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Follow-up of advanced diabetic neuropathy Useful variables and possible pitfalls

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Abstract *Background* The course of advanced diabetic neuropathy (DN) is largely unknown. *Aim* To find variables allowing the follow-up of late stages of DN. *Methods* Thirty diabetic patients with DN were observed. Patients were examined at intervals of 6 months over a period of 2 years. The compound muscle action potentials (CMAPs) were recorded in extensor digitorum brevis (EDB) and flexor hallucis brevis (FHB) muscles. Clinical severity of DN, nerve conduction studies (NCS), quantitative sensory testing (QST) and heart rate variability (HRV) were evaluated. The data were compared with age- and sex-matched controls. *Results* All measures were sensitive to the detection of DN.

Significant deterioration during follow-up was exclusively found in CMAP analysis of the EDB ($p < 0.05$) and FHB muscles ($p < 0.03$). NCS, QST and HRV remained unchanged within the 2 years of observation. Coincidental changes might occur, if only two time points are chosen for follow-up. *Conclusion* Our results indicate that ongoing axonopathy predominates in advanced DN. Repeated testing helps to minimize the impact of coincidental or chance changes in DN follow-up studies.

Key words diabetic neuropathy · compound muscle action potential · nerve conduction velocity · quantitative sensory testing · heart rate variability

Introduction

Diabetes mellitus is one of the most common chronic disorders affecting over 100 million people worldwide [9]. The occurrence of peripheral diabetic neuropathy (DN) depends on the duration of diabetes [17] and its incidence is 60 % in diabetic patients [27]. DN is electrophysiologically characterized as a combined neuropathy with demyelination (slowing of nerve conduction velocities (NCV)) [26], prolonged distal latency (DL) [28] and axonopathy (reduction of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs)). Accordingly, electromyographic studies show neurogenic reorganization with axon re-sprouting countervailing fiber loss. Sensory

NCV is sensitive to the detection of early neuropathies [13], as is quantitative thermal sensory testing (QST) and heart rate variability (HRV); the latter concerns autonomic fiber involvement [2]. A combination of several neuro-physiological methods may be of importance, since different classes of nerve fibers could be inhomogeneously affected in DN. NCV mainly reflects large fiber function, QST tests thinly or unmyelinated sensory C- and A δ -fibers and heart rate variability assesses parasympathetic reflexes.

Unless the underlying pathophysiology is reversed, e.g. by pancreatic transplantation, DN should be steadily but slowly progressing. In particular for treatment studies, diagnostic variables have to allow assessment of therapeutic effects within a restricted amount of time. Clinical evaluation is subjective and does not nec-

essarily reflect further nerve damage and might therefore be inappropriate for sensitive follow-up. Interestingly, discrepancies between subjective clinical improvement and NCV have been reported [29]. Most arguments dealing with this problem refer to the underlying further deterioration of DN. The failure of nerve conduction studies (NCS) to detect therapy effects may be connected with continuing deterioration of nerve function. On the other hand, NCV may well be within the pathological range before clinical symptoms of DN occur, and further deterioration of NCV might require 10 years or longer [22].

The aim of this study was to analyse the course of late DN. Our patients were neither treated with any “specific” medication aimed to slow the progression of DN nor extensively treated with anti-diabetic medication. We chose this type of patient because they represent the most important patient group in neurological outpatient clinics. Deterioration of neuropathy in these patients should be paralleled by similar changes in nerve function tests. The identification of the most sensitive diagnostic test could help in defining surrogate markers for therapy effects in future trials. In order to achieve stable results we investigated the patients 5 times over a period of 2 years. Therefore we could exclude occasional or seasonal variations, which would otherwise be misinterpreted as deterioration or improvement of DN. Motor NCV were assessed, the CMAPs were recorded, thermal and vibratory thresholds were measured, heart rate variability was tested and the clinical severity of DN was analysed.

Materials and methods

■ Patients and controls

Thirty patients with signs of peripheral DN (17 men, 13 women) with a mean age of 52.4 ± 2.5 years were investigated. Fourteen patients suffered from insulin-dependent diabetes mellitus (IDDM), 16 patients from non-insulin dependent diabetes mellitus (NIDDM). The mean duration of diabetes was 204.4 ± 24 months at the entrance of the study. The investigations were performed over a period of 24 months. The patients were examined at the beginning and thereafter in intervals of 6 months. The clinical severity of diabetic neuropathy was analysed by medical history and neuropathy impairment score (NIS) [7]. Diabetes control was assessed at the end of the study and was found to be suboptimal with a mean HbA1C of $8.1 \pm 0.34\%$.

For normal values, 34 age- and sex-matched healthy controls were tested (19 male, 15 female, mean age 50.6 ± 2.2 years). Control subjects were investigated once at the beginning of our follow-up study. We did not perform re-testing in the normal subjects group since there was no reason to suspect changes in nerve function.

Informed consent was obtained from all participants according to the declaration of Helsinki and the study was approved by the local ethics committee. All investigations were carried out in our temperature (23°C) and humidity (50% relative humidity) controlled laboratory. The time for acclimatization for all subjects was at least 1 hour before starting the study.

■ Nerve conduction studies

Nerve conduction studies were performed using standard surface recording techniques. Motor NCV and peak to peak CMAP of the peroneal and tibial nerves were assessed. Sensory nerve conduction velocity was not analysed systematically since only a minority of our patients ($n=7$, assessed orthodromically) had measurable sensory nerve potentials in the lower extremities.

■ Quantitative sensory testing (QST)

Vibratory, cold and warm perception thresholds were measured. Cold and warm perception thresholds were determined using a thermotester (Somedic, Sweden). A 5 cm^2 peltier element (thermode) was placed on the dorsum of the right foot. The method of limits [12] was employed to determine thermal thresholds in 6 consecutive measurements for warm and cold perception. In order to reduce variability, the first 2 measurements were excluded and the mean value of the remaining 4 was calculated.

Vibratory thresholds were assessed at the right medial ankle by an electromagnetic Vibrometer (Somedic, Sweden) with a stimulus frequency of 100 Hz. Vibration perception thresholds and vibration disappearance thresholds were identified [10] and the vibratory threshold (VT) was calculated as the statistical mean of 3 consecutive measurements [12].

■ Heart rate variability

Cardiac autonomic neuropathy (CAN) was assessed by evaluation of heart rate variability (HRV). HRV was recorded employing a Prosci-Card®-analyser (ProScience, MediSyst, Linden, Germany). Seven statistical values were obtained during rest, deep respiration and Valsalva maneuver while all subjects were resting in a comfortable seated position [8]. CAN was diagnosed if the results of 3 or more of these measures exceeded pre-determined normal values [31]. For follow-up statistics the variation coefficient to deep inspiration (VC) was selected. This has been shown to be sensitive and hardly influenced by the heart rate itself.

■ Statistics

Statistics were calculated using a SPSS (SPSS 10.1 for Windows, Chicago, Illinois, USA) software package. In order to identify significant differences within 2 years of follow up, a MANOVA for repeated measurements was performed with 5 consecutive measurements during follow up. Since sphericity could not be assumed in all data sets, Greenhouse-Geisser correction was employed.

Additionally, t-tests were used to fix differences between single measures of these follow-up investigations, in which MANOVA was insignificant. Values which were found to be insignificant in time series analysis but showed significance in single t-tests were classified as coincidentally significant.

All values are given as mean $\pm$ SEM. Statistical significance was considered at $p < 0.05$.

■ Missing values

The number of subjects included in the different measurements varies owing to the MANOVA requirement for complete data sets. This implies that the whole follow-up measurement was discarded if there was one missing value (e.g. heart rate variability could not be assessed because of cardiac arrhythmia).

Results

Clinical severity of DN

Clinical severity of diabetic neuropathy was analysed by medical history and neuropathy impairment score (NIS) [7]. The patients could be classified as follows: NIS 1 point: 6 patients, NIS 2 points: 17 patients, NIS 3 points: 7 patients. Despite the poor glycemic control, there was no clinical worsening: NIS scores, sensory disturbances (extension of hypesthesia and hypalgesia) and motor symptoms remained stable within our observation period.

Twenty-one patients suffered from neuropathic pain, which was described as dysesthesia or lancinating pain and 4 patients reported restless leg syndrome.

Nerve conduction studies

Motor NCV of the peroneal nerve within the patient group was significantly slowed as compared with controls ($p < 0.001$). Time series analysis revealed no further

deterioration within 2 years ($F = 0.521$, ns) (Fig. 1A) and no difference between patients with IDDM and NIDDM ($F = 1.114$, ns).

Tibial motor NCV also was significantly different between patients and controls ($p < 0.001$). As with peroneal NCV, time course analysis neither detected any significant changes within the follow-up period ($F = 1.806$, ns) (Fig. 1C) nor between IDDM and NIDDM patients ($F = 1.39$, ns).

CMAPs after peroneal and tibial motor stimulation were reduced compared with recordings in normal subjects (peroneal CMAP: $p < 0.001$, tibial CMAP: $p < 0.001$). By contrast to NCV studies, within 2 years a significant further and steady decline in CMAP amplitudes in the extensor digitorum brevis muscle ($F = 3.129$, $p < 0.05$) (Fig. 1B) as well as in the flexor hallucis brevis muscle ($F = 3.56$, $p < 0.03$) (Fig. 1D) could be detected. However, CMAP studies did not show a significant contrast between patients suffering from IDDM and patients diagnosed with NIDDM (peroneal CMAP: $F = 1.752$, ns; tibial CMAP: $F = 0.161$, ns).

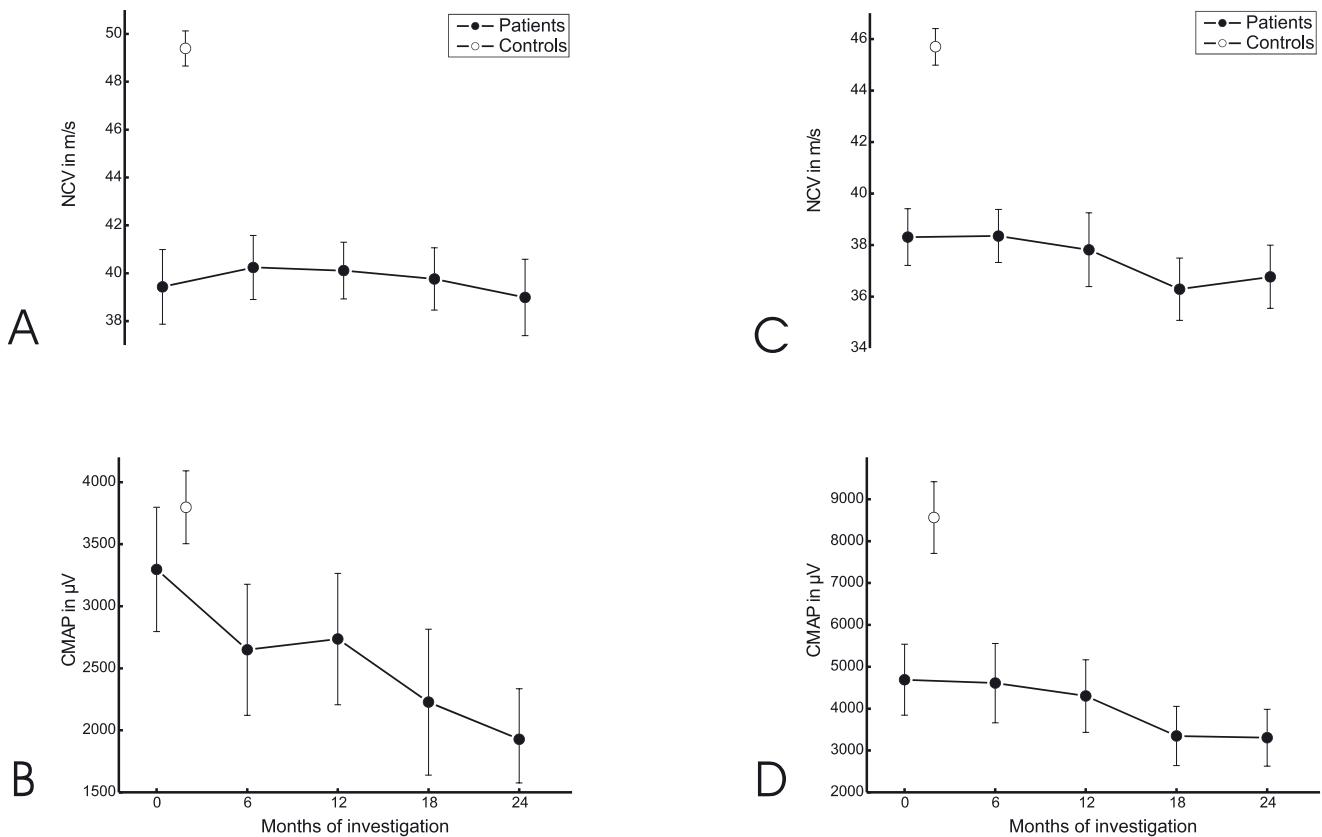


Fig. 1 Plotted are the variations in time of the peroneal (A) and tibial (C) NCV and the corresponding CMAP (Extensor digitorum brevis (EDB) muscle: B and Flexor hallucis brevis (FHB) muscle: D) within our patient series. Neither peroneal nor tibial NCV significantly changed within two years of follow-up. In contrast, a significant steady deterioration of the CMAP of the peroneal supplied EDB ($p < 0.05$, MANOVA) and the tibial supplied FHB ($p < 0.03$, MANOVA) can be observed. Filled circles represent DN patients, open circles control subjects

■ Quantitative sensory testing (QST)

Cold and warm perception thresholds (PT) were significantly decreased or increased, respectively in patients compared with controls (ColdPT: $p < 0.001$, WarmPT: $p < 0.001$), but differences between IDDM and NIDDM patients were not found (ColdPT: $F = 0.677$, ns; WarmPT: $F = 0.846$, ns). Standard deviations were high in the patients and therefore no significant deterioration could be found during the following 2 years (ColdPT: $F = 0.543$, ns, WarmPT: $F = 0.879$, ns) (Fig. 2). This also applies to VT which was significantly increased in the patients ($p < 0.001$); there was no difference between different patient groups recorded ($F = 0.986$, ns) and no further change could be detected ($F = 0.709$, ns) (Fig. 3).

■ Heart rate variability (HRV)

CAN was diagnosed in 10 patients: 5 patients suffered from IDDM and 5 patients were diagnosed with NIDDM. This number was unchanged during the follow-up. Accordingly, VC was reduced in patients ($p < 0.01$) and repeated testing revealed no further damage ($F = 0.509$, ns).

■ Assessment of “coincidentally significant” changes by t-tests

Those measures, which were insignificant in the time series analysis, were reassessed by comparing each single investigation. Using this simplistic approach, significant variations in tibial NCV, VC, ColdPT and VT can be de-

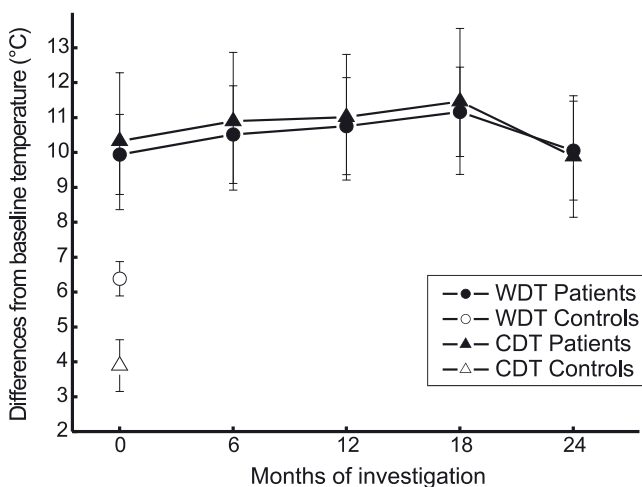


Fig. 2 Plotted are the differences from baseline temperature of warm (circles, WDT) and cold (triangles, CDT) perception thresholds over time. No significant changes within 2 years were recorded. Filled circles represent DN patients, open circles control subjects

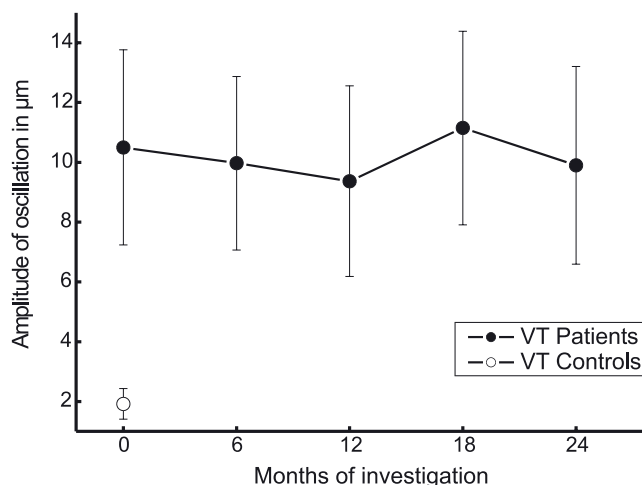


Fig. 3 Plotted is the time dependency of the vibration thresholds at the right internal malleolus in DN patients. No significant deterioration was observed. Filled circles represent DN patients, open circles control subjects

tested. We regard these results as incidental since the time series analysis was insignificant in these variables. Nevertheless, these coincidentally significant changes represent a source of error in follow-up studies.

Discussion

Diabetic neuropathy is slowly progressive. In the present study, we employed several neurophysiological investigations assessing different classes of nerve fibers. We found the CMAPs to be the only variable deteriorating within a 2 year observation period while the patients reported no further progression of their symptoms and the neuropathy impairment score and the extension of sensory and motor disturbances remained stable. This means that peripheral axon loss is the predominant pathological mechanism in advanced DN. Neither motor NCV, nor HRV, nor QST were sensitive in detecting further changes in DN. These measures might have become too severely deteriorated to be useful in follow-up studies in advanced DN.

The progression of DN mostly shows a gradual worsening but other courses do occur. Neuropathic symptoms in diabetes may be caused by axonopathy (reduced CMAP) or demyelination (slowed NCV or prolonged distal latency recordings, DL). Eventually axonopathy and impairment of the myelin sheath result in progressive fiber-loss and dying-back of the longest fibers innervating distal limbs (centripetal pattern). There is controversial debate about the major component of DN and about the sensitivity of assessment of either axonopathy or demyelination in diagnosis and follow-up [1]. Patients with early diabetes are usually free of neuropathic symptoms, but may present with slowing in

sensory NCV as an early symptom [13]. Further, NCV is useful in this stage of DN, as a good test-retest reliability has been proved [30]. This finding supports dysfunction of the myelin sheath to be one major pathomechanism of DN [11]. However, sensory and motor NCVs deteriorate very slowly. The latency for the detection of progression in NCV slowing has even been prolonged in studies of advanced DN. Almost 10 years may be necessary to detect further slowing of NCV in treated diabetics [22]. This time period would be unsuitable for the detection of therapy effects.

Changes in distal nerves can provide the first evidence of DN [23], while diabetic patients complaining of neuropathic symptoms may have normal routine NCS. In these patients, low sensory nerve action potentials (SNAPs) can be recorded by near-nerve needle techniques [19, 20], e.g. from interdigital nerves (IDN) [21]. This underlines the importance of axon loss (axonopathy) in DN and argues in favor of additional analysis of the action potentials after nerve stimulation. Electromyography may also be sensitive for the detection of axon loss in diabetes [2]. However, EMG changes are hard to quantify for follow-up purposes. Measurement of CMAP with surface electrodes is more practical. Despite some variability, the results of our study emphasize the possible predominance of axonopathy and the deterioration of CMAP as one major surrogate of late DN progression.

DN is a systemic disease and the majority of our patients were moderately affected (NIS: 2 points). The absence of clinical symptoms does not exclude changes in the upper extremities. However, in our study we focused on the lower extremities, where neuropathic symptoms were pronounced in order to find suitable follow-up variables representing clinically important nerve damage. We abandoned a systematic assessment of sensory NCV (SNCV), although this variable is known to be sensitive in detecting DN. However, in advanced DN SNAPs are often absent owing to degeneration of sensory fibers [13]. Indeed, we were able to record SNAPs in only 7 patients. That is, SNCV is sensitive in early DN but less suitable in follow-up of advanced DN.

QST is a routine test for evaluation of small-fiber dysfunction [24], which is sensitive and reproducible [25]. The latter applies in particular to healthy subjects. In DN, despite the use of QST for long term follow-up [5], there might be a high variability of QST results in neuropathy patients. Test – retest variation in VT was shown to be larger than in NCV [18]. Despite assessing similar fiber classes, there was a weak correlation between VT and NCV in DN [4]. However, levels of variance of VT (approximately 8%) [30] are even lower than of thermal thresholds (approximately 30%) [3]. QST is known to be sensitive in the detection of small-fiber damage in early stages of DN. Since sensory fibers are easily damaged by hyperglycemia, their impairment may be advanced even

in recently diagnosed DN. Because our patients suffered from advanced DN, vibratory and thermal threshold were already at the diagnostic limit at the entrance to our study. This is why no further deterioration of thermal and vibratory thresholds could be detected. These findings corroborate our finding that QST is less suitable for following up advanced DN.

Autonomic neuropathy emerges with increased duration of diabetes and poor glycemic control. Even in early stages of DN single parameters of HRV may be impaired [2]. Whether or not HRV may be useful for follow-up of DN has been a matter of debate for a long time. On the one hand, one previous study needed 9 years of observation to detect further HRV deterioration [15]. This would be in accordance with our results. On the other hand, a recent study suggested a significant deterioration of HRV within 2 years [14]. Vagal nerve function, which is reflected by HRV, must be assessed indirectly. Blood pressure, the heart rate itself and even cardiovascular changes might interfere with heart rate variation at different time points. Furthermore, HRV depends on the patients' active cooperation, e.g. deep breathing. These points explain the extensive variation of HRV and make this test less appropriate for follow-up studies [16].

We used repeated re-testing in our investigation to exclude or minimize seasonal, investigator, patient-related or chance variability. Our additional statistical analysis shows that obviously consecutive measurements have to be performed in order to avoid flaws. There would have been several "coincidentally significant" changes if just 2 time points had been chosen for evaluation of follow-up. The analysis of the whole series at all intervals eliminates such flaws since significant deterioration must include all measurements. We strongly believe that poor internal control is one of the major sources of the considerable variability of follow-up studies [6]. As discussed above, most parameters of nerve function remained unchanged for 2 years. This time period is further extended, if the patients are intensively treated. NCV may deteriorate during conventional therapy [34]. However, if intensified diabetes treatment becomes the standard, DN may occur later and progress more slowly. Because of this development, the demand for more sensitive tools to reliably analyse nerve damage in any stage of DN will increase. CMAP may be an objective marker of deterioration detecting changes in advanced DN within a reasonable time. This should help in planning future studies.

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