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Diabetic neuropathies

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Neuropathy is the most common "life-spoiling" complication of diabetes mellitus and the major cause of morbidity. While the primary long-term objective will be to find a cure for diabetes, in the immediate future the major goal is to prevent and reverse the chronic complications of the disease. The heterogeneity of diabetic neuropathy has for years escaped the attention of clinicians and investigators. Attempts have been made to distinguish the different clinical syndromes and the nerve fibre types affected without an in depth understanding of differences in pathogenesis.

An improved classification of diabetic neuropathies is required which recognizes more fully the heterogeneity of this disease, as well as the possibility that the pathogenesis and profile of neuropathies encountered in insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetic patients may be distinct. Recent human and experimental studies provide an increased understanding of the diversity of underlying pathophysiological and biochemical abnormalities in the IDDM and NIDDM disorders, and how these may relate to the diverse phenotypic expression of diabetic neuropathies. The recommended classification forges closer links between pathology, neurobiology, and immunology and aims to provide a firmer foundation for investigations into the aetiology and rational treatment of diabetic neuropathies. Animal and human data now show or strongly indicate, using end-points specific for participating neuropathies, that diabetic neuropathies may be amenable to immunotherapy and neurotrophic factor treatment. This group was convened to examine the current state of knowledge of the pathogenesis and limited success of past treatments. After considerations of the heterogeneity of neuropathies and their aetiopathogenesis, they have arrived at the following recommendations.

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Classification of diabetic neuropathies

A wide variety of disturbances of peripheral nerve function are encountered in patients with diabetes. These can be broadly classified into: 1) rapidly reversible neuropathy; 2) persistent neuropathies; 3) focal/multifocal neuropathies.

Rapidly reversible: Hyperglycaemic neuropathy

Persistent symmetric polyneuropathies: a) distal somatic sensory/motor polyneuropathies (DSPN) involving predominantly large fibres; b) autonomic neuropathies (APN); c) small fibre neuropathies.

Focal/multifocal neuropathies: a) cranial neuropathies; b) thoracoabdominal radiculopathies; c) focal limb neuropathies; d) proximal neuropathies; e) compression and entrapment neuropathies.

Clinical presentation and diagnosis

The spectrum of clinical neuropathic syndromes described in patients with diabetes includes dysfunction of almost every part of the somatic peripheral and autonomic nervous system. Its pathophysiologic, therapeutic and prognostic features can distinguish each syndrome. Initial neurologic evaluation should be directed toward the detection of the specific part or parts of the nervous system affected by diabetes. Diabetes may damage small fibres, large fibres, or both. Small nerve fibre dysfunction usually (although not always) occurs early and is often present before objective signs, or electrophysiologic evidence of nerve damage can be found. It is manifested first in the lower limbs by loss of thermal sensitivity and reduced sensations of light touch and pin prick. Pain and hyperalgesia are often present. Large fibre involvement is characterized by reduced vibration perception (often the first objective evidence of neuropathy) and position sense, weakness, muscle wasting and depressed tendon reflexes. Most patients with DSPN have a "mixed" variety with both large and small nerve fibre involvement. In DSPN, a "glove and stocking" distribution of sensory loss is almost universal. Early in the course of the neuropathic process, multifocal sensory loss may be found.

Proximal motor neuropathy can be clinically identified based on proximal muscle weakness and muscle wasting. It may be symmetric or asymmetric in distribution, and is sometimes associated with pain in the lateral aspect of the thighs. The condition is easily recognized clinically with prevailing weakness of the iliopsoas, obturator and adductor muscles, together with relative preservation of the gluteus maximus and minimus, and hamstrings. In contrast, if demyelination predominates and the motor deficit affects proximal and distal muscle groups, the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) should be considered. It is important to divide proximal syndromes into these two subcategories, since the CIDP variant shows good response to intervention, whereas amyotrophy runs its own course over months to years.

Involvement of the autonomic nervous system can occur as early as during the first year after diagnosis of diabetes and may involve any system in the body. The major manifestations of autonomic polyneuropathy (APN) are cardiovascular, gastrointestinal and genitourinary system dysfunction. Quantitative Autonomic Function Test (QAFT) consists of series of simple, non-invasive tests for detecting cardiovascular autonomic neuropathy. These tests are based on detection of heart rate and blood pressure reflex responses. Specific tests are used in evaluation of disordered regulation of gastrointestinal, genitourinary, and sudomotor function and peripheral skin blood flow induced by APN.

Means of quantitation

The 1988 San Antonio conference of Diabetic Neuropathy [1], and the 1992 conference of the American Diabetes Association and the American Academy of Neurology [2] concluded that in order to diagnose neuropathic abnormalities, one or more categories of clinical, electrophysiological and quantitative sensory testing was necessary. They recommended that at least one parameter from each of the following five categories are measured to classify diabetic neuropathy: symptom profiles, neurologic examination, quantitative sensory testing (QST), nerve conduction studies and autonomic function testing (QAFT). Suggested nerve conduction studies included motor and sensory evoked amplitudes and conduction velocities from the upper and lower extremities. The Nerve Disability Score (NDS), vibration threshold, motor and sensory nerve action potentials and motor nerve conduction velocities are quite reproducible over time. The least reliable measure is the Nerve Symptom Score (NSS). QST and QAFT are objective indices of neurological functional status. Combined, these tests cover vibratory, proprioceptive, tactile, pain, thermal and autonomic function. QST provides standardized procedures for evaluating neuropathy before symptoms appear. Vibration perception testing is the single most sensitive measurement of diabetic neuropathy when specificity is held greater than 90 %. In addition, the combination of thermal and vibratory modalities gives optimum sensitivity (92–95 %) and specificity (77–86 %), suggesting that the use of vibratory and thermal testing should be the primary screening tests for diabetic peripheral neuropathy. In the case of small-fibre neuropathy, QST is the only objective method of neurologic evaluation, since electrophysiologic measures are usually normal. Recent years have seen the development of a number of relatively inexpensive devices that allow suitable assessment of somato-sensory function, including vibration, thermal energy, and light touch perception. These types of instruments allow for cutaneous sensory functions to be assessed non-invasively, and their measurements are by definition correlates of specific neural fibre function. In addition to the above modalities, QST procedures are available for pain thresholds and cutaneous current perception.

Animal and human experimental results

Studies on neurotropic agents: Circulating insulin-like growth factors (IGFs) are reduced in IDDM and NIDDM patients and reduced to a greater extent in patients with neuropathy compared to those without [3]. IGF gene expression is reduced in peripheral nerves of diabetic rats with varying degrees of insulin deficiency and subcutaneous administration of IGFs

can prevent and/or reverse hyperalgesia and impaired nerve regeneration [4, 5]. Abnormal gene expression or axonal transport is observed for neurotropins such as nerve growth (NGF) and neurotrophin-3 (NT-3). Under normal conditions IGFs are believed to provide ubiquitous support for the nervous system, and neurotrophins provide support for specific classes of neurons. For example NGF targets the high affinity TrkA receptor responsible for pain and warm thermal perception and autonomic function, and NT3 targets the TrkC receptor responsible for integrity of large fibres subserving position sense and cold thermal perception. Therefore loss of neurotrophic support in the context of diabetes may play an important role in the aetiology of neuropathies.

In a randomized, double-blind, placebo-controlled study of 250 patients (age 18–60 years, 114 IDDM, 136 NIDDM, duration of diabetes 15 years, neuropathy 4.7 years, NGF was given s. c., three times per week, for 6 months to patients with symptomatic diabetic polyneuropathy demonstrating abnormalities of nerve conduction (NC) and quantitative sensory tests (QSTs). Significant improvements using the O'Brien's rank sum test were found with NGF compared with placebo. Composite score of nerve impairment score of the lower limb (NIS-LL), cold detection threshold (CDT) and heat pain (HP) $p = 0.005$ as well as the composite score of NIS-LL, CDT, vibration detection threshold (VDT) and HP $p = 0.032$ [6].

Differences in neuropathy in IDDM and NIDDM: Electrophysiologic and structural studies of peripheral nerves in human and animal models of the two major forms of diabetes demonstrate differences in the patterns of DSPN [7–9]. Fibre atrophy appears to be more severe in IDDM and there is a characteristic involvement of the nodal apparatus. Nerve fibre loss is more diffuse in IDDM compared with NIDDM in which there is focality of fibre loss. The electrophysiologic abnormalities are also more severe in IDDM than in NIDDM diabetes in rats with the same duration and severity of diabetes. These findings suggest that different pathogenetic mechanisms of neuropathy may exist in the two types of diabetes, and that future clinical trials should separate diabetic patients into IDDM and NIDDM categories for evaluation of responsiveness to interventions.

Studies using immunomodulatory agents: In non-randomized studies, 41 patients with proximal neuropathies presenting together with inflammatory infiltrates evident in nerve biopsies from the thigh, were treated with intravenous immunoglobulin. Treatment produced significant reduction in pain (visual analogue scale), weakness (MRC muscle strength score) and small fibre function (QST). Furthermore positive responses correlated with reduction in the capacity of serum from patients to provoke immune-mediated apoptosis of neuroblastoma cells in culture [10].

A specific algorithm for management of pain [11] based upon differences in pain mediated by C-fibres and A-8 has been shown to alleviate pain successfully in 95 % of patients.

Potential therapies requiring further evaluation

- Anti-advanced glycosylation end-product drugs
- Vasoactive agents
- Essential fatty acid supplementation
- Neurotropic growth factors
- Immunomodulatory measures
- Free radical scavengers

Future direction and recommendations

While hyperglycaemia is central to the development of diabetic neuropathy, once established, its normalization will not reverse diabetic polyneuropathy. In addition to hyperglycaemia, experimental evidence suggests a role for other pathogenetic factors such as type of diabetes, deficiencies of neurotrophic factors, and immune-mediated mechanisms.

It is essential that the particular type of diabetic neuropathy be identified so that treatments can be tailored accordingly. For diabetic sensory neuropathy, the development of sensitive new methods for documentation of abnormalities in different fibre populations now allow us to monitor longitudinally the involvement of different sensory modalities and response to therapy. Preliminary data indicate that immunomodulatory therapy and growth factor treatment targeted at specific nerve fibre populations may be effective.

It is recommended that:

- Further basic studies on underlying disease mechanisms should be undertaken to assess the roll of various types of diabetes, growth factors and immunopathogenetic mechanisms; and to define the reasons for failure of nerve regeneration.
- A repository of frozen and fixed human peripheral nerve tissue and skin from diabetic and non-diabetic patients with well-defined neurological and demographic profiles should be created.
- Funding should be provided to examine the clinical and biochemical data and biopsy material obtained in the placebo-arms of previous clinical trials to provide a larger body of information on the clinical correlates of histologic data as well as to provide information on the natural history of diabetic neuropathies.
- Specific double blind placebo-controlled trials be undertaken to evaluate therapies, e. g. nerve growth factor (NGF) for small fibre dysfunction,

neurotrophin-3 (NT-3) for large fibre involvement, and insulin-like growth factors (IGFs) for mixed.

- Controlled trials of intravenous human immunoglobulin should be instituted for proximal diabetic neuropathy in which inflammatory changes have been demonstrated.
- Systems need to be developed to deliver neurotrophic factors to their target tissues and to minimize side effects.
- Studies should be encouraged to identify genetic predispositions for the specific subtypes of diabetic neuropathies.
- Means should be developed for rapid translation of research findings into clinical application.

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