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Nerve conduction studies in diabetics presymptomatic and symptomatic for diabetic polyneuropathy

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ABSTRACT

Objective: We performed nerve conduction studies (NCS) on diabetics with and without symptoms of diabetic polyneuropathy (DPN) and evaluated correlations with glycaemic control and clinical features.
Methods: Consecutive patients were recruited in three groups: "normals" (nondiabetics without peripheral nerve disease); "presymptomatic diabetics" (diabetes without DPN); and "symptomatic diabetics". Clinical questionnaire and neurological examination were administered, and NCS were performed using standard techniques.
Results: 153 patients were recruited (51 normals, 50 presymptomatic diabetics, 52 symptomatic). Glycosylated haemoglobin and duration of DM were higher in symptomatic diabetics, with symptoms present for 1–60 months (mean 14.5). Alterations in NCS included prolonged latencies, lowered amplitudes and slowed conduction velocities, following a pattern of initially reduced sensory amplitudes and slowed motor velocities, with later reduced motor and sensory amplitudes and prolonged motor latencies. Neuropathic pain, clinical signs and glycosylated haemoglobin correlated with these changes.
Conclusions: Even in asymptomatic patients, NCS show diffuse changes, in a predictable pattern. Electrophysiological parameters correlate with neuropathic pain, physical findings and glycosylated haemoglobin levels.
Significance: We demonstrate that NCS changes in DPN follow a predictable pattern, correlating with clinical features and long-term glycaemic control.

1. Introduction

1.1. Diabetic polyneuropathy

Chronic complications of diabetes mellitus (DM) represent the major cause of morbidity and mortality from this disease in the modern era, with diabetic polyneuropathy (DPN), cardio-vascular disease, retinopathy and renal disease being most frequent (Chan, Terashima, Fujimiya, & Kojima, 2006; Dobretsov, Romanovsky, & Stimers, 2007). The current pandemic of DM makes these complications an obvious public health problem. By far the commonest cause of neuropathy, DPN is associated with a quarter of the total costs of diabetes care in the USA: over $4.6 billion annually (Callaghan, Cheng, Stables, Smith, & Feldman, 2012). The prevalence of peripheral neuropathy in diabetic subjects approaches 70% with three-fourths of these being DPN (Bansal, Kalita, & Misra, 2006; Dobretsov et al., 2007; Mythili, Dileep Kumar, Subrahmanyam, Venkateswarlu, & Butchi, 2010).

In patients with DM, DPN develops usually only if hyperglycaemia has been present for several years or more. This is true for both type 1 and type 2 DM; however, the time of onset of DM type 2 is seldom precisely known. Consequently, DPN may already be present at the time type 2 diabetes is formally diagnosed (Bansal et al., 2006). Moreover, emerging studies suggest that impaired glucose tolerance (IGT) may lead to polyneuropathy, particularly painful small-fibre neuropathy. Rates of IGT in patients with chronic idiopathic axonal polyneuropathies vary between 30% and 50% (Sinnreich, Taylor, & Dyck, 2005).

1.2. Electrophysiological studies in diabetic polyneuropathy

The fully expressed syndrome of DPN is a symmetrical distal lower-limb sensorimotor polyneuropathy with a variable degree of autonomic involvement. Almost without exception, sensorimotor involvement is restricted to the distal extremities of the lower limbs. By contrast, electrophysiological abnormalities can be found diffusely, even in nerves not affected clinically (Callaghan et al., 2012; Sinnreich et al., 2005; Vinik, 2004). As DPN is of insidious onset and often present at the time of diagnosis of type 2 DM, electrophysiological

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studies may be abnormal in diabetics even if they do not have any neuropathic symptoms. This study presents findings of motor and sensory nerve conduction studies (NCS) performed on diabetic patients with and without symptoms of DPN. We compare NCS parameters between these two groups and another group of persons without peripheral nerve disease, evaluate the relation between alterations in NCS in diabetic patients and glycaemic control, and correlate abnormalities in NCS with clinical features of somatic and autonomic neuropathy.

2. Methods

2.1. Patient enrolment and data collection

Patients were recruited over a period of one year from the out-patient clinics and in-patient wards in our centre. Patients without clinical signs of neuropathy and without systemic illness predisposing to neuropathy, including diabetes, were studied as the "normal" cohort with NCS being performed on one upper and one lower limb. Patients with diabetes but without symptoms and signs of peripheral neuropathy formed the asymptomatic diabetic group. Patients with diabetes and with two or more symptoms and signs attributable to the distal symmetric polyneuropathy of diabetes were included in the symptomatic diabetic group.

A detailed questionnaire was filled in every case, with a view to detecting symptoms and signs of peripheral nerve disease, describing and excluding confounding factors that may affect NCS results, and describing complications of diabetes. Exclusion criteria included age <18 years; asymmetric paresthesiae, sensory impairment or weakness in the lower extremities (other than that attributable to DPN); patients with any cause of neuropathy other than diabetes (including carpal tunnel syndrome, spine disease, alcoholism, liver or renal disease, toxic exposure, other endocrine, metabolic or nutritional disorders, inflammatory diseases, or trauma); pregnant women; patients with DM of specific aetiology or with diabetic emergencies and positive HIV serology.

2.2. Clinical and laboratory data

Clinical assessments were carried out by one examiner (RJS) on all patients, focusing specifically on sensory complaints and objective abnormalities in the upper and lower extremities. Glycosylated haemoglobin (HbA_{1c}) and fasting and postprandial blood sugar levels were estimated in all patients at the time of NCS.

2.3. Electrophysiological testing

NCS was performed by a single investigator (RJS) with standard surface stimulation and recording techniques on a Neurocare four-channel electromyograph (Biotech Ltd., Mumbai, India) with standard filter settings (2 Hz to 10 kHz) and a surface stimulator using a 0.1 ms square-wave pulse. Round silver cup electrodes with a diameter of 10 mm were used to record potentials. Electrodiagnostic techniques recommended by the Consensus Development Conference of Standardized Measures in Diabetic Neuropathy were employed to evaluate right-sided peroneal motor, median and ulnar motor and sensory, and sural sensory responses. Standard recording sites and stimulation to recording electrode distances were used: stimulation at the wrist and elbow for median and ulnar motor NCS recording from the abductor pollicis brevis and abductor digiti minimi respectively; stimulation at the wrist for median and ulnar antidromic sensory studies recording from the second and fifth digits respectively; stimulation at the ankle and fibular neck for peroneal motor NCS recording from the extensor digitorum brevis; and stimulation in the calf recording from the foot for sural studies. For motor NCS gain was kept at 2 mV/division, time sweep at 2 ms/division, and low and high frequency filters at 10 and 32 kHz respectively, while for sensory studies gain was at 20 μV/division and time sweep at 1 ms/division, with the same filter settings. Since the studies were performed in a tropical country where the ambient temperature at the time of performing NCS was always >25 °C, limb temperature was not monitored.

Compound muscle action potential amplitudes were measured from the baseline to negative peak, and onset latencies were measured for distal and proximal stimulation sites. Sensory nerve action potential (SNAP) amplitude was measured from the initial positive peak to the negative peak, or from the baseline to the negative peak if there was no initial positive peak. The results were calculated on the basis of average of ten or more responses. Conduction velocities were calculated from the onset latency and distance measurements. Motor conduction velocities were determined for the median nerve, the ulnar nerve, and peroneal nerves calculated by dividing the distance between proximal and distal stimulating cathodes by the latency. Sensory conduction velocity was calculated by dividing the distance between stimulating and recording electrodes by response latency. All nerve conduction recordings were reviewed by a neurologist (AS) to identify protocol violations, and amplitudes and latencies were remeasured to identify correctable problems such as transcription errors. The study received approval from the hospital ethics committee.

2.4. Statistical analysis

All data were entered in a database, and this was exported to statistical software (SPSS Inc, version 15) for analysis. Descriptive statistics such as mean, standard deviation, frequency, median, range and percentage were used to express data. Categorical variables were analysed using chi square test, while one-way analysis of variance and univariate analysis of variance were used for continuous variables. Logistic regression was employed to describe risk. A p value < 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical data

One hundred and fifty-three consecutive adult patients fulfilling the inclusion and exclusion criteria were included in this study. Of these, 51 did not have any history or examination findings suggestive of neurological disease and were designated as "normal subjects". Fifty had DM, but no history or findings on clinical examination to suggest neurological disease, and were designated as the "presymptomatic diabetic" group. The last group of 52 patients was designated the "symptomatic diabetic" group, and had diabetes mellitus as well as signs and symptoms of peripheral neuropathy. Demographic and laboratory data are shown in Table 1. Age, glycosylated haemoglobin levels and the duration of DM were significantly higher in the symptomatic group, with a much higher proportion of symptomatic diabetics having glycosylated haemoglobin values >9% (Fig. 1).

By definition, no patient in the presymptomatic group had sensory or motor symptoms in the limbs. In the symptomatic diabetic group, such symptoms were present from 1 to 60 months before enrolment (mean 14.5, SD 13.7 months) and were progressive after onset. Abnormal positive sensations (paresthesiae or pain) were present bilaterally in all 52 patients. 47.1% reported sensory loss in the feet. Weakness, which was uniformly bilateral, was noted by 74.5% of patients in the symptomatic diabetic group. Mild unsteadiness of gait was noted in 53.8%, although only 9.6% reported symptoms suggestive of sensory ataxia. On neurological examination the upper limb muscles were wasted distally in one patient, and the lower limb muscles in six. Distal upper limb weakness was seen in 21.2%, proximal upper limb weakness in 3.8%, distal lower limb weakness in 51.9% and proximal lower limb weakness in 23.1%. Upper limb