Beyond Glycemia

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Efforts to prevent the development or to retard progression of diabetic neurological complications by improving glycemic control have resulted in only partial success, suggesting that our understanding of the pathogenesis of diabetic neuropathy is still incomplete. For further advances in the treatment of diabetic neuropathy to occur, as well as the development of alternative therapeutic approaches, it will be necessary to fully characterize the causative and modulating factors.

A causative role of prolonged hyperglycemia in the pathogenesis of neuropathy was suggested 20 years ago by Pirart (1), who conducted a 25-year study of 4,400 unselected patients and provided an epidemiological link between the duration and severity of metabolic abnormalities and the presence of clinical neuropathy. The study was not, however, a prospective, double-blind, randomized one designed to determine the impact of glycemic control on complications.

The primary aim of the Diabetes Control and Complications Trial (DCCT) (2) was to evaluate the effects of intensive treatment (IT) in insulin-dependent, or type I, diabetes mellitus (IDDM). Patients with a disease duration of either no more than 5 years (primary prevention cohort without retinopathy) or no more than 10 years (secondary prevention cohort with mild retinopathy) were included (2). The outcome measures included an objective survey of retinal diabetic changes as a main parameter. Neuropathy was not a primary outcome measure.

The DCCT investigators reported that point prevalence rates for clinical and/or electrophysiological evidence of neuropathy were reduced by ±50% in those treated by IT at 5 years. At that stage in the study, 3% of the patients in the primary prevention cohort treated by IT showed at least minimal signs of diabetic neuropathy, compared with 10% of those treated by the conventional regime. The accumulated incidence rate for distal symmetric polyneuropathy is 4% after 5 years and 15% after 20 years (3). A median time from diagnosis of diabetes to development of neuropathy is 9 years (3). The disease duration of patients included in the DCCT was shorter (2), suggesting that a longer follow-up time might be necessary to determine the full effect of therapy on neurological complications. In addition, all those who had diabetic polyneuropathy at the baseline were subsequently excluded from the data analysis. If this data had been taken into account, the difference between the two groups might have been less significant. In the secondary prevention cohort, IT significantly reduced the prevalence of clinical neuropathy by 56% (7% in the IT vs. 16% in the conventional treatment group). No data on degree of improvement have been presented. Strikingly, the HbA_{1c} levels of intensively versus conventionally treated patients had significant overlap in the area where IT presumably was beneficial. If the outcome is equivalent in this area, then the beneficial effect of IT might be ascribed to effects other than glycemia. Lastly, IT failed to protect 44% of patients in the secondary prevention cohort. Several reasons may account for this failure.

A series of clinical vignettes serve to illustrate this hiatus in our knowledge. Here we present five cases suggesting that mechanisms other than hyperglycemia may be involved in the development of diabetic neurological complications, in at least certain subgroups of patients: *1*) in those with neuropathy occurring in the absence of hyperglycemia; 2) in those with progression of neuropathy despite the normalization of glucose metabolism by pancreas transplantation; and 3) in those with established neuropathy and signs of autoimmunity in their sera and nerve tissue.

A number of reports have suggested that a proportion of adults with diabetes have neuropathy before or at the time of diagnosis (1,4). The prevailing opinion was that such an early expression of neuropathy resulted from long-lasting unrecognized hyperglycemia. We carefully evaluated an identical-twin pair discordant for IDDM and found mild neuropathy in the nondiabetic sister.

Mrs. A.K. is a 57-year-old white female whose identical twin sister has had diabetes for 25 years and currently has distal symmetric neuropathy. Her history was unremarkable except for allergy to a variety of ubiquitous agents. Her physical examination was normal except for vitiligo and impaired vibration perception.

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CIDP, chronic inflammatory demyelinating polyneuropathy; DCCT, Diabetes Control and Complications Trial; DRG, dorsal root ganglion; GBS, Guillain-Barré syndrome; IDDM, insulin-dependent diabetes mellitus; IGF, insulin-like growth factor; IT, intensive treatment; NGF, nerve growth factor; PLA, phospholipid antibody.

Quantitative tests of sensory function showed impaired vibration perception (3.9 μm, $n^* < 2.1$ μm), indicative of large fiber dysfunction, typical of distal symmetric diabetic polyneuropathy. The levels of blood glucose and HbA_{1c} (5.9%, $n = 4.0–6.0\%$) were within normal limits.

The complexity of the relationship between control of hyperglycemia and diabetic neuropathy is illustrated by our observations of another patient. Mrs. S.S., a 52-year-old woman, has had IDDM for 23 years complicated by proliferative retinopathy, end-stage kidney disease, and diabetic neuropathy. She developed signs and symptoms of clinical diabetic neuropathy in the early 1980s. In 1990, she received a kidney and pancreas transplant and became normoglycemic shortly thereafter. Her insulin therapy was stopped, and she remained normoglycemic. In the period of four years after transplantation, signs and symptoms of diabetic neuropathy did not decrease. Contrary to expectations, she developed a left-sided Charcot's foot. There was a strong association between skeletal changes (bone mineral densities [g/cm^2] of anterior-posterior spine, femoral neck, and ultradistal radius were 1.056 [88% of *n*], 0.772 [79% of *n*], and 0.336 [89% of *n*], respectively) and deterioration of nerve function (increase in total neuropathy score from pretransplantation value of 7 on both sides to 19 on the right side and 20 on the left), including severe autonomic neuropathy (expiratory/inspiratory index 1.02 [$n > 1.12$], Valsalva index 1.06 [$n > 1.21$], and posture index 1.05 [$n > 1.04$]). These findings are similar to those in studies conducted in patients who received pancreas transplants, showing that euglycemia slows the rate of functional loss but does not normalize nerve dysfunction in diabetes (5).

The case history of Mrs. J.A., a 55-year-old white female, seen at the Diabetes Institutes (Norfolk, VA), provided us with clear evidence that neuropathy may precede the onset of hyperglycemia. Patient J.A. has had diabetes since 1992. She has a symptom complex of constant superficial and irregular deep pain, as well as numbness and paresthesia. In 1982, electroneurophysiological evaluation showed clear evidence of distal sensory neuropathy. The results of oral glucose tolerance tests were repeatedly within normal limits. She visited our outpatient clinic because of persistent neurological symptoms and signs, responding poorly to standard symptomatic treatment. We performed an extensive evaluation of possible autoimmune, metabolic, toxic, and nutritional causes of peripheral neuropathy. HbA_{1c} values were between 5.9% and 6.2%. Higher levels of IgG and IgA anti-phospholipid antibodies (PLAs) (49 GPL and 29 APL, respectively, $n < 10$) were detected in her sera.

The role of PLAs in the development of diabetic neuropathy has not been fully investigated. PLAs are a family of closely related immunoglobulins that interact with constituents of nervous tissues. PLAs are present in a number of autoimmune, neurological, and hematological disorders. PLAs were found in 88% of our diabetic population with neuropathy, compared to 32% in those diabetic patients without neurological complications and 2% in the general population (6). It is possible that cosegregation of PLAs and diabetes results in neuropathy through an independent, nonmetabolic mechanism, and neurological loss precedes clinical diabetes. The histopathological pattern of nerve damage in diabetic patients is consistent with multifocal ischemic damage. There is increasing pathological evidence that abnormal microvessels may play a role in the pathogenesis of diabetic neuropathy (8,9). Said et al. (10) reported on 10 patients with amyotrophy associated with distal symmetric polyneuropathy, 6 of whom had clear signs of inflammatory infiltration in biopsies of peripheral nerve. Two of them had a typical vasculitic picture (including typical vessel changes and ischemic pattern of centrofascicular fiber loss), consistent with isolated neuronal vasculitis. Signs of inflammation were combined with axonal and demyelinating changes in all six cases. All were treated with corticosteroids and showed a rapid improvement and better outcome. It is possible that PLAs induce intravascular thrombotic events as a result of interaction with an unknown endothelial cell surface antigen, resulting in a vasculitic process.

Much new data supports an association between diabetic neuropathy and signs of autoimmunity. In addition to PLAs, autoantibodies against sialo-GM1 and asialo-GM1 gangliosides as well as complement-fixing anti-sciatic nerve antibodies have been described in sera from IDDM patients (11). We have also detected deposition of immunoglobulins in nerve biopsies obtained from patients with sensorimotor diabetic polyneuropathy. One of these, patient M.G., is a 29-year-old white male who has had IDDM for 27 years and presented with a symptom complex typical for combined sensory and motor polyneuropathy, affecting both upper and lower extremities. He was being treated by an intensive insulin regime, and his HbA_{1c} values were essentially normal or near-normal (<6.5%). The symptoms of diabetic neuropathy appeared in 1992 after 25 years of diabetes and have been progressive. Standard symptomatic treatment did not significantly influence the course of his disease. Initial diagnostic evaluation at the Diabetes Institutes included quantitative sensory testing, quantitative autonomic testing, and electroneurophysiological evaluation. In addition to sensorimotor diabetic neuropathy, there was evidence for bilateral tarsal tunnel syndromes with medial plantar nerve compression. On 9 August 1994, M.G. underwent surgical release for bilateral compressive syndromes in the lower extremities. At the same time a sural nerve biopsy was done, which revealed deposition of IgM and IgG in the perineurium of nerve fascicles (Fig. 1). The association of immunoglobulin deposits with initiation or perpetuation of

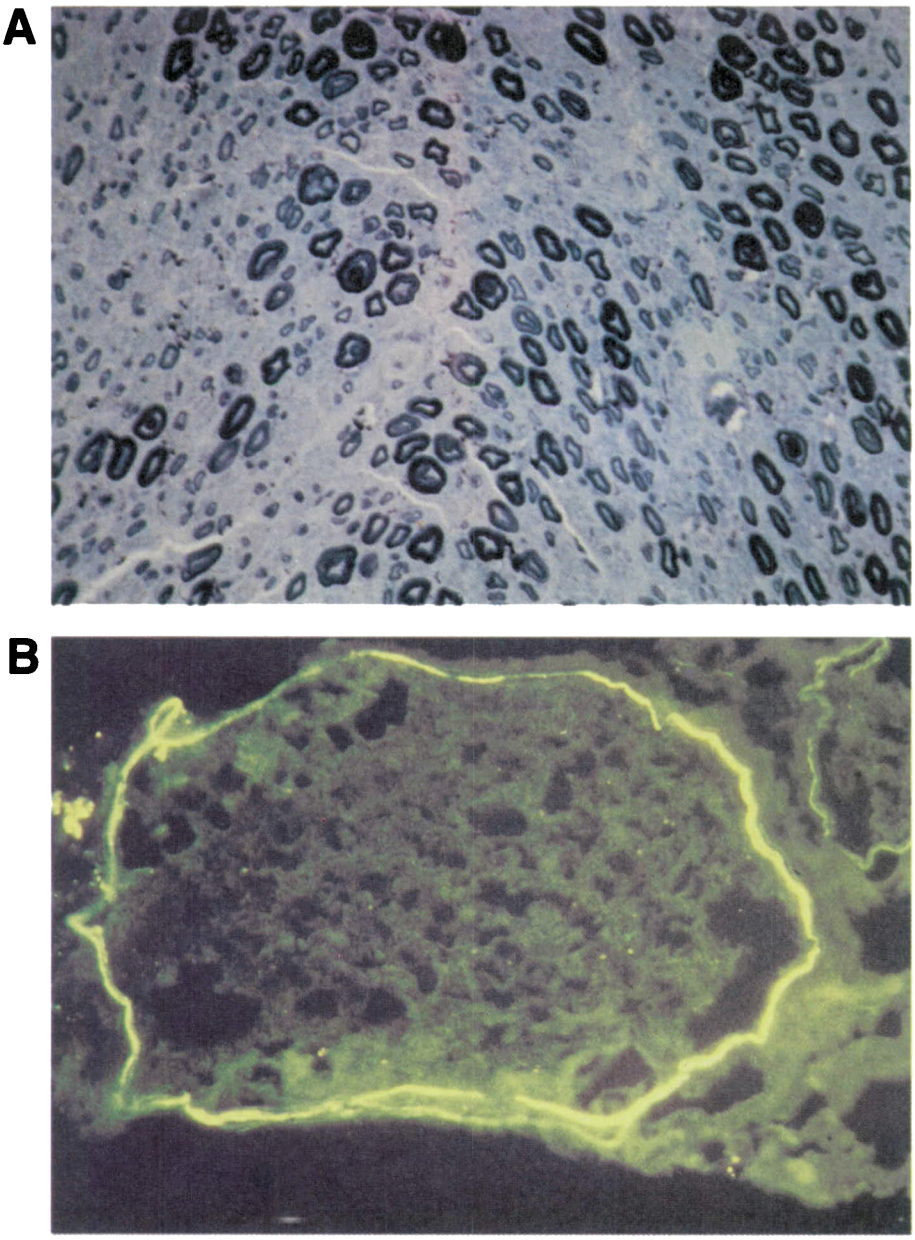

Figure 1—*Pathohistological findings in a nerve biopsy of patient M.G. showed mild axonal loss* (A). *Immunohistochemical analysis revealed IgG and IgM deposition in perineurium* (B).

neuronal destruction has been shown in patients with nondiabetic peripheral neuropathies, such as Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP). Recently, therapeutic success has been obtained with intravenous polyclonal human immunoglobulins, an immunomodulating agent, in the treatment of patients with GBS and CIDP, supporting the importance of autoimmunity in the pathogenesis of nondiabetic peripheral neuropathies (12, 13). Diabetic polyneuropathy shares certain pathological, clinical, and immunologic characteristics with this group of diseases, and nondiabetic neuropathy may even be erroneously ascribed to the diabetes.

Mr. L.H. is a 62-year-old white male with a 32-year history of NIDDM. Since 1989, he has been treated with insulin. He presented with a symptom complex indicative of sensorimotor peripheral neuropathy, with predominance of motor nervous system dysfunction (significant limb weakness, interosseous muscle wasting, and hammertoes). A sensorimotor pattern was confirmed by electroneurophysiological evaluation. Immunologic testing revealed a high titer of anti-ganglioside GM1 antibodies (90 EIA units, NV < 10 EIA) and a mild increase in anti-asialo-GM1 antibodies (13 EIA units, NV < 10 EIA). This antibody profile is frequently seen in individuals with multifocal motor neuropathy with a predominantly distal distribution of the nerve lesion.

Observations that suggest a role for autoimmunity in the development of sympathetic autonomic neuropathy are even more compelling than those for its role in somatic neuropathy. We and others (14–19) were able to detect complement-fixing antibodies specifically reacting with elements of the sympathetic nervous system. The autoantibody titer was also found to correlate with the degree of autonomic dysfunction reflected by orthostasis. We have also shown that circulating immunoglobulins bind to antigens on the surface of neuroblastoma cells in culture, inducing inhibition of proliferation or even apoptosis and cell death (20,21). Immunoglobulin fraction of diabetic sera is also responsible for lack of normal differentiation of these cells (20). Immunogenic evaluation has, furthermore, revealed a strong association between autonomic neuropathy and human leukocyte antigen DR3/DR4 heterozygocity (22).

Apart from the vascular and immunologic factors involved in the pathogenesis of neuropathy, there is data to support a role for growth factor deficiency. Many of the neuronal changes characteristic of diabetic neuropathy are similar to those observed following either removal of target-derived growth factors by axotomy or depletion of endogenous

growth factors by experimental induction of growth factor autoimmunity. Since neuronal growth factors can promote the survival, maintenance, and regeneration of neurons subject to the noxious effects of diabetes, the success of diabetic patients in maintaining normal nerve morphology and function may ultimately depend on the expression and efficacy of these factors (23).

It has been known for some time that sympathetic and dorsal root ganglion (DRG) neurons are developmentally dependent on nerve growth factor (NGF), but more recently, it has been shown that adult DRG and sympathetic neurons, both populations of neurons affected in diabetic neuropathy, are dependent on NGF for either their maintenance (24) or their survival (25). The effect of NGF depletion may be mediated through the downregulation of neurofilament gene expression (26) or mRNAs that encode the precursor molecules of substance P, both shown to be NGF dependent (27). Experimental data in diabetic animals has revealed lower NGF levels in tissue and in the bloodstream and reduced retrograde neuronal transport of the peptide (28,29), accompanied by reduced levels and retrograde transport of substance P (30). Low levels of NGF could be due to decreased production or transport of NGF in diabetes (28). In addition, autoimmunity may play a role in the NGF deficiency in diabetes by mechanisms related to immune neutralization of available NGF. There are structural and biochemical similarities between NGF and the insulin family of peptides (31,32), and it has been suggested that antibodies to insulin may cross-react with NGF, effectively reducing NGF available to nerves, thereby contributing to the development of neuropathy. Thus, insulin antibody formation, which might be secondary to insulin treatment but also occurs as a primary autoimmune phenomenon, may be contributing to diabetic neuropathy by binding with NGF and interfering with its biological action. That these abnormalities are only correctable in part by IT may explain the frustration of trying to reverse established neuropathy by improving only glycemic control.

The insulin-like growth factors (IGFs) IGF-I and IGF-II have also been implicated in the growth and differentiation of neurons, and IGF receptors are present in nerve tissues (i.e., neurons, Schwann cells, ganglia) involved in diabetes-associated nerve disorders. However, both IGFs and their binding proteins are present in the nervous system and are regulated by insulin and the glycemic state (23,33,34). It is therefore possible that the beneficial effects of IT in neuropathy may be related in part to the improved IGF status.

It is our belief that these vignettes reinforce our view that diabetic neuropathy is a complex group of disorders, which differ in their pathogenesis, epidemiology, clinical course, and response to current therapeutic approaches. To further ensure therapeutic successes, it will be necessary to better characterize the specific pathogenic factors in subgroups of neuropaths and to direct interventions toward these if the therapeutic gains are to exceed those achieved by investment in intensive glycemic control and those directed toward metabolic uncertainties.

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