PATHOLOGICAL FEATURES OF DIABETIC NEUROPATHY

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Abstract: *Peripheral neuropathy is the major reason for morbidity and mortality among diabetic patients. Unfortunately, the natural history and pathogenesis of the disease are not fully known. For a long time, hyperglicemia was viewed as a major, if not the sole factor responsible. It is obvious that diabetic neuropathy cannot be fully understood without considering factors besides hyperglycemia. Metabolic and vascular factors play an important role in the pathogenesis of the diabetic neuropathy. Detailed neurophysiological studies in diabetic patients have shown that demyelination precedes axonal loss. Experimental studies demonstrate progressive molecular alterations leading to nodal and paranodal degeneration with axo-glial dysjunction and axonal atrophy. These alterations have not been observed in diabetic patients. Unmyelinated fibres demonstrate both degeneration and regeneration in a variety of clinical syndromes of the diabetic neuropathy. The occurence of demyelination in the absence of morphologically apparent axonal damage suggest that the Schwann cell may be a primary target of damage in diabetic neuropathy. Epidermal small nerve fibre degeneration was demonstrated in the presence of normal vibration sensation and electrophysiology. Small fibres appear to be prone to early damage but retain the ability to repair themselves even in chronic end-stage neuropathy. Prior to clinically detectable neuropathy, endoneurial microangiopathy is characterised by membrane thickening and endothelial cell hyperplasia in diabetic patients.*

Cuvinte cheie: *neuropatie, demielinizare, degenerare axonală, dying back, microangiopatia*

Rezumat: *Neuropatia periferică este cea mai importantă cauză de morbiditate şi mortalitate în rândul pacienţilor diabetici. Din păcate, istoria naturală şi patogeneza bolii nu sunt pe deplin cunoscute. Pentru o lungă perioada de timp s-a crezut că hiperglicemia este cel mai important dacă nu şi singurul factor responsabil. Este însă evident că neuropatia diabetică nu poate fi perfect înţeleasă fără a considera implicarea şi a altor factori pe lângă hiperglicemie. Factorii vasculari şi metabolici joacă un rol important în patogeneza neuropatiei diabetice. Studii neurofiziologice detaliate la pacienţii cu diabet zaharat au arătat că demielinizarea precede pierderea axonală. Studii experimentale au demonstrat alterări moleculare progresive care duc la degenerare nodală şi paranodală cu disjuncţie axo-glială şi atrofie axonală. Aceste alterări nu au fost însă observate la pacienţii diabetici. Fibrele amielinice demonstrează atât degenerare cât şi regenerare într-o varietate de sindroame clinice ale neuropatiei diabetice. Apariţia demielinizării în absenţa afectării axonale morfologice arată că celulele Schwann pot fi prima ţintă a afectării în neuropatia diabetică. Degenerarea fibrelor epidermice cu diametru scăzut a fost demonstrată în prezenţa unei sensibilităţi vibratorii normale şi a unor teste electrofiziologice normale. Fibrele cu diametru scăzut par a fi predispuse la o afectare precoce, dar au însă capacitate de regenerare chiar şi în fazele terminale cronice de neuropatie. Înainte de apariţia neuropatiei detectabile clinic, microangiopatia endoneurială se caracterizează prin îngroşarea membranei bazale şi hiperplazia celulelor endoteliale la pacienţii diabetici.*

INTRODUCTION

Spinal Cord Structure and Function in Diabetes

The spinal cord lies within the blood–brain barrier. Glucose levels in the cerebrospinal fluid are substantially lower than those to which peripheral nerves are exposed, both in normal and hyperglycemic conditions. Consequently, the motor neuron cell bodies located in the ventral horn are relatively protected in comparison with the sensory cell bodies in the dorsal root ganglia and indeed relative to their own axons that leave the spinal cord and project to target organs. As hyperglycemia is widely regarded as a primary pathogenic mechanism for diabetic neuropathy, the regional variability in glucotoxic exposure may have important consequences for the manifestation of diabetic neuropathy (1).

Although the posterior columns are the most commonly reported site of injury in diabetes mellitus, lesions have also been documented in the spinocerebellar tracts and ventral columns with the lower segments of all regions affected more than the upper segments (2,3).

Diabetes-associated injury to the gray matter of the spinal cord is not as commonly reported as that in the white matter and, where reported, involves neuron shrinkage and loss, chromatolysis, and gliosis. More recently, neuroaxonal dystrophy has been described in the posterior spinal ganglia (4).

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Similar to peripheral neuropathy, radiculopathy is a frequently described manifestation of diabetes mellitus. Much of the debate related to diabetes-induced spinal cord injury has centered on whether myelopathy is an independent lesion or a secondary consequence of peripheral neuropathy and/or radiculopathy, the most frequently described neurological manifestations of diabetes mellitus. For example, abnormal cutaneous sensation, paresthesia, and ataxia clearly involve lesions in peripheral nerves and roots. However, alterations in proprioceptive sensation and lack of muscle coordination without profound changes in cutaneous sensation point to an independent lesion in the ascending tracts of the posterior column (5).

Distal peripheral neuropathy

The largest problem associated with distal peripheral neuropathy complicating its classification and treatment, is the variety of clinical presentations of the disease. Generally, is bilateral manifestation, distal to proximal advance and prevalence of sensory over motor impairment signs and symptoms. Positive symptoms include pain, paresthesias, allodynia and hyperalgesia. Negative symptoms consist of loss of sensory perception. Motor symptoms consist of muscle weakness, and thus they are also negative. Also negative sign is a decrease in nerve conduction velocity and amplitude of compound action potentials on electrophysiological study of peripheral sensory and motor nerves (6).

Abnormalities reported in diabetic neuropathy include axonal degeneration in nerve fibers, primary demyelination resulting from Schwann cell dysfunction, secondary segmental demyelination related to impairment of the axonal control of myelination, remyelination, proliferation of Schwann cells, atrophy of denervated bands of Schwann cells, onion-bulb formations, and hypertrophy of the basal lamina. Early morphological changes include minimal alteration of myelinated and unmyelinated fibers, and axonal regeneration (7,8).

Signs of demyelination of large peripheral fibers (decrease in nerve conduction velocity) may or may not co-exist with signs ans symptoms of large fiber axonopathy (decrease in amplitude of compound action potentials, loss of vibration sensation and/or loss of stretch reflexes). Loss of warm and cold perception, impairment of unmyelinated and small myelinated fibers, may or may not co-exist with signs of large fibers abnormalities. Furthermore, the pain normally conducted by small unmyelinated peripheral axons may or may not be present at the same time with any of the above mentioned symptoms. The pathogenesis of negative symptoms and signs of distal peripheral neuropathy is likely to be associated with demielination and axonal atrophy and degeneration. Failure of re-innervation will make these symptoms irreversible. Mechanisms of neuropathic pain, paresthesias and hyperalgesia are less understood (6).

At least at advanced stages, evidence for axonal, glial and vascular injuries are detectable in most cases of distal peripheral neuropathy. Distal peripheral neuropathy may be a manifestation of dying back degeneration, with the primary insult consisting of the impairment of synthesis or efferent axonal transport of proteins, therefore affecting the function of the longest axons in the body that are most dependent on these mechanisms. Failure of protein synthesis, including synthesis of some important neurotrophic molecules could result in impaired nerve regeneration and dying back axonopathy. Alternatively, accumulation of the effects of multiple injuries randomly located along the axon, for example demyelinating injures, may result in a clinical picture that is practically indistinguishable from dying back neuropathy. The longest axons in the body will most likely be hit by a critical number of such local insults and their function will fail first. Micro-vascular disease followed by local impairment of blood supply to the nerve fascicules may be a basis for random demyelinating insults progressing later to axonal degeneration. It is also conceivable that both mechanisms are operating at the same time (6).

Endoneurial capillaries often show signs of diabetic microangiopathy, with marked thickening of the basal lamina. The presence of multifocal nerve lesions and alterations of endoneurial capillaries have indicated a role for circulatory factors in symmetrical diabetic neuropathy. Dissociated sensory loss, severe autonomic dysfunction and predominant loss of unmyelinated axons cannot, however, be explained by nerve ischemia alone (8).

Focal and Multifocal Diabetic Neuropathies

In a patient with proximal neuropathy of the lower limbs, biopsy specimens of the intermediate cutaneous nerve of the thigh, that conveys sensation from the anterior aspect of the thigh, a territory commonly involved in diabetic neuropathy, showed lesions characteristic of nerve ischemia, associated with inflammatory infiltrates around epineurial and perineurial blood vessels. The inflammatory lesions consisted of B and T lymphocytes and macrophages. In patients with multifocal diabetic neuropathy, nerve biopsy showes asymmetric axonal lesions associated with vasculitis of perineurial and endoneurial blood vessels. It is not known why lesions predominate on lower spinal roots, the lumbar plexus and nerves of the lower limbs in proximal and multifocal diabetic neuropathies (8).

Punch Skin Biopsy in Diabetic Neuropathy

Measurement of unmyelinated C and A delta nociceptors through punch skin biopsy has been an important development in diabetic peripheral neuropathy over the past decade. The technique provides an objective pathological window into a population of fibers that is invisible to standard electrophysiological techniques. Epidermal nerve fibers are often lost early in diabetes or impaired glucose tolerance and can be the only objective measure of neuropathy in these patients. Historically, pathological examination of these fibers has been limited to nerve biopsies, primarily of the sural nerve. Further complicating interpretation of nerve biopsies is the difficulty to discern differences between somatic and autonomic small caliber unmyelinated nerve fibers (1).

The availability of antibody to protein gene product (PGP) 9.5, a neuronal ubiquitin hydrolase, rapidly led to sensitive immunohistochemical techniques to visualize nerve fibers in the skin (9).

Generally, skin biopsies are very well tolerated and result in negligible scarring in individuals without a predilection to keloid formation. In general, a distal location where there are abnormalities on examination, particularly decreased sensibility to pin prick or thermal sensation, or where the patient has symptoms is best. One distinct advantage of the technique is that nearly any site can be assessed in contrast to electrophysiology where testing is limited to specific nerves at specified sites (1).

Two biopsy techniques have been described: punch skin biopsy and skin blister formation. Punch biopsy is the most widely used and is performed with a 3-mm diameter circular biopsy instrument. Generally biopsies are performed to a depth of 2–3 mm. An alternative biopsy procedure is achieved by application of 300 mmHg negative pressure to a 3 mm blister capsule. This approach has the advantage of being less invasive though blister formation is dependent on maintenance of a tight seal for 20–40 minutes (1,10).

Evaluation of epidermal nerve fibers appear to be more sensitive, perhaps because of their further distance from the cell body, absence of a Schwann cell or collagen covering sheath, and the avascular nature of the epidermis that increase

their susceptibility to disease (11).

Intraepidermal nerve fibers density has been shown to be inversely related to diabetes duration in people with type 2 diabetes, but not to HbA1C levels (12).

In conclusion, skin biopsy with determination of epidermal nerve fiber density is a powerful tool that provides investigators insight into a population of nerve fibers that is prominently affected in diabetes and yet has been relatively under investigated. These features have allowed investigators to diagnose neuropathy earlier and to define an association between neuropathy and impaired glucose tolerance (12,13).

Because the spinal cord is the first site of integration of sensory input from the periphery and the last site of descending control of sensory and motor systems, disruption of spinal cord function has the capacity to impede appropriate CNS control systems and contribute to apparent peripheral neuropathy (14).

Multiple questions related to the pathogenesis of diabetic neuropathy remain unresolved. It is not clear why, in most cases of neuropathy, sensory symptoms prevail over signs of impairment to motor axons innervating the same distal areas of the human body. Neither of these mechanisms explains a variety of clinical presentations nor answers the question of why some diabetic patients live without any symptoms of diabetic neuropathy for years. The pathogenic triggers, the pathogenesis of individual symptoms, and the relationships among different symptoms and signs of the disease are not known yet (6).

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