ORIGINAL RESEARCH

A study on the role of High-resolution Ultrasonography in Leprosy neuropathy

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ABSTRACT

Background: Leprosy is a chronic infectious granulomatous disease predominantly involving skin and peripheral nerves, also one of the leading causes of treatable peripheral neuropathy in many developing countries.Nerve function impairment(NFI) is noted in almost 10-15% of new cases, of which a significant proportion of people develop lifelong functional disability.High-resolution ultrasonography (HRUS) is a non-invasive,safe,rapid technique that detects neuropathy before it manifests clinically. **Aims and objectives**: The study aims to evaluate the role of HRUS in diagnosing clinical and subclinical nerve involvement in leprosy. **Patients and methods**: This prospective observational study was conducted over 20 months at the DVL department in a tertiary health center. Fifty newly diagnosed leprosy cases and 50 age, sex-matched healthy controls were assessed. Clinical and sonographic data of 3 pairs of nerves (bilateral ulnar, median, and common peroneal) in each individual were recorded and analyzed. **Results**: Out of 300 nerves analyzed in leprosy patients, 97 showed clinical changes and 186 on HRUS. On HRUS, the changes noted were focal thickening (35%), diffuse thickening (13%), hypoechogenicity (46.3%), and increased vascularity (24.6%). The mean cross-sectional area of nerve in leprosy cases was higher and statistically significant compared to controls. **Conclusion:** The WHO global leprosy strategy 2021-2030, entitled 'Towards Zero leprosy,' focuses on reducing new cases with grade 2 disability by 90%. HRUS is a useful tool in the early diagnosis of NFI and prevention of disabilities.

Keywords: high-resolution ultrasonography, Leprosy neuropathy, nerve sonography, pure neuritic leprosy.

Abbreviations: HRUS – high-resolution ultrasonography, WHO – World Health Organization, SSS – slit skin smear, DVL – Dermatology, Venereology and Leprosy, MDT -multidrug therapy NFI – nerve function impairment, PNL- pure neuritic leprosy CSA- cross-sectional area

INTRODUCTION

Leprosy is a chronic infectious granulomatous condition caused by Mycobacterium leprae, which predominantly involves the skin and peripheral nerves. It corresponds to the most common treatable peripheral neuropathy in many countries of the world. More than half of the new leprosy cases are being reported from India.[1] Around 10% of newly detected cases present with nerve function impairment and a substantial proportion of people develop lifelong functional disability leading to economic and social seclusion[2]. Delay in detection is highly associated with an increased risk of nerve function impairment and disabilities.

A case of leprosy is defined by the World Health Organisation 8th Expert Committee as –an individual who has one of the following cardinal signs of leprosy[3] -

1. A definite loss of sensation in a hypopigmented or reddish skin patch
2. enlarged or thickened peripheral nerve with a loss of sensation in the area of supply and/or weakness of muscles supplied by the nerve
3. Positive Slit skin smear (SSS) - Presence of Acid-fast bacilli (AFB) in SSS

Pure Neuritic Leprosy(PNL) is a variant of leprosy where isolated nerve involvement is seen without skin lesions. This form is common in India, consisting of 4-18% of the total leprosy cases detected annually, and reportedly more common in South India with 18% of new cases[4]. Clinically, it may present as nerve thickening, nerve pain/tenderness, sensory-motor impairment, and occasionally nerve abscess.

Mononeuritis is the most common presentation and more frequently involving the upper limb nerves. This type of leprosy is negative for Slit Skin smear examination (SSS).

WHO classifies leprosy into paucibacillary and multibacillary based on the number of lesions and nerve involvement. Similarly, in India, under the NLEP (National Leprosy Eradication Programme),leprosy is classified into paucibacillary and multibacillary forms based on the number of affected nerves and skin lesions. Based on the type of leprosy, the government supplies the corresponding MDT blister packs monthly free of cost to the patients, which is mostly distributed at the field level.

Therefore, it is paramount to detect nerve involvement in Hansens to determine the type of leprosy,diagnose PNL, assign the therapeutic regimen, and decrease NFI. Here comes the role of imaging techniques like High-resolution ultrasonography, which helps to detect nerve involvement in leprosy.

Ultrasonography of peripheral nerves has been available for a few decades now, but its use in detecting neuropathy in Hansen's disease has been recognized widely for the past 15 years. With the advent of High-Resolution ultrasonography (HRUS), nerves could be examined objectively by capturing high-resolution morphological details. Color Doppler enables visualization of blood flow signals indicating inflammatory activity in acute neuritis before it manifests clinically [5,6].

On HRUS of a normal nerve, the fascicles are hypoechogenic round to oval structures surrounded by a hyperechogenic epineurium which appears as a rim. The perineural connective tissue is less echogenic than the epineurium. Thus, it gives a honeycomb appearance on a transverse plane and a bundle of straw appearance on a vertical plane.[7]

AIMS AND OBJECTIVES

The study aims to evaluate the role of HRUS in diagnosing clinical and subclinical nerve involvement in leprosy.

PATIENTS AND METHODS

This is a prospective observational study conducted over 20 months at the DVL department(outpatient and inpatient) in a tertiary health center. 50 newly diagnosed leprosy cases and age, sex-matched 50 healthy controls were assessed. Clinical and sonographic data of 3 pairs of nerves(bilateral ulnar, median, common peroneal) in each individual were recorded and analyzed.

INCLUSION CRITERIA

1. Newly diagnosed Leprosy cases who are willing to undergo study.

EXCLUSION CRITERIA

1. Patients with other causes of neuropathy such as HIV, thyroid dysfunction, diabetes mellitus, drugs causing neuropathy (vincristine, isoniazid, etc,), SLE, chronic alcoholism, familial neuropathies.
2. Patients with elbow and knee trauma, peripheral nerve biopsy, or surgery.
3. Patients under treatment for Hansen's disease and patients who are already treated or defaulters.
4. Patients not willing to undergo the study.

METHODOLOGY

After obtaining approval from the Institutional Ethics Committee, 50 cases and 50 controls were enrolled for the study. Informed and written consent was taken from the study groups. The demographic and clinical data were recorded after detailed history taking, thorough clinical examination, and necessary investigations. SSS(slit skin smear) for Acid Fast Bacilli was done in all cases and skin/nerve biopsy for histopathological examination was done in relevant cases for confirmation of diagnosis.

Every patient was examined carefully for the following - *skin lesions* (Maculoanesthetic patches, erythematous plaques, nodules, hypopigmented patches, and plaques, and umbilicated lesions), *Sensory impairment* (loss of temperature, pain, and touch sensations), *Motor impairment* (weakness of extremities and visible deformities), *Ulcers and autonomic changes* (xerosis, hair loss)

Both study groups underwent palpation of nerves to document enlargement and tenderness. The Ulnar nerve is palpated at the elbow, the Median nerve near the wrist, and the Common Peroneal nerve at the head of the fibula. Nerves were graded for thickness and tenderness. These groups were subjected to HRUS of peripheral nerves.

Anexperienced Radiologist in Musculoskeletal sonography performed HRUS. The sonographic examination was performed with a multifrequency musculoskeletal probe(>12MHz) using the highest frequency of 18MHz for bilateral Ulnar, Median, and Common Peroneal Nerves in both horizontal and vertical planes. The radiologist performing HRUS was blinded to the clinical details and diagnosis of the study participants.Thenerves were assessed throughout its course for Cross-Sectional Area (CSA, mm2), altered echotexture, any focal lesions (nerve abscess), and focal/diffuse thickening. The vascularity of the nerve was assessed with Colour Doppler.The statistical analysiswas performed using SPSS software and P(probability) values less than 0.05 were considered significant.

RESULTS

The HRUS of nerves in the control group showed a normal honeycomb appearance on a transverse plane and a bundle of straw appearance on the vertical plane (figure 1). There is no significant change in the echotexture or thickness of the nerves.

Of the 50 cases in the study group, males were 70%, females were 30%, and most patients were 30-40

years of age. Most cases belonged to the Borderline spectrum of leprosy(56%), and PNL constituted 32% of the cases in the study group. (Table I) Out of the 50 cases in the study group, 9 cases constituted Lepra reactions (type I—7 and type II—2).

A total of 6 nerves in each of the 50 cases were examined for clinical thickness and tenderness. A total of 97 nerves were thickened, of which 65 nerves showed tenderness and 25 nerves showed sensory or motor impairment. These 300 nerves were assessed sonographically, of which 186 (62%) showed changes. The various features noted on HRUS of nerves in the case study group were increased cross-sectional area (CSA), increased hypoechogenicity, loss or absence of fascicular pattern, increased hyperechogenicity, and neural vascularity.(table II)

The increased vascularity was assessed usingColor Doppler, and it was noted in 74 nerves, predominantly in cases of Lepra reaction. Increased vascularity is also noted in 2 cases of PNL, of which only one case showed clinical tenderness. HRUS could detect subclinical neuritis in clinically non-tender nerves.

The cross-sectional area(CSA) of the nerves in leprosy patients was significantly higher than that of the control group, with a P value of <0.05% .(table III)

Table No-I Distribution of clinical spectrum among cases.

Clinical Spectrum	Cases	Percentage (%)
TT	1	2.0
Borderline (BT/BB/BL)	***28***	***56.0***
LL	5	10.0
PNL (Pure Neuriticleprosy)	***16***	***32.0***
Total	50	100

TT- Tuberculoid leprosy, BT- Borderline Tuberculoid, BB- Mid borderline, BL- Borderline lepromatous, LL- Lepromatous leprosy

Table II– Ultrasonographic features of nerves in case study group

Sonographic features	No. of nerves(n=300)	Percentage
Thickening- Focal thickening	105	35%
Diffuse thickening	39	13%
Increased Hypoechogenicity or loss of fascicular pattern	139	46.33%
Dopplerchanges(intraneural and perineural vascularity)	74	24.66%
Fibrosis	2	0.66%
Total number of nerves showing any one or more of the above changes on HRUS	186	62%

Table III– Comparision of the cross-sectional area of cases and controls

Cross-sectional area	Right ulnar nerve	Left ulnar nerve	Right median nerve	Left median nerve	Right common peroneal nerve	Left common peroneal nerve
Cases	**17.35±6.22**	**17.7±7.8**	**16.23±5.6**	**15.45±4.90**	**11.49±5.93**	**11.37±3.46**
Controls	6.3±2.2	5.7±2	6.3±1.3	6.14±1.58	7.2±2.3	6.16±2.04
P value	**<0.002**	**<0.005**	**<0.003**	**<0.006**	**<0.004**	**<0.004**

Figure 1 – Images of nerves on ultrasonography

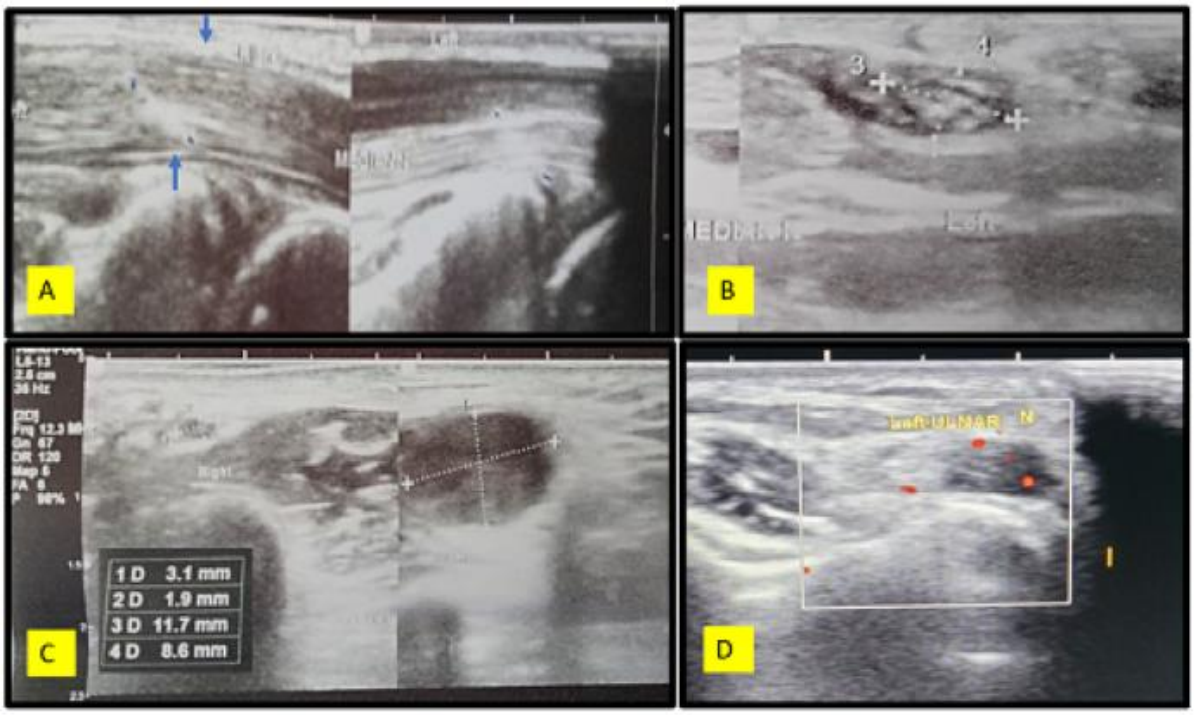

Figure 1- A, B – HRUS images of normal nerves in longitudinal and transverse planes respectively show a 'bundle of straw' and 'honeycomb appearance', image C – shows an enlargement of the left ulnar nerve compared to the right with the loss of fascicular pattern, image D shows increased vascularity detected on color doppler in a left ulnar nerve of a case of Hansen's disease.

DISCUSSION

Leprosy neuropathy is a complex clinical and diagnostic entity because of thepolymorphic aspect of its presentation, ranging from silent neuritis and mononeuropathy to symmetric polyneuropathy and rarely ataxia of leprosy ganglionitis[8].

The diagnostic difficulty posed by atypical manifestations can be avoided by a few diagnostic(imaging)techniques, such as high-resolution ultrasonography(HRUS).HRUS is easily available in many tertiary care hospitals and is time-saving and cost-effective.

Based on the existing data[9] and the present study, sonographically nerve echotexture could be classified into four groups – 1) normal, 2) more hypoechogenic (enlarged with fascicular abnormalities), 3) complete hypoechogenic (absence of fascicular pattern), 4) hyperechogenic (severe fibrosis)

The resolution of color Doppler is not high enough to capture the vascularity of nerves in physiological conditions, but in pathological conditions, the local inflammation increases blood flow,which is picked up by the colorDoppler. The intraneural or perineural Doppler activity is the first sign of active neuritis and a predictor of nerve damage and reactions[5,6].

In the present study,most of the borderline lesions were clinically over the upper extremities and trunk, and the corresponding nerves were thickened. However, on ultrasonography and color Doppler in Lepra reactions, the increased thickening and neural vascularity were detected in multiple nerves,even distant nerves from the site of the cutaneous lesions. These findings were similar to those of S Jain et al. 's study[9].

The maximum cross-sectional areas were recorded proximal to the osteofibrous tunnels for the ulnar and median nerves. These findings were consistent with a few other studies[10-13] on HRUS of nerves in leprosy.

The mean CSA of the ulnar nerve was comparable to L . Bathala et al[11] and Ashwini et al [12]study.L. Bathala[11] observed that male sex and advancing age were associated with more CSA, which could be the reason for higher values in our study when compared to the Sreejith et al. study.[10]

HRUS proved to be most beneficial in Pure neuritic leprosy, which poses diagnostic difficulty due to the absence of cutaneous lesions and negative slit skin smears. HRUS helps to elude nerve biopsy which can potentially damage nerve fibres. It can assess the CSA of nerves when they are clinically not confirmatory or equivocal,in patients where clinically sensory or motor deficit is evident but the nerves are not clinically thickened. It helps to diagnose nerve abscesses, fibrosis, and calcification[4].Increased blood flow detected on colorDoppler imaging could be correlated with edema and vascularity on histopathology[4].Thus HRUS helps in assessing the need for corticosteroid therapy in Pure neuriticleprosy (with subclinical neuritis) to prevent further nerve damage.

Concerning the data in the present study, HRUS is considered useful in the following situations –

1. Clinically difficult to palpate nerves where thickness is difficult to assess, like the *median nerve*- Due to its anatomic location, the thickening of the nerve cannot be easily ascertained proximally compared to the easy palpation of the ulnar nerve.
2. To confirm nerve thickening in equivocal cases or to avoid interobserver variation.
3. In Type I and II lepra reaction, to diagnose acute neuritis and nerve abscess.
4. To classify paucibacillary and multibacillary types based on the presence or absence of nerve involvement and the number of nerves involved. This is specifically useful in borderline forms where clinically skin lesions are less than 5 and the nerves are not thickened clinically.
5. Pure neuritic leprosy can be diagnosed by measuring the CSA and assessing nerve changes on HRUS, as nerve thickening is one of the cardinal signs for diagnosis of leprosy. In PNL, cutaneous lesions are absent, and SSS is negative; hence, demonstrating nerve involvement is the diagnostic criteria of PNL.
6. Detect subclinical nerve thickening- early detection of nerve enlargement even before it is clinically thickened and in nerves distant from the site of cutaneous lesions

LIMITATIONS OF THIS STUDY

The sample size was small, and it was a single-center study. We could not determine any statistically significant characters that could differentiate various types of leprosy, i.e., tuberculoid and lepromatous leprosy. Histopathological concordance with clinical and HRUS data could not be establishedin cases of Pure neuritic Hansens.

CONCLUSION

The WHO global leprosy strategy for 2021-2030 aims to reduce new cases of Grade 2 disability by 90%. Despite decreasing trends, India is still harboring many multibacillary cases, with a significant number constituting Pure neuritic Hansens. At this juncture, it is essential to detectneuritis early to prevent permanent and devastating disabilities.

HRUS emerged as a safe, non-invasive, objective diagnostic tool in assessing leprosy neuropathy. In leprosy, the clinically normal nerves may show significant enlargement on HRUS, one of the cardinal signs in diagnosing leprosy and a sensitive indicator of neuropathy in leprosy. HRUS can assess the nerve along the length of the nerve; even the clinically difficult-to-examine nerves are easily traced along the fascial planes, and the sites of maximum enlargementare mostly near or proximal to the osteofibrous tunnels.HRUS is also used to diagnose and localize nerve abscesses. Thus it helps in directing our therapeutic and surgical procedures.

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Declaration of patient consent

The authors validate that they have obtained the necessary and appropriate patient consent.

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None.

Conflicts of interest

There are no conflicts of interest.

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