DIABETIC NEUROPATHY

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Of the six million diabetics in the United States, between 5 and 60 per cent have been reported to be affected with peripheral neuropathy. The wide range in these figures reflects the lack of uniform criteria with which to diagnose and classify this complication of diabetes. Further complicating the matter is the fact that physicians may not recognize the various sensory, motor, and autonomic manifestations of the disease. This chapter reviews the forms, proposed etiologies, diagnosis, classification, and treatment of diabetic neuropathy with the hope that early recognition and treatment will improve the clinical management of these patients.

PATHOPHYSIOLOGY

Many physiological mechanisms have been proposed to explain the development of diabetic neuropathy. Simply stated, the function of the Schwann cells is impaired resulting in a loss of myelin. Even in those nerves which do not possess myelin, the relationship between the Schwann cell and the axon is quite intimate. The initial consequence is a reduction in nerve conduction velocity, but actual axon damage and degeneration follows (1).

Nerve tissue is unique as it does not require insulin for glucose to be absorbed into the cells. Consequently, the glucose levels within nerve axons will be directly proportional to that of the blood. Most authorities feel that the damage induced by the hyperglycemia is mediated through the polyol pathway. Glucose is transformed in the Schwann cell to sorbitol and fructose which eventually leads to numerous biochemical and functional abnormalities. Most important is the decreased concentration of myoinositol which is required for proper function of the axonal membranes. As the rate of the polyol pathway is directly dependent upon the level of glucose, persistent hyperglycemia feeds this process (Fig. 1)(2).

It has also been postulated that neuropathy is caused by occlusive vascular disease or infarcts which result in nerve ischemia. However, most authorities now tend to support a metabolic derangement such as that described above for most cases of neuropathy. Specific neuropathies which tend to develop due to ischemia or vascular infarcts will be noted.

CLASSIFICATION OF DIABETIC NEUROPATHY

With the onset of diabetic neuropathy a wide variety of manifestations may develop. The difficulty in adequately classifying this process is that mixed syndromes are frequent. Brown/Asbury (3) advocate using broad subdivisions as follows:

Distal symmetrical polyneuropathy:
Usually insidious in onset and progressive
Proximal symmetrical motor neuropathy:
"diabetic amyotrophy"
Focal neuropathies:
Rare, sudden, transient events.
-Asymmetrical proximal motor neuropathy
-Cranial neuropathy
-Mononeuropathy/mononeuropathy multiplex
-Entrapment neuropathy

The discussion that follows will focus on the various neuropathies that affect the lower limb.

Distal Symmetrical Polyneuropathy

This is the most commonly recognized form of diabetic neuropathy. The estimated prevalence of the various subtypes are provided in the table below (3).

Table 1

Subtype	% of cases
Mixed sensory-motor-autonomic	70
Predominately sensory	30
Predominately motor	<1
Predominately autonomic	<1

Perhaps the most striking feature of this classification is the large number of patients that will exhibit clinical manifestations of neuropathy in all three fiber types. Most clinicians have been keenly aware of sensory neuropathy, while other forms of nerve disease have not been fully appreciated. The discussions which follow are an effort to help those who treat diabetic patients to more readily distinguish the numerous characteristics of this mixed syndrome.

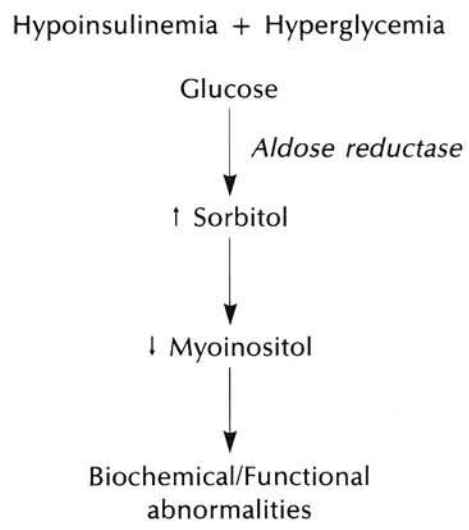

Fig. 1. Abbreviated and simplified model of relationships which lead to nerve damage. (Adopted from Clements RS, Bell DSH: Diabetic neuropathy: pathogenesis and classification. *Cardiovascular Reviews and Reports*, April, 1987, pp 18-23.

Sensory deficits and symptoms appear in the most distal portions of the extremities and progress in a "stocking and glove" distribution. The first symptoms may be numbness and paresthesias in the feet, most marked in the evening. They are often relieved by ambulation, massage, and hot or cold soaks. The paresthesias may be variously described as coldness, burning, tingling, ache, cramplike, or crushing. Often a patient relates a sensation of walking on air or pillows, or feeling that their feet are swollen. With progression of the neuropathy, pain in the lower limbs may become the most prominent feature, although this does not seem to be the case in the majority of instances. Many patients will not recall any specific symptoms, yet fail to recognize the degree to which sensation has been impaired. Sensory neuropathy is appropriately detected in most instances, and much has already been written about this particular neuropathy.

While a majority of the symptoms and signs in the legs may be sensory, muscle weakness almost invariably accompanies the sensory loss. In evaluating diabetic patients at the Institute it has been the authors' finding that a consistent number will present with a variable pattern of lower extremity muscle weakness. The loss of a grade of muscle strength may initially seem benign, but in this patient population the effect is greater than imagined. Many of the patients will present with muscle weakness which exceeds one grade. The motor neuropathy usually involves the interosseous muscles of the feet and results in claw toe contractures and increased pressure beneath the metatarsal heads. One may also see the weakness involving the anterior leg muscles which may be profound enough to cause a dropfoot.

Milder forms of weakness may not be as readily detected, yet still lead to a distinct dynamic imbalance which creates or exacerbates an ankle equinus deformity. Equinus not only increases the forces affecting the metatarsal area, but places additional stress on the mid- or rearfoot which may cause Charcot collapse. When combined with a concurrent sensory loss the patient is at a higher risk for developing ulceration. When present with autonomic neuropathy, bone which has already been weakened due to hyperemia may not be able to withstand these additional forces and may eventually collapse.

Autonomic neuropathy, or autosympathectomy, occurs in up to 70% of diabetics (3). Evidence indicates that the autonomic component of the peripheral neuropathy may precede the onset of either sensory or motor involvement. Sympathetic fibers supply the small arteries and arterioles of the lower extremity, the sweat glands, and the arrectores pilaris muscles. Autonomic dysfunction results in vascular calcification resembling Monckeberg's medial calcific sclerosis, anhidrosis, and eventually loss of hair growth.

The vascular implications of autonomic neuropathy are great. Loss of sympathetic tone results in a vasodilation of the vessels causing an increased blood flow to the skin, subcutaneous tissues, and bone. Numerous studies have shown that the neuropathic foot is extremely well perfused (4-6). Many patients may possess a foot which demonstrates neuropathic edema due to the shunting of blood at the arteriovenous anastamoses (7). Vascular calcification should not be interpreted as occlusive disease as Edmonds, et.al., have noted that the only explanation for this phenomena is neuropathy (8). At times the calcification may make palpation of the pulses impossible.

Typically, the diabetic limb has been felt to suffer from microangiopathy, however, no objective evidence has been found to support the presence of a microvascular occlusive disease. Yet many diabetics may not receive adequate foot care due to the misconception concerning the vascular status of the lower extremity (9,10). Unless proximal large vessel disease is present, the patient who possesses autonomic neuropathy will present with a good blood supply to the foot.

Autonomic neuropathy will usually affect the lower extremity first, then may exhibit more proximal manifestations as well. This facet of the disease may affect many organ systems. Although beyond the confines of the lower extremity, evidence of the more proximal aspects of the disease confirm the fact that autosympathectomy is present in the lower extremity. The anhidrotic skin found in the foot and leg may be contrasted with a compensatory increase in perspiration over the trunk. This

hyperhidrosis is required to offset the reduced ability of the lower limb to dissipate heat. The patient may complain of heat intolerance or sweating attacks. Gustatory sweating may occur over the face, head, and neck within seconds of eating spicy foods.

Cardiac function may be affected by autonomic neuropathy and initially result in a resting tachycardia. However, if the skin and splanchnic beds are diseased the patient is prone to postural hypotension. The heart rate is typically fixed and fails to show the typical change to position and exertion. This may result in orthostatic hypotension which is quite disturbing. Some authorities also attribute the prevalence of silent myocardial infarction in diabetics to autonomic neuropathy (11).

The gastrointestinal and urinary systems may demonstrate a variety of problems including diabetic gastroparesis (early satiety, abdominal fullness, nausea, and vomiting), diabetic diarrhea with involvement of the small bowel, or constipation when the colon is affected. Bladder disturbances are occasionally present and may result in incomplete voiding, decreased frequency of voiding, incontinence, and impotence (11).

Treatment of symmetrical polyneuropathy

The treatment of peripheral neuropathy is best centered upon preventing the initial nerve damage. An improved metabolic control with near normal daily blood glucose profiles is the first and foremost step. Although clinical trials have really not demonstrated that this makes a definitive long term difference, most experts continue to support the need for tight glucose control (12).

Various pharmacologic agents have also been studied to determine if neuropathy may be prevented by blocking the polyol pathway. If this metabolic process could be arrested, then one might prevent the accumulation of noxious substances within the nerve. Specifically the medications most commonly employed to date have been agents which inhibit the enzyme aldose reductase (Alrestatin, Sorbinil, Tolrestat). Although theoretically of value, these drugs have yielded only equivocal results in clinical trials. Two studies have found significant improvement in nerve conduction velocity as well as subjective assessments of patient symptoms (13,14). Other investigators have been unable to reproduce these results (15,16). However, the effectiveness of these drugs may be related to the degree of nerve damage present when pharmacologic therapy is instituted. Those patients who have benefited the most in the clinical trials were younger and exhibited less established disease.

One must also be concerned over potential side effects of this type of medication and whether or not the potential benefits outweigh the long term risks. Aldose reductase catalyzes a number of other metabolic reactions in the body and it is not known if the inhibition of these processes is of consequence (17).

Another agent which has been used for diabetic neuropathy is myoinositol. This substance is an important component of neuronal cell membranes. In diabetic laboratory rats the nerve content of myoinositol is diminished. Normalization by oral supplements results in an increase in nerve conduction velocity. However, clinical trials in humans so far have been disappointing (18).

The "antineuritic" vitamins, thiamine, pyridoxine and vitamin B 12 have all been experimentally used in diabetics. The supposition was that they may be beneficial if some correlation was present with alcoholic or nutritional neuropathies. However, deficits of these vitamins has never been found in diabetic subjects. Most current researchers feel that there is no objective data to justify the use of neurotrophic vitamins (12).

Unfortunately, we have to deal with a large group of patients who either possess, or will possess, varying degrees of neuropathy. Several things can be done to minimize the risk for complications in these individuals. Adequate protective measures must be taken with shoes and/or orthotic devices. The device should be designed to accommodate the excessive forces acting on the foot. Often one may forget the benefit of adding a rocker sole to the shoe to assist in protecting the metatarsal area (19). Muscular imbalances (equinus) must be accommodated as well. This may be accomplished by adding an appropriate size heel lift to the shoe. In most cases between 3/4" to 1 1/4" will be adequate. Despite other supportive measures, failure to recognize and protect the foot from equinus still leaves the foot at risk for Charcot joint collapse.

Muscle imbalance may be improved through the use of a controlled physical therapy program. Generally the authors recommend that the patient be seen by a physical therapist as most patients lose interest in exercising on their own. Specifically, one is attempting to strengthen the anterior leg muscles, while stretching the posterior group. Stretching should be done gently, so as not to encourage excessive stress within the foot. The danger is that the foot may be used as a lever against the triceps. If Charcot collapse has already taken place then physical therapy may have to be limited to strengthening of the anterior muscle group.

Symmetrical Proximal Motor Neuropathy

Other somatic manifestations of diabetic neuropathy may occur in the hip and thigh muscles. Here weakness

may be associated with aching thigh pain. Most affected individuals are middle-aged or older who will give a history of recent weight loss. The proposed etiology of this process is felt to be metabolic in nature owing to the concommitant history of weight loss and/or poor glycemic control. This syndrome has also been associated with alcoholism (20).

Generally these individuals recover motor function to some degree, although the intervening period may be quite distressing. Ambulation, stair-climbing, and arising from a sitting position may all become difficult if not impossible to perform. Several such patients in our practice have responded to physical therapy, while others, with more protracted weakness have failed to demonstrate significant improvement.

Focal and Multifocal Neuropathies

Asymmetrical proximal motor neuropathy primarily affects the cranial and intercostal nerves, although it may also be seen in the lower extremity. Generally speaking the evidence seems to support an acute ischemic process as the etiology for these clinical syndromes. The onset of the neuropathy is usually rather rapid and pain is usually associated with the loss of strength. In the lower extremity this syndrome may resemble a radiculopathy and most commonly affects the femoral, obturator, and sciatic nerves. However, such presentations should not be casually dismissed as "diabetic radiculopathy" since this is a diagnosis assigned after other pathologies have been excluded. Overall the prognosis is good, although recovery of function may take months.

Nerve entrapments are also more common in diabetics. Generally speaking the entrapment neuropathy is felt to be due to compression. The patient who already possesses some degree of nerve damage will be more vulnerable to any compressive effects or strictures about a nerve. In the lower extremity compression of the lateral femoral cutaneous nerve may result in meralgia paresthetica, pain and numbness overlying the lateral thigh. The common peroneal nerve is also reported to occasionally manifest with entrapment syndromes. However, the authors have yet to witness this presentation. Carpal tunnel syndrome is seen with greater frequency in diabetic patients (3).

Treatment for each of these entrapment neuropathies is the same as that for nondiabetic patients with resolution occurring in a similar manner.

Painful Diabetic Neuropathy

Pain may be a feature of any type of diabetic neuropathy. Focal neuropathies will result in a sharp, sudden onset along the course of the nerve which is afflicted. Typically it is asymmetrical and lasts for weeks or months before spontaneously disappearing.

Pain in peripheral polyneuropathy usually starts insidiously and may be symmetrical. However, in the authors' experience most patients have presented with unilateral complaints. Several types of symptoms may be described including spontaneous episodes of generalized discomfort, contact sensitivity, shooting or stabbing, burning, or a deep aching. Although the onset may occur at any time of the day, most patients relate that they are particularly uncomfortable in the evening, and often can not sleep through the night (21).

It is paradoxical that insensitivity to pain and spontaneous pain coexist. Although not fully understood, the most logical explanation for the discomfort appears to be damage to the small nerve fibers which causes a subsequent increased activity of these units. It has been shown that regenerating nerve fibers fire rapidly and at abnormally low thresholds. Depolarization of these damaged or regenerating fibers may be the mechanism which elicits pain (3).

Treatment of Painful Diabetic Neuropathy

One of the best means of treating this condition is through effective, strict blood glucose control. Hyperglycemia is felt to enhance pain sensitivity and relief of symptoms is often obtained after several weeks of stable metabolic control. However, in some individuals painful neuropathy may be induced by rapid normalization of hyperglycemia (21).

Chronic pain has been treated by a variety of pharmacologic agents. Tricyclic antidepressants have been used with success in a number of patients, although critics point out that no controlled, double-blind studies have been performed. Generally these medications work best for deep, aching pain. However, if orthostatic hypotension is a problem for the patient (as it may often be in those with autonomic involvement in the heart), then tricyclic medications may aggravate the condition (3,21). Those with shooting or stabbing pains appear to respond more favorably with either phenytoin or carbamazepine (3). Carbamazepine is the only drug which has been shown effective in a controlled clinical trial (22). Phenytoin has a less demonstrable effect and high doses tend to inhibit insulin secretion. Trazodone, a nontricyclic antidepressant also has its advocates (23). Others have tried combinations of tricyclic antidepressants and phenothiazines (3).

Unfortunately, many patients fail to find relief with any of the medications described above. Other conservative methods which may help to a certain degree are the ap-

plication of cool towels or dressings, or the use of a mildly compressive stocking.

CONCLUSION

Peripheral neuropathy like other diabetic complications are characterized by early functional reversible changes followed by later permanent structural damage. It is possible that some of the agents currently undergoing evaluation may at some point induce positive effects related to early functional disease. Currently only early preventive treatment in the primary stages of diabetes have yielded any success. Early, tight and near normalization of blood glucose levels appears to be the most effective means of limiting diabetic neuropathy as well as other organ system disease.

Appropriate protection of the foot with education of the patient and physical therapy as required appear to be the best preventive measures to date.

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