

## Sonographic characteristics of median nerve neuropathy in Hansen's disease: a case-control study

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### Summary

**Background and objectives** High-resolution ultrasonography (HRUS) has become a vital imaging tool in the management of leprosy. This case-control study analyzed the sonographic data on median nerves in leprosy and healthy controls to identify the features characteristic of leprosy.

**Methods** Newly diagnosed and treatment naïve Hansen's patients of both sexes and aged >16 years were included in the study. The control group included prospectively enrolled healthy subjects. Nerve conduction studies were performed in all. HRUS of the median nerve was performed using a Philips HD15 machine. HRUS parameters studied included cross-sectional area (CSA) of the nerve, fascicular architecture and abnormal blood flow (by colour Doppler). CSA was measured at the wrist (S1), 5 cm above the wrist (S2), 10 cm above the wrist (S3), mid-forearm (S4) and at the elbow (S5).

**Results** 30 median nerves from 22 cases of leprosy and 30 nerves from 15 healthy subjects were compared. Among cases, 8 were borderline tuberculoid, 9 borderline lepromatous, 3 lepromatous leprosy, and 2 indeterminate leprosy. Abnormal motor (76.7%) and sensory conduction (96.7%) was noted in the patient group. The mean CSA was 18.5 mm<sup>2</sup> at S1, 20.3 mm<sup>2</sup> at S2, 14.1 mm<sup>2</sup> at S3, 9.1 mm<sup>2</sup> at S4, and 8.1 mm<sup>2</sup> at S5. The CSA at S1 and S2 were significantly higher compared to other sites. CSA values were significantly higher in patients compared to controls. The fascicular architecture was distorted in patients - grade II (33.3%), III (40.0%) and IV (20%), and hypervascularity was noted in 26.6%.

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**Conclusion** HRUS depicted characteristic features of the median nerve in leprosy - maximum enlargement in the distal forearm with distorted fascicular architecture.

**Keywords:** Hansen's disease, median nerve, nerve enlargement, distorted fascicular architecture, hypervascularity

## Introduction

Hansen's disease, commonly known as leprosy, is a chronic debilitating disease of the skin and peripheral nerves caused by infection with *Mycobacterium leprae*.<sup>1</sup> Despite the reduced incidence of this neglected tropical disease in most countries worldwide, India is one of the substantial contributors to the global disease burden of leprosy. According to the recent WHO report, India reported 120,334 newly diagnosed patients with leprosy in 2018 and is the country with the highest incidence rate of leprosy in the South East Asia region.<sup>2</sup>

During the clinical course of the disease, *M. leprae* infects Schwann cells located in the peripheral nerves, leading to damage to these nerves, ultimately manifesting irreversible deformities and functional disabilities of limbs.<sup>3</sup> The peripheral nerve enlargement occurs early in the disease course, even before the initial clinical symptoms, and if left undiagnosed and untreated, may result in irreversible nerve damage. Therefore, early detection of nerve damage is the most crucial aspect in the management of patients with leprosy.<sup>4</sup>

High-resolution ultrasonography (HRUS) has gained prominence as a novel non-invasive imaging technique for assessing nerve morphology.<sup>5,6</sup> The ability of HRUS to assess the extent of nerve damage and treatment efficacy in leprosy has made this technique an indispensable tool in managing this disease.<sup>7,8</sup> Sonographic features of active leprosy include extensive nerve enlargement, distorted fascicular architecture, abnormal vascularity and epineural thickening.<sup>9</sup>

The most commonly involved nerve in Hansen's disease is the ulnar nerve. Several previous case-control studies have provided evidence validating the use of HRUS in the early diagnosis of ulnar neuropathy in leprosy and differentiating it from other causes.<sup>10,11</sup> It was shown that extensive enlargement of the ulnar nerve above the medial epicondyle is characteristic of leprosy.<sup>12</sup> However, until now there is only one study describing sonographic median nerve enlargement systematically in Hansen's disease.<sup>13</sup> Therefore, in the present case-control study, we aimed to study the characteristic features of median neuropathy due to leprosy on HRUS.

## Patients and methods

This study is a retrospective analysis of patients with Hansen's disease who visited the Outpatient Department of Neurology, CARE hospital, Hyderabad, Telangana state, India, between May 2015 and July 2019. Data from healthy controls for comparison were collected prospectively. The study was conducted following the ethical principles in the Declaration of Helsinki. The Institutional Ethics Committee approved the study protocol (Ref. No. IEC/CARE/20455/2020/IIS; approved on 13-May-2020). Written informed consent was obtained from all the healthy participants; however, a consent waiver for the retrospective cases was approved by IEC.

## SUBJECTS

Patients with newly diagnosed, untreated Hansen's disease aged more than 16 years were included, irrespective of gender. The diagnosis of leprosy was made by slit-skin smear

or skin biopsy. The latter was done in selected patients in those with negative slit-skin smears. Median neuropathy was confirmed by clinical examination. Patients with a history of mechanical trauma or surgery around the region of the median nerve or those with other polyneuropathies including alcoholism, diabetes, amyloidosis, and neurofibromatosis were excluded from the study. Fifteen age and sex-matched healthy subjects were included in the control group. Patients were categorized by the Ridley–Jopling classification system based on clinical features. In those who underwent skin biopsy, classification was done based on histopathological findings.

#### CLINICAL AND ELECTROPHYSIOLOGICAL EVALUATION

All patients and healthy controls underwent detailed clinical evaluation by the neurologist (YMR) for any symptoms and signs of median nerve disease. Symptoms of thenar muscle weakness were noted and graded by the modified research council (MRC) scale. Positive and negative sensory symptoms and objective sensory deficits of the lateral half of palm, thumb and index finger were also noted. All patients were categorised according to the Ridley–Jopling classification. Nerve conduction studies of median motor nerves and median sensory nerves were carried out in all subjects as per the American Academy of Neuromuscular and Electrodiagnostic Medicine (AANEM) protocol on a Synergy electrodiagnostic system by a senior qualified neuro-technologist (KESS). Sensory conduction study was done by orthodromic technique. The electrodiagnostic evaluation was done with the skin temperature kept at 32 °C.

#### HIGH-RESOLUTION ULTRASOUND EXAMINATION

HRUS was performed using a Philips HD15 ultrasound system (Massachusetts, USA) with a 12–3 MHz linear array probe. The sonographic examination of all patients was conducted by a senior neurologist trained in neuromuscular ultrasound (YMR) on the same day as the nerve conduction studies and before starting anti-leprosy treatment. The sonographer was not blinded as to whether the subject belonged to the patient or the control group. The median nerve was traced from the wrist proximally until the mid-arm, with the subject placed in the supine position. The maximum cross-sectional area (CSA) of the nerve was measured by the freehand delimitation technique at the inner hyperechoic rim of the nerve. The CSA was measured at five locations—proximal wrist crease (S1), 5 cm above S1 (S2), 10 cm above S1 (S3), mid-point of the line joining elbow crease and S1 (S4), and at elbow crease (S5). The fascicular architecture was graded 0, I, II, III and IV based on the echogenicity at the maximum swelling point of the nerve. The regular honeycomb fascicular pattern was graded as 0, mild hypoechogenicity (<50%) as grade I, obvious hypoechogenicity (≥50%) as grade II, complete loss of echogenicity (100%) as grade III and hyperechogenicity as grade IV (Figure 1A–E). Doppler evaluation of the nerve was done using colour Doppler with the pulse repetition frequency of 0.7–1 kHz and Doppler gain of 55–60. Any intraneural or perineural vascularity was recorded. All measurements were done in the transverse section.

#### STATISTICAL ANALYSIS

Data were analyzed using SPSS version 23.0. Quantitative variables were presented as mean (standard deviation (SD)), and qualitative variables were presented as frequency, and percentage. An unpaired *T*-test was done as a test of significance for continuous data. A test result was considered significant if the *P*-value was ≤0.05.



**Figure 1.** Fascicular grading with examples grade 0 (A); grade 1 (B); grade 2 (C); grade 3 (D); grade 4 (E).

## Results

### DEMOGRAPHIC DATA

Thirty median nerves (cases) from 22 Hansen's patients were included in the analysis. Among the cases, 18 were men, and 4 were women. The mean (SD) age was 41.7 (15.4) years.

**Table 1.** Assessment of sonographic parameters

Parameters	Cases ( <i>n</i> = 30)	Controls ( <i>n</i> = 30)	<i>p</i> -value
Mean CSA at (mm <sup>2</sup> )			
Wrist	18.5 (6.8)	7.4 (1.2)	<0.001
5 cm above wrist	20.3 (6.8)	6.1 (0.9)	<0.001
10 cm above wrist ( <i>n</i> * = 20)	13.3 (4.8)	5.5 (0.8)	<0.001
Mid forearm ( <i>n</i> * = 22)	8.1 (3.2)	5.4 (0.9)	0.001
Elbow ( <i>n</i> * = 21)	8.8 (3.8)	5.7 (0.6)	<0.001
Fascicular architecture, <i>n</i> (%)			
Grade I	2 (6.6)		
Grade II	10 (33.3)	–	–
Grade III	12 (40)		
Grade IV	6 (20)		
Hypervascularity, <i>n</i> (%)	8 (26.6)	–	–

Data presented as mean (SD), unless otherwise specified.

*n*\*, represents number of cases for each parameter.

CSA, cross-sectional area; SD, standard deviation.

8 (36.4%) were classified as borderline lepromatous (BL), 9 (40.9%) as borderline tuberculoid (BT), 2 (9.09%) as indeterminate (IN) and 3 (13.6%) as lepromatous leprosy (LL), as per the Ridley–Jopling classification. Skin biopsy findings were used for classifying in 5 (22.7%) cases, of which three were BT, and two were IN. 30 median nerves from 15 healthy volunteers were included as controls; in the control group, the mean (SD) age was 39.9 (12.4) years, 12 were men, and 3 were women.

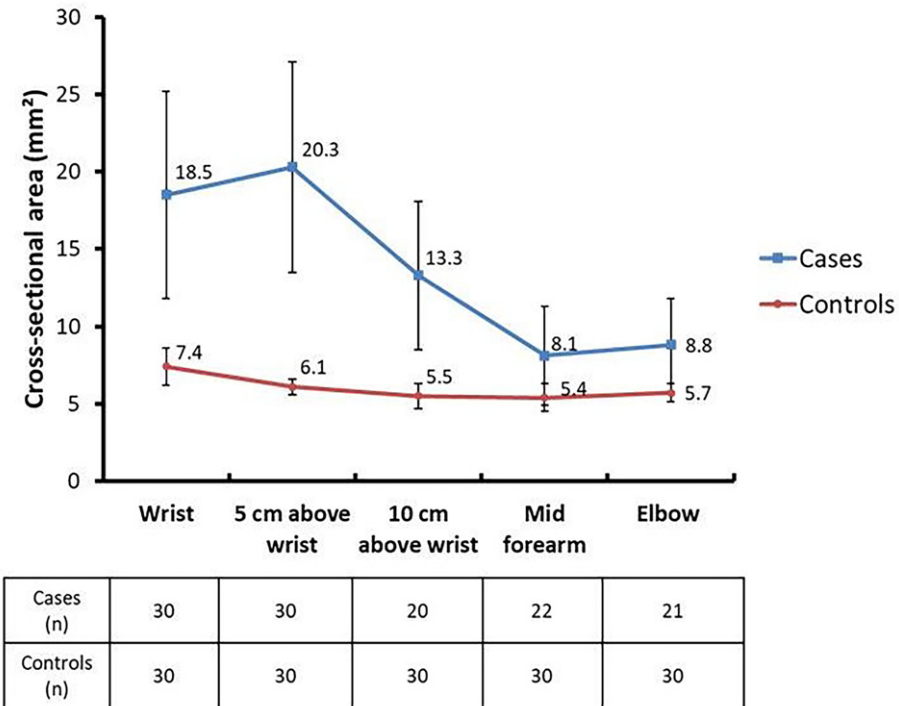
#### CLINICAL AND ELECTROPHYSIOLOGICAL FINDINGS

On clinical examination, combined sensory and motor deficits were noted in 25 (83.3%), and sensory deficit alone was noted in 5 (16.7%). Three (10%) had pain and tenderness of the median nerve in the distal forearm and wrist. Seven (23.33%) reported pain and tenderness along the median nerve in the distal forearm. In nerve conduction studies, of the thirty nerves (cases), both motor and sensory conduction abnormalities were found in 23 (76.6%), only sensory abnormalities in 6 (20%). One nerve (3.33%) showing normal conduction study results had sensory deficits in the median nerve distribution on examination.

#### HRUS FINDINGS

Data on median nerve CSA for cases at S3, S4 and S5, were available only for 20, 22 and 21 nerves, respectively. HRUS observations showed that the average (SD) median nerve CSA was 18.5 (6.8) mm<sup>2</sup> at S1, 20.3 (6.8) mm<sup>2</sup> at S2, 13.3 (4.8) mm<sup>2</sup> at S3, 8.1 (3.2) mm<sup>2</sup> at S4, and 8.8 (3.8) mm<sup>2</sup> at S5 (Table 1). The comparative analysis of CSA values between cases and control groups showed significantly higher mean CSA (*p* < 0.001) at each site in cases than in the control group (Figure 2). Comparing the CSA values among different sites showed that CSA at S1 and S2 were significantly higher (*p* < 0.001) compared to other sites.

The fascicular pattern analyses of nerves showed that the majority of nerves were classified as grade II in 10 (33.3%) cases and grade III in 12 (40.0%) cases, whereas 6 (20%) nerves showed hyperechogenicity (IV). Abnormal vascularity was noted on Doppler examination in eight (26.6%) median nerves (Table 1). Nerve CSA and fascicular grade at five sites in the whole cohort are shown in the bubble diagram (Figure 3). A hand sketch of the median nerve based on these results (Figure 4) and HRUS pictures (Figure 5) highlight maximum nerve enlargement in the distal forearm.



**Figure 2.** Comparison of the CSA at various sites between cases and control groups.

**Discussion**

Peripheral neuropathy due to leprosy is a well-established fact.<sup>3</sup> Sonographic observations from peripheral nerves using HRUS help to understand the location and degree of nerve enlargement, fascicular architectural pattern and vascularity of the nerve.<sup>12,14</sup> Although, several previous studies have reported a unique pattern of morphological changes of the ulnar nerve, the studies evaluating median nerve pattern are scant at global and national levels. Given this lacuna, the present study assessed sonographic features of median nerve neuropathy in a cohort of patients with Hansen’s disease from a hospital situated in the southern part of India.

In the present study, overall observations indicate two unique aspects of median nerve enlargement in Hansen’s disease. Firstly, the median nerve is diffusely enlarged compared to healthy controls. The median nerve was two-fold larger at the wrist, three-fold larger at 5 cm above the wrist, two-fold larger at 10 cm above the wrist and 1.5-fold larger at mid-forearm and elbow in patients with Hansen’s disease compared with the control group. Secondly, the median nerve is enlarged more at the wrist and 5 cm above the wrist than 10 cm above the wrist, mid-forearm, and elbow in leprosy, suggesting maximum enlargement in the distal forearm. The median nerve can be involved either as an isolated mononeuropathy or as part of a polyneuropathy. Common causes of mononeuropathy include entrapments such as carpal tunnel syndrome, pronator syndrome, varying degrees of trauma, tumours (including Schwannoma, neurofibroma, neurosarcoma and neurilemmoma), and ganglion cysts. Common causes of polyneuropathies include vasculitis and immune-mediated neuropathies such as inflammatory demyelinating neuropathies, sarcoidosis, and hereditary neuropathies, apart

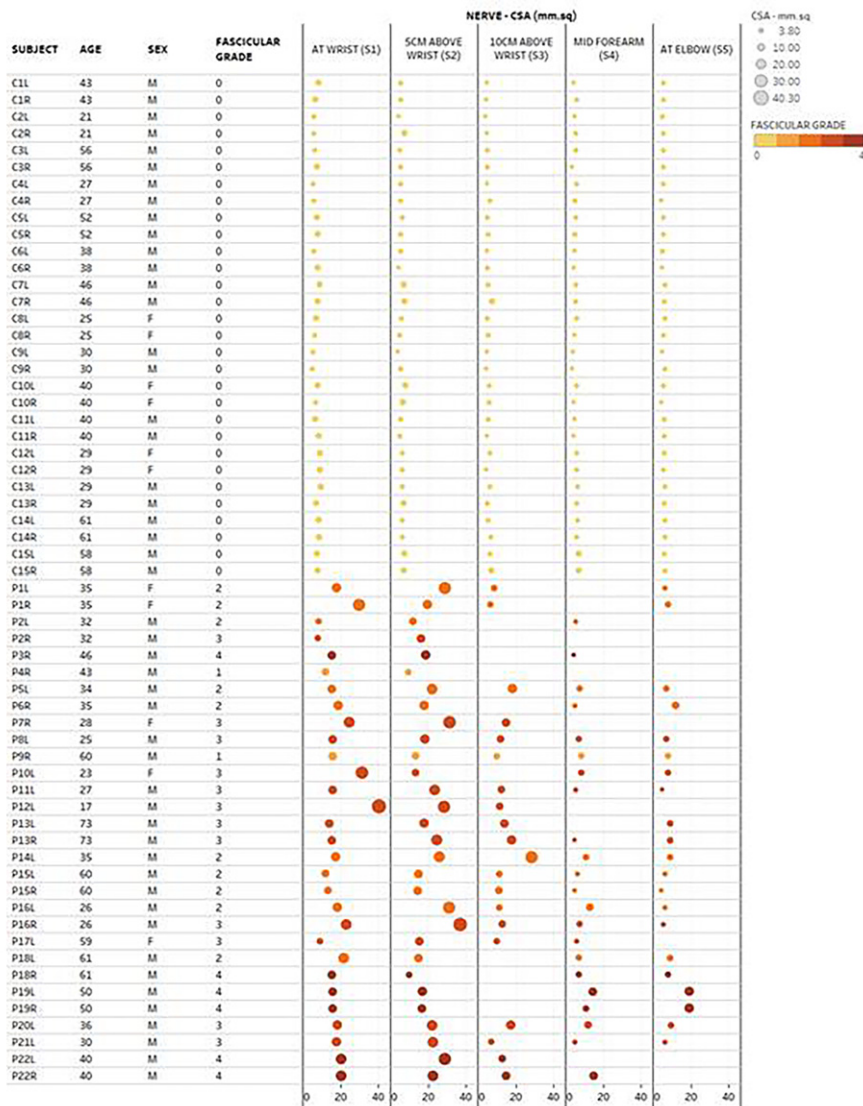
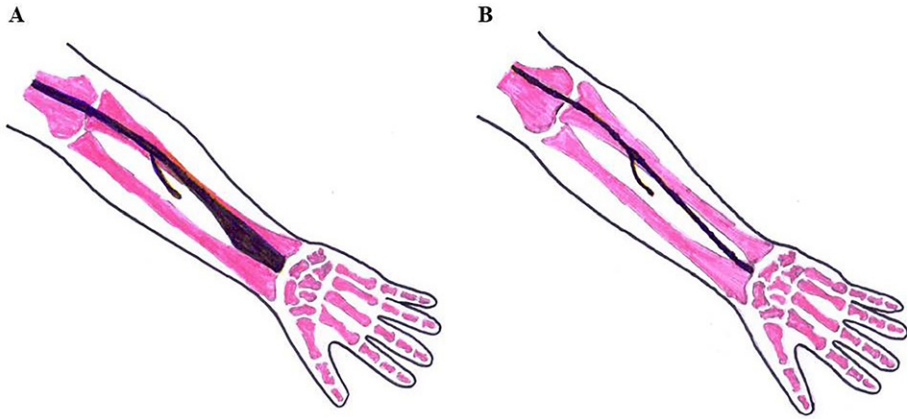
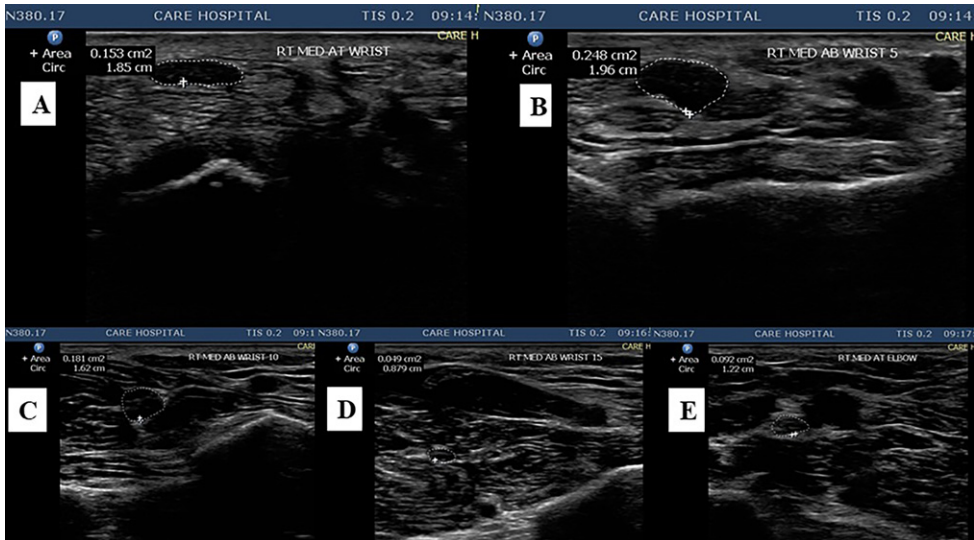


Figure 3. Bubble diagram depicting CSA and fascicular pattern of whole cohort.

from leprosy.<sup>15</sup> While enlargement is very focal in entrapments, tumors and trauma, it is diffuse, multifocal and more proximal in non-Hansen’s polyneuropathies.<sup>16,17</sup> Therefore, the peculiar enlargement pattern identified in this paper appears unique to leprosy. Nagappa *et al.* showed that the median nerve in leprosy was maximally enlarged proximal to wrist crease with gradual tapering proximally while it enlarged most at the distal wrist crease in carpal tunnel syndrome.<sup>13</sup> The median nerve is a deep nerve and is not easily palpable, unlike the ulnar, radial, common peroneal and posterior tibial nerves. Therefore, HRUS is of immense value in detecting median nerve enlargement and in evaluating the echo texture and blood flow as highlighted in our study. This enlargement pattern of the median nerve, which is more



**Figure 4.** (A, B) Hand drawn sketch showing the pattern of median nerve enlargement in leprosy (A) and healthy control (B).



**Figure 5.** (A–E) HRUS images of median nerve in a Hansen's patient showing enlargement at S1, S2, S3, S4 and S5 along with distorted fascicular architecture.

prominent proximal to the fibro-osseous carpal tunnel, is similar to studies of the ulnar nerve, which shows maximal enlargement proximal to the cubital tunnel.<sup>18–20</sup> Bathla *et al.* compared the HRUS pattern of ulnar nerve enlargement in 30 nerves of leprosy patients with 30 healthy controls. They concluded that the increase in ulnar nerve CSA occurred throughout the arm in patients compared with controls, and reported the maximum enlargement between the ulnar sulcus and axilla, peaking at four centimetres above the sulcus.<sup>18</sup> Gupta *et al.* compared the ulnar nerve CSA at three levels in leprosy patients—four centimetres above the elbow, deep to the cubital tunnel and below the medial epicondyle between flexor carpi ulnaris and flexor



digitorum profundus—with controls, finding that the ulnar nerve was enlarged at all three sites in leprosy. Larger CSA values were noted above the elbow.<sup>19</sup>

In this study, most of the median nerves showed moderate to severe distortion of fascicular architecture, and nearly 30% showed abnormal intraneural vascularity. These findings, though not specific features of the median nerve in leprosy, indicate severe nerve damage and a disrupted blood-nerve barrier. Previous studies on leprosy neuropathy reported a range of fascicular abnormalities from mild hypoechogenicity to complete loss of architecture and hyperechogenicity.<sup>12,14</sup> Intraneural vascularity is often seen in patients with active neuritis, but rarely without it.<sup>21,22</sup> Jain *et al.* reported abnormal colour flow in 25% of the tested median nerves with active disease.<sup>14</sup> A longitudinal study by Lugao *et al.* showed intraneural vascularity diminishing after anti-leprosy therapy. They also showed in the same study a case with subclinical intraneural vascularity that progressed to develop active neuritis later. Intraneural vascularity, therefore, can be the first sign of nerve damage, and it may have a role in predicting reactions.<sup>7</sup> These additional findings, in the presence of enlarged nerves in the distal forearm segment, appear to be typical of Hansen's disease and could prove very useful, especially in patients with a pure neuritic form of leprosy and those with isolated median nerve involvement.

NCS was normal in one of our patients. However, he had sensory deficits on clinical examination and an enlarged nerve on HRUS. Elias *et al.* reported three cases of ulnar neuropathy due to leprosy with abnormal HRUS and normal NCS. These findings suggest that HRUS may detect nerve involvement earlier than electrophysiology in leprosy.<sup>23</sup>

Our study is unique in many aspects. Firstly, we included newly diagnosed and treatment naïve patients with leprosy. Many published reports are cross-sectional studies and include patients already on anti-leprosy therapy. These may have affected the findings. Secondly, we used a grading system to report the fascicular abnormalities, unlike many other studies. This grading system is helpful to know the severity of nerve damage. Thirdly, we have compared the nerve CSA at different locations along the course and showed intraneural variability, which is less often reported in other nerves except for studies of the ulnar nerve. However, our study has some limitations. Firstly, the study's retrospective design limits the data collection for various additional parameters that would have been helpful. We did not have all data in the patient group at S3, S4 and S5. Secondly, the median nerve data of the arm segment was very scanty and therefore excluded deliberately to maintain uniformity of the data. Thirdly, the unblinded assessment of nerve on HRUS could have led to some bias. Fourthly, the small sample size makes our findings only suggestive.

## Conclusion

Overall observations indicate that HRUS depicted characteristic features of leprosy in the median nerve. Recognising the unique sonographic enlargement pattern along with distorted fascicular architecture and abnormal colour flow could help clinicians identify median nerve damage quite early in Hansen's disease. Therefore, HRUS can be considered an essential diagnostic tool to determine median nerve neuropathy among patients with leprosy; however, large-scale prospective studies are necessary to validate these findings.

## Review board approval

Obtained (Ref. No. IEC/CARE/20455/2020/IIS; approved on 13-May-2020).

### Conflict of interest

Authors report no conflict of interest.

### Funding

No funding was paid for this research.

### Contributorship

YMR has conceptualised the paper, done the clinical examination and sonography of all subjects and controls, written the manuscript. JMKM has contributed patient information and revised the manuscript; SKJ and LP have contributed patient information; KESS has done the electrodiagnostics; AP and RN have compiled the data; SK has done the statistical analysis.

### Patient consent

Consent was taken from all healthy controls. Consent waiver was approved by Institutional Ethics Committee for patients.

### Data sharing statement

The supporting data for this article can be obtained from the corresponding author on request.

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