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A clinicopathological and electrophysiological study of nerve involvement in leprosy in a tertiary care centre in South India

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Summary
Objectives and Methods To correlate the clinical spectrum of Hansen's disease with the histopathological spectrum in skin and nerve and to study the electrophysiological changes in peripheral nerves in Hansen's disease. Thirty-five consecutive attendees with leprosy were recruited for the study from a tertiary dermatology clinic.
Results Clinically, borderline tuberculoid (BT) classification was the commonest subtype with 34% cases, followed by borderline lepromatous (BL) and lepromatous (LL). The incidence of multibacillary (MB) cases was high (83%) and grade 2 disability was seen in 23% cases. Concordance between clinical diagnosis and skin histopathology was 75.8%, while between clinical diagnosis and nerve histopathology was 68%. Skin and nerve histopathology were in concordance in 60% of cases. Electrophysiological assessment revealed derangement in 88.5% of cases with sensory nerve conduction parameters being the commonest and earliest to be affected. Analysis revealed a significant association between deranged parameters and thickness of the superficial peroneal nerve, sural and common peroneal nerves. Subclinical involvement was high in most nerves studied. Cases at the tuberculoid end of the spectrum showed more of segmental demyelination, whereas lepromatous cases showed a mixture of axonal and demyelinating changes.
Conclusion A high degree of concordance was seen between dermal and nerve histopathologies, especially towards the poles of the leprosy spectrum. With an increasing trend towards MB cases and grade 2 disability, our study validates nerve

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conduction study to be a very sensitive screening tool to detect Hansen's disease in its early stages and also to identify the type of nerve degeneration. Nerve histopathology may be considered as the gold standard for confirmation of the diagnosis of leprosy.

Keywords: Leprosy, histopathology, peripheral nerves, nerve enlargement, nerve conduction study

Introduction

Hansen's disease is a chronic infectious disease caused by *Mycobacterium leprae*, primarily affecting the peripheral nervous system, skin and certain other tissues.[1] It continues to be an important public health problem in many parts of Africa, Latin America and Asia. On December 30th, 2005, India declared elimination of leprosy as a public health problem after achieving a nationwide prevalence of less than 1 case/10,000 population.[2] However, the trends of two important indicators of the National Leprosy Eradication Program, India, namely, the Annual New Case Detection Rate (ANCDR) and the Prevalence Rate (PR) have been almost static since 2006–2007,[3] thus necessitating a periodic updating of our knowledge about the disease.

Timely diagnosis and treatment before nerve damage has occurred, is the most effective way of preventing disability due to leprosy. While the skin histology continues to be the standard tool in confirming the diagnosis and classification of leprosy, studies have shown that nerve histology gives more information about the exact classification.[4] The entire spectrum of leprosy has been observed in nerves. Clinical electrophysiological studies significantly help in early diagnosis as well as detection of neuropathies in leprosy. A stage of functional blockade of nerve conduction always precedes visible pathological changes in the nerve.[5]

Materials and methods

This was an observational study of 35 consecutive patients with Hansen's disease attending the department of Dermatology at the Government Medical College, Kottayam in South India, over a period of 14 months from 2015 to 2016. A clinical diagnosis of leprosy was made according to criteria propounded by the WHO Expert Committee on leprosy (1997).[6] Informed consent was taken before enrolment. We included both new and relapsed cases of leprosy, irrespective of age and sex and excluding those cases where neuropathy due to other causes was suspected.

A detailed history, dermatological and neurological examinations were carried out in all patients. Basic neurological examination was done as follows, with special attention to the following parameters: nerve palpation, voluntary muscle testing (VMT) and sensory examination. Patients were classified according to the Ridley Jopling classification and disability grading was done according to the WHO disability grading system of 1988.[7] Slit skin smears were taken from two sites (active skin lesion and ear lobe). Skin biopsy and nerve biopsy were done from those who consented.

Skin biopsy and nerve biopsy were done at the same sitting. In pure neuritic (PNL) cases, a skin biopsy was taken from the anaesthetic area supplied by the corresponding nerve. Nerve biopsy was taken from a thickened nerve, if present. Purely cutaneous sensory nerves were selected. In cases where a thickened sensory nerve was not present, a biopsy was taken from the radial cutaneous or ulnar cutaneous nerve, irrespective of the site of the lesion.

NERVE CONDUCTION STUDIES

Electrophysiological conduction studies were done at the Department of Neurology using the Nihon Kohden EMG/NCV/EP system. The following nerves were analysed

(a) Motor nerve conduction velocity (MNCV) study of:

(i) Ulnar nerve,
(ii) Median nerve
(iii) Common peroneal nerve (CPN)
(iv) Posterior tibial nerve (PTN)

(b) Sensory nerve conduction velocity study of:

(i) Ulnar nerve
(ii) Median nerve
(iii) Sural nerve
(iv) Superficial peroneal nerve (SPN)

Distal latency, Amplitude, Conduction velocity of Compound Muscle Action Potential (CMAP), and Sensory Nerve Action Potential (SNAP) were studied. Normal adult values of nerve conduction study were used for comparison[8] and any deviation from this was considered as abnormal.

Other investigations, including routine blood and urine examination, FBS/PPBS, Liver Function Tests and Renal Function Tests were done in all cases.

Statistical Analysis: Qualitative data were analysed using percentages and proportions. Quantitative data were analysed using means and standard deviations. For testing the association between qualitative variables chi-square test was used.

Results

35 Cases of Hansen's disease satisfying the criteria were enrolled in the study. Mean age was 46 years and males (74%) outnumbered females.

On classifying clinically, borderline tuberculoid (BT) constituted the largest group with 12 cases (34%), followed by borderline lepromatous (BL) and lepromatous (LL); 7 cases each (20%); PNL constituted 17% (6 cases) and tuberculoid (TT), 3 cases. There were 29 multibacillary (MB) cases (83%) and 6 paucibacillary (PB) cases (17%).

Peripheral nerve thickening was observed in 32 cases (91.42%). Among the 136 thickened nerves, the ulnar nerve was the commonest to be involved (20%), followed by the radial cutaneous nerve (16%) and common peroneal nerve (13%). A nerve abscess was seen in a single case of PNL.

As many as 48.5% of our patients had disability with 22.8% presenting with grade 2 disability (Table 1). The largest number of patients with disability belonged to the BL and pure neuritic groups.

Type 1 reaction was observed in 5 cases including 4 BT and 1 LL subpolar case, while the two Type 2 reactions were both in the LL group.

CLASSIFICATION BASED ON HISTOPATHOLOGY

Tables 2 and 3 shows the comparison between clinical diagnosis and histopathological diagnosis in skin and nerve, respectively. Overall concordance between clinical diagnosis and skin

Table 1. Disability grading among the clinical groups

Type of leprosy	Grade -1 Disability	Grade 2 Disability	Total
BT	2	1	3
BL	4	1	5
LL	1	3	4
Neuritic	2	3	5
Total	9	8	17

Table 2. Comparison of clinical diagnosis with skin histopathological diagnosis

Clinical Diagnosis	Histopathology of skin						
	I	TT	BT	BB	BL	LL	Normal finding
TT (3)		3					
BT (12)	1	2	9				
BB (0)							
BL(7)				1	4	2	
LL(7)					1	6	
PNL(6)							6
	1	5	9	1	5	8	6

Table 3. Comparison of clinical diagnosis with nerve histopathological diagnosis

Clinical diagnosis	Histopathology of nerves					
	TT	BT	BL	LL	Normal findings	Biopsy deferred
TT (3)	2	1			–	
BT (12)		7	2		1	2
BL (7)			4	2	1	
LL (7)				4	1	2
P.Neuritic (6)	2	4			–	
Total	4	12	6	6	3	4

histopathological diagnosis was 75.86% (22/29 cases; excluding 6 PNL cases). There was 100% correlation in TT, 75% in BT, 57% in BL and 85.7% in LL cases. Skin biopsies from the anaesthetic area along the distribution of the nerve in all 6 PNL cases showed normal skin histology.

Nerve biopsies were obtained from 31 patients who gave consent. On comparing nerve histology with clinical diagnosis, concordance was seen in 17 out of 25 cases i.e., 68%. The concordance was 66.7% in TT, 70% in BT, 57.1% in BL and 80% in LL cases. Among the 6 clinically diagnosed PNL cases, 2 were histologically BT and 4 were histologically TT.

Concordance between nerve and skin histopathology was 60% with maximum correlation in LL and BT cases (71.4%), followed by BL (60%) while it was only 50% in TT.

NERVE CONDUCTION STUDY (NCS)

Abnormal nerve conduction parameters was seen in 31 out of 35 cases (88.5%). Maximum abnormality was seen in sensory nerve conduction(SNC) study (93.5%), while motor nerve conduction(MNC) study showed abnormality in 80.65% cases (Table 4). The ulnar nerve showed the highest abnormality among both motor and sensory studies (Table 4).

Table 4. Abnormal sensory and motor studies in various peripheral nerves (%)

	Abnormal SNC study	Abnormal MNC study	Nerve thickening
Ulnar nerve	45 /70 cases (64%)	38 /70 cases (54%)	27/70 (38.5%)
Median nerve	33/70 cases (47%)	10/70 (14%)	2/70 (2.8%)
Sural nerve	14/70 (20%)	–	9/70 (12%)
Superficial peroneal	16/70 (23%)	–	15/70 (21%)
Common peroneal	–	26/70 (37%)	18/70 (25%)
Posterior tibial	–	32/70 (45%)	9/70 (12.8%)

Table 5. Comparison between thickened and non-thickened nerves with abnormal SNC

Type of nerve (Sensory)	Prolonged latency		Total	*P* value	Reduced velocity		Total	*P* value
	Thickened nerve	Non-thickened nerve			Thickened nerve	Non-Thickened nerve		
Ulnar	5/26 (19%)	11/44 (25%)	16/70	0.403	12/26 (46%)	20/44 (45.5%)	32/70	0.57
Median	2/2 (100%)	23/68 (34%)	24/70	0.124	1/2 (50%)	28/68 (41%)	29/70	0.66
Sural	4/11 (36%)	6/59 (10%)	10/70	0.044	2/11 (18%)	2/59 (3.4%)	4/70	0.114
Superficial peroneal	5/15 (33%)	5/55 (9%)	10/70	0.031	5/15 (33%)	4/54 (7%)	9/70	0.018

Table 6. Comparison between thickened and non-thickened nerves with abnormal MNC

Type of nerve (Motor)	Reduced NCV		Total	*P* value	Reduced Amplitude		Total	*P* value
	Thickened nerve	Non-thickened nerve			Thickened nerve	Non-thickened nerve		
Ulnar	14/26 (54%)	18/44 (41%)	32/70	0.211	3/26 (11.5%)	2/44 (4.5%)	5/70	0.404
Median	0/2	13/68 (18%)	13/70	0.661	1/2 (50%)	9/68 (13%)	10/70	0.267
Posterior tibial	0/9	15/61 (24.5%)	15/70	0.098	0/9	6/61 (10%)	6/70	0.423
Common peroneal	5/18 (28%)	2/52 (4%)	7/70	0.010	8/18 (44%)	8/52 (13.5%)	16/70	0.016

Velocity reduction was the commonest abnormality both among sensory and motor nerves, while reduced amplitude was the least common derangement. Also, amplitude reduction was more common among motor nerves (66%) while velocity changes were marginally higher among sensory nerves.

Tables 5 and 6 show comparison between thickened and non-thickened nerves with abnormal SNC and abnormal MNC results, respectively.

There was a statistically significant difference in all three nerve conduction parameters for the superficial peroneal nerve (SPN) between thickened and non-thickened nerves. The difference in latency prolongation between thickened (36%) and non-thickened (10%) nerves in the sural nerve was also found to be statistically significant with a p-value of 0.044. The CMAP amplitude lowering among thickened CPN nerves was found to be statistically significant compared to non-thickened nerves with a p value of 0.01.

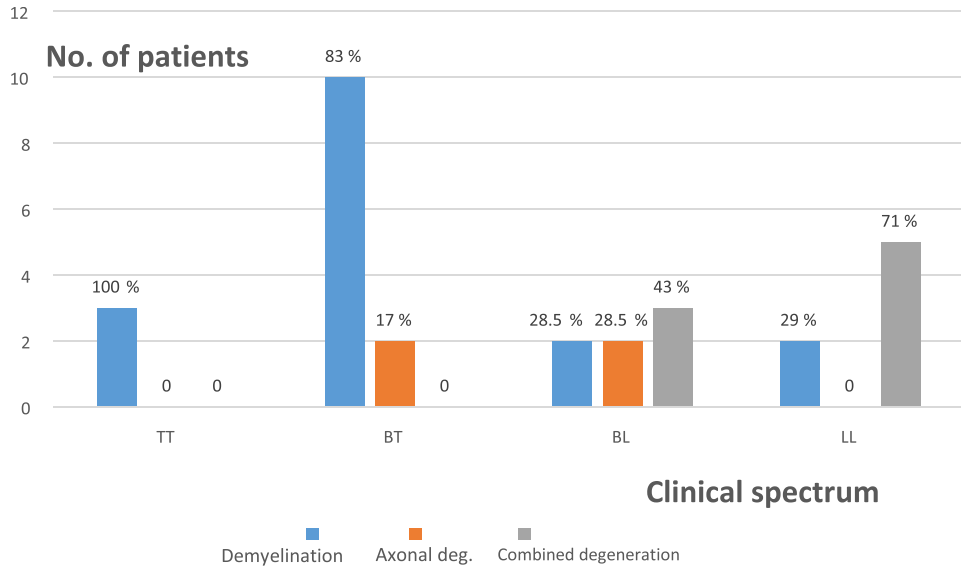

Figure 1. Type of nerve degeneration across the clinical spectrum.

Complete absence of responses was seen in a total of 20 nerves studied. This was seen in 5 LL cases and a single pure neuritic case, which was found to be a BT case on nerve biopsy. Demyelinating changes are characterized by prolonged latency and reduction in velocity, whereas axonal degeneration is characterized by a reduction in amplitude. Accordingly, the type of nerve degeneration across the clinical spectrum is depicted in Figure 1.

Discussion

When leprosy was eliminated from India in 2005, it was heralded as a golden chapter in the history of leprosy. But soon it was realized that the future was not as rosy as expected. The ANCDR and PR remained almost static and even showing an upward trend over the past one decade. The data presented in this study throw some light on the current scenario of Hansen's disease in south India.

In our study of 35 patients, the largest group of patients belonged to the BT subtype (34%). Many other studies have shown BT to be the commonest subtype on the clinical spectrum of Hansen's disease.[9–11]

The incidence of LL and BL is high in our study, so is the number of MB cases (83%). A recent study has shown LL cases to constitute up to 46%.[12] This trend has been noted by Kumar *et al.*[13] in the post elimination era with a rise in number of multibacillary cases. It has been attributed to lack of active surveillance and delay in diagnosis. There seems to be a lack of leprosy cases presenting in the early stages, resulting in late voluntary reporting, when the disease has progressed to advanced stages, resulting in a gradually increasing MB ratio. This seems to have happened with integration of leprosy services within the general health system.[13] The national MB ratio has increased from 25.9% in 1994 to 51.48% in 2014.[5] Ours being a tertiary care centre the incidence of MB cases will be even higher.

Notably, there were 6 cases (17%) of PNL in our study. This is in concordance with reports that the prevalence of pure neuritic leprosy in India ranges from 4 to 18%.[14] The fact that skin

lesions may occur in up to 20% of pure neuritic leprosy over months and years of observation indicates that this is a form of leprosy with initially pronounced nerve trunk involvement followed by cutaneous manifestations in a good proportion of cases.[15] Hence, categorizing pure neuritic leprosy as a separate group and clinically diagnosing these cases early equates to identifying leprosy before the skin is involved.

The overall concordance between clinical diagnosis and dermal histopathology was around 75%. The highest parity was in the polar regions of the spectrum (TT and LL) while major discordance was seen in the borderline groups. Similar observations were seen in studies by Bhusan *et al.*,[16] Kalla *et al.*[17] and Nadakarni *et al.*[18]

In all 6 clinically diagnosed cases of pure neuritic leprosy, the histopathology of the corresponding area of sensory loss on the skin revealed normal histology. A similar study by Suneeta *et al.*[15] among 196 pure neuritic leprosy patients showed histological changes in the skin due to leprosy in 32.1%. This study shows that there is a cutaneous component to primary neuritic leprosy and the disease is not totally confined to nerves. The absence of visible patches in these patients is probably related to the deep location of the dermal inflammation.

In our study histological changes in nerves were studied in 31 patients, of which 90% showed evidence of Hansen's disease. The nerve spectrum correlated with the clinical spectrum only in 17 cases (68%) with maximum correlation in LL cases (80%). In a study by Khan *et al.*,[19] the correlation between nerve histopathology and clinical diagnosis was 60%, which is similar to our study. Studies by Ashok Kumar *et al.* observed concordance in 44% cases.[20]

In our study, nerve histopathology was analysed in thickened nerves lying close to a skin lesion whenever possible. The nerve conduction study report was also used to assess an affected nerve before doing the nerve biopsy. Hence features of Hansen's disease were observed in 90% of nerves biopsied. Nerve histology may not be positive in all patients even if the nerves subjected to biopsy are carefully chosen. This is because that particular nerve fascicle may not have been affected and the disease may be in its early stages, causing symptoms without showing demonstrable pathological changes.[21]

All cases of pure neuritic leprosy showed evidence of Hansen's disease in this study. Among them 2 had features of TT disease, while 4 had features of BT. Pure neuritic cases generally show a narrow histological spectrum ranging from TT to BB, but sometimes it is not uncommon to find the entire spectrum of leprosy.[22]

Dermal and neural histology were correlating in 15 out of 25 cases (60%). Concordance between histology of skin and nerve tissue was lower in other studies, ranging from 38% to 44%.[19,20]

In our study the highest concordance was seen in BT and LL cases (71%), while the lowest was seen in TT cases (50%). Reddy *et al.*[23] showed that in early lesions there appears to be a dichotomy in immunological grading between the skin and nerve and this needs to be explored in greater detail. The nerve histology showed features lower down the spectrum compared to skin histology in 20% cases. These findings are also confirmed in other studies. The importance of neural histology lies in the fact that it might show a higher BI and a lower histological grading in several cases and if not performed it may result in inadequate treatment, drug resistance and even relapse.

NERVE CONDUCTION STUDIES

Abnormal nerve conduction parameters were seen in 88.5% cases and among them SNC was the commonest and earliest to be affected (93.5%), while MNC abnormality was seen in

80.65%. Similar findings were seen in studies by Khambatti *et al.*,[24] Kar *et al.*[25] and Husain *et al.*[26] while in a study by Gupta *et al.*,[27] MNCV was more affected than SNCV.

Overall, the highest level of sensory abnormality was seen in the ulnar nerve (64%), followed by median nerve (47%). This is comparable to the finding of 77.5% with sensory abnormality in the ulnar nerve observed by Ramadan *et al.*[28] Motor studies also revealed the highest derangement in the ulnar nerve (54%), followed by the posterior tibial nerve (45%) and common peroneal nerve (37%). Though velocity reduction was the commonest abnormality seen, amplitude reduction was also seen in a high percentage of patients (66%).

Interestingly, SNC of the median nerve was impaired in 33/70 cases (47%), while only two median nerves were clinically thickened and sensory loss in its distribution was seen in only one patient. The reduction in velocity in clinically normal nerves probably represents a preclinical stage of damage which manifests when a defined quantum of nerve fibres becomes non-functional.

The study of the posterior tibial nerve (PTN) also highlights the finding that electrophysiological changes are more pronounced than what is seen clinically. 100% of PTN with reduction in amplitude were clinically normal. Higher involvement of the PTN might be because of its superficial location at a trauma prone site in the legs. According to Croft *et al.*[29] the posterior tibial nerve is the most commonly affected nerve.

From Tables 5 and 6, it is evident that less than half of the nerves with clinical involvement showed abnormal nerve conduction velocity. Many authors have noted that normal sensory and motor conduction velocities can be found in the diseased nerves which could be explained by involvement of certain fascicles of the affected nerve with little or insignificant involvement of others. Since nerve conduction velocity is calculated on the basis of fast conducting fibers, it may be normal if slow conducting fibers are predominantly damaged.[30]

Amplitude reduction was considered a more important feature of motor nerve abnormality by many workers,[31,32] which is in accordance with our findings. Amplitude changes were well correlated with nerve thickening, compared to other parameters.

Overall, a clinico-electrophysiological correlation was seen in sensory studies of the superficial peroneal (SPN) and sural nerves, and in the motor study of CPN. In a similar study by Vashisht *et al.*,[33] significant correlation between deranged parameters and nerve thickening was seen for ulnar, common peroneal and posterior tibial nerves.

There are only a handful of studies involving SNC of the superficial peroneal nerve in the literature and not much data is available regarding its electrophysiological involvement.

Absent responses were observed in 5 LL patients and in a single case of pure neuritic leprosy. This is comparable to observations of Soysal *et al.*[34] wherein the number of absent or very low CMAPs or SNAPs was found to be more common in lepromatous leprosy patients than in the other cases.

TYPE OF NERVE DEGENERATION ACROSS THE CLINICAL SPECTRUM

All 3 TT cases in our study showed features suggestive of segmental demyelination. Among the 12 BT cases, a majority showed segmental demyelination. In the LL cases, a majority showed features of mixed demyelination and axonal degeneration. At the tuberculoid pole, nerves showed segmental demyelination alone, whereas as we move towards the lepromatous pole of disease there is both axonal degeneration and segmental demyelination. Our findings correlate with the findings of Shetty *et al.*,[35] which show that in early leprosy regardless of the type, segmental demyelination predominates and Wallerian degeneration appeared only later with both types of degeneration seen concomitantly in patients with evident sensory

impairment. This is in contrast to the findings of Job[36] and Dastur and Razak[37] according to which in lepromatous cases, segmental demyelination predominated, while in the tuberculoid type Wallerian degeneration was principally seen.

LIMITATIONS OF STUDY

(1) A larger sample size, with controls, would allow more significant conclusions.
(2) The study was done in a tertiary centre, rather than as a population-based study.
(3) Errors can occur while estimating electrophysiological parameters because of limitations inherent in the technique.

Conclusion

In this study there was a high degree of concordance between clinical and histopathological findings, both in skin and nerve. Also, among the discordant cases, the majority showed a histologically lower spectrum of disease in the nerves.

Nerve conduction studies showed abnormalities in 89% of patients, with sensory NCS showing the earliest and greatest involvement. Tuberculoid cases showed more segmental demyelination, whereas the lepromatous cases showed mixed axonal and demyelinating changes. Thus nerve conduction studies provide a simple and non-invasive method of detecting early nerve involvement in Hansen's disease and also of identifying the type of nerve degeneration. There is an increasing trend towards grade 2 disability which is in turn due to a delay in diagnosis and delay in therapy. Hence nerve conduction studies could be a very sensitive screening tool for early detection of Hansen's disease. But histopathology may be considered the gold standard for confirmation of cases.

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Conflicts of interest

There are no conflicts of interest among the authors of the article.

Authors' contributions

All authors contributed to the planning, conduct and reporting of the work.

Guarantor

Dr. Ameena Jaleel.

Ethics approval

Institutional Review Approval obtained from Govt. Medical College, Kottayam, Kerala on 22-12-2015 (IRB No.66/2015).

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