Idiopathic Neurotrophic Feet in Blacks
A Pathological Study
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SUMMARY
The pathological findings in tissues obtained from 6 patients with idiopathic neurotrophic feet are described. The salient features were those of a neuropathy characterized by gross demyelinization and marked changes in the distal blood vessels. The vascular changes included medial and intimal hypertrophy with luminal narrowing. It is proposed that both the neural and the vascular changes were secondary to chronic alcoholism.


Idiopathic neurotrophic feet in Blacks is a well-known clinical entity. The pathology of this condition has, however, received scant attention. The purpose of this article is to describe its pathological features and to suggest a hypothesis for the neural and vascular changes observed.

PATIENTS AND METHODS
The tissues examined in this study were derived from 6 patients between 28 and 45 years old who had had amputations at Baragwanath Hospital during 1976. As in previous studies, all patients were men. The extent of the amputations varied from a single toe to an entire foot. In every instance several sections of the amputated tissue were examined, particularly those proximal to the line of surgical excision, so as not to include tissue affected by the infection which is inevitably present in the distal parts. All sections were stained with haematoxylin and eosin, elastic Masson, Luxol fast blue and periodic acid-Schiff (PAS).

Case 1
A 28-year-old man presented with pain in the right foot and a history of heavy alcohol consumption. He was pellagrous and the pulses in both feet were good. The feet were also warm. The specimen received in the laboratory consisted of an amputated left foot without the big toe. Microscopical examination showed demyelinization of the nerves with almost total loss of myelin and evidence of axonal degeneration (Figs 1 and 2). Some of the nerves showed marked perineural fibrosis. There was a marked degree of infection with abscess formation and necrosis and in these areas the blood vessels showed prominent endarteritis. Some of the blood vessels were almost completely occluded by young granulation tissue containing numerous capillaries. The internal elastic lamina was generally intact. There was smooth-muscle hyperplasia of the media and in many instances also of the intima (Fig. 3). Although thickening of the walls of the blood vessels was often present in inflamed areas, it was also seen in non-inflammatory foci. Some blood vessels showed prominent oedema of the wall with large, clear, cyst-like spaces in the media and intima (Fig. 4).

Fig. 1. Normal nerve showing myelin staining (Luxol fast blue × 900).

Fig. 2. Complete demyelinization of a nerve (Luxol fast blue × 900).

Case 2
A 31-year-old man presented with a cold, painful, right first toe and a swollen right leg. The pulses were normal and amputation of the right first toe was performed.
Microscopical examination showed marked demyelinization of all nerves. There was also a considerable amount of inflammation with necrosis, abscess formation and occluded blood vessels in the vicinity of the inflammation. However, these changes were also present in the proximal part of the specimen, where there was no inflammation. The neural and vascular changes were essentially similar to those observed in case 1.

Case 3

Angiography revealed some remarkable features in this 34-year-old man. The large blood vessels were normal with no evidence of occlusion. However, the angiographic pattern in the feet showed marked increase in vascularity with dilated blood vessels so prominent as to almost suggest a 'tumour blush'. There was demyelinization of nerves and evidence of axonal degeneration. Apart from the thickening of walls of the blood vessels and the endarteritis, similar to that observed in the previous patients, the small blood vessels, including the capillaries and arterioles, were extremely prominent and appeared to be increased in number (Fig. 5). These vessels, as well as the larger arteries, showed thickening of their walls with prominent endarteritis and narrowing of the lumen. In some of the larger vessels there was medial hypertrophy with prominence of the smooth muscle. Fragmentation of the internal elastic lamina could also be seen.

Case 4

A 34-year-old man was admitted with a gangrenous right big toe, which was amputated. There was an ulcer under the proximal phalanx of the left big toe. The striking microscopical feature in this patient, as in all the others, was the gross demyelinization of all the nerves with prominent axonal degeneration. Many of the nerves showed perineural fibrosis and in some instances the nerves themselves appeared to be undergoing a globular hyaline change (Fig. 6). These areas stained negatively for collagen and amyloid. As in the other cases, the blood vessels showed prominent endarteritis.

Fig. 3. Digital artery showing marked smooth muscle hyperplasia of the intima and media with endarteritis almost completely occluding the lumen. There is some fraying of the internal elastic lamina (elastic Masson × 225).

Fig. 4. Cystic change due to oedema in the wall of a blood vessel (H and E × 225).

Fig. 5. Prominent dilated blood vessels (elastic Masson × 225).

Fig. 6. Globular hyaline areas in a nerve showing marked perineural fibrosis (H and E × 225).
Case 5

A 48-year-old man presented with clinically evident pellagra and malnutrition. The left big toe had started to become necrotic and the right foot also showed areas of necrosis. Normal pulses were present in both feet and angiography showed normal major vessels. However, angiography showed numerous tortuous digital arteries in both feet. The specimen received in the laboratory consisted of a big toe. Histological examination again showed gross demyelination of all the nerves with perineural fibrosis. Some of the nerves also showed globular foci similar to those observed in case 4. The blood vessels again showed endarteritis with narrowing of the lumen and smooth muscle proliferation in both intima and media.

Case 6

The patient was a 45-year-old man. His left big toe had been amputated and was submitted to the laboratory. Most of the sections taken from this specimen were unfortunately associated with severe surrounding infection. However, there was gross demyelination with axonal degeneration and the blood vessels showed marked endarteritis with narrowing of the lumen. The interpretation of the latter finding was uncertain in this case because of the severe associated infection.

DISCUSSION

Idiopathic neurotrophic feet in Blacks is generally referred to by the descriptive term 'vrot foot'. The term 'vrot foot' refers to the decayed appearance of the neglected feet when first seen, characterized by ulceration of the soles in the region of the metatarsal heads, painless destruction of the bones of the feet and peripheral neuropathy. The clinical features of this condition have been well described by Perdikis and Bremner. All the patients thus far reported have been men, generally below the age of 50 years. Most were considered heavy drinkers who mostly drank home-brewed alcoholic beverages. There is often a perforating ulcer on the underside of the foot with evidence of bony resorption and clawing. Most patients show a shortening of the toes and in some only stubs remain. This change is supposedly due to infection with osteolysis and absorption and also to the neuropathy which apparently induces increased vascularity of the bone, with resultant rarefaction. With progressive neuropathy there is eventual extension at the metatarsophalangeal joints and flexion at the interphalangeal joints. The metatarsal head is pushed through the skin of the ball of the foot, resulting in the perforating ulcer. A number of patients also have clinical evidence of pellagra. Evidence of a vascular deficit has been found very rarely but there is generally a neurological deficit affecting mainly light touch, pain and temperature. Perdikis and Bremner and Trope and Crookes suggest that the condition is the result of excessive ingestion of alcohol, resulting in central and peripheral nerve degeneration. Clinically, the lesion is similar to diabetic neuropathy and the primary presentation is usually that of a peripheral neuropathy.

The studies, including angiography, in these 6 cases, did not point to a vascular deficit, and the striking histological finding in all cases was gross demyelination and evidence of axonal degeneration. Some nerves had undergone globular hyaline degeneration, and in advanced cases there was perineural fibrosis. A diffuse neuropathy was therefore present and the underlying cause was gross demyelination similar to that observed in diabetic neuropathy. These findings therefore confirm the clinical assessment of a peripheral neuropathy.

The vascular changes were a surprising finding. The large blood vessels were always patent, with no suggestion of atherosclerosis or Buerger's disease. The changes were confined to the radicles of the smaller distal digital blood vessels, which were increased in number and filled with blood. The latter may be so prominent as to resemble a 'tumour blush' on radiographs. Pathologically, this was represented by the marked increase in the number of small blood vessels, including arterioles and capillaries, although the increase may not have been real but may have reflected dilatation and prominence of existing blood vessels. In addition, the small arteries and arterioles showed thickening of their walls, particularly of the intima, with hyperplasia of the smooth muscle of the media and intima. The lumina of many of the blood vessels were markedly narrowed. In some instances the vascular changes, particularly the endarteritis, were also present in the intima of inflammatory cell infiltration into the walls of the blood vessels and the internal elastic lamina was generally intact, although in one or two instances there was slight fraying. Some blood vessels showed prominent oedema of the wall with cystic clear spaces in the media and intima.

What is the possible explanation of the vascular changes? It does not seem likely that the neural changes were secondary to the vascular alterations, as has been suggested for diabetic neuropathy by Fagerberg. He maintains that intraneural vascular lesions cause diabetic neuropathy through ischaemia and suggests that a vascular affection specific for diabetes alone or in combination with atherosclerotic lesions underlies the neurological complications. However, this cannot apply to subjects with idiopathic neurotrophic feet, since they do not present with vascular deficit and the pulses are normal. The hypothesis I would propose is that both the neuropathy and the vascular changes are secondary to chronic alcoholism.

Factor, in describing the intramyocardial small vessels in chronic alcoholism, noted that there was vascular oedema of both intracellular and extracellular type. There was separation of individual cells within the vessel walls by clear spaces. Perivascular fibrosis was prominent and many of the vessels showed striking intimal proliferation with oedema and medial sclerosis. Major narrowing of the lumen was seen when the sclerosis affected the entire vessel wall in a symmetrical fashion. The sclerosis was often asymmetric. In some instances the internal elastic lamina was disrupted and duplicated. It is, however, of
interest to note that despite these marked vascular changes in the hearts of chronic alcoholics, these patients had never had any clinically evident symptoms of cardiac disease. Experimental evidence suggests that oedema in the vessel wall is secondary to endothelial cell damage, widening of intercellular gaps and diffusion of plasma into the vascular wall. Pintar et al. reported essentially similar findings in the hearts of chronic alcoholics. In contrast to the large- and medium-sized branches, the walls of the small branches of the coronary arteries were arranged in less organized layers with an increase of collagen in the adventitia. Subendothelial plaques of PAS-positive material were present. Some of the small blood vessels showed marked narrowing of the lumen due to subintimal accumulation of PAS-positive material which produced inward bulging of the intima, suggesting possible leakage of blood through the intima into the vessel wall. These authors suggested that chronic alcoholism produces an increase in vascular permeability with changes in vascular tone and resultant interstitial oedema in the myocardium and in the vessel wall. These observations are of significance in view of the clinical finding of oedema of the affected limbs in many subjects with idiopathic neurotrophic feet. It is also of significance that Benchimol and Schlesinger, in a study of heart disease associated with beriberi, found that vascular oedema was the most prominent abnormality.

The hypothesis proposed is that subjects with idiopathic neurotrophic feet are chronic alcoholics who develop a peripheral neuropathy which accounts for the clinical symptomatology, but that in addition marked vascular alterations affect the distal arteries and arterioles. The vascular alterations are also produced by chronic alcoholism.

Alcohol consumption plays an important role in this disease. Of the 15 patients reported by Trope and Crookes, 13 admitted to heavy drinking and 2 to light alcohol consumption. These authors also pointed out that many of their subjects had no homes of their own and lived in hostels, environments that predispose to heavy drinking.

Bureau and Barriere reported a series of cases which they termed 'ulcerating and mutilating trophic lesions of the lower limbs'. They described 26 men and 1 woman, all adults varying in age from 30 to 56 years, who were all severely addicted to alcohol and who presented with perforating ulcers and a progressive deformity of the whole foot. Changes were not observed in the upper limbs. In their cases arteriography of the small vessels of the legs showed arteriovenous communications producing tufts, the number of which was proportional to the severity and duration of ulcerated lesions.

The smooth muscle hyperplasia in the media and intima of patients with idiopathic neurotrophic feet is of considerable interest. Most authorities agree that smooth muscle proliferation occurs early in the development of atherosclerosis. The mechanism is not entirely clear but it has been suggested that chronic hypercholesterolaemia injures the endothelium and leads to focal desquamation, that platelet adherence and aggregation occur at the injured sites and that disintegrating platelets release a substance that stimulates smooth muscle proliferation. 'Chalones' in the arterial wall may act as inhibitors of smooth muscle proliferation. Theoretically, therefore, this stage in atherogenesis may be due to stimulation of smooth muscle or to a failure of inhibitors to restrain this hyperplasia. However, in atherosclerosis the changes are present predominantly in larger blood vessels. Recently Ledet also showed that serum from young diabetics contains a factor or factors which promote an excessive growth of arterial smooth-muscle cells. The factor is not a lipid, glucose, an amino acid, fructose or a ketone.

What are the possible causes of the smooth-muscle hyperplasia in the blood vessels of these subjects with idiopathic neurotrophic feet? It is possible that the alcohol, by itself or in combination with the associated malnutrition, may either stimulate smooth muscle hyperplasia or, alternatively, suppress the activity of the chalone inhibitors.

I should like to thank Mr M. Ulrich for the photomicrographs, Mr D. Treurnich for technical assistance and Miss N. M. Mazamisa for secretarial assistance.

REFERENCES