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Review Articles

The Diabetic Leg

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Summary. Many clinical problems arise as a result of tissue pathology in the diabetic leg. Neuropathic or vascular ischaemic syndromes are readily identified but on occasions differentiation of the two may be difficult. This survey reviews the aetiological background of neuropathy and ischaemia, examines the relationship of physiological blood flow abnormalities to both areas and comments on management of the clinical states encountered, including the common problem of the ulcerated diabetic foot.

Key words: Arteriovenous anastamoses, blood flow velocity, diabetic neuropathies, electrophysiology, ultrasonics.

Neuropathic Problems

Peripheral nerve damage is much more common in the legs than in the arms of the diabetic, and this damage leads to a variety of clinical syndromes – the diabetic neuropathies [1]. There is no satisfactory report relating the type of pathological change in nerve to the clinical features although there is some electrophysiological evidence that painful symptoms of diabetic neuropathy are related to damage to small fibres, whereas the painless syndromes are associated with loss of large myelinated fibres [2]. Sensory syndromes with pains and a variety of unpleasant sensations (tingling, cramps, coldness, deadness) are typical of the insidious type of neuropathy, nocturnal exacerbation being profound, but in such cases a marked muscle wasting of thighs and small muscles of the feet is also common. Sudden onset of generalised wasting and weakness of muscles may occur, usually relating to times of poor metabolic control [3]. Asymmetric wasting of the thigh muscles with considerable pain was described by Garland (amyotrophy) [4], this suggesting a more proximal neuropathy although there is always evidence of a diffuse symmetrical neuropathy as well. With muscle wasting there will often be a significant sensory element. Many diabetic legs are totally lacking in pain sensation although at the same time experiencing a variety of painful sensations – the 'painful–painless' leg. Foot drop due to pressure on the vulnerable damaged diabetic nerve is described, but the incidence would not seem to be greater than in the non-diabetic.

In no other complication of diabetes is the evidence of a relationship with blood glucose control so strong as in the neuropathies [5] although other critical factors must trigger the pathological changes of segmental demyelination [6], axonal degeneration [7, 8] and structural changes in the Schwann cell itself [9–11]. Metabolic abnormalities consist of altered patterns of myelin lipid [12], accumulation of sorbitol and fructose [13], deficiency of myo-inositol [14] and decreased retrograde transport of axonal proteins [15]. In the more acute syndromes it seems more likely that metabolic factors are of prime importance, especially in those cases where acute pain and wasting of a leg resolve within a few months.

Vascular changes certainly occur in the vasa nervorum. Fagerberg [16] was the first to postulate sclerotic small vessels as a cause of nerve damage. The demonstration of platelet abnormalities in diabetes and in diabetic neuropathy [17] and the occurrence of cerebral small vessel damage in ketoacidosis [18] led to a reappraisal of the vascular hypothesis and indeed occlusion of small vessels with fibrin and platelets has been demonstrated in one-third of nerves studies [19, 20]. Fresh fibrin deposits in vasa nervorum following ketosis point to the dynamic changing nature of vessel status within nerve although it must be admitted that the presence of some occluded vessels does not neces-

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sarily mean that such obstruction is a direct cause of nerve pathology. In long standing neuropathy, vessel changes could be secondary to the pathological process in nerve itself. Certainly such obstructed vessels are seen in long standing neuropathy without overtly poor metabolic control.

Treatment of the neuropathies, especially pain, is unrewarding. The more acute the onset of pain and symptoms, the more likely is there to be eventual recovery and such a fact should be used as an encouragement to the patient. However, many of the unpleasant neuropathic sensations in the legs do indeed remain over many years. Reassessment of pain scores in neuropathic subjects after 5 years of a prospective clinical analysis revealed that 25 out of 34 patients reported either no change or indeed more severe pain (unpublished observations). Routine analgesics, Carbamazepine, Phenytoin, tricyclic anti-depressants and anti-platelet agents have all been tried without significant success. Returning to the question of the role of blood glucose control, it is encouraging that in nine patients with severe long-standing painful neuropathy, improvement in pain, motor conduction velocity and vibration perception have now been reported following meticulous blood glucose control [21].

Vascular Ischaemic Problems

Ischaemic syndromes seen in the non-diabetic occur commonly in the diabetic. Intermittent claudication is a classical symptom occurring more commonly in the diabetic subject [22]. As the claudication distance falls, the development of rest pain leads to the need for medical action. The presence of diabetes should not deny these patients the investigative studies which would normally apply in peripheral vascular disease in the non-diabetic subject. The need for arteriography and surgical treatment should be considered, for vascular reconstruction achieves a very acceptable success rate in the diabetic compared with the non-diabetic subject. The use of the Doppler ultrasound system and stethoscope provides a non-invasive method of assessing the flow through proximal major vessels in the leg [23]. The ratio of leg systolic pressure to arm systolic pressure (the ankle pressure index) of greater than 1.0 indicates good proximal flow, whereas a ratio around 0.6 is seen in intermittent claudication and a ratio around 0.4 will often occur when rest pain is being experienced. The knowledge of such ratios alerts the physician to assess at which point more active surgical help should be sought. Using a similar system, it was shown that foot lesions in the diabetic were more common in patients with abnormal ratios of this nature [24].

The more distal nature of arterial degeneration in diabetes [25] with an increased incidence of vascular calcification undoubtedly adds to the technical difficulties in surgery and the need often to perform amputation at a higher level. Moreover, the extent of vessel disease seems to allow infection to develop in the stump, sometimes with unpleasant gas forming organisms. There is a need to establish whether more adequate control of blood glucose in the peri-operative period would reduce the incidence of such infection.

Factors leading to diabetic atherosclerosis in part are much the same as in the non-diabetic subject. It is not known why vascular calcification should be so much more common nor why distal vessels are so badly affected. The presence of such distal vessel disease may not give rise to painful symptoms in many patients for it has been shown that disease and obstruction of tibial and more distal vessels do not seem to cause typical intermittent claudication [26]. The frequent occurrence of autonomic damage in the diabetic leg would suggest that lumbar sympathectomy would not be a logical or satisfactory procedure in such patients and this operation is now an uncommon event in the diabetic wards. There is no convincing evidence that any vaso-dilator agents are effective in symptom relief or on the progression of peripheral vascular disease in the legs.

Blood Flow Abnormalities

It is clear that blockage of proximal vessels leads to a poor and inadequate flow of blood so that early on collateral channels are established. In the neuropathic leg, in the absence of signs of ischaemia below the knee and with palpable foot pulses, it is usually assumed that blood flow is normal. Recent evidence indicates that there are marked abnormalities of blood flow in such legs, suggesting increased velocity of flow and raising the possibility of arterio-venous shunting [27, 28]. Forearm blood flow has been shown to be increased in juvenile diabetic patients, this increase being more marked at times of poor metabolic control [29].

By use of the Doppler ultrasound principal and system [30] using sophisticated probes, a blood velocity wave form can be drawn. Thus Figure la represents the normal wave form with a small diastolic back flow element, and Figure 1 b represents a poor blood flow in proximal vessel disease with a 'sluggish' wave form. Figure 1 c shows a high positive take off, a broad base and loss of the important diastolic back flow phase, which is typical of the wave form found in patients with ulcerated neuropathic feet [27, 32]. Simply

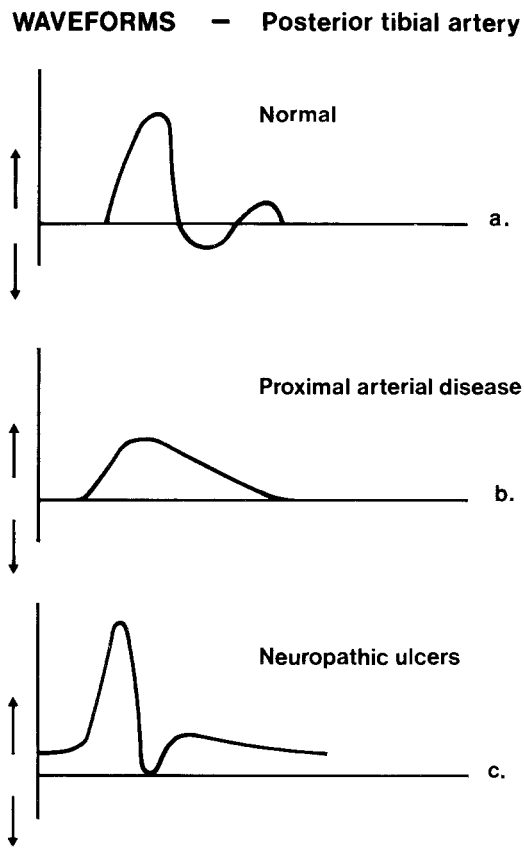

Fig. 1 a–c. Examples of ultrasonic wave forms in: a) normal b) proximal disease c) neuropathic ulcer

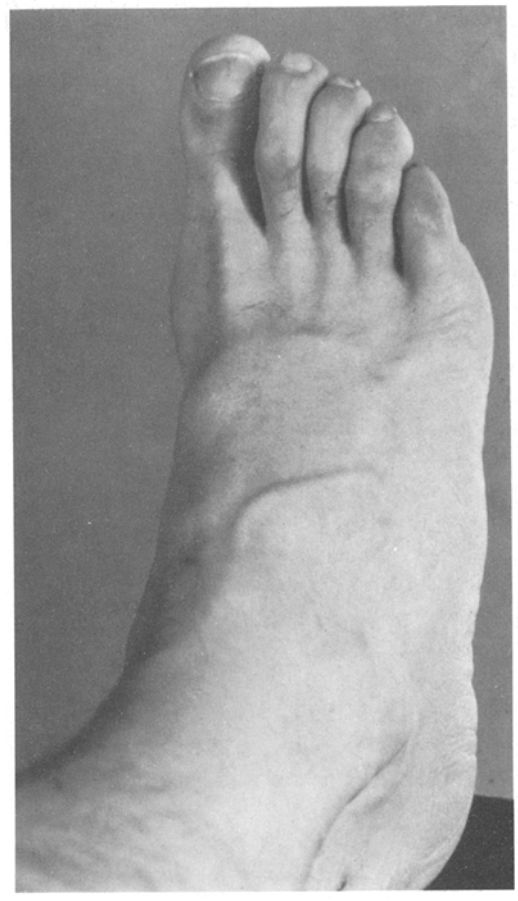

Fig. 2. Turgid distended veins on the dorsum of a non-ulcerated neuropathic foot

speaking there is a continued, rapid and increased forward flow of blood in such feet. From this tracing, a pulsatility index may be calculated and this is seen to be abnormal compared with normal non-diabetic feet or other forms of non-ulcerated diabetic feet [31, 32]. With the addition of a frequency time analyser and an electrocardiogram impulse, the transit time – pulse wave velocity – may be calculated and again this is seen to be abnormal in the neuropathic foot [27]. The use of the more simple Doppler ultrasound stethoscope allows the demonstration of an abnormality in this condition. Here the ratio (normally 1–1.12) may be as high as 1.5. Prospective studies of the use of this simple measurement in the recognition of vulnerable neuropathic legs and the benefits of prophylactic treatment are needed.

Such ultrasound blood flow abnormalities could be due to rapid shunting of blood away from distal tissues and support for this view is provided by the demonstration that the oxygen concentration of blood sampled from veins in such neuropathic feet is increased to approaching arterial oxygen saturation [33]. Indeed, although to a lesser degree, the venous oxygen concentration is elevated in diabetic patients in general when compared with normal subjects. Clinical support for the presence of arterio-venous shunting of blood is provided by the personal observation that in such ulcerated feet, or indeed in feet with a history of healed ulcers, the veins over the dorsum of the foot are distended and turgid in the recumbent position. In some, if blood is sampled from the vein, the plunger of the syringe is moved without the assistance of the investigator. Along with such turgid veins the dorsalis pedis pulse is palpable and indeed often visibly bounding. Figure 2 shows such distended foot veins in a diabetic neuropathic foot with high venous oxygen concentration in which no ulcer has ever been present.

The exact reason for the presence of such shunting is not clear. The wave form abnormalities of blood flow described above suggest shunts but could be due to rigid arterio-sclerotic vessels [27, 34–36]. Such is certainly the case in many neuropathic feet and there seems to be a relationship between vascular calcifica-

tion and foot ulceration. Moreover, in simple vascular occlusive calcification the Doppler leg/arm ratio (ankle pressure index) is elevated in a similar fashion to that described in the neuropathic foot [37].

However, it does seem more likely that genuine arterio-venous shunts have formed and indeed there is evidence of such shunting in forms of neuropathic foot ulceration such as leprosy, sensory neuropathy and diabetes, in which radio-labelled human albumin microspheres have been injected intra-arterially with subsequent counting in the lung circulation [38]. It is known that there are many shunts present in the tissues of the foot [39] which may open up in response to increased blood flow [40]. Sympathetic innervation of such vessels is undoubted and there is good evidence for the presence of autonomic dysfunction in the legs of diabetic patients [32, 41]. Clinically, the legs of patients with long-standing diabetes and an element of neuropathy are warm and dry and heating of the trunk does not lead to reflex sweating. Galvanic skin resistance, a measure of the integrity of sweating reactions in the legs, is abnormal, especially so in diabetic feet with neuropathic ulcers [42]. Galvanic skin resistance is seen to correlate well with autonomic dysfunction, although this measurement is more often abnormal in ulcerated feet than tests of systemic autonomic function. In animal experimentation sympathectomy, infective reactive hyperaemia and α-adrenergic blockade resulted in arterio-venous shunting [43].

Although relatively unusual, the Charcot diabetic foot is the end stage and the most gross example of neuropathic destruction. The appearance is of a squat, flat foot with complete loss of all contours due to wasting of muscles and collapse and destruction of the mid-tarsal joint. Osseous lesions in bone have been described in the absence of any penetrating ulcers, the suggestion being that this is due to increased blood flow [44]. In such feet all measurements of blood flow, as described earlier in this section, are grossly abnormal and further evidence of the role of abnormal blood flow is provided by the demonstration of a high uptake of radio-active material in and around the damaged mid-tarsal and ankle joint [45].

In the obviously badly ulcerated diabetic foot of this extreme form of Charcot foot, the abnormalities of blood flow, as demonstrated by ultrasound abnormalities and venous oxygenation, are probably related to a number of inter-related factors – dilated vascular bed due to sympathetic dysfunction, rigid and calcified blood vessels, numerous small vessel occlusions forcing blood away from peripheral tissues and some metabolic component related to poor control of the diabetic state.

Assessment of Diabetic Leg Pain

Basic differentiation of unpleasant and painful sensations will lie between the neuropathic and the vascular. In clinical practice it may not often be essential to be certain of the exact cause of pain if expectant observation is to be the clinical policy. In many instances, the pain might genuinely have a dual cause. However, if the understanding of the aetiology of nerve damage or peripheral vascular disease in the legs is to be expanded and if trials of various forms of treatment in the painful diabetic leg (glucose control, sorbitol blockage, myo-inositol feeding, vaso-dilator agents) are to be attempted, it is important to make every effort to ensure that a group of patients diagnosed as having 'neuropathy' or 'ischaemia' really do warrant the particular diagnosis. In the past, with regard to neuropathy, there have been far too many clinical reports in which the diagnosis is based on trivial symptomatology or physical signs or even on nerve conduction velocity measurements alone, a view supported by recent reports [46, 47]. The presence of ankle jerks, with or without patchy sensory loss, has been shown to be identical in a group of elderly diabetic patients diagnosed as having neuropathy when compared with a matched group in which no such diagnosis had been made [48]. Even the presence of significant sounding symptoms may, on occasions, be misleading. In personal clinical practice, the 'correct' diagnosis of diabetic neuropathy in the presence of the following other pathologies has led to a complicated clinical picture or indeed to a delay in the diagnosis of these other pathologies – spinal stenosis, lumbar disc protrusion, osteomyelitis of a lumbar vertebra, and neurofibroma of the cauda equina. Although these are unusual clinical problems, the physican should always be alert when assessing pain in the diabetic leg, especially when the pain is more marked proximally. Claudication symptoms in the diabetic patient may on occasions not be due to overt proximal major vessel disease, but are perhaps another manifestation of neuropathy [49].

The following strict *criteria* are therefore recommended for the selection of patients to be studied for whatever reason and labelled as diabetic neuropathy.

Symptoms: These are the most important component of the clinical assessment. Typically, pains and paraesthesia are common in the feet but may occur in any part of the leg with nocturnal exacerbation and bed clothes irritation. Lesser degrees of tingling should be assessed and, if possible, the pain discomfort score should be expressed graphically – e. g. on a 10 cm horizontal scale [50]. If pain is to be assessed serially, the patient should be interviewed by a physician not di-

rectly involved with the management of the patient or in the trial study itself. Symptoms should have been present for a period of no less than one year so that the more acute problems related to times of poor glucose control and shorter-lived syndromes are eliminated. In a way, the patient should be regarded as being in 'real trouble' with his neuropathy.

Physical Signs: Extensive muscle wasting and reflex loss are common in long-standing cases, as are areas of sensory loss and vibration sense impairment, and assist greatly in the diagnosis. However, it is doubtful whether detailed serial sensory mapping is reliable enough to provide accurate objective data. Lesser degrees of such abnormalities are acceptable if symptom assessment is strongly in favour of a neuropathic process. Occasionally patients with severe symptoms are seen in whom reflexes are present. Clearly, if a painless punched out pressure neuropathic ulcer is present or is documented in the past, this allows inclusion although the lack of pain in many patients with neuropathic ulcers will mean that this subjective clinical measure has been removed.

Electrophysiological Assessment: Some assessment of electrical nerve function should be made. It has been common in the past to rely on measurements of motor conduction velocity, although many of the syndromes of diabetic neuropathy have a major sensory component. Increasing attention is being paid to measurements of sensory nerve conduction [51, 52], although in many legs with significant diabetic neuropathy it may not be possible to achieve measurable sensory conduction velocities. The combination of motor and sensory velocity, measured in a serial fashion, does give some quantitative measure of changing nerve function and should be part of any study in diabetic neuropathy. Investigators in such studies should establish their own normal range of values for motor and sensory conduction velocities and in any grouping of neuropathic patients velocities below the normal range for that group should be demanded. In reviewing the literature of conduction velocities in diabetes it seems that with improved blood glucose control a constant increased motor conduction velocity is reported, suggesting that this measurement only relates to a small percentage of nerve function and could lead one to suggest that it tells us very little about nerve structure and function.

Vibration Perception Threshold: Using a biothesiometer, a simple objective measurement can be made of the sensory pathways involved in vibration sensation and levels below normal ranges should be required. In the normal limb in which arterial supply is occluded by a cuff, loss of vibration sensation and electrical action potentials is rapid, but in the diabetic leg there is resistance to such loss for a considerable period [53, 54].

Vascular Factors: In defining the neuropathic patient, it is important to exclude any possibility of a contribution towards symptoms from vascular ischaemic elements. Careful symptom assessment will lead to exclusion of suspicious cases as will inability to palpate foot pulses. The measurement of the Doppler ratio of the ankle pressure index will add further accuracy to neuropathic assessment.

Role of Nerve Toxins: Any patient who is known to have been exposed to nerve toxins should certainly not be included in a prospective study, although many patients with long-standing painful legs do tend to have a high alcohol intake. Exposure to heavy metals and industrial organic solvent use should be carefully assessed.

The Diabetic Foot

Ulceration and infection of the diabetic foot forms the biggest single problem within any Diabetic Unit, certainly with regard to hospital bed usage. A brief review of the factors leading to this unhappy state and their logical avoidance or correction provides an excellent practical summary of the facts laid out in this review.

The diabetic foot, being painless, readily allows the small cut or pressure blister to expand and develop. The situation is further aggravated by the fact that the patient is often in an isolated social situation with poor eyesight so that even if he could see the lesion he would not wish to do anything about it. Certainly he has made no attempt to assess or adjust his own footwear, the ill fitting nature of which may have been at the root of the initial lesion. As the lesion begins to break down, there are the beginnings of embarrassment to the distal circulation although the medical attendant is reassured about the vascular state of the foot because it is warm and has an easily palpable pulse. Further circulatory embarrassment develops and infection intervenes, this itself aggravating the shunting of blood away from the distal tissues and digits and also by compressing blood flow through vessels as oedema and cellulitis develop. What blood does filter down to smaller vessels finds its passage impeded by a lumen occluded by endothelial swelling and the rather sticky platelets then find it agreeable to adhere and clump together to form a basis of an intraluminal obstruction which further impairs the flow

of blood. The longer such a state is allowed to progress, the more chance there is of wide areas of gangrene leading to loss of a large part of the foot, the leg or to septicaemia and possible death of the patient.

Treatment of this condition should be expectant and early, attempting to reverse as many of the described processes as possible with rest, antibiotics, good blood glucose control and any necessary surgical treatment of tissue and drainage of pus as seems necessary in the important joint medical-surgical assessment of the patient. The more typically neuropathic the problem with the demonstration of good proximal blood flow (clinically and by the use of the Doppler ultrasound stethoscope), the more likely will be the success of local conservative surgical procedures and the salvaging of a useful amount of functional foot. Major amputation should rarely be necessary as the initial procedure unless life threatening infection is present.

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