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Reference values for nerve function assessments among a study population in northern India – I: Vibration perception thresholds

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Abstract

Objective: This paper presents normal reference values for vibration perception thresholds for a study population in northern India. The work was in preparation for the INFIR Cohort Study, a prospective study of people newly diagnosed with multibacillary leprosy which sought to identify early changes in nerve function predictive of new onset impairment and reactions. To establish the limits of normal function we collected data on subjects with no known neurological condition and computed the reference values defining the limits of normal function. *Methods:* Data on vibration perception in 5 bilateral nerves was collected from 362 healthy subjects stratified by sex and by age and drawn from the same general population as the subsequent leprosy-affected cohort. Reference values were computed from log-transformed data after the exclusion of outliers. *Results:* Normal reference values are presented in the form of 95th percentiles for vibration perception thresholds among normal subjects for 5 peripheral nerves within 8 age and sex groupings and by centre. The reference values are compared with those published for other populations. The incidence of impairment at diagnosis among the leprosy-affected cohort is described and illustrated.

INTRODUCTION

This is a report of normal values of vibration perception thresholds (VPT) for ulnar, median, radial cutaneous, posterior tibial and sural nerves in the healthy populations served by two specialist leprosy referral centres in northern India. The research was carried out in advance of a 24 month prospective cohort study of newly diagnosed multibacillary leprosy patients resident in the same geographical area, the objective being to assess changes in vibration perception as an early indicator of clinical changes in nerve function associated with leprosy reactions. In the leprosy context normal practice is to use monofilament and voluntary muscle testing for nerve function assessments.

Normal sensory and motor nerve function is affected by age and by a wide range of neurological and medical conditions. Assessment of nerve function therefore has an established role in diagnosis and monitoring.[1] Vibrometry testing is one of several physiologic tests known collectively as quantitative sensory testing (QST).[2-4] Testing vibration perception thresholds (VPT) is a sensitive and reliable method of nerve function testing[5] and in staging the severity of diabetic neuropathy.[6] While loss of sensory and motor function is the major contributor to the secondary disabilities and deformities associated with leprosy, only limited use has been made of QST. Histological evidence indicates that in early leprosy, small unmyelinated fibres are affected early, with a consequent reduction in the mediation of pain, temperature sensation and autonomic function.[7] The present paper provides the reference values needed to assess the impact of *M. leprae* on larger myelinated fibres assessed by VPT.

METHODS

The research was centred on the specialist leprosy referral centres in Naini and Faizabad, Uttar Pradesh state, northern India, run by The Leprosy Mission International. The equipment used in

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each field centre was a Vibrameter Type IV, manufactured by Somedic in Sweden. These are a development from biothesiometers and measure the amplitude of displacement in a vibrating probe in micrometers (μM). They include a built-in pressure transducer that measures the application force, which is shown as an indicator on the control panel, allowing the tester to keep the force within narrow limits. The equipment includes a manual control used by subjects to signify their response to the test. However, early trials with the equipment demonstrated that many subjects lacked the co-ordination needed to respond promptly. We therefore relied on the verbal response of subjects.

Subject selection and sample size

In order to achieve a close match with individuals recruited to the cohort study we planned to recruit subjects from among the healthy relatives accompanying individuals attending general and dermatology outpatient clinics at the two participating centres, applying inclusion and exclusion criteria as follows:

Inclusion criteria: Since VPT is reported to be age-related, we selected equal numbers of subjects within four age bands up to 60 years, the maximum age for recruitment to the subsequent cohort study. We also assessed equal numbers of men and women within each age band.

Exclusion criteria: Since the diagnosis of leprosy can only be made on clinical grounds all subjects were screened by an experienced leprologist leading to the exclusion of anyone exhibiting any clinical signs or symptoms of leprosy. Subjects with any known neurological disorder, previous contact with leprosy or a history of diabetes were also excluded. Individuals aged above 60 years or those less than 10 years were excluded.

Sample Size: To ensure adequate precision we planned to assess 40 subjects within each of four age bands for men and for women. The overall target for the number of subjects was therefore 320, equal numbers to be recruited in each centre.

Protocol for testing and data recording

Because neuropathy in leprosy is understood to be localised and non-homogeneous, we decided to test VPT on soft tissue rather than bony prominences. The latter spread the sensation more widely, allowing unaffected sensory fibres at some distance from the test site to pick up the stimulus and thus produce a false negative result. The bilateral nerves and test sites were the hypothenar eminence representing the ulnar nerve, the thenar eminence representing the median nerve, the dorsal first web space representing the superficial radial nerve, the plantar surface of the great toe for the posterior tibial nerve and the mid-lateral border of the foot representing the sural nerve. The same sites were tested in the subsequent cohort study. The detailed instructions on the use of the vibrometers are described in Table 1.

Vibrometry testing was undertaken by a team of physiotherapists in each centre. Physiotherapists were instructed to repeat assessments at each site until three comparable readings were obtained. These were recorded and the procedure repeated for left and right test sites on each of the five nerves tested. Subject ID, demographic data and each data triplet were entered into a Microsoft Access database.

To ensure reliable and reproducible results, we provided training for the 8 physiotherapists and one physio-technician involved in the study, 5 in Naini and 4 in Faizabad. To assess inter-rater reliability we recruited subjects with a variety of neurological conditions. Within each centre each pairing of physiotherapists completed blinded assessments of 20 to 30 volunteer subjects. In Faizabad, intraclass correlation coefficients (ICC) ranged from 0.702 to 0.995. In Naini, two of the ICCs were below 0.75, each pairing involving an individual who subsequently had only a limited involvement in the project.

Choice of reference values

We noted considerable variation in the literature concerning the choice of percentiles used to define reference values.[1] The choice of percentile is dependent on a combination of clinical, disease-specific, personal and financial factors.[10] Presented here are reference values based on the 95th percentile. Since at the time of the study the extent of impaired vibration perception among people affected by leprosy was unknown we also calculated 97.5th and 99th percentiles and made these available to the analysis of the data from the Cohort Study.

Identification of outliers and computation of normal reference values

The analysis involved checking of data entry, identifying and excluding outliers and computing reference values. Assessments of 5 bilateral nerves from 362 subjects produced more than 3,400

Table 1: Instructions in the use of the vibrometers

1. Check that the pressure indicator properly balances when the pressure is applied
2. The subject should be comfortably seated, or lying on a bed, with as few disturbing factors in the surroundings as possible.
3. Relaxation of the test site (hand, foot, etc) should be ensured by providing support with a rice cushion. (A small sack of soft cloth, filled with household rice or a sandbag).
4. Explain the procedure to the subject. Explain that the test will in no way be painful, but that the subject may feel an uncommon buzzing sensation.
5. The examiner should be seated in a unstrained position with comfortable access to, and visual contact with the subject, the test site and the vibrometer.
6. During measurement, place the probe of the vibrator perpendicularly to the test site, to provide smooth, painless contact. Preferably there should be no tendons between vibrator and bone. The placement should be checked during the measurements, to verify that the vibrator stays in the correct position.
7. Adjust the application pressure to centre the vibrometer pressure indicator (small variations, like one or two indicator steps from the centre, can be tolerated) and keep this application pressure as constant as possible during the measurements.
8. Start with no vibration and tell the subject that "this is the feeling of the pressure from the vibrator". Then increase the vibration amplitude to a supra threshold level and ask him/her if (s)he can feel a vibrating (buzzing) sensation. When these two initial sensations are defined, and recognised, sometimes after repeated trials, you have a coarse indication of the person's threshold, and (s)he starts to be used to the measurement procedure.
9. Now you instruct the subject to tell you (or press the response button) as soon as the vibration first appears. (This is the definition of vibration perception.)
10. VPT is to be recorded three times at the same test site, with the probe preferably removed between the measurements and reapplied at a nearby, or the same, location. If the three recordings differ in order of magnitude, further readings should be taken until three readings in the same range have been obtained. The average of these three recordings constitutes the final VPT value.
11. Continue until the thresholds for all sites have been determined and saved.
12. Replace the vibrator on the control unit and thank the person for his/her cooperation.
13. The result is copied *immediately after each test* from the digital readout into the appropriate box on the vibrometry form. This is repeated three times, as above.

data triplets. To check the accuracy of data entry we compared a random sample of 10% of data forms with the data on computer. This identified just 3 data entry errors arising from the omission or misplacement of a decimal point or the misreading of data forms. We then used a database query that contrasted the maximum and minimum differences within each data triplet to identify and correct similar errors in the full data set. Finally we computed the mean for each triplet.

In view of age-related changes in VPT, we identified outliers using regression analysis of log-transformed VPT on age. The procedure was carried out separately within four groups defined by centre and sex. Any assessments for which the standardised residual exceeded 2.58 were identified as outliers and excluded from all further analysis. Where a subject was found with 3 or more outliers all assessments were excluded. Following the first round of screening a judgement was made on the need to remove further outliers. Where necessary, this was achieved by repeating the same procedure. Compared to the earlier analysis and thresholds applied in work already published, this procedure is more sensitive to differences between age and sex groups and results in a more conservative elimination of outliers.

Having excluded outliers we used analysis of variance on log-transformed data to assess differences between sexes, between age groups, between left and right sides and between centres. Subject to finding no differences between left and right sides we planned to pool remaining assessments, effectively doubling the sample size and then to use regression analysis of log transformed data on age within each sex and centre grouping to compute reference values. These were then reverse-transformed to the original units of amplitude. Reference values for VPT based on the 95th percentiles were computed as the predicted value for age plus 1.64 times the standard deviation of regression estimates and

then reverse transformed and tabulated by sex and by age band.

Application of reference values

These reference values were then applied to classify nerve function in a prospective cohort study of 303 newly diagnosed cases of multibacillary leprosy, the INFIR Cohort Study, the objective being to identify early changes in nerve function predictive of new onset impairment and reactions. Recruitment for this study was completed in the 16 months up to May 2002 and the last 2-year follow-up visits were completed in May 2004. Routine clinical assessments were made at each visit, including assessments of sensory function of ulnar, median, radial cutaneous, posterior tibial and sural nerves and motor function using voluntary muscle testing of ulnar, median, radial and lateral popliteal nerves. The same nerves were also assessed for vibration perception thresholds, warm and cold sensation and nerve conduction. Findings from the study have been published[8,9,18,19,20], including impairment rates. However, the method of calculation of reference values reported here is based on a re-analysis of the normative data using methods that show greater sensitivity to differences relating to sex, age and centre. Other papers in the present series[21, 22] describe reference values for thermal sensation and for parameters of sensory and motor nerve conduction.

All the analysis was carried out using STATA.

Ethical approval

Ethical approval for all aspects of the INFIR study was obtained from the Indian Council of Medical Research, through the Research Ethics Committee of the Central JALMA Institute for Leprosy in Agra. Written consent was obtained from subjects enrolled in the Cohort Study and verbal consent from individuals participating as subjects in the normal and reliability studies.

RESULTS

The total number of subjects assessed was 362, 191 in Faizabad and 171 in Naini. Two rounds of screening for outliers resulted in the exclusion of all data from 3 subjects and the exclusion of 11 single assessments, 1.2% of the total number of assessments. The age and sex distribution of the 359 subjects contributing data to the analysis is presented in Table 2.

In Faizabad there were relatively fewer female subjects and fewer in the oldest age group. This is reflected in differences in mean age between centres. The average age of men in Faizabad was 32.8 years (sd 13.54) compared with 40.1 years (13.08) in Naini ($p<0.001$). The equivalent figures for women were 35.0 (13.95) for Faizabad and 39.8 (13.22) for Naini ($p<0.05$).

Table 3 presents the mean, standard deviation and median VPT by centre, sex, age group and side for all five nerves tested. The total number of assessments excludes a small number of missing values relating to missed tests or errors in recording. We used analysis of variance of log-transformed data to assess the statistical significance of differences between sexes, between age groups, between sides and between centres. In all nerves VPT increased with age ($p<0.001$) and was higher among men than among women ($p<0.01$ in upper limb nerves and $p<0.05$ in lower limb nerve). The importance of these sex and age-related differences is illustrated in Figure 1. There was a statistically significant interaction effect between age and sex only in ulnar ($p<0.05$), radial cutaneous ($p<0.001$) and posterior tibial nerves ($p<0.05$), drawing attention to high VPTs amongst the oldest men. Mean right side VPT for all five nerves was marginally higher than that for the left side but none of these differences reached statistical significance. Including a variable representing the test centre in the analysis did not affect these findings but between-centre differences reached statistical significance in all 5 nerves ($p<0.001$).

Since none of the comparisons between left and right side reached statistical significance we concluded that we could compute reference values based on pooled left and right side assessments, effectively doubling the sample size. We completed separate regression analyses to identify centre-specific age-related reference values for men and for women for each of the five nerves assessed (Table 4). (Reference values based on 97.5th and 99th percentiles are available from the authors).

Figure 1 presents scatter plots for ulnar and posterior tibial nerve VPT in which the line of the 95th percentile is based on data from combined centres and the shaded area draws attention to the difference between centre-specific 95th percentiles. The charts illustrate how the percentiles vary with age and facilitate comparisons between men and women and between upper and lower limb nerves.

To illustrate the application of these reference values we computed impairment rates among the

Table 2: Age and sex distribution plus row and column percentages for subjects assessed in each centre

Faizabad					
	Age groups (years)				
Sex	**<=30 yrs**	**31-40 yrs**	**41-50 yrs**	**51-60 yrs**	**Total**
Female	31 39.7, 38.3	22 28.2, 41.5	18 23.1, 52.9	7 9.0, 33.3	78 41.3
Male	50 45.1, 61.7	31 27.9, 58.5	16 14.4, 47.1	14 12.6, 66.7	112 58.7
Total	81 42.9	53 28.0	34 18.0	21 11.1	189

Naini					
	Age groups (years)				
Sex	**<=30 yrs**	**31-40 yrs**	**41-50 yrs**	**51-60 yrs**	**Total**
Female	23 27.4, 52.3	20 23.8, 48.8	19 22.6, 45.2	22 26.9, 51.2	84 49.4
Male	21 24.4, 47.7	21 24.4, 51.2	23 26.7, 54.8	21 24.4, 48.8	86 50.6
Total	44 25.9	41 24.1	42 24.7	43 25.3	170

303 individuals newly diagnosed with MB leprosy who were recruited to the INFIR cohort study at the same two field centres. Full details of the cohort have been published elsewhere.[8] Centre, age and sex-specific rates for impaired function beyond these reference values for each nerve at time of diagnosis are presented in Table 5.

The charts in Figure 2 illustrate the impact of *M.leprae* on nerve function. High proportions of cases presented with VPT well outside the normal range, providing evidence of early nerve involvement in leprosy. We also note that the impaired rate was substantially higher than that identified using a standard set of five monofilaments.

DISCUSSION

This is the first major study to produce reference values for VPT for a study population in northern India. Our inclusion and exclusion criteria ensure that these are applicable across similar areas of India. They may be applied in studying the impact of a variety of neurological conditions in which VPT is a recognised clinical measure of nerve function.

In planning our research and interpreting our findings we were aware of a lack of consensus in published work concerning the relationship between VPT and variables such as sex, height, weight, occupation and dominant side. Bartlett *et al*[11] found that vibration sensation deteriorates with age while any sex effect is confounded by height. The same authors found no effect relating to skin temperature. Only in the foot was VPT associated with height. Others have confirmed these findings. [5, 12]

Sosenko *et al*[13] and de Neeling *et al* [14] reported an association between height and VPT while Meh and Denislic[15] found substantial heating (5°C) and substantial cooling (10°C) influenced vibration perception thresholds. Hilz *et al* found no relationship with height or with skin temperature.[5] All our vibrometry assessments were conducted in air-conditioned rooms with temperature within the range 22°C to 26°C. Since the study population was relatively homogeneous with regard to height and weight, we judged that

Table 3: N, mean, standard deviation and median vibration perception threshold by nerve, centre, sex, age group and side.

Age Group	Side	Ulnar	Median	Radial Cutaneous	Posterior Tibial	Sural
			VPT for male subjects by age group in Faizabad			
<=30 yrs	**Right**	49, 0.91 (0.61), 0.72	50, 0.88 (0.48), 0.75	50, 0.66 (0.30), 0.62	50, 1.41 (1.33), 1.06	49, 0.85 (0.41), 0.75
	Left	50, 0.74 (0.39), 0.61	50, 0.80 (0.43), 0.64	50, 0.64 (0.35), 0.53	50, 1.12 (0.73), 0.94	50, 0.86 (0.50), 0.67
31-40 yrs	**Right**	31, 1.14 (0.67), 0.97	31, 1.54 (1.06), 1.23	31, 1.02 (0.64), 0.83	31, 2.85 (2.98), 2.04	31, 1.99 (1.88), 1.29
	Left	31, 1.07 (0.54), 0.90	31, 1.28 (0.68), 0.99	31, 1.07 (0.69), 0.80	31, 2.58 (2.41), 1.81	31, 2.04 (1.63), 1.47
41-50 yrs	**Right**	16, 1.54 (0.83), 1.33	16, 1.25 (0.51), 1.11	16, 1.00 (0.61), 0.89	16, 3.22 (2.93), 2.39	16, 1.97 (1.39), 1.60
	Left	16, 1.37 (0.90), 1.22	16, 1.39 (0.86), 1.09	16, 1.16 (0.68), 0.94	16, 3.69 (4.30), 2.51	16, 2.51 (2.21), 2.08
51-60 yrs	**Right**	14, 2.00 (1.14), 1.80	14, 1.98 (1.06), 1.91	14, 1.49 (1.30), 0.94	14, 5.34 (5.83), 2.68	14, 4.99 (4.32), 2.94
	Left	14, 1.65 (0.98), 1.29	14, 1.68 (1.01), 1.30	14, 1.20 (0.82), 0.96	14, 4.99 (5.54), 2.87	14, 6.10 (10.67), 3.07
			VPT for female subjects by age group in Faizabad			
<=30 yrs	**Right**	31, 0.83 (0.45), 0.67	31, 0.99 (0.85), 0.72	31, 0.70 (0.49), 0.48	31, 1.57 (1.19), 1.19	31, 1.18 (1.07), 0.85
	Left	30, 0.81 (0.58), 0.64	30, 0.78 (0.32), 0.69	30, 0.74 (1.04), 0.51	31, 1.56 (1.25), 1.12	31, 1.23 (1.12), 0.95
31-40 yrs	**Right**	21, 0.82 (0.40), 0.76	22, 1.09 (1.14), 0.76	22, 0.87 (0.81), 0.58	22, 1.68 (1.70), 1.29	22, 1.46 (1.41). 1.18
	Left	22, 0.87 (0.53) 0.69	22, 0.91 (0.73), 0.67	22, 0.71 (0.51, 0.58	22, 1.70 (1.36), 1.29	22, 1.29 (0.88), 1.11
41-50 yrs	**Right**	17, 1.46 (1.32), 1.06	18, 2.23 (2.24), 1.18	18, 1.31 (1.54), 0.66	18, 3.76 (3.51), 1.93	18, 3.84 (4.41), 1.55
	Left	18, 1.61 (1.68), 1.07	18, 1.88 (1.78), 1.16	18, 1.57 (2.34), 0.81	18, 3.63 (3.38), 2.27	18, 4.04 (5.19), 1.52
51-60 yrs	**Right**	7, 2.38 (1.43), 1.99	7, 2.60 (1.46), 2.41	7, 2.76 (1.11), 2.63	7, 6.64 (2.79), 7.65	7, 3.94 (1.93), 4.17
	Left	7, 2.15 (1.47), 1.48	7, 2.20 (1.39), 1.69	7, 2.72 (2.13), 1.79	7, 5.99 (2.25), 6.49	7, 4.81 (2.72), 3.62
			VPT for male subjects by age group in Naini			
<=30 yrs	**Right**	21, 0.72 (0.23), 0.63	21, 0.86 (0.30), 0.77	21, 0.76 (0.22), 0.66	21, 1.37 (0.64), 1.16	21, 1.12 (0.55), 0.90
	Left	21, 0.70 (0.21), 0.62	21, 0.87 (0.37), 0.74	21, 0.74 (0.25), 0.69	21, 1.36 (0.73), 0.96	21, 1.17 (0.77), 0.89
31-40 yrs	**Right**	21, 0.67 (0.18), 0.63	21, 0.74 (0.25), 0.68	21, 0.72 (0.18), 0.71	21, 1.35 (0.59), 1.19	21, 1.31 (0.56), 1.37
	Left	21, 0.66 (0.21), 0.62	21, 0.74 (0.28), 0.65	21, 0.73 (0.22), 0.65	21, 1.31 (0.64), 1.25	21, 1.07 (0.47), 0.95
41-50 yrs	**Right**	22, 0.71 (0.25), 0.66	23, 0.96 (0.48), 0.85	23, 0.99 (0.61), 0.84	22, 2.89 (3.17), 1.65	22, 2.58 (4.00), 1.08
	Left	22, 0.75 (0.30), 0.68	23, 0.93 (0.46), 0.84	23, 0.88 (0.47), 0.65	22, 2.84 (3.59), 1.36	22, 2.30 (3.12), 1.12
51-60 yrs	**Right**	21, 0.92 (0.35), 0.88	21, 1.12 (0.56), 1.05	21, 0.97 (0.45), 0.87	21, 2.42 (2.46), 1.61	21, 3.02 (4.80), 1.40
	Left	21, 1.01 (0.56), 0.83	21, 1.10 (0.60), 0.92	21, 0.88 (0.34), 0.81	21, 2.79 (2.67), 1.69	21, 3.01 (4.62), 1.53
			VPT for female subjects by age group in Naini			
<=30 yrs	**Right**	23, 0.59 (0.22), 0.51	23, 0.67 (0.32), 0.62	23, 0.62 (0.26), 0.55	23, 0.89 (0.42), 0.76	23, 0.79 (0.48), 0.56
	Left	23, 0.56 (0.23), 0.48	23, 0.55 (0.18), 0.49	22, 0.56 (0.18), 0.52	23, 0.89 (0.45), 0.72	23, 0.75 (0.42), 0.64
31-40 yrs	**Right**	20, 0.68 (0.28), 0.61	20, 0.65 (0.23), 0.64	20, 0.68 (0.35), 0.57	20, 1.51 (0.94), 1.26	20, 1.17 (0.64), 1.08
	Left	20, 0.64 (0.21), 0.57	20, 0.67 (0.31), 0.57	20, 0.60 (0.17), 0.56	20, 1.57 (0.85), 1.57	20, 1.16 (0.67), 1.04
41-50 yrs	**Right**	19, 0.80 (0.33), 0.69	19, 0.88 (0.41), 0.79	19, 0.80 (0.33), 0.68	19, 2.08 (1.53), 1.79	19, 1.69 (1.77), 1.17
	Left	19, 0.73 (0.28, 0.63	19, 0.80 (0.29), 0.79	19, 0.82 (0.35). 0.72	19, 2.08 (1.76), 1.38	19, 1.70 (1.71), 1.22
51-60 yrs	**Right**	22, 1.15 (0.58), 1.09	22, 1.34 (0.89), 1.13	22, 1.56 (1.26), 1.32	22, 3.71 (3.52), 2.43	22, 3.10 (2.24), 2.39
	Left	22, 1.13 (0.55), 0.99	22, 1.12 (0.54), 0.91	22, 1.24 (0.63), 1.21	21, 2.84 (1.83), 2.40	22. 3.46 (3.86), 2.51

Table 4: Normal reference values for five nerves based on the 95th percentile, presented as mid-points of four 10 year age bands and calculated by sex, by centre and by combined centres.

	Ulnar		Median		Radial Cutaneous		Posterior Tibial		Sural	
Faizabad	M	F	M	F	M	F	M	F	M	F
25 years	1.80	1.66	1.89	2.08	1.72	1.93	4.05	4.04	2.58	3.06
35 years	2.36	2.24	2.47	2.93	2.14	2.82	6.20	6.09	4.22	4.38
45 years	3.12	3.07	3.24	4.19	2.67	4.15	9.57	9.28	7.05	7.23
55 years	4.14	4.26	4.27	6.05	3.34	6.13	14.85	14.23	11.90	11.24
Naini										
25 years	1.18	0.94	1.50	1.01	1.31	0.96	4.32	2.39	4.07	2.05
35 years	1.29	1.21	1.66	1.32	1.44	1.31	5.18	3.55	4.94	3.23
45 years	1.40	1.58	1.83	1.76	1.59	1.86	6.20	5.32	5.99	5.16
55 years	1.53	2.09	2.02	2.38	1.74	2.71	7.39	8.01	7.22	8.34
Combined centres										
25 years	1.68	1.34	1.82	1.61	1.51	1.43	4.18	3.34	3.08	2.76
35 years	1.96	1.74	2.16	2.12	1.77	1.96	5.62	4.79	4.38	4.13
45 years	2.30	2.28	2.56	2.83	2.07	2.73	7.60	6.90	6.28	6.26
55 years	2.71	3.03	3.04	3.81	2.43	3.84	10.29	10.00	9.05	9.55

these variables were unlikely to have an important influence and did not record this information. By separate analysis of data from men and women we eliminated some height-related bias. Our analysis found the expected relationship between age and VPT.[5,11,12,13,16] We also found statistically significant difference between sexes.

While traditional values are now changing in India, historical norms have discouraged left-handedness. We did not therefore identify the dominant hand for our subjects. Our analysis found that right side VPT was marginally higher in all five nerves tested, though in none of these did the difference reach statistical significance. Hilz *et al*[5] had similar findings.

From examination of the scatter plots (Figures 1 and 2) it is apparent that both subjects and cases showed a strong preference to report

Table 5. Impairment rates for five nerves among 303 newly diagnosed cases of MB leprosy, presented by sex and by centre. Impairment rates for Faizabad cases are based on Faizabad-specific reference values. Impairment rates for Naini cases are based on Naini-specific reference values. Impairment rates for all combined centres are based on reference values computed from combined centres.

	Ulnar		Median		Rad. Cut.		Pos. Tib.		Sural	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Faizabad	17.0	15.9	22.5	13.6	22.0	11.4	35.4	22.4	37.5	27.3
Naini	17.1	24.4	15.1	21.8	18.0	31.2	20.9	28.2	17.2	32.5
Combined centres	13.4	16.9	15.9	13.3	19.6	14.5	26.8	22.7	26.9	25.5

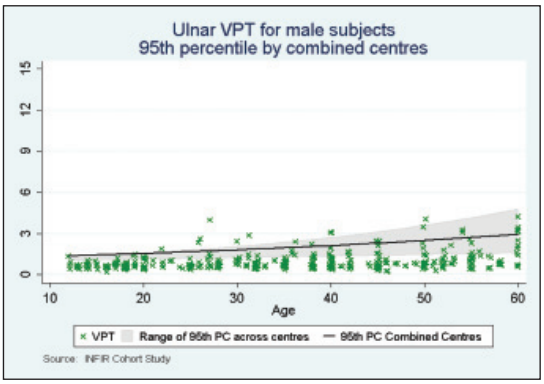

Figure 1a. Normal reference values for ulnar VPT by age for male subjects in combined centres

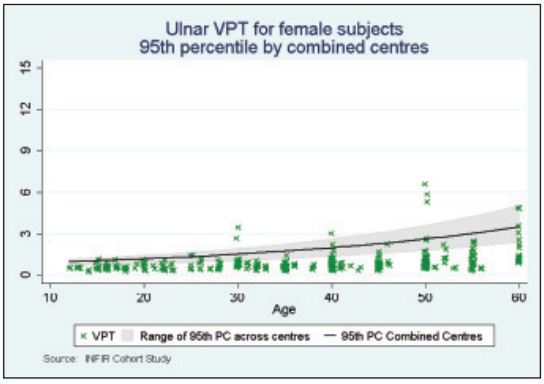

Figure 1b. Normal reference values for ulnar VPT by age for female subjects in combined centres

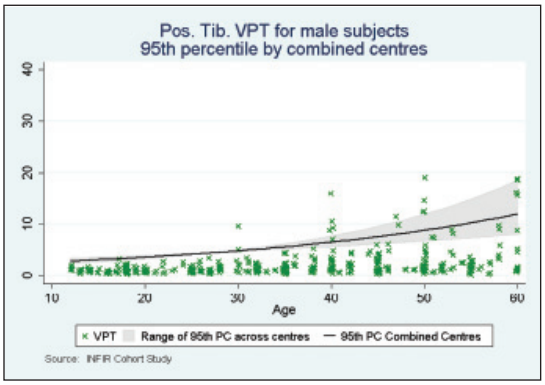

Figure 1c. Normal reference values for posterior tibial VPT by age for male subjects in combined centres

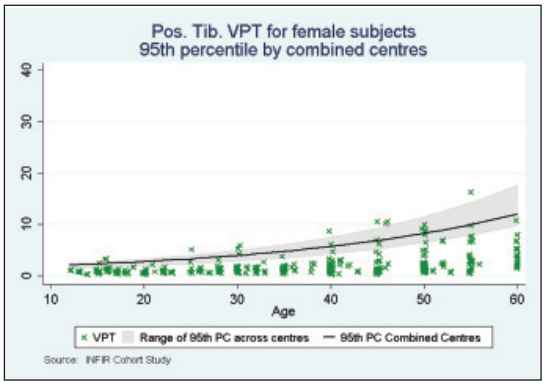

Figure 1d. Normal reference values for posterior tibial VPT by age for female subjects in combined centres

Figure 1. Scatter plots of ulnar and posterior tibial vibration perception thresholds for normal subjects by age and by sex with reference values in the form off 95th percentiles based on combined centres plus shaded area highlighting the difference between centre-specific 95th percentiles

age to the nearest five or ten years. Uncertainty concerning the date or year of birth is not uncommon in India, particularly among older people. A tendency for under-estimation would explain the extreme assessments found among some of the oldest subjects, in turn suggesting the need for reanalysis excluding subjects giving their age as 60 years. This might aid comparison with published data on other populations, but would reduce the value of the reference values in the Indian context. In absence to any clear evidence to the contrary, we have to consider that age may be under-estimated or over-estimated. By accepting self-reported ages we have produced reference values that can be used in the local context without the need to determine a more precise estimate of age.

Comparison of data collected at the two participating field centres identified statistically significant differences in VPT across each sex and age group (Table 3). Subjects assessed in Faizabad tended to have more extreme mean scores and show greater variation than those assessed in Naini. We note that the Naini centre is situated on the edge of the major city of Allahabad and serves a mixed urban and rural population while the Faizabad centre is situated close to the town of the same name and serves a more rural population. Published work has identified factors that may be relevant to the observed differences between centres, including life style, smoking status, nutrition and general health status[13], however, we did not record such data on our subjects. The data we have on 220 men recruited to the subsequent cohort study shows 63% of cases in Faizabad working as labourers compared with 57% in Naini, however, this difference is not statistically significant.

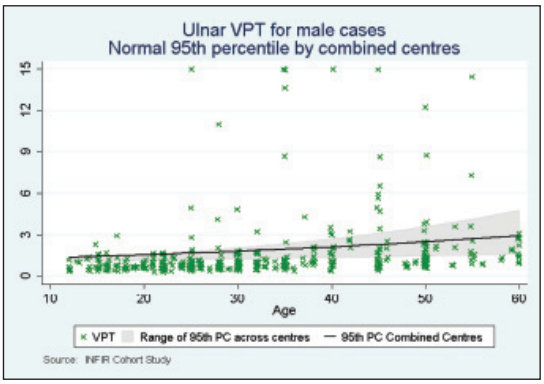

Figure 2a. Ulnar VPT for newly diagnosed male MB leprosy cases plus reference values based on 95th percentiles in combined and individual centres

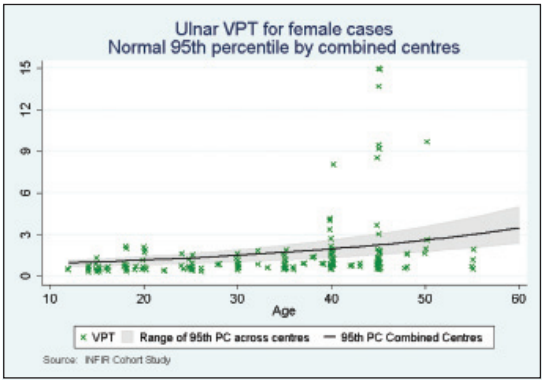

Figure 2b. Ulnar VPT for newly diagnosed female MB leprosy cases plus reference values based on 95th percentiles in combined and individual centres

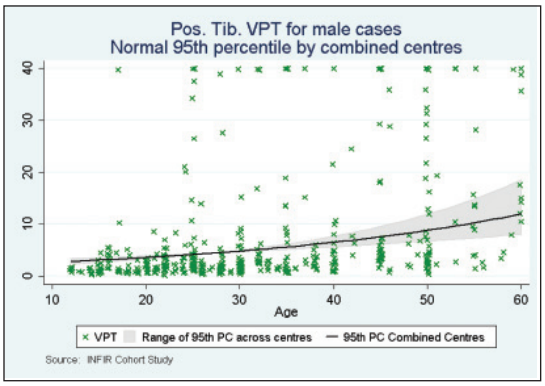

Figure 2c. Posterior tibial VPT for newly diagnosed male MB leprosy cases plus reference values based on 95th percentiles in combined and individual centres

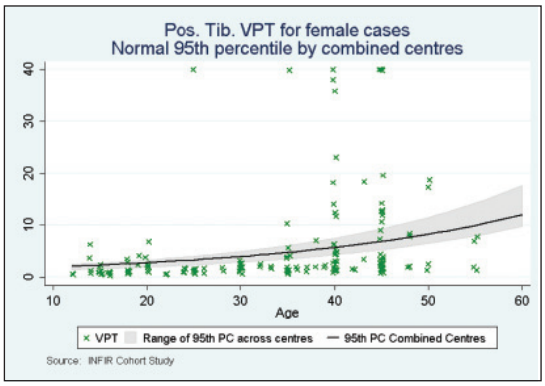

Figure 2d. Posterior tibial VPT for newly diagnosed female MB leprosy cases plus reference values based on 95th percentiles in combined and individual centres

Figure 2. Scatter plots of ulnar and posterior tibial vibration perception thresholds for cohort cases by age and by sex with normal reference values in the form of 95th percentiles based on combined centres plus shaded area highlighting the difference between centre-specific 95th percentiles

Further analysis of the data excluded the possibility that one or more of the physiotherapists recorded assessments that were out of line with others. We considered the possibility of other differences between the centres, for example, in calibration of the vibrometers, in test procedures or in working environment. However, since we identified similar between-centre differences in thermal sensation and in sensory and motor nerve conduction testing, we concluded that these differences reflect real differences between the populations served by the two centres, most likely relating to local differences in occupation or nutritional status. With this in mind, in the analysis of data from the Cohort Study we applied centre-specific reference values throughout.

As part of a study of patients with a variety of upper limb disorders in Denmark, Larsen *et al*[17] reported the vibration perception thresholds for a group of 50 Controls using the same Somedic vibrometer as used in the present study. They found no significant differences between left and right side assessments and a strong age-related effect. Mean values for right /left sides and ranges were 0.48/0.49 (0.19-0.77/0.25-0.98) for ulnar nerve, 0.70/0.68 (0.47-1.16/0.38-1.52) for median nerve and 0.45/0.46 (0.24-0.90)/0.19-0.84) for radial nerve. Mean ulnar VPT for the youngest age group (age up to 35 years) was of the order 0.38 compared with 0.57 for age 51+. The equivalent for median was 0.55 and 0.78 and for radial 0.35 and 0.50. Comparison with data in Table 3 makes

it apparent that ulnar nerve VPT reported in the present study are substantially higher than those reported from Denmark, the mean VPT for our subjects approaching the maximum observed values for the Danish subjects. Together with the present finding of differences between our two centres in northern India this draws attention to a wide spectrum of "normal" VPT and stresses the importance of obtaining locally appropriate reference values, as opposed to applying values based on different population groups. Further research would identify the specific contributory factors.

In conclusion, the reference values presented here reflect the limits of normal vibration perception in a study population in UP State, northern India. As such they are of value in the assessment of nerve function in a wide range of neurological conditions.

Comparison with data from the leprosy cohort illustrates the high rates of impaired function among people newly diagnosed with leprosy. Further analysis of data from the Cohort Study will determine if detecting change in VPT during multi-drug therapy is an indicator for the onset of clinical changes in nerve function associated with leprosy reactions.

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