

# Inflammatory Neuropathies

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We discuss two of the most common of the acquired inflammatory neuropathies: Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy, as well as their variants. We review their clinical presentation, electrophysiologic findings, and management, highlighting knowledge gained from the recent literature. Unfortunately, although treatments exist for both Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy, none are completely curative and all have significant potential side effects and/or expense. Better understanding of the underlying pathophysiology of these diseases is needed in order to develop more targeted therapies.

## Introduction

The acquired demyelinating neuropathies are an important cause of weakness and disability seen by neurologists. In contrast to many of the other neuropathies, they are treatable but also potentially life-threatening if not recognized and managed appropriately. The diagnosis of Guillain-Barre syndrome (GBS) usually becomes apparent shortly after the onset of symptoms. However, chronic inflammatory demyelinating polyneuropathy (CIDP) can be much more difficult to diagnose, as there is no simple diagnostic test and many patients do not meet all of the classically described criteria. Unfortunately, treatment, particularly for CIDP, involves the use of immunosuppressant medications with all their attendant side effects. Thus, anxiety about missing a potentially treatable diagnosis must be tempered with the risk of overdiagnosis. In some variants of CIDP (*ie*, those associated with an IgM monoclonal gammopathy), response to treatment is poor, and in these cases the risks of unproven immunosuppressive treatments must be seriously considered. We describe the various clinical presentations of the acquired demyelinating neuropathies and review the current knowledge with regard to therapy.

## Guillain-Barre Syndrome

### Epidemiology

Guillain-Barre syndrome is the most common cause of acute generalized weakness, with an annual incidence of 1 to 4 per 100,000 of population. It can occur at any age and is slightly more prevalent in men. Approximately two thirds of GBS patients report a preceding viral or bacterial illness. In most cases, the infectious agent is never identified. Of the identified antecedent pathogens, *Campylobacter jejuni* is most common [1,2]. Cytomegalovirus, Epstein-Barr virus, and *Mycoplasma pneumoniae* are other commonly identified antecedent pathogens [1,2]. There also appears to be an association with HIV infection. Although common teaching is that GBS has a predilection for occurring at the time of human immunodeficiency virus (HIV) seroconversion, it can in fact occur at any stage of the disease. A mild cerebrospinal fluid (CSF) pleocytosis should alert one to the possibility of concurrent HIV infection; however, in most HIV-associated cases, no pleocytosis is found [3]. GBS has also been associated with bone marrow transplants, leukemia, and lymphoma [4]. Many other identified pathogens have been reported as antecedents to GBS; however, in most cases these are anecdotal reports or small series without statistically valid evidence.

The link between vaccination and GBS remains controversial. A small increased risk of developing GBS was identified following immunization with the swine-flu influenza vaccine in 1976 and 1977. However, an epidemiologic study evaluating the risk of influenza vaccine-associated GBS in subsequent years showed a risk of slightly more than one additional case of GBS per million persons vaccinated [5]. Also controversial is the role of vaccination in persons with a history of GBS. Although the risk of recurrent GBS following vaccination appears to be low, there is a paucity of epidemiologic data to either confidently support or refute its use in this population of patients [6,7]. Decisions in this regard must be made on a case by case basis. We do not advocate routine influenza vaccination in patients with a prior history of GBS. However, we recommend the vaccine in patients with a high likelihood of complications if they were to contract influenza (*ie*, patients with significant respiratory and/or cardiovascular disease).

### Clinical features

Guillain-Barre syndrome can be divided into three subtypes: 1) acute inflammatory demyelinating polyneuropathy (AIDP), which is the most common form in Western

countries; 2) acute motor axonal neuropathy (AMAN); and 3) acute motor and sensory axonal neuropathy (AMSAN). All present with the acute onset of generalized symmetric weakness, which typically reach their nadir within 2 to 4 weeks. AMAN is more common in China and Japan, where it makes up 40% to 80% of GBS cases, compared with less than 10% in Europe and North America. AMSAN is very rare, with the incidence being less than 10% that of AMAN [2]. Approximately 90% of GBS cases seen in North America and Europe are of the AIDP subtype. Early symptoms are typically sensory and involve paresthesias in the hands and/or feet and often aching in the back with radicular type pain. Progressive symmetric weakness usually ensues and is the primary complaint in most patients. Most commonly, the weakness begins in the legs and progresses to involve the arms, trunk, head, and neck, but variations (eg, onset with bulbar and/or upper extremity weakness) do occur. Mild facial weakness is apparent in at least 50% of patients and up to 15% may develop ophthalmoparesis. Respiratory failure develops in approximately 30% of patients. Neck flexion strength correlates well with diaphragmatic strength and thus is important to follow closely. Cardiovascular autonomic involvement is not uncommon. Diminished or absent deep tendon reflexes are the rule. Elevated CSF protein levels accompanied by no or only a few mononuclear cells are the characteristic laboratory finding and are evident in over 80% of patients at 2 weeks. However, within the first week of symptoms, CSF protein levels are normal in approximately one third of patients.

At least 50% of patients reach their nadir within 2 weeks of onset, and progression beyond 4 weeks is unusual. Progression beyond 8 weeks suggests the diagnosis of CIDP. Patients whose signs and symptoms progress for 4 to 8 weeks fall into a gray zone between GBS and CIDP, often called subacute demyelinating polyneuropathy. However, in a recent study, the majority of these patients' clinical course was similar to that of GBS [8]. After the disease reaches its nadir, symptoms remain stable for 2 to 4 weeks before starting to improve. Although the majority of patients recover satisfactory function, the overall mortality rate is about 5% to 10%, and approximately 20% of patients have severe residual disability. Sixty to seventy percent of patients recover completely or with only mild residual deficits [9]. The prognosis is worse for patients over 60 years of age and for those requiring mechanical ventilation [10].

Acute motor axonal neuropathy differs clinically from AIDP in that there are typically no sensory signs or symptoms, although we have seen the occasional patient with very mild sensory abnormalities. AMAN appears to have a rapid progression and earlier nadir compared with AIDP [11]. Interestingly, reflexes may be preserved, or in some cases even increased, in AMAN despite profound weakness. In contrast to AIDP, autonomic involvement is

rarely observed. Also, in contrast to AIDP, where recovery proceeds at a steady pace, some patients with AMAN recover relatively quickly whereas others experience a slow and poor recovery [12]. It is thought that the rapid recovery pattern may be due to resolution of functional conduction block at the nodes of Ranvier (see discussion of pathophysiology in this article), whereas the slow recovery pattern occurs when extensive axonal loss takes place.

The clinical presentation of AMSAN is essentially indistinguishable from that of AIDP. However, most patients progress to requiring ventilator support and the prognosis of AMSAN is poorer than AIDP, with most patients having a slow and incomplete recovery. AMSAN appears to be similar to AMAN pathophysiologically but involves sensory as well as motor nerves.

### Electrophysiology

Abnormalities may not be seen on nerve conduction studies for several weeks. However, once present, they are helpful in differentiating the subtypes of GBS. The earliest abnormalities in AIDP, consistent with early involvement of nerve roots and the distal nerve terminal, are prolonged or absent late responses (H-reflex, F-waves) and prolongation of distal latencies. Later in the disease, one sees slowed conduction velocities in intermediate segments and conduction block. If damage is severe, electrophysiologic changes consistent with secondary axonal loss may be seen. In contrast, in AMSAN, there are reduced amplitudes of sensory nerve and compound muscle action potentials with preservation of the distal latencies and conduction velocities. Likewise, AMAN demonstrates a reduction in motor amplitudes without features of primary demyelination and with sparing of sensory nerves.

### Pathophysiology

The underlying pathogenesis of all subtypes of Guillain-Barre syndrome remains incompletely understood. It is considered an autoimmune disease with both cell-mediated and humeral immune system involvement. Recent research highlights the role of molecular mimicry with antibodies to a foreign antigen believed to cross-react against various gangliosides. The lipopolysaccharide from *C. jejuni*, the most commonly associated antecedent pathogen, contains a tetrasaccharide identical to that of ganglioside GM1, and serum samples from patients with GBS following infection with *C. jejuni* have demonstrated high titres of antibodies against a number of gangliosides, including GM1, GM1b, and GD1a [13]. In AIDP, complement-activation products are found on the outermost surface of the Schwann cells [14], whereas in AMAN and AMSAN, the target for complement activation products appears to be at the nodes of Ranvier and in the periaxonal spaces of motor fibers [15]. However, the exact mechanism by which this antibody binding disrupts neural transmission remains unknown.

### Treatment

Many trials have demonstrated the efficacy of plasma exchange and intravenous immunoglobulin (IVIg) in the treatment of GBS. Both treatments are equally effective in hastening recovery. Additionally, a meta-analysis of four studies for which the outcome was available demonstrated increased likelihood of recovery of full muscle strength after 1 year in patients treated with plasma exchange when compared with control subjects [16••]. The risk of adverse events, however, appears somewhat higher with plasma exchange as compared with IVIg. For this reason, we advocate the use of IVIg unless unavailable or contraindicated. Relative contraindications for IVIg are renal failure and/or a history of stroke, myocardial infarction, or other thrombotic event. Adverse events associated with plasma exchange include hemodynamic instability, sepsis, pneumonia, and clotting abnormalities.

We give IVIg at a dosage of 2 g/kg for 5 days in patients presenting within 2 weeks of onset of symptoms or in patients who are continuing to progress at the time of presentation. The value of IVIg once symptoms have reached a plateau is unknown. Patients who present with mild symptoms and signs and who appear to have reached a plateau have a good prognosis. We tend not to treat patients who remain ambulatory without need for an assistive device because the risk of adverse events from IVIg, although low, is not zero. When plasma exchange is used, we recommend a regimen involving the exchange of one plasma volume, or 50 mL/kg, on five separate occasions over 1 to 2 weeks.

Both clinicians and patients need to be aware of the time-frame for improvement after treatment with IVIg or plasma exchange. In the various studies, the mean time to improvement of one clinical grade varied from 6 to 27 days; thus, the absence of any immediate observable improvement does not indicate treatment failure and should not discourage physicians or patients. Combining the two treatments does not improve outcome over either treatment alone [17], and steroid treatment given alone or in combination with IVIg is not beneficial [18].

In the absence of curative therapy, supportive therapy remains essential. GBS patients, if bedridden, are at risk of deep vein thrombosis, pneumonia, atelectasis, and decubitus ulcers. Hemodynamic instability related to autonomic dysfunction must also be monitored and treated appropriately. Neck flexion strength and forced vital capacity should be monitored for signs of impending respiratory failure. Most authorities advocate elective intubation once forced vital capacity reaches 20 mL/kg or less.

## Chronic Inflammatory Demyelinating Polyneuropathy

### Epidemiology

Despite their apparent similarities, CIDP is a different disease from GBS. It most commonly presents in adults,

with a peak incidence from 40 to 60 years of age. As in GBS, there is a slight male predominance. Unlike GBS, however, there is no consistent evidence of association with antecedent infection.

### Clinical features

Chronic inflammatory demyelinating polyneuropathy is characterized by the insidious onset of symmetric proximal and distal weakness progressing over at least 2 months. This progression may be gradual, step-wise, or relapsing. The majority of CIDP patients also experience sensory symptoms (numbness and/or paresthesias), particularly in their hands and/or feet. As in AIDP, hyporeflexia or areflexia is the rule. However, autonomic, respiratory, and cranial nerve involvement, although they do occur, are not as commonly seen as with AIDP.

The diagnosis rests primarily on clinical criteria, with electrophysiologic and laboratory data used to support the clinical diagnosis. Nerve conduction studies demonstrate changes consistent with primary demyelination. F-waves, if present, are typically prolonged. There is slowing of motor and sensory nerve conduction velocity out of proportion to loss of amplitude. The presence of conduction block or temporal dispersion is also helpful in supporting a diagnosis of acquired demyelinating neuropathy. Despite the typical symmetry of the clinical examination, conduction velocities may vary considerably between segments and between nerves. Many patients with CIDP do not meet strict electrophysiologic criteria for the diagnosis as defined by an ad hoc committee of the American Academy of Neurology [19]. These criteria were developed to insure specificity of the diagnosis for research purposes. However, strict adherence to these guidelines in routine clinical situations will result in underdiagnosis.

Elevated CSF protein levels are found in 90% of patients with CIDP [20]. CSF leukocyte count should be less than  $10/\text{mm}^3$  except in patients with concurrent HIV infection, where leukocyte counts up to  $50/\text{mm}^3$  may be seen. Sural nerve biopsy, which was at one time advocated in the workup of CIDP, is no longer routinely recommended. In cases with a typical clinical presentation, which includes evidence of demyelination on nerve conduction studies and cytoalbuminemic dissociation, nerve biopsy is not indicated. However, in patients with atypical features and a concern for vasculitis, amyloidosis, or lymphoma, we would recommend sural nerve biopsy.

Chronic inflammatory demyelinating polyneuropathy may be associated with concurrent systemic illness, including HIV, systemic lupus erythematosus, hepatitis B or C, lymphoma, monoclonal gammopathy of uncertain significance, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes), Castleman disease, diabetes, and inflammatory bowel disease. There is also an association with organ or bone marrow transplantation. We screen the serum and urine with immunofixation looking for a monoclonal

gammopathy in all CIDP patients. Serum and urine protein electrophoresis is not sufficient, as a small monoclonal protein can be missed by this technique. If a monoclonal gammopathy is found, the patient should undergo further work-up (skeletal survey and possible bone marrow biopsy) to exclude lymphoma, Castleman's disease, plasmacytoma, multiple myeloma, and osteosclerotic myeloma, which are associated with POEMS syndrome. Although POEMS syndrome itself is relatively rare, CIDP is typically the presenting symptom. In contrast, CIDP is rarely a presenting feature of the other hematologic malignancies. Other blood-work should be undertaken as clinically indicated.

### Pathophysiology

The pathogenic basis of CIDP is presumably autoimmune. Both humoral and cell-mediated mechanisms appear to contribute to the pathogenesis; however, the exact mechanism is unknown. Endoneurial inflammatory changes with T-cell infiltrates are seen in the acute phase [21]. Myelin degradation appears to be initiated by macrophages, as no consistent changes have been identified in fibers that are not in contact with these cells [22]. Although some evidence for molecular mimicry has been identified in GBS, no such correlation has yet been demonstrated in CIDP.

### Treatment

Randomized controlled trials have demonstrated the efficacy of corticosteroids [23], plasma exchange [24,25], and IVIg [26,27,28•]. In general, either IVIg or prednisone is used as initial therapy. A clinical trial of IVIG versus prednisolone for 6 weeks demonstrated no significant difference between these two treatments in the short term [29]. If using prednisone, we recommend starting with a dosage of 1 to 1.5 mg/kg/d (maximum of 100 mg) for 2 to 4 weeks and then switching to alternate-day dosing. Patients are maintained on stable alternate-day dosing until their improvement plateaus, at which point a gradual taper is instituted (by 5 mg every 2 to 3 weeks to 20 mg every other day and then by 2.5 mg every 2 to 3 weeks). When using IVIg, we start with a dosage of 2 g/kg given over 2 to 5 days and repeat this monthly for 3 to 4 months, at which point we will attempt to increase the interval between treatments as tolerated. Unfortunately, most patients never achieve complete medication-free remission.

Although plasma exchange could be used as a first-line treatment, it is generally reserved for patients who do not respond adequately to either prednisone and/or IVIg. We also use plasma exchange in combination with high-dose prednisone for acute treatment of severely disabled patients (*ie*, those unable to walk at the time of presentation) based on our impression that the response to plasma exchange occurs earlier than with the other therapies. Other immunomodulating therapies (*ie*, azathioprine, mycophenolate mofetil, cyclosporine, and cyclophosphamide) can be used in patients who do not adequately

respond to prednisone, IVIg, or plasma exchange. However, evidence to support their use in CIDP is based on small retrospective studies and/or case reports.

### Chronic inflammatory demyelinating polyneuropathy variants

Whether the following diseases are significantly different from typical CIDP remains a matter of some controversy. However, they fall under the rubric of acquired idiopathic demyelinating neuropathies, and thus until we have a better understanding of their underlying pathophysiology, should be included in discussions of CIDP.

#### *Distal acquired demyelinating symmetric neuropathy*

These patients present with primarily large fiber sensory symptoms. The most common complaints are of distal sensory loss and sensory ataxia. Distal motor weakness can occur but is not as prominent. Interestingly, tremor is a common feature. Symptoms are slowly progressive. Nerve conduction studies are not significantly different from those seen in typical CIDP. Although not specific, significant prolongation in distal motor latency is typically present [30]. Unlike CIDP, conduction block does not occur. CSF protein is usually elevated.

This phenotype is commonly associated with an IgM monoclonal gammopathy and anti-myelin-associated glycoprotein antibodies [31•]. The presence of an IgM monoclonal gammopathy and/or anti-myelin-associated glycoprotein antibodies predicts a poor response to immunomodulating therapy. Although IVIg, plasma exchange, corticosteroids, and various immunosuppressive agents have been tried in this neuropathy, the response is modest, if at all, and the slow nature of the disease process and frequent side effects of these treatments usually mitigate against such treatment [31•,32–36].

#### *Multifocal acquired demyelinating sensory and motor neuropathy*

The term multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) refers to a markedly asymmetric variant of CIDP. It is also known by the eponym Lewis-Sumner syndrome after the clinicians who first described this neuropathy. Patients present with a mononeuropathy multiplex pattern of weakness and sensory loss [37]. Onset is insidious and progressive and typically painless. Symptoms usually start in the arms, although occasionally the legs are the site of initial involvement. There is a 2:1 male predominance. CSF protein is typically moderately elevated, although normal CSF protein is seen more commonly than in CIDP. Electrophysiologic studies demonstrate changes consistent with demyelination in clinically affected nerves (*ie*, slowed conduction velocities, prolongation of distal latencies and F-waves, and conduction block and temporal dispersion). Both sensory and motor involvement is evident clinically and electrophysiologically. Like CIDP, MADSAM responds

to steroid treatment and to IVIg. We recommend a similar treatment regimen to that outlined previously for typical CIDP patients.

## Conclusions

Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy and their variants represent an important group of potentially treatable disorders that all clinical neurologists will eventually encounter. As GBS is more common than CIDP and tends to follow a stereotyped clinical course, it is generally fairly easily recognized. CIDP is more variable in presentation and can be more difficult to identify as well as to treat. Although there are a multitude of immunomodulating drugs available, none has proven curative and all have a large spectrum of potentially harmful side effects. Despite clear advances in our understanding of the pathophysiology of these diseases, we unfortunately have not yet developed the more targeted therapies needed for optimizing cure rates while minimizing side effects. This remains an important goal for future research in these diseases.

## Acknowledgment

Dr. Briemberg can be contacted at the Neuromuscular Diseases Unit, Vancouver General Hospital, in Vancouver, Canada.

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