

Managing inflammatory diabetic neuropathies



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Practice Points

- Radiculoplexus neuropathies (neuropathies that involve the roots, plexus and peripheral nerve) occur in people with and without diabetes mellitus and are of three types, lumbosacral (lower limb), thoracic (trunk) and cervical (upper limb), and can occur in isolation or in combination.
- Radiculoplexus neuropathies in diabetes mellitus classically begin focally with pain followed by weakness of a lower limb (lumbosacral), but spread to become bilateral and involve the upper limbs (cervical) or the trunk (thoracic), and can also occasionally be painless.
- The nerve pathology of diabetic radiculoplexus neuropathies is characterized by axonal loss/degeneration, ischemic injury, inflammation, and microvasculitis.
- In a controlled study, corticosteroids have been found to improve pain in diabetic radiculoplexus neuropathies.
- Earlier treatment of diabetic radiculoplexus neuropathies may result in a better and quicker response.
- Patients with diabetes mellitus and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) tend to have more axonal electrophysiological features than patients with CIDP alone, which may be partially secondary to coexisting diabetic polyneuropathy.
- The first line treatments for CIDP are corticosteroids, intravenous immunoglobulins, and/or plasma exchange, but multiple other agents have shown efficacy in some patients, although data is limited.
- CIDP in diabetic patients is immunotherapy responsive in most patients, although the benefit may be less than in idiopathic CIDP, likely because of greater axonal loss and/or an underlying diabetic polyneuropathy.

ABSTRACT Most diabetic neuropathies are felt to be related to metabolic and microvascular complications from prolonged periods of hyperglycemia, the classical example being diabetic polyneuropathy. Diabetic polyneuropathy is a symmetric slowly progressive distal predominant, sensory greater than motor neuropathy, commonly seen in neurological practice. However, there are subtypes of diabetic neuropathy, inflammatory in origin, which are important to identify, as the fundamental approach to treatment is different. The main categories of inflammatory diabetic neuropathy, which we will discuss in detail, including clinical presentation, evidence for an inflammatory pathophysiology, and the treatment strategies, are the different forms of radiculoplexus neuropathies (diabetic lumbosacral radiculoplexus neuropathy, diabetic cervical radiculoplexus neuropathy, diabetic thoracic radiculoneuropathy and painless motor and lower limb predominant neuropathy) and diabetic chronic inflammatory demyelinating polyradiculoneuropathy.

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Diabetic neuropathies are extremely common and many are directly related to microvascular and metabolic causes, such as diabetic polyneuropathy (DPN). The best management strategies for these types of neuropathy are an emphasis on good glycemic control, with the goal of reducing rate or degree of progression. Compressive neuropathies such as carpal tunnel syndrome and ulnar neuropathy at the elbow also occur frequently in diabetic patients, and can be managed conservatively with splinting, or more aggressively through local corticosteroid injections or surgical decompressions. Inflammatory diabetic neuropathies are much rarer, but their identification as such is critical for appropriate management, as many cases will be immunotherapy responsive. It is important to be able to differentiate diabetes-related inflammatory neuropathies from other mimickers (Box 1). We will present a review of the clinical features, pathophysiology, and management options for the known types of inflammatory diabetic neuropathy.

Diabetic lumbosacral radiculoplexus neuropathy

One of the more well known of the inflammatory diabetic neuropathies is diabetic lumbosacral radiculoplexus neuropathy (DLRPN), which is described in the literature under several different names, including diabetic polyradiculopathy [1], diabetic amyotrophy [2], diabetic mononeuritis multiplex [3] and proximal diabetic neuropathy [4,5], among others. The differing names are reflective of historical controversy over the primary site of nerve injury in these patients. Over time, it has become clear that while there are common patterns of nerve damage, the underlying process can involve nerves at multiple levels, including nerve roots, lumbar and/or sacral plexus, and peripheral nerve (radiculoplexus neuropathy). We prefer the DLRPN designation as it reflects the breadth of anatomic localization more precisely.

DLRPN is a rare complication of diabetes mellitus, with a population-based study showing that 'proximal asymmetric neuropathy' occurred in 1% of both insulin-dependent and noninsulin-dependent diabetic patients [6]. A later prospective study of 33 patients with DLRPN found that nearly all (32) had Type 2 diabetes mellitus [7]. While diabetic polyneuropathy has been associated with longer duration of diabetes mellitus and with other diabetic complications (diabetic retinopathy and nephropathy), DLRPN

tends to occur in patients with shorter duration of diabetes (median 4.1 years [7]). Most patients with DLRPN do not have diabetic retinopathy or nephropathy, which has raised the clinical suspicion of a separate underlying pathophysiology from DPN. For these reasons, it would appear unlikely that DLRPN is primarily due to metabolic factors (glucose dysregulation).

While DPN is characterized by slowly progressive, distal greater than proximal symmetric sensory loss with or without, and a less prominent motor component, DLRPN presents in a distinctly different fashion. DLRPN has a subacute, and in most cases, a much more severe presentation. The usual pattern is one of unilateral involvement, with severe pain in a lower extremity, generally proximally involving the hip or thigh. However, pain can involve any part of the lower extremity including the leg and foot. This is followed by the development of weakness in that extremity, which generally becomes the longer-term source of disability. Typically there is proximal weakness so patients have difficulty getting out of low chairs or climbing stairs but distal weakness such as footdrop is also common. The weakness is of a large degree and causes significant morbidity. The marked asymmetric weakness, prominent pain component, and subacute presentation are hallmarks of DLRPN and, in most cases, should be easily distinguishable clinically from DPN.

In Dyck's [7] prospective series of 33 personally seen patients with DLRPN, 16 of them were in wheelchairs at the time of evaluation and all but three needed gait aids (walker, cane or ankle foot orthosis) to walk. DLRPN was often (90% of cases) associated with weight loss (on average about 30 lbs), and about half of DLRPN patients had associated autonomic symptomatology (e.g., orthostatic hypotension, evidence of gastrointestinal dysmotility, and urinary or erectile dysfunction). While there was typically a unilateral presentation, most cases eventually became bilateral, with a median time to bilaterality of 3 months, although these cases usually remained asymmetric [7]. In the Dyck *et al.* [7] study, the median age of onset was 65 years and the median hemoglobin A1c was 7.5%. When compared with the Rochester Diabetic Neuropathy Study data, the patients affected with DLRPN had a significantly better hemoglobin A1c and significantly lower BMI than the general diabetic population studied. Nerve conduction studies/electromyography on these

Box 1. TITLE.***Differential diagnosis diabetic radiculoplexus neuropathy***

- Focal/multifocal chronic inflammatory demyelinating polyradiculoneuropathy (Lewis–Sumner syndrome)
- Other inflammatory process (e.g., postsurgical, parainfectious)
- Sarcoidosis
- Other vasculitic process (e.g., connective tissue associated)
- Infectious (e.g., Lyme disease)
- Malignant involvement (metastatic or locally invasive)
- Peripheral nerve sheath tumor (benign or malignant)/perineurioma
- Trauma

Differential diagnosis chronic inflammatory demyelinating polyradiculoneuropathy

- Lower motor neuron amyotrophic lateral sclerosis
- Inflammatory polyradiculopathy
- Infectious polyradiculopathy (e.g., from cytomegalovirus)
- Leptomeningeal disease (e.g., malignancy, sarcoidosis) involving nerve roots
- Hereditary motor and sensory neuropathy type 1/X
- Painless diabetic radiculoplexus neuropathy

patients showed an axonal-predominant neurogenic process, which involved the lower extremities in an asymmetric pattern, and interestingly, the neurogenic findings tended to be more diffuse than the clinical presentation would have suggested. The sensory nerve action potentials were reduced and lumbosacral paraspinal muscles showed fibrillation potentials confirming the anatomical localization of root and nerve involvement. Cerebrospinal fluid protein tended to be elevated with a normal cell count.

In the Dyck *et al.* [7] study of DLPRN nerve pathology, there was widespread evidence of ischemic injury – of 33 nerve specimens, 19 showed focal or multifocal fiber loss/injury, 24 had focal thickening/scarring of the perineurium, 12 had injury neuroma and 21 had neovascularization; all had findings of epineurial perivascular and vascular inflammatory collections. Nearly half had findings either diagnostic or suggestive of microvasculitis, and a majority had hemosiderin deposition in nerve. Based on the findings, it was felt that the primary pathophysiological process in DLPRN is a microvasculitis, which leads to ischemic injury and axonal degeneration, with secondary demyelinating changes due to underlying axonal atrophy.

These findings are supported by other pathological studies. LLewelyn *et al.* [8] performed biopsies of the intermediate cutaneous nerve of the thigh in 14 cases of DLPRN and a sural nerve biopsy in a 15th patient. In four patients (three intermediate cutaneous nerve of the thigh and the one sural nerve) there was evidence of

microvasculitis and an additional patient had nonvasculitic epineurial inflammation. Said *et al.* [9] had the intermediate cutaneous nerve of the thigh biopsied in ten patients with a DLPRN phenotype, and found ischemic lesions in three (two of which had inflammation and vasculitis), and four others showed mild inflammatory changes. Kelkar *et al.* [10] studied nerve and muscle biopsies of 15 patients with a DLPRN phenotype, and found that four had small vessel vasculitis of nerve, six others had epineurial perivascular inflammation without vasculitis, and another showed recanalized vessels in a pattern that could indicate a healed vasculitis; the muscle biopsies all showed neurogenic changes, and a single muscle biopsy also showed endomyxial inflammation.

Another study directly addressed the presence of inflammatory markers in nerve itself, with immunostaining of sural nerve biopsies for ICAM-1, TNF- α , IL-6 and NF- κ B. Nerve biopsies of patients with DLPRN, nondiabetic LRPN and control patients were evaluated. The authors found that there were a significantly greater number of ICAM-1 and NF- κ B positive vessels in both diabetic and nondiabetic LRPN than in control patients, again supportive of an inflammatory basis for DLPRN [11].

Coppack and Watkins [12] studied the natural history of this condition in 27 patients, with a median follow-up period of 62 months, and reported that some recovery was noted after 3 months, and was usually completed by 18 months. Two patients in their group had

relapses. Importantly, though the natural history is one of recovery, they noted that half the patients still had some residua of the disease, albeit minor. Said *et al.* [13] reported on four patients with painful proximal diabetic neuropathy, not treated with immunotherapy, and noted that one of the patients followed for more than 2 years and another for nearly 1 year, no longer had neuropathic symptoms, while two patients had mild residual proximal weakness. In the Dyck *et al.* [7] study, at final telephone follow-up of 31 patients, three were wheelchair bound, and 16 still used an assistive device for walking; only two of the patients reported that they were back to their previous normal state. Despite the fact that the natural history would indicate improvement over time, the significant residua experienced by many patients as well as the shorter term disability of severe pain and weakness warrants search for an effective treatment.

Symptomatic therapy (e.g., pain control measures), physical therapy and gait assistive devices (when necessary) are important parts of the therapeutic regimen in all DLRPN patients. However, given the findings of inflammation and microvasculitis on nerve biopsy, the hope would be that immunotherapy would be effective.

Unfortunately, the data to support immune suppression are limited. Chan *et al.* [14], in a Cochrane review, did not find evidence to support recommendation for immunotherapy in these patients. However, there have been mixed results in the literature, with some findings to suggest immunotherapy may be beneficial. Dyck *et al.* [15] carried out a prospective randomized double-blind trial of intravenous methylprednisolone versus placebo in 75 DLRPN patients, with 12 weeks of tapering treatment; the primary end point was time to improvement in Neuropathy Impairment Score (Lower Limb) by 4 points. There was no statistically significant difference for the primary end point, although the methylprednisolone group met this end point over a month sooner. There was a statistically significant difference in secondary end points of pain and positive neuropathic symptoms, in favor of the methylprednisolone-treated group. The authors indicated that one of the factors in the lack of a difference in the primary end point may have been an extended delay (several months) between symptom onset and initiation of treatment. They concluded that intravenous methylprednisolone was an effective treatment

for pain in DLRPN and that an earlier treatment trial for impairment (weakness) was needed. Pascoe *et al.* [16] did a retrospective review of 44 patients with DLRPN, termed 'subacute proximal diabetic neuropathy', either treated with immunotherapy (prednisone, IVIG or plasma exchange) or not. There was no significant difference in improvement between the two groups, though nine out of 12 treated patients improved, and 17 out of 29 untreated patients improved. The authors noted, however, that the treated group seemed to improve to a greater extent than the untreated group.

The issue of timing in the efficacy of immunotherapy was directly addressed by Kilfoyle [17] who reviewed ten episodes (in nine patients) with diabetic amyotrophy treated with oral or intravenous corticosteroids and compared their course with the natural history of the disease. They noted that in patients treated within 2 months there was a quick improvement in pain, while patients treated within 4 weeks of symptom onset had quick improvements in both pain and strength. This supports the idea that there is a critical period early in the illness when immunotherapy may provide the best results.

There are also individual case reports of diabetic amyotrophy, which noted significant improvement with intravenous corticosteroids [18] and IVIG [19–21].

The practice of the authors is that if a patient appears clinically and electrophysiologically to be in an early, active phase of disease without spontaneous improvement, to treat with a short course of intravenous methylprednisolone (often weekly for 12 weeks) or if there are reasons steroids cannot be given to use a similar course of IVIG. Our practice has been to not further escalate immunotherapy. If the patients are clinically improving we advise not treating with immunotherapy and following them clinically. We re-evaluate the patient at 12 weeks after treatment. If there is no response to corticosteroids or IVIG, the patient is likely in an inactive phase of the disease, and no further immunotherapy is offered. If the patient has clinical improvement with treatment (less pain and improved strength and sensation on neurological examination), we will still typically discontinue the immunotherapy, as the disease is expected to be monophasic and not further progressive. There is a great deal of clinical practice variability in the treatment or lack thereof of the radiculoplexus neuropathies. Larger clinical trials of patients

in an early stage of disease would be helpful in developing a standardized practice.

Although the vast majority of the cases are painful, Garcés-Sánchez *et al.* [22] have expanded on the descriptions of the clinical presentation of DLRPN, by reporting on 23 cases of painless DLRPN. The authors attempted to better characterize the clinical phenotype and pathology of painless, motor and lower limb predominant diabetic neuropathy. While sharing some characteristics with classic DLRPN as described above (e.g., similar median age: 62.2 years, associated weight loss, more prevalent among Type 2 diabetics), there are several distinct characteristics. These patients tend to have a more slowly progressive process developing over weeks to months of a motor-predominant neuropathy with a length-dependent presentation. While in 'classical' DLRPN the thigh is most frequently involved, this type of DLRPN has bilateral foot drop as the most common presentation, with upward spread of weakness, which frequently includes the upper extremities. The severity of the weakness differentiates it from DPN, which is sensory predominant, and the patients with painless DLRPN were markedly weak, with approximately half these patients being wheelchair bound at the time of presentation. Most (22 out of 23) did have some degree of sensory loss and a significant minority (nine out of 23) had autonomic symptoms. Nerve conduction studies/electromyography (EMG) showed findings of axonal polyradiculoneuropathy, without findings of temporal dispersion and conduction block. There tended to be mildly slowed conduction velocities and prolonged F-wave latencies, but in the context of decreased compound muscle and sensory nerve action potential amplitudes, arguing that this would not represent a 'diabetic CIDP'.

The nerve biopsy findings in these patients were similar to the 'classical DLRPN' cohort earlier described, with all biopsies showing perivascular and vascular inflammation, mostly involving epineurial vessels. In total, 15 out of 23 had inflammation in vessel walls, and three had destruction of blood vessel walls diagnostic of microvasculitis. Only a single biopsy showed frequent onion bulbs. In total, 13 of the 16 patients with follow-up at the same institution were treated with immunotherapy (IVIg, intravenous methylprednisolone or plasma exchange). When looking at this group as a whole, similar to classical DLRPN, there was improvement in

the clinical syndrome over time, including in both treated and nontreated patients, although the number of nontreated patients in this study was very small. The findings would suggest that like the painful DLRPN, this too is a monophasic process, with a probably natural history of improvement. That being said, the long-term data for this particular variant is limited, and further study needs to be performed regarding long-term rate of recurrence/progression, and relative utility of immunotherapy, as well as relative response to treatment compared with classical DLRPN patients, given the greater severity of weakness found in the painless variant group. This study helped increase our understanding of the clinical spectrum of the inflammatory radiculoplexus neuropathies.

Dyck *et al.* [23] reported on a nondiabetic variant, referred to simply as nondiabetic lumbosacral radiculoplexus neuropathy, with similar presentation to classical DLRPN, with asymmetrical lower extremity pain and weakness. The median age was 70 years old, the majority had weight loss, and approximately a half had autonomic symptoms. In total, 26 out of 57 had some milder upper extremity involvement. Nerve conduction studies and EMG showed low amplitude sensory nerve and compound motor action potentials, and nerve biopsies showed findings consistent with ischemic and microvasculitis. Natural history showed improvement, albeit incomplete, and only three of the patients reported complete recovery over time. Ten of these patients were treated with corticosteroids, with reported improvement. Only two of the 57 patients developed diabetes mellitus over time, one 5 years and the other 7 years after presentation for their neuropathy, suggesting that this syndrome does not merely reflect a very early diabetic phenomenon.

Diabetic cervical radiculoplexus neuropathy

As previously discussed, DLRPN has been found in some cases to have more diffuse neuropathic findings outside the lumbosacral distribution. In the Dyck *et al.* [7] study of DLRPN, three patients were identified who had associated asymmetric but bilateral cervical radiculoplexus neuropathies. Katz *et al.* [24] reported that in 60 patients with DLRPN, nine also had upper extremity involvement, which was one sided in five but bilateral in four; most of the upper extremity symptoms improved over a several-month period.

In some cases, upper extremity involvement occurs in isolation, or is the predominant neuropathic feature; these cases have been termed diabetic cervical radiculoplexus neuropathy. Massie *et al.* [25] described 85 patients with upper limb involvement, usually pain followed by weakness, more common in Type 2 diabetic patients. In total, 25 of these had a pan-plexopathy. There was not a predilection for a particular nerve trunk in this syndrome. Many had involvement of other segments of nerve, and 30 of these patients had contralateral findings. Nerve conduction studies/EMG showed an axonal process. CSF proteins were elevated. Nerve biopsies showed ischemic injury, inflammation, and in some, microvasculitis.

The data on diabetic cervical radiculoplexus neuropathy treatment are even more limited than for DLRPN, but since the underlying pathological findings are similar, one would anticipate that therapeutic interventions would be similarly effective. In the Massie *et al.* [25] study, 32 patients received immunotherapy and half of these noted some benefit, with pain the primary area of improvement. Wada *et al.* [26] described a single patient with bilateral shoulder girdle weakness, followed by lower extremity weakness, which was felt to be an upper limb predominant diabetic amyotrophy, who had 'marked improvement' with IVIG.

Diabetic chronic inflammatory demyelinating polyradiculoneuropathy

CIDP is an immune-mediated disorder of the myelin sheath surrounding peripheral nerves, which can progress over time to cause secondary axonal injury, leading to greater long-term disability. CIDP is, in its classical form, a motor-predominant, symmetrical, proximal and distal neurogenic syndrome, which clinically manifests as diffuse weakness. It can be progressive, usually slowly, or relapsing–remitting and is a chronic disorder (neurological worsening for more than two months in duration). Large fiber sensory loss is often present, although weakness is generally the predominant symptom. Pain should not be a prominent feature, although some patients do experience pain. The diagnosis of CIDP is based mostly on clinical grounds, although electrophysiological studies are also important, and should show evidence of demyelination (e.g., slowed conduction velocities, prolonged distal and F-wave latencies, and often temporal dispersion and/or conduction block). Often there are

changes of secondary axonal loss/denervation (e.g., low motor and sensory amplitudes, long duration poorly recruited motor units, fibrillations and/or positive sharp waves). There are several criteria proposed in the literature for the diagnosis of CIDP [27–30].

A major differential diagnostic consideration is hereditary motor and sensory neuropathy type 1 (Charcot-Marie-Tooth disease Type 1), which is an inherited primary demyelinating neuropathy, though family history and clinical course should be very helpful in distinguishing CIDP from this. Connexin-32 genetic abnormalities, producing an X-linked Charcot–Marie–Tooth disease, may also appear similarly electrophysiologically (temporal dispersion and conduction block). Conventional wisdom holds that temporal dispersion and conduction block are most predictive of an acquired rather than an inherited neuropathy, whereas inherited neuropathy usually will have uniform demyelination but this does not always hold true. The diagnosis of CIDP can also be difficult when there is accompanying marked axonal loss, and the distinction between whether the demyelinating or the axonal process is primary may be unclear. In addition, while the classical CIDP described symmetrically involves the peripheral nervous system from nerve roots down to distal peripheral nerve, there are multiple subcategories of focal CIDP identified (e.g., multifocal acquired demyelinating sensory and motor neuropathy, also known as Lewis–Sumner syndrome, chronic inflammatory demyelinating mononeuropathy and chronic inflammatory sensory radiculopathy). The natural history and treatment responsiveness of many of these subtypes is yet to be clearly defined.

There is an entity reported as 'diabetic CIDP', which is controversial as it may be a coincidental occurrence given the frequency of diabetes mellitus in the general population. Furthermore, some of the cases called diabetic CIDP may really have a diabetic radiculoplexus neuropathy. Another complicating issue is the frequent coexistence of electrophysiological findings of axonal loss and demyelination in diabetic polyneuropathy, which, in some cases, could be overinterpreted as CIDP. Given the clinical findings of DPN in most cases being predominantly sensory, Uncini *et al.* [31] suggested that the diagnosis of CIDP could be made in a diabetic patient, whose symptoms were primarily motor, and met three quarters of the electrophysiological

criteria for demyelination outlined in the *Ad Hoc* Subcommittee of the American Academy of Neurology AIDS Task Force [27]. They also indicated that if only two of the criteria were met, that an empiric trial of immunotherapy could be considered.

Sharma *et al.* [32] reviewed patients with and without diabetes mellitus who presented in their electrodiagnostic laboratory and looked for frequency of CIDP in those populations, and estimated that the odds of CIDP were 11 times higher in the diabetic population. Laughlin *et al.* [33] did a population-based study of CIDP in diabetes mellitus. The authors emphasized the clinical features over the electrophysiological features since diabetic polyneuropathy can suggest demyelination on nerve conduction studies. They reported that there was no increased prevalence of CIDP in diabetic patients in a large population-based study, although they noted a small effect could not be excluded. The authors felt that the perceived association of CIDP and diabetes mellitus may be due to misclassification of other forms of diabetic neuropathy (especially of diabetic radiculoplexus neuropathy) as CIDP. Most of the diabetic neuropathies thought to have CIDP that in the end were due to a different cause still had inflammatory neuropathies.

In a study addressing potential mimickers of CIDP in diabetic patients, Garcés-Sánchez *et al.* [22] evaluated the pathological cause of painless, motor and lower limb predominant diabetic neuropathy in 23 biopsied cases. The authors noted that CIDP usually involves large myelinated fibers most severely, and these fibers are motor predominant and that pain fibers are usually not significantly involved. Therefore, if there is a diabetic CIDP, it should be a motor predominant neuropathy without a significant pain component. The nerve biopsies showed evidence of ischemic injury (multifocal fiber loss, perineurial thickening, neovascularization and injury neuroma) from an inflammatory vasculopathy (inflammatory collections, hemosiderin-macrophages and microvasculitis) and little evidence of inflammatory demyelination. The authors concluded that the painless, motor predominant neuropathy can also be part of the spectrum of diabetic radiculoplexus neuropathies and does not necessarily represent CIDP.

We conclude that CIDP clearly occurs in diabetic patients but it is less clear if the diabetes mellitus is important in the pathogenesis of the inflammatory demyelinating neuropathy.

The treatment of ‘classical CIDP’ (symmetrical, motor predominant, proximal and distal weakness neuropathy) has primarily consisted of corticosteroids, intravenous immunoglobulins and plasma exchange [34]. Dyck *et al.* [35] performed a trial in which 28 CIDP patients were given oral prednisone for 3 months, and showed some improvements in strength. Lopate *et al.* [36] studied CIDP patients who had received intravenous methylprednisolone and found improvement in strength in 81% of these patients, not significantly different from treatment with IVIG or oral prednisone or cyclosporine.

IVIG is frequently used in CIDP, both because of its efficacy and in an attempt to avoid the long-term side effects of corticosteroid use, the downside being that this is a more expensive agent. Hughes *et al.* [37] performed a large placebo-controlled trial with a routine follow-up period, a crossover component for nonresponders and an extension component for responders. After a 24-week period, 54% of IVIG-treated patients, and 21% of the placebo patients showed an improvement in INCAT disability score, which was statistically significant in favor of IVIG. There was only a 13% probability of relapse with IVIG treatment during the 24-week extension phase, with a 45% probability of relapse in the placebo group.

Dyck *et al.* [38] performed a prospective placebo-controlled trial of plasma exchange in CIDP, with 29 patients given either plasma exchanges or sham exchanges for 3 weeks, with significant improvement in combined nerve conduction measures in the treated patients. Hahn *et al.* [39] performed a double-blind controlled crossover trial of PLEX in 18 patients with CIDP; of the one patient who completed the trial, 80% had a significant improvement with treatment. Another study by Dyck *et al.* [40] compared treatments with IVIG and plasma exchange and did not show a significant difference in outcomes. The authors concluded that both treatments were effective in CIDP.

In addition to corticosteroids, IVIG, and plasma exchange, several other immunomodulatory agents have been tried for the treatment of CIDP; the data for most of these individual agents are limited. Azathioprine is a commonly used steroid-sparing agent, and there have been some reports of efficacy, with four out of five treated patients (with concomitant use of corticosteroids/adrenocorticotropic hormone allowed) showing sustained improvement in the

Pentland *et al.* [41] study, and Dalakas and Engel [42] reporting efficacy in three of four patients. However, a randomized controlled trial of prednisone versus prednisone and azathioprine did not show a significant difference in response [43], although the azathioprine dosing and length of follow-up may have been suboptimal.

A randomized controlled trial of methotrexate or placebo (in patients already on corticosteroids or IVIG) failed to show a significant difference in the primary end point of 20% reduction in mean weekly dose of either the corticosteroid or IVIG by the end of the trial (40 weeks) [44]. A smaller retrospective study of methotrexate in CIDP showed some improvement of muscle strength in seven out of ten patients [45]. There has been mixed data regarding mycophenolate mofetil, with Umapathi and Hughes reporting on four patients with CIDP, two of whom were felt to have only a minimal response, and both subsequently stopped mycophenolate mofetil because of side effects [46]. Gorson *et al.* reported on 13 patients with CIDP on mycophenolate mofetil and did not find significant improvements in strength, sensation or disability, but did comment that three of the patients had some clinical improvement [47].

Rituximab has shown promise, with a retrospective study of 13 CIDP patients either refractory or prior immunotherapy or requiring frequent courses of IVIG or PLEX for management showing a good response in nine of those patients treated with rituximab (375 mg/m² weekly for 4 weeks) [48]. Cocito *et al.* [49] reviewed CIDP patients who did not have good response to conventional therapy, who were then treated with different second-line agents, and identified 18 patients treated with rituximab, 33% of whom had a good response.

Other agents not as commonly used, except for more refractory cases, because of side-effect profile, include cyclosporine and cyclophosphamide. Both Barnett *et al.* [50] and Matsuda *et al.* [51] found improved disability scores in treatment-refractory CIDP patients with the use of cyclosporine, and Mahattanakul *et al.* [52] found benefit in three out of eight CIDP patients treated with cyclosporine. Good *et al.* [53] found that 11 out of 15 CIDP patients treated with intravenous cyclophosphamide had a complete remission, and Brannagan *et al.* [54] reported on four patients with only partial response to alternate immunotherapy who were treated with cyclophosphamide and showed improvements.

Very rarely, stem cell transplantation has been used, with individual cases reported with good outcome [55,56], and good outcome followed by relapse 5 years later [57].

A recent randomized clinical trial of intramuscular interferon β -1a in patients with IVIG-dependent CIDP treated 67 patients with either placebo or one of four different dose regimens of IFN- β 1a, with discontinuation of IVIG half-way through the trial and reinstatement of IVIG as needed based on clinical response. Unfortunately, there was no significant difference in the primary outcome, which was amount of IVIG needed in the second half of the trial (weeks 16–32) [58]. Alemtuzumab was used for treatment of seven patients with refractory CIDP and found to cause reduction of mean monthly IVIG use by 25%; two patients had a prolonged remission, two had a partial remission and three had no benefit. Importantly, three patients were felt to have immune-mediated complications, one with an isolated elevation of anti-TPO antibodies, one with elevated anti-TPO antibodies who subsequently developed Graves' disease, and another with an autoimmune hemolytic anemia, with difficult management, who died shortly after splenectomy [59]. Another case report of a treatment-refractory patient with CIDP reported some clinical response to alemtuzumab, although with ongoing clinical relapses [60].

The data for treatment of idiopathic CIDP provide important guidelines regarding the first-line options and several possible second-line options. However, the data for treatment of CIDP in the context of diabetes are much more limited. Since the underlying pathophysiological process of immune-mediated demyelination should be similar, if not the same, one would postulate the above data for idiopathic CIDP should hold true for diabetic CIDP. There is limited literature regarding responsiveness (and relative responsiveness) of CIDP in diabetic patients.

Stewart *et al.* [61] reported on seven diabetic patients who developed progressive distal greater than proximal lower extremity motor weakness and atrophy over an 8-month to 2.5-year period; the weakness was quite severe, and four were wheelchair bound. All patients had some sensory loss over the course of their syndrome. Electrodiagnostic studies showed demyelinating features, as well as some degree of denervation/reinnervation changes. All patients were treated with immunotherapy (corticosteroids, IVIG,

plasma exchange, and/or azathioprine) and all had improvements (all but 1 by at least 2 modified Rankin scale grades).

Gorson *et al.* [62] published a thoughtful retrospective study comparing the clinical course, electrophysiological features, and treatment responsiveness between 14 patients with both diabetes mellitus and CIDP and 60 patients with idiopathic CIDP. The clinical features of the two groups were similar with the exception of an older age, and more imbalance in the diabetic group. The electrophysiological features showed more changes of axonal loss in the diabetic group. The authors note that similar proportions of patients responded to the various immunotherapies attempted (corticosteroids, IVIG, plasma exchange, cyclophosphamide), but that the extent of improvement was less in the diabetic CIDP group, which they believe is secondary to the greater amount of axonal loss in the diabetic group. This finding may be due to a coexisting diabetic polyneuropathy.

Haq *et al.* [63] retrospectively compared ten patients with idiopathic CIDP and nine patients with diabetes mellitus and demyelinating polyneuropathy, who had similar clinical, electrodiagnostic findings. Nerve biopsy findings in both groups showed similar rates of demyelination and remyelination on teased fibers, subperineurial and endoneurial edema, presence of onion bulbs and perivascular mononuclear inflammation, although the number of fibers with demyelination was significantly higher in the idiopathic CIDP group. In total, eight of the idiopathic and six of the diabetic patients were felt to be affected severely enough to warrant immunotherapy and were treated with prednisone with or without plasma exchange, IVIG or azathioprine. A positive treatment response was defined by the authors as if “patients were cured, significantly improved, or able to return to their previous occupation and were functioning independently for a minimum of 3 months”. All the treated patients in the idiopathic and diabetic groups showed a positive treatment response.

Sharma *et al.* [64] performed an open-label trial of 26 patients with diabetes mellitus and CIDP, who were given IVIG (0.4 g/kg for 5 days), the mean Neuropathy Impairment Score significantly improved by the end of a 4-week period. In total, 80.8% of their group showed an improvement.

Given the rarity of the combination of diabetes mellitus and CIDP, there will likely continue

to be limitations in acquiring enough patients for larger, more definitive, prospective, randomized and controlled trials to determine the best types of immunotherapy in diabetic CIDP patients. The current, retrospective, noncontrolled data would suggest that the typical first-line agents used in idiopathic CIDP are effective in diabetic CIDP patients as well. The choice of a first-line agent will likely be determined by multiple factors, including the severity of underlying diabetes mellitus and ability to tolerate the side effects (including but not limited to hyperglycemia) of corticosteroids, as well as the cost and availability of treatment. At this stage, there are not enough data to make recommendations regarding choice of second-line agents, and this should be determined on a case-by-case basis, relating to severity of underlying disease, refractoriness to first-line agents, and other comorbidities (e.g., renal or hepatic disease). As noted above, it is not clear that diabetes mellitus and CIDP are causally linked.

Conclusion & future perspective

Inflammatory diabetic neuropathies are very important to recognize, as their management and prognosis are different from the more common diabetic neuropathies, such as DPN and compressive neuropathies. Radiculoplexus neuropathies are of three types – lumbosacral, cervical and thoracic and can occur alone or in combination. They have an inflammatory pathophysiology and are due to microvasculitis from ischemic injury and in most cases, appear to be monophasic, with a natural history of improvement over time, although improvement is incomplete in many. Supportive therapies and pain control are important, and while the data are mixed, immunotherapy, specifically intravenous methyl-prednisolone, is likely to be beneficial, particularly in pain relief. The apparent disconnect between the inflammation seen on nerve biopsy and the limited clinical response to immunotherapy in controlled trials described in the literature may be secondary to timing of treatment. The authors feel it is likely that immunotherapy earlier in the course of the disease process would provide benefit, but further controlled trials need to be done to more definitively address this question.

Diabetic CIDP is still a controversial entity, and it is unclear if this is just the coincidental occurrence of two separate disease processes; the literature is controversial regarding the

frequency of CIDP in diabetic versus non-diabetic patients. It is the authors' view that there likely is not a pathophysiological association between the two conditions and that some of the cases called diabetic CIDP have forms of radiculoplexus neuropathy such as the painless, motor and lower limb predominant neuropathy. Nonetheless, those patients who are diagnosed with diabetic CIDP likely have an inflammatory neuropathy that should be treated with immunotherapy. The data available would indicate that CIDP in diabetic patients is responsive to the typical first-line agents used for idiopathic CIDP – corticosteroids, IVIG and plasma exchange. Benefit may be limited by a separate DPN with associated axonal loss, which would not be expected to be

immunotherapy responsive. Further comparative data with larger populations of idiopathic and diabetic CIDP patients would be helpful to see if there are consistent differences between the two groups and to assess for differences in treatment responsiveness.

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