Upright Posture and the Microvasculature in Human Diabetic Neuropathy

A Hypothesis

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Despite many years of study, no clear understanding of the pathogenesis of nerve damage in diabetes has yet emerged. Clinical studies in human subjects are bedeviled by the lack of an agreed definition, and extreme difficulties arise in interpreting the neuro- and electrophysiological abnormalities of peripheral nerve in their relationship to pathogenesis and clinical status. As a result, much of our understanding of the metabolic and functional state of diabetic nerve is gained from animals—the streptozotocin diabetic rat (1) and the BB Wistar rat (2). Such studies for many years have focused primarily on the metabolic hypothesis with little emphasis on the microvasculature, for apparently the diabetic rodent does not develop capillary disease. This is certainly not the case in human subjects.

METABOLIC FACTORS

The dominant field of research has focused on increased flux through the polyol pathway associated with depression of Na^+-K^+-ATPase and *myo*-inositol (3). Claims have been made that these changes are related to observed pathological changes in animal nerve and the well-recognized slowing of nerve conduction velocity (4). The whole pathway is controlled by the enzyme aldose reductase, inhibition of which results in control of the biochemical abnormalities of the polyol pathway, regardless of the level of blood glucose, and associated protection of nerve structure and function (5). The great hope therefore based on this theory was that a demonstrable pathological pathway in diabetic nerve could be blocked by an inhibitor unrelated to blood glucose control and hence prevent nerve damage in diabetic subjects. Sadly, the use of aldose reductase inhibitors in human subjects with diabetic neuropathy has been disappointing, with only minimal improvement in conduction velocity and little change in clinical symptoms (6,7).

Other features of abnormal biochemistry relate to the glycation of nerve protein and collagen, with some evidence that the use of aminoguanidine to block this increased glycation results in improved nerve function (8). Nerves require growth factors to assist growth, regeneration, and repair. Interesting animal work suggests that these factors are impaired in animal diabetic neuropathy, and it could well be that no therapeutic intervention in human neuropathy will be effective if the imbalance of growth factors remains uncorrected (9).

MICROVASCULAR CHANGES

It is now well established that structural and functional microvascular abnormalities are present in established cases of human diabetic neuropathy. Fagerberg (10) was the first to describe sclerosis of the vasa nervorum, and further human sural nerve biopsy studies demonstrated a wide variety of abnormalities of endothelial capillaries, including significant thickening of the basal lamina, swelling of the endothelial cells with occlusion of vessels, and occasional deposits of degranulating platelets (11). Subsequently, diabetic neuropathic nerve was shown to be hypoxic by the direct insertion of glass platinum microelectrodes (12), and that finding was followed by the demonstration of gross arteriovenous abnormalities of the epineurial vessels, consisting of sclerosis, venous tortuosity, and arteriovenous shunting (13). Intravenous injection of fluorescein into such subjects demonstrated extremely poor flow and appearance of fluorescein in the nerves compared with non-neuropathic diabetic subjects.

Further biopsy studies have not only confirmed the presence of endothelial swelling and basal lamina thickness but shown a significant relationship of the severity of vessel change to the degree of clinically measurable neuropathy (14). It must be stressed that the thickening of the basal lamina is gross and much more than that seen in capillaries from skin and muscle biopsies taken at the same time in the same subjects. This strongly suggests that a neurochemical vascular interaction causes such gross disease in the neural vessels, and indeed, so specific is this effect that significant change is observed between vessels in the endoneurium and the surrounding vessels in the sheath of perineurium (15). Although the extreme of these abnormalities is seen in subjects with advanced diabetic neuropathy, lesser but significant changes are also observed in subjects with "mild neuropathy" and even in subjects without obvious clinical neuropathic problems (16).

Vessel disease within and on the nerve surface is therefore a major feature of established diabetic neuropathy. The main questions remaining are when and why these changes occur in the human situation. There is no evidence of anything approaching such changes in the diabetic animal model.

By far the most common clinical picture of diabetic neuropathy is the distal symmetrical sensory motor neuropathy

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of a glove-and-stocking distribution but predominantly affecting the distal aspects of the lower limbs, and this picture is commonly described as a symmetrical dying back neuropathy (17). The increased length of the axons to the lower limbs is the reason given for the occurrence of neuropathic disease in the legs. Indeed, height does seem to relate to neuropathy in some studies, and presumably axonal length is a factor in pathogenesis (18). However, no attention has been paid to the obvious fact that the human subject is upright and the animal model is not. The hypothesis suggested, therefore, is that diabetic neuropathy occurs in the lower limbs because of our upright posture, the microvessels being particularly vulnerable because of impairment of the control mechanisms of vasoconstriction that would normally protect vessels from back pressure when standing.

NERVE BLOOD FLOW IN ANIMALS

Although no similar vessel disease is seen in diabetic rodents, many studies have now conclusively shown that in this rodent model, sciatic nerve blood flow is significantly decreased (19). A number of conditions are likely to lead to this depression of nerve blood flow.

Oxidative stress. Oxidative stress results from the deficient action or release of nitric oxide (endothelial-derived relaxing factor), thus removing its dilatating properties and allowing increased vascular reactivity and increased potency of angiotensin II and endothelin I (20). Constriction of vessels is therefore prominent in such a situation and ischemia results, with the production of oxygen free radicals, further damaging endothelial cells and producing more ischemia. Moreover, glycated end products (21) and activity of the polyol pathway (22) also result in oxygen free radical production and have been shown to directly impair nerve blood flow. All these changes of depressed nerve blood flow are associated with a depression of nerve conduction velocity (19). Administration of antioxidants to such animals (vitamin E, ascorbic acid, glutathione, probucol, α-tocopherol) prevents the impairment of nerve blood flow and the associated conduction velocity defects (23). Moreover, use of aldose reductase inhibitors and aminoguanidine also achieves such beneficial effects (19).

Vasoactive prostanoids. The production of prostanoids has to be balanced, with thromboxane from the endothelium encouraging constriction (24) and the prostacyclin from platelets encouraging dilatation. Deficiency of γ-linolenic acid in the pathway from linoleic acid to arachidonic acid results in an imbalance that leads to constriction and further impairment of nerve blood flow. Flow and conduction velocity are increased by the administration of γ-linolenic acid (25).

How relevant these deficits are to the human situation is not known, for we have no way of measuring human nerve blood flow. Certainly at the onset of IDDM, when hyperglycemia is similar to that in the diabetic animal, significant neuropathy is not observed, suggesting either that these pathways are irrelevant or that there are sufficient compensatory mechanisms present to protect the nerve from severe fiber damage. It is quite possible, however, that such ischemia may be present to a degree and damaging nerve fibers early on in certain susceptible individuals.

Another potential area for damage is within the lumina of vessels—namely, hemorrheological factors that may become more prominent as the endothelium becomes more diseased and the chronic back pressure has an effect on flow characteristics. There is indeed some evidence that abnormalities of hemorrheological factors relate to neuropathy in that basal lamina thickness relates to abnormalities of fibrinogen and thromboxane B2 production (26).

VASA NERVORUM AND THE UPRIGHT POSTURE

The vasa nervorum have a distinct small-fiber (autonomic) innervation, and there is evidence of damage to these axons in the transperineurial sleeve, with accumulation of perineurial cell basement membrane and thickening of the wall of transperineurial arterials (27). Here, therefore, is a potential for further imbalance in the vasoactive state of the nerve vasculature. Damage of small autonomic fibers, by direct ischemic insult or relating to metabolic damage, will lead to impairment of flow, allowing the development of arteriovenous shunts and the distinct tendency to vasodilatation (28). Indeed, it is known that sympathetic function is impaired in human diabetic subjects. Through the technique of microneurography, small-fiber function has been shown to be impaired at a relatively early stage in diabetes (29), and a number of clinical experiments have demonstrated impairment of postural vasoconstriction (30), paradoxical decrease in skin blood flow, and reduced neurogenic flare response and axon reflexes (31).

In human subjects, the state of upright posture has led to incredibly complex and efficient mechanisms to protect the vasculature from the associated back pressure (32). Many of the studies in this area have been carried out by Tooke et al., who have clearly demonstrated that the microcirculation is effectively protected from the increased hydrostatic pressure of standing. Pressure and flow are regulated by vessel diameter, and there are intrinsic mechanisms to regulate pre- and post-capillary resistance. Pre-capillaries are undoubtedly under neurogenic control associated with sympathetic axon reflexes, and any increase in venous pressure induces reflex capillary vasoconstriction and hence protection.

It is likely that the situation is even more complex. The known increased capillary permeability present in diabetes may further aggravate endothelial damage in the pressurized endoneurial capillaries, and impaired regulation of splanchnic blood flow also may play its part (33,34).

The hypothesis therefore can be summarized in the following way (Fig. 1): small-vessel flow is under neurogenic con-

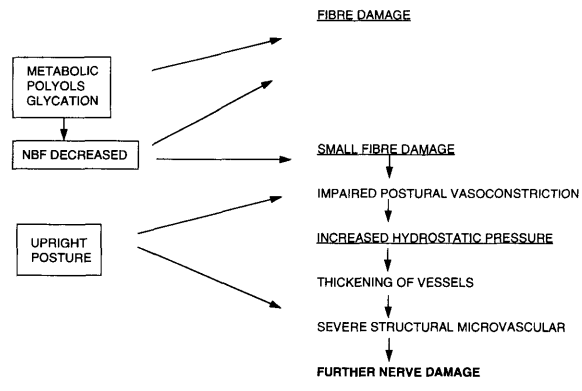

FIG. 1. Proposed pathogenetic pathway.

trol, and relaxed or deficient sympathetic tone encourages shunts with the known impairment of postural regulation of blood flow in people with sympathetic nerve damage. The axons supplying the vasa nervorum are damaged. Since there is impairment of postural vasoconstriction on standing, the microcirculation is chronically exposed to increased transmural pressure, hence the extremely thick capillary walls seen in diabetic sural nerves.

Such increased transmural pressure transmitted to small vessels in nerve could lead to the major thickening of the vessel wall so clearly described. The reason for greater degrees of thickening in endoneurial capillaries could relate to the different chemical environment of these vessels; but it could also relate to the fact that the vessels in the endoneurium may be more compressed and unable to take up the increased pressure, whereas vessels in the perineurium and other tissues are more naturally distensible. Increased intraluminal pressure is therefore acting as an extreme pressure stress on the endothelium and associated basal lamina.

Although the quality of metabolic control has an important part to play in the development of nerve damage in diabetes, clearly some subjects are more susceptible than others. As yet, no genetic or other marker has been identified to allow recognition of such subjects. The following pathway leading to nerve damage in diabetes is therefore proposed. At some stage in the diabetic state, small sympathetic nerve fibers are damaged, possibly by a direct metabolic effect but equally possibly by changes in nerve blood flow associated with oxidative stress and imbalance of the prostanoids. The situation can perhaps be aggravated if there is any abnormality of growth factor production or action. Eventually, this degree of ischemia affecting small fibers leads to impairment of vasoconstriction and the tendency for back pressure to be more profoundly damaging to small vessels aggravated in many subjects who are standing. Certain groups of people who regularly stand for long periods may therefore be more at risk of nerve damage. This back pressure, causing thickening, eventually leads to visible microvascular change, which encourages the presence of shunts between the epineurium, perineurium, and endoneurium and further severely damages nerves as a result of very severe ischemia of the nerve.

If any therapeutic strategy is to benefit already diseased nerve fibers or prevent such damage, then it must relate to logical understanding of the pathogenetic mechanism leading to the final clinical state. The potential for damage to small sympathetic fibers that is therefore likely to lead to microvascular structural and hemodynamic effects could lead to more rational therapy.

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