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Journal of Skin and Sexually Transmitted Diseases

*Review Article*

# High resolution ultrasound, nerve conduction study, and other non-invasive investigations in leprosy

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Received : 05 January 2021
Accepted : 14 February 2021
Published : 14 October 2021

**DOI**
10.25259/JSSTD_1_2021

**Quick Response Code:**

## ABSTRACT

Leprosy is a chronic infectious condition caused by *Mycobacterium leprae* and is endemic in many regions of the world. The diagnosis of this condition is usually clinical except in some situations where investigations are necessary to confirm the diagnosis of leprosy or classify its clinical form. Histopathology is the usual modality for conformation of diagnosis. This review focuses mainly on high resolution ultrasound, nerve conduction study, and other non-invasive investigations in leprosy.

**Keywords:** High resolution ultrasound, Infrared thermography, Nerve conduction study, Ninhydrin sweat test, Quantitative sensory testing

## INTRODUCTION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* that affects mainly skin and peripheral nerve.[1] It has a wide spectrum of clinical manifestations depending on the degree of immunity of the host to the bacillus.[2] Patients with strong cell mediated immunity to *M. leprae* manifest tuberculoid (TT) and borderline tuberculoid (BT) disease while those with minimal or non-existent immunity to *M. leprae* develop borderline lepromatous (BL) or lepromatous leprosy (LL). Individuals who's immunity to *M. leprae* lies between the same noted in TT and lepromatous groups manifest mid-borderline (BB) leprosy.

## DEFINITION OF A CASE OF LEPROSY

According to the WHO 8th expert committee, leprosy is diagnosed in the presence of at least one of the following cardinal signs:[3]

1. Definite loss of sensation in a hypopigmented or erythematous skin lesion.
2. A thickened or enlarged peripheral nerve, with loss of sensation with/without weakness of muscles supplied by that nerve.
3. Presence of acid fast bacilli in a slit skin smear.

Diagnosis of leprosy is most commonly based on these cardinal signs. Only in rare instances, there arises a need to use laboratory and other investigations to confirm a diagnosis of leprosy. Histopathology is the usual modality for confirmation of a clinically doubtful case of leprosy. However, other procedures such as skin testing with M. *Leprae* antigen (lepromin), antibody responses of the host to *M. Leprae*, molecular techniques to detect the components

of *M. Leprae* in the lesions, and non-invasive investigations such as nerve conduction study (NCS) and high resolution ultrasound have also been used for diagnosis of leprosy. This article is a review of the non-invasive diagnostic modalities in leprosy.

## NCS

The most important consequence of leprosy is due to the direct involvement of the peripheral nerves. Nerve damage in leprosy may present as silent neuropathy without overt signs and symptoms or clinically manifest with weakness, atrophy, or contracture. Glove and stocking pattern of sensory impairment results from damage to the Type C fibers that discriminate heat and cold, the earliest sensation lost during the course of the disease. Anhidrosis is seen if there is associated sympathetic nerve involvement.[4]

Common methods used to detect sensory nerve function impairment (NFI) are monofilament testing (MFT) and ballpoint testing; both asses touch sensation on hand and feet. For detection of motor function impairment, voluntary muscle testing is performed.[5]

Functional derangement of nerves can be detected by nerve conduction studies before the appearance of clinical signs and symptoms.[6] Disability and deformity could be minimized if NFI is detected and treated early. Although the usefulness of NCS was reported in 1990, NCS was not used commonly. With the availability of modern, affordable and portable electrophysiology machines, these days, trained technicians take less time for each study.[7]

NCS involves the recording, display, measurement, and interpretation of action potentials arising from the peripheral nerves.

### Principles of NCS

NCS involves application of a depolarizing square wave electrical pulse to the skin over a peripheral nerve producing,

1. A propagated nerve action potential recorded at a distant point over the same nerve.
2. A compound muscle action potential (CAMP) arising from activation of muscle fibers in a target muscle supplied by the nerve.

Nerve may be stimulated through the skin with a surface stimulator or through a needle placed close to a nerve or a nerve root.

Surface electrodes are designed to give information about the whole of a muscle stimulated. Needle electrodes give very accurate conduction time, but since they record from only a small area of muscle or nerve, numerical analysis becomes difficult. Needle recordings are most appropriate when severe muscle wasting has occurred or when the depth of a muscle under study makes a surface recording impossible.[8]

## SPECIFIC NCS TECHNIQUES

### Motor nerve conduction studies

Motor studies are performed by electrical stimulation of a nerve and recording the CMAP from surface electrodes overlying a muscle supplied by that nerve.[8]

#### *NCS interpretation*

Latency is the time from stimulus artifact to the onset of the response.

In motor nerve studies, this latency includes nerve conduction time and neuromuscular transmission time. Proximal latency starts at the proximal stimulation point and ends at the first deflection from baseline. Distal latency is measured from the distal stimulation point to the first deflection from the baseline.

Amplitude is dependent on the number of axons that conduct impulses from the stimulus point to the muscle, number of functioning motor endplates and muscle volume. The amplitude is measured from the baseline to the negative peak.

Conduction velocity (CV) is calculated by dividing the length of the nerve segment between the two stimulation points by the difference between the proximal and distal latency. It is calculated as follows:

$$CV\,(m/s) = \frac{Distance\,(mm)}{Proximal\ latency - Distal\ latency}$$

Motor conduction velocity calculated in this manner reflects the conduction in the fastest motor axons.[9]

### Sensory conduction studies

The sensory nerve action potential (SNAP) is obtained by electrically stimulating sensory fibers and recording the nerve action potential at a point further along that nerve. The stimulus must be supramaximal.

Recording the SNAP orthodromically refers to distal nerve stimulation and recording more proximally (the direction in which physiological sensory conduction occurs). Antidromic testing is the reverse. Different laboratories prefer antidromic or orthodromic methods for testing different nerves.

#### *NCS interpretation*

Latency is the time from the stimulus to the first positive peak of SNAP.

Amplitude of the SNAP should be measured from the base line to the negative peak.

Sensory nerve conduction (SNC) in peripheral nerves does not involve synaptic transmission, so stimulation of the nerve at a single site, suffices to calculate CV. The CV is calculated by dividing the length of the nerve segment from the stimulus point to the recording point by the positive peak latency.[9]

Abnormalities in NCS

1. Axonal degeneration – Results in reduction in SNAP or CMAP amplitudes.
2. Demyelination – Prolonged distal latency and slowing of CV.
3. Mixed patterns with primary demyelination and secondary axonal loss.
4. Focal conduction block – Loss of CMAP amplitude at the site of block and normal amplitudes above and below the segment.

**NCS and leprosy**

Nerve functioning is assessed using distal latency (myelination), amplitude (number of axons), and velocity (myelination).

NCS can detect subclinical leprosy neuropathy, which is helpful for prevention of clinical neuropathies.[10] Husain and Malaviya observed that even though clinically normal, 16% of ulnar and 20% of median nerves were electrically abnormal in leprosy.[11] Study by Hackett found slowing of MNCV in patients without any clinical abnormality.[12]

Slowing of sensory velocity and motor nerve conduction velocity (NCV) is observed in patients without any clinical abnormality. Reduced conduction velocities in clinically normal nerves probably represent the preclinical stage (without symptoms and signs) of damage which becomes manifest when certain defined quantum of nerve fibers becomes non-functional. Ramadan *et al*. in their study found significant reduction in MNCV, prolongation of distal latency, and reduction of amplitude.[13] Normal sensory-motor conduction velocities recorded in diseased nerves may be explained by the involvement of some fascicles of the affected nerve with little or insignificant involvement of others. Since nerve CV (NCV) is calculated on the basis of fast conducting fibers, it may be normal, if slow conducting fibers are predominantly damaged as damage to C and A-delta fibers precedes the involvement of A-alpha fibers in leprosy.[11] Rao *et al*. and Verghese *et al*. observed no statistically significant difference in the electrophysiological parameters between the clinically thickened nerve and its non-thickened counterpart, in the early stages of the disease.[14,15]

The conduction velocities never reach zero (some conduction continues to occur in cases which showed no response on clinical testing for sensory-motor functions). It might be due to discharges from the regenerating nerve fibers or due to the survival of certain fibers.[11,16]

In a study by Sunki *et al*., amplitudes were the most affected parameter among both sensory and motor nerves. In sensory nerves, amplitudes (46.7%) were the most affected, followed by their velocities (7%) and latencies (5.1%). In motor nerves also, amplitudes (37.4%) were more affected, followed by their velocities (13%) and latencies (8.4%).[17]

In studies conducted by Samant *et al*., Donde *et al*., and Pandya *et al*., sensory nerves were involved much earlier in leprosy and showed more quanta of changes in conduction velocities as compared to motor nerve fibers in the early stages of damage. However, amplitude changes were much more marked for motor nerve fibers.[18-20]

Wim *et al.* in their study found abnormalities in SNC (particularly amplitude) and warm perception as the most sensitive markers of sub-clinical neuropathy. In SNC, both distal latency and amplitude became abnormal at least 12 weeks prior to the clinical manifestation of sensory impairment. The early changes were less obvious in MNC. CMAP velocities and amplitudes were lower in many cases than in controls at least 12 weeks before the clinical manifestation of deficit, but they were above or near the normal threshold in about half of the nerves.[21]

***Applications of NCS[22]***

1. To detect subclinical neuropathy.
2. Management of neuritis

Carayon and Rigal outlined several guidelines for surgical indications in leprosy, based on EMG and NCV.[23] These may be summarized as:

- Recent neuritis – If NCV drops and EMG worsens, it is a sign of failure of medical treatment and an indication for surgery. When neuritis is subclinical, and NCV/EMG is stable, medical treatment alone should be pursued.
- Long-standing neuritis – If there is clinically complete sensory-motor deficits and EMG/NCV results are abnormal, surgery is contraindicated; if EMG shows some intact motor units and signs of regeneration, surgery may be useful. Surgery is worthwhile only when NCV is more than 25–30 m/s.

3. Monitoring the medical treatment
   - Improvement in NCV with treatment was noted in several studies.[23-25]
   - MNCV can be used to monitor drug efficacy in leprosy reactions.[26]
4. To detect thalidomide-induced peripheral neuropathy

Leprosy patients on thalidomide may develop peripheral neuropathy due to disease *per se* or due to thalidomide. NCS can differentiate between the two. The electrophysiological features of thalidomide induced neuropathy include, reduction in SNAP amplitude, and relative conservation of nerve conduction velocities.[22,27]

Early identification of NFI and prompt treatment are crucial in prevention of disabilities. Neurophysiological examination should be done along with clinical examination at the time of diagnosis, as these studies are more sensitive than the clinical examination. NCS is a rapid, safe and non-invasive technique.[22] In clinically suspected cases of peripheral neuropathy due to pure neuritic leprosy, NCS is recommended to determine the extent and the type of nerve involvement. It helps in early diagnosis of NFI ensuring early initiation of treatment so as to prevent disabilities.[7]

## HIGH RESOLUTION ULTRASONOGRAPHY (HRUS) IN LEPROSY

Ultrasonography is a non-invasive modality useful for studying changes in nerve and is more cost-effective than other imaging procedures, such as magnetic resonance imaging. Technological developments have improved the image quality and brought out devices that are smaller in size and are portable. It has become a useful tool where leprosy is endemic.[28] Ultrasonography uses the piezoelectric effect which converts electric energy to sound waves. The ultrasound unit comprises of a transducer, transmitter, and image visualization and image storage devices. The B mode ultrasound is based on the brightness of a grid of grey dots that deciphers various anatomical structures.[29] In leprosy, clinical examination of nerves is subjective and inaccurate. HRUS can provide an objective measure of nerve damage by demonstrating the nerve thickening, altered echotexture, and abnormal vascularity. In nerves with clinical features of impairment of function, HRUS was able to detect more extensive changes than those diagnosed clinically. Moreover, many clinically normal nerves showed features of nerve involvement in HRUS analysis.[28]

HRUS can calculate the cross-sectional areas of peripheral nerves.[29] It helps to study the structural changes in nerve sites that cannot be biopsied for histopathology, especially the mixed nerves (risk of muscle palsy). Furthermore, the HRUS can examine the nerve for a longer length than MRI. Evaluation by MRI is limited to defined segments.[30]

HRUS measurement of increased nerve size is a sensitive indicator of the presence of neuropathy in leprosy.[31] The nerves are palpably enlarged in leprosy, especially superficial nerves in areas that are typically cooler than the core body temperature, such as ulnar nerve at the elbow and fibular nerve at the fibular head.[32] In a study on the correlation between clinical signs and sonographic findings, 90% of leprosy patients who had no clinical evidence of nerve involvement showed nerve enlargement by HRUS.[33]

Fusiform enlargement or loss of fascicles, edema and increased neural vascularity can be seen by Doppler mode on ultrasound. A normal nerve, in transverse section, shows small hypoechoic areas separated by hyperechoic septae, giving it a "honeycomb-like" appearance.[30] The longitudinal sections reveal fascicular architecture, leading to a "bundle of straws" appearance. The nerve shows sliding movement over the muscles and tendons on dynamic examination. Any contour deformity during movement of nerve or altered movement gives us a clue to the underlying pathology. The echo reflectivity of nerves assessed on imaging is arbitrarily graded as follows:
Mild = Some hypo-reflectivity
Moderate = Obvious hypo-reflectivity
Severe = Absence of any fascicular pattern

Wilder-Smith *et al*. showed that color Doppler measurements of blood flow in the ulnar artery by ultrasound are sensitive and specific in identifying small fiber autonomic dysfunction in patients with leprosy.[34] Normally, perineural and intraneural vasculature are not visualized on Doppler imaging modalities due to low blood volume and slow flow velocities. Reactions and neuritis in nerve are associated with hemodynamic changes in both epineurium and perineurium of nerve fascicles. The increased neural vascularity with interfascicular edema reflects immune-mediated inflammation in leprosy reactions.[28]

Studies reveal that there is no feature to differentiate TT from lepromatous forms of leprosy on imaging. HRUS showed greater disruption of nerve architecture in frequent and severe reversal reactions.[30]

In summary, the definite advantages of HRUS include the ability to assess multiple nerve sites and the ability to examine a longer section of the same nerve for localized thickening. These, in turn, help in early recognition of nerve involvement in leprosy.

## QUANTITATIVE SENSORY TESTING (QST)

QST is a newer modality to assess sensory neuropathy. The thermal threshold and vibration perception threshold (VPT) are the commonly tested parameters. Thermal testing assesses warm sensation mediated by small, unmyelinated C-fibers, and cold sensation mediated by small, unmyelinated and myelinated Aδ fibers. Vibrometry assesses large, myelinated Aβ fibers.[21]

## VPT TESTING

VPTs are assessed by Vibrameter. The instrument provides application force-controlled measurements of VPTs by slowly

increasing the vibration amplitude, until the person tested feels the vibration. The testing sites are:
Thenar eminence – Median nerve
Hypothenar eminence – Ulnar nerve
Dorsal first web space – Radial cutaneous nerve
Plantar surface of big toe – Posterior tibial nerve
Mid-lateral border of foot – Sural nerve
All the tests are done on both sides.[21]

## THERMAL THRESHOLD TESTING

Thermal thresholds are evaluated using a thermal sensory analyzer. Warm detection thresholds (WDT) and cold detection thresholds are measured relative to a baseline thermode temperature of 32°C. 10°C is set as the measurable limit of cold and 50°C as the limit of warm perception. Test sites are the same as for vibrometry (as described above).

QST is not used commonly. Van Brakel *et al*. did not find any additional advantage for vibrometry over established methods of sensory testing in the INFIR Cohort Study. But they noted that WDT could detect sensory deficit even 12 weeks before an abnormal monofilament test.[21]

## NINHYDRIN SWEAT TEST

Autonomic dysfunction is observed early in leprosy. The routinely used sweat tests involve injection of a cholinergic drug followed by the use of a color indicator. Ninhydrin test is a non-invasive test. It detects and grades thermal sweating. The autonomic function assessed by the ninhydrin sweat test is as follows:-

Punches of Schleicher and Schuell (S and S) filter paper/ Whatman filter paper are used. These punches are placed in a dry bowl and few drops of 1% ninhydrin in acetone are added to soak the filter paper, and these are then allowed to dry. These filter paper punches are transferred to the adhesive side of a piece of Scotch tape and then applied to the skin lesion (test site) and the corresponding normal site.

The patient is asked to walk in the sun to induce thermal sweating and sweat function is graded after ½ an hour. The gradings are:[35]
0 – No color change.
1 – Just perceptible blue-purple color change.
2 – Color change in between 1 and 3.
3 – Intense blue purple color change.

Markandeya and Srinivas found the test to be effective in detecting and grading sweat function in different types of leprosy. The test could detect normal sweating in 16 patients with hypopigmented lesions due to causes other than leprosy.[36]

Different stimulating agents have been used to assess sweat response such as epinephrine injections by Wade (1940), pilocarpine by Muir (1938), methacholine by Arnold (1944) and acetylcholine by Parekh *et a*l., (1966), Sehgal (1976), and Matur *et al*. (1971). These tests are invasive, cumbersome and therefore not commonly used. The degree of sweat function impairment cannot be graded by these tests whereas ninhydrin test is simple, can be undertaken at any place, and loss of sweat function can be graded. It is also useful in uncooperative patients, in children and for face lesions, where it is difficult to assess sensory nerve function.[35]

## INFRARED THERMOGRAPHY

The intensity of infrared radiation emitted by objects is mainly a function of their temperature. Infrared thermography uses this feature for multiple purposes. It is a potential tool for early detection of autonomic neuropathy in leprosy, assisting in the prevention of major neural damage, deformities, and disabilities.[37]

Temperature changes in patients' hands can be detected by infrared thermography. The patient is made to sit with palms upward in his/her lap. Filming of hands is done with the infrared camera for 5 minutes.[37] During filming, after the initial 3 seconds, vasomotor reflex test (autonomic response of the vessel) is performed where a cold stress is delivered on the palms. A cold jet is splashed on the palm to observe the autonomic response of hand's vessels to cold stress (done in both controls and cases). The temperature is recorded at 0 minutes (initial temperature), 2 minutes and 30 seconds, and 5 minutes (final temperature).[37]

The control group and those with lepromatous leprosy showed difference in temperature between the areas supplied by the ulnar and the median nerves, but no difference was noted between the limbs. BL and BB showed a significant difference between the temperatures of the right and left hands, but no difference was noted between the areas supplied by the ulnar and the median nerves. In BT, no difference was noted in the mean temperature recorded with respect to the nerve supply or the limb.[37]

The temperature difference after the cold stress also differed significantly between the clinical types of leprosy. After the cold stress, BT group could return to and reach a higher than the initial temperature while the lepromatous group was unable to return to the initial temperature in 5 minutes.[37]

## CONCLUSION

Despite the declared "elimination of leprosy as a public health problem" in December 2005, India, still contributes to more than 60% of the global leprosy case load. These non-invasive methods can play a great role in the early detection of NFI due to leprosy which may help in the early diagnosis of the disease and the prevention of disability due to the

disease. Judicious use of these under-utilized, non-invasive techniques may improve the accuracy of diagnosis of leprosy and NFI due to the disease.

### Declaration of patient consent

Not required as there are no patients in this article.

### Financial support and sponsorship

Nil.

### Conflicts of interest

Dr Kunjumani Sobhanakumari is on the editorial board of the Journal.

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**How to cite this article:** Indu Krishnan MU, Sobhanakumari K, Jose P, Amitha NP, Irimpan KJ. High resolution ultrasound, nerve conduction study, and other non-invasive investigations in leprosy. J Skin Sex Transm Dis 2021;3:136-42.