Current Concepts in Diabetic Neuropathy

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Abstract

Diabetic neuropathies are classified, for the sake of convenience, into four groups. First are the distal symmetrical variety that may be predominantly motor or predominantly sensory. Second are the mononeuropathy syndromes of cranial or somatic nerves. Third are the automatic group and finally, any combination of two or three varieties. Etiopathology of these neuropathic syndromes takes into consideration the biochemical alterations and ischemic changes. The most recent understanding of the role of aldose reductase in the polyol pathway is presented briefly, as is, in the hyperglycemic state, sorbitol accumulation, which resuls in the decrease of AT-Pase activity and slowing of nerve conduction. In the treatment of diabetic neuropathies, aldose reductase inhibitors are being used in many centers and their release for general use is anxiously awaited.

Key words: *Diabetic neuropathy, aldose reductase, sorbitol, aldose-reductase inhibitors*

Diabetic neuropathy is a fairly common condition and has been recognized for more than a century.[1,2] Our understanding of its causation, however, is still incomplete. Nevertheless, recent biochemical advances seem promising and are very likely to influence our approach to the treatment of this condition.

Since there are many neuropathy syndromes associated with diabetes mellitus, it is more appropriate to speak of "diabetic neuropathies" rather than neuropathy. In considering the association of these two conditions, it should be recognized that the neuropathy may sometimes make its clinical appearance even before diabetes manifests itself.[3] This raises the question of whether neuropathy is a part of diabetes or a complication thereof.

There are many ways to classify diabetic neuropathies.[4] The following grouping of these conditions is given only for convenience of discussion:

I) Distal symmetrical polyneuropathy (sensorimotor)
   a) Painful type: predominantly sensory, generally affecting the lower extremities.
   b) Painless type: predominantly motor, generally affecting the distal parts of the extremities.

II) Mononeuropathy syndromes
   a) Mononeuropathy (any somatic nerve, eg, median, femoral or peroneal)
   b) Cranial mononeuropathy (eg, 3rd, 4th, or 6th nerves)
   c) Mononeuropathy multiplex.
   d) Proximal mononeuropathy (Diabetic amyotrophy)

III) Autonomic neuropathy

There are many autonomic neuropathy syndromes. The following list is by no means complete.

   a) Gastro-intestinal
      1) Esophageal dysfunction
      2) Gastro-paresis
      3) Diabetic diarrhea
   b) Genito-urinary
      1) Cysto-paresis [with overflow incontinence]
      2) Male impotence
   c) Cardiovascular
      1) Postural hypotension
      2) Arrhythmias

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d) Pupilary and sweating abnormalities

IV) Mixed Neuropathies, ie, any combination of two or more of the above syndromes.

Clinical Features

It is not our purpose to review the clinical features of all the the conditions mentioned above except to mention some of the less common or less well understood conditions. Numbness, neuritic pain and dysesthesias are easily recognized.

A mononeuropathic syndrome is frequently heralded by pain and paresthesia; the important thing to remember is that the prognosis is uniformally good, although recovery may take two years or more. Thoracic neuropathy or radiculopathy[5] presents with acute chest pain or upper abdominal pain. Its early recognition may prevent an unnecessary surgical procedure. Truncal polyneuropathy[6] and polyradiculopathy[7,8] have also been described in diabetics.

Diabetic amyotrophy[9] is the term applied to the syndrome of acute onset of pain and weakness in one or both lower extremeties, especially the thigh muscles such as the quadriceps and psoas. Rapid wasting develops in the quadriceps and sometimes other muscles such as the glutei, hamstrings, etc. There is gradual recovery over a period of one to two years. The facts that (1) Hugh Garland described this syndrome first as diabetic myelopathy,[10] later corrected to amyotrophy,[11] and that (2) the clinical findings of these patients are not limited to the muscles supplied by the femoral nerves has resulted in multiple names. These include "symmetrical proximal motor neuropathies",[12] "femoral neuropathy",[13] etc. This also illustrates the difficulty in placing this syndrome in the usual classification. The exact pathology of this particular condition is not understood.

Diabetic neuropathic cachexia[14] is the condition of diffuse motor neuropathy with generalized wasting of muscles and some pain. It is generally considered a self-limited condition with good prognosis.

Pain in these patients may not necessarily be of neuropathic type, but may be due to degenerative arthritis.

When sensory neuropathy has been present for a prolonged time, complications such as Charcot's arthropathy, due to decreased nocifensive reflex, may develop.

Autonomic neuropathies are found in 20 to 40% of diabetic patients if looked for carefully.[15] Pupilary and sweating abnormalities are usually of no serious consequence other than the production of Argyll-Robertson - like pupil, causing difficulties in differential diagnosis. Postural hypotension and "silent" myocardial infarction[16] or arrythmias[17] are clearly worthy of attention. Nocturnal episodic diarrhea of the diabetics is known to respond to antibiotics[18] and gastro - paresis is helped by metoclopramide.[19] Impotence is reported in as many as 50% of the diabetic male population.[20] For diagnosis and treatment, a very careful history, especially of erectile and ejaculatory functions, is essential.

Pathology and Pathogenesis

The diabetic changes observed in axons, myelin, and Schwann cells are nonspecific. There has been a debate over whether segmental demyelination or axonal degeneration is the primary event. More recently, electroneuromyographic studies have suggested that injury to the axon is the primary structure event.[21]

The pathogenetic mechanisms that result from hyperglycemia have been studied for many decades.[22] For details, Low's description in "Muscle and Nerve"[23] may be consulted.

It may be useful at this juncture to recapitulate very briefly the anatomic physiology and biochemistry. A nerve fiber consists of three elements:

a) Axon

b) Myelin Sheath

c) Schwann cells.

The myelin sheath is composed of fatty structures and some proteins. It is wrapped around the axon longitudinally in an "onion skin" fashion. One Schwann cell is located in each internode (the nodes of Ranvier divide the entire length of the fiber into many internodes of various lengths). Saltatory conduction of the nerve impulse depends upon the integrity of the myelin sheath. Axonal filaments have their own flow of nutritive materials running from the cell body to the termination of the axon.

The energy required to maintain the nerve conduction velocity (physiological measure of the integrity of nerve function)[24] depends upon the ATPase activity in the nerve fiber. Also, myoinositol, a glucose isomer, helps in electrolyte and aminoacid transport in the nerve fibers.

In normal glucose metabolism hexokinase activity is the major activity in the nerve fiber, whereas aldose-reductase activity of the polyol pathway has a minor role. In the diabetic nerves, however, due to sustained high levels of glucose, the hexokinase activity becomes saturated and aldose-reductase activity is increased. As seen in the equation below, aldose-reductase converts glucose, in the presence of NADPH, into sorbital, which in turn is converted to fructose by dehydrogenase.

$$\text{Glucose} \xrightarrow[\text{NADPH}]{\text{Aldose reductase}} \text{Sorbital}$$

$$\text{Sorbital} \xrightarrow{\text{Dehydrogenase}} \text{Fructose}$$

This result in an accumulation of sorbital and fructose, which in turn decreases myoinositol; hence, activity of sodium-potassium-ATPase is decreased. Required energy consumption in the nerve fiber is reduced with a resultant decrease in the nerve conduction velocity.[23]

Involvement of vasa nervorum due to diabetic microangiopathy[25] producing ishemia will decrease the turnover of myelin and slow down the axonal transport system.[26] It is conceivable that all these factors, singly or in combination, acting over a long period of time may result in structural damage to the nerves in diabetics.

Treatment

From the above description, it seems plausible that reducing the activity of aldose-reductase may improve or prevent neuropathy in diabetics.[27] During the last five years, various diabetic centers have attempted trials of aldose-reductase inhibitors, both experimentally and in patients with diabetic neuropathy. Although the results have not been uniformly impressive, this line of treatment appears to have clear promise for the control of diabetic neuropathy in the future.

Treatment of painful neuropathy with drugs such as diphenyl hydantoin and carbamazepine is well established. Anti-depressive medications, such as amitriptyline alone or in combination with a phenothiazine, have been used more recently for the control of pain.[28,29] As far as the use of narcotic analgesics is concerned, caution should be exercised as these conditions generally have good prognosis. We anxiously wait for the release of aldose-reductase inhibitors such as sorbinil or tolrestat for the treatment of diabetic neuropathy.

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