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Treatment of Diabetic and Nondiabetic Lumbosacral Radiculoplexus Neuropathy

Pariwat Thaisetthawatkul, MD[1]
P. James B. Dyck, MD[*]

Address
*Peripheral Nerve Research Laboratory, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
Email: Dyck.PJames@mayo.edu
[1]Department of Neurological Sciences, 982045 Nebraska Medical Center, Omaha, NE 68198–2045, USA

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Opinion statement

Lumbosacral radiculoplexus neuropathy (LRPN) is a multifocal, asymmetric, painful neuropathic disorder affecting multiple levels of lumbosacral plexus, nerve roots, and distal nerves that emerge from the plexus. The disorder was first described in diabetic patients (DLRPN) and was later found to occur in nondiabetic patients as well. There have been debates as to the pathogenesis of DLRPN and LRPN. Recent detailed and extensive pathologic studies, however, have shown that the main pathogenesis is inflammation and microvasculitis affecting various components in the peripheral nerves, resulting in ischemic injury to the nerves. Even though studies on the natural history of this disorder have shown that the majority of patients recover within a few years after the attack without any treatment (although recovery is incomplete in many cases), it is a common practice, based on the pathophysiology and case series, to administer immunotherapy. Preliminary data from a controlled clinical trial failed to show significant improvement in outcomes measured by neurologic deficits (as judged by the Neuropathy Impairment Score) but did show improvement in symptoms (pain and positive sensory symptoms). Choices of immunotherapy include corticosteroids, intravenous immunoglobulin, plasma exchange, or a combination. Pain management, physical therapy, and treatment of depression remain mainstays for managing this disorder.

Introduction

Lumbosacral radiculoplexus neuropathy (LRPN) is an acute or subacute neuropathic syndrome affecting lower limb nerves at the lumbosacral nerve roots, plexus, and the distal nerves that emerge from the plexus. The clinical picture is that of unilateral or asymmetric bilateral pain, weakness, and sensory loss in the lower limbs. The disorder most commonly occurs in diabetes as diabetic lumbosacral radiculoplexus neuropathy (DLRPN), but LRPN can also occur in nondiabetic patients. DLRPN was initially described in patients who had diabetes mellitus [1] and was called *diabetic amyotrophy* [2] because it was frequently associated with weight loss and muscle atrophy. The disorder was later described under different names, including *diabetic myelopathy* [1], *diabetic neuropathic cachexia* [3], *diabetic femoral neu-*

ropathy [4], *diabetic proximal femoral neuropathy* [5], and *diabetic proximal neuropathy* [6].

There was much debate among early investigators about pathogenesis. Metabolic derangement and ischemic nerve injury were the major theories [7]. Early histopathologic studies frequently showed nonspecific findings in nerve biopsies [3, 8]. The term *proximal diabetic neuropathy* was used to reconcile the debate between cases with rapidly evolving disease from ischemic injury and those with slowly progressive disease from metabolic injury [6]. A later histopathologic study showed evidence of inflammation, ischemia, and vasculitis in the rapidly evolving, severe cases and evidence of metabolic damage in the milder cases [9]. A detailed clinicopathologic study at the Mayo Clinic showed that perivascular epineurial inflammation from microvasculitis was seen in virtually every case of this disorder, and the term *diabetic lumbosacral radiculoplexus neuropathy* was first used to describe this condition because of the involvement of the nerves at the levels of lumbosacral roots, plexus, and peripheral nerves [10]. The study also showed that the segmental demyelination seen in this condition is secondary to axonal degeneration and atrophy caused by ischemic injury and is not related to metabolic derangement, as initially suspected [10]. The study also revealed important clinical features including pain at the onset, followed by weakness; the pain then subsided. Contrary to previous beliefs, DLPRN was not a pure motor syndrome, and sensory and autonomic involvement could be prominent. Most cases occurred while diabetes was under good control, and significant weight loss was seen in most patients with this disorder. Most of the patients improved over time.

A later study on LRPN, a less common variety, revealed clinical symptom profiles and histopathology similar to those in DLPRN [11]. Another study of DLRPN revealed similar distinctive pathologic changes suggestive of an inflammatory cause [12]. Because of the pathology suggesting an immune-mediated process, the authors at the Mayo Clinic recommended that treatment with immunosuppressive therapy should be considered, including corticosteroids, intravenous immunoglobulin (IVIg), or plasmapheresis [13]. A recent study of inflammatory mediators in DLRPN and LRPN also showed upregulation of inflammatory mediators, such as tumor necrosis factor α (TNF-α), nuclear factor κB (NF-κB), and intercellular adhesion molecules, that target different cells at different stages [14].

Treatment

- Even though immunotherapy may seem to improve the condition, based on pathophysiology, a clinical trial has not yet proved its efficacy in significantly improving neurologic deficits. Nevertheless, it is considered a good practice to treat patients with immunotherapy, especially pulsed intravenous methylprednisolone, if the patients are seen early in the course of the illness. It is important to identify patients early in the disease course if improvement with treatment is desired.

Pharmacologic treatment

Corticosteroids

- There has been only one prospective randomized, double-blind, multicenter controlled trial using intravenous methylprednisolone (IVMP) in DLRPN. This study has been presented in abstract form only and has not been fully published [15, Class I]. In that study, 75 patients were

randomized to IVMP ($n=49$) or placebo ($n=26$). The dose of IVMP was 1 g three times weekly, with decreasing dosage and frequency over 12 weeks. The primary outcome measure (improvement in Neuropathy Impairment Score in the lower limbs) was not significantly different between the IVMP group and the placebo group over 104 weeks. However, neuropathic symptoms, especially pain symptoms, improved significantly more in the IVMP group [15, Class I].

- Case series have documented improvement with corticosteroid treatment in patients with DLRPN. In one study, three patients were treated with prednisone, and pain quickly subsided after the treatment. One patient developed gastric ulcer. Strength improved in a few months [9, Class IV]. In another study, two DLRPN patients who had vasculitis or perivascular inflammation confirmed by a nerve biopsy were treated with prednisone at 80 mg/d. Both improved in 2–3 months [16, Class IV]. In another study, two of three patients who received prednisone (50–60 mg/d) had significant improvement, to the point that they were able to walk with help or a cane [17, Class IV]. A retrospective study looked at nine patients with ten episodes of DLRPN receiving treatment with IVMP ($n=7$) or oral methylprednisolone ($n=3$) compared with the published natural history of the disorder [18, Class III]. The dose of methylprednisolone was 500 mg on 2 consecutive days every 2 weeks up to 3 months. The mean symptom duration before treatment was 1.8 months (range, 1 week to 5 months). In all episodes, there was significant improvement within 6 months after treatment [18, Class III].
- In LRPN, there was one open study using IVMP in 11 patients during the time of worsening [19, Class IV]. The dose of IVMP was 1 g/wk for 8–16 weeks. The median pretreatment symptom duration was 5 months (range, 1–48 months). Assessment using the Neuropathy Impairment Score found improvement in all 11 patients during the treatment period. Nine patients judged their improvement as marked. The Neuropathy Impairment Score was significantly improved after treatment.

Intravenous immunoglobulin

- No controlled clinical trials of the use of IVIg in either DLRPN or LRPN have been published. There is one ongoing, randomized, double-blind, placebo-controlled study on the use of IVIg in DLRPN, comparing low-dose IVIg, high-dose IVIg, or placebo. The result is not known at this time [20••].
- Case series have documented improvement in patients with DLRPN who were treated with IVIg. In one study, six patients received IVIg alone and seven patients received a combination of IVIg and prednisone [16, Class IV]. All but one patient improved significantly. The other patient needed azathioprine to maintain improvement. In another study, three of four patients receiving IVIg improved significantly after treatment [17, Class IV]. There are no published studies on the use of IVIg in LRPN.

Other treatments

Plasma exchange

- No controlled clinical trial on the use of plasma exchange in either DLRPN or LRPN has been published. One case series documented improvement in five patients with DLRPN after plasma exchange alone [17, Class IV]. One patient received plasma exchange and prednisone but died, and one received plasma exchange but did not respond and had to switch to IVIg [17, Class IV].

Pain management

- Apart from immunotherapy, pain management remains an important aspect in managing patients with LRPN or DLRPN. Pain is the most common symptom at onset, and usually the most severe [10]. The pain may be lancinating, burning, or tightness. It can last for many months and becomes disabling.
- Evidence from the clinical trial shows that the use of immunotherapy such as IVMP helps relieve the pain early and effectively [15, Class I]. In the long run, however, antiseizure or antidepressant medications such as gabapentin, duloxetine, pregabalin, amitriptyline, nortriptyline, or imipramine can be used to manage neuropathic pain. Pain management clinics are helpful for many patients.
- In patients who have longstanding pain or weakness, depression may become an important issue and needs to be managed accordingly.

Physical/speech therapy and exercise

- Physical therapy and rehabilitation are important in managing patients with these disorders because of the marked asymmetric weakness in the lower limbs.

Assistive devices

- Wearing an ankle brace can help walking and prevent falls for patients with foot drop.

Prognosis

- Improvement occurs in almost all patients with both DLRPN and LRPN, even though recovery is delayed and is incomplete in many cases [13]. For most patients, the recovery is incomplete even at 2 years, although most patients are much improved [13]. A potential problem in a controlled study was that recruitment occurred late (6 months after symptom onset), so the maximal deficit may already have been reached and improvement may just have reflected the natural history of the disorder [15, Class I]. Future clinical trials should consider recruiting patients at an early stage of the disease.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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A recent, in-depth review on therapeutic options in these disorders.