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The diabetic foot syndrome, diagnosis and consequences
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2002

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 7

Early polyneuropathy in diabetes: concurrent sensory and motor disturbances

J.W.G. Meijer, F. Lange, T.P. Links, J.H. van der Hoeven

Submitted.
Abstract

Introduction  Diabetic polyneuropathy (PNP) is supposed to be a primary disorder of sensory nerves. Hypoxic neuropathy has been held as important pathogenetic factor. Study hypothesis: (1) PNP starts before any sign of micro- or macroangiopathy is detectable, and (2) sensory and motor dysfunction occurs concurrently and not sequentially.

Methods  12 male patients (8 type 1, 4 type 2 diabetes; mean age 35.8 yrs SD 10.6), without forms of micro- or macroangiopathy, were studied by clinical and neurophysiological testing including invasive muscle fiber conduction velocity (I-MFCV) estimation.

Results  Sensory nerve conduction velocity (SNCV) of the sural nerve was abnormal in 6 subjects. I-MFCV of the tibialis anterior muscle showed abnormal results in 6 subjects (5 had also low SNCV).

Conclusion  Half of the subjects showed a combination of sensory and I-MFCV abnormalities, suggesting concurrent and not sequential motor and sensory involvement in early diabetic PNP, before micro- or macroangiopathy is detectable.
7.1 Introduction

Distal symmetric polyneuropathy (PNP) is the most common form of diabetic neuropathy in diabetes mellitus (DM), and is supposed to be primary a disorder of sensory nerves \(^1\). At an early stage of the disease, the disturbances are detectable by sensory nerve conduction studies, which have been taken as evidence for (sensory) PNP \(^2\). Later on, motor dysfunction becomes evident, manifesting with clinical force loss of distally located (leg) muscles \(^3\,^4\). Electromyography (EMG) may reveal chronic axonal loss, which is generally not detectable by (motor) nerve conduction studies, because axonal sprouting will compensate the loss of nerve fibers. Studies in diabetic patients with specialised EMG techniques such as macro EMG and single fiber EMG suggest a much earlier involvement of motor axons in diabetes \(^5\,^6\,^7\). However, the increase of motor unit area and fiber density are both the result of axonal sprouting and reinnervation, which is only secondary to muscle fiber denervation. This suggests an earlier, subclinical start of motor neuropathy, probably together with the evolution of sensory neuropathy. In a previous study invasive muscle fiber conduction velocity (MFCV) testing was shown capable to detect muscle fiber conduction slowing due to chronic and acute neurogenic lesions. Acute axonal loss resulted in a progressive slowing of MFCV, mainly resulting from muscle fiber atrophy \(^8\). Disturbances in the microvasculature supplying the nerve resulting in hypoxic neuropathy has been hold as important pathogenetic factor \(^9\). This would imply a relation between angiopathy and the appearance of PNP. In this pilot study we tested the hypothesis (1) that PNP starts at a subclinical level before any sign of micro- or macroangiopathy is detectable, and (2) that sensory and motor dysfunction in DM occur concurrently and not sequentially. We investigated a group of asymptomatic diabetic patients without clinical signs of PNP, nor signs of retinopathy, nephropathy or other forms of micro- or macroangiopathy. All patients were tested by a symptom and examination score for PNP, dynamometry, and electrodiagnostic studies including MFCV testing of the tibial anterior muscle.

7.2 Patients and Methods

Patients

12 male patients, (8 type 1 and 4 type 2 DM) were selected from the diabetes outpatient clinic of the University Hospital Groningen. Inclusion criteria: absence of known signs of neuropathy or retinopathy, normal clinical neurological examination, in combination with negative sores on quantitative sensory examination: Semmes Weinstein Monofilaments \(^10\) and Vibration Perception Threshold \(^11\) tests. The mean age was 39.9 yrs.
(SD 12.8), with a mean duration of DM of 10.0 yrs (SD 6.1). The mean HbA1c value was 7.7 (SD 1.3). HbA1c levels were relatively constant during the 18 months preceding the study. All were normoalbuminuric, normotensive and had no other forms of micro- or macroangiopathy. Additionally, 51 age matched healthy controls were investigated to get normal values for the MFCV determination in tibialis anterior muscle.

**Methods**
After inclusion, all subjects were tested by the Diabetic Neuropathy Symptom (DNS) score, the Diabetic Neuropathy Examination (DNE) score, dynamometry and electrodiagnostic studies.

**DNS-score**
The DNS-score is a symptom score with the following items: neuropathic pain, paraesthesia, numbness and unsteadiness in walking. Items are scored as present (1 point) or absent (0 points). The maximum score is 4 points. A positive score is defined as ≥ 1 point.

**DNE-score**
The DNE-score is a standardised physical examination score for diabetic polyneuropathy with 8 items tested on the right side, scored from 0 (no deficit) to 2 (severe deficit). The maximum score is 16 points. A positive score (suspected neuropathy) is defined as > 3 points.

**Dynamometry**
Hand-held dynamometry was performed according to a standardised protocol, in 10 proximal and distal arm and leg muscle groups on both sides. Tested muscle groups consisted of shoulder abductors, elbow flexors, elbow extensors, wrist extensors, hand grip (3 - point grip), hip flexors, hip abductors, knee extensors, knee flexors and foot extensors. All measurements were performed during isometric muscle contraction using the “break” technique, in which the resistance of the patient gradually is overcome.

**Electrodiagnostic studies**
The same investigator (JHvdH) performed the electrodiagnostic and force measurements. Nerve conduction studies were performed with standard surface stimulation and recording techniques using Nicolet Viking IIe and IV EMG equipment with standard filter settings. All measurements were performed after warming in hot water (38 °C) of forearm and lower legs during at least 15 minutes. Peak-peak amplitude values were used. Motor nerve conduction velocity (MNCV) was measured on the left forearm segment of the median nerve (thenar), and the left peroneal nerve (ext. dig. brevis and tibial anterior muscle). Minimal F-wave latencies were acquired.
from the same recording and distal stimulation points, from at least 8 tracings. F-wave conduction velocity (FCV) was calculated as described elsewhere. Sensory nerve conduction velocity (SNCV) was measured antidromically with ring electrodes placed around the thumb (median and radial nerve), middle finger (median nerve) and little finger (ulnar nerve) and stimulation at the wrist. Sural nerve was tested at both sides antidromically after stimulation lateral of the Achilles tendon, 10-12 cm proximal from the active electrode. The electrodiagnostic results were defined as abnormal when lying outside the 2SD border. Reference values from our own laboratory were used.

A nerve conduction sum (NCS) score, consisting of summated number of abnormal conduction velocity results (or complete absence of potentials) on the above-mentioned tests was calculated. Each abnormal test counted for 1 point, maximum score (only abnormal results) 12 points.

Invasive MFCV (I-MFCV) measurements were performed in the tibialis anterior muscle at rest by means of needle electrodes adapted from the method as described previously. In short, muscle fibers were stimulated in the distal part of the tibial anterior muscle by a small monopolair needle electrode (cathode) using a surface electrode as anode. Filter settings 500 Hz-10 kHz, stimulation 0.2 ms, 1-2 mA, stimulation frequency 1 Hz. The uptake electrode was placed proximally at a known distance (50-60 mm) by a small concentric needle electrode (see Figure 1).

Figure 1: Muscle Fiber Conduction Velocity measurement

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After optimal positioning action potentials, supposed to represent individual muscle fibers, were identified, and the resulting conduction velocities were calculated. As parameters the mean I-MFCV and the fastest/slowest ratio representing the scatter of conduction velocities were used. Concentric needle EMG was performed directly afterwards with the same uptake electrode at the same location.

Statistics
The statistical package SPSS-PC was used to compute the descriptive statistics. To test significance of differences between the study and reference groups and the correlation, the student T test and Spearman's correlation coefficient have been used. Statistical significance was accepted at a level of 5%.

7.3 Results

The individual patient results of the main parameters are shown in Table 1.

DNS- and DNE-score and dynamometry
Two out of 12 patients scored positive on the DNS-score, respectively 1 patient 1 point and 1 patient 2 points. There were no patients who scored more than 3 points on the DNE-score. The positive scores on the DNS- and DNE-score were related to sensory or autonomic function. Force values as measured with hand-held dynamometry, were within the normal range in all subjects, in proximal as well as in distal muscle groups.

Electrodiagnostic studies:
Table 1 shows some results of the individual patients. Median MNCV was abnormal in 2 subjects (subject 6 and 11). Amplitudes were all within the normal range. Peroneal MNCV of the tibialis anterior muscle was abnormal in 1 patient (subject 6), amplitudes were all within the normal range. F-waves of the median nerve were abnormal in 3 subjects (subject 6, 11 and 12), the peroneal nerve showed 1 abnormal F wave result (subject 6). Sensory testing showed abnormal SNCV or no responses at all in at least one nerve of the hand (median, radial or ulnar nerve) in 8 patients (1, 3, 6, 7, 8, 9, 11 and 12). The mean, median and fastest I-MFCV were normal in all patients, the slowest I-MFCV was abnormal in subject 12. In 6 patients the F/S ratio was abnormal, 5 of these patients also had abnormal sural nerve SNCV.
### Table 1: Patient Characteristics

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<th>duration DM (yrs)</th>
<th>HbA1c (%)</th>
<th>DNS &lt;1</th>
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<th>MNCV EDB CV &gt; 41</th>
<th>NCS &lt;1</th>
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**reference values (rv):**

- **sncv sural:** sensory nerve conduction velocity of the sural nerve
  - CV: 47.4 SD 3.6
- **mncv EDB:** motor nerve conduction velocity of the extensor digitorum brevis muscle
  - CV: 47.3 SD 3.0
- **MFCV:** muscle fiber conduction velocity of the tibialis anterior muscle
  - slowest: 2.6 SD 0.4
  - F/S ratio: 1.47 SD 0.2
- **CV:** conduction velocity
- **NCS:** nerve conduction sum score
As shown in Table 2, mean values of mean and fastest MFCV were not significantly different between patients and controls. There was a significant difference for the F/S ratio and slowest MFCV.

**Table 2: Results of I-MFCV measurements in tibialis anterior muscle**

<table>
<thead>
<tr>
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<th>patients</th>
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<td>I-MFCV ms⁻¹</td>
<td>3.17 (±0.40)</td>
<td>3.27 (±0.40)</td>
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<tr>
<td>F/S ratio</td>
<td>1.47 (±0.20)</td>
<td>1.89 (±0.46) *</td>
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<td>I-MFCV (fastest) ms⁻¹</td>
<td>3.78 (±0.49)</td>
<td>4.16 (±0.31)</td>
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<tr>
<td>I-MFCV (slowest) ms⁻¹</td>
<td>2.60 (±0.40)</td>
<td>2.32 (±0.57) *</td>
</tr>
</tbody>
</table>

* :significant difference (p<.05)

Needle EMG findings were abnormal in 1 patient (increase of MUP duration). Signs of denervation (fibrillations and positive waves) were not found in any of the patients.

Figure 2 shows the relation between the nerve conduction sum score and the SNCV of the left sural nerve (r -.97, p<.001), MNCV of the extensor digitorum brevis muscle (r -.67, p<.05) and the mean I-MFCV (r -.79, p<.01). Furthermore, the relation between SNCV of the left sural nerve and the mean I-MFCV is shown (r -.80, p<.01).

**Figure 2a: Relation of NCS-score with the SNCV of the left sural nerve**

r -.97, p<.001

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Figure 2b: Relation of NCS-score with the MNCV of the extensor digitorum brevis muscle

Figure 2c: Relation of NCS-score with the mean I-MFCV

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Figure 2d: Relation of the mean I-MFCV with the SNCV of the left sural nerve

$r = -.80, p < .01$
7.4 Discussion

We investigated a group of male diabetic patients without clinical signs of PNP, nor signs of retinopathy, nephropathy or other forms of micro- or macroangiopathy to study the sequence of changes in early distal symmetric polyneuropathy. The main findings were (1) half of the patients showed electrodiagnostic sensory nerve involvement before any sign of micro- or macroangiopathy was detectable, and (2) 5 out of 6 patients with sensory involvement had concurrent abnormalities on MFCV testing. This finding suggests combined sensory and motor involvement in early diabetic PNP.

The pathophysiology of PNP in DM is until now not completely clear. Hypoxic neuropathy, caused by disturbances in the microvasculature supplying the nerve, has been hold as important pathogenetic factor. This would imply a relation between angiopathy and the appearance of PNP. However, none of our patients showed signs of angiopathy. This suggests that PNP in these cases is the first detectable consequence of microangiopathy, or, alternatively, that PNP in DM is (partly) caused by other factors. Animal studies suggest a multifactorial cause, involving closely interrelated metabolic alterations occurring sequentially. Endoneurial ischaemia forms in this view only one of the elements in the pathways leading to PNP. The abnormalities in motor and sensory conduction and MFCV in our patients, without any sign of angiopathy, argues in favour of the second hypothesis.

Although five patients scored some positive items on the DNS- and DNE-score, none of them was known with clinical signs of PNP, and force values were within the normal range. There was no correlation between DNS- and DNE-scores and electrodiagnostic studies. This means that the abnormalities found by electrodiagnosis are mainly at subclinical level. The unimpaired force, as measured with dynamometry, points to normal motor function in our patient group as well.

Diabetic PNP is characterised by axonal loss, and secondary demyelination and remyelination. Loss of motor neurons causes denervation and muscle fiber atrophy. Collateral reinnervation and muscle fiber hypertrophy compensates denervation and preserves muscle strength despite of loss of up to 90% of the motor units. Conventional concentric needle EMG testing may reveal partial denervation as an early sign of motor axon loss. However, spontaneous muscle activity (fibrillations, positive sharp waves) are seldom found in, slight, slow progressive PNP. Qualitative motor unit action potential (MUAP) changes at visual inspection are difficult to interpret in
Studies with specialised EMG techniques such as macro EMG and single fiber EMG (sfEMG) suggests a much earlier involvement of motor axons in diabetes. The increase in motor unit area by macro EMG and the increase of fiber density as shown by sfEMG are the result of axonal sprouting and reinnervation, manifesting the reshaping of the motor unit. Using these techniques, a close relation between the degree of reinnervation and distal muscle strength was found in advanced neuropathy. However, such techniques are not capable in showing denervation of single muscle fibers. Increased jitter values as found with sfEMG point to instability of the neuromuscular junction. Although a highly sensitive method, increased jitter, as a measure of end-plate function, does not discriminate between dying back neuropathy and early reinnervation, and merely reflects dynamic changes in metabolic status. Invasive MFCV testing, on the contrary, is designed to detect abnormalities in muscle fiber conduction. This method was shown highly sensitive to detect muscle fiber conduction changes due to chronic neurogenic lesions. Axonal loss results in a progressive slowing of MFCV, which has been attributed to muscle fiber atrophy. Additionally, high conduction velocities indicate hypertrophic muscle fibers. Slow conducting fibers and the (related) increase of fast/slow (F/S) ratio, can therefore be used as marker for the presence of muscle fibers diameter changes. Our findings of an increased F/S-ratio in combination with the decrease of the slowest I-MFCV in the study group strongly suggests the presence of hypotrophic muscle fibers in the anterior tibialis muscle, however, without clear increase in fast conducting fibers. This indicates motor axon loss at a stage when compensatory motor unit reshaping is not yet present. In that respect invasive MFCV determination offers a highly sensitive method to detect early motor neuropathy.

In conclusion, we showed in clinically asymptomatic DM patients that (1) half of the subjects had sensory nerve involvement before any sign of micro- or macroangiopathy was detectable, and (2) that almost all patients with sensory involvement had abnormalities on MFCV testing, despite normal concentric needle EMG and normal force. This finding suggests concurrent sensory and motor involvement in early diabetic PNP.
7.5 References


