The natural history of painful diabetic neuropathy—a 4-year study

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Summary

Thirty-nine patients with painful diabetic peripheral neuropathy were selected for a follow-up study to determine the natural history of this condition. Symptoms, motor conduction velocities (MCV) and ankle pressure indices were recorded at the initial assessment and after a mean study period of 4.7 years. Thirty-six patients completed the study and showed no significant changes in symptoms, but there was a significant fall in median nerve MCV. It is concluded that symptoms of established diabetic neuropathy persist for several years, and the changes in MCV may reflect continuing deterioration in nerve function.

KEY WORDS: diabetic neuropathy, diabetic complications.

Introduction

Although peripheral neuropathy is probably the commonest long-term complication of diabetes (Ellenberg, 1982), little is known of its natural history and prognosis. The few reported studies have produced conflicting results (Fry, Hardwich and Scott, 1962; Mayne, 1968; Bischoff, 1981) and, have usually involved all groups of neuropathy, including mononeuropathy and autonomic neuropathy. These different conditions may have a variable prognosis (Ellenberg, 1982; Thomas, Ward and Watkins, 1982; Ewing, Campbell and Clarke, 1976). Since the commonest manifestation is painful peripheral neuropathy of the lower limbs, we have identified and followed 39 patients with these symptoms in order to determine the natural history of this condition.

Materials and methods

Thirty-nine patients (29 males) with sensorimotor diabetic neuropathy were selected for study between

1976 and 1978. There were 12 insulin-dependent diabetics and 27 non-insulin-dependent diabetics, mean age 55.5 years (range 40-72 years) and duration of diabetes 10.9 years (range 1-34 years). All subjects were outpatients, were assessed independently by two investigators before their selection, and satisfied the following strict criteria for diagnosis of neuropathy:—

- (1) Painful symptoms in both legs for at least 6 months before the study. All patients experienced one or more of the following symptoms: paraesthesiae, numbness, burning pains with nocturnal exacerbation, hyperaesthesiae.
- (2) Motor conduction velocity in peroneal nerve less than 40 m/sec.
- (3) No symptoms or signs of peripheral vascular disease: ankle pressure index greater than 1.0 (Yao, Hobbs and Irvin, 1969).

In addition, none had a history of alcohol abuse (McCulloch *et al.*, 1980) and all had a haemoglobin greater than 12 g/dl. Other diabetic complications were present in 14 patients: 10 had background retinopathy and 4 had proliferative changes.

All subjects were asked to score their painful symptoms on a 10 cm horizontal graphic rating scale (no pain = 0; maximum pain = 10) (Scott and Huskinson, 1976). This scale consists of a 10 cm horizontal straight line, each end representing the extreme, either maximum symptoms or no symptoms. Subjects were asked to mark the scale at a point corresponding with their symptoms. The point was then measured, giving a score of between 0 and 10; the higher the score the more severe the symptoms. The same pain scale was used for the follow-up appointment, so that any change in symptoms could be indicated by the patient. Motor conduction velocities (MCV) were measured in the right median and peroneal nerves as previously described (Ward *et al.*, 1971), and the ankle pressure index, the ratio of posterior tibial

systolic pressure to brachial systolic pressure was recorded using a Doppler ultrasound stethoscope (Yao *et al.*, 1969). The subjects were followed for a mean period of 4.7 years (range 2–5 years) during which they continued to attend the diabetic clinic. They received symptomatic treatment for their neuropathic symptoms, which generally consisted of simple analgesics, aspirin and dipyridamole or tricyclic antidepressants. A blood glucose level was recorded at most clinic visits (glucose oxidase technique) and the mean number of results available for each patient during the study was 22 (range 7–36).

There were no changes in diabetic management during the study, with the exception of 5 subjects who changed to insulin therapy because of poor diabetic control on maximum doses of sulphonylurea drugs. Two patients died within a year of the initial assessment, one following a cerebral infarct and the other of a myocardial infarction. A third patient emigrated, and the follow-up study therefore included 36 patients. All the initial investigations were repeated at the follow-up appointment, and the subjects were asked to score current neuropathic symptoms on their original 10 cm graphic rating scale. This enabled changes in the severity of symptoms during the study to be assessed.

Wilcoxon's signed rank test, the Chi squared test and the sign test were used for statistical analyses: all results are shown as mean $\pm$ s.d.

Results

The results of the investigations are summarised in Table 1. No significant changes in symptom scores were found during the 4-year study and furthermore, no subject experienced complete resolution of symptoms, though some improvement was noted by 11 subjects (Fig. 1). There was no significant difference between the clinic blood glucose levels in the subjects who experienced improvement of symptoms during the study ($9.7 \text{ mmol/litre} \pm 2.6$), when compared with those experiencing no changes in symptoms ($9.8 \text{ mmol/litre} \pm 2.4$), or worsening of symptoms ($10.2 \text{ mmol/litre} \pm 2.3$). Moreover, there was no significant

difference in blood glucose levels after starting insulin therapy in the 5 subjects whose treatment was changed during the study. One of these subjects experienced improvement in symptoms, 2 noted worsening and the other 2 experienced no change in symptoms. There was a small, though non-significant fall in ankle pressure index during the study period (Table 1). Five patients developed symptoms and signs of peripheral vascular disease with ankle pressure index less than 1.0 on review, and one required an above knee amputation for peripheral gangrene, despite easily palpable pulses on entry into the study. Motor conduction studies showed a significant decrease in the median nerve, though there was no significant change in peroneal nerve MCV.

Discussion

No significant changes in symptoms and few significant changes in objective tests were found during the 4-year study. This conclusion is in broad agreement with that of Bischoff, who followed 30 patients with symmetrical sensory neuropathy for an average of 5.6 years (Bischoff, 1981). In an earlier study, Fry *et al.* (1962) reported 39 patients with symmetrical neuropathy, and concluded that only one-third of patients showed a satisfactory improvement. Conversely, Mayne (1968), in his series of 73 patients followed for an average of 3 years, concluded that symptoms of neuropathy tended to improve. However, in these 3 earlier studies subjects with peripheral neuropathy were grouped with other patients suffering from mononeuropathy and autonomic dysfunction. A follow-up of such a broad group may well produce conflicting results, as the mononeuropathies have been shown to carry a good prognosis (Ellenberg, 1982; Thomas *et al.*, 1982), whereas Ewing *et al.* (1976) have demonstrated that established autonomic neuropathy carries a significant mortality. Furthermore, these earlier studies used questionnaires and interviews to assess the severity of symptoms. We chose to use the most reliable, semiquantitative method available to assess changes in symptoms (Scott and Huskisson, 1976).

TABLE 1. Results of investigations in 36 neuropathic patients

	Initial assessment	Follow-up assessment	P
Pain score (cm)	5.3 $\pm$ 2.0	5.6 $\pm$ 2.5	NS
Ankle pressure index	1.27 $\pm$ 0.25	1.20 $\pm$ 0.34	NS
Median nerve MCV (m/sec)	45.8 $\pm$ 6.6	42.7 $\pm$ 6.1	<0.025
Peroneal nerve MCV (m/sec)	36.2 $\pm$ 5.2	36.0 $\pm$ 4.8	NS

MCV = motor conduction velocity; NS = not significant.

FIG. 1. Changes in symptom scores during the study. Subjects noting improvement in symptoms are represented by a thick line, those showing no change or deterioration of symptoms by a thin line.

A recent study of 8 patients with severe painful neuritis has suggested a very good prognosis (Archer *et al.*, 1982) but symptoms resolved within 10 months of onset and such patients would not have satisfied our strict criteria for established diabetic neuropathy. Moreover, each of these patients had severe and incapacitating pain associated with marked weight loss. Greene *et al.* (1981) have recently emphasised the importance of strict criteria in the selection of subjects with neuropathy for clinical studies. They also expressed major reservations concerning the relevance of nerve conduction studies to symptomatic changes in neuropathy. However, as many investigators still use changes in MCV as major determinants of success in clinical trials, we chose to assess symptoms together with measurement of MCV. It thus appears that, whereas symptoms of short duration may carry a good prognosis (Archer *et al.*, 1982) established neuropathic symptoms do not resolve spontaneously and may persist for many years. Although 11 of our subjects noted some improvement (Fig. 1), none experienced complete resolution of painful symptoms. Nerve conduction studies may reflect deterioration in nerve function during such time.

A study of the natural history of untreated diabetic neuropathy would be unethical: however, as neither the use of aspirin and dipyridamole, nor tricyclic antidepressants has been shown to influence neuro-

pathic symptoms significantly (Thomas *et al.*, 1981; Ward *et al.*, 1981), the present study probably reflects the natural history of this condition. Despite strict selection criteria, several patients developed symptoms and signs of peripheral vascular disease. The differentiation between neuropathic and vascular symptoms can be very difficult (Ward, 1982) and even an ankle pressure index of greater than unity does not necessarily exclude patients with early large vessel disease (Boulton *et al.*, 1981). Earlier studies have stressed the importance of diabetic control in the management of peripheral neuropathy (Goodman *et al.*, 1953; Fry *et al.*, 1962; Mayne, 1968), but methods of assessment of control in such studies are now known to be suspect (Molnar *et al.*, 1979). Thus, no conclusion as to the effect of diabetic control on the natural history of neuropathy can be made from the present study, as routine use of home blood glucose monitoring and glycosylated haemoglobin measurement was not available until 1980. An estimate of the degree of control can, however, be achieved by the analysis of multiple random blood sugar results, as has recently been demonstrated by Dornan, Mann and Turner (1982). From such results, it is apparent that, in the present study, there was no significant difference in control between groups that showed improvement, deterioration or no change in symptoms. Boulton *et al.* (1982a,b) have recently confirmed the importance of strict glycaemic control in the aetiology and management of neuropathy using more valid measurements of control. However, no group in the present study achieved near normalisation of blood glucose as reported by Boulton *et al.* (1982b). Thus, though we conclude that symptoms of diabetic neuropathy frequently persist for several years, recent studies suggest that glycaemic control may offer symptomatic relief to such patients. Further similar longitudinal studies with strict blood glucose control are now required.

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