Editorial

Aetiopathogenesis of Diabetic Peripheral Nerve Disease and Problems Concerning the Diabetic Foot

A J M BOULTON*

Journal of the Ceylon College of Physicians, 1991, **24**, 14–16

The diabetic neuropathies remain one of the commonest longterm complications of both main types of diabetes. Previous estimates of the prevalence of neuropathy have been extremely disparate due to the differences in diagnostic criteria and classifications adopted. Although complex classifications based upon presumed aetiology have been proposed, in this paper clinical classification will be used where splits neuropathies into polyneuropathies and mononeuropathies[1]. Whereas the latter tend to be of vascular aetiology and carry a good prognosis, the vast majority of neuropathies are indeed polyneuropathies, that may be subdivided into the sensorimotor neuropathies, the autonomic neuropathies, proximal motor and finally truncal polyneuropathies. The remainder of this paper will refer mainly to the sensorimotor and autonomic neuropathies.

Prevalence of the Sensory Polyneuropathies

A recent survey of the literature showed a prevalence varying from 10–16% depending upon criteria used to define neuropathy. In a survey of clinic population of insulin treated patients, aged under 60 years, I previously reported the prevalence of 11% for symptomatic sensorimotor neuropathy which increased to 20% if patients with signs but no symptoms were included. It is therefore generally accepted that the prevalence of clinically relevant neuropathy in the average diabetic clinic including older patients with Type 11 diabetes is around 33%. If one was to include patients with electrophysiological abnormalities, the prevalence of neuropathy in the average diabetic population would approach 90%.

Aetiopathogenesis

It seems that our views of the aetiology of diabetic neuropathy change with each decade and this new decade will be no exception. There is strong and compelling evidence to suggest that both metabolic and vascular factors are contributory to the aetiology[2 3]. A number of observations have suggested a pivotal role of chronic hyperglycaemia in the causation of the diabetic polyneuropathies. Activation of the polyol pathway in the presence of an elevated blood glucose provides a possible mechanism for the neurotoxicity of glucose. Recent evidence has furthered our understanding of the polyol pathway abnormalities though the connection between increased activity of this pathway and abnormalities of myoinositol and sodium potassium ATPase is less clear.

* *Consultant and Senior Lecturer in Medicine, University of Manchester, UK.*

However, studies with aldose reductase inhibitors which inhibit the rate limiting enzyme of the polyol pathway have demonstrated some efficacy both clinically and morophologically and studies of early intervention are urgently required.

In addition to metabolic abnormalities, widespread microvascular abnormalities in sural nerve biopsies have been demonstrated in diabetic neuropathy and my group has recently demonstrated that both electrophysiological and structural changes similar to those seen in diabetic neuropathy are also seen in patients with chronic hypoxia of non-diabetic aetiology[4]. In addition we demonstrated that some of the cardinal features of diabetic neuropathy which are present in chronic hypoxia correlate with the prevailing arterial pO_2s suggesting that endoneurial hypoxia may be a crucial and early feature in the evolution of diabetic neuropathy, though the causation of this hypoxia remains speculative.

In summary, the diabetic neuropathies are a heterogeneous group of disorders and strong evidence exists to implicate both metabolic and ischaemic/hypoxic factors in their aetiology[5].

Treatment

A structured approach to the patient with symptomatic diabetic polyneuropathy is proposed[1,6].

1. Exclude other causes of neuropathy.
2. Aim for optimal stable control of diabetes realizing that insulin is not necessarily required in Type 11 diabetes.
3. If symptoms persist despite good control, a trial of simple analgesics or non-steroidals is suggested.
4. Specific therapies available at present include the tricyclic drugs which must be considered the treatment of choice as these have been demonstrated in 2 good control trials to be efficacious in the relief of symptoms.
5. Other drugs that may be helpful include phenytoin and carbamazepine.
6. Drugs under investigation include the aldose reductase inhibitors, the gangliosides and essential fatty acids.

Natural History of Diabetic Neuropathy

A small sub-group of patients with a sensory neuropathy have florid symptoms of acute onset that often follow a metabolic upset. This small sub-group of acute sensory neuropathy carries a very good prognosis. A typical patient with insidious onset of symptoms must carry a guarded prognosis as longterm studies have showed that symptoms have tended to persist together with gradual deterioration of electrophysiological measurements. These patients may ultimately lose symptoms but may be left with the insensitive foot, that is so at risk of insensitive ulceration.

Diabetic Foot Ulceration

Our understanding of the aetiopathogenesis of diabetic foot problems has progressed in recent years. Experimental support aetiology of foot ulceration can be found in studies from Poland some 18 years

ago when workers demonstrated that canine hind paw ulceration only occurred if both sciatic and sympathetic nerve trunks were transected. However these authors failed to remark that it was a combination of insensitivity and autonomic dysfunction together with pressures that led to ulceration. Recent data from my unit and others confirm the importance of neuropathy in the aetiopathogenesis of around 90% of diabetic foot ulcers. The commonest scenario is a combination of neuropathic and vascular dysfunction though purely neuropathic ulcers can account for up to 40% of lesions in any one clinic. Peripheral autonomic dysfunction with sympathectomy is commonly present in these patients that, in the absence of large vessel disease will lead to increased peripheral blood flow with arteriovenous shunting. Thus, the warm insensitive foot is as much at risk of ulceration as the cold ischaemic foot. It was work from pioneers such as Milroy Paul from Sri Lanka that recognised the importance of peripheral insensitivity in the aetiology of foot ulceration in conditions such as leprosy.

In my unit we have demonstrated that it is a combination of peripheral insensitivity and mechanical pressure that leads to ulceration in the majority of cases. Mechanical pressures can come from foreign bodies or equally from inappropriate footwear purchased by the patient. We have demonstrated in several studies the importance of abnormal pressures and loads on the diabetic foot, in the aetiopathogenesis of ulceration in those already insensitive from peripheral neuropathy. More recently Fernando working in my unit has demonstrated the pivotal role of limited joint mobility in the aetiology of abnormal foot pressures in the diabetic patient[5 7].

As diabetologists, our main role is in the identification of patients at risk of foot ulceration. In addition to those who have peripheral neuropathy and peripheral vascular disease, those considered at risk must include patients with any history of foot ulceration, mechanical problems of the foot whether of orthopaedic or other aetiology and the elderly especially if living alone and confused. It is our duty to provide them with sufficient education to enable them to avoid the development of these ultimately preventable lesions. The management of those patients who develop foot ulceration will be considered elsewhere.

In summary it is estimated that up to 50% of amputations in diabetic patients could be prevented with the application of simple preventive medicine which relies upon the early identification of those at risk of foot ulceration.

REFERENCES

1. Boulton A J M, Ward J D. Diabetic Neuropathy and Pain. *Clinics in Endocrinology and Metabolism* 1986; **15**: 917-931.
2. Greene D A, Lattimer S A, Sima A A F. Pathogenesis and prevention of diabetic neuropathy. *Diabetes/Metabolism Reviews* 1988; **4**: 201-222.
3. Low P A. Recent advances in the pathogenesis of diabetic neuropathy. *Muscle and Nerve* 1987; **10**: 121-128.
4. Malik P A, Masson E A, Sharma A K et al. Hypoxic neuropathy: relevance to human diabetic neuropathy. *Diabetologia* 1990; **33**: 311-318.
5. Boulton A J M. The Diabetic Foot — of neuropathic aetiology? *Diabetic Medicine* 1990; **7**: 852-858.
6. Young R J, Clarke B F. Pain relief in diabetic neuropathy: the effectiveness of Imipramine and related drugs. *Diabetic Medicine* 1985; **2**: 262-266.
7. Boulton A J M. The Diabetic Foot. *Medical Clinics of North America* 1988; **72**: 1513-1530.