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Review Articles

Sympathetic Nerve Failure in Diabetes

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Summary. Sympathetic damage is a striking feature of diabetic neuropathy, probably much more common and important than previously suspected. Degeneration of arterial medial smooth muscle with subsequent medial calcification is a feature of diabetic neuropathy and represents a structural abnormality probably resulting from sympathetic denervation. Loss of vasomotor control is responsible not only for postural hypotension but also for the remarkable increase of peripheral blood flow and arteriovenous shunting in the neuropathic foot. Demineralisation of bones and neuroarthropathic bone and joint destruction may result. Intractable oedema is another consequence of these haemodynamic abnormalities, while in other cases there is a close association of sympathetic defects with painful neuropathies. The possibility of new treatments using sympathomimetic agents to reverse these abnormalities now exists, and ephedrine has already been shown to be highly effective in reducing neuropathic oedema.

Key words: Diabetic autonomic neuropathy, Charcot joints, ephedrine, heart denervation, hypotension, isotope bone scans, sympathetic nerves, ultrasound blood flow.

Autonomic defects are common in diabetic neuropathy as a consequence of damage to small nerve fibres. Indeed many years ago, Lawrence, in his famous book 'The Diabetic Life', suggested that "the first attack is on non-medullated autonomic nerve fibres and the symptomatology due to their degeneration" [1]. Few other neuropathies cause clinical symptoms like those seen in diabetes, and these have been extensively reviewed [2–7].

The importance of parasympathetic, vagal neuropathy has been emphasized during the last decade, and some abnormalities, such as loss of heart rate variability or acceleration on standing, have been used as simple bed-side tests of autonomic function [8]. Sympathetic failure, though well-known from many observations such as loss of spontaneous variations of peripheral blood flow [9] or postural hypotension, was thought to occur late in the natural history of the disease, and usually after parasympathetic damage. New approaches suggest that sympathetic defects occur earlier and more frequently than previously suspected, and that they may cause structural and physiological changes. This review describes these sympathetic defects together with new methods of examination of sympathetic nerve function.

Measurement of Sympathetic Function

Direct measurement of sympathetic function has only recently been achieved as a result of work by Hagbarth and Wallin in Sweden [10, 11]. Using percutaneously inserted intraneural microelectrodes, sympathetic activity in post-ganglionic C fibres can be recorded in awake unanaesthetised man. Different sympathetic impulses in muscle and skin nerve fascicles are identifiable. Muscle vasoconstriction impulses vary with transient changes in blood pressure and may be important in buffering temporary blood pressure changes, while skin nerve activity includes sudomotor and vasoconstrictor impulses governed by thermoregulatory and emotional stimuli. By recording reflex latency following various stimuli, an indirect measurement of conduction velocity of the unmyelinated post-ganglionic C fibres can be obtained. This varies in different types of fibres but is, on average, about 1 metre/s.

Measurement of sympathetic activity in diabetic patients with neuropathy has been reported [12]. When it could be detected at all, the impulses appeared normal, and calculated nerve conduction times were neither reduced, nor correlated with motor nerve conduction times. However, failure to detect any sympathetic

activity was much more common in diabetic neuropathy (64% of cases) than in various other forms of polyneuropathy (19%), and occurred most frequently in those with the lowest motor nerve conduction velocity, again in contrast to other neuropathies where intact sympathetic function was often found even when motor nerve conduction was severely reduced. As a result of these first direct measurements, it has been proposed that sympathetic failure is characteristic of diabetic as distinct from many other neuropathies, and that it may be an early feature.

Cardiac Denervation

Sympathetic denervation of the heart appears to follow vagal denervation. Sympathetic function is however much more difficult to assess than that of the vagus which is so easily undertaken at the bedside by measurement of heart rate variability [8, 13–15]. Sympathetic failure is shown only by complex stimulatory or inhibitory tests including sudden noise, the Valsalva manoeuvre, amyl nitrite administration, or lack of response to beta-blockade. These tests are often still normal even when vagal damage is advanced. Heart rate changes on standing are simpler to measure, but again the more obvious defect is the loss of overshoot of cardiac acceleration, a vagal effect. The slower subsequent heart rate increase is mediated by sympathetic nerves, and inhibited by beta-blockade [8, 16] but is only rarely completely absent. In advanced neuropathy, however, the heart becomes effectively deprived of both parasympathetic and sympathetic innervation [17, 18].

The clinical consequences of cardiac denervation are reflected by abnormalities of heart rate. Persistent tachycardia resulting from vagal damage is relatively common in neuropathic patients, but as sympathetic neuropathy progresses, it has been suggested that heart rate decreases, so that many of those with severe neuropathy do not have a tachycardia [18]. The totally denervated heart has a fixed rate unresponsive to any stimuli with the possible exception of exercise [17]. Failure of the heart to accelerate on standing probably exacerbates postural hypotension. Denervation also limits cardiac responses to exercise [5].

Postural Hypotension

Sympathetic failure causes loss of peripheral and splanchnic vasoconstriction, and in diabetes this is the chief cause of postural hypotension. The contribution from impaired baroreceptor afferent impulses is not known, and although a reduction of fibres in the intermedio-lateral columns of the spinal cord has been reported in severe diabetic autonomic neuropathy [19], the role of the central nervous system is still uncertain. Postural hypotension is a feature only of advanced diabetic neuropathy. Symptoms from postural hypotension occur infrequently and were present in only eight of the 125 patients with neuropathy studied by Rundles [20]. Debilitating symptoms are very rare and then the standing systolic pressure is usually < 70 mmHg, and may be unrecordable.

Postural hypotension varies to a remarkable degree and symptoms are often intermittent [21]. The precise cause of these fluctuations is uncertain but at least two responsible factors are known. Fluid retention from any cause alleviates hypotension, and may happen spontaneously when renal impairment develops. In contrast, insulin administration exacerbates hypotension in patients with neuropathy, and may even cause it in those who do not normally suffer from it [21]. Insulin also induces hypotension in sympathectomised patients [22]. The mechanism of this effect is uncertain but insulin is known to reduce right atrial pressure and cardiac output in patients with neuropathy [23], and reduces plasma volume of diabetic subjects (though not that of diabetic patients with neuropathy) [24]. Insulin-induced hypotension may cause unconsciousness which on very rare occasions can be confused with a hypoglycaemic episode.

Treatment is seldom needed. In severe cases, however, it is difficult and a combination of techniques is required. First, all drugs which exacerbate hypotension should be stopped, and these include diuretics, tranquillisers, antidepressants and glyceryl trinitrate. The head of the bed should be raised, and full length elastic stockings worn. Increasing plasma volume by high salt intake and fludrocortisone (up to 0.4 mg daily) is the best treatment, but nonetheless often fails, and frequently causes disagreeable oedema. Other methods are unreliable, but worth attempting in difficult cases. They include indomethacin, a combination of flurbiprofen and ephedrine together with fludrocortisone [25], or administration of pindolol which is a beta-blocker with intrinsic sympathomimetic effects [26]. Atrial tachypacing has also been described [27].

Medial Vascular Calcification

Sympathetic denervation may cause structural damage to peripheral arteries. Sympathectomy is known to cause atrophy of smooth muscle with foci of necrosis [28], and long-term sympathetic denervation also leads to structural changes in arterial smooth muscle [29]. Morphological changes also occur in ciliary muscle and iris after autonomic denervation, and unique eosinophilic bodies have been observed in smooth muscle from different organs taken at autopsy examination of several of our most severe cases of autonomic neuropathy [19, 30].

An association between diabetic neuropathy and medial vascular calcification (Monckeberg's sclerosis) has been demonstrated recently by Edmonds et al. [31], who suggested that sympathetic denervation could cause this form of medial degeneration. Substantial calcification, best seen in a lateral radiograph of foot and ankle, was seen in 16 out of 20 patients with severe neu-

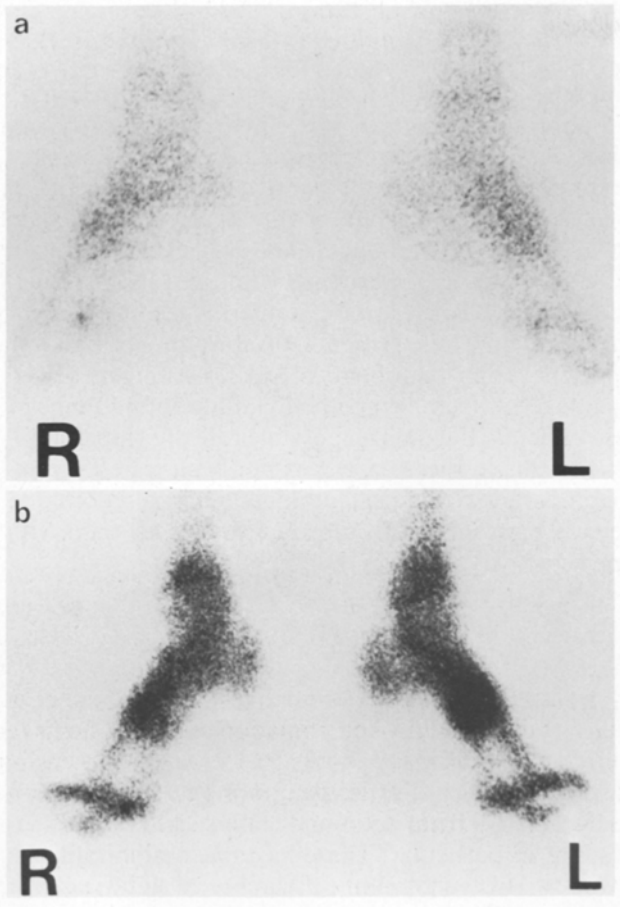

Fig. 1 a and b. Visualisation of isotope uptake in the feet of a normal person (**a**) and of a diabetic woman, aged 35 years, with severe neuropathy (**b**). X-rays of the feet were normal

ropathy between 22 and 50 years of age, all of whom had neuropathy sufficient to cause foot ulceration, many of whom had Charcot's arthropathy. In two large series of cases of Charcot's arthropathy, vascular calcification was present in up to 90% [32]. While it has long been known that vascular calcification is more common in diabetic than non-diabetic subjects [33], this is the first time that the association with another diabetic complication, namely neuropathy, has been described.

The functional effects of medial calcification are not well understood; stiffening of the arterial wall is probably responsible for haemodynamic abnormalities which have recently been described, including raised arterial pressures in the ankle and foot, and shortened transit times in the arteries of the leg [34–36].

These observations lead to the suggestion that sympathetic neuropathy may be responsible for structural vascular abnormalities.

Peripheral Blood Flow in Neuropathy

Sympathetic neuropathy results in loss of vasomotor control and increase of peripheral blood flow. There is now ample direct and indirect evidence for increased blood flow in the neuropathic foot, recently reviewed by Ward [36]. Doppler sonograms show high diastolic flow and evidence for opening of arteriovenous shunts [34–36]. Studies showing that intra-arterially injected radioactive labelled albumin microspheres pass more readily to the veins in subjects with neuropathy [37], and others demonstrating a raised venous partial pressure of oxygen in blood from distended veins on the dorsum of the neuropathic foot [38], support the presence of arteriovenous shunts. Blood flow measurements by plethysmography show that flow is increased on average fivefold above normal, while skin temperature in these feet with raised blood flow is higher (mean 33.5 °C) than normal (mean 25.8 °C) (A. G. Archer, unpublished observations).

The raised blood flow in the neuropathic foot on the one hand increases understanding of bony abnormalities of the foot, and may also explain the intractable oedema which sometimes occurs; while on the other hand, the possibility of reducing blood flow by use of sympathomimetic agents may offer prospects of new forms of treatment.

We have shown, by use of isotope scans, that blood flow in the bones of the neuropathic foot is considerably increased, even in the absence of radiological abnormalities (Fig. 1) [39]. There is a remarkable uptake of the isotope (technetium methylene diphosphonate) which is greatest in those with neuropathic Charcot joints. Although standard 4 h isotope uptake reflects both osteoblastic activity as well as blood flow, the increased early uptake (2 min) most probably indicates that the bone blood flow is raised. Demineralisation of bone is a likely consequence, as it is in other cases with increased flow such as the paralysed limbs of paraplegics. It is suggested that the evolution of the destructive bony changes in these cases is as follows: sympathetic denervation of arterioles causes an increase of blood flow which in turn causes rarefaction of bone, making it prone to damage even after minor trauma. Loss of sensation from somatic neuropathy, in particular reduction of pain sensation, permits abnormal stresses which would normally be prevented by pain. Relatively minor trauma can therefore cause major destructive changes in susceptible bones.

Neuropathic Oedema and Ulceration

Peripheral oedema, sometimes of considerable severity and resistant to treatment, is a rare feature of some cases of diabetic neuropathy [20, 40]. It has hitherto been unexplained. The high blood flow, vasodilatation and arteriovenous shunting, which result from sympathetic denervation, could lead to abnormal venous pooling and cause the oedema. The use of sympathomimetic agents might, by stimulating vasoconstriction, be expected to reduce this form of oedema. Edmonds et al. [41] have recently described the effect of ephedrine in such cases and demonstrated a rapid decrease in weight, reduction in peripheral diastolic flow, and increase in sodium excretion all associated with a remark-

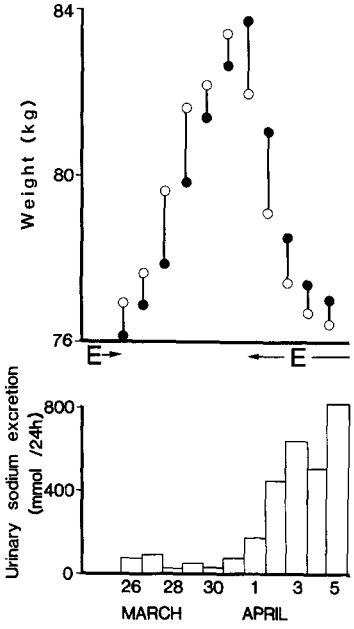

Fig. 2. Weight changes and urinary sodium excretion in a case of neuropathic oedema on ephedrine treatment (*E*) following withdrawal and then reinstitution of ephedrine [41]. (•=morning weight, ○=evening weight). (Reproduced by kind permission of the Lancet)

able diminution of oedema (Fig. 2). Several patients have now been treated using, on average, 30 mg three times daily, without evidence of tachyphylaxis and usually without side effects. The effect of ephedrine is probably complex and as well as its peripheral effects it may reduce aldosterone secretion either by an effect on the kidney or by acting directly on the adrenal cortex.

The genesis of the neuropathic ulcer is not yet fully understood. Loss of sensation, especially awareness of pain is required, but there is evidence from experiments on dogs that somatic denervation alone is insufficient to cause ulceration, and that sympathetic denervation is also necessary before ulceration occurs [42, 43]. All our patients with neuropathic foot ulceration also have autonomic defects, and perhaps sympathetic denervation is indeed a prerequisite to the development of foot ulcers.

Painful Neuropathy

Sympathetic fibres are found among small myelinated and unmyelinated nerve fibres which also carry impulses signalling pain and temperature. Involvement of these small fibres (as well as others) [44, 45] occurs in some cases of diabetic neuropathy with associated pain and autonomic disturbances. The typical burning pain with cutaneous hyperaesthesia witnessed in some diabetic patients bears a striking similarity to some types of causalgic pain where sympathetic abnormalities may be important. High peripheral blood flow and increased warmth result from sympathetic failure in the limbs of these patients (Fig. 3). The possible role of sympathomimetic agents in these cases has not been tested yet, although paradoxically guanethidine block is reported to alleviate pain in certain types of cutaneous pain with hypersensitivity.

Other Sympathetic Defects

A wide range of cardiovascular, hormonal and metabolic defects result from autonomic failure and sympathetic failure in particular. These have been admirably reviewed by Hilsted [5]. While their clinical significance is not always clear, some defects are obviously important. Exercise-induced responses of heart rate, blood pressure and catecholamines are abnormal; cardiac stroke volume is lower as is the increase in hepatosplanchnic vascular resistance during exercise. Orthostatic catecholamine responses are impaired, and some report renin response to be abnormal. Hypoglycaemia is an established stimulus of autonomic function. Thus, failure of adrenaline responses (but not noradrenaline), and of several pancreatic hormones, notably glucagon, to hypoglycaemia have been recorded. Hilsted concluded that sympathetic defects are likely to develop in parallel with parasympathetic neuropathy.

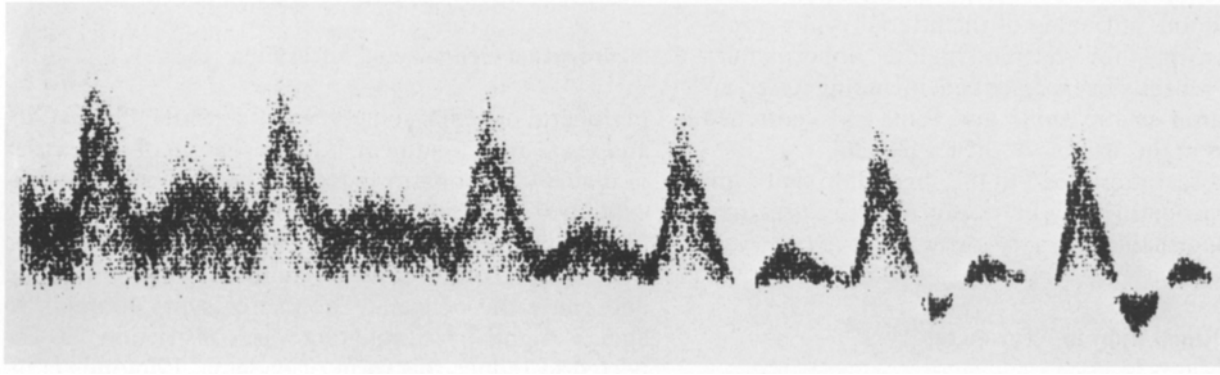

Fig. 3. Doppler ultrasound sonogram from the posterior tibial artery of a young female patient with painful neuropathy. On the left, the pattern of the sonogram is that typical of neuropathy, showing the normal upward deflection of forward flow followed by continuous forward flow throughout diastole with complete loss of the expected reversed flow; after sympathetic stimulation (by coughing) the appearance of the sonogram becomes normal (on the right) showing the typical triphasic appearance – upward deflection of forward flow followed by reversed and later again forward flow in diastole. (A.G. Archer, unpublished observation)

Conclusion

We conclude that sympathetic damage in diabetic neuropathy is much more common and important than previously suspected. There now exists the exciting prospect that at least some of the functional disturbances may be reversed.

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