Diabetic Amyotrophy or Proximal Diabetic Neuropathy
an Immune-mediated Condition?

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Diabetic amyotrophy is a relatively rare condition in which unilateral or bilateral muscular weakness acutely or subacutely develops mainly around the hip and thigh in mild type 2 diabetes (1). It often accompanies pain around the buttock and hip, while paresthesia and allodynia are lesser symptoms. Although the name bears the condition like a myogenic disorder, it is a genuine neuropathic condition. To describe this condition, varieties of terms have been applied; proximal diabetic neuropathy (PDN), diabetic femoral neuropathy, and diabetic lumbosacral plexopathy are popular terms to describe this disorder. Dyck et al (2) proposed the term of diabetic lumbosacral radiculoplexus neuropathy, since it seems the most accurate for the known anatomical distribution of the lesion in this condition.

The pathogenesis of PDN has been understood to be due to nerve/plexus ischemia as a consequence of diabetic microangiopathy. Evidence provided by a histological study showing multifocal infarcts of the proximal nerve trunks and lumbosacral plexus strongly supports the ischemic pathogenesis of PDN (3). Multifocal nerve fiber loss has been frequently described in the biopsied cutaneous nerve, too. In 1994 Said et al (4) found necrotizing vasculitis in the cutaneous nerves biopsied from two patients with PDN, and perivascular infiltrates in four patients, in addition to multifocal fiber loss attributed to nerve ischemia. Other investigators then reconfirmed the presence of vasculitis or perivasculitis in biopsied nerves from PDN (5, 6).

On the other hand, Pascoe et al (7) reported that inflammatory infiltrates were less common in the sural nerve specimen from 44 PDN patients of Mayo Clinic. Since minor foci with cellular infiltrates in and around the perineurium were sometimes seen in any peripheral neuropathies, many investigators wondered if these changes were due to some kind of metabolic effects of diabetes.

Recently, Dyck et al (2) prospectively studied distal cutaneous nerves (sural and superficial peroneal) of 33 PDN patients in Mayo, and confirmed perivascular inflammation in all nerves examined, vessel wall inflammation in 15 nerves, and previous bleeding in 19 nerves, all of which suggested microscopic vasculitis as a primary event of PDN. Small arterioles, venules, or capillaries were mainly involved. Kelkar et al (8) found polymorphonuclear small-vessel vasculitis affecting epineural vessels and IgM deposits along the endothelium and in affected vessels. Activated complement deposition was seen along the endothelium of small vessels. From these distinct findings, an immune-mediated inflammatory theory has rapidly emerged as the primary event in PDN.

In this issue Ogawa (9) reported the dramatic effect of high-dose intravenous immunoglobulin (IVIg) on the proximal muscular weakness of a 49-year-old patient with PDN.

She had walking difficulties with subacute progression for two or three months, and showed severe muscular wasting in both thighs. Although a nerve biopsy was not performed, the femoral nerve conduction study revealed a fall in motor conduction velocity and marked reduction in the amplitude of compound muscle action potential, suggesting both demyelination and severe axonal loss. Conduction studies in other nerves showed relatively mild changes. The most striking event in this patient was that the efficacy of IVIg treatment was so rapid and dramatic.

The clinical efficacy of IVIg based on controlled trials is now established in many autoimmune neuromuscular diseases, e.g. Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), myasthenia gravis, Lambert-Eaton myasthenic syndrome, dermatomyositis, and others. Although it was an open trial, Krendel et al (10) reported the efficacy of IVIg in the treatment of PDN and CIDP-like demyelinating neuropathy in diabetic patients. Since the efficacy of steroid administration, plasma cleaning therapy, or IVIg treatment had already been confirmed in CIDP of unknown background, it was not absolutely new to recognize the effect of IVIg for diabetes-associated CIDP, however, its efficacy for the case of PDN was rather surprising. As some immune-mediated background was strongly suspected, and if the mechanisms of action of IVIg are mainly explained by immune-modulating actions such as supply of idiotypic antibodies, suppression of antibody production, acceleration of catabolism of immunoglobulin, the suppression of pathogenic cytokines, inhibition of complement binding, prevention of membranolytic attack complex formation, and modulation of Fc receptors or T-cell function (11), PDN should be understood as a condition developing on an immune-mediated inflammatory basis, and could be treatable by means of immune-modulating therapy. IVIg treatment is of course a potent candidate for PDN.

According to a recent paper by Dyck et al (12), the pathologic alteration after microvasculitis may be a common pro-
cess in lumbosacral radiculoplexus neuropathies with and without diabetes. If so, PDN may not be a true diabetic or hyperglycemic complication, but diabetes may simply be one of the risk factors or precipitating conditions of proximal neuropathy of the lower limb.

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References