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The effect of corticosteroid usage on the bacterial killing, clearance and nerve damage in leprosy: A prospective cohort study: Part 1 – Study design and baseline findings of 400 untreated multibacillary patients

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Summary
Objective To investigate possible adverse effects of therapeutic usage of corticosteroids on the killing and clearance of *M. leprae* and the clearance of granuloma, in patients with multibacillary (MB) leprosy.
Design A cohort of 400 untreated MB patients were sub-grouped into those to be treated with corticosteroids (prednisolone 40 mg daily tapered to 5 mg over 12 weeks) along with MB-MDT for reaction and/or neuritis or silent neuropathy (SN) of <6 months duration (group A), and those with no reaction and to be treated with MDT only (group B). Clinical, bacteriological, histopathological and neurological test findings at fixed time points were compared. Analysis was performed using SPSS version 10.0. The significance of association was tested using Chi-square test.
In the current report, we describe the study design and baseline findings of 400 untreated MB patients, with special emphasis on differences between patients in groups A and B.
Results At baseline, applying Ridley-Jopling classification, 39% patients were BT, 20% BB, 24% BL, 12% sub-polar LL and 5% pure neural (PN). Overall, 60% patients were slit skin smear (SSS) negative and 33% presented with disability either grades 1

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or 2. Overall 140/400 (35%) patients presented with reaction and/or neuritis and 11/400 (3%) presented with SN of <6 months duration.
Comparing groups A and B, the percentage of patients presenting with DG2 was significantly higher in group A (43%). By clinical tests, monofilaments (MF) and voluntary muscle testing (VMT), the percentage of patients and nerves showing functional impairment was also significantly higher in group A. However, in the more sensitive nerve conduction velocity (NCV) test, the percentage of patients that showed nerve abnormalities was closely comparable; 94% and 91% in groups A and B respectively while number of affected nerves was higher in group A.
Conclusion At baseline, as recorded by NCV, peripheral nerve function abnormality was observed in almost all the MB patients regardless of reaction; but among those presenting with reaction or neuritis, the nerve damage was more severe and extensive.

Introduction

Corticosteroids by virtue of their dual anti-inflammatory and immunosuppressive actions, are the drugs of choice in the treatment of reactions and neuritis in leprosy.[1] They help in reducing the cutaneous and intraneural oedema, leading to a rapid improvement in some patients and also reduce post-inflammatory scar formation during the prolonged healing phase.[2] Their chief effect is to suppress the T-cell driven inflammatory response to *M. leprae*/ antigens within skin and nerves.[3]

About half the patients that either present with or develop reaction or neuritis during the course of the disease receive steroids.[4] In addition to these, since differentiation between relapse and late reversal reaction may be difficult under field conditions, patients with late reversal reactions occurring after the end of MDT are often given a therapeutic course of corticosteroids.[5,6] Precipitation of reversal reactions is assumed to be due to delayed type hypersensitivity reaction (DTH) to persisting dead bacterial products[7] or host factors.[8]

The effects of corticosteroids in varying doses and duration on nerve damage[9–11] and in reducing the recurrence of reaction[12] have been well studied in India and elsewhere[2,3,13] and have been reviewed in detail recently by Naafs.[14] Some complications of steroid therapy such as moon face, fungal infections, acne and gastric pain requiring antacid as well as some major complications like psychosis, glaucoma, cataract, osteoporosis, diabetes and hypertension have been documented.[15]

However there is a dearth of information with regard to the precise relationship between corticosteroid usage and the killing and clearance of bacteria and the clearance of granuloma. The main question is, does the usage of corticosteroids in any way hinder the killing of bacteria, clearance of antigens and thereby increase the risk of relapse and late reversal reaction and/or nerve damage in the long run. In the current strategy, the scant emphasis on follow up and surveillance makes it difficult to know the exact incidence of relapse or recurrence of lesions. A field-based study has shown that overall around 5% of MB patients present with recurrence of lesions[16] while the documented relapse rates vary from 1% to 20%.[17–20]

In tuberculosis, use of steroids is known to accelerate the multiplication of dormant organisms.[21] In leprosy, failure of drugs to kill *M. leprae* and persistence of viable *M. leprae* are the main cause of relapse.[17,22] As peripheral nerves are the major reservoir of *M. leprae*[23,24] and if prevention of nerve damage is a priority with any kind of intervention, it is important to ascertain that the intervention used does not add to the problems.

AIM

To investigate possible adverse effects of the therapeutic usage of corticosteroids on the pathogen and pathological process. The following parameters were studied as outcome measures and compared at fixed time points in two broadly matched group of patients, those who receive steroids along with 12 months MB-MDT and those who receive only MB-MDT; (a) Clinical regression of lesions, (b) Clearance of *M. leprae* and its antigens from the lesions, (c) Regression of granuloma, (d) Changes in nerve function, (e) Determination of bacterial viability using mouse foot pad (MFP).

The findings of the study will be presented in 3 parts:

(1) The study design and clinical, bacteriological, histopathological and neurological findings at baseline of 400 untreated MB patients recruited for the study.
(2) Clinical, bacteriological and neurological observations recorded at 6 monthly intervals, during and after treatment, up to 18 months.
(3) Rate of clearance of antigens, regression of lesions, changes in nerve function and occurrence of viable *M. leprae* assessed approximately 6 months after the release from 1 year MB-MDT in 100 pair matched MB patients, treated with and without steroids.

In the current report we describe the Part-1 findings as mentioned above, with special emphasis on differences between patients presenting with and without reactions and/or neuritis or SN of <6 months.

Definitions

Type 1 reaction (T1R): Patients presenting with erythema and oedema of skin lesions. There may be accompanying neuritis and oedema of the hands, feet and face.

Type 2 reaction (T2R): Patients presenting with crops of tender subcutaneous skin lesions. There may be accompanying neuritis, iritis, arthritis, orchitis, dactylitis, lymphadenopathy, oedema and fever.

Neuritis (N): Patients presenting with acute inflammation of one or more peripheral nerve trunk detectable by swelling and/or functional impairment with spontaneous nerve pain and/or nerve tenderness on palpation. Nerve pain or tenderness may or may not be accompanied by paraesthesia.

Nerve function impairment (NFI): Clinically detectable impairment of sensory and/or motor nerve function.

Silent neuropathy (SN): Patients with clinically detectable sensory and/or motor impairment but without spontaneous complaints of nerve pain, paraesthesia and/or nerve tenderness on palpation and with no evidence of reaction (either T1R or T2R). In this study, patients with 'silent neuropathy' of <6 months duration have been considered for steroid treatment.

Group A: Patients who receive corticosteroids along with MDT (MB patients presenting with either T1R or T2R with or without neuritis or neuritis alone or with SN of <6 months duration).

Group B: Remaining MB patients treated with MDT only.

Patients and Methods

STUDY DESIGN

This was a cohort study of newly registered MB patients. The patients were then followed up every 6 monthly intervals for 18 months.

STUDY POPULATION

This included 400 newly registered MB leprosy patients requiring a full course of MB-MDT.

STUDY SUBJECTS

Eligibility criteria

Leprosy patients of either sex, aged 12–60 years, presenting with 6 or more skin lesions or with a positive slit skin smear or with more than one thickened peripheral nerve were recruited for the study between February 2001 to April 2005.

Exclusion criteria

- Any patient for whom MDT was contraindicated.
- Patients with history of diabetes.
- Patients with serious additional infection or condition, such as tuberculosis, HIV/AIDS.

TREATMENT REGIMEN

MDT treatment

All the patients under study were treated with 12 months MB-MDT regimen as per the WHO/NLEP guidelines.[25]

Treatment for reaction and/or neuritis or SN of < 6 months

Patients presenting with or developing type1 or type2 reactions with or without neuritis, neuritis alone and the patients presenting or developing SN of < 6 months, were treated with corticosteroids (Prednisolone – 40 mg daily tapered to 5 mg daily over 12 weeks as per WHO recommendation.[25] 40 mg, 30 mg, 20 mg, 15 mg, 10 mg, 5 mg for 2 weeks each (daily dose). The same course was given when the patient developed a further episode. We used a rigid steroid regimen to ensure uniformity in the treatment among the study patients.

Examination and investigations at intake

Detailed history taking using a standard protocol created at the Foundation for Medical Research, systematic physical and neurological examinations were done and recorded with special attention to signs and symptoms of reactions (type 1 or type 2) with or without neuritis, or neuritis alone or SN of < 6 months duration.

WHO disability grading

Grading disability grades 1 and 2.[26]

Slit skin smear (SSS)

These were obtained, using scalpel blade no. 11, from both ear lobes, one forehead and from the edge of two active skin lesions. Smears on glass slides were heat fixed and stained by Ziehl-Neelsen's method and graded microscopically for bacteriological index (BI), using the Ridley-Jopling scale (0–6+).[27]

Manual nerve palpation (MNP)

The peripheral nerves most commonly affected in leprosy (ulnar at the elbow, median at the wrist, radial cutaneous, common peroneal, posterior tibial, sural) and their branches were palpated bilaterally at the sites of predilection to record the thickening and tenderness and graded as 0 (no thickening), 1+ (thick), 2+ (very thick), 3+ (visibly thick) by co-author S.DG.

NERVE FUNCTION ASSESSMENTS

Touch sensibility testing using monofilaments (MF)

Touch sensibility was tested with a standard set of five coloured Semmes-Weinstein monofilaments (MF) as described by Bell Krotoski.[28] When applied with a force sufficient to bend the filament, these were respectively equal to application forces of 50 mg – score 5, 200 mg – score 4, 2 g – score 3, 4 g – score 2, and 300 g – score 1. A score of 5 was given when the thinnest filament was felt, and zero if the thickest filament was not felt. Normal reference values were up to 200 mg for hands and 2 g for the foot.[29] The nerves tested were bilateral ulnar (3 sites, normal score = 11–15), median (3 sites, normal score = 11–15), radial cutaneous (1 site, normal score = 4–5), sural (1 site, normal score = 4–5) and posterior tibial (12 sites including the heels, normal score = 40–60). Any nerve scoring below the normal score was considered impaired.

Test sites For ulnar nerve – hypothenar eminence, 5th metacarpal head and distal phalanx of the little finger. For median nerve – 2nd metacarpal head, distal phalanx of the thumb and distal phalanx of the index finger. For radial cutaneous nerve – dorsal on the thumb at the site of the motor point. For posterior tibial – distal phalanx of toes, metacarpal head of each toe and lateral heel of foot. For sural – dorsal lateral aspect of foot.

Voluntary muscle testing (VMT)

This was done using the modified Medical Research Council (MRC) scale.[30] The muscle tested per nerve were; for ulnar nerve – abductor digiti minimi, for median nerve – abductor pollicis brevis, for common peroneal nerve – tibialis anterior and extensor of toes, for posterior tibial nerve – peroneus longus and small muscles of feet.

Grading criteria was as follows:

5 – full range of movement of the joint, normal resistance
4 – full range of movement but less than normal resistance
3 – full range of movement but no resistance
2 – partial range of movement with no resistance
1 – perceptible contraction of muscles not resulting in joint movement
0 – complete paralysis

Criteria for motor impairment was, any muscle scoring less than grade 4.

Sensory nerve conduction measurements (SNC)

Sensory action potential (SAP) parameters were measured by co author G.DC, (using Neurocare 2000 EMG machine, Biotech Ltd, Mumbai), bilaterally in four major sensory nerves (ulnar, median, radial cutaneous and sural) at a fixed stimulation recording distance of 14 cm. The ulnar and median nerves were stimulated at little and index fingers respectively with pick up at wrist while radial cutaneous nerve action potential was picked up at the first web space and stimulated at the radial side of the forearm. The sural nerve was picked up behind the lateral malleolus and stimulated at mid calf.

Motor nerve conduction measurements (MNC)

Compound muscle action potential (CMAP) parameters were measured (using Neurocare 2000 EMG machine, Biotech Ltd, Mumbai) bilaterally in 4 motor nerves (ulnar, median, common peroneal and posterior tibial) following stimulation at standard distal and proximal sites. Abductor digiti minimi muscle served as pick up for ulnar nerve, which was stimulated at wrist, below and above the sulcus; the distance between below and above sulcus being 10 cm. Abductor pollicis brevis muscle was the pick up for median nerve, which was stimulated at wrist and elbow. Extensor digitorum brevis muscle was the pick up for the common peroneal nerve, which was stimulated at the ankle and behind the capitulum fibulae. Abductor hallucis brevis muscle was the pick up for posterior tibial nerve, which was stimulated behind the medial malleolus and at the popliteal fossa. The Window-driven software stores the evoked responses as traces in a database for reference. The measured value for latency, amplitude, and conduction velocity were stored in a separate Access database. Skin temperatures were measured electronically at wrist and ankle and the measured latencies and velocities normalised for a temperature of 33° C at the time of analysis using standard formulae.[31]

NORMAL VALUES

Normal values were obtained by studying 25 normal subjects in the age group 23–52 years. Sensory conduction velocity for all the nerves sampled was >50 m/s ($68{\cdot}47 \pm 14{\cdot}15$). Amplitude value was $>10\,\mu$V ($18{\cdot}6 \pm 6{\cdot}7$) for median, radial cutaneous and sural nerves while it was $>4\,\mu$V ($7{\cdot}1 \pm 2{\cdot}8$) for the ulnar nerve. Motor conduction velocity for median and ulnar nerves was >47 m/s ($59{\cdot}06 \pm 11{\cdot}3$) while that for common peroneal and posterior tibial nerves was >40 m/s ($46{\cdot}25 \pm 6{\cdot}5$). Amplitude was >10 mV ($15{\cdot}06 \pm 3{\cdot}75$) for median and ulnar, >10 mV ($17 \pm 7{\cdot}2$) for posterior tibial and >4 mV ($6{\cdot}8 \pm 2{\cdot}8$) for common peroneal nerve.

CORRELATION BETWEEN CLINICAL AND ELECTROPHYSIOLOGICAL TESTS

Findings of the three clinical testing methods employed for assessing nerve function impairment; MNP, MF and VMT were compared with SNCV and MNCV measurement findings to determine the sensitivity and suitability of these testing methods. (Note: These clinical tests are routinely used by us at clinic level).

Biopsy

An incisional skin or a nerve biopsy (using local anaesthesia) was taken in 391 patients at entry to the study. Amongst the 21 pure neural patients, one of the affected nerve was biopsied in five (three radial cutaneous and two sural nerves), and a skin biopsy from an anaesthetic or hypoaesthetic area was obtained in 11 patients while 5 PN patients were unwilling for the biopsy.

A second biopsy was obtained from 220 patients at 6 months post release from treatment (RFT), from a site showing maximum bacterial index (by slit skin smears) or clinical activity.

The biopsies thus obtained, were divided into three parts to study as follows:

(a) *Histopathology*: One part of the biopsy was fixed in formal Zenker and embedded in paraffin. Sections were stained with Trichrome modified Fite Feracco (TRIFF), leprosy classification, grading of cell types, tissue bacterial index and granuloma index, were done using a semi quantitative approach.[32] Paraffin sections were also used for staining with Anti – Bacillus Calmetto Guerin (BCG) by Peroxidase – Anti Peroxidase technique[33] for determining the antigenic load. This method of detecting antigen load has been found to be more sensitive than AFB detection.[23] In the case of nerve biopsies one part of nerve was fixed in glutaraldehyde, followed by osmium tetroxide and embedded in araldite for the fine structural studies.

(b) *Assessment of bacterial load/gram weight and mouse foot pad (MFP) test for viability determination*: The second part of skin or nerve biopsy was homogenised and bacterial load/gram wt. of tissue was determined using the standard procedure.[34] The homogenate was inoculated into the hind footpads of immuno-competent Swiss White (SW) mice using the standardised protocol. Fold increase in the footpads confirming viability of *M. leprae*, were recorded through regular harvests.[34,35]

The third part of the skin biopsy was frozen and stored at -70° C.

FOLLOW UP INVESTIGATIONS

Physical, neurological examinations (including SNCV and MNCV) and slit skin smears were repeated at 6 monthly intervals in all the patients reporting for follow up and as and when a patient presented with reaction episode.

DATA ANALYSIS

Analysis was performed using SPSS version 10.0. The significance of association was tested using Chi-square test.

ETHICAL APPROVAL

No financial incentives were given to the patients. Travel expenses were refunded to the patients on occasion. The study followed the International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS/WHO, 1993). The study had the clearance from the Institutional Ethics Committee. This included permission for the skin and nerve biopsies. Written consent was obtained from individual study subjects before inclusion in the study, using a standard consent form.

Committee for the Purpose of Control and Supervision of experiments on animals (CPCSEA) cleared the use of animals in the study. The Foundation for Medical Research is registered with CPCSEA and has a valid registration number 423/01/1/CPCSEA.

Results

BASELINE FINDINGS IN 400 NEWLY DETECTED MB PATIENTS

Of the 400 patients recruited for the study, 86 (22%) were females. Age ranged from 12–60 years with mean of 31·4 years. The patients were classified clinically and histopathologically using Ridley-Jopling scale.[36] There was some discrepancy noted between the clinical and histopathological classification in the BT and BB group of patients. Twenty three BT and three BB patients showed indeterminate pathology in the biopsied lesions. For the study, a classification was arrived at after considering the clinical, bacteriology and histopathological features. Accordingly, 39% patients were borderline tuberculoid (BT), 20% mid borderline (BB), 24% borderline lepromatous (BL), 12% subpolar lepromatous (LLs) and 5% were pure neural (PN) (Table 1). Some of the tests could not be done in few patients for technical reasons; hence some of the tables contain figures less than 400.

Table 1. Characteristics of the patients at baseline (Cohort of 400 patients)

Variable	Frequency	Percentage
Sex		
Males	314	78
Females	86	22
Age group (yrs)		
12–20	102	26
21–30	112	28
31–40	92	23
41–50	59	15
51–60	35	09
Classification		
BT	157	39
BB	79	20
BL	95	24
LLs	48	12
PN	21	05

Key: BT – borderline tuberculoid, BB – mid borderline, BL – borderline lepromatous, LLs – sub polar lepromatous, PN – pure neural.

Table 2. Bacteriological findings. Slit Skin Smear findings in leprosy types

	BI range			
Class	0	1+	2–3+	4–5+
BT	157	0	0	0
BB	63	14	02	0
BL	0	06	64	25
LLs	0	0	10	38
PN	21	0	0	0
Total	241 (60)	20 (05)	76 (19)	63 (16)

BACTERIOLOGICAL FINDINGS

Overall, 60% patients under study were negative in SSS examination, which included all the BT, all PN and 71% of BB patients (Table 2).

In the mouse foot pad test, 38% and 75% of SSS negative and positive patients respectively, showed unequivocal growth, proving the presence of viable bacteria in the biopsied lesion (Table 3).

Comparison of BI and viability status with tissue granuloma index (GI) was obtained in 372 patients. Amongst the BI + ve patients, 25/37 (68%) with GI (0·1–0·3), 51/64 (80%) with GI (0·4–0·6) and 36/49 (73%) patients with GI (0·7–1·0) tested positive in the MFP. On the other hand, amongst the BI − ve patients, 33/91 (36%) with GI (0·1–0·3), 33/93 (35%) with GI (0·4–0·6) and 18/38 (47%) with GI (0·7–1·0) showed MFP +ve (Table 3).

WHO DISABILITY GRADE (DG1 & 2)

A WHO disability grade of either 1 or 2 was seen in a total of 131 (33%) patients of which 103 were males and 28 were females. There was no difference in the proportion of males (33%) and females (33%) presenting with disability. The majority of them (82%) had DG2. Among the patients with DG2, 74% had a single disability and 26% had more than one disability. Going by the leprosy type, 30% of BT, 33% BB, 37% BL, 18% LLs and 67% of PN patients presented with either DG1 or 2 (Table 4).

Ulnar claw was the commonest DG2 (81%) (Table 5).

Table 3. Viability test (MFP) findings in relation to BI and GI (Total No. of patients assessed = 372)

	No. (%) scoring +ve in MFP		
	GI range		
BI	0·1–0·3	0·4–0·6	0·7–1·0
0	33/91 (36)	33/93 (35)	18/38 (47)
1+	3/7 (43)	2/2	5/8 (63)
2–3+	8/14 (57)	29/38 (76)	13/19 (68)
>4+	14/16 (88)	20/24 (83)	18/22 (82)

Key: BI – Bacteriological index, GI – Granuloma index, MFP – mouse foot pad.

Table 4. No. (%) of patients presenting with WHO disability (Disability grade 1 and 2 in leprosy types)

	WHO disability grades		
Class	0	1	2
BT	110 (70)	10 (06)	37 (24)
BB	53 (67)	03 (04)	23 (29)
BL	60 (63)	04 (05)	31 (32)
LLs	39 (81)	04 (08)	05 (10)
PN	07 (33)	03 (14)	11 (52)
Total	269 (67)	24 (06)	107 (27)

Total patients with disability (DG1 + 2) = 131/400 (33%).
DG1 = 24/131 (18%), DG2 = 107/131 (82%).
No. with single DG2 = 79 (74%).
No. with multiple DG2 = 28 (26%).

MANUAL NERVE PALPATION (MNP) FINDINGS

This was assessed in 388 patients of which 329 (85%) patients showed definite thickening of one or more nerves. Overall, 55% of nerves showed thickening (1+ to 3+). The ulnar nerve was the most frequently thickened (74%) followed by common peroneal (65%), radial cutaneous (55%), sural, posterior tibial (50% each) and greater auricular (45%) nerves (Table 6).

MONOFILAMENTS (MF) AND VOLUNTARY MUSCLE TESTING (VMT)

Assessments with MF and VMT were made in 397 patients, of which 191 (48%) showed abnormal nerve function (Table 7).

Impaired nerve function was highest among the PN (76%) patients, followed by LLs (60%), BL (52%), BB (50%) and least among BT (39%) patients (Table 7).

Overall, of the 3910 sensory and 3136 motor nerves examined using MF and VMT, 918 (23%) and 182 (6%) respectively showed impairment (Table 8).

Sural (28%), posterior tibial-sensory (27%) and ulnar-motor (18%) were the most frequently and severely impaired nerves (Table 8).

Table 5. No. (%) of patients presenting with different DG2 disabilities.

Type of disability (DG2)	No. (%)
Ulnar claw	87 (81)
Median claw	06 (06)
Ulnar + median	05 (05)
Foot drop	03 (03)
Resorption	02 (02)
Lagophthalmos	02 (02)
Ulcer	02 (02)

Key: DG – disability grade.

Table 6. Manual nerve palpation results (Total No. of patients assessed = 388)

	Grades of thickening			
Nerves	0	1+	2+	3+
G. auricular	449 (58)	210 (27)	111 (14)	06 (01)
Ulnar	200 (26)	265 (33)	260 (34)	51 (07)
Median	429 (55)	232 (30)	103 (13)	12 (02)
R. cutaneous	353 (45)	265 (35)	135 (17)	23 (03)
Sural	389 (50)	240 (31)	134 (17)	13 (02)
C. peroneal	275 (35)	243 (32)	225 (29)	33 (04)
P. tibial	390 (50)	262 (34)	111 (14)	13 (02)
Total	2485 (45)	1717 (32)	1079 (20)	151 (03)

Key: 0 – not thickened, 1+ – thick, 2+ – very thick, 3+ – visibly thick.

Table 7. Nerve function impairment findings. No. (%) of patients showing NFI by MF and/or VMT tests, in different leprosy types (Total No. of patients assessed = 397)

	Variables			
Class	N	S	M	S + M
BT	95 (61)	20 (13)	11 (07)	29 (19)
BB	40 (50)	14 (18)	02 (03)	23 (29)
BL	47 (48)	18 (21)	07 (08)	22 (23)
LLs	19 (40)	12 (24)	06 (13)	11 (23)
PN	05 (24)	05 (23)	01 (05)	10 (48)
Total	206 (52)	69 (17)	27 (07)	95 (24)

Key: N – normal, S – pure sensory, M – pure motor, S + M – sensory and motor.

Table 8. Nerve function impairment findings: No. (%) of nerves showing impairment by MF and/or VMT tests

	By MF			By VMT		
Nerves	N	0	Ab	N	0	Ab
Ulnar	600 (77)	47 (06)	130 (17)	645 (82)	28 (04)	111 (14)
Median	648 (83)	32 (04)	104 (13)	762 (97)	07 (01)	15 (02)
R. cutaneous	605 (78)	51 (06)	128 (16)	NA	NA	NA
Sural	565 (72)	95 (12)	124 (16)	NA	NA	NA
C. peroneal	NA	NA	NA	773 (98)	04 (01)	07 (01)
P. tibial	574 (73)	76 (10)	131 (17)	774 (98)	04 (01)	06 (01)
Total	2992 (76)	301 (08)	617 (16)	2954 (94)	43 (02)	139 (04)

Key: N – normal, 0 – total loss of sensations by MF or total muscle weakness by VMT, Ab – abnormal sensations or muscle strength, NA – not applicable.

Table 9. No. (%) of patients showing abnormal nerve function by SNCV & MNCV in different leprosy types (Total No. of patients assessed = 365)

	Variables			
Class	N	S	M	S + M
BT	17 (11)	28 (21)	08 (05)	87 (63)
BB	08 (11)	12 (16)	05 (07)	49 (66)
BL	04 (05)	17 (20)	0	62 (75)
LLs	0	05 (11)	0	42 (89)
PN	0	02 (10)	01 (05)	18 (86)
Total	29 (08)	64 (18)	14 (04)	258 (70)

Key: N – normal nerve function, S – pure sensory, M – pure motor, S + M – sensory + motor.

CONCORDANCE BETWEEN DISABILITY AND VMT/MF ABNORMALITY

All the 130 patients with disability had sensory and/or motor impairment. By contrast, 15% of patients that had sensory and or motor impairment did not have disability (data not shown).

NERVE CONDUCTION VELOCITY (SNCV AND MNCV) FINDINGS

Assessments using SNCV and MNCV were done in 365 patients, of which 336 (92%) showed abnormal nerve function of one or more parameters in the nerves tested. Abnormality of a single nerve was seen in 13 (4%) of patients, of 2–4 nerves in 87 (26%) and of >5 nerves in 237 (70%) patients.

Going by the leprosy type, all the LLs and PN patients, 95% of BL and 89% each of BB and BT patients showed abnormal nerve function (Table 9).

Overall, of the 2920 sensory and motor nerves examined using SNCV and MNCV, 1532 (52%) and 1078 (37%) respectively showed impairment (Table 10).

Sural (72%) and ulnar – motor (67%) were the nerves most frequently and severely affected.

Table 10. No. (%) of nerves showing impairment by SNCV & MNCV

	N	0	D	A	D + A
SNCV					
Ulnar	360 (49)	164 (22)	13 (02)	75 (10)	118 (16)
Median	438 (60)	108 (15)	42 (06)	83 (11)	59 (08)
R. cutaneous	389 (55)	185 (25)	08 (01)	129 (17)	19 (02)
Sural	201 (28)	349 (48)	39 (05)	69 (09)	72 (10)
Total	1388 (48)	806 (28)	102 (03)	356 (12)	268 (09)
MNCV					
Ulnar	321 (44)	21 (03)	289 (40)	09 (1)	90 (12)
Median	488 (67)	11 (02)	74 (10)	60 (08)	97 (13)
C. peroneal	534 (74)	59 (08)	10 (01)	109 (15)	18 (02)
P. tibial	499 (68)	35 (05)	09 (01)	146 (20)	41 (06)
Total	1842 (63)	126 (04)	382 (13)	324 (11)	246 (08)

Key: N – normal nerve function, 0 – no conduction, D – slow conduction, A – reduced amplitude, D + A – slow conduction + reduced amplitude.

Table 11. No. (%) of patients presenting with reaction in different age groups among males and females

Age group (yrs)	Males (No. = 314)	Females (No. = 86)
12–20	17 (16)	12 (28)
21–30	30 (28)	06 (14)
31–40	25 (23)	07 (16)
41–50	21 (19)	14 (33)
51–60	15 (14)	04 (09)
Total (%) with reaction	108 (34)	43 (50)

The proportion of patients as well as nerves affected by SNCV was two-fold higher than MF and MNCV was six-fold higher than VMT proving NCV to be the more sensitive in detecting NFI.

REACTION TYPE

One hundred and forty (35%) patients presented with reaction of type 1 or 2 and/or neuritis. 11/400 (3%) presented with SN of <6 months and were also considered for steroid treatment as per protocol. The proportion of females (43/86 = 50%) with reaction and/or neuritis or SN of <6 months was higher than that of males (108/314 = 34%) ($P < 0{\cdot}005$). Though not statistically significant, occurrence of reaction with/without neuritis or SN <6 months was more common in the age group 21–40 yrs among males ($\sim$28%) while 12–20 (28%) and 41–50 (33%) among females (Table 11).

The majority of them (107/140 = 76%) had T1R with or without neuritis, 8/140 (6%) had T2R with or without neuritis, while 25/140 (18%) had neuritis alone. Total of 66 (47%) patients had neuritis with or without T1R or T2R, which was graded as very severe in 5 (8%) patients, moderate in 15 (23%) and mild in 46 (70%). Occurrence of NFI was more common among patients with neuritis (Table 12).

The prevalence of reaction and/or neuritis or SN <6 months combined was 35% in BT, 39% BB, 41% BL, 33% in LLs and 43% in PN patients. Though not statistically significant, it was highest among PN followed by BB and BL than BT and LLs patients (Table 13).

Table 12. No. (%) of patients presenting with different types of reaction and NFI

			NFI	
Variable	Frequency	Percentage	Frequency	Percentage
Nil	249/400	62	105	40
T1R	71/140	50	33	46
T1R + Neu	36/140	26	18	50
T2R	03/140	02	02	–
T2R + Neu	05/140	04	04	–
Neu	25/140	18	18	72
SN <6 months	11/400	03	11	100

Key: T1R – type 1 reaction, T2R – type 2 reaction, Neu – neuritis, SN – silent neuropathy.

Table 13. No. (%) of patients presenting with reaction in different leprosy types

Class Variable	BT	BB	BL	LLs	PN
No reaction	101 (65)	48 (61)	56 (59)	32 (67)	12 (57)
T1R	28 (18)	19 (24)	21 (22)	03 (06)	0
T1R + Neu	16 (10)	08 (10)	10 (11)	02 (04)	0
T2R	0	0	0	03 (06)	0
T2R + Neu	0	0	0	05 (11)	0
Neu	07 (04)	03 (04)	05 (05)	03 (06)	07 (33)
SN <6 months	05 (03)	01 (01)	03 (03)	0	02 (10)

Key: T1R – type 1 reaction, T2R – type 2 reaction, Neu – neuritis, SN – silent neuropathy.

COMPARISON OF FINDINGS IN PATIENTS WITH REACTION AND/OR NEURITIS AND SN OF <6 MONTHS (GROUP A) AND OTHERS (GROUP B) AT ONSET

Groups A and B were comparable for age and sex (Table 14).

Table 14. Comparison of findings in Group A and Group B

Variables	Group A	Group B	X^2 value, significance
(a) Male:female ratio	No. (%)	No. (%)	
Males	108 (72)	206 (83)	
Females	43 (28)	3 (17)	
(b) No. (%) of patients showing WHO disability grade in Grs. A & B			
Grade 0	79 (52)	190 (76)	24·55, $P < 0.001$
Grade 1	07 (05)	17 (07)	0·8, $P < 0.25$
Grade 2	65 (43)	42 (17)	32·87, $P < 0.001$
(c) No. (%) of patients showing impairment by MF & VMT in Grs. A & B			
N	65 (43)	141 (57)	7·6, $P < 0.005$
S	17 (11)	52 (21)	6·36, $P < 0.01$
M	13 (09)	14 (06)	1·25, $P < 0.25$
S + M	56 (37)	39 (16)	23·17, $P < 0.001$
(d) No. (%) of nerve showing impairment by MF & VMT in Grs. A & B			
Test			
MF	440/1498 (29)	478/2412 (20)	46·90, $P < 0.001$
VMT	112/1192 (09)	71/1944 (04)	43·29, $P < 0.001$
(e) No. (%) of patients showing abnormal nerve function by SNCV & MNCV in Grs. A & B			
N	08 (06)	21 (09)	1·19, $P < 0.25$
S	09 (07)	55 (24)	17·49, $P < 0.001$
M	08 (06)	06 (03)	2·5, $P < 0.5$
S + M	110 (81)	148 (64)	12·05, $P < 0.005$
(f) No. (%) of nerves showing abnormality by SNCV & MNCV in Grs. A & B			
Test			
SNCV	613/1040 (59)	919/1880 (49)	26·94, $P < 0.001$
MNCV	480/1040 (46)	598/1880 (32)	59·02, $P < 0.001$

Key: N – normal, S – pure sensory, M – pure motor, S + M – sensory + motor, MF – monofilaments, VMT – voluntary muscle testing, SNCV & MNCV – sensory and motor conduction velocity.

Bacteriological status

In group A, 12 (8%) patients had BI of 1+, 33 (22%) had 2+ to 3+ and 22 (15%) had $> 4+$. In group B, 8 (3%) patients had BI of 1+, 43 (17%) had 2+ to 3+ and 41 (16%) had $>4+$. Remaining 84 (56%) in group A and 157 (63%) in group B were bacteriologically negative.

WHO disability grade

In both groups, there were more patients with grade 2 than grade 1 disability. The majority in both the groups had ulnar claw (group A – 82%, group B – 88%).

Number of patients showing DG2 was significantly higher in group A than group B ($P < 0{\cdot}001$). Sixteen patients in group A and 12 in group B had more than one DG2, the remaining had single disability.

MF AND VMT TEST FINDINGS

Number of patients showing impaired nerve function (MF + VMT) was significantly higher in group A (57%) than group B (43%). Similarly percentage of impaired sensory and motor nerves was also significantly higher in group A (29% and 9%) than group B (20% and 4%) respectively (in both $P < 0{\cdot}001$).

SNCV AND MNCV FINDINGS

Number of patients showing abnormal nerve function was comparable in two groups (group A = 94% and group B = 91%). However, percentage of affected sensory and motor nerves was significantly higher in group A (59% and 46%) than group B (49% and 32%) respectively ($P < 0{\cdot}001$ for both).

In both the groups, affected sensory nerves (assessed using MF & SNCV) was significantly higher than motor nerves (assessed using VMT & MNCV).

Discussion

This baseline data are of 400 untreated MB patients, presenting with >6 skin lesions or more than 1 palpably enlarged peripheral nerve or positive slit skin smears. MB patients are at a higher risk of reaction and NFI than PB patients.[37] Females formed a small proportion (22%) of the cohort due to selection bias. When the Ridley-Jopling classification was applied, 39% of patients conferred to BT leprosy. Overall, 60% of patients were SSS negative of whom 38% showed growth in the mouse foot pad. Notably, among the BT patients, occurrence of viable *M. leprae* was higher in lesions with GI ($>0{\cdot}7$) which in turn implies that these granulomatous cells failed to kill the bacilli.

WHO DISABILITY GRADE

Disability graded 1 or 2, was seen in 33% of patients, which is less than that recorded in a recent study on MB patients (50%) in northern India by Van Brakel *et al.*[38] However the proportion of patients showing DG2 was higher than DG1 indicating delay in diagnosis, that is unlike the findings of Van Brakel[38] and is much higher than the currently quoted overall

national figure for disability of less than 2%.[39] The occurrence of disability was highest among pure neural patients, although the numbers were small. A field study carried out at Agra in India also recorded a high incidence of ulnar claw deformity, among MB and pure neural patients.[40]

NERVE FUNCTION IMPAIRMENT (NFI)

NFI is an important measure of disease outcome in leprosy. The most commonly used and time-tested clinical tests to record nerve function impairment include graded MF and VMT both of which were used in this study, along with MNP, SNCV and MNCV measurements.

Nerve thickening at the site of predilection is one of the characteristic features of leprosy. Manual nerve palpation (MNP) is a subjective process[41] and is not considered a very reliable test by some, as there are no widely accepted quantitative normal limits. Other rare clinical abnormalities like neurofibromatosis,[42] primary amyloidosis,[43] chronic inflammatory demyelinating polyneuropathy[44] influence nerve enlargement while obesity, occupation and size of the contralateral nerve influence the assessment of nerve thickness.[45] In this study, nerve thickening recorded by the clinician was seen in 85% of patients and most showed more than one thickened nerves (1+ to 2+ to 3+). The ulnar nerve at the sulcus was the most frequently thickened (74%), concordant with the high rate of ulnar claw disability, followed by common peroneal nerve (65%). One to one comparison showed a good positive correlation of MNP with NCV test findings (results not shown).

By MF and/or VMT tests, 48% of patients showed impaired nerve function, whereas by NCV 92% of patients showed nerve abnormalities. In terms of number of nerves, the proportion of sensory and motor nerves showing abnormal nerve function by SNCV and MNCV were two and four-fold higher than by MF and VMT respectively. Higher sensitivity of NCV test in detecting pre-clinical neuropathy and its diffuse nature in leprosy have been documented in the past.[41,46] Discordance between MF and SNCV was particularly high for radial cutaneous and sural nerves which may be due to, as pointed out by Van Brakel *et al.*,[38] that for these nerves only a single site is tested by MF while multiple sites are tested for ulnar and median nerves which increases the sensitivity of MF, and gives a better concordance with NCV. Moreover it has been shown that $>30\%$ of fibres in a nerve are destroyed before any clinical sensory deficit can be elicited.[47] Similarly the discordance between VMT and MNCV was high, and maximum nerves showed abnormal conduction by MNCV but normal strength by VMT. The findings reiterate that the abnormality observed by MNCV may be pre-clinical and may not translate into motor weakness. Secondly in case of peroneal and tibial nerves, the VMT of the foot primarily tests strength of the tibialis anterior, extensor of toes, peroneus longus, and small muscles respectively, while MNCV recordings were taken from the extensor digitorum brevis and abductor hallucis brevis respectively. This apart, the trends noted were very similar in both clinical and NCV tests, suggesting a good agreement between the two tests.

The disability and impairment of sensory and/or motor nerve function assessed by MF and VMT also showed a good agreement in that all the patients showing disability, showed abnormal MF and/or VMT. However over 15% of patients showing impaired nerve function by MF and/or VMT, were not covered by the WHO disability grades, confirming the higher sensitivity of MF and VMT tests.

Sensory neuropathy predominated over motor, which has been a consistent finding in all our studies.[46,48] A study by Brown *et al.*[41] also recorded predominance of sensory

neuropathy, whereas Van Brakel *et al.* report that motor nerves were as frequently affected as sensory.[38]

Sural and ulnar were respectively the most frequently and severely affected sensory and motor nerves. Electrophysiological studies carried out on a small number of patients at this centre[48] and the recent large study of MB patients by Van Brakel *et al.* also record the sural as the most frequently affected sensory nerve.[38] The sural nerve can be useful as an early detection marker, and is also the most amenable nerve for biopsy. The ulnar nerve on the other hand is functionally important and is the most frequently studied nerve. Sabin and Swift[49] and Kumar *et al.*[40] also note that paralysis is more common in the ulnar nerve distribution as compared to other nerves, in leprosy.

Reduced amplitude, indicating axonal damage was the commonest abnormality detected by NCV amongst all the sensory nerves, while slowing of conduction indicating demyelination was recorded maximum (~40%) in the ulnar nerve across the elbow that is suggestive of site specific abnormality. Three prior studies of early leprosy have also identified slowing of conduction across the elbow as the most frequent ulnar conduction abnormality.[50–52] Cool temperature, increased bacillary infiltration, repetitive trauma and bony impingement are implicated as underlying causes.[41] Abnormalities of sensory and/or motor nerves detected by NCV were highest among LLs, PN (all patients by NCV) and BL (95%) patients followed by BB and BT (89% each) patients, which indicate that borderline leprosy is the most widespread and crippling form.[53]

Isolated abnormalities of motor nerves, though not common, have been previously reported.[54] In this study 7% of patients showed pure motor impairment by VMT (Table 7). However, all these patients showed mixed nerve abnormalities by NCV studies. On the other hand, 4% of patients showed abnormality of one or more MNCV parameters (Table 9), while SNCV as well as MF and VMT were normal.

COMPARISON OF FINDINGS IN GROUPS A AND B

WHO disability grade

The proportion of patients showing DG2 was significantly higher in group A (43%), however, more important is the finding that 17% of patients in group B also had DG2, and 29% among them had more than one disability, that is attributable to silently occurring nerve damage.

Nerve function impairments (NFI)

As assessed by clinical tests (MF and VMT), the percentage of patients showing impaired nerve function was significantly higher in group A than group B (Table 14). However the more sensitive NCV test, showed that the proportion of patients with abnormal nerves was the same in the 2 groups (94% and 91% in group A and group B respectively) reiterating that neuropathy is present in almost all patients regardless of reaction. Other notable findings, both by clinical as well as electrophysiological tests, were that a larger proportion of patients in group B showed pure sensory impairment and that in both the groups; mixed (sensory and motor) nerve abnormalities was more common than pure sensory impairment.

Also the number of affected sensory and motor nerves was significantly higher in group A than group B, in both clinical and NCV tests, showing an association between reaction episode and magnitude of NFI as recorded by Van Brakel *et al.*[55] The sensory nerve

abnormalities was significantly higher than motor, showing the predominance of sensory neuropathy in both the groups.

The most important finding of this baseline study is that while peripheral nerve damage can be demonstrated in almost all the patients with leprosy, a reaction episode increases the severity of the problem in terms of extent of nerve damage and visible grade 2 disability. Future publications building on this baseline data will focus on: a) clinical, bacteriological and neurological observations during and after the treatment. b) the effect of corticosteroid usage on the rate of clinical regression, clearance of *M. leprae* and its antigens, regression of granuloma, changes in nerve function and occurrence of viable bacteria, assessed approximately 6 months post release from 1 year MB-MDT in 100 pair matched patients treated with and without steroids.

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