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The INFIR Cohort Study: assessment of sensory and motor neuropathy in leprosy at baseline

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Summary

Aim: To compare different method(s) to detect peripheral neuropathy in leprosy and to study the validity of the monofilament test (MF) and the voluntary muscle test (VMT) as standard tests of nerve function.

Design: A multi-centre cohort study of 303 multibacillary (MB) leprosy patients.

Methods: Newly registered MB patients requiring a full course of MDT were recruited in two leprosy outpatient clinics in North India. Controls were people without leprosy or neurological conditions, attending the dermatological outpatient departments of the same clinics. Nerve function was evaluated electrophysiologically using standard parameters for sensory and motor nerve conduction (NC) testing, warm and cold detection thresholds (W/CDT), vibration perception thresholds, dynamometry, MF and VMT. The latter two defined the outcomes of sensory and motor impairment.

Results: 115 patients had nerve damage or a reaction of recent onset at diagnosis. Sensory and motor amplitudes and WDTs were the most frequently abnormal. Among

the nerves tested, the sural and posterior tibial were the most frequently impaired. In the ulnar nerve, sensory latencies were abnormal in 25% of subjects; amplitudes in 40%. Ulnar above-elbow motor conduction velocities were abnormal in 39% and amplitudes 32%. WDTs were much more frequently affected than CDTs in all nerves tested. The thresholds of all test parameters differed significantly between controls and patients, while only some differed between patients with and without reaction. Good concordance was observed between MF results and sensory latencies and velocities (direct concordance 80% for the ulnar). However, a proportion of nerves with abnormal MF results tested normal on one or more of the other tests or *vice versa*. Concordance between VMT and motor conduction velocities was good for the ulnar nerve, but for the median and peroneal nerves, the proportion impaired by VMT out of those with abnormal motor conduction was very low.

Conclusions: Concordance between monofilaments and other sensory function test results was good, supporting the validity of the monofilaments as standard screening test of sensory function. Concordance between VMT results and motor nerve conduction was good for the ulnar nerve, but very few median and peroneal nerves with abnormal conduction had an abnormal VMT. A more sensitive manual motor test may be needed for these nerves. Of the nerve assessment tests conducted, NC amplitudes and warm sensation were the most frequently affected. Therefore, nerve conduction studies and WDT measurements appear to be most promising tests for early detection of leprosy neuropathy. The pattern of concordance between tactile and thermal sensory impairment failed to support the hypothesis that small fibre neuropathy always precedes large fibre damage. Warm sensation was more frequently affected than cold sensation. This could indicate that unmyelinated C fibres are more frequently affected than small myelinated A δ fibres.

Introduction

Leprosy is known for the neuropathy it causes. Different methods have been used to detect leprosy-related nerve function impairment (NFI).¹⁻⁵ More sophisticated methods for assessing nerve function such as vibrometry,⁶ laser Doppler flowmetry^{7,8} and thermal threshold testing⁹ have been shown to detect different modalities of leprosy neuropathy. However, it is not known which of these testing methods would detect the neuropathy earliest. To determine this, the methods needed to be compared in a carefully planned prospective study.

Many nerve conduction (NC) studies of subjects with leprosy have been reported, particularly in the 1960s and 1970s. Among the earliest were those of Hackett *et al.*,¹⁰ Magora *et al.*,¹¹ Verghese *et al.*,¹² Antia *et al.*,¹³ McLeod *et al.*,¹⁴ and Singh *et al.*¹⁵ With the exception of the studies of Magora *et al.* and Samant *et al.*,¹⁶ all these studies were cross-sectional in nature. The great majority of the studies were small and often a limited number of nerves was studied, e.g. only ulnar nerves in the study of Hackett *et al.*, the radial cutaneous nerve by Antia *et al.*,¹⁷ the ulnar and median nerves by Verghese and colleagues or single-sided nerves, as in the more recent study of Brown *et al.*,⁴ Samant *et al.* did not find parameters in NC studies that helped predict reactions.¹⁸ However, this study had a small sample size, so associations may have been present, but not statistically significant. Generally, investigators concluded that nerve conduction studies were very useful and could potentially detect pre-clinical neuropathy.

Quantitative sensory testing has opened up new possibilities for the study of sensory neuropathy.^{19,20} The most commonly used methods are thermal testing and testing of vibration sense. Thermal testing assesses small, unmyelinated C-fibres that mediate warm sensation and small unmyelinated and myelinated A δ fibres mediating cold sensation.²¹ Vibration 'sense' is mediated by large afferent A $\alpha\beta$ fibres.²² The sensory receptor most sensitive to vibration stimuli in the glabrous skin is the Pacinian corpuscle.²²⁻²⁴ Dyck *et al.* introduced automated electronic testing of thermal and vibration perception thresholds in 1978.²⁰ They used a two-alternative forced-choice algorithm to determine the perception thresholds. Systems have been refined and are now much easier to use. They have been shown to be a sensitive measure of peripheral sensory function in toxic neuropathies,²⁵ multiple sclerosis²⁶ and diabetes.²⁷⁻³¹ and are widely used in the clinical management of people with diabetes.^{21,28,31-36} These newer techniques hold promise for the study of neuropathy in leprosy, since there is evidence that small, particularly unmyelinated fibres may be affected first.³⁷⁻³⁹ Discrimination of warm and cold has been used extensively as a sensory test in leprosy. However, testing with warm and cold test tubes was cumbersome and the results only qualitative.^{4,40-45} Electronic thermal testing has been reported, but the study was cross-sectional and detailed results were not presented.⁹ Vibrometry has been shown to be useful in several studies on leprosy, but not necessarily more so than testing with monofilaments. Hammond and Klenerman reported several studies conducted in India, in which they found vibration thresholds measured with a biosthesiometer useful for predicting the risk of plantar ulcers,⁶ risk of tarsal disintegration,⁴⁶ and for diagnosing sensory impairment in skin lesions.⁴⁷ They showed that vibration sense was affected in 90% of feet at risk of ulceration. Similar sensitivity was found for abnormal monofilament thresholds. Feenstra *et al.*, also investigating risk factors for plantar ulceration, concluded that 'vibrometry was . . . no better than graded filaments . . . in identifying those at risk'.⁴⁸

Despite several recent major studies on the epidemiology of neuropathy in leprosy, many questions remain as yet unanswered. This is partly because much of the current knowledge of neuropathy in leprosy reactions has come from cross-sectional studies. Little is known about the longitudinal changes in neurological parameters over time. We do not know which test of nerve function, is the most sensitive to detect early nerve function impairment and which is the most dynamic in reflecting the ongoing neuropathogenic processes relating to outcome events and/or therapy. Nor do we know how well tests of touch sensation, such as the monofilaments and the ballpoint test, reflect the underlying neuropathy. A recent randomized trial failed to show a benefit from detecting sensory impairment with monofilaments before the ballpoint test became abnormal.⁴⁹ However, does monofilament testing reflect well the changes in nerve function during steroid treatment? Can treatment outcome be predicted on the basis of a particular test or combination of tests? Answers to these and other questions may point to better methods to prevent and treat neuropathy in leprosy.

We have investigated the detection and pathogenesis of neuropathy in leprosy in a large prospective study. The current report describes the results of neurological examination of the patients in this cohort at registration, specifically looking at 1) the sensitivity of the different tests to detect peripheral neuropathy in leprosy and 2) the validity of the monofilament test (MF) and the voluntary muscle test (VMT) as standard tests of nerve function. Results of the prospective part of the study will be reported elsewhere.

Materials and methods

Details of the methods have been given in a parallel publication; only a brief summary will be given here.⁵⁰

DESIGN

This was a cohort study of newly-registered MB patients. The patients were then followed up monthly for 1 year and every 2nd month during the 2nd year.

STUDY POPULATION

The study population included newly registered multibacillary leprosy patients requiring a full course of MDT.

STUDY SUBJECTS

All newly diagnosed patients who were being registered for MDT and who were smear positive and/or had six or more skin lesions and/or had two or more nerve trunks involved were eligible for inclusion. Patients who had a reaction or sensory or motor impairment at diagnosis were not excluded from the study, but were given steroid treatment (or other anti-inflammatory treatment as appropriate). Control subjects were people without leprosy or neurological conditions, attending the dermatological outpatient departments of the same clinics.

OUTCOME EVENTS

The following are counted as outcome events: neuritis, silent neuropathy (SN), type 1 or reversal reaction (T1R), erythema nodosum leprosum (ENL or T2R), sensory impairment (SI), motor impairment (MI). The definitions are given in the Appendix.

OUTCOME MEASURES

- Association between nerve function test results and outcome events.
- Median or mean values of test parameters, as appropriate.
- Percentage of patients testing positive for a given measure or marker.
- Odds ratio of a given measure adjusted for the effect of other measures that have a significant influence on the outcome.
- Early detection of sensory or motor impairment.

The sensitivity and specificity of each test compared with clinically significant NFI diagnosed with MF or VMT.

GENERAL EXAMINATION AT INTAKE

A standardized history using a checklist was taken from all patients admitted to the study. A systematic physical and neurological examination was done, giving particular attention was given to signs and symptoms of type 1 reactions, ENL and peripheral neuropathy.

TREATMENT REGIMEN

All patients were put on WHO multidrug therapy as described before.⁵⁰

NERVE FUNCTION ASSESSMENT (NFA)

The study employed a number of tests of nerve function that are not routinely used in the examination of people affected by leprosy. The outcome events motor and sensory impairment were defined on the basis of an abnormal VMT or monofilament test result, because these are standard tests that are widely used. NFA was done using the following methods.

Motor nerve function

Voluntary muscle testing (VMT) using the 0–5 modified MRC scale.⁵⁰

Grip dynamometry, key pinch and pulp-to-pulp pinch testing The dynamometer was made of a sphygmomanometer cuff inserted in a cylindrical cotton cover and inflated to a baseline pressure of 20 mmHg. Pinch strength was measured in a similar way using a neonatal sphygmomanometer cuff.⁵

Motor nerve conduction measurements (MNC) Compound muscle action potentials (CMAP) parameters were measured on three nerves bilaterally in three nerves following stimulation at standard distal and proximal sites: ulnar (wrist and above-elbow; abductor digiti minimi muscle), median (wrist and elbow; abductor pollicis brevis muscle) and peroneal (ankle and fibular head; extensor digitorum brevis muscle), using Neurocare 2000 EMG machines (BioTech Ltd, Mumbai). The Windows-driven software stores the CMAP traces in a database for future reference. The measured values for latency, amplitude and conduction velocity were stored in a separate Access database. Skin temperatures were measured electronically at both wrists and ankles and the measured latencies and velocities normalized for a temperature of 33°C at the time of analysis using standard formulae.⁵¹

Sensory nerve function

Sensory testing was done using a standard set of coloured Semmes–Weinstein monofilaments (MF)2 The monofilaments used were 200 mg, 2 g, 4 g, 10 g and 300 g. Normal reference values were 200 mg for the hand and 2 g for the foot (excluding the heel).⁵² The test sites and scoring methods are given in a previous publication.⁵⁰

Sensory nerve conduction measurements (SNC) Antidromic sensory action potential (SAP) parameters were measured bilaterally on 4 nerves (radial cutaneous, ulnar, median and sural at a fixed stimulation-recording distance of 14 cm) using the same equipment and temperature correction procedure as described under MNC.

Vibration perception threshold (VPT) testing VPTs were testing with a Vibrameter II (Somedic, Sweden). The instrument provides application force-controlled measurements of the VPTs in microns of skin displacement, using an algorithm of limits (slowly increasing vibration amplitude, until the person tested indicates that (s)he can feel the vibration. The test sites were the thenar and hypothenar eminences (soft tissue), for testing the median and ulnar nerve, respectively, the dorsal first webspace for the radial cutaneous nerve, the plantar pulp

of the big toe (posterior tibial) and the mid-lateral border of the foot (sural). All tests were done bilaterally. Details of the testing procedure will be published elsewhere.

Thermal threshold testing Thermal thresholds were evaluated with a Thermal Sensory Analyzer (TSA II; Medoc, Israel). Warm detection thresholds (WDT) and cold detection thresholds (CDT) were recorded relative to a baseline thermode temperature of 32°C. A thermode with a surface of 30 × 40 mm was used. The algorithm used for determining the threshold was the 'method of levels'.⁵³ The test sites were the same as for vibrometry, described above. Details of the testing procedure will be published elsewhere.

ANALYSIS OF RESULTS

The thresholds for impairment of NC, VPT, WDT and CDT are based on the normative studies done as part of this project and which will be reported in separate publications. From these, age and sex-group-specific normal thresholds were calculated as the 97.5th percentile of the log-transformed data. Temperature-corrected latencies and nerve conduction velocities were used for analysis.⁵¹ Each measured nerve function test value in individual patients was then compared with the appropriate age, sex and centre-specific normal threshold to determine whether the modality was impaired or not. Cases with an outcome were matched for leprosy type, bacteriological index, age and sex, although matching on all four variables was not always possible.

The significance of associations between outcome and predictor variables was tested using the Chi-squared or Fisher's exact test. Differences between proportions were tested with the *z*-test for differences between proportions. Differences between medians were tested with the Kruskal-Wallis test for unpaired or the Wilcoxon signed-rank test for paired comparisons.⁵⁴ Comparisons between the performance of the new tests and the reference tests (MF and VMT) are presented as two-by-two tables. Each top left hand cell corresponds to the co-positivity ('positive concordance') and each lower right hand cell to co-negativity ('negative concordance') of the new test and the reference test.⁵⁵ The term 'concordance' is used to describe the direct agreement between the results of two tests in terms of 'impaired' and 'not impaired'. Analyses were performed using Stata for Windows software, vs. 7 and 8.

ETHICAL CONSIDERATIONS

Written consent was obtained from individual study subjects before inclusion in the study, using a standard consent form. No financial incentives were given to participants. Further details are available in a previous publication.⁵⁰

Results

A total of 303 subjects were enrolled in the study. The mean age was 32.8 years (range 12–60). The sex and age distribution of the cohort are presented in Table 1. Altogether 115 subjects had a reaction or NFI event at registration. For the results reported below, the number of tests was not always the same for each instrument, because of occasional equipment failure or occasional failure to record the results.

The frequency of sensory and motor impairment detected by the various tests used is shown in Table 2. The most frequently affected were SAP and CMAP amplitudes and WDTs. Interestingly, only in the above-elbow measurements of the ulnar nerve, were CMAP latencies and velocities more frequently affected than amplitudes. A sensory conduction block (no measurable latency or amplitude) was observed in a substantial proportion of nerves (from 10% in the left median nerve to 46% for the left sural nerve). Pooling results for right and left for nerves where a response was recorded, ulnar sensory latency and amplitude were abnormal in 60/452 (13%) and 139/452 (31%) of subjects (data not shown). In the case of motor conduction, total conduction block was much less frequent (0.4–6.6%). Ulnar motor latency, conduction velocity and above-elbow amplitudes were abnormal in 177/511 (35%), 196/511 (38%) and 157/511 (31%), respectively. A large discrepancy was found between the frequency of motor impairment detected by VMT and MNC. This was particularly pronounced in the median and peroneal nerves. Overall, on the sensory tests, the sural and posterior tibial nerves were the most frequently impaired. WDTs were affected as least twice as often as CDTs in the ulnar and median nerves. This difference was less pronounced on the lower limb. If non-conducting nerves were included, SAP amplitudes were significantly more often abnormal than WDT (e.g. 43% versus 19% for the right ulnar, $P < 0.0001$), while, except in the right ulnar nerve, the latter was significantly more often affected than the monofilament test (Table 2). It is noteworthy that 119/522 ulnar nerves (23%) had impairment of one or more MNC parameters, while SNC was normal (data not shown). Out of these 119, a further 22 had an abnormal WDT and/or CDT. When comparing VMT and MF results, 21/606 ulnar nerves (3.5%) had an abnormal motor function, while sensation was normal.

Table 3 compares the results of nerve conduction testing, WDT, CDT, VPT and dynamometry of the ulnar nerve, between controls, patients with and patients without reaction at the time of registration. For all tests, the difference between controls and patients was highly statistically significant. Significant differences were observed also between reaction and non-reaction patients in SAP distal latency and velocity, in CMAP latencies and amplitudes at the wrist, above-elbow CMAP amplitudes, and in VPTs. Differences in median WDT and CDT were significant between the controls and non-reaction patients, but the magnitude of the differences was very small. The mean strength in each of the dynamometry parameters recorded (grip, key pinch and pulp-to-pulp pinch) differed significantly between patients with and without a reaction.

Table 1. Characteristics of the subjects in the INFIR Cohort Study ($n = 303$) at the time of registration

Variable	Frequency	Percentage
<i>Sex</i>		
Men	220	72.6
Women	83	27.4
<i>Age group</i>		
12–20	56	18.5
21–30	97	32.0
31–40	71	23.4
41–50	61	20.1
>50	18	6.0

Table 2. Number and percentage of nerves scoring impaired, compared to age and sex-specific normal thresholds, on the various nerve function tests used in the INFIR Cohort Study at the time of registration ($n = 303$, unless stated otherwise)

Test*	Ulnar		Median		Radial cutaneous		Sural		Peroneal		Posterior tibial	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left, $n = (302)$
MF	44 (14.5)**	34 (11.2)	22 (7.3)	18 (5.9)	20 (6.6)	19 (6.3)	82 (27.1)	91 (30.0)			90 (29.7)	91 (30.0)
VMT	28 (9.2)	33 (10.9)	3 (0.99)	2 (0.66)					2 (0.66)	2 (0.66)		
SNC	$(n = 263)$		$(n = 263)$		$(n = 262)$	$(n = 261)$	$(n = 259)$					
No conduction	37 (14.1)	37 (14.1)	32 (12.2)	26 (9.9)	51 (19.5)	52 (19.9)	115 (44.4)	119 (46.0)				
Latency (ms)	70 (26.6)	64 (24.3)	59 (22.4)	51 (19.4)	91 (34.7)	86 (33.0)	127 (49.0)	127 (49.0)				
Amplitude (μ V)	114 (43.4)	99 (37.6)	100 (38.0)	91 (34.6)	158 (60.3)	140 (53.6)	166 (64.1)	172 (66.4)				
Velocity (m/s)	69 (26.2)	64 (24.3)	58 (22.1)	51 (19.4)	91 (34.7)	86 (33.0)	127 (49.0)	127 (49.0)				
MNC	$(n = 263)$		$(n = 262)$						$(n = 260)$	$(n = 259)$		
<i>Wrist</i>									<i>Ankle</i>			
No conduction	4 (1.5)	5 (1.9)	2 (0.8)	1 (0.4)					11 (4.2)	17 (6.6)		
Latency (ms)	42 (16.0)	36 (13.7)	23 (8.8)	20 (7.6)					34 (13.1)	40 (15.4)		
Amplitude (mV)	64 (24.3)	55 (20.9)	64 (24.4)	65 (24.8)					85 (32.7)	93 (35.9)		
<i>Elbow</i>									$(n = 256)$			
No conduction	4 (1.5)	5 (1.9)	1 (0.39)	1 (0.38)					<i>Fibula</i>			
Latency (ms)	98 (37.4)	88 (34.1)	48 (18.5)	33 (12.6)					12 (4.7)	13 (5.1)		
Amplitude (mV)	91 (34.7)	75 (29.1)	69 (26.6)	70 (26.8)					44 (17.2)	37 (14.5)		
Velocity (m/s)	110 (42.0)	95 (36.8)	46 (17.8)	41 (15.7)					87 (34.0)	90 (35.3)		
WDT ($n = 297$)	57 (19.2)	68 (22.9)	58 (19.5)	80 (26.9)	$(n = 296)$	$(n = 295)$	151 (51.2)	159 (53.9)			$(n = 293)$	$(n = 295)$
CDT ($n = 297$)	25 (8.4)	35 (11.8)	31 (10.5)	38 (12.8)	120 (40.5)	109 (37.1)	123 (41.7)	137 (46.4)			142 (48.5)	153 (51.9)
VPT	55 (18.2)	48 (15.8)	52 (17.2)	53 (17.6)	88 (29.7)	81 (27.7)	91 (30.0)	92 (30.7)			109 (37.2)	106 (36.1)
					66 (21.8)	62 (20.6)					$(n = 301)$	$(n = 299)$
											100 (33.2)	88 (29.4)

* MF = monofilament test, VMT = voluntary muscle test, MNC = sensory nerve conduction, WDT = warm detection threshold, CDT = cold detection threshold, VPT = vibration perception threshold.

** Number (%).

Table 3. Results (medians) of nerve conduction testing and quantitative sensory testing of the ulnar nerve, comparing results of controls and patients with and without reaction in the INFIR Cohort Study at the time of registration

Test*	No. (nerves)	Controls	No. (nerves)	No reaction**	Reaction**	Difference, controls vs no reaction +	Difference, no reaction vs reaction++
<i>SNC</i>							
No conduction				13	31		
Latency (ms)	534	2.1 (2.08–2.13)#	135	2.26 (2.21–2.31)**	2.4 (2.3–2.5)	0.0001	0.035
Amplitude (µV)	534	29.5 (28.1–31.8)	135	19.5 (17.0–23.4)	16.8 (14.3–20.7)	0.0001	0.30
Velocity (m/s)	534	57.1 (56.3–57.6)	135	53.0 (52.0–54.3)	49.7 (48.2–52.2)	0.0001	0.041
<i>MNC</i>							
<i>Wrist</i>							
No conduction				0	5		
Latency (ms)	528	2.54 (2.50–2.59)	169	2.76 (2.64–2.83)	2.88 (2.76–3.04)	0.0001	0.001
Amplitude (mV)	528	15.8 (15.3–16.4)	169	15.0 (14.0–15.8)	13.7 (13.1–14.7)	0.0001	0.0023
<i>Elbow</i>							
No conduction				0	6		
Latency (ms)	514	5.2 (5.1–5.3)	165	5.80 (5.60–5.94)	5.84 (5.70–6.0)	0.0001	0.31
Amplitude (mV)	514	14.6 (14.2–15.0)	165	13.2 (12.0–13.9)	11.5 (10.6–12.8)	0.0001	0.0023
Velocity (m/s)	514	63.0 (62.5–63.7)	165	57.4 (56.2–60.2)	57.5 (55.5–59.2)	0.0001	0.62
WDT	603	33.1 (33.1–33.2)	220	33.8 (33.6–34.0)	33.6 (33.2–33.6)	0.0001	0.15
CDT	604	31.1 (31.1–31.2)	219	31.0 (30.8–31.1)	31.1 (31.0–31.2)	0.0018	0.29
VPT	655	0.71 (0.68–0.75)	230	0.87 (0.78–0.94)	0.98 (0.92–1.10)	0.0001	0.016
<i>Dynamometry</i>							
Grip (mmHg)		##	114	240 (220–260)	202 (180–220)		<0.0001
Key pinch			114	150 (142–160)	132 (120–146)		0.0026
Pulp-to-pulp pinch			114	106 (100–110)	92 (90–102)		0.014

*SNC = sensory nerve conduction, MNC = motor nerve conduction, WDT = warm detection threshold, CDT = cold detection threshold, VPT = vibration perception threshold.

**Matched for leprosy type, age and sex.

+ *P*-values of significance of the difference between median, based on the Kruskal-Wallis test.

++ *P*-values of significance of the difference between median, based on the Wilcoxon paired signed rank test.

#Median + binomial 95% confidence interval.

##Normative study was not done.

Tables 4 and Table 5 show the concordance between motor and sensory impairment diagnosed with the VMT and MNC results and monofilament testing and results of SNC and quantitative sensory testing. Good concordance was observed, particularly between VMT results and distal motor latency, although positive concordance was highest with CMAP amplitudes (Table 4). Overall concordance was also good for the median and peroneal nerves, however, of the nerves testing impaired on MNC, hardly any were impaired by VMT.

Concordance between monofilament results and SNC varied per type of nerve, but was generally good (Table 5). Overall concordance was best for SAP latency and velocity, CDTs and VPTs, while the highest positive concordance was seen between MF results and SAP amplitudes. Combining impairment of any of the three SNC parameters in one variable did not improve co-positivity with the MF test, over that of individual SAP parameters, while co-negativity and overall concordance was substantially lower. These findings indicate that, most of the time, if touch sensation is affected, one of the SNC parameters will be abnormal also. Exclusion of non-conducting nerves further improved negative concordance, but dramatically decreased positive concordance (data not shown).

Positive concordance between monofilaments and thermal thresholds was better for the radial cutaneous, sural and posterior tibial nerves than for the ulnar and median (Table 5), but the difference was only statistically significant for the sural nerve. Good positive concordance indicates that, if touch sensation was impaired, often, thermal sensation was affected also. This was not true for concordance between MF and VPT, where negative concordance was much stronger than positive concordance. Negative concordance was generally strong, showing that if the MF test was normal, most of the time, other tests were normal also. Although the tests agreed in the large majority of nerves, substantial discordance was observed in both directions. Nerves testing abnormal on the MF sometimes tested normal on one or more of the other tests, while up to 61% of nerves with a normal MF result had one or more abnormalities in sensory nerve conduction testing. Similar results were observed for the motor assessments.

Discussion

In this study, six nerves commonly affected in leprosy were studied, bilaterally and prospectively over a period of 2 years from the time of diagnosis in a cohort of 303 patients. In the current report, we compared sensory and motor nerve conduction results in patients with reaction against those without reaction and healthy control subjects at baseline only. We also compared the results of the neurophysiological tests against the monofilament and voluntary muscle test.

DIFFERENCES BETWEEN HEALTHY CONTROLS AND PATIENTS

Consistent differences in neurological test results were observed between our samples of healthy control subjects and subjects with leprosy. This highlights the fact that peripheral neuropathy is a characteristic of leprosy, even though it may not always be detectable with current routine nerve function tests used in leprosy control programmes. It also shows that neuropathy is often already well established before the development of reactions.

Table 4. Concordance between VMT results and motor nerve conduction testing in the INFIR Cohort Study at the time of registration

Test*		Left ulnar		Right ulnar		Left median		Right median		Left peroneal		Right peroneal	
		VMT impaired	VMT not impaired	VMT impaired	VMT not impaired	VMT impaired	VMT not impaired	VMT impaired	VMT not impaired	VMT impaired	VMT not impaired	VMT impaired	VMT not impaired
MNC		(n = 23)	(n = 240)	(n = 24)	(n = 239)	(n = 1)	(n = 261)	(n = 2)	(n = 260)	(n = 2)	(n = 257)	(n = 1)	(n = 259)
<i>Wrist/ankle</i>													
Latency	Impaired	57 (13)**	10 (23)	58 (14)**	12 (28)	0	8-0 (20)	50 (1)	8-0 (22)	100 (2)	15 (38)	100 (1)	13 (33)
	Not impaired	43 (10)	90 (217)	42 (10)	88 (211)	100 (1)	92 (241)	50 (1)	92 (238)	0	85 (219)	0	87 (226)
Amplitude	Impaired	78 (18)	15 (37)	88 (21)	18 (43)	100 (1)	25 (64)	50 (1)	24 (63)	100 (2)	35 (91)	100 (1)	32 (84)
	Not impaired	22 (5)	85 (203)	12 (3)	82 (196)	0	75 (197)	50 (1)	76 (197)	0	65 (166)	0	68 (175)
<i>Elbow/fibula</i>													
Latency	Impaired	(n = 22)	(n = 236)	(n = 24)	(n = 238)	(n = 1)	(n = 261)	(n = 2)	(n = 257)	(n = 2)	(n = 253)	(n = 1)	(n = 255)
	Not impaired	68 (15)	31 (73)	67 (16)	34 (82)	0	13 (33)	0	19 (48)	100 (2)	14 (35)	100 (1)	16 (43)
	Impaired	32 (7)	69 (163)	33 (8)	66 (156)	100 (1)	87 (227)	100 (1)	81 (209)	0	86 (218)	0	84 (212)
Amplitude	Impaired	86 (19)	23 (56)	100 (24)	28 (67)	100 (1)	27 (69)	50 (1)	27 (69)	100 (2)	35 (88)	100 (1)	34 (87)
	Not impaired	14 (4)	77 (183)	0 (0)	72 (171)	0	73 (191)	50 (1)	73 (190)	0	65 (165)	0	66 (169)
Velocity	Impaired	73 (16)	33 (79)	63 (15)	40 (95)	0	16 (41)	0	18 (46)	100 (2)	19 (47)	100 (1)	22 (57)
	Not impaired	27 (6)	67 (157)	37 (9)	60 (143)	100 (1)	84 (219)	100 (2)	82 (211)	0	81 (206)	0	78 (198)

*MNC = motor nerve conduction.

**Column % (number of nerves).

Table 5. Concordance between impairment by monofilament test, sensory nerve conduction testing and quantitative sensory testing of five sensory nerves in the INFIR Cohort Study at the time of registration

Test*		Right ulnar		Right median		Right rad cutaneous		Right sural		Right posterior tibial	
		Impaired	Not impaired	Impaired	Not impaired	Impaired	Not impaired	Impaired	Not impaired	Impaired	Not impaired
SNC		(n = 40)	(n = 223)	(n = 20)	(n = 243)	(n = 19)	(n = 243)	(n = 68)	(n = 191)		
Latency	Impaired	73 (29)**	18 (41)	70 (14)	19 (45)	84 (16)	31 (75)	93 (63)	34 (64)		
	Not impaired	27 (11)	82 (182)	30 (6)	81 (198)	16 (3)	69 (168)	7·0 (5)	66 (127)		
Amplitude	Impaired	78 (31)	37 (83)	80 (16)	35 (84)	100 (19)	57 (139)	94 (64)	53 (102)		
	Not impaired	22 (9)	63 (140)	20 (4)	65 (159)	0	43 (104)	6·0 (4)	47 (89)		
Velocity	Impaired	73 (29)	18 (40)	70 (14)	18 (44)	84 (16)	31 (75)	93 (63)	34 (64)		
	Not impaired	27 (11)	82 (183)	30 (6)	82 (199)	16 (3)	69 (168)	7·0 (5)	66 (127)		
SNC	Impaired	78 (31)	43 (95)	85 (17)	39 (94)	100 (19)	61 (149)	96 (65)	55 (105)		
Combined***	Not impaired	22 (9)	57 (128)	15 (3)	61 (149)	0	39 (94)	4·0 (3)	45 (86)		
		(n = 43)	(n = 254)	(n = 21)	(n = 276)	(n = 19)	(n = 277)	(n = 80)	(n = 215)	(n = 83)	(n = 210)
WDT	Impaired	53 (23)	13 (34)	57 (12)	17 (46)	79 (15)	38 (105)	91 (73)	36 (78)	77 (64)	37 (78)
	Not impaired	47 (20)	87 (220)	43 (9)	83 (230)	21 (4)	62 (172)	9·0 (7)	64 (137)	23 (19)	63 (132)
					(n = 275)						
CDT	Impaired	42 (18)	3·0 (7)	38 (8)	8·0 (23)	79 (15)	26 (73)	89 (71)	24 (52)	72 (60)	23 (49)
	Not impaired	58 (25)	97 (247)	62 (13)	92 (252)	21 (4)	74 (204)	11 (9)	76 (163)	28 (23)	77 (161)
Thermal	Impaired	53 (23)	15 (39)	57 (12)	19 (53)	79 (15)	42 (117)	96 (77)	41 (89)	80 (66)	42 (89)
combined	Not impaired	47 (20)	85 (215)	43 (9)	81 (222)	21 (4)	58 (160)	4·0 (3)	59 (126)	20 (17)	58 (121)
		(n = 44)	(n = 259)	(n = 22)	(n = 281)	(n = 20)	(n = 283)	(n = 82)	(n = 221)	(n = 88)	(n = 213)
VPT	Impaired	50 (22)	13 (33)	68 (15)	13 (37)	55 (11)	19 (55)	59 (48)	19 (43)	70 (62)	18 (38)
	Not impaired	50 (22)	87 (226)	32 (7)	87 (244)	45 (9)	81 (228)	41 (34)	81 (178)	30 (28)	82 (175)

*SNC = sensory nerve conduction, SNC comb = combination of abnormal latency or amplitude or velocity, WDT = warm detection threshold, CDT = cold detection threshold, VPT = vibration perception threshold.

**Column % (number of nerves).

*** Combined = impairment in any of the NC or thermal testing parameters.

SENSORY AND MOTOR CONDUCTION

NC measurements in the current study revealed that motor fibres were almost as frequently affected as sensory fibres. The same was found by Ramadan *et al.*⁵⁶ Others reported more frequent SNC impairment.^{4,16} Comparing VMT and MF results in the ulnar nerve, 3.5% had isolated motor impairment. Using nerve conduction tests, 23% of ulnar nerves had evidence of motor impairment, while sensory conduction was normal. These findings support earlier clinical reports of isolated motor function impairment in leprosy patients.^{57–59} The current findings show that this phenomenon is not an artefact of lack of sensitivity of sensory testing instruments used in the field.

We found a high percentage of concordance between VMT and MNC parameters in the ulnar nerve, supporting the validity of the ulnar VMT. For the median and peroneal nerves, negative concordance was high, indicating that most nerves with a normal MNC result also had a normal VMT. However, of the median and peroneal nerves testing 'impaired' by MNC, hardly any had impairment by VMT. In addition, a substantial proportion of nerves testing normal on the VMT had abnormal MNC (8–40%). These observations could have two explanations. First, as observed by Dyck *et al.*, results of nerve conduction tests do not necessarily correlate well with motor function.⁶⁰ The impairment observed by MNC thus may be subclinical and may not translate (yet) into motor weakness. The second possibility is that the VMT for these nerves (respectively, thumb opposition and foot dorsiflexion) is not sensitive enough to detect early damage. In the case of the peroneal nerve, however, it should be noted also that the VMT primarily tests muscle strength in the tibialis anterior muscle, while CMAP recordings were taken from the extensor digitorum brevis.

Concordance between MF and SNC was good and was highest with SNC latency and velocity, confirming earlier findings by Breger.⁶¹ However, a substantial proportion of nerves impaired by VMT or monofilaments (Tables 4 and 5) were not impaired by MNC or SNC. Maybe the VMT/MF detect functionally important impairment not necessarily reflected in nerve conduction, which is studied over a relatively short segment of the peripheral nerve. It is known that the severity of abnormality of conduction velocity does not relate well to global severity of neuropathy.⁶⁰ In the present study, except for the radial cutaneous and sural nerves, negative concordance was comparatively high, i.e. if VMT or monofilaments were negative, NC results were often also normal. The same was reported by Brown *et al.*⁴ The higher positive concordance and relatively lower negative concordance of the radial cutaneous and sural NC may be due to the fact that for these nerves, only a single site was tested with monofilaments, while multiple sites were tested for the ulnar, median and posterior tibial nerves. Fifty-five to 61% of the radial cutaneous and sural nerves that tested normal on the MF were impaired on SNC, while this was 39–43% for the median and ulnar nerves. This suggests that testing only one site for a given nerve may be insufficient, leading to more under-diagnosis of sensory impairment. However, a proportion of the nerves testing normal on VMT or on multiple monofilaments test sites also had abnormal nerve conduction. This has also been observed by other investigators^{4,10,14} and may indicate a pre-clinical stage of neuropathy, as suggested by Hackett *et al.* and Brown *et al.*^{4,10} Whether this is the case may become clear from the analysis of the longitudinal data from current study (van Brakel *et al.*, in preparation).

QUANTITATIVE SENSORY TESTING: THERMAL TESTING AND VIBROMETRY

The Thermal Sensory Analyzer II used in this study was very easy to operate. The test is highly relevant in leprosy, because lack of warm sensation frequently causes injury in people with sensory impairment. The 'levels' algorithm provided highly reliable threshold results (to be reported elsewhere), but sometimes took a long time to complete, particularly in people with incomplete sensory impairment on the feet. In such situations, the test could take more than an hour to complete on five nerves bilaterally.

On grounds of histopathological evidence, indicating that small, unmyelinated fibres are the first to be affected in leprosy,³⁷⁻³⁹ we had postulated that thermal sensation would be impaired before touch sensation. In the current cross-sectional analysis, this would have meant that all nerves impaired on the monofilament test would also have impaired thermal sensation. In addition, a proportion on nerves would have impaired thermal sensation, but normal touch sensation. The association between temperature sensation and touch sensation was strong, but did not follow the expected pattern. This may have four explanations. First, the patchy nature of leprosy neuropathy causes different levels of impairment at different sites and in different people, despite the fact that small fibres are affected before the large ones. This effect may have been exaggerated by the way the tests were performed. The ulnar-innervated area on the palm was tested at three different sites with the monofilament test, while only the hypothenar eminence was tested for thermal sensation. Both are standard testing practice. If sensory impairment is localized, due to the inhomogeneous nature of the neuropathy, it is possible that the monofilaments picked up impairment at the 5th metacarpophalangeal joint or little finger tip missed by the thermal test. Support for the latter explanation may be found in the fact the positive concordance between the two tests was considerably higher for the radial cutaneous and sural nerves, both of which were monofilament-tested at only one site. If this explanation were true, it would support the practice of testing at least two or three sites per nerve, rather than only one. Second, we have not tested small fibres responsible for autonomic innervation. It is therefore possible that those patients who had impaired touch, but normal thermal sensation, had autonomic neuropathy. Perhaps it is not likely that leprosy would affect thermal sensation selectively in some and autonomic function in others, but this possibility cannot be excluded on the basis of the current data. Third, small fibres serving thermal sensation may recover more readily than large fibres. Thus, nerves currently showing impaired touch sensation without thermal impairment may have had such impairment initially, but this may have recovered, while tactile impairment has not. Fourth, it is possible that no association exists between the two modalities and fibre systems with regard to the sequence of being affected; in some patients touch sensation is impaired first, in others thermal sensation.

Monofilament and vibration tests both assess large afferent fibre function. It was therefore expected that vibrometry results would correlate closely with the monofilament test. However, as with thermal testing, not all nerves with impaired touch had impaired vibration sense. One explanation again would be the discrepancy in the number of test sites between MF (usually 3-4) and vibrometry (1). Support for this reasoning can be found in the high co-negative concordance: if the monofilament test was normal, VPTs were also normal in the great majority of nerves. Vibrometry is therefore not necessarily more sensitive for detecting sensory neuropathy in leprosy than monofilament testing.

DYNAMOMETRY

Dynamometry was done with ‘appropriate technology’ grip and pinch meters made of an adult and neonatal sphygmomanometer cuff, as described by Soares *et al.*⁵ These have been shown to give reliable results (to be published elsewhere). We found significant differences in grip and pinch strength between those with a reaction event and age and sex-matched leprosy controls. Because of large between-subject variations observed during reliability testing, no normative study had been done. Instead we planned to use a subject as his or her own control during the prospective analysis. Schreuders showed that the ulnar nerve has a large influence on grip strength.⁶² This would support the use of grip dynamometry in leprosy.

In the current analysis, nerve conduction testing and warm detection thresholds showed the highest prevalence of impairment. This may indicate that these methods are the most sensitive for detecting neuropathy in leprosy. However, analysis of the prospective cohort data will need to confirm this. An important finding is the good concordance between monofilament and voluntary muscle testing on the one hand and the more sophisticated tests of nerve function on the other. This supplies additional evidence of their validity to assess sensory and motor neuropathy. We recommend the use of graded monofilaments and voluntary muscle testing as standard screening tests for nerve function in the clinical management of people affected by leprosy. Programme managers and leprosy supporting agencies should investigate ways to improve the supply of cheap, but standardized monofilaments to hospitals and health workers responsible for diagnosis and monitoring treatment of nerve damage.

CONCLUSIONS

- Concordance between MF and other sensory function tests results was good, supporting the validity of the monofilaments as standard screening test of sensory function.
- Concordance between VMT results and MNC was good for the ulnar nerve, but very few median and peroneal nerves with abnormal conduction had an abnormal VMT. A more sensitive motor function test may be needed for these nerves.
- Of the nerve assessment tests conducted, NC amplitudes and WDTs were the most frequently affected. Therefore, NC studies and WDT measurements appear to be most promising tests for early detection of leprosy neuropathy.
- The pattern of concordance between tactile and thermal sensory impairment failed to support the hypothesis that small fibre neuropathy always precedes large fibre damage.
- Warm sensation was more frequently affected than cold sensation. This could indicate that unmyelinated C fibres are more frequently affected than small myelinated A δ fibres.

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Appendix: definitions and diagnostic cut-offs

Non-conducting nerve: A nerve for which the measured latency was less than 1.0 ms for sensory and less than 3.0 ms for motor nerves.

Neuritis: a leprosy patient has neuritis if he/she has any of the following:

- Spontaneous nerve pain, paraesthesia or tenderness
- New sensory or motor impairment of recent onset (defined below)

Mixed signs neuritis: neuritis may be mild or severe (see below), acute (< 1 month duration), sub-acute (2–6 months) or long-standing (> 6 months). During the monthly study follow-ups, only acute neuritis was regarded as an outcome.

Silent neuropathy (SN): a patient has silent neuropathy when he/she has sensory and/or motor impairment of recent onset (< 6 months duration) in an area innervated by one or more nerve without signs of a reaction (RR or ENL) or nerve pain and with or without tenderness.

Type 1 or reversal reaction (TIR): a type 1 reaction is diagnosed when a patient has erythema and oedema of skin lesions. There may be accompanying neuritis and oedema of the hands, feet and face. The skin signs are obligatory; the nerve and general signs optional.

Erythema nodosum leprosum (ENL): a patient has ENL if he/she has crops of tender subcutaneous skin lesions. There may be accompanying neuritis, iritis, arthritis, orchitis, dactylitis, lymphadenopathy, oedema and fever. The skin signs are obligatory; the nerve and general signs optional.

Sensory impairment: a patient is diagnosed as having sensory impairment in any of the following situations: the monofilament threshold is increased by three or more levels (filaments) on any site, OR two levels on one site and at least one level on another site, OR one level on three or more sites for one nerve.

Motor impairment: a patient is diagnosed as having motor impairment if the VMT score for any muscle is less than four on the 0–5 (modified) MRC scale.

New additional sensory or motor impairment: where the baseline showed *partial or full longstanding* impairment for two or more consecutive assessments, then if the difference in 'levels' (between now and the baseline) is 3 or more for monofilaments or 2 or more for VMT, then the patient has additional recent impairment and should be considered as having an outcome event.

Paraesthesia: nerves are marked positive for paraesthesia if the patient reported sensations of tingling, pricking or something equivalent while the nerve was gently palpated.