When to Suspect Amyotrophy in Your Diabetes Patients

Common among diabetics, this condition can be surprisingly difficult to detect. Here are diagnostic clues and a look at the prospects for medical intervention.

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Case Presentation

A 59-year-old Caucasian woman with controlled type II diabetes mellitus (DM) that was diagnosed 10 years earlier developed sudden severe right thigh pain and weight loss. Within weeks, the pain improved but right quadriceps weakness and atrophy were noticed. A few weeks later she developed similar symptoms in the left leg. Two months later she became wheelchair dependent. Over the following 6-8 weeks, she developed bilateral asymmetric proximal arm weakness and pain, which continued to worsen for one year. Examination revealed the following MRC grades: quadriceps and iliopsoas 1+ in the right and 2+ in the left, feet extensors 2/5, deltoids and biceps 3+. Sensation was decreased symmetrically in the feet to all modalities and DTRs are diffusely absent.

Cervical and lumbosacral MRIs revealed chronic changes attributed to multiple back surgeries. HbA1c was 6.8, sed rate was 18mm/hour, ANA titer was negative, CSF protein was 70mg/dl. NCS findings are shown in Table 1. EMG revealed many fibrillations and positive sharp waves, high amplitude long duration units, and neurogenic firing in the proximal and distal leg and arm muscles in a patchy fashion, more severe in the right leg.

The thoracic and LS paraspinal muscles were involved as well. Left biceps biopsy revealed neurogenic atrophy. Left Sural nerve biopsy revealed axonal and demyelinating neuropathy and rare inflammatory foci. There was inflammation of the wall of several small blood vessels. There was no mural necrosis or thrombosis.

- *What is the diagnosis and differential diagnosis?*
- *What is the prognosis?*
- *Does intervention help?*

Expert Opinion

The diagnosis is diabetic amyotrophy (DA), also called Burns-Garland syndrome, diabetic myelopathy, diabetic mononeuritis multiplex, diabetic polyradiculopathy, proximal diabetic neuropathy, diabetic lumbosacral radiculoplexus neuropathy (DLRPN), multifocal diabetic neuropathy and diabetic femoral neuropathy.

Since its description by Burns in 1890, our clinical and pathological understanding of this syndrome has remarkably improved. Diabetes mellitus turned out to be merely a risk factor; an identical syndrome in non-diabetics is recognized, supporting the vascular and inflammatory nature of the disease. Microvasculitis is found to be the pathological hallmark, and therapeutic trials with immunomodulators are ongoing and promising. Similar disorders in diabetics should be differentiated.

The initial right thigh pain in a diabetic was suggestive of DA, although L3 or L4 radiculopathy or LS plexopathy could not be excluded with confidence. The spread of the symptoms to the left thigh, although occurring in 30 percent of DA cases, also pointed to LS plexitis and raised the possibility of vasculitis, especially in light of the weight loss.

While normal ESR and ANA are uncommon in systemic vasculitis, they are usually normal in isolated PNS vasculitis. Bilateral foot drop, proximal arm weakness and diffuse areflexia suggest CIDP. Some myopathies have predilection for anterior thigh muscles, but preceding pain is unlikely.

Mildly elevated CSF protein is common in DA and a higher level is expected in CIDP. Severe widespread and asymmetric denervation is typical for DA and very rare in early CIDP. Mild demyelinating features (prolonged distal latencies, prolonged F- responses, motor slowing) are typically seen in CIDP but are also common in DA. Mixed demyelinating and axonal features in nerve biopsy are not specific and can be seen in both, but microvasculitis is more indicative of DA.

Clinical features and Course of DA

DA is a disabling neuropathy that usually occurs in patients with type 2 DM in middle or old age. Concomitant weight loss is frequent. Patients usually have not been diabetic for very long and glycemic dysregulation is not severe. Interestingly, DA is the presenting manifestation of DM in about a third of cases. Even when DM is present, long-term diabetic complications such as diabetic retinopathy and nephropathy are rare. The clinical presentation is characterized by sudden, sharp and asymmetric pain that usually starts in one hip and thigh and subsequently spreads to the other side within weeks to months.

Weakness starts distally in a third of cases, leading to unilateral or bilateral foot drop. As the pain improves, weakness becomes the major symptom, affecting both proximal and distal muscles of the legs. In about a third of cases, weak-

Table 1. NCS Results

	Onset	Normal	Ampl	Segment	CV	Normal	F-response	CB
L.Peroneal M	4.7	<6	0.4	F-A	25	<40	68	no
L.Tibial M	8.2	<7.2	1.8	K-A	31	<40	71	no
L.Median M	6	<4.6	6	EW	41	<50	36	no
R.Median M	7	<4.6	4.6	EW	36	<50	36	no
L.Ulnar M	3.7	<3.6	5.6	E-W	38	<50	34	no
R.Ulnar M	4	<3.6	4.3	EW	40	<50	34	no

L/R Sural S, L/R Ulnar S, L.Median S, L. Ulnar S = NR

ness spreads to the proximal arm muscles and is attributed to cervical radiculoplexopathy. Approximately 12 percent of patients develop thoracic radiculopathy, leading to radiating belt-like chest or abdominal pain and intercostal weakness that causes pseudohernia.

Initially, the disease progresses relentlessly; half of patients become wheelchair bound and almost all require assistance with ambulation. Progression may continue up to 18 months following onset. Recovery is usually remarkable and spontaneous but slow and incomplete. While only nine percent of patients will still need a wheelchair after two years, only 10 percent of patients achieve full recovery for the same period of time.

CSF protein is frequently elevated. Nerve conduction studies usually reveal marked reduction of the amplitudes of the compound muscle action potentials of the affected motor nerves in a very asymmetrical fashion, low amplitudes (more frequently absent) sensory nerve action potentials in the affected regions, and mild slowing of the nerve conduction velocities. Needle examination shows spontaneous activity, reduced recruitment of the motor units potentials (MUPs), and long duration and high amplitude MUPs in muscles supplied by multiple nerve roots and different peripheral nerves. Paraspinal muscles are usually affected.

These neurophysiologic findings indicate a multifocal axonal injury. The EMG abnormalities tend to be much more prevalent and widespread than the clinical picture suggests. Findings related to an underlying diabetic polyneuropathy (DPN) are common.

While metabolic derangement is considered the primary mechanism of generalized diabetic neuropathies, a vascular mechanism is suggested to explain the acute onset and focal nature of DA. Dyck compared 33 sensory nerve biopsies of DA patients with those of DPN patients and found perivascular inflammation in all sampled nerves, mural invasion (microvasculitis) in half and Hemosidirin-laden macrophages in half. The latter finding indicates previous bleeding.

Said reported similar findings of necrotizing vasculitis of perineurial and endoneurial blood vessels in 6/22 and perivascular inflammation in 21/22 nerve biopsies from DA patients. He also found endoneurial red blood cells in 11/22, endoneurial hemorrhage in 5/22 and ferric deposits (another sign of previous bleeding) in 7/22 of these biopsies. In contrast, nerve biopsies from 30 patients with severe distal DPN demonstrated only mild epineurial mononuclear cells infiltration in one biopsy and endoneurial red blood cells in another.

Interestingly, muscle biopsies from Said's 22 patients displayed inflammatory infiltrate in three cases and vasculitis in one case. The lack of fibrinoid necrosis of vessel walls as opposed to the systemic vasculitis may be due to the very small size of the involved vessels in the former. DA thus seems to be a form of non-systemic vasculitis isolated to the peripheral nerves.

The cause of inflammation in DA remains elusive. An immune reaction against altered wall of small endoneurial blood vessels is possible. The cause(s) of such alteration may be diverse.

Treatment Options

The above-mentioned pathological findings prompted several investigators to treat DA as an inflammatory syndrome. In addition, the reported favorable response of the non-diabetic LRPN to IVMP suggests that its diabetic counterpart may respond similarly. Said treated two DA patients with biopsy-proven vasculitis using prednisone; outcomes were favorable.

Krendel treated 15 patients: seven with intravenous immunoglobulin (IVIG) and prednisone, five with IVIG, two with prednisone and cyclophosphamide, and one with prednisone alone. All improved, five markedly. In view of the monophasic and self-limiting nature of the disease, these results provide only preliminary information and support the inflammatory nature of the disease. They also pave the way for prospective controlled studies.

In a recent multicenter trial, two thirds of patients received IVMP and a third received placebo in a dose of one gram three times per week, followed by less frequent doses over 12 weeks. Patients were followed for two years. The final outcome measure was four-point improvement in the NIS. The study is completed and results are pending. **PN**

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