ORIGINAL RESEARCH PAPER

Volume-8 | Issue-7 | July - 2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

SONOLOGICAL & DOPPLER EVALUATION IN ASSESSING THE PATTERN OF NEURONAL DAMAGE IN PATIENTS WITH LEPROSY

Radiodiagnosis

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ABSTRACT

OBJECTIVE: To assess the morphological changes in the nerves & to grade the damage of nerve based on the sonological appearance.
MATERIALS & OBJECTS: The Study was done between 2016-2017 in the hospital based population in Dr. PSIMS & RF. Study sample total 15 patients were included in the study who are presented to radiology department with nerve pain & thickening. All the patients were examined with frequency ranging (7-12 MHz) & assessed with Doppler .
RESULTS: Of the 12 patients 2 patients presented with increased thickness of the peripheral nerves & 2 patients were presented with unilateral ulnar nerve thickening rest all presented with involvement of both the ulnar & common peroneal nerves bilaterally. In all the 12 patients 3 patients had increased vascularity on colour Doppler. All the patients commonly presented with thickening of ulnar nerve mainly in the medial epicondylar region.

KEYWORDS

Leprosy is a chronic granulomatous immune response to infection caused by *Mycobacterium leprae*, which resides in macrophages and Schwann cells and is the only bacterium known to affect myelination and cause peripheral neuropathy. This involves the peripheral nerves, skin, and upper respiratory tract and corresponds to the most common treatable neuropathy in many regions of world, mainly in developing countries in the tropical and subtropical zones.

Nerve damage, affecting mainly the ulnar (UN), median (MN), common peroneal nerve (CPN) and posterior tibial (PTN) nerves, results in nerve enlargement.

Leprosy presents as a clinico-pathological spectrum ranging from the localized paucibacillary tuberculoid form with anaesthetic hypopigmented skin patch (TT) to the generalized multibacillary, lepromatous leprosy. Between these poles are unstable forms of borderline tuberculoid, borderline borderline and borderline lepromatous leprosy.

These states include type 1 (reversal reaction), where only the skin patch shows inflammation with tenderness in the associated nerve, and type 2 [Erythema Nodosum Leprosum (ENL)] reaction, manifesting with systemic symptoms of fever, erythematous nodules and joint pains.

Though some nerve involvement may be seen in all types of leprosy, leprosy reactions lead to severe morbidity and acute neuritis requiring immediate treatment.

Diagnosis of leprosy is based on the presence of 1 or more of 3 cardinal signs: hypopigmented skin lesions with definite loss of thermalgesic sensation, involvement of the peripheral nerve system, as shown by definite thickening of the nerve trunks with sensory or motor loss, and the presence of acid-fast bacilli on skin smears or biopsy material. Histologic diagnosis, when available, is deemed the standard diagnostic reference.

The main objectives of all leprosy health programs are to stop transmission and prevent impairment, disability, and deformity related to nerve damage by identifying patients who are in the early stage of neural involvement for treatment.

Hence, the most important goal in the management of leprosy is the prevention of disability via early detection of nerve impairment.

Nerve conduction studies or warm perception testing may improve early detection strategies, but these are usually not available in leprosy centers.

Since the hallmarks of leprosy are nerve enlargement and inflammation, we decided to use high-resolution sonography to demonstrate nerve morphological changes (even subclinically) and inflammation.

Inflammation can be detected by increased blood flow signals in the epi- and endoneurium of the involved nerves in leprosy patients.

The application of sonography in the evaluation of peripheral nerve anatomy and pathologic conditions has been described for more than 10 years. High-resolution sonography has increasingly been used for noninvasive assessment of peripheral nerve diseases.

Objective

The purpose of this study was to evaluate the diagnostic role of peripheral nerve sonography in establishing morphologic changes of leprosy neuropathy.

Therefore, we performed an extensive sonographic study in 14 leprosy patients and compared the sonographic findings with 12 healthy Indian controls.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board. Written informed consent was obtained from all patients and volunteers.

Ultrasonography and color doppler

All sonographic examinations were performed with a Philips HD ultrasound system and a multi frequency (7–10 MHz) electronic real time linear array transducer using the highest frequency of 10 MHz for all examinations. All examinations were performed and documented by a specialized radiologist with experience in musculoskeletal sonography.

All patients were examined in a supine position.

Ulnar nerves were scanned from the axilla through the hand along their transverse and longitudinal axes, and their identification was based on analysis of their echo texture as well as on detection of anatomic landmarks.

Patients and Volunteers

This study was performed between June 2018 and November 2018, and during this period, 14 new patients with leprosy were admitted for diagnostic confirmation and ambulatory treatment in our institution. Exclusion criteria were previous recurrent elbow trauma, ulnar nerve biopsy or surgery, systemic lupus erythematosus, alcoholism, familiar neuropathies, and any previous peripheral neuropathies.

The study group was composed of 14 consecutive patients with leprosy (12 men and 2 women; age range, 20-45 years) who were prospectively examined with diagnostic sonography of the peripheral nerves.

A leprosy diagnosis was established in all patients on the basis of clinical, bacteriologic, and histopathologic criteria.

The reference standard for ulnar neuropathy in this study was clinical symptoms or signs (anesthesia or paresthesia in the peripheral nerve distribution, nerve palpation, motor abnormalities, and corresponding deformities) in patients with proven leprosy.

All patients were classified as having multibacillary or paucibacillary leprosy as well as having a polar tuberculoid, borderline tuberculoid, polar lepromatous, borderline lepromatous, or pure neuritic form, as described by Ridley and Jopling[8].

Nerve characteristics

I. Nerve enlargement:

The greatest cross-sectional area (CSA) of the ulnar nerve was measured in each of 2 different regions defined as region A, above the medial epicondyle; region B, at the level of medial epicondyle.
The CSA of the nerve was obtained with freehand delimitation at the inner borders of the echogenic rim of the nerve.

II. Nerve echotexture:

The ulnar nerve echo texture was also classified as normal or abnormal. The normal sonographic pattern included hypoechoic fascicular tubular structures with intervening echogenic perineural tissue.

III. Nerve vascularity:

Neural vascularity was assessed with the use of color doppler.
The presence of blood flow signals in the perineural plexus or intrafascicular vessels indicated hypervascularity of the nerve during color doppler imaging.

Nerves were classified as abnormal if the sonographic study showed complete hypoechoic morphology or if focal thickening, loss of the fascicular pattern and increased vascularity were documented.

Bilaterally, the UN at the elbow and proximal to the medial epicondyle, CPN at the fibula head and PTN nerves at the ankle and proximal to the medial malleolus were examined and abnormality of the nerve was determined by the presence of abnormal size and echo reflectivity of the nerves.

All nerves were measured on transverse sections at a point where the nerve thickness was maximum in the visualized segment of the nerve.
On transverse scans, the cross sectional area of the nerve was determined from that area by one measurement within the hyperechoic rim surrounding the nerve.

RESULTS

Of the 14 patients, 7 were classified as having tuberculoid form, 5 as having lepromatous form and 2 as having pure neuritic form.

Ulnar nerve CSAs measured by sonography in the control and patient groups were statistically different.

The average ulnar nerve CSA measured by sonography was significantly larger in the patient group than in the control group.

The mean ulnar nerve CSAs were high at the level of medial epicondyle than above that level in 11 cases. One case had significant ulnar nerve thickening in region A compared to that of region B.

In region B, the mean ulnar nerve CSAs was 6.09 mm^2 in the control group and 12.63 mm^2 in the leprosy group.

Ulnar nerve CSA measurement differences were significant for each of the 2 evaluated regions and for the maximum cross-sectional area (Max CSA) measurements, always with greater nerve thickening in the leprosy group compared with the control group.

The receiver operating characteristic curve analysis showed that the best discrimination could be achieved with the MaxCSA, and choosing 9.0 mm^2 as the cutoff for the MaxCSA.

Three patients had a MaxCSA of less than 9.0mm^2.
One control patient had a Max CSA of more than 9.0 mm^2.

A normal ulnar nerve echo texture was found in all 12 control participants.

Of the 72 examined nerves, 83% of ulnar nerves, 58% of common peroneal nerves and 8% of posterior tibial nerves showed focal thickening.

Of the 72 examined nerves, 54% of ulnar nerves show hypo echogenicity, 8% of common peroneal nerve show hypo echogenicity and 8% of posterior tibial nerve show hypo echogenicity.

Of the 72 examined nerves, 50% of ulnar nerves had loss of the fascicular pattern, 8% of common peroneal nerves had loss of the fascicular pattern and 8% of posterior tibial nerves had loss of the fascicular pattern.

Of the 12 patients, only 1 patient had increased vascularity of ulnar and common peroneal nerves on color doppler.

DISCUSSION

Efforts to diagnose early (or subclinical) neuritis could ameliorate the nerve damage leading to functional impairment of limbs, ulcer formation and stigmatizing deformities. Careful clinical testing is useful, but can only detect the presence of neuropathy.

This study demonstrates the usefulness of US in detecting nerve damage in leprosy.

Our findings may have clinical and therapeutical consequences.

Peripheral nerves are often enlarged in leprosy, and these are more accurately assessed by US than by clinical palpation.

UN is the most commonly involved nerve.

Nerve enlargement is more often present in patients with type 1 or type 2 reaction and the nerves of these patients often showed an increased vascularity in both the clinically involved nerves and innerves far distant from those clinically affected.

There is a growing interest in US as a diagnostic tool for diseases of the peripheral nervous system including mononeuropathies, polyneuropathies and peripheral nerve tumors.

US is noninvasive, amenable to studying structural changes in nerve sites that cannot be biopsied for histopathology, and is more cost effective than magnetic resonance imaging.

Moreover, with US the nerve can be probed for a longer length than MRI examination which is limited to defined segments.

Technical developments leading to improved image quality and reduced sizes of US equipment together with a reduction in price will make it possible for US to become a tool that can be used in countries where leprosy is still endemic.

Martinoli et al.[2] examined the median, ulnar and posterior tibial nerve in 23 leprosy patients (58 nerves) both with sonography and MRI.

Based on the sonographic (or MR) imaging appearance, nerve could be classified as normal (group I), enlarged with fascicular abnormalities (group II) or having no fascicular structure at all (group III). The nerves in group II were thicker than in group III. The nerve swelling found in group II was gradual and fusiform, and typically occurred proximal to osteofibrous tunnels. However, their main finding was that nerves which showed a reversal reaction towards a more intense immune response had a hypervascular pattern demonstrated by Doppler studies (or by a marked T2 intensity and increased gadolinium enhancement on MR).

That study had some limitations.

Only affected clinical nerves were examined by sonography or MRI, while we examined the UN, CPN and PTN nerves systematically in all leprosy patients.

As expected, we also found that nerves are often enlarged in leprosy patients, especially in patients with a type 1 or 2 reaction.

One of the three key signs of leprosy is the presence of enlarged nerves. Ascertaining the presence of enlarged nerves can be difficult, and for some nerves this is impossible because of their location.

Additionally, it is impossible to assess the length of nerve abnormality by palpation.

It has to be emphasized that palpation of nerves in our study was performed by very experienced clinicians.

We conclude that clinical examination of enlarged nerves is subjective and inaccurate, whereas sonography provides an objective measure of the nerve dimensions in addition to revealing structural changes over a longer length of the nerve.

Besides enlargement, nerves in leprosy patients exhibited varying degrees of structural abnormalities such as fusiform enlargement or loss of fascicles, edema and increased neural vascularity.

Nerves that showed increased blood flow signals in the endo/ perineurium belonged to patients with leprosy reactions, as Martolini et al. also demonstrated.

As compared to the nerve size or echotexture, the above feature discriminates leprosy reactions from non-reaction leprosy.

We found that the more enlarged the nerve, the more often CD flow signals were present. Possibly, an increased blood flow signal in the nerve is the first sign of possible nerve damage.

For example in one of the leprosy patient in the present study, the ulnar and common peroneal nerves showed CD flow signals while no sensory or motor nerve impairment was observed.

Sonographic findings of major peripheral nerves of upper & lower limbs in 14 patients

Characteristics	Ulnar nerve	Common peroneal nerve	Posterior tibial nerve
Focal thickening	13	08	01
Echo reflectivity (Hypoechoic)	10	01	01
Loss of fascicular pattern	09	01	01
Increased CD	02	01	01

Ulnar nerve diameters in leprosy group

S.no.	Right Ulnar nerve diameter (mm)	Cross sectional area (mm^2)	Left Ulnar nerve diameter (mm)	Cross sectional area (mm^2)
01	4.8 x 2.5	12.00	5.0 x 2.0	10.00
02	4.6 x 2.9	13.34	4.0 x 2.5	10.00
03	4.6 x 2.3	10.58	4.0 x 3.0	12.00
04	4.9 x 3.1	15.19	3.5 x 2.7	09.45
05	5.0 x 3.0	15.00	6.0 x 4.0	24.00
06	5.0 x 3.6	18.00	5.1 x 3.3	16.83
07	3.9 x 2.5	09.75	2.4 x 1.9	04.56
08	5.7 x 2.1	11.97	6.7 x 4.1	27.47
09	4.3 x 2.9	12.47	4.7 x 2.7	12.69
10	2.5 x 1.9	04.75	2.3 x 2.1	04.83
11	4.4 x 3.2	14.08	3.8 x 3.2	12.16
12	4.1 x 2.3	09.43	4.0 x 2.4	09.60
13	5.2 x 2.8	14.56	4.9 x 3.0	14.70
14	3.6 x 3.2	11.52	5.6 x 2.5	14.00

Ulnar nerve diameters in control group

S.no. T-2	Right Ulnar nerve diameter (mm)	Cross sectional area (mm^2)	Left Ulnar nerve diameter (mm)	Cross sectional area (mm^2)
01	3.3 x 1.8	5.9	3.3 x 1.7	5.6
02	2.1 x 1.8	3.7	2.3 x 1.6	3.6
03	2.8 x 2.0	5.6	3.1 x 2.0	6.2
04	2.9 x 1.7	4.9	2.6 x 1.7	4.4
05	3.6 x 2.4	8.6	3.2 x 2.1	6.7
06	3.6 x 2.2	7.9	3.5 x 1.9	6.6
07	3.5 x 2.0	7.0	3.9 x 2.4	9.3
08	3.2 x 1.8	5.7	3.3 x 1.8	5.9
09	2.1 x 1.6	3.3	2.3 x 1.8	4.1
10	2.8 x 2.0	5.6	3.1 x 2.0	6.2
11	3.6 x 2.1	7.5	3.2 x 2.4	7.6
12	3.6 x 1.9	6.8	3.5 x 2.2	7.7

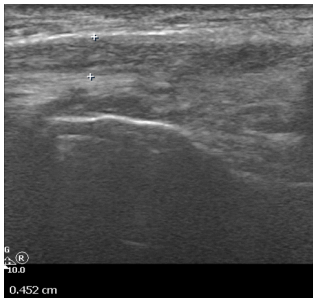
Control group

S.no. T -4	Right Common peroneal nerve diameter(mm)	Cross sectional area (mm^2)	Left Common peroneal nerve diameter(mm)	Cross sectional area (mm^2)
	5.6 x 3.0	16.80	4.4 x 3.2	14.00

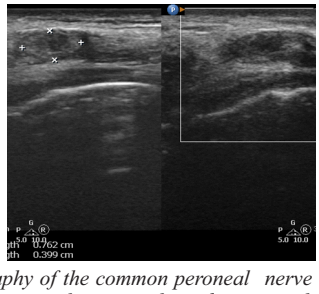
Leprosy group

S.no. T -4	Right Common peroneal nerve diameter(mm)	Cross sectional area (mm^2)	Left Common peroneal nerve diameter(mm)	Cross sectional area (mm^2)
	7.6 x 3.9	29.60	9.0 x 4.7	42.30
	10.9 x 4.7	51.23	8.2 x 5.1	41.82

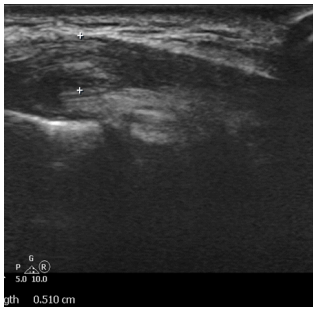
Characteristics	Ulnar nerve (28 nerves)	Common peroneal nerve (28 nerves)	Posterior tibial nerve (28 nerves)	All nerves (84 nerves)
Focal thickening	25 (89%)	14 (50%)	02 (7%)	41 (48.9%)
Hypoechoic	17 (60%)	02 (7%)	02 (7%)	21 (25%)
Loss of fascicular pattern	16 (57%)	02 (7%)	02 (7%)	20 (23.8%)
Increased vascularity	04 (14.2%)	02 (7%)	02 (7%)	08 (9.5%)



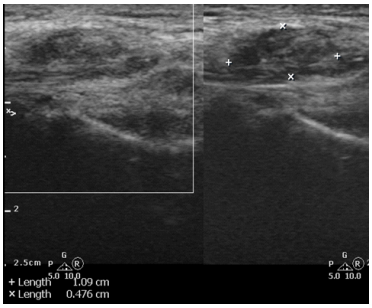
Ultrasonography of the ulnar nerve in longitudinal section showing the thickened nerve with hypoechogenecity and loss of fascicular pattern.



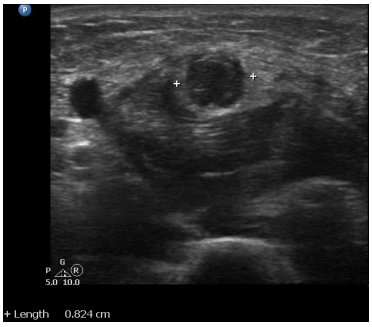
Ultrasonography of the common peroneal nerve in leprosy patient. Transverse section showing enlarged nerve with hypoechogenecity and loss of fascicular pattern. Longitudinal section showing the thickened nerve with no evidence of internal vascularity.



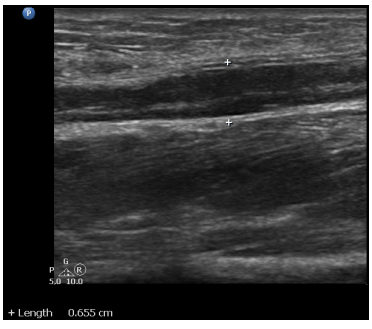
Ultrasonography of the ulnar nerve in longitudinal section showing the thickened nerve with hypoechogenecity and loss of fascicular pattern.



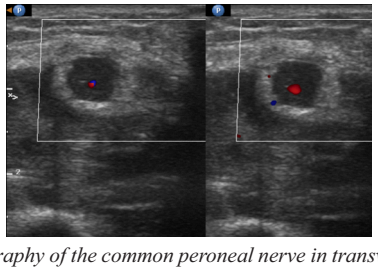
Ultrasonography of the common peroneal nerve showing the thickened nerve with hypoechoic echotexture and loss of fascicular pattern.



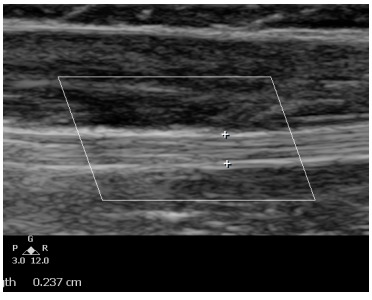
Ultrasonography of the ulnar nerve in transverse section showing the thickened nerve with hypoechogenecity and loss of fascicular pattern.



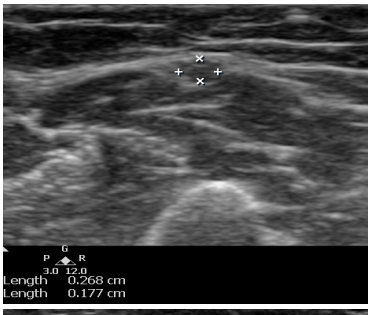
Ultrasonography of the ulnar nerve in longitudinal section showing focal thickening of nerve with hypoechoic echotexture and loss of fascicular pattern.

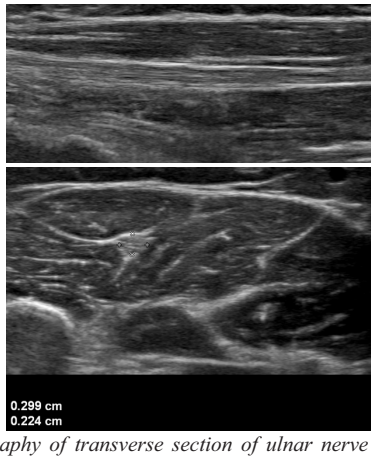


Ultrasonography of the common peroneal nerve in transverse section showing the thickened nerve with hypoechogenecity and minimal increased vascularity.

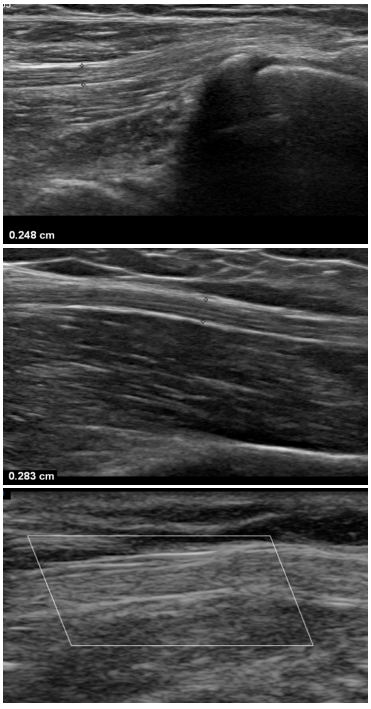


Ultrasonography of the ulnar nerve in longitudinal section showing the normal nerve showinghyperechoic perineural sheaths within the nerve.

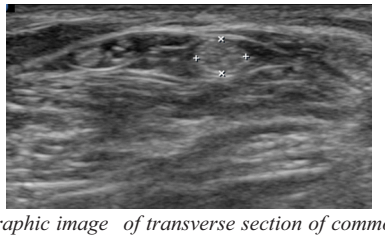




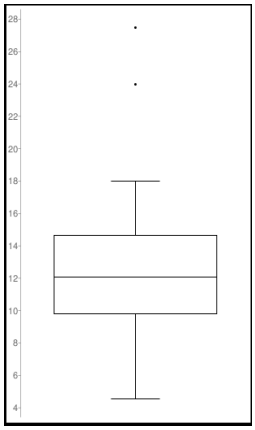
Ultrasonography of transverse section of ulnar nerve in a control caseshowing normal caliber of nerve with internal hyperecoic perineural sheaths surrounding hypoecoic nerve fasciculus.



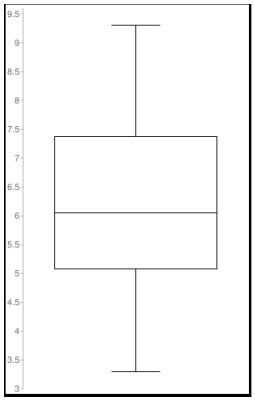
Ultrasonography of longitudinalsection of common peroneal nerve in a control patientshowing normal caliber and echogenicity of nerve.



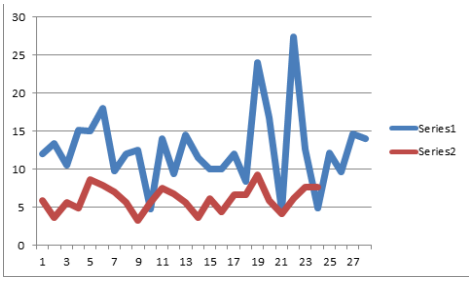
Ultrasonographic image of transverse section of common peroneal nerve in a control patientshowing normal caliber and echogenicity of nerve.



Box plot distribution of leprosy cases showing the median value of ulnar nerve CSA at 12.0



Box plot distribution of control subjects showing the median value of ulnar nerve CSA at 6.0



Line diagram depicting the distribution of ulnar cross section areas in cases(Blue) and control groups(Red).

The increased neural vascularity taken together with inter fascicular edema may reflect immune-mediated inflammation known to occur during leprosy reactions.

Cross References:

Jain et al[1] in their study evaluated the peripheral nerves of 20 leprosy patients and observed that the nerves were significantly thickened in leprosy patients as compared to healthy controls(p value<0.0001 for each nerve).They concluded that sonography provides objective measure of nerve damage in leprosy neuropathy by showing increased vascularity, distorted echotexture and enlargement.

Jarge Elias et al.[3] evaluated the diagnostic usefulness of ulnar nerve sonography in leprosy neuropathy.

Martinoli et al.[2] examined the median, ulnar and posterior tibial nerves in 23 leprosy patients (58 nerves) both with sonography and MRI and obtained similar results.

High-resolution sonography is useful in characterizing peripheral nerve lesions and can complement other diagnostic investigations such as the nerve conduction study. It is easily available and has the potential to become the first modality for the evaluation of focal peripheral nerve disorders as observed by Muhammed Afsal, Veena Chowdhury[6].

Xiaohua Chen et al.,[7] evaluated peripheral neural impairment in leprosy patients by ultrasonography (US)and found that for the nerves located in upper limbs, the CSAs were significantly increased in the leprosy patients vs the controls.

Pitfalls

One major limitation of our study was the absence of correlation between nerve anatomical changes and nerve function abnormalities.

Another limitation of the study was the relatively small sample size.

It was not possible to biopsy the ulnar nerve to confirm the neuropathy in most of the cases.

CONCLUSION

Ultrasonography helps to delineate the morphological changes of peripheral nerves in leprosy patients even in subclinical presentations and early nerve damage cab be assessed, thereby preventing neurologic deficit.

Doppler sonography also helps to identify the acute inflammatory process within the nerves.

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