia and need for mechanical ventilation. Weakness is usually first noted in the legs and ascends to the arms, trunk, head and neck. Ropper reported 56% had onset of weakness in the legs, 12% in the arms, and 32% simultaneously in the arms and legs. Mild facial weakness is also often apparent in at least half of the patients during the course of the illness. Ophthalmoparesis and ptosis develop in 5-15% of patients. Occasionally, there is a descending presentation with onset in the cranial nerves with subsequent progression to the arms and legs. The bowel and bladder are usually spared, although they may become involved in particularly severe disease states. Muscle stretch reflexes progressively diminish or become unobtainable. Autonomic instability is common in AIDP with hypotension or hypertension and occasionally cardiac arrhythmias.

The neuropathy usually progresses over the course of 2-4 weeks. At least 50% of patients reach their nadir by 2 weeks, 80% by 3 weeks, and 90% by 4 weeks. Progression of symptoms and signs for over 8 weeks excludes GBS and suggests the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) . Subacute onset with progression of the disease over 4 to 8 weeks and has been termed subacute inflammatory demyelinating polyneuropathy (SIDP). Patients with SIDP may have a monophasic illness like AIDP or may behave like CIDP and continue to progress unless treated with immunosuppressive or immunomodulating agents. Approximately 30% of patients with AIDP develop respiratory failure. Because the immune attack of AIDP has an early predilection for the nerve roots, neck flexors and extensors and shoulder abductors, which are innervated by cervical roots close to the phrenic nerve (C3C4), correlate well with diaphragmatic strength and are thus important to closely follow. Once the disease nadir is reached, there is a plateau phase of several days to weeks followed by gradual recovery over several months. However, 50 -85% of patients have some degree of residual deficits as many as 7 years after disease onset with 5 to 10% of patients having disabling motor or sensory symptoms including severe fatigue. The mortality rate is about 5% with patients dying as a result of respiratory distress syndrome, aspiration pneumonia, pulmonary embolism, cardiac arrhythmias, and sepsis related to secondarily acquired infections. Risk factors for a poorer prognosis (slower and incomplete recovery) are age greater than 50 to 60 years, abrupt onset of profound weakness, the need for mechanical ventilation, and distal CMAP amplitudes less than 10-20% of normal.

Laboratory features

Albuminocytological disassociation with elevated CSF protein levels accompanied by no or only a few mononuclear cells is present in over 80% of patients after two weeks. However, within the first week of symptoms, CSF protein levels are normal in approximately one-third of patients. When CSF pleocytosis of more than 10 lymphocytes/mm3 (particular with cell counts greater than 50/mm3) is found, AIDP-like neuropathies related to Lyme disease, recent HIV infection, or sarcoidosis need to

be considered. Elevated liver function tests are common and may be attributed to viral hepatitis (A, B, and C), EBV, or CMV infection.

Enhancement of the nerve roots may be appreciated on magnetic resonance imaging of the spine.

Antiganglioside antibodies, particularly anti-GM1 IgG antibodies, are found in some patients and correlates with recent *Campylobacter jejuni* infection. Serological evidence of recent antecedent *Campylobacter jejuni* infection is evident in 15 to 45% of patients. Molecular mimicry between gangliosides expressed on nerve fibers and glycolipids present on *Campylobacter jejuni* may account for their association with AIDP, and may play a role in the pathogenesis of the disorder.

Electrophysiologic findings

Various electrophysiologic criteria for demyelination have been developed to aid in the diagnosis of AIDP, the most commonly one used is the AAN criteria (Table 1). The electrophysiological hallmarks of demyelination include prolonged distal latencies, slow conduction velocities, temporal dispersion, conduction block, and prolonged F-wave latencies.

Motor conduction studies

Slowing of nerve conduction may be preferentially localized to distal nerve segments, proximal nerve segments, or diffusely throughout the peripheral nervous system. I always perform F-wave studies in both the upper and lower limbs in patients suspected of having AIDP because of the early predilection for the proximal nerve segments and spinal roots. Prolonged or absent F-waves and H-reflexesare found in 80-90% of patients during the course of AIDP. It is also possible to demonstrate conduction block at the nerve root level by using nerve root stimulation techniques.

Research criteria for electrophysiological evidence of demyelination require only a 20% reduction in the CMAP amplitude or negative peak area between proximal and distal sites of

Table 1.
Electrodiagnostic medicine criteria forperipheral nerve demyelination*

I. Conduction Velocity Reduced in Two or More Nerves
1. If CMAP amplitude is > 80% of lower limit of normal (LLN) then the NCV must be < 80% of LLN.
2. If CMAP amplitude < 80% of LLN, then the NCV must be < 70% of LLN.

II. CMAP Conduction Block or Abnormal Temporal Dispersion in 1 or More Nerves
1. Regions to examine for these findings include:
   a. Peroneal nerve between fibular head and ankle
   b. Median nerve between wrist and elbow
   c. Ulnar nerve between wrist and below elbow

2. Partial Conduction Block Criteria
   a. CMAP duration difference between the above noted proximal and distal sites of stimulation must be < 15%; and
   b. A > 50% drop in CMAP negative spike duration, or baseline-to-peak amplitude.

3. Abnormal Temporal Dispersion and Possible Conduction Block
   a. CMAP duration difference between the above proximal and distal sites of stimulation is > 15%; and
   b. A > 20% drop in CMAP negative spike duration, or baseline-to-peak amplitude.

III. Prolonged Distal Motor Latencies (DML) in 2 or More Nerves
1. If CMAP amplitude is > 80% of the LLN; then the DML must be > 125% of the upper limit of normal (ULN).
2. If the CMAP is < 80% of the LLN, then the DML must be > 150% of the ULN.

IV. Prolonged Minimum F-Wave Latency or Absent F-Wave
1. F-waves performed in 2 or more nerves (10-15 trials)
2. If the CMAP amplitude is > 80% of the LLN, then the F-wave latency must be > 120% of the ULN.
3. If the CMAP amplitude is < 80% of the LLN, then the F-wave latency must be > 150% of the ULN.

*: Three of the four features must be present.46,245

stimulation as evidence of conduction block. However, other studies have employed stricter criteria (e.g., 30 or 40% reduction in CMAP amplitude or area) and computer simulation studies suggest a 50% drop in amplitude would be more appropriate for the electrophysiologic evidence of conduction block. Importantly, there must be less than a 15% increase in the negative peak duration when comparing the proximal to distal response to ensure that a reduction in amplitude is not a result of excessive temporal dispersion and phase cancellation producing pseudoconduction block. If there is found to be excessive temporal dispersion, it is difficult to state with assurance as to whether conduction block is present or not. True conduction block may occur without demyelination or prior to demyelination as a result of antibodies blocking ion channels at the nodes of Ranvier. It is conduction block of nerve impulses that result in actual weakness and sensory loss. Later, weakness and sensory loss may occur due to secondary axonal degeneration. Conduction block is noted in 74% of patients within the first two weeks. The smaller myelinated nerve fibers may be affected first by conduction block with the subsequent involvement of the larger fibers. Conduction block is often appreciated at common sites of entrapment or compression such as the carpal tunnel (median nerve), cubital tunnel (ulnar nerve), and fibular head (peroneal nerve). In patients with rapid recovery, particularly following plasmapheresis or intravenous immunoglobulin, the improved clinical status is likely a result of conduction block resolution rather than remyelination or regeneration of the axons.

Within the first week, motor conduction studies can be normal or show only minor abnormalities. The maximum degree of motor conduction abnormality occurs within tree to eight weeks with 80-90% of patients with AIDP having abnormalities in at least one of the motor nerve parameters (distal CMAP latency, F-wave latency, conduction velocity, conduction block) within five weeks of onset. Meulstee and colleagues applied the electrophysiological criteria for demyelination designed by Albers et al, Barohn et al, and Asbury and Cornblath to 135 patients with AIDP sequentially studied during the Dutch-GBS PE (plasma exchange) and IVIG trials. The sensitivity of the criteria for diagnosing demyelination ranged from 3 to 36% during the first study (performed at a median of 6 days, range 2-15 days after onset) to 13 to 46% during the third study (performed at a median of 34 days, range 29-49 days after onset).

It is difficult to state with certainty the most sensitive motor conduction parameter in confirming a diagnosis of AIDP because the specific nerves that were studied, the various motor conduction parameters, the timing of the studies in relationship to disease onset, and the definition of "abnormal" varied in the different published studies. Some have suggested that conduction block is the earliest recognizable electrophysiological abnormality in AIDP. However, Albers and colleagues found that prolonged distal latencies and diminished CMAP amplitude was the earliest abnormality. Within one week of symptoms, the mean distal CMAP amplitudes were reduced to approximately 50% of normal and declined further over the next several weeks. This is our experience as well. The North American Guillain-Barré Syndrome Study Group reported prolonged distal motor latencies and prolonged or absent F-waves as the earliest abnormal features-findings that reflect the early predilection for involvement of the proximal spinal roots and distal motor never terminals in AIDP. Slowing of conduction velocities, temporal dispersion of the CMAP waveforms, and conduction block become apparent later in the course. The motor conduction abnormalities remain at their nadir for approximately one month and then gradually improve over the next several weeks to months, but it may take a year or more for normalization. There is no correlation between the nerve conduction velocities or distal motor latencies and clinical severity of the neuropathy, although distal CMAP amplitudes less than 10-20% of normal are associated with a poorer prognosis.

Sensory conduction studies

Multiple sensory nerves should be examined in both the upper and lower limbs. Of note, upper limb SNAPs, particularly the median nerve, can be affected more severely and earlier than the sural SNAPs. The exact explanation is multifactorial. It has been suggested that recognized entrapment sites are more prone to being affected, accounting for slowing of the median SNAP across the carpal tunnel. In addition because AIDP is s multifocal demyelinating disorder rather than a length-dependent process typical of most axonal neuropathies the median SNAP may be affected prior to the sural SNAP.

About 40-60% of patients eventually demonstrate either amplitude reduction or slow conduction velocities. It can take about 4-6 weeks for SNAP abnormalities to peak, at which time significant and easily identifiable SNAP parameter alterations become obvious. The parameter most adversely affected is the SNAP amplitude, which is usually diminished or absent by the third or fourth week. Reduced SNAP amplitudes can be the result of secondary axonal degeneration, conduction block, or phase cancellation related to differential

demyelination and slowing of the sensory nerve fibers. Sensory conduction velocities can be slow and distal latencies prolonged.

Rarely, some persons may present with what appears to be pure sensory symptoms and signs, however, careful investigation may reveal subtle motor nerve conduction abnormalities. With a pure sensory presentation, other disorders (acute sensory neuronopathy or ganglionopathy) must be ruled out, and detailed neurophysiologic studies performed to attempt to detect subclinical motor abnormalities.

Needle electromyographic (EMG) examination

The earliest abnormality on EMG is a reduced recruitment of MUAPs. A reduced number of normal appearing MUAPs firing at rapid rates may be observed during low levels of force production particularly in clinically weak muscles. Spontaneous potentials in the form of positive sharp waves and fibrillation potentials may first be seen between weeks two and four peaking at about the six through 15 weeks with those potentials located in proximal muscles maximizing earlier than in distal muscles. Myokymia may be appreciated, especially in facial muscles.

Autonomic testing

Autonomic instability can be assessed by looking at heart rate variability with deep breathing or Valsalva maneuvers with about 35% of patients demonstrating an abnormality. Sympathetic skin response may be absent is has poor sensitivity.

Histopathology

Nerve biopsies are not routinely performed in cases suspected of having GBS. Nonetheless, studies have demonstrated that perivascular mononuclear cell infiltrate consisting of macrophages and lymphocytes may be seen on light microscopy. The entire peripheral motor and sensory nervous systems, including cranial nerves, may be involved from the most proximal aspects of the ventral and dorsal roots to the terminal regions of the intramuscular and sensory nerve fibers. There may be an initial preference for the nerve root region, areas where peripheral nerves are commonly entrapped (e.g. carpal and cubital tunnels), and the motor nerve terminals. The earliest pathophysiologic features are often appreciated at the nodes of Ranvier with loosened paranodal myelin and subsequent demyelination of the internodal segments. Monocellular infiltrates may be appreciated in areas of segmental demyelination. Polymorphonuclear cells, in addition to monocytes, may be associated with axonal degeneration in severe cases. During the recovery phase, remyelination is appreciated. Myelin thickness is reduced and the number of internodes is increased compared to normal peripheral nerve. Immunohistochemistry studies show increased expression of matrix metalloproteinases MMP-7 and MMP-9 around blood vessels in the epineurium and endoneurium. MMP-9 is also increased in the serum and levels correlate with the clinical severity in GBS. These matrix metalloproteinases are zinc-dependent endoproteinases, which may play a role in the inflammatory response in AIDP by digesting the basement membrane and disrupting the nerve-blood barrier.

Autopsy studies of patients in China who died early in the course of their illness have shed light on the pathology of GBS, including AIDP, AMSAN, and AMAN. In two patients who died at 7 and 9 days after onset of the neuropathy, autopsies revealed completely demyelinated peripheral nerves accompanied by extensive lymphocytic infiltrate. However, in a patient who died only 3 days after symptom onset, the peripheral nerves had only scant inflammatory infiltrate and just a few of the nerves were completely demyelinated. Markers of complement activation were demonstrated on the outermost surface of the Schwann cells and early vesicular changes in the myelin sheaths, beginning in the outer lamellae was appreciated on electron microscopy (EM).

Pathogenesis

A T-cell mediated process may play a role given the inflammation apparent in the nerves, markers of T-cell activation (e.g., soluble interleukin-2 receptor and interferon-γ) in the serum, and the resemblance to experimental allergic neuritis. The humoral arm of the immune system has been implicated by the demonstration of antiganglioside antibodies in may patients and the clinical improvement following plasmapheresis. Further, injection of serum from patients with AIDP into nerves of animal models induces complement-dependent demyelination and conduction block. Serum from 10 patients with GBS applied to mouse hemidiaphragm revealed depressed presynaptic transmitter release using a macro-patch-clamp technique, and in some cases, the activation of postsynaptic channels. The neuromuscular blockade was independent of complement and there was no link to the presence (in 6 patients) or absence (in four patients) of antibodies to GM1 or GQ1B.

The nature of the epitope is not known but probably is a glycolipid. Molecular similarity between the myelin epitope(s) and glycolipids expressed on *Campylobacter*, *Mycoplasma*, and

other infectious agents, which precede attacks of AIDP, may be the underlying trigger for the immune attack. Antibodies directed against these infectious agents may cross-react with specific antigens on the Schwann cell because of this molecular mimicry. These autoantibodies may bind to the Schwann cells and then activate the complement cascade leading to lysis of myelin sheaths. Inflammatory cells are subsequently recruited to complete the demyelinating process.

Treatment

Plasma Exchange (PE) and intravenous immunoglobulin (IVIG) are proven effective treatments of AIDP (Table 2).[Hughes 2003, 2004] In the North American Trial PE reduced the time

Table 2
Guillain Barré Syndrome: Plasmapheresis and IVIG Trials.

	Plasmapheresis Group	Control Group	IVIG Group
1. North American Trial			
number of patients	122	123	
time to improve 1 clinical grade	19 days	40 days	
time to walk unaided (all patients)	53 days	85 days	
time to walk unaided (ventilator patients)	97 days	169 days	
time on ventilator	9 days	23 days	
% improved at 1 month	59%	39%	
% improved at 6 months	97%	87%	
2. French Trial			
number of patients	109	111	
% of patients on ventilator after study	18 days	31 days	
time to wean from ventilator	70 days	111 days	
time to walk unaided	28 days	45 days	
time in hospital	21%	42%	
3. Dutch IVIG Trial			
number of patients	73		74
% of patients improving 1 clinical grade after 4 weeks	34%		53%
time to improve 1 clinical grade	41 days		27 days
time to Clinical Grade 2	69 days		55 days
ventilator dependent by week 2	42%		27%
number of multiple complications	16		5
4. PE/Sandglobulin Trial Group			
number of patients	121		130
mean change in clinical grade after 4 wks	0.9		0.8
time to wean from ventilator	29 days		26 days
time to walk unaided	49 days		51days
number of patients wks unable to walk after 48	19 (16.7%)		21 (16.5%)

North American Trial: Guillain- Barré Study Group: Plasmapheresis and acute Guillain-Barré syndrome. Neurology 1985;35:1096-1104.

French Trial: 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;22:753-761.

Dutch IVIG Trial: van der Meche' FGA, Schmidtz PIM, and the Dutch Guillain- Barré Study Group. A randomized trial comparing intravenous immunoglobulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992;326:1123-1129.

*Plasma Exchange / Plasma Exchange / Sandoglobulin Guillain-BarreSyndrome Trial Group. Sandoglobulin GBS Randomized trial of plasma exchange, intravenous immunoglobulin,Trial Groupand combined treatments in Guillain-Barré syndrome. Lancet 1997;349:225-230.

** This trial also had 128 patients randomized into a treatment group which received plasmaphesis (PE) followed by IVIG. There was no statistically significant improvement in any outcome measures in this group compared to the groups which received PE or IVIG alone.*

necessary to improve one clinical grade, time to walk unaided, time on a ventilator, and the percentages of patients improving after one and six months compared to the control group. The French Plasmapheresis Group confirmed that PE was efficacious in GBS. The exact mechanism is unclear but is likely that PE removes autoantibodies, immune complexes, complement, or other humoral factors involved in the pathogenesis of AIDP. The standard course of PE is 200 to 250 ml/kg of patient body weight over 10 to 14 days. Thus, a 70 kg patient would receive 14,000 to 17,500 mL (14 to 17.5 L) total exchange which can be accomplished by four to six alternate day exchanges of 2 to 4 liters each.

IVIG has replaced PE in most centers as the treatment of choice of AIDP. IVIG was shown to be at least as effective as PE in non-ambulatory adults treated within the first two weeks in a prospective trial (Table 2). Importantly, there is no added benefit of IVIG following PE and it certainly makes to sense to give IVIG and then perform PE. The dose of IVIG is 2.0 gm/kg body weight infused over two to five days. Randomized trials are needed to decide the effect of intravenous immunoglobulin in children, in adults with mild disease and in adults who start treatment after more than two weeks. IVIG may inhibit the binding of antiganglioside antibodies to their respective antigens, thereby preventing complement activation and subsequent pathophysiological effects.

Treatment with IVIG or PE should begin within the first seven to 10 days of symptoms. Improvement with PE and IVIG is often not immediate with the mean time to improvement of one clinical grade in the various controlled, randomized PE and IVIG studies ranging from six days to as long as 27 days. There is no evidence that PE beyond 250 mL/kg or IVIG greater than 2 gm/kg is of any added benefit in patients with AIDP and stable deficits. Further, as noted above, there is no indication for PE followed by IVIG or vice versa. However, as many as 10% of patients treated with either PE or IVIG develop a relapse following initial improvement. In patients who suffer such relapses, we give additional courses of PE or IVIG.

Unlike chronic inflammatory demyelinating polyneuropathy, corticosteroids do not appear beneficial in the treatment of GBS, and in fact, some patients have done worse. A small study of 25 patients treated with IVIG and intravenous methylprednisolone did better than a historical control group treated with IVIG alone. However, a much larger British study of 142 patients treated with methylprednisolone or placebo (approximately half the patients in each group were also treated with PE) failed to demonstrate the efficacy of corticosteroids. A double-blind, placebo-controlled randomized study of IVIG plus intravenous methylprednisolone compared to IVIG plus placebo in 233 patients with GBS revealed no significant difference between treatment with methylprednisolone and IVIG and IVIG alone. Thus, there is indication for supplemental corticosteroid use in patients with GBS. Also, a small double-blind, randomized, placebo-controlled safety trial of interferon beta 1a (IFN[beta]-1a) (Rebif) in 19 patients with GBS also treated with IVIG revealed no added benefit of IFN-Beta-1a.

Childhood AIDP

Children with AIDP have clinical, laboratory, and electrophysiologic findings in children similar to affected adults. An antecedent infection within two months of the attack is appreciated in approximately 75% of children have. Most children present with back and extremity pain. Generalized weakness including respiratory failure, sensory loss (including sensory ataxia, and autonomic dysfunction can develop. Laboratory evaluation is remarkable for an elevated CSF protein. Sural nerve biopsies in children with GBS demonstrate similar histopathological abnormalities as those described in adults.

In large series of children with AIDP, electrophysiological studies demonstrated prolonged or absent F-waves in 81-88% within the first few weeks of symptoms. Also, during these first two weeks, 83-100% of the children had reduced CMAP amplitudes and 22- 60% had mean CMAP amplitudes less than 20% of the lower limit of normal. In addition, temporal dispersion or conduction block of CMAPs was found in 61-74% of cases. Slow nerve conduction velocities was noted in two or more nerves in 48% of patients and in at least one nerve in 70-84% of individuals. Prolonged distal motor latencies were evident in at least one nerve in 57-75% of children. Abnormal SNAPs were reported in about 70% of patients with decreased or absent responses in 52-61% and prolonged distal latencies or slow conduction velocities in 9-54%. Needle electromyographic examination revealed fibrillation potentials and positive sharp waves in at least one muscle in 27% of children. Fortunately, the majority of children with AIDP demonstrate a satisfactory recovery, even those with significant reductions in CMAP amplitude. It is essential to look for ticks, particularly children, as tick paralysis can mimic GBS. Removal of the tick leads to improvement of strength and function.

AXONAL GBS: ACUTE AXONAL MOTOR-SENSORY NEUROPATHY (AMSAN)

Clinical Features

Feasby and colleagues were the first to detail an axonal variant of GBS in 1986. Initially, the

existence of an axonal variant was met with early skepticism, however, subsequent autopsy studies confirmed that AMSAN is a real disease entity. Clinically and often by early electrodiagnostic studies, patients with AMSAN are indistinguishable from those with AIDP. Usually, sensory symptoms are begin in the hands or feet and later progress. Sensation to all modalities are reduced and complete areflexia is usually evident. Patients with AMSAN develop rapidly progressive and severe generalized weakness over only a few days, as opposed to progression over a couple of weeks in most patients with AIDP. Ophthalmoplegia may , dysphagia, and respiratory muscle weakness can occur. Blood pressure instability and cardiac arrhythmias may complicated AMSAN as well. Recovery of strength and function is slow and often incomplete compared to AIDP. Only a few children have been reported with AMSAN and there is some suggestion that the prognosis is better than in adults.

Laboratory features

Albuminocytologic dissociation of the CSF protein is usually seen. Evidence of a recent infection with *Campylobacter jejuni* and antibodies directed against anti-nerve gangliosides, particularly GM1 antibodies, are demonstrated in many patients with AMSAN. Some have suggested that *Campylobacter jejuni* infection and GM1 antibodies are more commonly associated with axonal forms of GBS (i.e., AMSAN and AMAN) and poorer prognosis, but this is controversial. Some patients with antecedent *Campylobacter jejuni* infection and GM1 antibodies have typical AIDP and a good recovery.

Electrophysiologic Findings

Nerve conduction studies reveal markedly diminished amplitudes or absent CMAPs and SNAPs within 7-10 days of onset. As discussed in the AIDP section, low amplitude CMAPs are one of the earliest electrophysiological abnormalities noted in AIDP, thus, low amplitude CMAPs does not necessarily imply axonal degeneration. Distal conduction block with or without demyelination also leads to low amplitude distal CMAPs. Initially if is often impossible, to distinguish AIDP from AMSAN by nerve conduction studies, however, serial nerve conduction studies may be helpful. Most patients with AIDP will eventually develop other features of demyelination (e.g., significantly prolonged distal latencies and f-wave latencies, slow CVs, more proximal conduction block or temporal dispersion). The distal latencies of the CMAPs and the nerve conduction velocities, when obtainable, should be normal or only mildly affected in AMSAN. Needle EMG demonstrates markedly abnormal reductions in recruitment. Several weeks after the presentation of major motor weakness, abundant fibrillation potentials and positive sharp waves can be detected in most muscles, especially those located in the distal regions of the limbs.

Histopathology

Nerve biopsy performed early in the course of the disorder is the only way to differentiate "axonal" GBS from "pseudoaxonal" GBS because of their clinical, laboratory, and electro-physiological similarities; however, this is rarely indicated in clinical practice. Nerves biopsied late in the disease course of AIDP oar AMSAN may show axonal degeneration and it can be difficult to distinguish a primary axonopathy from secondary axonal degeneration. Sensory and motor nerve biopsies in several patients with inexcitable motor and sensory conduction studies revealed severe demyelination rather than primary axonal degeneration. Nevertheless, some patients with inexcitable CMAPs and SNAPs have features that suggest a primary axonal insult. Unlike AIDP, demyelination and lymphocytic infiltrates are absent or only minimally present on nerve biopsy or at autopsy in patients with AMSAN; rather, prominent axonal degeneration affecting the ventral and dorsal roots and the peripheral nerves is appreciated. As many as 80% of teased fibers reveal axonal degeneration, while demyelinating features are rare. A marked loss of both myelinated and unmyelinated axons is evident. Griffin and colleagues reported the autopsies of three patients with AMSAN who died early in the course of their illness demonstrated prominent axonal degeneration of the spinal roots and peripheral nerves without demyelination or significant inflammation. Numerous macrophages were present in the periaxonal space of myelinated internode as were rare intraaxonal macrophages. Similar histological abnormalities are seen in AMAN but are not typically noted in AIDP. An autopsy on another patient with AMSAN demonstrated inflammatory cell infiltrates comprising lymphocytes and macrophages in the spinal cord.

Pathogenesis

The pathogenic basis of AMSAN is unknown but is most likely do to an immune-mediated attack directed against epitopes on the axon. AMSAN often follows *Campylobacter jejuni* infection and may lead to the production of the antiganglioside antibodies (e.g., GM1 or GM1a). These gangliosides are present on the nodal axolemma and may be the target of the immune attack due to molecular mimicry. Early in the

course or with mild disease, binding of the antibodies to neural epitopes may result in only physiological conduction block. However, complement activation on nodal and later internodal axolemma and recruitment of macrophages could result in axonal degeneration.

Treatment

There have been prospective treatment studies specifically for AMSAN, however we treat patients with IVIG or plasma exchange.

ACUTE MOTOR AXONAL NEUROPATHY (AMAN)

Epidemiology

McKhann and colleagues initially described this variant in patients with seasonal outbreaks of acute flaccid paralysis in northern China. They initially named the disorder the "Chinese paralytic syndrome" but because similar cases subsequently were described throughout the world, the term "acute motor axonal neuropathy (AMAN)" is more appropriate. In northern China, AMAN is the most common variant of GBS and although it is less frequent in other areas of the world, AMAN is still quite common. In this regard, 27 of the 147 (18%) of the patients enrolled in the Dutch GBS trial comparing IVIG to PE were later classified as having AMAN. An antecedent illness occurs in 30 to 85% of patients with AMAN- most often a gastrointestinal infection. In addition, 67 to 92% of patients have serologic evidence of a recent *Campylobacter jejuni* infection.

Clinical features

AMAN occurs in children and adults and similar to AMSAN, it presents as an abrupt onset of generalized weakness. The distal muscles are often more severely affected than proximal limb muscles, while cranial nerve deficits and respiratory failure requiring mechanical ventilation can be seen in up to one-third of patients. Unlike AIDP and AMAN, there are no sensory signs or symptoms. However, autonomic dysfunction (e.g., cardiac arrhythmias, blood pressure fluctuations, and hyperhidrosis) may occur. Deep tendon reflexes may be normal or absent, but of note some patients develop hyperactive reflexes during the recovery period. The median time of recovery is similar to that seen in typical AIDP and they generally make a good recovery within one year, but residual distal limb weakness is common. The mortality rate is less than 5%. Second attacks of the illness have been described in northern Chinese patients, but the actual recurrence rate is not known.

Laboratory features

As with AIDP and AMSAN, albuminocytological dissociation in the CSF is seen and the absence of prominent CSF pleocytosis helps distinguish AMAN from poliomyelitis, which it would otherwise mimic. Serology evidence of recent *Campylobacter jejuni* infection and anti-GM1 and anti-GD1a antibodies are commonly detected in patients with AMAN are demonstrated the majority of patients.

Electrophysiological findings

NCS reveal low amplitude or unobtainable CMAPs with normal SNAPs. When CMAPs are obtained, the distal latencies and conduction velocities are normal as are F-waves when unobtainable. The decreased CMAP amplitudes may be a reflection of distal conduction block, degeneration only of the distal motor nerve terminal, or widespread axonal degeneration. Rare cases of proximal conduction block without other features of demyelination have also been reported. EMG reveals fibrillation potentials and positive sharp waves and decreased recruitment of MUAPs. Autonomic studies are relatively spared in AMAN compared to AIDP.

Histopathology

The earliest histological abnormalities abnormality is lengthening of the nodal gaps. Immunocytochemistry reveals deposition of IgG and complement activation products (i.e., C3d and C5b-9) on the nodal and internodal axolemma of motor fibers that axonal degeneration. In contrast, there is early deposition of immunoglobulin and complement on Schwann cells rather than the axons in AIDP. Macrophages are recruited into the affected nodes of Ranvier and periaxonal space via complement-derived chemotropic factors. The macrophages migrate through the Schwann cell basal lamina into the nodal gap where they dissect beneath the myelin sheath into the periaxonal space. As they enter the perixonal space, the axon retracts away from the adaxonal Schwann cell. In severe cases, the axons then begin to degenerate but the innermost myelin sheath (adaxonal lamella) appears intact. Active degeneration and severe loss of large myelinated intramuscular nerve fibers can also be demonstrated on motor point biopsy. An autopsy on a patient with AMAN demonstrated inflammatory cell infiltrates comprising lymphocytes and macrophages in the spinal cord.

Pathogenesis

AMAN is most likely caused by an immune-mediated attack against an unknown epitope(s) on the nodal axolemma. Perhaps the antibodies are directed against GM1 or GD1a gangliosides that cross-

react with the lipopolysaccaride membrane of *Campylobacter*. The binding of antibodies to the nodal axolemma may decrease the sodium current or increase the potassium current, thereby resulting in conduction block. Experimental studies demonstrate that GBS sera containing anti-ganglioside cause neuronal cell lysis by targeting specific cell surface gangliosides, and secondly, that this cell lysis is complement dependent. The GD1a cell membrane pool appeared to be more susceptible to anti-ganglioside antibody-mediated injury than the GM1 pool. Of note, IVIG significantly decreased this complement-dependent cytotoxicity.

Treatment

There have not been any treatment trials devoted to AMAN, although 27 of the 147 (18%) of the patients enrolled in the Dutch GBS trial comparing IVIG to PE were later classified as having AMAN. Subgroup analysis of the AMAN group suggested that the IVIG-treated patients may recovery faster than PE-treated patients. However, there was no significant difference in outcome regardless of treatment (IVIG, PE, or PE followed by IVIG) between AIDP and AMAN in a subgroup analysis of 369 patients.

OTHER GBS VARIANTS

Besides AMSAN and AMAN, there are several other variants of GBS including the Miller Fisher syndrome (comprised of ataxia, areflexia, and ophthalmoplegia), idiopathic cranial polyneuropathy, pharyngeal-cervical-brachial weakness with or without ophthalmoparesis, and paraparetic weakness. These disorders may represent oligosymptomatic or forme-fruste of AIDP. Of these possible GBS variants, the Miller Fisher syndrome is best characterized. Other disorders that might be considered variants of GBS include acute sensory ganglionopathies and acute autonomic neuropathies.

MILLER FISHER SYNDROME

Clinical features

Miller Fisher syndrome is characterized by ataxia, areflexia, and ophthalmoplegia in 1956. 96,418,1115 Hung 2004 The mean age of onset is in the early 40s, but it can occur in children. There is a 2:1 male predominance. As with other forms of GBS an antecedent infection is common occurring in over two-thirds of the cases. Double vision is the usually the earliest symptom (39%), followed by unsteadiness and incoordination due to a sensory ataxia (21%). Asymmetric oculomotor weakness may be seen but this often progresses to complete ophthalomoplegia. Ptosis also occurs but pupillary involvement is uncommon. Other cranial nerves are also affected with facial weakness evident in 57%, dysphagia in 40%, and dysarthria in 13% patients. Approximately 50% of the patients complain of paresthesias of the face and distal limbs during the course and areflexia is evident on examination in over 80%. Mild proximal limb weakness may develop in approximately one-third of cases and some patient's progress to develop severe generalized weakness similar to typical AIDP. Recovery usually begins within about 2 weeks following the onset of symptoms and a full return of function is usually seen within 3-5 months.

Laboratory features

CSF protein is usually elevated without significant pleocytosis. Serological evidence of recent infection by *Campylobacter jejuni* and antiganglioside antibodies, in particular anti-GQ1b, are evident in many patients. A large study of 123 patients with MFS demonstrated CSF albuminocytological dissociation in 59% of patients during the first 3 weeks of illness, while serum anti-GQ1b IgG antibody was positive in 85%. While the incidence of CSF albuminocytological dissociation increased from the first to second weeks, anti-GQ1b IgG antibody peaked in the first week.

Histopathology

Nerve biopsy and autopsy data are limited and need to be viewed cautiously as some of the cases began with ophthalmoplegia, ataxia, and areflexia but later evolved to severe quadriparesis characteristic of more typical AIDP. The brainstem appeared normal or revealed only secondary chromatolysis of the oculomotor, trochlear, or abducens nuclei. Demyelination and mild inflammatory infiltrates were noted along the course of these cranial nerves and in the sensory ganglia of peripheral nerves.

Pathogenesis

The pathogenic basis for the disorder is not known, although it is likely autoimmune with preferential early attack directed against the sensory ganglia and oculomotor fibers. Recent antecedent infections (e.g., *Campylobacter jejuni*,) suggest autoantibodies directed against these infectious agents cross-react with neuronal epitopes (e.g, GQ1b). In this regard, oculomotor fibers and the sensory ganglion are enriched in GQ1b and antibodies directed against this protein are detected in most patients with MFS. Immunohistochemistry studies reveal anti-GQ1b antibodies stain sensory neurons in the dorsal root as well as cerebellar

nuclei. In mice infused with serum from patients with MFS, the GQ1b antibodies also bind to neuromuscular junctions and in a complement-dependent process, this resulted in massive quantal release of acetylcholine from nerve terminals and eventually blocked neuromuscular transmission.

Electrophysiological findings

NCS reveal reduced amplitudes of SNAPs out of proportion to any prolongation of the distal latencies or slowing of sensory conduction velocities. CMAPs in the arms and legs are usually normal. However, mild to moderate reduction of facial CMAPs amplitudes is evident in over 50% of patients with MFS. A loss or mild delay of R1 and R2 responses may be appreciated on blink reflex testing.

Treatment

There are no controlled treatment trials of patients with MFS, although we treat patients with either IVIG or PE IVIG inhibits the binding of anti-GQ1b antibodies to GQ1b, thereby preventing complement activation and subsequent pathophysiological effects in ex vivo mouse models suggesting that it might be beneficial (Jacobs 2003).

IDIOPATHIC SENSORY NEURONOPATHY / GANGLIONOPATHY

Background

This disorder is believed to be caused by an autoimmune attack directed against the dorsal root ganglia, The differential diagnosis of sensory neuronopathy includes a paraneoplastic syndrome, which is typically associated with anti-Hu antibodies, and a sensory ganglionitis related to Sjögren's syndrome. Certain medications or toxins, infectious agents, and other systemic disorders are also associated with a sensory neuronopathy. Despite extensive evaluation, many cases of sensory neuronopathy have no clear etiology, so-called idiopathic sensory neuronopathy. The acute cases may represent a variant of GBS, although the onset can be insidiously progressive as well.

Clinical features

Idiopathic sensory neuronopathy is a rare disorder that usually presents in adulthood (mean age of onset 49 years with range 18-81 years) and has a slight female predominance. Symptoms can develop over a few hours or evolve more insidiously over several months or years and the course can be monophasic with a stable or remitting deficit, chronic progressive, or chronic relapsing. Unlike typical GBS, only a few patients report a recent antecedent infection. The presenting complaint is numbness and tingling face, trunk, or limbs which can be painful. Symptoms begin asymmetrically and in the upper limbs in nearly half the patients suggestive of a ganglionopathy as opposed to a length-dependent process. Usually, the sensory symptoms become generalized, but they can remain asymmetric. Patients also describe clumsiness of the hands and gait instability.

On examination, marked reduction in vibration and proprioception are found, while pain and temperature sensations are less affected. Manual muscle testing is usually normal. Some muscle groups may appear weak, but this is usually secondary to impaired modulation of motor activity due to the proprioceptive defect. Most patients have sensory ataxia, which can be readily demonstrated by having the patient perform the finger-nose-finger test with their eyes open and then closed. Patients may have only mild dysmetria with their eyes open, but when their eyes are closed, they consistently miss their nose and the examiner's stationed finger. Pseudo-athetoid movements of the extremities may also be appreciated. Patients exhibit a positive Romberg sign and, not surprising, describe more gait instability in the dark. Deep tendon reflexes are decreased or absent, while plantar reflexes are flexor.

Idiopathic sensory neuropathy is a diagnosis of exclusion. A detailed history and examination is essential to exclude a toxin-induced neuronopathy, paraneoplastic syndrome, or disorder related to a connective tissue disease (i.e., Sjögren's syndrome). Importantly, the sensory neuronopathy can precede the onset of malignancy or SICCA symptoms (i.e., dry eyes and mouth), therefore these disorder should always be kept in mind. Pertinent laboratory and malignancy work-up should ordered. We refer patients to ophthalmology for Rose Bengal stain and a Schirmer's test. A lip or parotid gland biopsy is obtained in all suspected patients. Subacute sensory neuronopathy has also been associated with recent Epstein-Barr virus infection.

Laboratory features

The CSF protein is normal or only slightly elevated in most patients. However, the CSF protein can be markedly elevated (reportedly as high as 300 mg/dl) when examined within a few days in cases with a hyperacute onset. Only rare patients exhibit CSF pleocytosis. MRI scan can reveal gadolinium enhancement of the posterior spinal roots or increased signal abnormalities on T-2 weighted images in the posterior columns of the spinal cord. Some patients have a monoclonal gammopathy (IgM, IgG, or IgA). Antiganglioside antibodies, particularly anti-GD1b antibodies, have been demonstrated in some cases

of idiopathic sensory neuronopathy associated with IgM monoclonal gammopathy.

Antineuronal nuclear antibodies (e.g., anti-Hu antibodies) should be assayed in all individuals with sensory neuronopathy to evaluate for a paraneoplastic syndrome. Likewise, antinuclear, SS-A, and SS-B antibodies should be ordered to look for evidence of Sjögren's syndrome, which can also present with a sensory neuronopathy.

Histopathology

Sensory nerve biopsies may reveal a preferential loss of large myelinated fibers compared to small myelinated fibers or similar loss of both large and small diameter nerve fibers. Mild perivascular inflammation may be seen but prominent endoneurial infiltrate is not appreciated. There is no evidence of segmental demyelination.

An autopsy performed five weeks after onset of idiopathic sensory neuronopathy in one man revealed widespread inflammation involving sensory and autonomic ganglia with loss of associated neurons and Wallerian degeneration of the posterior nerve roots and dorsal columns was evident.536 The motor neurons and roots appeared normal. Immunohistochemical analysis suggested a CD8+ T cell-mediated cytotoxic attack against the ganglion neurons.

Pathogenesis

Autoimmune sensory neuronopathies are caused by an autoimmune attack directed against the dorsal root ganglia. Serum from affected patients immunostain dorsal root ganglia cells in culture and inhibit neurite The neuronal epitope is unknown, but the ganglioside GD1b has been hypothesized to be the target antigen. GD1b localizes to neurons in the dorsal root ganglia and antibodies directed against this ganglioside have been detected in some patients with idiopathic sensory neuronopathy. Further, rabbits immunized with purified GD1b develop ataxic sensory neuropathy with loss of the cell bodies in the dorsal root ganglia and axonal degeneration of the dorsal column of the spinal cord without demyelination or an inflammatory infiltrate.

Electrophysiologic findings

The most prominent NCS abnormality is absent or low amplitudes SNAPs. When SNAPs are obtainable, the distal sensory latencies and nerve conduction velocities are normal or only mildly abnormal. In contrast, Motor nerve conduction studies are either normal or reveal only mild abnormalities. In addition, H-reflexes and blink reflexes typically may unobtainable. An abnormal blink reflex favors a non-paraneoplastic etiology for a sensory neuronopathy, but does not exclude an underlying malignancy. The masseter reflex or jaw jerk is abnormal in patients with sensory neuropathy but is usually preserved in patients with sensory neuronopathy. This is because the masseter reflex is unique amongst the stretch reflexes in that the cell bodies of the afferent limb lie in the mesencephalic nucleus within the CNS. This differs from the sensory cell bodies innervating the limbs, which reside in the dorsal root ganglia of the PNS. The afferent cell bodies lie in the Gasserian ganglia that is outside the CNS, which explains why the blink reflex can be impaired in sensory ganglionopathies.

Treatment

Various modes of immunotherapy have been tried including corticosteroids, PE, and IVIG.[However, there have been no prospective, double-blinded, placebo-controlled trials. Occasionally, patients appear to improve with therapy, however some improve spontaneously and many stabilize without treatment. In our experience, most patients have not experienced a dramatic improvement following treatment, Perhaps, this is because once the cell body of the sensory neuron is destroyed, it will not regenerate. However, in patients seen in the acute setting or those who have a chronic progressive deficit, a trial of immunotherapy may be warranted.

Acute Small Fiber Sensory Neuropathy
Clinical features

Small fiber neuropathies typically present insidious with slowly progressive burning pain and paresthesia in the legs that may later involve the arms. Most are idiopathic in nature but diabetes mellitus, amyloidosis, Sjorgrens' syndrome, and hereditary sensory and autonomic neuropathy need to be excluded. Rarely, patients present acutely with symptoms suggestive of a small fiber neuropathy. An antecedent infection is common. neurological examination disclosed normal muscle strength, symmetric glove and stocking type sensory loss for pain and temperature, normal proprioception, and vibration senses with normal or brisk tendon reflexes. The burning dysesthesia usually disappear within 4 months, however, the numbness and objective sensory loss tended to persist longer.

Laboratory features

CSF examination may reveal albuminocytological dissociation.

Electrodiagnostic studies

Routine motor and sensory conduction studies that primarily assess large fiber function are normal. Autonomic testing may be abnormal.

Histopathology

No nerve biopsy data has been reported in these

Pathogenesis

The acute clinical presentation often following an infection and CSF findings suggest that this is a rare variant of GBS.

Treatment

A trial of IVIG would seem warranted in patients who present in the acute phase of the illness.

AUTOIMMUNE AUTONOMIC NEUROPATHY

Clinical features

Young et al were the first to report a detailed clinical, laboratory, and histological description of a patient with acute pandysautonomia. Subsequently, there have been a number of small reports of idiopathic autonomic neuropathy. Many of these cases are presumed to have an autoimmune basis. This is a heterogeneic neuropathy in terms of onset, the type of autonomic deficits, the presence or absence of somatic involvement, and the degree of recovery. A Mayo Clinic series of 27 cases of idiopathic autonomic neuropathy followed for a mean of 32 months found approximately 20% of patients had selective cholinergic dysfunction, while 80% had various degrees of widespread sympathetic and parasympathetic dysfunction. The most common symptom is orthostatic dizziness or lightheadedness occurring in about 80% of patients. Gastrointestinal involvement is present in over 70% with patients complaining of nausea, vomiting, diarrhea, constipation, ileus, or postprandial bloating. Heat intolerance and poor sweating is also present in the majority of patients. Blurred vision, dry eyes and mouth, urinary retention or incontinence, and impotence are common. Numbness, tingling, and dysesthesia of the distal extremities are evident in about 30% of patients, but muscle strength is normal. Most patients have a monopathic course with progression followed by a plateau and slow recovery or a stable deficit. Although some patients exhibit a complete recovery, it tends to be incomplete in most.

Laboratory features

The CSF often reveals slightly elevated protein without pleocytosis. Supine plasma norepinephrine levels are not different, but standing levels are significantly reduced, when compared to normal controls. In a large study of patients with idiopathic autonomic neuropathy 18/106 (18 %) had high levels of ganglionic acetylcholine receptor (AChR) autoantibodies. The seropositive group had a significant overrepresentation of abnormal pupillary responses, sicca complex, and lower gastrointestinal tract dysautonomia. A subacute mode of onset was more common in the seropositive group. Rabbits immunized with a neuronal AChR alpha3 subunit fusion protein produce ganglionic AChR antibodies and develop autonomic failure. Immunohistochemical staining of superior cervical ganglia and myenteric plexus neurons reveals intact presynaptic nerve terminals and postsynaptic neurons containing cytoplasmic nAChR, but lacking surface AChR.

Electrophysiologic findings

Routine motor and sensory nerve conduction studies and electromyography are usually unremarkable. Quantitative sensory testing may reveal abnormalities in thermal thresholds. Autonomic testing can be helpful . Orthostatic hypotension and reduced variability of the heart rate on deep breathing are evident in over 60% of affected individuals. An abnormal response to valsalva maneuver (i.e., exaggerated fall in blood pressure during early phase II of the response, absent recovery of systolic and diastolic blood pressure during late phase II, or reduced or absent overshoot of systolic and diastolic pressures during phase IV) has been demonstrated in over 40% of patients. Sympathetic skin response may be absent.

Abnormal quantitative sudomotor axon reflex test (QSART) scores are seen in 85% of patients. Most patients have abnormal thermoregulatory sweat tests with areas of anhidrosis in 12-97% of the body. Gastrointestinal studies may reveal hypomotility anywhere from the esophagus to the rectum.

Histopathology

Nerve biopsies reveal reduced density of mainly small diameter myelinated nerve fibers along with stacks of empty Schwann cell profiles and collagen pockets. Scant epineurial perivascular inflammation may be seen.

Pathogenenesis

The disorder is suspected to be the result of an autoimmune attack directed against peripheral autonomic fibers or the ganglia. A subset of patients may have antibodies directed against calcium channels, which are present on presynaptic autonomic nerve terminals.

Treatment

PE, prednisone, IVIG and other immunosuppressive agents have been tried with variable success. The most important aspect of management is supportive therapy for orthostatic hypotension

and bowel and bladder symptoms. Fluodrocortisone is effective at increasing plasma volume but is administered only in the morning or in the morning and at lunch to avoid nocturnal hypertension. We begin treatment at 0.1 mg per day and increase by 0.1 mg every 3-4 days until the blood pressure is controlled. Midodrine, a peripheral a1 adrenergic agonist, is also effective and can be used in combination with fluodrocortisone. Midodrine is started at 2.5 mg per day and can be gradually increased to 40 mg per day in divided doses (every 2 to 4 hours) as necessary. Gastrointestinal hypomotility can be treated with metaclopramide, cisapride, or erythromycin. Bulking agents, laxatives, and enemas may be need in patients with constipation. Urology should be consulted in patients with neurogenic bladders. Patient may require cholinergic agonists (e.g., bethanechol), intermittent self-catheterization, or other modes of therapy.

REFERENCES

Modified with permission from: Amato AA, Dumitru D. Acquired Neuropathies. In: Dumitru D, Amato AA, Swartz MJ (Eds.). Electrodiagnostic Medicine. 2nd Ed. Philadelphia: Hanley & Belfus, Inc.; 2002, p. 937-1041.

Bril V, Ilse WK, Pearse R, et al. Pilot trial of immunoglobulin versus plasma exchange in patients with Guillain-Barré syndrome. Neurology 1996; 46: 100-3.

Castro LHM, Ropper AH. Human immune globulin infusion in Guillain-Barré syndrome: worsening during and after treatment. Neurology 1993; 43: 1034-6.

Cornblath DR, Mellits ED, Griffin JW, et al. Motor conduction studies in Guillain-Barré syndrome: Description and prognostic value. Ann Neurol 1988; 23: 354-9.

Cornblath DR. Electrophysiology in Guillain-Barré syndrome. Ann Neurol 1990; 27(Suppl): S17-S20.

Dalakas MC. Autoimmune ataxic neuropathies (sensory ganglinopathies): are glycolipids the responsible autoantigens? Ann Neurol 1996; 39: 419-42.

Dutch Guillain-Barré Study Group. Treatment of Guillain-Barré syndrome with high-dose immune globulins combined with methylprednisolone: a pilot study. Ann Neurol 1994; 35: 749-52.

Feasby TE, Gilbert JJ, Brown WF, et al. An acute axonal form of Guillain-Barré polyneuropathy. Brain 1986; 109: 1115-26.

Feasby TE, Hahn A, Brown W, Bolton CF, Gilbert JJ, Koopman WJ. Severe axonal degeneration in acute Guillain-Barré syndrome: evidence of two different mechanism? J Neurol Sci 1993; 116: 185-92.

Feasby TE, Hughes RAC. Campylobacter jejuni*, antigangliosides antibodies, and Guillain-Barré syndrome. Neurology 1998; 51: 340-2.*

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.

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

Griffin JW, Li CY, Ho TW, et al. Guillain-Barré syndrome in northern China: The spectrum of neuropathologic changes in clinically defined cases. Brain 1995; 118: 577-95.

Griffin JW, Li CY, Ho TW, et al. Pathology of the motor-sensory axonal Guillain-Barré syndrome. Ann Neurol 1996; 39: 17-28.

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

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

Guillain G, Barré JA, Strohl A. Sur un syndrome de radiculo-nevrite avec hyper albiminose du loquide cephalo-rachiden sas reaction cellulaire. Remarques sur les caracteres cliniques et graphiques des reflexes tendeneux. Bulletins et memories de la societe medicale des hospitaux de Paris. Masson et Cie 1916; 40: 1462-70.

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

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

Hartung HP, Pollard JD, Harvey GK, Toyka KV. Immunopathogenesis and treatment of the Guillain-Barré syndrome. Part I. Muscle Nerve 1995; 18: 137-53.

Hartung HP, Pollard JD, Harvey GK, Toyka KV. Immunopathogenesis and treatment of the Guillain-Barré syndrome. Part II. Muscle Nerve 1995; 18: 154-64.

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

Irani DN, Cornblath DR, Chaudry V, Borel C, Hanley DF. Relapse in Guillain-Barré syndrome after treatment with human immune globulin. Neurology 1993; 43: 1034-6.

Jackson CE, Barohn RJ, Mendell JR. Acute paralytic syndrome in three American men. Arch Neurol 1993; 50: 732-5.

Low PA, Dyck PJ, Lambert EH, et al. Acute pandysautonomic neuropathy. Ann Neurol 1983; 13: 412-17.

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: 347-53.

McKhann GM, Cornblath DR, Ho TW, et al. Clinical and electrophysiological aspects of acute paralytic disease of children and young adults in northern China. Lancet 1991; 338: 593-7.

McKhann GM, Cornblath DR, Griffin JW, et al. Acute motor axonal neuropathy in northern China: The spectrum of neuropathologic changes in clinically defined cases. Brain 1995; 118: 577-95.

Mericle RA, Triggs WJ. Treatment of acute pandysautonomia with intravenous immunoglobulin. J Neurol Neurosurg Psychiatry 1997; 62: 529-31.

Meulstee J, van der Meche', the Dutch Guillain-Barré Study Group. J Neurol Neurosurg Psychiatry 1995; 59: 482-6.

Miller RG, Peterson GW, Daube JR, et al. Prognostic value of electrodiagnosis in Guillain-Barré syndrome. Muscle Nerve 1988; 11: 769-74.

Plasma Exchange/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.

Smith AA, Vermeulen M, Koelman J, Wielman J, Wieling W. Unusual recovery from acute pandysautonomia after immunoglobulin therapy. Mayo Clin Proc 1997; 72: 333-5.

van der Meche' FGA, Schmidtz PIM, the Dutch Guillain- Barré Study Group. A randomized trial comparing intravenous immunoglobulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992; 326: 1123-9.

van Koningsveld R, Schmitz PI, Meche FG, Visser LH, Meulstee J, van Doorn PA. Dutch GBS study group. Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barre syndrome: randomised trial. Lancet 2004; 363(9404): 192-6.

Van den Bergh PY, Pieret F. Electrodiagnostic criteria for acute and chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 2004; 29(4): 565-74.

Hung PL, Chang WN, Huang LT, Huang SC, Chang YC, Chang CJ, Chang CS, Wang KW, Cheng BC, Chang HW, Lu CH. A clinical and electrophysiologic survey of childhood Guillain-Barre syndrome. Pediatric Neurology 2004; 30(2): 86-91.

Hughes RA, Wijdicks EF, Barohn R, Benson E, Cornblath DR, Hahn AF, Meythaler JM, Miller RG, Sladky JT, Stevens JC. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: immunotherapy for Guillain-Barre syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2003; 61(6): 736-40.

Pritchard J, Gray IA, Idrissova ZR, Lecky BR, Sutton IJ, Swan AV, Willison HJ, Winer JB, Hughes RA. A randomized controlled trial of recombinant interferon-beta 1a in Guillain-Barre syndrome. Neurology 2003; 61(9): 1282-4.

Tekgul H, Serdaroglu G, Tutuncuoglu S. Outcome of axonal and demyelinating forms of Guillain-Barre syndrome in children. Ped Neurol 2003; 28(4): 295-9.

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.

Kwa MS, van Schaik IN, De Jonge RR, Brand A, Kalaydjieva L, van Belzen N, Vermeulen M, Baas F. Autoimmunoreactivity to Schwann cells in patients with inflammatory neuropathies. Brain 2003; 126: 361-75.

Seneviratne U, Gunasekera S. Acute small fiber sensory neuropathy: another variant of Guillain-Barre syndrome? J Neurol Neurosurg Psychiatry 202; 72: 540-2.