

# Diabetic Neuropathy Part 2

## Proximal and Asymmetric Phenotypes

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### KEYWORDS

- Diabetic asymmetric neuropathies • Diabetic amyotrophy
- Focal diabetic neuropathy • Diabetic lumbosacral radiculoplexopathy
- Symmetric diabetic amyotrophy

### KEY POINTS

- Diabetic neuropathy presents with varied manifestations, including proximal and asymmetric types.
- Except for entrapments, diabetic amyotrophy is the most common form of asymmetric diabetic neuropathy.
- Diabetic amyotrophy can present asymmetrically or symmetrically, with a rapid or insidious onset.
- Symmetric form of diabetic amyotrophy can be indistinguishable from chronic inflammatory demyelinating polyneuropathy.
- Treatment of diabetic amyotrophy with intravenous immunoglobulin or immunosuppressive drugs is controversial.
- Truncal radiculopathy can cause abdominal muscle weakness.
- Patients with diabetes can develop third, fourth, sixth, and seventh cranial nerve palsies.
- Patients with diabetes are more susceptible to compression mononeuropathies than those who are not diabetic.
- Muscle infarction can also be seen in diabetic individuals and is clinically distinct from diabetic amyotrophy.
- Treatment is mostly strict diabetic control and supportive in most of these conditions.

### INTRODUCTION

Distal symmetric polyneuropathy is most common type of neuropathy associated with diabetes; however, many subtypes of diabetic neuropathies were defined even as early as in the 1800s.<sup>1-4</sup> Included in these descriptions are patients with proximal

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diabetic neuropathy, truncal neuropathy, limb mononeuropathies, and cranial neuropathies (**Box 1**). Bruns<sup>5</sup> focused further on the entity of proximal diabetic neuropathy. Various theories have been proposed for the pathogenesis of these neuropathies. Treatment in most cases is tight and stable glycemic control and pain management. A practical approach to the diagnosis and management of asymmetric and focal diabetic neuropathies is reviewed in this article.

## ASYMMETRIC/FOCAL NEUROPATHIES

### *Diabetic Lumbosacral Radiculoplexopathy (Diabetic Amyotrophy, Bruns-Garland Syndrome, Proximal Diabetic Neuropathy)*

The most common, and often misdiagnosed, multifocal asymmetric diabetic neuropathy is the lumbosacral radiculoplexopathy syndrome (DLSRP).<sup>6</sup> This disorder has been referred to by many names, including proximal diabetic neuropathy, ischemic mononeuropathy multiplex, femoral or femoral-sciatic neuropathy, and most often, diabetic amyotrophy and the “Bruns-Garland syndrome,” after the 2 physicians who first reported this entity.<sup>5–21</sup> Bruns<sup>5</sup> first described diabetic patients with asymmetric proximal weakness and pain in 1890. Later, Garland,<sup>13</sup> in the 1950s, used the term diabetic amyotrophy because of the muscle atrophy in the thighs. But this term can falsely imply that the primary lesion is on the muscle and therefore we use the term DLSRP.

#### **Clinical presentation**

DLSRP syndrome affects an older group of diabetic individuals, more frequently men, usually older than 50, but occasionally we have seen the syndrome in middle-aged diabetic individuals. Most patients have type 2 diabetes mellitus; however, this can occur even in individuals with type 1 diabetes. In a series of 27 patients reported by Coppack and Watkins,<sup>22</sup> 24 patients had type 2 diabetes mellitus and 3 had type 1 diabetes mellitus. The development of this neuropathy is often unrelated to glucose control or the duration of glucose intolerance. DLSRP can be the presenting manifestation leading to the initial diagnosis of diabetes.

This neuropathy begins with severe unilateral pain in the back, hip, or thigh, which subsequently spreads to the other side within weeks to months.<sup>6,19,22</sup> Patients are frequently misdiagnosed as having a compressive lumbosacral radiculopathy. Some patients undergo unnecessary lumbar surgery despite minor changes on lumbar magnetic resonance imaging (MRI) scan. Given the associated weight loss, patients are often suspected to have a pelvic tumor. Within days to weeks of the pain onset, patients develop weakness in typically proximal and, to a lesser extent, distal leg muscles.

#### **Box 1**

##### **Clinical classification of asymmetric diabetic neuropathies**

###### *Asymmetric/Focal and Multifocal Diabetic Neuropathies:*

Diabetic lumbosacral radiculoplexopathy (Bruns-Garland syndrome; diabetic amyotrophy; proximal diabetic neuropathy)

Truncal neuropathies (thoracic radiculopathy)

Cranial neuropathies

Limb mononeuropathies

On examination, there is weakness of hip flexors, adductors and extensors, knee flexors and extensors, and ankle dorsiflexors and plantar flexors of varying degree. Profound atrophy of the thigh and at times distal lower extremity muscles develops. Weakness usually encompasses multiple root or plexus levels and is rarely isolated to an individual root or peripheral nerve. Thus, in cases in which knee extension weakness is prominent and the possibility of a diabetic “femoral neuropathy” is considered, if one looks closely at other L2–L4 muscles either on the neurologic examination or with needle electromyography (EMG), the disease process can usually be found in these adjacent areas. Similarly, if there is a significant foot drop, there is also usually evidence of involvement in tibial or other L5 innervated muscles, and the process is actually not confined to the peroneal nerve. There is usually distal sensory loss, but this is often indistinguishable from the sensory abnormalities of distal symmetric polyneuropathy (DSPN), which often is present before the development of the radiculoplexopathy. Loss of knee and ankle reflexes is common.

Although the condition usually begins in one leg, spread to the other leg within weeks or months is rather frequent. The disorder worsens in a gradually progressive or stepwise manner. Cases have been documented in which there is worsening for 18 months.<sup>6</sup> Eventually, the process stabilizes and gradually improves, although the recovery may take many months. In many cases, some degree of permanent weakness may persist (**Fig. 1**).<sup>6</sup>

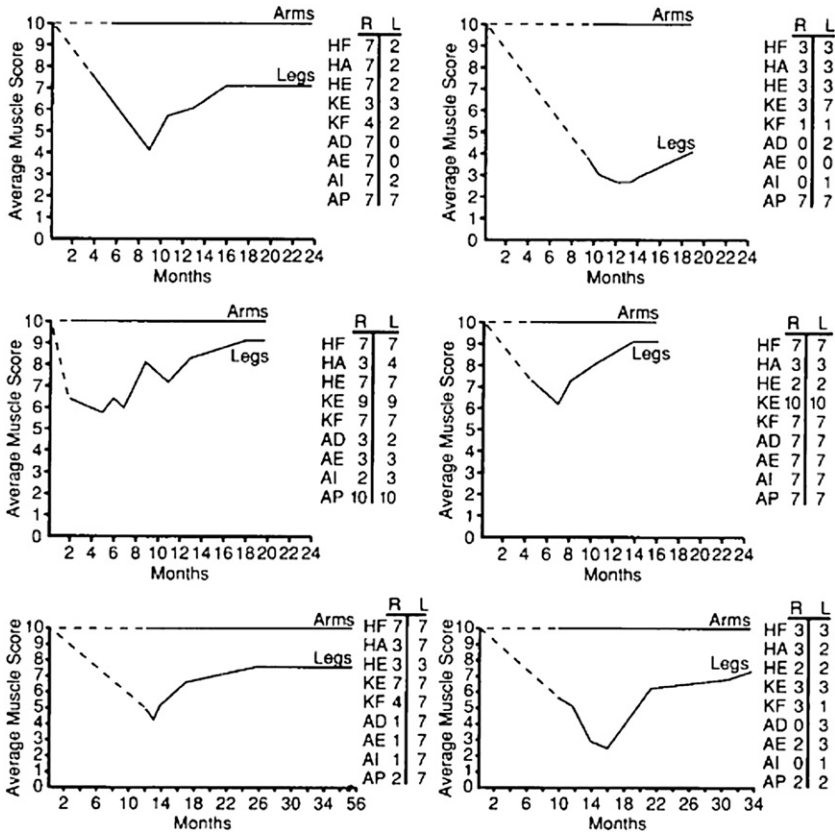
In about one-third of the cases, weakness spreads to proximal arm muscles and is attributed to cervicobrachial radiculoplexopathy.<sup>11,19,23</sup> Approximately 12% of patients develop thoracic radiculopathy, leading to radiating pain in the chest or abdomen and intercostal muscle weakness.<sup>24,25</sup> Respiratory weakness has also been described with this neuropathy.<sup>26</sup>

### **Diagnostic workup**

Electrophysiologically, nerve conduction study findings may not differentiate DLSRP neuropathy from DSPN, except for an asymmetric reduction of the femoral compound muscle action potential amplitudes in unilateral cases. However, the needle EMG reveals abundant fibrillation potentials in weak proximal and distal leg muscles, as well as in the lumbosacral paraspinal muscles.<sup>6</sup> The cerebrospinal fluid (CSF) protein is often elevated, usually between 60 and 100 mg/dL, but occasionally as high as 400 mg/dL. The erythrocyte sedimentation rate may be elevated as well, but is usually less than 50 mm/h. MRI with gadolinium may show nerve root enhancement.<sup>27</sup>

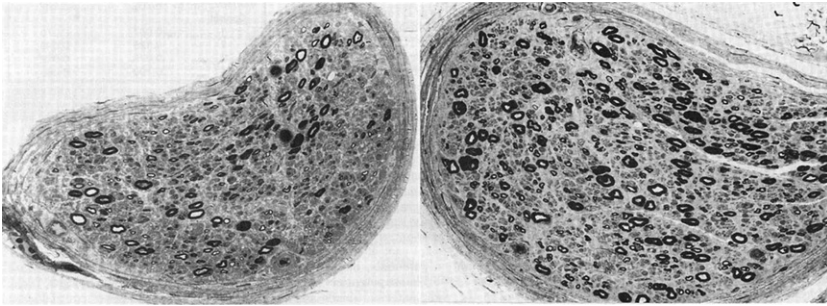
Sural nerve biopsy is not essential to the diagnosis of DLSRP syndrome. When done to exclude mimics, it shows significant fiber loss, often in an asymmetric fashion within and between fascicles, resembling focal ischemia (**Fig. 2**).<sup>6,9–11</sup> An ischemic pathogenesis was documented by Raff and colleagues<sup>7,8</sup> in an autopsy study showing infarcts of proximal nerve trunks of the leg and lumbosacral plexus. Asymmetric fiber loss in sural nerve may support this theory; however, it should be remembered that even patients with typical DSPN may show this multifocal pattern at times. The presence of occasional thinly myelinated fibers on plastic-embedded sections or short, thin segments on teased nerve fiber preparations should not lead the physician to diagnose a demyelinating neuropathy, as these findings can be seen in DSPN as well. However, it should be emphasized that the electrophysiologic, biopsy, and laboratory features are often not particularly helpful, and the diagnoses of DLSRP is primarily clinically based on the history and neurologic examination.

There is probably a small subset of diabetic patients with amyotrophy who develop a painless, symmetric proximal neuropathy involving the lower extremities. Asbury,<sup>21</sup>



**Fig. 1.** Course of muscle strength in 6 patients showing progressive leg weakness. Broken lines represent the period before the initial evaluations. Solid lines represent the course during our serial examinations. The average muscle score, shown in the table adjacent to each graph, is based on a modified Medical Research Council scale expanded to a 10-point scale (see text). The scores for leg strength are those at the nadir of the illness. AD, ankle dorsiflexion; AE, ankle eversion; AI, ankle inversion; AP, ankle plantar flexion; HA, hip abduction; HE, hip extension; HF, hip flexion; KE, knee extension; KF, knee flexion; L, left; R, indicates right. (From Barohn RJ, Sahenk Z, Warmolts JR, et al. The Bruns-Garland syndrome (diabetic amyotrophy): revisited 100 years later. *Arch Neurol* 1991;48:1130-5; with permission.)

favoring the term proximal diabetic neuropathy, considered that there was a spectrum ranging from asymmetrical cases with a rapid onset to patients with symmetric proximal weakness of insidious onset. Chokroverty and colleagues<sup>16,17</sup> emphasized insidious bilateral onset of proximal weakness. Pascoe and colleagues<sup>11</sup> published a Mayo clinic series of 44 patients with symmetric proximal weakness that has a more restricted distribution and seems to be monophasic and self-limiting, differentiating from chronic inflammatory demyelinating neuropathy (CIDP). However, the symmetric presentation seems to be uncommon and tends to occur more often in young type 1 diabetic individuals who are having poor glycemic control. Therefore, we have divided the proximal diabetic amyotrophies (DAM) into 2 forms: DAM-1 and DAM-2 (Table 1).<sup>28</sup>



**Fig. 2.** Cross sections of sural nerve fascicles, 1- $\mu$ m thick. Nonrandom fiber loss is more apparent and more severe in the left than in the right. (From Barohn RJ, Sahenk Z, Warmolts JR, et al. The Bruns-Garland syndrome (diabetic amyotrophy): revisited 100 years later. *Arch Neurol* 1991;48:1130-5; with permission.)

If asymmetric diabetic neuropathies occur in only about 1% of the diabetic population, we think the painless, symmetric form of diabetic amyotrophy (DAM-1) is even more uncommon. This form superficially resembles idiopathic CIDP. We believe that for every 10 to 20 patients with asymmetric/painful amyotrophy (DAM-2) seen at a tertiary care neuromuscular centers, only one DAM-1 patient will be seen. Whether or not the pathogenesis of DAM-1 is different from DAM-2 and is more in line with metabolic dysfunction is unknown.

### Management

Treatment is centered around pain control and strict glycemic control. Both groups spontaneously improve over a period of months. Physical therapy can assist in improving functional mobility.

Controversy involving DLSRP is whether or not there is an immune-mediated pathogenesis component and if patients respond favorably to immunomodulating therapy. This concept was first introduced by Bradley and colleagues<sup>29</sup> in 1984 in their report of 6 patients with a painful lumbosacral plexopathy, elevated sedimentation rate, mild

Table 1 Diabetic amyotrophy: 2 presentations		
	DAM-1	DAM-2
Type of DM	Type 1 >2	Type 2 >1
Onset in legs and progression	Bilateral/Insidious Chronic	Unilateral/Acute Stepwise/Goes to other leg
Distribution	Symmetric proximal	Asymmetric proximal and distal
Pain	No	Yes
Sensory symptoms	No	Yes
Poor DM control	Yes	Yes
Weight loss	Yes	Yes
Spontaneous improvement	Yes	Yes
Frequency	Very, very rare	Uncommon: ~1%
Spread to arm	Yes: ?Common	Yes: 10%

*Abbreviations:* DAM, diabetic amyotrophy; DM, diabetes mellitus.

perivascular inflammation on sural nerve biopsy, and asymmetric nerve fiber loss. Five were treated with immunosuppressive drugs (prednisone alone or prednisone and cyclophosphamide) and 4 improved or stopped progressing. They did not believe the diabetic individuals had typical DLSRP because “they continued to deteriorate and to have pain for several months despite careful control of the diabetes, and only began to improve following treatment with prednisone, although this therapy worsened their diabetes.” Thus, Bradley and colleagues<sup>29</sup> felt the diabetes in their patients was incidental. Of course, others have also reported idiopathic lumbosacral plexitis in nondiabetic patients (analogous to idiopathic brachial plexitis).<sup>30,31</sup> Interestingly, in the earlier reports of idiopathic lumbosacral plexitis, patients improved spontaneously. Verma and Bradley<sup>32</sup> advocated the use of intravenous immunoglobulin (IVIG) for idiopathic lumbosacral plexitis.

Krendel and colleagues<sup>33</sup> (in 1995) reported their experience using immunotherapy in 21 patients with diabetic neuropathy. They divided their patients into 2 groups: Group A consisted of 15 patients who had “multifocal axonal inflammatory vasculopathy” and most of these patients seemed to correspond to what we described previously as DLSRP. Group B patients consisted of 6 diabetic individuals who had both arm and leg involvement, and although in 3 patients the process was asymmetric, the investigators stated this group had “demyelinating” neuropathy by electrophysiologic criteria. Group A patients had perivascular inflammation on nerve biopsy and group B patients had “onion bulbs” but no inflammation. All patients received some form of immunomodulatory therapy (15, IVIG; 13, prednisone; 5, cyclophosphamide; 3, plasma exchange; 1, azathioprine) in various combinations, and all improved. Krendel and colleagues<sup>33</sup> conclusion was that there are 2 forms of immune-mediated neuropathy in diabetic patients that responds to treatment. Younger and colleagues<sup>34</sup> reported their experience finding evidence of inflammation in 20 patients with diabetic neuropathy: 4 had DSPN, 12 had “proximal diabetic neuropathy,” and 4 had mononeuropathy multiplex. All patients with proximal diabetic neuropathy and mononeuropathy multiplex had asymmetric features and we would currently consider them as having DLSRP. As noted in the pathogenesis section see the article by Pasnoor and colleagues elsewhere in this issue, 12 of 20 had some evidence of inflammatory cells, including 2 with DSPN. Younger and colleagues treated 8 patients with IVIG (2 DSPN, 1 mononeuropathy multiplex, 5 proximal diabetic neuropathy), all of whom had perivascular inflammation, and they reported that all improved.

In the Mayo Clinic group series by Pascoe and colleagues,<sup>11</sup> 3 of 9 patients undergoing sural nerve biopsy had a multifocal distribution of fiber loss, and 2 had perivascular mononuclear inflammatory infiltrates. Twelve were treated with IVIG, and 9 improved. Of the 29 untreated patients, 17 spontaneously improved. They concluded that the “efficacy of immunotherapy is unproven but such intervention may be considered in the severe progressive cases or ones associated with severe neuropathic pain.”

The experience of the French group led by Gerard Said is important to note. In an article published in 1994, they reported inflammatory and ischemic lesions in nerve biopsy specimens of the intermediate cutaneous nerve of the thigh in patients with DLSRP.<sup>9</sup> Three patients with “severe and prolonged painful disability” improved dramatically with corticosteroid treatment. In a subsequent report in 1997 of 4 patients with DLSRP, Said and colleagues<sup>10</sup> described patients who had symptoms for 4, 6, 12, and 18 months before biopsy. Although all patients showed perivascular inflammation on nerve biopsy, to the investigators’ surprise, all became pain free with subsequent improvement of their weakness shortly following the biopsy. They concluded that despite the treatment with prednisone they used in their initial article, that

DLSRP “is self-limited and does not require the use of corticosteroids or immunomodulators.” In a series by Dyck and colleagues,<sup>35</sup> all 33 patients with DLSRP had some evidence of microvasculitis on nerve biopsy, and nearly all improved spontaneously. A report by the group from Houston found 18 of 19 patients with DLSRP had substantial improvement without immunomodulating therapy.<sup>36</sup>

Despite many months of persistent symptoms or progression in some patients with DLSRP, eventually all patients spontaneously have resolution of pain and slow improvement of weakness (see **Fig. 1**).<sup>6</sup> Treatment with IVIG or other immunosuppressive drugs is controversial. In a prospective case series, 5 patients with severe pain received IVIG after having no response to symptomatic therapy for pain and corticosteroids.<sup>37</sup> Four had a decrease in pain. In contrast, Zochodne and colleagues<sup>38</sup> in 2003 reported a patient who developed DLSRP while on immunosuppressive regimen consisting of cyclosporine and myophenolate mofetil for an allograft cardiac transplant and 2 patients with DLSRP who did not respond to IVIG treatment, arguing that immunosuppressive therapy did not prevent onset of DLSRP. In our opinion, we do not believe IVIG should be used in patients with DLSRP. At this time, we are not convinced that this form of immunomodulating therapy is indicated. Perhaps this question can be resolved with a controlled trial, but such a trial will be difficult, as each center sees a handful of patients annually and it will be difficult to get the pharmaceutical industry and the Food and Drug Administration to support a large multi-center IVIG trial in this rare disorder.

On the other hand, the experience of Said and Bradley with the improvement of pain with prednisone should not be ignored. According to a recent Cochrane review of immunotherapy for diabetic amyotrophy (DA) only one completed controlled trial using IV methylprednisolone in DA was found.<sup>39,40</sup> High doses of corticosteroids may lead to improvement of severe pain in some patients with DLSRP, and this may be analogous to the improvement of neuropathic pain in patients who are believed to have reflex sympathetic dystrophy.<sup>41,42</sup> Perhaps breaking the pain syndrome in this manner may subsequently allow patients to begin moving their weak extremities easier. Presently, there is no convincing evidence from randomized trial to support any recommendation on the use of any immunotherapy treatment in DLSRP.<sup>39</sup>

We believe one should be cautious about jumping to the conclusion that finding mild perivascular inflammation on biopsy, or demyelination features on either electrophysiology or pathology suggest that DLSRP is a disease that is primarily immune-mediated and will respond to immunomodulating therapy. We cautioned previously about the danger of heavily relying on electrophysiologic evidence of demyelination on nerve conduction studies (NCS) of diabetic patients, as some will fulfill research electrophysiologic criteria for CIDP even though the clinical pattern does not correspond to CIDP, but actually is that of DLSRP. Similar caution should be used with data from nerve biopsies of patients with DLSRP in concluding these patients have either vasculitis or a demyelinating neuropathy. In routine clinical practice, we do not recommend either nerve biopsy or immunomodulating therapy in patients with typical DLSRP. Finally, we would also caution clinicians about splitting patients with otherwise typical DLSRP because of nerve root enhancement on lumbar MRI scan.<sup>27</sup> If other etiologies are excluded by CSF analysis, the mere finding of root enhancement on MRI in DLSRP should not necessarily lead to the initiation of immunomodulating therapy.

### Other DLSRP caveats

**Cervical brachial radiculoplexopathy** Although cervical/brachial plexus involvement is uncommon, it does occur.<sup>11,23</sup> In the classic early Mayo Clinic series of “diabetic

polyradiculopathy” reported by Bastron and Thomas<sup>19</sup> in 1981 of 105 patients, 81 had lower extremity involvement, 15 had upper extremity involvement, and 12 had thoracic/abdominal involvement. Obviously, a few patients had involvement of more than one region. As mentioned previously, in the Mayo Clinic series of Pascoe and colleagues,<sup>11</sup> all 44 patients had (by definition) leg weakness, and 12 of these also had arm weakness (7 bilateral, 5 unilateral). Occasionally, patients with DLSRP develop arm pain and weakness days to weeks after the initial leg symptoms.<sup>43,44</sup> The arm involvement is usually proximal and distal, similar to the pattern of weakness seen in the legs. Interestingly, the arm symptoms can begin or continue to progress after the leg symptoms have plateaued or begun to improve.

Thus, whereas cervical/brachial root and plexus involvement has not been emphasized a great deal in diabetic radiculoplexopathy, the clinician should be aware of this possibility. We do believe that in this setting, a more extensive workup probably is to exclude other disease entities. All of these patients should have a CSF examination for infectious and neoplastic diseases, and nerve biopsy is probably warranted to exclude true vasculitic neuropathy.

**CIDP in diabetic patients** Diabetic patients can develop typical CIDP but, as mentioned previously, there is no increased risk of CIDP in diabetic patients.<sup>45–48</sup> The clinical features of gradually progressive, usually painless, proximal and distal symmetric weakness and numbness in the arms and legs should be sufficient to distinguish CIDP from the typical symmetric and asymmetric diabetic neuropathies; however, the laboratory results in this setting may not be particularly helpful, especially the CSF protein. If there is an underlying diabetic DSPN on NCS and needle EMG, electrophysiologic results can also be relatively unhelpful unless clear-cut and ample features of an acquired, markedly demyelinating neuropathy are present. In addition, nerve biopsy in many diabetic neuropathies can show thinly myelinated fibers, and therefore we usually do not pursue nerve biopsy in this setting. Diagnosis is usually based on the clinical presentation and it is reasonable to proceed with immunomodulating therapy when CIDP is strongly suspected.

**True mononeuritis multiplex in diabetes: does it exist?** Finally, a comment should be made regarding “mononeuritis multiplex” in diabetic patients. We suspect that most of these patients have diabetic radiculoplexopathy, usually lumbosacral, but rarely cervical-brachial. It is uncommon for diabetic patients to develop a true mononeuritis multiplex in which individual distal peripheral nerves (eg, femoral, peroneal, tibial, ulnar, median or radial) are “picked-off” in a subacute or acute fashion. It is difficult to find good documentation of this in the literature. Although the early articles by Raff and colleagues<sup>7,8</sup> use the term “mononeuropathy multiplex,” if one reads of clinical description of their 7 cases, they all had typical DLSRP with proximal and distal involvement not confined to an individual nerve. If a diabetic patient develops a true mononeuritis multiplex, the usual causes need to be pursued (vasculitis, infectious, and hereditary). We believe that if one wants to include diabetes mellitus in the differential diagnosis of true mononeuritis multiplex, it should be at the bottom of such a list.

## OTHER ASYMMETRIC NEUROPATHIES

### *Truncal Radiculopathy*

Another common focal form of diabetic radiculopathy involves isolated thoracic roots.<sup>49–52</sup> This is presumably a focal diabetic radiculopathy that is similar to DLSRP except for the location on the trunk, thorax, or abdomen.



**Clinical presentation**

Patients develop abrupt pain over days to weeks with severe dysesthesias in a dermatomal pattern. In some patients, the pain may not radiate entirely around the trunk in a full radicular pattern, but the symptoms and signs may occur in smaller, restricted regions that imply damage of the dorsal or ventral rami or their medial or lateral branches.<sup>25</sup> Multiple thoracic dermatomes can be involved. Although most cases are unilateral at onset, it can evolve bilaterally, much like DLSRP. In fact, in our experience, it is not uncommon during the evaluation of a patient with typical DLSRP to uncover that at some point over the preceding year or 2 the patient had an episode of truncal pain and dysesthesias, or was diagnosed with truncal “shingles” without a rash. Patients can occasionally develop weakness of the rectus abdominus muscles. Some patients may present with pseudohermia caused by weakening of the abdominal musculature.<sup>49,53</sup>

On the other hand, although most patients do not demonstrate obvious motor involvement, needle EMG can reveal abnormalities in the paraspinous or abdominal wall muscles.

**Diagnostic workup**

Nerve conductions may reveal abnormalities related to distal symmetric polyneuropathy. Needle EMG findings include fibrillations in the paraspinous or abdominal wall muscles.<sup>51,54,55</sup>

**Management**

Treatment is directed at symptomatic pain management, see the article by Pasnoor and colleagues elsewhere in this issue on DSPN, in this volume. Truncal radiculopathy should be distinguished from the wedge-shaped midline area of symmetric truncal sensory loss that can occur in advanced DSPN<sup>50</sup> and from rare discogenic thoracic radiculopathy.

**Prognosis**

The natural history is similar to DLSRP, with persistence of sensory symptoms for weeks to months, with gradual resolution.

**Cranial Neuropathies**

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Diabetic patients can suddenly develop a unilateral third, fourth, sixth, or seventh cranial nerve palsy. The oculomotor nerve was found to be most frequently affected in one study by Greco and colleagues<sup>56</sup> looking at 61 patients with diabetic cranial nerve palsies. The hallmark of diabetic third nerve palsy is pupillary sparing in most cases.

**Clinical presentation**

Retro-orbital pain accompanies about half of the cases. Sparing of the pupil in diabetic third nerve palsies is due to sparing of axons at the periphery of the nerve involved in pupillary function. Pathologic evidence supports the concept that the process is probably attributable to an ischemic watershed phenomenon in the central part of the nerve.<sup>57–60</sup>

It has been suggested that patients with diabetes are more likely to develop a seventh cranial nerve palsy.<sup>61</sup> However, Bell palsy is a common event and it is difficult to substantiate if it is indeed more prevalent in diabetes.<sup>62</sup> It is interesting to note that in the Rochester Diabetic Neuropathy Study, neither cranial mononeuropathies nor truncal radiculopathies were more common in diabetic patients compared with control subjects.<sup>63</sup>

**Diagnostic workup**

Imaging studies may be necessary to rule out stroke in some cases; however, history alone without additional testing is sufficient in most of these patients.

**Management and prognosis**

The main risk factors for the development of cranial neuropathies are duration of diabetes and the patient's age.<sup>64</sup> Treatment should be mainly focused on management of diabetes.

Most patients make a full recovery, with some early evidence of improvement within 2 to 3 months.

**Isolated Mononeuropathies**

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**Clinical presentation**

It is generally believed and established in studies that diabetic individuals are more susceptible to compression injuries compared with nondiabetic individuals.<sup>65</sup> This would include the median nerve at the carpal tunnel, ulnar nerve at the elbow, the peroneal (fibular) nerve at the fibular head, and perhaps the lateral cutaneous femoral nerve (meralgia paresthetica) at the hip. In the early study by Mulder and colleagues<sup>66</sup> in 103 cases of diabetes, 16 had mononeuropathies affecting 29 nerves as follows: common peroneal, 13; median nerve (carpal tunnel), 9; ulnar nerve, 5; lateral femoral cutaneous nerve, 1; and femoral nerve, 1, the latter being likely due to DLSRP. Meralgia paresthetica (mononeuropathy of the lateral femoral cutaneous nerve) is associated with diabetes mellitus irrespective of obesity and advanced age.<sup>67</sup>

In a study from Rochester, Minnesota, there was evidence that carpal tunnel syndrome is more common in diabetes mellitus than in the general population.<sup>68</sup> In another Rochester Diabetic Neuropathy Study, approximately one-quarter of patients had subclinical carpal tunnel syndrome on NCS, but only 7.7% were symptomatic.<sup>63</sup>

**Diagnostic workup**

Diagnosis is usually established with electrophysiologic testing; however, electrophysiologic diagnosis of carpal tunnel or other mononeuropathies is sometimes difficult in individuals with diabetic polyneuropathy. One study showed that segmental and comparative median nerve conduction tests in combination with standard nerve conduction resulted in more accurate diagnosis of carpal tunnel syndrome in patients with diabetic polyneuropathy.<sup>69</sup>

**DIABETIC MUSCLE INFARCTION**

In the context of discussing the various diabetic neuropathies, it is relevant to review another neuromuscular complication of diabetes in which the muscle itself is the target organ rather than the nerve. It is an underdiagnosed complication of long-standing diabetes.<sup>70</sup>

**Clinical Presentation**

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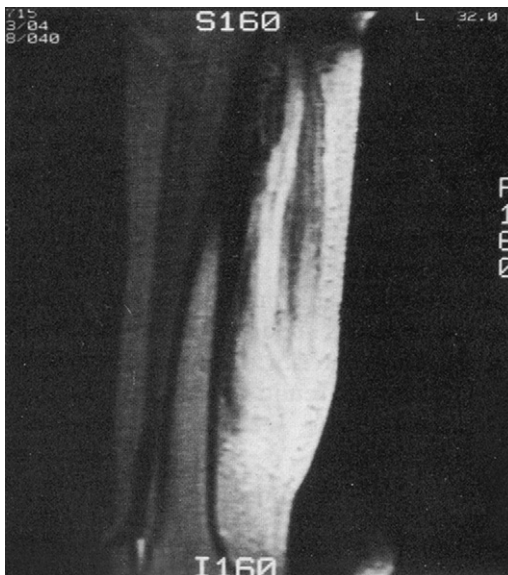
Diabetic muscle infarction (DMI) begins with the abrupt onset of thigh pain, tenderness, and swelling.<sup>71–76</sup> Over a period of days, a firm mass develops in nearly half of cases. The muscles most frequently involved are the vastus lateralis and medialis, thigh adductors, and biceps femoris. Calf involvement is reported in up to 20% of cases and bilateral involvement in 8% of cases.<sup>77</sup> Compared with 130 cases, there are 5 case reports of DMI affecting muscles of the upper limb of patients, particularly in patients with type 2 diabetes with end-stage renal disease.<sup>78</sup> Edema from the

swelling can extend to the knee and mimic a joint effusion.<sup>70</sup> DMI tends to occur in younger, poorly controlled diabetic patients with other end-organ complications. There are no associated systemic symptoms or signs indicative of infection and no skin discoloration suggesting cellulitis or thrombophlebitis. The painful mass persists for weeks, occasionally with exacerbation of symptoms, and then spontaneously resolves over weeks to several months. Contralateral involvement of the other thigh can occur, even after the initial episode resolves. Up to 50% of cases will recur, mostly involving previously unaffected muscle groups.<sup>77</sup>

### Diagnostic Workup

Creatine kinase can be normal or modestly elevated. Needle EMG demonstrates fibrillation potentials in the involved muscles with a loss of voluntary motor unit potentials in the most affected areas. Remaining motor unit potentials may be brief and short, reflecting fragmentation of the motor unit. MRI scan of the limb muscle reveals increased signal on T2-weighted images in the involved thigh muscles, indicative of marked muscle edema extending into the perifascicular and subcutaneous tissues (**Fig. 3**).<sup>72,73,79</sup> Gadolinium contrast administration is contraindicated in those with renal impairment. Radionuclide imaging with Technetium-99 demonstrates radiopharmaceutical accumulation and muscle ultrasound shows hyperechoic signal in the mass.<sup>73</sup>

Biopsy of the region consists of large confluent areas of muscle necrosis and edema, with loss of the normal architectural pattern. A muscle biopsy is often not needed because it may prolong recovery and is indicated only when the presentation is atypical, response is poor, or diagnosis is uncertain. Biopsy, when performed,



**Fig. 3.** Sagittal view of left thigh by T2-weighted MRI scan. There is diffuse high signal in the biceps femoris, semimembranosus, and semitendinosus muscles, whereas the bone and anterior compartment muscles appear normal. (From Barohn RJ, Kissel JT. Case-of-the-month: painful thigh mass in a young woman: diabetic muscle infarction. *Muscle Nerve* 1992;15:850–5; with permission.)

	<b>DLSRP</b>	<b>DMI</b>
Pain	+	+
Focally tender	–	+
Swelling/mass	–	+
Progression	+	+
Bilaterally	+	+
Atrophy	+	–
Distal weakness	+	±
Sensory symptoms	±	–
MRI muscle	Normal	Abnormal
EMG	Neuropathic	Myopathic

*Abbreviations:* DLSRP, diabetic lumbosacral radiculoplexopathy; DMI, diabetic muscle infarction; EMG, electromyogram; MRI, magnetic resonance imaging; +, present; –, absent; ±, maybe present or absent.

shows pale muscle on gross examination and areas of muscle necrosis and edema surrounded by muscle fibers in various stages of degeneration and regeneration, with hyalinosis and thickening of arterioles.<sup>71</sup>

The differential diagnosis of DMI includes, in addition to DLSRP, infection (abscess, pyomyositis, necrotizing fasciitis), focal myositis, venous thrombosis, and tumor. Both DMI and DLSRP syndromes begin with the abrupt onset of lower extremity pain that can ultimately involve the opposite side. In DLSRP the pain is usually localized to the low back, hip, or buttocks with radiation into the thigh; whereas, in DMI, the pain is more focal and associated with swelling and a firm mass. Patients with DLSRP develop dramatic weakness and atrophy in proximal, and usually distal lower extremity muscles. Sensory symptoms (other than pain) do not result from DMI unless there is a prior distal symmetric polyneuropathy. Whereas the imaging studies of the thigh will be focally abnormal with swelling and infarction in DMI, they may show diffuse denervating changes and atrophy on T2 sequences of the hip, thigh, and leg muscles in DLSRP. The EMG in DLSRP is different in that it is characterized by widespread fibrillations in many muscles (usually including the paraspinal muscles), with long-duration, polyphasic motor unit potentials and decreased recruitment pattern. NCS may not be helpful in distinguishing the disorders, as both may show evidence of a distal symmetric polyneuropathy.

Although there are obvious differences between DMI and DLSRP (**Table 2**), the abrupt onset of both syndromes, and pathologic evidence for probable focal ischemia in the muscle (DMI) and nerve (DLSRP) supports the theory that both entities have a primary vascular microangiopathic etiology.

### **Management and Prognosis**

The treatment of DMI is supportive. No evidence-based recommendations are available on management of this condition; however, a retrospective analysis supports conservative management with bed rest, leg elevation, and adequate analgesia. Activities should be avoided to avoid increasing the pain. There is no evidence to support the use of corticosteroids or surgery. Short-term prognosis is good, but the recurrence rate is high (40%), and recurrences may not affect the same muscle group.<sup>80</sup>

**Case study**

A 62-year-old diabetic man on an oral hypoglycemic treatment developed sudden severe pain that started in the lower back and radiated to the right leg. Within 3 days, he experienced weakness in the same leg. After 1 month, similar pain and weakness occurred in the left leg. Symptoms persisted for 4 months, during which time the patient had a 9-kg unintentional weight loss. Neurologic examination revealed asymmetric proximal and distal weakness in both legs. There was asymmetric atrophy of the quadriceps and hamstring muscles. A stocking pattern of loss of pinprick, light touch, and vibration sense was found. Tendon reflexes were absent at the ankles and trace at the knees bilaterally. Upper extremities had normal motor and sensory function.

At the time of initial evaluation, fasting glucose was mildly elevated (140 mg/dL), with a glycosylated hemoglobin of 7.5% and fasting blood sugar of 135 mg/dL. Peroneal motor conduction velocity was reduced at 36 m/s, and compound motor action potential was reduced at 300  $\mu$ V. Tibial nerve conduction was 38 m/s, and sural potentials were absent. Median and ulnar nerve conduction velocities were normal. Bilateral femoral motor conduction studies showed an amplitude of 3 mV on left and 1 mV on right. An EMG revealed active denervation potentials in proximal (quadriceps, adductor longus, gluteus medius, and hamstrings), distal (gastrocnemius and anterior tibial), and lumbosacral paraspinal muscles bilaterally.

His recovery was protracted. Diabetes mellitus was managed by his primary care physician and he achieved better control of his diabetes. He required a right knee brace for ambulation and was treated with gabapentin (Neurontin) for pain control. Leg weakness progressed for 3 additional months before subsequent gradual improvement of strength. At the 6-month follow-up, the pain had almost resolved; however, he still had considerable residual weakness.

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