Update Article

REGENT ADVANCES IN DIABETIC NEUROPATHIES

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Definition

The following operational definition of diabetic peripheral neuropathy was adopted in : San Antonio Conference on Diabetic neuropathy[1] held on February 8-10, 1988 :

"Diabetic neuropathy is a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system".

Pathogenesis

The precise cause of diabetic neuropathy is not known. Following possible mechanisms have been suggested :

1. Endoneurial hypoxia : Sural nerves from patients with diabetic neuropathy have been shown to exhibit statistically significant increase in the percentage of capillaries closed as compared to those without neuropathy and controls[2]

2. Nonenzymatic glycosylation of myelin components : It has been demonstrated that the amount of nonenzymatic glycosylation in whole peripheral nerve from diabetic rats and dogs is increased twofold above the normal[3]. Vogt et. al.[4] demonstrated that nonenzymatic glycosylation also occurs in human peripheral nervous tissue. Peripheral nerve myelin isolated from diabetic rat has been shown to have a greater than fivefold increase in the amount of glycosylation present when compared with normal peripheral nerve myelin[5].

3. Defects of axonal transport : In experimental diabetes, a reduction in the transport velocity of slow component a (SCa), axonal dwindling and reduction in the amount of material transported per unit time have been found[5]-[10]. Gel electrophoretic studies have shown a corresponding decreased transport velocity of two neurofilament subunits in diabetic mice[11]. Two pathological alterations occur in relation to changes in the neurofilament transport at the site of damming of transport a swelling of the axon occurs while a decrease of transport leads to axonal atrophy[12].

4. Inter-related fall in nerve myo-inositol due to increased polyol (sorbitol) pathway activity : Hyperglycemia-induced increased polyol pathway activity and reduced tissue myoinositol content in peripheral nerves are two commonly invoked biochemical pathogenetic mechanisms for diabetic neuropathy. Recently, their possible inter-relationship has been explored. Studies in streptozotocin diabetic rats have shown that administration of aldose reductase inhibitor (sorbitol) completely

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prevented the fall in nerve myoinositol, thereby implicating increased polyol pathway activity as a likely factor in the fall in nerve myoinositol content in experimental diabetes[13].

Clinical Assessment

In the last two years, several substantial advances in clinical assessment of diabetic polyneuropathy have been made[1] :

a) Careful studies have shown a close correlation between clinical manifestations of diabetic polyneuropathy and neuropathologic abnormalities.

b) Several ongoing studies show concordance between clinical dysfunction and objective continuous measures such as electrodiagnostic studies (EDX), autonomic function testing (AFT), and quantitative sensory testing (QST) nonetheless, each may be abnormal in the absence of clinical correlates.

c) The incidence and severity of polyneuropathy correlate with duration of disease and age.

Electrodiagnosis

A complete electrodiagnostic evaluation plays an important role in diagnosing diabetic neuropathy. In monitoring the course of the disease, however, conduction studies of selected nerves suffice. Conduction studies have widespread availability and acceptance in the assessment of diabetic neuropathy, particularly sequential studies. In multiple mononeuropathies, affected nerves should be tested to characterize the abnormalities. As nerve conduction studies primarily reflect functional status of large myelinated sensory and motor nerve fibres normal results do not rule out neuropathy[1].

Electromyography may reveal partial denervation in intrinsic foot muscles as an early sign of diabetic neuropathy. Needle studies also elucidate focal or asymmetric clinical findings not detectable by conduction studies. As one of the most sensitive indication of motor axonal degeneration, this technique demonstrates early abnormality in asymptomatic diabetic patients. It also helps document the presence or absence of polyradiculopathy or other peripheral disorders superimposed on diabetic neuropathy[1].

More sophisticated methods e.g. near nerve recovding, somatosensory evoked potentials, motor unit count, or measures of refractory periods have recently been utilized to asses diabetic neuropathy.

Autonomic Function Testing

Several objective measurements of autonomic function have been developed during the last few pears. These tests measure end-organ responses to activation of neural reflex arcs. They can be influenced by end-organ failure, intercurrent illness, drugs and age. Such tests include non-invasive tests like the tests of heart rate control, blood pressure control, sudomotor control etc, invasive tests of cardiovascular function, gastrointestinal motility, bladder function and other biochemical, physiologic and pharmacologic studies like plasma norepinephrine response to standing, pupillometry etc.

Measures of autonomic function particularly lend themselves to staging system because there is a hierarchy of levels of sensitivity of these measures. For example, an abnormality of heart-rate variability alone may be the earliest stage, an abnormality of Valsalva response

define an intermediate stage, and the presence of postural hypotension might define the severe stage.

Management

In the last few years, the studies have tried to define the role of aldose reductase inhibitors in diabetic polyneuropathy. Earlier clinical trials have involved treatment for up to 6 months. In a randomized, double-blind, cross-over trial on 39 asymptomatic patients it was shown that during nine weeks of treatment with sorbinil (250 mg per day), nerve conduction velocity was greater than that during a nine week placebo period[14]. In a study of 30 patients with long-standing diabetes treated with aldose reductase inhibitor (Alrestatin) for 12 weeks, beneficial effect was reported[16] parti-cularly for autonomic functions, although in many instances there have been no demonstrable changes in nerve function. Relief of pain[16] and paresthesiae[17] has been described but this has not been reproduced in other studies[13] and more detailed investigations are required. The effects of an aldose reductase inhibitor, sorbinil, on neuropathy in 39 diabetics were studied in a 12 month double-blind placebo controlled trial[19]. The results indicate that aldose reductase inhibitors are not effective in the treatment of established diabetic neuropathy. Whether these have any role in prevention or delaying the onset of diabetic neuropathy is yet to be studied.

References

1. Special report. Report and recommendations of the San Antonio Conference on Diabetic Neurology 1988; 38 : 1161-1165.
2. Dyck PJ, Hansen S, Karnes J, O'Brien P, Yasuda H, Windebank A, ZimmermanB. Capillary number and percentage closed in human diabetic sural nerve.Proc Natl Acad Sci USA 1985; 82 : 2513-2517.
3. Vlassara H, Brownlee M, Cerami A. Nonenzymatic glycosylation of peripheral nerve protein in diabetes mellitus. Proc Natl Acad Sci 1981; 78 : 5190-5192.
4. Vogt. BW Scnleicher ED, Weilard OH. Epsilon Amino-lysine-bound glucose in human tissues obtained at autopsy: increase in diabetes mellitus. Diabetes 1982; 31 : 1123-27.
5. Gregersen *G*. Diabetic neuropathy; influence of age, sex, metabolic control, and duration of diabetes on motor conduction velocity. Neurology (Minneapolis) 1967; 17 : 972-980.
6. Jakobsen J, Sidenius P. Decreased axonal transport of structural proteins in streptozotocin diabetic rats. J. Clin Invest 1980; 66 : 292-7.
7. Jakobsen J, Axonal dwindling in early experimental diabetes. I. A study of cross sectioned nerves. Diabetologia 1976; 12 : 539-46.
8. Jakobsen J. Early and preventable changes of peripheral nerve structure and function in insulin-deficient diabetic rats. J Neurol Neurosurg psychiatry 1979; 42 : 509-18.
9. Sharma AK, Bajada S. Thomas PK. Influence of streptozotocin-induced diabetes on myelinated nerve fibre maturation and on body growth in the rat. Acta Neuropathol (Berl) 1981; 53 : 257-65.

10 Sidenius P, Jakobsen J. Reversibility and prevent ability of the decrease in slow axonal transport velocity in experimental diabetes. Diabetes 1982; 31:689-93.

11. Vitadello M. Filliatreau G- Gupont JL, Hassig R, Gorio A, Di Giamberardino L Altered axonal transport of cytoskeletal proteins in the mutant diabetic mouse. J. Neurochem 1985; 45 : 860-8.

12. Jakobsen J, Sidenius P, Braendgaard H. A proposal for a classification of neuropathies according to their axonal transport abnormalities. J. Neurol Neurosurg Psychiatry 1986; 49 : 986-990.

13. Finegold D, Lattimer SA, Noll S, Bernsstein M, Greene DA. Polyol pathway activity and myoinositol metabolism : a a suggested relationship in the pathogenesis of diabetic neuropathy. Diabetes 1983; 32 : 988-992.

14. Judzewitch RG. Jaspan JB, Polonsky KS, Weinberg CR, Halter JB, Halar E, Pfeifer MA, Vukadinovic C, Bernstein L, Schneider M, Liang KY. Gabby KH, Rubenstein AH, Porte J Jr Aldose reductase inhibition improves nerve conduction velocity in diabetic patients. N Engl J Med 1983; 308 : 119-125.

15. Fagius J, Jameson S Effects of aldose reductase inhibitor treatment in diabetic polyneuropathy- a clinical and neurophysiological study. J Neurol Neurosurg Psychiatry 1981; 44 : 991-1001.

16. Jaspan J. Maselli R, Herold K, Bartkus C Treatment of severely painful diabetic neuropathy with an aldose reductase inhibitor : relief of pain and improved somatic and autonamic function. Lancet 1983; II : 758-762.

17. Shand DG and the Tolrestat painful neuropathy study group. The effect of Tolrestat, a new aldose reductase inhibitor, on nerve conduction and painful symptoms in diabetic neuropathy. Diabetic Medicine 1986; 3 : 559 (Abstract).

18. Lewin IG, O'Brien IBD, Morgan MH, Corrall RJM Clinical and neurophysiological studies with the aldose reductase inhibitor, sorbinil, in symytomatic diabetic neuropathy. Diabetologia 1984; 26 : 445-448.

19. Guy RJC, Gilbey SG, Sheehy M, Asselman P, Watkins PJ. Diabetic neuropathy in the upper limb and the effect of twelve months sorbinil treatment. Diabetologia 1988; 31 : 214-220.