

AFTER THE SWEET COMES THE BITTER. TIME TO HALT THE DIABETIC NEUROPATHY EPIDEMIC

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ABSTRACT

Diabetes is the leading cause of neuropathy in industrialized countries and possibly worldwide. The most common form is distal symmetrical polyneuropathy. Diabetes affects the nerves even before being recognized. The disease continues to expand in parallel with the incorrect lifestyle habits typical of modern society. The cardinal symptoms of peripheral nervous system diseases may be indicative of motor, sensory, autonomic and trophic lesions. Diabetic neuropathy also has significant economic costs to society. The high rate of diabetic neuropathy causes substantial morbidity from recurrent infections of the lower limbs, ulceration and amputation. Electromyographic examination of the distal muscles of the lower extremities may reveal acute and chronic denervation. Some alterations of the paraspinal muscles, such as spontaneous activity, are similar to those of disease in the spinal nerve roots.

Keywords: diabetes, diabetic neuropathy, diabetic complications, diabetic prevention, diabetic therapy.

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Introduction

Diabetes is the leading cause of neuropathy in industrialized countries and possibly worldwide. Inadequate control or long duration of diabetes are among the main risk factors for neuropathy. One of the features that set neuropathy apart from other neurological illnesses is its clinical polymorphism^(1,2), the most common form being distal symmetrical polyneuropathy (DSP), but many patterns of nerve injury can occur⁽³⁻⁴⁾.

Diabetic neuropathy continues to expand in parallel with the incorrect lifestyle habits typical of modern society. Several pathogenic noxae selectively damage Schwann cells or membranes that form the myelin sheaths and cause peripheral nerve

demyelination leaving relatively intact axons. Alternatively, specific axonal damage may affect the cell body or complex axonal transport system⁽⁵⁻¹⁰⁾. The typical symptoms of peripheral nervous system (PNS) diseases may be indicative of motor, sensory, autonomic and/or trophic lesions^(1,2,11,12).

Accurate early diagnosis of diabetes is crucial because the patient's prognosis and the choice of treatment depend on the extent of the metabolic disorder. This is supported by the fact that recent attention has focused on a possible association between an undiagnosed nerve injury and impaired glucose tolerance in the absence of manifest diabetes (prediabetes)⁽¹³⁻¹⁵⁾.

This study aimed to:

1 Establish a diagnosis of diabetes or predia-

betes excluding any other known aetiology of neuropathy ;

2 Establish a diagnosis of neuropathy by clinical assessment (impaired reflexes, loss of proprioception and perception of vibration, wasting of small muscles of hands and feet, weakness in feet, impaired sensation of warm and cold temperatures and 10-g monofilament testing) and instrumental evaluation [16]: nerve conduction study and sympathetic skin response (SSR);

3 Evaluate the effects of treatment (including dietary and calorie intake restrictions) on the evolution of neuropathy at time 0 (first visit), time 1 (after 6 months) and time 2 (1 year after the first visit) to evaluate the reversibility of the diabetic neuropathy monitoring the clinical symptoms and signs and neurophysiological alterations (motor and sensory conduction velocity (MCV and SCV), SSR, presence/absence or changes in late responses (F-wave parameters) and EMG alterations in all four limbs;

4 Evaluation of somatosensory evoked potentials (SEPs) to disclose a possible alteration of the preganglionic component of the somatosensory pathways, assessing the presence/absence of P40, its symmetry and central conduction time (CCT).

Materials and methods

In a longitudinal observational clinical study we recruited 60 patients (35 men and 25 women) aged between 47 and 78 years presenting typical signs and symptoms of PNS impairment such as hypoaesthesias, paraesthesias, pins and needles, pinprick sensations, electric shocks, local or diffuse reductions in muscle strength in subjects with diabetes or prediabetes.

Patients were in various disease stages and were classified into three groups on the basis of disease severity:

Group A: Twenty patients with prediabetes or mild diabetes of at least two years' duration (HbA1C=6/7.5%, 42/58 mmol/ml);

Group B: Twenty patients with diabetes of at least two years' duration, aware of the average severity of their disease (HbA1c=7.5/9.5%, 58/80 mmol/ml);

Group C: Twenty patients with more severe diabetes of at least two years' duration under insulin or mixed oral and insulin treatment (HbA1c=>9.5%, >80 mmol/ml).

Patients were evaluated for PNS effects, bearing in mind the degree of therapeutic disease control. All patients underwent clinical and neurophysiological investigations recording: motor conduction velocities (upper limb median and ulnar nerves, lower limb peroneal and tibial nerves); distal latencies and F-wave latencies; SCV (upper limb median, ulnar and radial nerves, lower limb sural nerve); electromyography if necessary (axonal neuropathies) in one proximal (biceps/quadriceps) and one distal muscle (first dorsal interosseous/tibialis anterior) in all four limbs; SEPs in all limbs; metabolic control (fasting blood glucose, glycated haemoglobin). All tests were performed at: Time 0 (t0) (baseline), Time 1 (t1) (six months after time 0) and Time 2 (t2) (12 months after time 0).

Results

The patient drop-out rate was high and only ten patients in each group were considered for the final assessment. Tables 1-3 summarise the results for the three groups. All patients presented chronic distal sensorimotor polyneuropathy (DSP) in the lower limbs. DSP was absent in the upper limbs only in Group A patients with mild diabetes (70%) or prediabetes (30%) (with normal fasting blood glucose levels but elevated glycated haemoglobin) (HbA1c =<7.5%).

	SNCV	MNCV	DL	FL	EMG	SEPs (CCT)	SEPs (P40 L) SSR
To	↓	-↓	↑	↑	-	↑	↑ -
T1	↓	-↓	-↑	-↑	-	↑	↑ -
T2	-↓	-↓	-↑	-	-	-↑	-↓ -

Table 1: (Group A): ten patients (HbA1c =<7.5%)T0: Basal assessment; T1: Intermediate assessment (after 6 months); T2: Final assessment (after 12 months).

HbA1c= glycated haemoglobin; DL= distal latency; FL= F-wave latency; SNCV= sensory nerve conduction velocity; MNCV= motor nerve conduction velocity; EMG= electromyography: -= normal, imp.=impairment; SEPs= somatosensory evoked potentials, CCT= central conduction time; P40 L= P40 latency; ↑,↑↑, ↑↑↑ = mild (<30% respect to upper limits), mean (<50% respect to upper limits) or severe (>50% respect to upper limits) impairment, respectively; SSR -= sympathetic skin response present; SSR 0= sympathetic skin response absent.

	SNCV	MNCV	DI	FL	EMG	EP(CCT)	EP(P40 L)	SSR
To	↓/↓↓↓	↓/↓↓↓	↑↑/↑↑↑	↑↑/↑	↑↑	-/Imp.	↑/↑↑↑	-/0
T1	↓/↓	↓/↓	↑/↑↑	↑/↑↑↑	-/Imp.	↑/↑	↑/↑↑	-/0
T2	-/↓	-/↓	↑/↑	↑/↑	-/Imp.	-/↑	-/↑	-/0

Table 2: (Group B): ten patients (HbA1c = 7.5/9.5%) T0: Basal assessment; T1: Intermediate assessment (after 6 months); T2: Final assessment (after 12 months).

HbA1c= glycated haemoglobin; DL= distal latency; FL= F-wave latency; SNCV= sensory nerve conduction velocity; MNCV= motor nerve conduction velocity; EMG= electromyography: -= normal, imp.=impairment; SEPs= somatosensory evoked potentials, CCT= central conduction time; P40 L= P40 latency; ↑,↑↑, ↑↑↑ = mild (<30% respect to upper limits), mean (<50% respect to upper limits) or severe (>50% respect to upper limits) impairment, respectively; SSR -= sympathetic skin response present; SSR 0= sympathetic skin response delayed/absent.

	SNCV	MNCV	DI	FL	EMG	EP(CCT)	EP(P40 L)	SSR
To	↓/↓/↓↓	↓/↓/↓↓	↑↑/↑↑↑	↑↑/↑↑↑	-/Imp	↑/↑	↑↑/↑↑↑	0
T1	↓/↓↓	↓/↓↓	↓/↓↓	↓/↓↓	-/Imp	↑/↑	↑↑/↑↑↑	0
T2	↓/↑	↑/↓	↑/↑	↑/↑	-/Imp	↑/↑	↑/↑↑	-/0

Table 3: (Group C): ten patients (HbA1c = >9.5%) T0: Basal assessment; T1: Intermediate assessment (after 6 months); T2: Final assessment (after 12 months).

HbA1c= glycated haemoglobin; DL= distal latency; FL= F-wave latency; SNCV= sensory nerve conduction velocity; MNCV= motor nerve conduction velocity; EMG= electromyography: -= normal, imp.=impairment; SEPs= somatosensory evoked potentials, CCT= central conduction time; P40 L= P40 latency; ↑,↑↑, ↑↑↑ = mild (<30% respect to upper limits), mean (<50% respect to upper limits) or severe (>50% respect to upper limits) impairment, respectively; SSR -= sympathetic skin response present; SSR 0= sympathetic skin response delayed/absent.

In addition to DSP, the main clinical and instrumental findings in our cohort were the following:

High frequency of uni/bilateral carpal tunnel syndrome (associated metabolic and traumatic injury) with a right-sided prevalence in unilateral forms. Right>left bilateral carpal tunnel syndrome was also present in patients with occupations not deemed at risk: 30% in Group A, 60% in Group B, 80% in Group C;

L5-S1>L4-L5 lumbar radiculopathy: 20% in Group A, 40% in Group B, 90% in Group C. This condition was closely correlated with advanced age and physically demanding occupations (building, farming and road maintenance workers) probably associated with metabolic and traumatic injury;

Prevalence of sensory, hypoaesthetic, paraesthetic or mixed damage over motor injury in all three patient groups;

Prevalence of demyelinating over mixed (demyelinating and axonal) or axonal neuropathy (42%, 34% and 24% respectively), often with single or double series of pre-F A-waves or post-F A-waves, reflecting a demyelinating process⁽¹⁷⁾;

Prevalence of neuropathic damage in the lower limbs (internal popliteal sciatic nerve>external popliteal sciatic nerve>femoral nerve) with respect to the upper limbs (median nerve>ulnar nerve);

Concomitant altered SEPs in the lower limbs (tibial nerve) >upper limbs (ulnar nerve) due to increased bilateral P40 latency from mild to moderate and an increased peripheral component and CCT (2,4/3,7 ms>upper limits), in some cases due to intervertebral disc disease (especially in elderly patients). In patients without disc disease we postulated that metabolic injury to the pre- and post-ganglionic fibres of the somatosensory pathway was responsible for the typical electroneurographic changes (increased SCV/MCV, increased distal latency and increased F-wave latency);

The most common autonomic nervous system impairments disclosed on history-taking were erectile dysfunction, irregular bowel movements and bladder function which remained largely unchanged throughout the study.

Discussion

As shown in Tables 1-3, the long duration and severity of diabetes are correlated with the frequency and extent of PNS effects: longer disease duration and poorer metabolic control are more often associated with major complications. In our experience, chronic sensorimotor polyneuropathy can be observed in patients still unaware of their diabetes, as in our three cases of prediabetes. These patients had no clinical hallmarks of the disease and presented normal fasting blood glucose values. They were surprised at the diagnosis of diabetic neuropathy documented by their DSP and HbA1c levels.

A key finding in our patients disclosed on history-taking was the onset of diabetic neuropathy with carpal tunnel syndrome, more frequent on the right (right-handed patients). This symptom is known to be even more common in subjects with diabetes occupationally exposed to wrist joint injury (butchers, house painters, bricklayers, pneumatic drill users, housewives), probably due to associated trauma in subjects with abnormal glucose metabolism. Carpal tunnel syndrome is even more suggestive of diabetes if the symptoms fluctuate (alternating left and right) as they did in many of our patients.

Another history-taking finding in our patients was recurrent or fluctuating (right/left or vice versa) facial paralysis, sometimes even years before the diagnosis of diabetes. This supports our conviction that impaired glucose metabolism can damage the PNS even when it is mild but long-lasting and that the diagnosis of diabetes is only the end result and not the onset of a longstanding underlying illness unknown to the patient and his/her doctor. It is essential to identify the underlying metabolic disorder to prevent repercussions, sometimes exacerbated or maintained by frequent corticosteroid administration. This type of disease onset will evolve into generalised neuropathy, first sensory and then sensorimotor, in patients whose diabetes status is unknown or poorly controlled. Through different mechanisms and sites of injury the complications of diabetes may also lead to severe language disorders, namely dysarthria⁽¹⁸⁾.

The lumbosacral region is another recurrent site of neuropathy manifesting with sciatic nerve pain (affecting the external or internal popliteal sciatic nerve), first unilateral and/or fluctuating, then bilateral. A similar traumatic/metabolic pathogenetic combination can also be postulated in these cases. Again, failure to recognize the metabolic disorder entails high morbidity rates and recurrent recourse to lumbosacral surgery, resulting in increased healthcare spending, working days lost and deterioration in quality of life.

Demyelinating neuropathy was more common than axonal or mixed impairment in our cohort. Lower limb neuropathy is thought to be more common after median nerve entrapment at the wrist, typically presenting with paraesthesias at onset and subsequently extending to the upper limbs.

The results of clinical and neurophysiological investigations in our patients varied widely in all three groups. Despite our dietary and therapeutic rec-

ommendations, disease progression was encountered in some patients due to elevated glycated haemoglobin levels. Other patients showed a marked improvement in clinical symptoms paralleled by a stable correction of metabolic impairment, the most favourable condition for improvement.

Diabetic neuropathy may be reversible but this is uncommon. We believe the most important factor undermining patients' prognosis is poor compliance with dietary restrictions in the early stage of diabetes, also for the purposes of weight loss, the main objective in the prevention, control and possible remission of diabetes and its complications. Early diagnosis, lifestyle changes and patient compliance are crucial factors impacting on the reversibility of neuropathy⁽¹⁹⁾. Nonetheless, this is difficult to achieve as only a small percentage of patients, from 26% to 37% in our three groups, complied with dietary/therapeutic instructions. The remainder either failed to understand (or preferred to ignore) the importance of diet, treatment and physical activity, with the resulting impact on disease persistence or progression. Reversibility is also strictly linked to the anatomopathological type of neuropathy: exclusively demyelinating forms are more likely to improve than axonal neuropathy, and initial mild forms may even be cured⁽²⁰⁾.

Plainly, other cardiovascular risk factors such as hypertension, hyperlipidaemia, obesity, sedentary lifestyle, alcohol abuse, thrombophilia, and advanced age also reduce the chances of reversibility, especially when patients present multiple risk factors which act synergistically to cause DNA damage, endoplasmic reticulum stress, mitochondrial dysfunction, cellular injury, and irreversible damage⁽¹⁾.

The main findings of our study can be summarised as follows:

1 Neuropathy can be encountered sometimes in advanced stages even in subjects unaware of their metabolic illness;

2 Fasting blood glucose levels have a poor diagnostic sensitivity as they are often normal or within the upper limits of normal in subjects presenting full-blown symptoms of neuropathy;

3 Neuropathic damage is closely related to disease duration;

4 Many patients with diabetic neuropathy present uni/bilateral carpal tunnel syndromes with a right-sided prevalence, evolving into generalised neuropathy in all four limbs, first sensory than mixed sensorimotor;

5 Lumbar radiculopathies are common in diabetic patients (associated metabolic and traumatic damage);

6 Recurrent or fluctuating facial paralysis may signify disease onset;

7 Prevalence of demyelinating damage over mixed or axonal injury;

8 Prevalence of sensory over motor neuropathy;

9 Prevalence of neuropathic damage in the lower with respect to the upper limbs;

10 Greater reversibility of neuropathic damage only in mild forms, and only in patients with sensory neuropathy as opposed to those with concomitant sensorimotor damage. Reversibility depends on compliance with dietary restrictions and lifestyle modifications;

Greater reversibility of demyelinating neuropathic damage;

11 Major pathogenetic synergistic effect of other cardiovascular risk factors (hypertension, hyperlipidaemia, obesity, sedentary lifestyle, alcohol abuse, thrombophilia);

12 High rates of concomitant altered SEPs, prevalent in the lower limbs due to unilateral or bilateral increased P40/CCT latency caused by intervertebral disc disease, disc-joint damage or scoliosis and possible preganglionic metabolic impairment of the somatosensory pathway;

13 Rare finding of axonal responses in axonal neuropathies confined to the lower limbs, with rare acute and chronic spontaneous activity in the distal territories (sharp waves, fibrillations, fasciculations);

14 Detection of risk factors for ocular surface disorders in patients with type 2 diabetes and other disimmune disorders⁽²¹⁻²⁴⁾;

15 Major difficulties in making changes to patients' dietary habits in terms of quality and quantity to reduce calorie intake for the primary/secondary prevention of diabetic neuropathic changes. Food addiction is a major problem (in women>men).

Conclusion

Further studies on larger cohorts are needed to confirm our findings. It is our hope that national health authorities will gain awareness of the importance of early health education starting in primary school and continuing to high school designed to provide community-based primary prevention to stop diabetes⁽²⁵⁾, obesity and their micro/macroan-

giopathic and metabolic complications (neurological, ocular, cardiovascular, cognitive, neoplastic disorders) becoming an outright metabolic epidemic. Children and adolescents need to be convinced that not only drugs and alcohol are harmful given their dramatic short-term effects, but the abuse of sugar, salt and fats concealed in myriad foods advertised daily is also hazardous to health. In addition to schools, preventive education in television programmes for children and adolescents should be broadcast with the same commitment dedicated to the prevention of infectious diseases and cancer. This would radically limit diabetes-induced disability, amputations and deaths with an improvement in quality of life and reduced healthcare expenditure.

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