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Multifocal Motor Neuropathy, Multifocal Acquired Demyelinating Sensory and Motor Neuropathy and Other Chronic Acquired Demyelinating Polyneuropathy Variants

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Abstract

Chronic acquired demyelinating neuropathies (CADP) are an important group of immune neuromuscular disorders affecting myelin. These are distinct from chronic inflammatory demyelinating polyneuropathy (CIDP). Classically, CIDP is characterized by proximal and distal weakness, large fiber sensory loss, elevated cerebrospinal fluid (CSF) protein content, demyelinating changes nerve conduction studies or nerve biopsy, and response to immunomodulating treatment. In this chapter we discuss CADP with emphasis on multifocal motor neuropathy (MMN), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), distal acquired demyelinating symmetric (DADS) neuropathy and conclude with less common variants. While each of these entities has distinctive laboratory and electrodiagnostic features that aid in their diagnosis, clinical characteristics are of paramount importance in diagnosing specific conditions and determining the most appropriate therapies. Unlike CIDP, MMN is typically asymmetric and affects only the motor nerve fibers. MMN is a rare disease that presents chronically, over several years of progression affecting the arms are more commonly than the legs. Men are more likely than women to develop MMN. MADSAM should be suspected in

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patients who have weakness and loss of sensation in primarily one arm or leg which progresses slowly over several months to years. It is important in patient with multifocal demyelinating clinical presentation to distinguish MMN from MADSAM since corticosteroids are not effective in MMN where the mainstay of therapy is intravenous gammaglobulin (IVIg). DADS can be subdivided into DADS-M (associated with M-protein) and DADS-I which is idiopathic. While DADS-I patients respond somewhat to immunotherapy, DADS-M patients present with distal predominant sensorimotor demyelinating neuropathy phenotype and are notoriously refractory to immunotherapies regardless of antibodies to myelin-associated glycoprotein (MAG). Our knowledge regarding pathogenesis, diagnosis and management continues to expand, resulting in improved opportunities for identification and treatment.

Keywords

Multifocal motor neuropathy; multifocal acquired demyelinating sensory and motor neuropathy; distal acquired demyelinating symmetric; CANOMAD; CISP; diagnosis; nerve conduction testing; treatment

Historical Note

The first case of recurrent neuritis was published by Eichhorst in 1890¹. In 1958, Austin described the steroid responsiveness of this recurrent polyneuropathy.² The frequent occurrence of elevated CSF protein levels was subsequently observed. Dyck et al described the first large series of 54 patients which they termed chronic inflammatory polyradiculoneuropathy.³ In addition to inflammatory pathology and demyelinating electrophysiology, these cases exhibited clinically a variety of neurologic deficit patterns including monophasic progression over 6 months, recurrent weakness, steady deterioration or stepwise progression. A decade later, Dyck and Arnason underscored the demyelinating nature of this disorder and coined the term chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).⁴

In addition to classic CIDP, other phenotypes sharing some clinical and pathologic features, laboratory findings, and in most cases response to immunomodulatory therapies have been described under the rubric of chronic acquired demyelinating polyneuropathies (CADP) (see Table 1).^{8, 9} The four categories of CADP are largely based on the phenotypic differences. Symmetrical proximal and distal weakness with or without sensory loss is highly suggestive of CIDP (see CIDP and Symmetrical Variants chapter). The pattern of symmetrical distal weakness and sensory loss should raise suspicion of distal acquired demyelinating symmetric (DADS) neuropathy.¹⁰ When weakness is asymmetric, further classification hinges around the presence or absence of sensory signs. Asymmetric distal weakness without sensory loss is indicative of multifocal motor neuropathy (MMN) whereas sensory loss would suggest multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy (Lewis-Sumner syndrome).¹¹⁻¹⁴ About half of the MMN patients also have serum GM-1 antibodies and most DADS patients have an IgM monoclonal protein in the serum, often accompanied by antibodies to myelin-associated glycoprotein (MAG). In a report of 25 patients with the MADSAM phenotype about half of the patients had ganglioside antibodies detected¹⁴ although in our earlier series, and two other series these

antibodies were not detected in any MADSAM patients.^{12, 13, 15} The benefit of placing the CADPs into various phenotypes is that it helps clinicians identify potentially treatable neuropathies in choosing the most appropriate therapy, and in determining the prognosis.

Multifocal Motor Neuropathy (MMN)

Clinical Presentation

In 1988, Parry and colleagues demonstrated the presence of multifocal conduction block in 5 patients with purely motor neuropathies, cramps, and fasciculations and relatively preserved reflexes suspicious for motor neuron disease, and pointed out that this electrodiagnostic finding distinguished these cases from motor neuron disease.¹⁶ Around that same time, reports of similar patients emerged, often associated with the presence of anti-GM1 serum antibodies, and this entity became known as multifocal motor neuropathy (MMN) with conduction block.¹⁷⁻²¹ However, our group as well as others subsequently reported that neither the presence of anti-GM1 antibodies nor conduction block are necessary to diagnose MMN.²²⁻²⁵

MMN is an immune-mediated demyelinating neuropathy that presents with chronic asymmetric distal limb weakness atrophy and fasciculations affecting the distal arm more frequently than the leg, usually in the distribution of individual peripheral nerves with limited or no sensory symptoms.^{16-22, 26-31} There is a male-to-female ratio of approximately 3:1 with most cases beginning in the fifth decade of life but the age of symptom onset ranging from childhood to the eighth decade of life. Most patients present with insidious intrinsic hand weakness, wrist drop, or foot drop which progresses over the course of several years to involve other limbs and weakness will rarely affect cranial innervated muscles. The lack of atrophy in muscles weakened by conduction block should heighten suspicion of MMN. However, patients with MMN may develop secondary axon loss with resultant denervation atrophy leading to a misdiagnosis of amyotrophic lateral sclerosis (ALS). However, weakness in the latter is in a myotomal pattern whereas in MMN it follows a peripheral nerve distribution. Deep tendon reflexes may be diminished but are often normal in unaffected nerves but occasionally can be brisk. Clonus, spasticity, and extensor plantar responses are not observed. In our experience, the incidence of MMN is much less than that of ALS.

More recently sensory loss of a variable degree has been described in patients with otherwise typical MMN.^{32, 33} Five of eleven cases fulfilling AANEM diagnostic criteria MMN at the onset of disease developed sensory loss associated with electrophysiological sensory abnormalities while being treated with IVIg.³² The mean time to appearance of objective sensory signs was 7.2 years, being preceded by intermittent paresthesias in the same nerve territories as the motor involvement in 3/5 cases. Anti-GM1 IgM antibodies were positive in four patients. Though these 5 cases overlap with MADSAM, they were closer to MMN on clinical and therapeutic grounds. Therefore, the Joint Task Force of the European Federation of Neurological Societies/Peripheral Nerve Society 2010 revised guideline on MMN³⁴ requires that there would not be any objective sensory abnormality except for minor vibration sense abnormalities in the lower limbs but allows for sensory signs and symptoms that may develop over the course of MMN.

Laboratory Testing

As in Table 1 and in contrast to CIDP, the CSF protein level in most cases of MMN is normal and a significantly elevated CSF protein level should suggest an alternate diagnosis such as MADSAM or CIDP.³⁵ Though most patients do not have a serum M-protein, polyclonal IgM GM1 antibodies are detected in the sera of 40-80% of MMN cases, and the relationship of these antibodies to pathogenesis is unclear.^{20, 36-41} Very high titers of IgM anti-GM1 antibodies appear to be specific for MMN⁴², but the sensitivity of standard anti-GM1 antibody testing is at best 50%.^{22, 43, 44} Low titers of anti-GM1 antibodies are not specific to MMN as they can be found in other neuropathies such as GBS and CIDP.^{40, 45} Reports of very high sensitivity and specificity using a specialized ELISA technique⁴⁶ could not be reproduced by others investigators.⁴⁷ In a patient presenting with the MMN phenotype, the presence of anti-GM1 antibodies is supportive of, but not essential to, the diagnosis and these antibodies do not predict response to treatment.

Pestronk and colleagues recently identified serum IgM binding, using covalent antigen linkage to ELISA plates, to a disulphated heparin disaccharide (NS6S) in 43% of 75 motor neuropathy cases with mostly distal predominant asymmetric arm weakness and objective sensory loss mostly of the distal legs in 28 cases.⁴⁸ Motor conduction block was present in 42 patients, other features of demyelination in 3 while 30 had motor axon loss without evidence of demyelination without detailed description of weakness pattern. They found that high titers ($>$ or $=$ 7,000) of serum NS6S or GM1 antibody in motor neuropathy increased sensitivity from 43% based on GM1 antibody positivity alone to 64% when either antibody is detected. While none of the ALS or CIDP cases had an abnormal titer, 21% of 56 patients with sensory neuropathy had highly elevated NS6S antibody titers. Additional review of the 2113 sera revealed 27 patients with IgM GM1 positivity, of whom two had mild cryptogenic sensory neuropathy and high titers of IgM binding to NS6S, thereby suggesting 93% specificity. Given the retrospective approach, presence of thoracic paraspinal denervation in 11 of the 25 patients tested cases, sensory neuropathy in 21% of cases and the lack of detailed clinical data on 30 motor axon loss cases, the value of NS6S IgM antibody in clinical practice is yet to be determined.

Electrophysiologic findings

Although motor conduction block has been considered the electrophysiologic hallmark of MMN,⁴⁹ some otherwise typical MMN cases have no detectable CB. This may be due to proximal location of the conduction block making it difficult to confirm electrophysiologically or to the activity-dependence of these blocks.⁵⁰ In addition, we and others described prolonged distal latencies, temporal dispersion, slow conduction velocity, and delayed or absent F-waves on motor NCS in MMN.^{22, 25, 29, 51, 52} Conduction block is not essential to the diagnosis of MMN if other features of demyelination are detected.^{22, 25} In our series of MMN patients,²² only 31% had conduction block; 44% had temporal dispersion, and 94% had other electrodiagnostic features of demyelination with superimposed axonal degeneration (Table 2). We and others found that response to treatment was no different between patients with or without conduction block.²²⁻²⁴

Vucic et al described needle cervical root stimulation (CRS) findings in 13 MMN cases meeting the American Academy of Electrodiagnostic Medicine (AAEM) criteria of either possible (n=7) or definite MMN (n=6).⁵³ The sensitivity of the established neurophysiologic criteria for definite MMN was 46.1% with conventional NCS and after CRS all patients exhibited either CB, prolonged CMAP onset latency or both, thereby establishing the diagnosis of MMN.

The AANEM consensus criteria for definite or probable MMN⁴⁹ include patients without objective sensory loss, with normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block and normal sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested. Therefore, sensory NCS are predicted to be normal in MMN patients. In a retrospective study, significant reduction of at least one sensory potential amplitude in a cohort of 21 MMN patients within a follow-up of at least 3 years, defined according to the 2001 ENMC International Workshop Report, was noted in 13 patients (62%), 4 of whom had abnormalities of two or more sensory potentials.³³ Comparison of the 13 cases to 8 patients who had no sensory abnormality revealed no significant differences in gender, age at onset, number of involved motor nerves, CSF protein level, presence/absence of anti-GM1 serum antibodies and response to IgIV.

Multifocal motor neuropathy by definition typically involves clinical and electrical abnormalities in more than one nerve. However, an intriguing report described three patients with an acquired, presumably immune mediated neuropathy in a single motor nerve (median or peroneal or ulnar) that improved with IVIg therapy.⁵⁴ Our group reported 9 patients with the phenotype of MMN but who had only axonal features on electrodiagnostic studies.⁵⁵ We termed this phenotype multifocal acquired motor axonopathy - MAMA. Three of six treated patients showed improvement. Recently, another group confirmed our observations by demonstrating five of six MAMA patients responded to IVIg.⁵⁶

Pathology

Sensory nerve biopsies from patients with MMN are usually unrevealing^{57, 58} and is not a routine test in the evaluation of MMN. While one study has shown evidence for demyelination without inflammatory cell infiltrates at the site of motor conduction block,⁵⁹ another pathological study of 7 patients demonstrated multifocal axonal degeneration without any overt signs of demyelination.⁶⁰ These findings suggest that an antibody-mediated attack directed against components of axolemma at nodes of Ranvier could cause transient conduction block that is rapidly reversible with IVIg and axonal degeneration and regeneration. T2-weighted MRI scans of the brachial plexus may show increased signal intensity associated with a diffuse nerve swelling of the brachial plexus.^{61, 62}

Therapy

While corticosteroids and PE may improve rare MMN patients, other MMN cases have deteriorated with these treatments.^{63, 64} Several studies have demonstrated the efficacy of IVIg in MMN, including two small randomized controlled trials.^{65, 66} Intravenous immunoglobulin (IVIg), a pooled gammaglobulin product from several thousand blood donors, has a complex immunomodulatory mechanism of action. It is thought to involve

pathogenic autoantibodies production modulation and binding inhibition, pro-inflammatory cytokine suppression, Fc receptor blockade, macrophage colony stimulating factor and monocyte chemotactant protein-1 increase, alteration in T cell function, decreased in circulating CD54 lymphocytes and inhibition of cell transmigration into the muscle. More recently, investigators from the Rockefeller found that Fc core polysaccharide sialylation mediates the anti-inflammatory properties the IVIg.⁶⁷ They also determined the precise IgG Fc fragment N-linked glycan requirements for this anti-inflammatory activity and could recapitulate in vitro the anti-inflammatory property of IVIg in a 2,6 sialylated IgG Fc recombinant molecule at a much reduced dose.⁶⁸ They demonstrated that these sialylated Fcs require a specific C-type lectin, SIGN-R1, (specific ICAM-3 grabbing non-integrin-related 1) which is expressed on macrophages in the splenic marginal zone.⁶⁹ Anthony and colleagues found that, in transgenic mice, IVIg suppresses inflammation through a novel TH2 pathway.⁷⁰ Administration of Fc fragments with glycans terminating in α 2,6 sialic acids resulted in the production of IL-33, which, in turn, induces expansion of IL-4-producing basophils that promote increased expression of the inhibitory Fc receptor Fc γ RIIB on effector macrophages. Systemic administration of the TH2 cytokines IL-33 or IL-4 upregulated Fc γ RIIB on macrophages. In untreated CIDP patients, these Fc γ RIIB receptors have lower expression levels on naïve B cells, compared to demographically-matched healthy controls.⁷¹ Following clinically effective IVIG therapy, Fc γ RIIB protein expression is upregulated and partially, restored on B cells and monocytes. Therefore, modulating Fc γ RIIB function might be another promising therapeutic approach in CADP.

Most MMN patients respond to IVIg with improvement typically beginning within several days and lasting several weeks to months. Most responders show improvement after the first treatment and will have a long-term response to IVIg.⁷²⁻⁷⁴ However, over time, axon loss and disability may accrue.⁷⁵ In a detailed study looking at the effect of IVIg in 11 MMN patients given regularly for 4 to 8 years, most of the improvement was noted in the first several months. Also, strength tended to decrease slightly over time, although patients were still significantly better at the last follow-up compared to pre-treatment.⁷⁶ Conduction block in some nerves resolved, but in other nerves, despite treatment, conduction block or evidence of axonal loss appeared. Another group reported their experience treating 10 MMN patients with IVIg for 5 to 12 years.⁷⁷ Only 2 patients maintained maximal improvement; 8 worsened despite IVIg treatment. The decline started between 3 to 7 years into the therapy. Therefore, while IVIg often has a significant benefit initially, the response declines over time.

In a cross-sectional descriptive study of 88 MMN cases, ninety-four percent responded to IVIg therapy. Non-responders had longer disease duration before the first treatment.⁷⁸ Over the 6-year median IVIg maintenance duration, the median IVIg dose increased from 12 to 17 g per week. Independent determinants of worse weakness and disability were axon loss and longer disease duration without IVIg. Early IVIg treatment may postpone axonal degeneration and permanent deficits. Most recently, a large 15-month multicenter cross-over trial of 10% IVIg for the treatment of multifocal motor neuropathy was concluded. (<http://clinicaltrials.gov/ct2/show/NCT00666263?term=motor+neuropathy&rank=2>). The forty-four enrolled cases from 17 sites had 3 stabilization phases on IVIg with 2 blinded phases on

10% IVIg or placebo and 41 completed the study. Accelerated switch to open-label IGIV, 10% was allowed if grip strength decreased 50% in the more affected hand or intolerable functional deterioration was objectified. The preliminary results of this study were presented at the 2012 American Academy of Neurology annual meeting.⁷⁹ There was a substantially greater decline from baseline (34%) in the mean grip strength in the more affected hand following placebo administration, as compared to IGIV ($p=0.005$). A greater proportion of subjects had a 30% decline in grip strength of the more affected hand (43% vs 5%; $p<0.001$), as well as the less affected hand (31% vs 0%; $p<0.001$), following placebo vs IVIG treatment. Sixty-nine percent of subjects required accelerated switch while on placebo, compared to only 1 accelerated switch (2.4%) on blinded IVIG. Therefore, IVIG was demonstrated to be safe, well-tolerated and an effective treatment for MMN in this phase III study.

We closely monitor patients with the first infusion, starting at a very slow rate of 25 to 50 cc/hr for 30 minutes and increasing it progressively by 50 cc/hr every 15 to 20 minutes up to 150 to 200 cc/hr. Mild reactions (headache, nausea, chills, myalgia, chest discomfort, back pain) occur in 10% and are improved with slowing the infusion rate and are preventable with pre-medication with acetaminophen, benadryl and if need be IV methylprednisolone. Moderate rare reactions include chemical meningitis and delayed red, macular skin reaction of the palms, soles and trunk with desquamation. Acute renal failure is uncommon and related to patient dehydration and the sucrose or maltose diluent. Other severe and rare reactions are anaphylaxis, stroke, myocardial infarction or pulmonary emboli due to hyperviscosity syndrome. The latter is more likely to occur in old age, immobility, diabetes, thrombocytopenia, hypercholesterolemia, hypergammaglobulinemia, and cryoglobulinemia. We avoid using IVIG in patients with several of these risk factors and place IVIG recipients on low dose aspirin prophylactically. Two papers discussed stroke as a complication of IVIg. In the report by Caress et al, all but one of the 16 cases had risk factors for stroke.⁸⁰ Okuda et al successfully treated 3 of 4 patients who had a vascular complication from IVIg (three strokes; one leg ischemia) with tissue plasminogen activator (tPA).⁸¹ They recommend using only 5 percent solutions and limiting the maximum infusion rate to 15 g/hr in order to minimize the viscosity changes. The extremely rare patients with total IgA deficiency should not be receiving IVIG. While we generally infuse IVIg no faster than 150 to 200 cc/hr, a recent report described infusion rates of up to 800 cc/hr in 50 patients, which was reasonably well tolerated.⁸² In this study, the complication rate was 26 percent, but most of these consisted of headaches, malaise, or nausea and all recovered without sequelae. Patients were pre-medicated with acetaminophen and diphenhydramine.

Though there is no data from prospective randomized controlled trials,⁸³ there are several reports of benefit from rituximab, a monoclonal anti-CD20 antibody.⁸⁴⁻⁸⁸ The largest published case series is a 2-year open-label study of rituximab in 14 MMN patients with the control group consisting of 13 cases that were not treated as a result of patient choice, lack of insurance coverage, or evaluation and follow-up before rituximab.⁸⁵ Quantitative strength measures improved by 13% to 22% in the rituximab group at 1 and 2 years and remained essentially unchanged in the control subjects. This was associated with 45% reduction in anti-GM1 antibody titers at 2 years. However, most patients with initial benefit developed recurrent weakness at 3 to 9 months after treatment and received a second set of treatment

then one infusion every 10 weeks to maintain benefit. Clearly not all patients with MMN neuropathy will respond to this novel therapeutic approach and further study of rituximab in MMN is needed. Intravenous cyclophosphamide is effective in over 70% of MMN cases.^{20, 30, 41} In patients with significant deficits who are unresponsive to IVIg or rituximab, we consider monthly pulses of intravenous cyclophosphamide 0.5 to 1.0 mg/m² with or without PE for 6 months.

Lee et al treated 2 CIDP patients with subcutaneous infusion of immunoglobulins (SCIG) after IVIg therapy was shown to be effective. Application of SCIG was well tolerated and led to stabilization of the disease course.¹²⁷ In a recent study of 9 patients with MMN,⁸⁹ short-term infusion of subcutaneous immunoglobulin (SCIG) preserved muscle strength for a few months of treatment. Five patients preferred to continue SCIG after the trial and another patient chose to start SCIG. These 6 cases were enrolled in a long-term SCIG maintenance therapy study for 2 years.⁹⁰ Side effects consisted of mild and transient local skin reactions. The neuropathy impairment and disability scores remained unchanged and isokinetic muscle strength was stable. In another study,⁹¹ four out of five patients treated with a SCIG dose equivalent to the IVIg maintenance had stable muscle strength over the 6 months follow-up. Besides local adverse events, mild systemic adverse events were reported mostly in the first week of treatment. Finally,⁹² an open-label multi-centre study assessed the efficacy, safety, and convenience of SCIG in 8 MMN patients over 6 months, as an alternative to IVIG. Although one patient deteriorated and was withdrawn, muscle strength, disability, motor function, and health status were unchanged in all seven study completers. Despite these encouraging data, the role of SCIG in MMN is uncertain. A large prospective randomized controlled trial of SCIG in MMN has yet to be done.

In a randomized controlled trial,⁹³ 28 MMN patients responding to IVIg treatment were eligible for randomization to mycophenolate mofetil (MMF) or placebo for 12 months. After 12 months IVIg reduction did not differ significantly between the two treatment groups and anti-GM1 antibody titers did not change. Adjunctive treatment of MMN patients with MMF at a dose of 1 g twice daily was found to be safe but did not allow significant reduction of IVIg doses.

Multifocal Acquired Demyelinating Sensory and Motor (MADSAM) Neuropathy

Clinical Presentation

In 1982, Lewis, Sumner and colleagues⁹⁴ described several patients with chronic demyelinating sensorimotor neuropathy, mononeuritis multiplex, and persistent multifocal conduction block on electrophysiological studies; all had a generally favorable response to corticosteroids. This report is erroneously cited as the first description of MMN. However, these patients had objective sensory abnormalities setting apart from MMN. Oh and colleagues⁹⁵ were the first to point out the important clinical differences between patients with MMN and those with multifocal demyelinating sensory and motor neuropathy. In order to distinguish it from MMN, we proposed the descriptive term “multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy” (Table 1).¹¹ Other terms

describing identical patients include “focal upper limb demyelinating neuropathy”, “upper limb predominant, multifocal chronic inflammatory demyelinating polyneuropathy”, and “multifocal inflammatory demyelinating neuropathy.”^{62, 96, 97} It is apparent that MADSAM neuropathy is a multifocal variant of CIDP, and that both diseases are distinct from MMN.

MADSAM patients have a chronic sensorimotor mononeuropathy multiplex with typically an insidious onset and slow progression. Initial involvement is usually in the arms, with later spread to distal legs. Patients can present initially with involvement of single nerves that progress to confluent and symmetrical involvement.^{94, 98} Up to one-half of patients with MADSAM may evolve into a typical pattern of generalized CIDP.¹² Many patients experience pain and paresthesias. Cranial neuropathies have been reported, including optic neuritis and oculomotor, trigeminal, and facial palsies.^{11, 94, 95} Muscle stretch reflexes are reduced or absent in a multifocal pattern with progression to areflexia late in the disease.

Laboratory and electrodiagnostic testing

CSF protein is elevated in up to 82% of patients with MADSAM neuropathy.¹¹ Unlike MMN, MADSAM neuropathy is not associated with anti-GM1 antibodies.^{11, 95-97} As in MMN and CIDP, nerve conduction studies in MADSAM neuropathy shows conduction block, temporal dispersion, prolonged distal latencies, slow conduction velocities and delayed or absent F-waves in one or more motor nerves (Table 2). In contrast to MMN, sensory NCS are also abnormal at the outset. These clinical features and laboratory features overlap with hereditary neuropathy with liability to pressure palsies (HNPP) which should be considered, especially if there is history of recurrent compressive palsies, foot deformities or family history of compression or generalized neuropathies.

Pathology

In general, sensory cutaneous nerve biopsies show prominent demyelinating features with many thinly myelinated large-diameter fibers, scattered demyelinating fibers, and onion bulbs, similar to the findings in CIDP.^{11, 94- 97} Teased-fiber preparations reveal evidence of demyelination or remyelination,¹¹ with asymmetric pathologic findings within and between fascicles.^{99, 100}

Therapy

Though prospective randomized controlled studies have not been performed, retrospective series have demonstrated improvement in response to IVIg in treatment more than 70% of MADSAM neuropathy patients.^{11, 62, 94-97, 99, 100} In contrast to MMN, most patients with MADSAM neuropathy have also shown response to corticosteroid treatment. Therefore it is important to distinguish MADSAM neuropathy from MMN since the former is steroid-responsive while the latter is not. Prednisone therapy is initiated with 100 mg orally once daily in the morning. When improvement begins, usually within 2-4 weeks, patients can be switched to alternate day therapy. When strength has returned to normal or improvement has plateaued, usually within 3-6 months, the prednisone dose is slowly tapered by 5 mg every 2-3 weeks. Although a minority of patients can eventually be tapered completely off of prednisone, many patients relapse. It is important for both the patient and physician to realize MADSAM is a chronic disorder and may require immunosuppressive therapy for one

or more years. Some patients will require a steroid-sparing agent to facilitate a downward prednisone taper (see below).

Because the risks of long-term corticosteroids (CS) therapy are numerous, discussing those with the patient as well as establishing a monitoring plan in collaboration with the primary care physician is integral to the management plan. Before CS initiation we place a PPD skin test to identify the need for isoniazid in previously exposed cases. As we start CS, we obtain a baseline bone DEXA scan and request the patient to seek an ophthalmologic examination, with yearly follow-up for both. We maintain patients on oral calcium 500 to 600 mg two to three times daily with vitamin D 400-800 IU daily. If there is osteopenia or osteoporosis, or there are fractures, we recommend starting an antiresorptive agent such as alendronate. If patients develop gastric irritation, we instruct them to use H2-blockers or proton pump inhibitors. We ask patients and their family to be alert about personality changes and psychiatric side effects. We inform our patients to reduce the salt and carbohydrate in their diet and visit regularly with the primary care physician for blood pressure, serum glucose and potassium and measurements. We advocate the pneumococcal vaccine and yearly flu shots but caution against live vaccines which are contraindicated.

A recent retrospective chart review from the Washington University neuromuscular group suggests that intravenous, high-dose methylprednisolone may be an effective treatment for CIDP and this may be an option for MADSAM cases.¹⁰¹ One gram of methylprednisolone was administered daily for 3-5 days, weekly for 4-8 weeks, and then monthly based on clinical course. Treatment of patients with CIDP using high-dose intermittent IV methylprednisolone resulted in improved strength equal to that with IVIg and oral prednisone. This favorable response was observed in 13 of 16 patients at 6 month follow-up. In addition, patients treated with intravenous methylprednisolone had less weight gain and cushingoid features adverse effects when compared with those treated with daily oral prednisone. To further investigate the potential to reduce CS side effects, an open-label prospective study of pulse oral weekly methylprednisolone was recently conducted.¹⁰² All 10 CIDP patients were started on oral methylprednisolone 500 mg once a week, for 3 months and the dose was adjusted every 3 months by 50 to 100 mg. All improved and off-treatment remission occurred in 60% of patients. Treatment was fairly well tolerated with many side effects being short-lasting following methylprednisolone ingestion (1-2 days), but steroid-induced osteoporosis remained a problem in 5/9 cases.

Plasma exchange (PE) was demonstrated to be more effective than “sham” pheresis for CIDP in two important studies.^{103, 104} PE is typically used if patients are severely weak, if they relapse on prednisone or IVIg, or they are unresponsive to these therapies and makes sense to use in MADSAM neuropathy. However, IVIg may also be effective in severely weak patients. Risks of PE include those of central venous indwelling catheter, hypotension, allergic reaction to albumin, hypocalcemia, anemia, thrombocytopenia and citrate toxicity. The response obtained with plasma exchange is faster than that from prednisone or IVIg. Five to 10 treatments are usually performed over 2-4 weeks at the initiation of therapy. Unlike the situation in Guillain-Barre Syndrome, there is no benchmark goal of how much total fluid to remove. The effects of plasma exchange are transient, usually lasting 4-8 weeks, but sometimes only 1-2 weeks. Therefore, unless another immunomodulatory

treatment such as prednisone is given, PE will need to be performed indefinitely, something not typically pursued because of cost, risk to the patient, and often the need for a long-term indwelling vascular access device. When initiating plasma exchange in a patient already on prednisone but who has worsened, we usually increase the steroid dose or add a second oral immunosuppressive agent; otherwise, the patient may relapse once the effect of plasma exchange has worn off.

When a patient does not respond to or cannot tolerate the first-line agents (IVIg, CS, PE), other medications may prove beneficial. Azathioprine, cyclophosphamide, cyclosporine, interferon-alpha, interferon-beta, mycophenolate mofetil, and methotrexate have all been reported to be beneficial in CIDP patients not responsive to initial therapies.^{42, 105-120} For the most part, however, these studies were not prospective, randomized, or blinded. In a small controlled trial, patients randomly assigned to azathioprine 2 mg/kg and prednisone did no better than those assigned to glucocorticoids alone.¹⁰⁵ Besides azathioprine, mycophenolate mofetil, cyclosporine, and methotrexate are often used as steroid sparing agents.

In a retrospective review of the efficacy of mycophenolate mofetil, three patients with CIDP (30%) improved, allowing the reduction of steroid or IVIg therapy.¹¹³ In another retrospective case series of 8 CIDP patients, the average Neuropathy Impairment Score improved from baseline after mycophenolate mofetil therapy.¹²¹ Six of these eight patients were either able to stop corticosteroid or intravenous immunoglobulin or reduce their doses and frequency by 50%. Caution in using mycophenolate mofetil with corticosteroids is important since three out of 10 treated dermatomyositis cases are reported to have had associated opportunistic infections, leading to death in one patient.¹²²

More recently a negative randomized controlled trial of oral methotrexate 15 mg weekly was reported in CIDP.¹²³ Fifty-two percent of those taking methotrexate and 44% of those on placebo had a greater than 20% reduction in mean weekly dose of corticosteroids or intravenous immunoglobulin (adjusted odds ratio 1.21, 95% CI 0.40-3.70). Perhaps a higher methotrexate weekly dose would have been more effective. A recent study evaluated whether treatment with intramuscular interferon-beta-1a (Avonex) at low (30 micrograms weekly), intermediate (30 micrograms twice weekly or 60 micrograms weekly) and high dose (60 micrograms twice weekly) would permit the discontinuation of IVIg in CIDP patients receiving regular IVIg maintenance therapy.¹²⁴ Participants were maintained on IVIg through week 16, when IVIg was discontinued and patients who worsened were restarted on IVIg. The primary outcome was total IVIg dose (g/kg) administered from week 16 to 32. Due to a >20% patient dropout rate, this randomized controlled Class I study by design trial was downgraded to Class II evidence. Unfortunately, it did not show a significant benefit of adding intramuscular interferon-beta-1a to IVIg in CIDP. In progressive demyelinating neuropathy patients with IgM monoclonal gammopathy of unknown significance, oral treatment with fludarabine was well-tolerated and induced stabilization and improvement in modified Rankin scale at 1 year follow-up in 5/16 patients.¹²⁵

In comparison to the 2006 EFNS/PNS joint task force report,¹²⁶ the most recent treatment recommendation upgrades the use of IVIg in CIDP to a Level A recommendation, while downgrading corticosteroids therapy in sensory and motor CIDP to Level C and retaining the Level A recommendation for PE when IVIg and corticosteroids are ineffective.¹²⁷ Good practice points include IVIg as the initial treatment in pure motor CIDP as well as combination therapy or adding an immunosuppressant drug if the therapeutic response is inadequate or the maintenance dose of the initial treatment are high. This is in addition to symptomatic treatment and multidisciplinary management.

Distal Acquired Demyelinating Symmetric (DADS) Neuropathy

Clinical Presentation

This entity is characterized by a distal, symmetric demyelinating neuropathy phenotype. DADS neuropathy is a slowly progressive disorder that is typically sensory and ataxic, with frequent tremor. Features distinguishing DADS neuropathy from classic CIDP are listed in Table 1. The majority (2/3) of patients with DADS neuropathy phenotype will have a MGUS, which is almost exclusively IgM Kappa and are labeled DADS-M.¹⁰ Many of these cases have been reported in the literature under such names as “CIDP-MGUS” or “IgM-MGUS neuropathy.”¹²⁸⁻¹³² More than 90% of DADS-M cases are men, with onset in the sixth decade or later. When motor signs are present they are usually confined to the distal (toes, ankles, fingers, wrists) limb musculature. Mild ankle dorsiflexion and plantarflexion weakness is present in 60% of cases. DADS-M patients typically have predominantly sensory symptoms and signs despite prominent demyelination on motor NCS. Because of profound sensory involvement, gait unsteadiness and tremor are frequent findings.

Laboratory and electrodiagnostic testing

Serum antibodies reactive against myelin-associated glycoprotein (MAG) are frequently present in 10/15 patients with DADS-M neuropathy.¹⁰ However, the clinical phenotype and treatment response are dictated by the presence of IgM Kappa monoclonal gammopathy regardless of MAG status. Therefore, it remains uncertain whether there are any practical differences with regards to management, prognosis, or pathophysiology between MAG-positive and MAG-negative IgM-MGUS neuropathy cases.^{10, 132-135} CSF protein is elevated in most patients. Motor NCS demonstrate widespread symmetric slowing, most accentuated in distal sensory and motor nerves (Table 2). Conduction block is uncommon. In most cases, distal latencies are dramatically prolonged, resulting in a short terminal latency index (TLI) which has been suggested as an electrodiagnostic hallmark of anti-MAG neuropathy.^{136,137} Some,¹³⁶ but not all¹⁰ reports have found that a short TLI can reliably distinguish anti-MAG neuropathy patients from those with other chronic demyelinating neuropathies.

Pathology

Nerve biopsies have a characteristic finding consisting widely spaced myelin outer lamellae that is only seen on electron microscopy. In addition to deposits of IgM and complement on sural nerve myelinated fibers, skin biopsies from anti-MAG neuropathy patients have demonstrated IgM deposits on dermal myelinated fibers in all cases, with a greater

prevalence at the distal site of the extremities and a decrease in epidermal nerve fiber density reflecting associated axonal loss.¹³⁸

Therapy

DADS-M neuropathy patients respond poorly to immunomodulatory therapy. Despite treatment with prednisone, IVIg, PLEX and cyclophosphamide, none demonstrate objective improvement. In our series,¹⁰ only 30% showed any improvement. Most had only sensory manifestations, making objective assessments of treatment responses difficult. In the literature, IgM-MGUS polyneuropathies are not categorized by clinical phenotype or evidence of demyelination but by the presence of an antibody and its type. However, there is general consensus that IgM-MGUS and MAG-positive patients either do not respond or respond poorly to immunomodulatory therapy.¹³⁹⁻¹⁴³ Most of these cases correspond to the DADS phenotype.

There have been only three randomized, placebo-controlled trials assessing immunomodulatory therapies in IgM-MGUS polyneuropathy. PE was no better than “sham” plasma exchange in IgM-MGUS polyneuropathy patients, whereas active treatment produced a superior response among IgG- and IgA-MGUS cases.¹⁴¹ Dalakas and colleagues found a response rate of 18% for IVIg in IgM-MGUS patients.¹⁴⁴ In a placebo-controlled trial, no benefit for interferon-alpha was detected.¹⁴⁵

Despite other investigators reporting a response to open-label use,^{83, 84, 146-148} our experience with rituximab in DADS-M has not been positive.¹⁴⁹ Rituximab is a chimeric monoclonal antibody that specifically binds to CD20 antigen, expressed from pre-B-cell stage to mature B-cell stage, on normal and malignant B-lymphocytes. It reduces peripheral B-lymphocyte counts by approximately 90% within 3 days and cell counts begin to recover within 90 days. Another proposed mechanism of action of rituximab has to do with it acting as a cellular decoy.¹⁵⁰ This is through binding of tens of thousands of rituximab-IgG molecules to B cells, generating cellular immune complexes that efficiently attract and bind Fcγ receptor-expressing effector cells. This in turn reduces effector cell recruitment at sites of immune complex deposition thereby reducing tissue inflammation. Benedetti et al. found that improvement in the mean INCAT sensory sumscore was significant at 12 months in anti-MAG neuropathy and correlated with lower anti-MAG antibody at entry and at follow-up.¹⁵¹ Investigators from Utrecht studied the effect of rituximab in 17 patients with polyneuropathy and IgM monoclonal gammopathy.¹⁵² Rituximab induced an improvement of ≥ 1 point on the Overall Disability Sum Score in 2/17 patients, an improvement of $\geq 5\%$ in the distal MRC sum score in 4/17 and in the sensory sum score in 9/17 patients. The presence of antibodies to MAG and a disease duration shorter than 10 years predicted treatment response.

More recently, a randomized controlled trial in 26 anti-MAG neuropathy cases compared rituximab to placebo.¹⁵³ The primary endpoint measure was a change ≥ 1 point in the INCAT leg disability scale score at month 8. There was no statistically significant difference between placebo response (0/13) and that to rituximab (4/13). After excluding a rituximab case who in retrospect may have had an INCAT score of 0 rather than 1 at entry, this difference became significant. The time to walk 10 meters was reduced in the rituximab

group from 8.3 ± 3.2 at baseline to 7.4 ± 2.5 seconds after treatment. However, identifying the minority of anti-MAG patients that may respond to rituximab remains to be a challenge.

Since the clinical deficit in most IgM-MGUS polyneuropathy patients is primarily sensory and significant progression over time may be minimal, even without treatment, the risks of aggressive management should be weighed against this relatively benign course.¹⁴² Recent guidelines jointly issued by the European Federation of Neurological Societies and the Peripheral Nerve Society advocate withholding immunomodulatory therapy from DADS-M patients who do not have significant disability¹⁵⁴ since potential benefit should be balanced against possible side effects and the usually slow disease progression.

Other groups continue to show that patients with IgG or IgA monoclonal gammopathy and neuropathy are different from these with IgM monoclonals. Magy et al found that patients with IgM monoclonals were more likely to have predominantly sensory clinical manifestations, including ataxia, and were more likely to have evidence of distal demyelination on motor nerve conduction studies, essentially confirming the DADS phenotype.¹⁵⁵ The IgA/IgG group was in general much more heterogeneous with some axonal and some demyelinating cases. Isoardo and colleagues again showed that patients with MAG antibodies are more likely to have a sensory phenotype despite severe demyelination findings on motor nerve conduction studies, particularly distally.¹⁵⁶

The remaining one-third of patients with the DADS phenotype do not have an M-protein and are referred to as idiopathic DADS neuropathy (DADS-I). These cases do not have the striking older age and male preponderance of DADS-M patients. Individuals classified as DADS-I are heterogeneous and show a response to treatment that is intermediate between DADS-M and CIDP.¹⁰ Patients corresponding to DADS-I have been labeled in the literature as “sensory CIDP” because they have only sensory symptoms or signs even though there is electrodiagnostic evidence of motor demyelination.¹⁵⁷⁻¹⁵⁹ These patients may respond to immunomodulatory therapy, but this can be difficult to measure if there are only sensory manifestations.

Less Common CADP Variants

Other less common variants include chronic inflammatory sensory polyradiculopathy (CISP) with normal NCS but abnormal somatosensory evoked potentials¹⁶⁰ and chronic ataxic neuropathy with ophthalmoparesis, M protein, cold agglutinins and disialosyl ganglioside antibodies (CANOMAD).¹⁶¹ In the Mayo clinic series of 15 CISP cases, 3 were confined to a wheelchair and 5 relied on a cane (87). CSF protein was increased in 13/14. Despite normal nerve conduction studies in all, 12/12 patients had abnormal SSEP: 7/12 had prolonged median nerve N13 latencies or N9-N13 interpeak latencies and 9/12 had delayed tibial nerve scalp responses (with absent cervical and lumbar responses) and 2 had absent tibial responses. Out of 5 cases with radiologic evidence of lumbar nerve root thickening, 3 did not have an evoked potential study. Lumbar sensory rootlet biopsies in 3 cases showed thickened rootlets, decreased density of large myelinated fibers, segmental demyelination, onion-bulb formation, and endoneurial inflammation. All 6 patients requiring aided

ambulation responded markedly and with within a few months to intravenous steroid (n=2) or IVIg (n=4).

CANOMAD is another rare ataxic variant with a heterogeneous mode of presentation.¹⁶¹ In addition to weakness in 14/18 cases, 16 had variable degrees of ophthalmoparesis, 15 had gait and limb ataxia while one had ataxia confined to limbs. Less commonly the facial and trigeminal nerves were affected. One case presented only with limb paresthesia and bulbar dysfunction. The course was slowly progressive with 13/18 experiencing relapses in ocular (n=10), sensory (n=9) bulbar (n=8) or motor (n=4) symptoms. One had a respiratory relapse requiring temporary mechanically assisted ventilation. Some degree of demyelination on nerve conduction studies was ultimately present in 12/18 cases. CSF protein was elevated in 11/16 cases and 2/8 imaged cases had multifocal brain white matter lesions without any oligoclonal band. An M protein was found in 17/18 cases and 8 had cold agglutinins. A variety of IgM anti-ganglioside antibodies were detected in all 18 cases with 17 cases having identifiable GD1b (n=16) and/or GQ1b (n=17) antibodies. A single case had isolated GD3 antibody elevation. At last assessment, 5 were wheelchair bound and only 3 walked unaided. Patients may respond to IVIg or PLEX. To avoid agglutination in the extracorporeal arm, the replacement fluid temperatures of PLEX should be controlled carefully.

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Key Points

- CADP are a heterogeneous group of immune-mediated neuromuscular disorders affecting myelin that include MMN, MADSAM, DADS and other less common variants.
- MMN presents with asymmetric weakness affecting the arms are more commonly than the legs.
- Though sensory loss is limited at the onset to toe vibratory impairment, MMN patients may over several years of progression develop sensory loss in the territory of affected motor nerves.
- Markedly elevated GM1 antibody titers are detectable in the blood up to 50% of MMN patients.

While MMN is refractory to corticosteroids, most patients respond to IVIg.

- MADSAM cases have weakness and of sensory loss at the onset and an elevated CSF protein.
- -It is important to recognize MADSAM since corticosteroids are also effective in addition to IVIg.

DADS-M patients are refractory to CS, IVIg and rituximab.

Table 1
Comparison of the Chronic Acquired Immune-Mediated Demyelinating Polynuropathies

	CIDP	DADS Neuropathy	MADSAM Neuropathy	MMN
Clinical Features				
Weakness	Symmetric; Proximal + Distal	Symmetric; Distal only; Mild or no weakness	Asymmetric; Distal > Proximal; Upper limbs > Lower limbs	Asymmetric; Distal > Proximal; Upper limbs > Lower limbs
Sensory Deficits	Yes; Symmetric	Yes; Symmetric	Yes; Multifocal (distribution of individual nerves)	No
Reflexes	Reduced or absent symmetrically	Reduced or absent symmetrically	Reduced or absent (multifocal or diffuse)	Reduced or absent (multifocal or diffuse)
Electrophysiology				
Abnormal CMAPs:				
Demyelinating features	Usually symmetric	Usually symmetric Prolonged distal latencies	Asymmetric (multifocal)	Asymmetric (multifocal)
Conduction Block	Frequent		Frequent	Frequent
Abnormal SNAPs	Usually symmetric	Uncommon Usually symmetric	Asymmetric (multifocal)	SNAPs are normal
Laboratory Findings				
CSF Protein	Usually elevated	Usually elevated	Usually elevated	Usually normal
Monoclonal Protein	Occasionally present; Usually IgG or IgA	IgM-κ present in the majority; 50-70% are MAG positive	Rarely present	Rarely present
Anti-GM1 Antibodies	Rarely present	Not present	Rarely present	Frequently Present (50%)
Sensory nerve biopsy:				
Demyelination/remyelination	Frequent	Frequent	Frequent; Sometimes asymmetrical	Occasional; Minimal findings
Treatment Response				
Prednisone	Yes	Poor*	Yes	No
Plasma Exchange	Yes	Poor*	Possible (more study needed)	No
IVIg	Yes	Poor*	Yes	Yes
Cyclophosphamide	Yes	Poor*	Possible (more study needed)	Yes

* When associated with an IgM-MGUS.
Treatment responses in DADS neuropathy patients without a MGUS are more similar to those with CIDP.
CIDP = chronic inflammatory demyelinating polynuropathy
CMAPs = compound motor action potentials

CSF = cerebrospinal fluid

DADS = distal acquired demyelinating symmetrical

IVIg = intravenous immunoglobulin

MADSAM = multifocal acquired demyelinating sensory and motor

MAG = myelin associated glycoprotein

MMN = multifocal motor neuropathy

SNAPs = sensory nerve action potentials

Table 2
Nerve Conduction Study Values Needed to Be Considered “Demyelinating”

	NCV (m/sec)		DL (msec)		F WAVES (msec)		
	LLN	<80% ¹	<70% ²	ULN	> 125% ¹	>150% ²	>150% ²
Median	49	39.2	34.3	4.5	5.6	6.7	46.5
Ulnar	50	40.0	35.0	3.6	4.5	5.4	48.0
Peroneal	41	32.8	28.7	6.6	8.2	9.9	87.0
Tibial	41	32.8	28.7	6.0	7.5	9.0	87.0

¹ = If Amp > 80% LLN

² = If Amp < 80% LLN

If: Median CMAP LLN 4.5 mV; then 80% LLN = 3.6 mV

Ulnar CMAP LLN 5.0 mV; then 80% LLN = 4 mV

Peroneal CMAP LLN 2.0 mV; then 80% LLN = 1.6 mV

Tibial CMAP LLN 4.0 mV; then 80% LLN = 3.2 mV