A STUDY ON THE DIAGNOSTIC SIGNIFICANCE OF NERVE CONDUCTION STUDIES IN EARLY DETECTION OF PURE NEURITIC HANSEN'S DISEASE

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CERTIFICATE

This is to certify that the dissertation **entitled "A study on diagnostic significance of nerve conduction studies in early detection of Pure Neuritic Hansen's disease"** is a bonafide original work of DR.R.JEYARAMAN , in partial fulfillment of the requirements for D.M. Branch– I (NEUROLOGY) Examination of the Tamil Nadu Dr. M.G.R Medical University to be held in AUGUST 2012, under our guidance and supervision.

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DECLARATION

I hereby solemnly declare that this dissertation titled **"A STUDY ON THE DIAGNOSTIC SIGNIFICANCE OF NERVE CONDUCTION STUDIES IN EARLY DETECTION OF PURE NEURITIC HANSEN'S DISEASE"** was done by me in Institute of Neurology, Madras Medical college and Rajiv Gandhi Government General Hospital, Chennai -3, under the guidance and supervision of **Prof. R.M. BHOOPATHY**, M.D, D.M, Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-3 . This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirement for the award of D.M Degree Branch I (NEUROLOGY).

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CONTENTS

ABBREVIATIONS

TT TUBERCULOUS TUBERCULOID

BT BORDERLINE TUBERCULOID

BL BORDERLINE LEPROMATOUS

BB BORDERLINE BORDERLINE

LL LEPROMATOUS LEPROSY

RNA RIBONUCLEIC ACID

kDa KILO DALTON

HLA HUMAN LEUCOCYTE ANTIGEN

CD CLUSTER DIFFERENTIATION

MHC MAJOR HISTOCOMPATIBILITY COMPLEX

TNF TUMOUR NECROSIS FACTOR

IL INTERLEUKINS

ENL ERYTHEMA NODOSUM LEPROSUM

PGL PHENOLIC GLYCOLIPID

MF MONOFILAMENTS

NCS NERVE CONDUCTION STUDIES

SNC SENSORY NERVE CONDUCTION

NFI NERVE FUNCTION IMPAIRMENT

HD HANSEN'S DISEASE

VDRL VENEREAL DISEASE RESEARCH LAB

HIV HUMAN IMMUNODEFECIENCY VIRUS

DIAGNOSTIC SIGNIFICANCE OF NERVE CONDUCTION STUDIES IN EARLY DETECTION OF PURE NEURITIC HANSEN'S DISEASE

ABSTRACT

AIM

To study the diagnostic significance of nerve conduction studies in early detection of pure neuritic hansen's disease.

INTRODUCTION

Hansen's disease is diagnosed by presence of skin lesions. However, in case of pure neuritic hansen's the diagnosis is delayed because of absence of skin lesions. The delay in diagnosis leads to delay in treatment which leads to formation of deformities. This study is aim that whether nerve conduction studies are helpful in subjecting the patient to early nerve biopsy.

MATERIALS AND METHODS

This study is a descriptive study of analysing the patients with clinical suspicion of pure neuritic Hansen's electro physiologically and later corrlating with the nerve biopsy results.

70 patients attending neurology OPD with clinical suspicion of pure neuritic hansen's disease were selected.

Patients were evaluated for other diseases which can mimic Hansen's disease.

Patients were subjected to sural nerve biopsy and then the findings were correlated with electro physiology.

RESULTS

16 out of 70 patients were diagnosed to have Hansen's disease by biopsy. The most common mimickers for Hansen's were Diabetic Neuropathy, HMSN and connective tissue disorders.

Nerve conduction studies including sympathetic skin response were abnormal in all patients with Hansen's disease. It was also abnormal in other diseases like Diabetic Neuropathy and connective tissue disorders.

CONCLUSION

All the patients with biopsy proven Hansen's disease showed abnormal nerve conduction studies.

Since nerve conduction studies were also abnormal in other diseases it is not specific for Hansen's and based on that alone we cannot subject the patients for nerve biopsy.

Nerve biopsy clinches the diagnosis.

INTRODUCTION

Leprosy is a chronic granulomatous infection, principally affecting the skin and peripheral nerves, caused by the obligate intracellular organism Mycobacterium leprae. Leprosy is the most common treatable cause of neuropathy. It is one of the oldest diseases endemic in India. It continues to be an important health problem worldwide but is most prevalent in India, Brazil, Democratic Republic of Congo, Tanzania, Nepal, Mozambique, Madagascar, Angola, and the Central African Republic.[1].The clinical range from tuberculoid to lepromatous leprosy is a result of variation in the cellular immune response to the mycobacterium. The resulting impairment of nerve function causes the disabilities associated with leprosy. It is of high social concern as its complications leads to deformities which leads to social stigma and decreased quality of life. The diagnosis is often delayed because of the prolonged incubation period. The compliance of the patients with respect to treatment is also poor because of the prolonged treatment period. The diagnosis is further delayed when the disease presents as the pure neuritic form in which there are no skin lesions. A stage of functional blockade of conduction of nerve impulse almost always precedes visible pathological changes in the nerve. The role of electrophysiological evaluation of nerve function in the diagnosis and assessment of different neuropathies is well established A significant decline of motor nerve

conduction velocities has also been reported in clinically normal nerves in leprosy. This study is aimed at whether electrophysiology can help in the early detection of nerve involvement in pure neuritic disease which may aid in the early treatment of the disease decreasing the morbidity. This study also tries to correlate the clinic electrophysiological findings with that of the nerve biopsy.

AIM AND OBJECTIVES

1. To study the diagnostic significance of nerve conduction studies in early detection of Pure Neuritic Hansen's disease

2. To study the correlation between sympathetic skin response and nerve biopsy.

3. To study the electrophysiological correlation in biopsy proven Hansen's disease

REVIEW OF LITERATURE

INTRODUCTION

The earliest report of Leprosy dates back to 600 bc. In 1864 G. Armour Hansen reported his observations on tissue from a Norwegian patient and became the first to link a bacterium to human disease. This organism, which later came to be known as Mycobacterium leprae, is one of the important causes of treatable neuropathy worldwide. The most likely mode of transmission is through nasal

secretions and skin contact. The disease is thought to be of low infectivity. In most populations, over 95% of individuals are naturally immune.[2]. Leprosy was recognized in the ancient civilizations of China, Egypt and India.

PATHOGENESIS

M. leprae multiplies very slowly and the incubation period is about five years. Symptoms can take as long as 20 years to appear. Nerves, which are generally resistant to bacterial infections are consistently invaded by M. leprae. Another extraordinary feature is that the critical temperature required for multiplication of M. leprae. It fails to multiply at core body temperature of 37 ◦C and optimal growth occurs at 27–30 ◦C which is responsible for the

occurrence of leprosy in superficial and cooler areas such as skin, nerves, testis and upper respiratory tract. Peripheral neuropathy is the main cause of morbidity in leprosy and responsible for most of the disabilities and deformities displayed by many leprosy patients [3,4.]

The nerve damage affects sensory, motor, and autonomic fibers. These nerve lesions are characterized by a chronic or subacute inflammatory infiltrate containing epithelioid cells or M. leprae-glutted macrophages. This infiltrate will occupy the endoneurium, perineurium and epineurium which leads to progressive impairment of unmyelinated and myelinated neural fibers followed by a replacement of the peripheral nerve parenchyma with fibrous tissue [5,6]. Necrotic caseation in tuberculoid granulomas can lead to abscess formation and complete destruction of the nerves [7]. Pure neuritic form of neuropathy may present without skin lesions. Pure neuritic form has a varied incidence among the total number of cases in an endemic leprosy population comprising 4–10% of patients. Males are significantly more affected than females [8,9]. In this neuropathy, the small nerve fibers conducting pain and temperature sensations are affected significantly before the large myelinated fibers that conduct vibration sense, position sense, and motor impulses. This selective sequential involvement of the nerve fibers impairs the detection of leprosy neuropathy at the initial stages of the disease by neurophysiological evaluation since routine nerve conduction studies only record potentials originating from fibers wider than 7μm in diameter. Histologic preparations

in these patients usually show changes compatible with borderline or tuberculoid leprosy [3,10].

Clinical features:

Leprosy mainly affects the skin and nerves and resembles many dermatologic and neurologic conditions. If left untreated the disease is progressive and results in permanent damage to the skin, nerves, limbs and eyes.

Classification:

Leprosy can be classified according to the number of skin lesions present and the number of bacilli found on slit-skin smear examination.

Paucibacillary disease (indeterminate, tuberculoid tuberculoid (TT) and borderline tuberculoid (BT) forms) is defined as fewer than six skin lesions with no bacilli on slit-skin smear testing. Multibacillary disease (borderline borderline (BB), borderline lepromatous (BL) and lepromatous leprosy (LL) forms) is characterized by six or more lesions with or without positive skin smear results. To avoid treatment failure in PB patients with positive skin-slit smears it is recommended that such cases should be classified as multibacillary disease [11]. Skin manifestations and neurological involvement depends on the stage of disease and immunological status of the patient.

Table .1

Clinical features of different stages in leprosy

Type	Skin lesions	Nerve lesions
Lepromatous (little/no cellular immunity,anergic)	Wide and symmetrical distribution	Nerve damage slow and progressive
	Slight pigmentation or erythema	Hypoesthesia over extensor surface of the legs,feet, forearms and hands
	Smooth and shiny surface Late features-impaired sweating, hair growth, loss of sensation Dry, scaly appearance Impairment of sweating	Distal weakness-intrinsic muscles of hands and feet
Tuberculoid (strong cell-mediated immunity, lymphocytic infiltration)	<6 lesions	Enlargement of single nerve is common
	Asymmetric distribution	Marked nerve damage can occur
	Well circumscribed	May result in wrist drop, clawing of the hand and foot

		drop
	Elevated margins	Commonly involves the greater auricular, radial cutaneous, ulnar, common peroneal posterior tibial nerve
	Marked hypopigmentation Lesions typically hairless anesthetic	
Indeterminate (intermediate immunity status)	Hypo-pigmented	Nerve involvement irregular and asymmetrical
	Ill-defined Heal on their own in 75% cases Ignored by patients	Early anesthesia
Borderline (intermediate immunity status)	Abundant Various degree of symmetry, definition and pigmentation	

Lepromatous leprosy (LL):

Lepromatous leprosy is a generalized disease with multisystem involvement, sparing only the central nervous system. Most strikingly involves the skin, mucous membranes, nerves and reticuloendothelial systems. Lesions involving the skin are multiple, bilateral, and symmetrical. Typically these lesions are hypopigmented (sometimes mildly erythematous), shiny with ill-defined margins and merges imperceptibly with surrounding skin. Characteristically it involves eyebrows, nose, and lips, along with flattening of the bridge of the nose resulting in classical 'leonine facies'. Nerve involvement results in progressive bilateral symmetrical cutaneous sensory loss. The nerve trunks tend to be bilaterally and symmetrically thickened and tender [12,13]

Tuberculoid tuberculoid (TT):

Tuberculoid tuberculoid leprosy is characterized by a well-defined uniformly circular or oval erythematous/ hypopigmented plaque with maximal induration of the margins sloping towards the centre and appearing like "a saucer the right way up". The surface is bald, dry and scaly, and completely anaesthesthetic. These lesions usually number from one to three in a patient and a thickened (sometimes tender) nerve in the vicinity is usually palpable [12,13].

Indeterminate (I) leprosy

This expression of the disease is a prelude to the determinate forms of the disease. It is diagnosed when there is a single lesion or only a few macules, with well or ill-defined margins and variably impaired sensations. The surface may be smooth or mildly scaly, and a thickened nerve supplying the lesion(s) may or may not be palpable clinically. Seventy-five percent of the lesions in indeterminate leprosy heal spontaneously and they are ignored by many patients.

Borderline lepromatous (BL)

Borderline lepromatous leprosy shares features of BB; however lesions resembling BT are out-numbered by lepromatous (LL) type of lesions. The lesions have variable sensory loss, tend to vary in number from countable to uncountable, and they are bilaterally distributed with a tendency towards symmetry. Symmetrical involvement of the nerves in the form of thickening and/or tenderness along with sensory loss not limited to clinically apparent skin lesions are features that help in the diagnosis [12,13].

Borderline tuberculoid (BT)

Borderline tuberculoid leprosy is recognized as hypopigmented and/or erythematous macules or plaques with well-defined irregular margins. The surface of the lesion(s) is bald, dry, and scaly with variable sensory loss. The number of lesions in a patient may vary from 3 to 10, and satellite lesions are a cardinal feature. Cutaneous nerves within the area of skin lesion may be thickened, tender, or both [12,13].

Borderline borderline (BB)

Mid borderline (BB) leprosy manifests the clinical morphology of BT as well as borderline lepromatous (BL) disease. The number of BT-type lesions tends to equal the number of lepromatous type lesions. Nerves tend to be affected bilaterally and asymmetrically; may be thickened, tender, or both. There is variable/partial sensory loss over different types of lesions, but the loss tends to be coterminous with the clinically apparent skin involvement [12,13].

Histoid leprosy

This is the uncommon presentation of multibacillary leprosy that has distinct clinical, bacteriologic, and histopathological features. Patients with this type of disease may present de novo or as a result of secondary drug resistance,

with cutaneous and/or subcutaneous nodules and plaques over surrounding apparently normal skin [12,14].

Pure Neuritic leprosy

This is a type of leprosy that manifests with neural signs and/or symptoms without any clinically evident skin involvement. It accounts for a significant proportion of leprosy in Indian subcontinent, nearly 5 – 10% 0f the patients with leprosy [15]. Patients with neuritic leprosy have signs and symptoms of sensory impairment, parasthesia, nerve enlargement, nerve pain, and muscle weakness, without skin manifestations [14,16]. The extent and distribution of nerve involvement is variable and commonly affected nerves are ulnar, radial, median, lateral popliteal, posterior tibial, facial, and sometimes trigeminal [17]. Mononeuritis or mononeuritis multiplex are the most common presentations. In patients with mononeuritis single nerve is usually enlarged and the others may appear thickened. In few cases there is distal symmetric neuropathy with temperature and pain anesthesia without muscle weakness. In these cases the tendon reflex may be retained and electromyography (EMG) may be normal [2,7,8]. These case are difficult to diagnose as it will need sophisticated diagnostic procedures such as bacilloscopy, electroneuromyography and nerve biopsy. Approach to the neuritic leprosy will depend on its clinical characteristics, nerve biopsy, and histological

appearance of dermatological and neurological lesions. Inflammatory infiltrate in the nerves may be distinct from the ones in the cutaneous lesions, being multibacillary in the nerves and paucibacillary in the skin [18–20].

RECENT ADVANCES IN PURE NEURITIC LEPROSY

Leprosy is a disease where Mycobacterium leprae is primarily directed against specific targets in the peripheral nerves [21-23]. Recent research has clearly demonstrated the gap between clinical and histopathological disease definition. The majority of patients with pure neuritic leprosy are now known to have histological evidence of involvement beyond neural tissues. Simple histological examinations of nasal mucosa and dermatologically normal skin from hypesthetic regions may be used to reveal the characteristic changes of leprosy[24-27].

Due to the embedding of nerves in the skin, pathophysiological processes naturally spill over to involve the surrounding tissues even early on in the disease process. In patients with pure neuritic leprosy established on clinical examination, typical histological involvement of extra neural tissues occurs frequently. Samples taken from hypesthetic skin and nasal mucosa, show specific changes of leprosy in more than 50%.[25-27]. Abnormalities are typically seen surrounding the deep dermal nerves and the neurovascular complexes.[25] Changes seen in the nasal mucosa range from macrophage

granulomas with acid-fast bacilli, to epithelioid granulomas and nerve inflammation.[25]

UPDATES IN THE BIOLOGY OF MYCOBACTERIUM LEPRAE

The genomic sequencing of M leprae is a major advance, which assist in elucidation of the unique biology of the organism[28].

M leprae is an acid-fast gram-positive bacillus and an obligate intracellular. parasite with tropism for macrophages and Schwann cells. The bacilli show preference for growth in cooler regions of the body. The M leprae genome includes 1605 genes encoding proteins and 50 genes for stable RNA molecules.[28] More than half of the functional genes in the M tuberculosis genome are absent and have been replaced by many inactivated genes or pseudogenes. M leprae seems to have jettisoned genes normally required for replication ex vivo and assumed a unique ecological niche with a very limited host range and the need for growth within cells. This gene decay has removed entire metabolic pathways and regulatory genes, particularly those involved in catabolism, but the genes essential for the formation of a mycobacterial cell wall have been retained.[29] The leprosy bacillus might therefore be dependent on host metabolic products, which could explain its long generation time and inability to grow in culture.[28]. The unique predilection of M leprae for Schwann cells is probably determined by the mycobacterium's binding to the G domain of the 2 chain of laminin 2, which

is a component of the basal lamina of Schwann cells.[30]. This form of laminin is restricted to peripheral nerves, which explains the specific tropism of M leprae. The subsequent uptake of M leprae by the Schwann cell depends on α-dystroglycan, which is the receptor for laminin within the cell membrane, and other intracellular components.[31] Several candidate molecules on the surface of M leprae bind to this complex, including the specific terminal trisaccharide of PGL-I and a 21 kDa protein;[32,33] however, the specificity of these interactions has not been fully resolved.[34] Once inside the Schwann cell, the leprosy bacilli replicate slowly over years. At some stage, specific T cells recognise the presence of mycobacterial antigens within the nerve and initiate a chronic inflammatory reaction. The Schwann cells can express HLA class 2 molecules and play an active part in the immunological reaction by presenting mycobacterial peptides to HLAclass- 2-restricted CD4-positive T cells.[35] Swelling within the inflexible perineurium leads to ischaemia, further nerve damage, and eventually fibrosis with axonal death. [36].

Host response:

Host genetic factors have a partial effect on both the development of leprosy and the pattern of disease. Whole-genome screening has identified susceptibility loci on chromosome 10p13, close to the gene for the mannose receptor C type 1, a phagocytic receptor on macrophages, and on chromosome 6 within the MHC.[37] Within this region linkage has been

shown to HLA class II genes in Indian patients with leprosy and to the gene for tumour necrosis factor (TNF) in Brazilian patients[38]

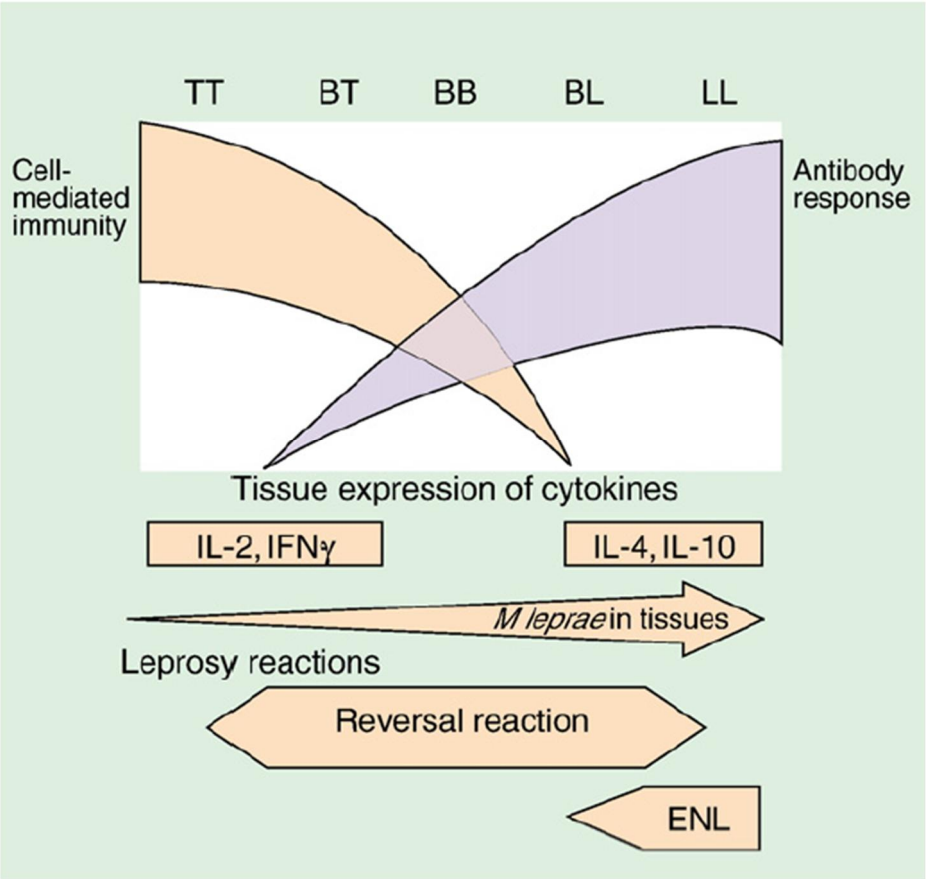


Fig 1. Clinical-immuno pathological range of leprosy.

IL=interleukin; IFN=interferon; ENL=erythema nodosum leprosum.

The varying clinical forms of leprosy are determined by the underlying immunological response to M leprae [39] (figure 1).

At one pole, patients with tuberculoid leprosy (TT) have a vigorous cellular immune response to the mycobacterium, which limits the disease to a few well-defined skin patches or nerve trunks.[40] The lesions are infiltrated by interferon-γ and TNF α-secreting CD4-positive T lymphocytes, which form well-demarcated granulomas, containing epithelioid and multinucleate giant

cells, around dermal nerves.[41] Few, if any, acid-fast mycobacteria can be found in the lesions. Strong cellular immunity is confirmed by T-cell proliferative and cytokine responses to M leprae antigens in vitro and by skin-test reactivity to soluble preparations of M leprae and to dead whole M leprae organisms (Mitsuda reaction). Antibody responses to M leprae antigens are absent or weak.

At the other pole, lepromatous leprosy (LL) is characterised by the absence of specific cellular immunity but intact immunity to the related M tuberculosis. There is therefore uncontrolled proliferation of leprosy bacilli with many lesions and extensive infiltration of the skin and nerves. The dermis contains foamy macrophages filled with many bacteria, but few CD4-positive and CD8- positive T lymphocytes and no organised granulomas.

There are high titres of antibodies to PGL-I and protein antigens specific for M leprae, and mycobacterial antigens are readily identified in the urine and blood.[42,43,44] Most patients have the intermediate forms of borderline tuberculoid (BT), mid-borderline (BB), and borderline lepromatous (BL) leprosy. These forms are characterized by a progressive reduction from BT to BL leprosy in cellular responses, associated with an increasing bacillary load, more frequent skin and nerve lesions, and higher antibody titres. The borderline forms are clinically unstable, and patients either show slow

change towards the lepromatous pole or experience sudden type I or reversal reactions.

NERVE DAMAGE

Damage to the nerves occurs in two settings

Peripheral nerve trunks and small dermal nerves.

Peripheral nerves are affected in fibro-osseous tunnels near the surface of the skin, including the great auricular nerve (neck), ulnar nerve (elbow), radial-cutaneous nerve (wrist), median nerve (wrist), lateral popliteal nerve (neck of the fibula), and posterior tibial nerve (medial malleolus). The posterior tibial nerve is the most commonly affected, followed by the ulnar, median, lateral popliteal, and facial nerves.[45,46] Involvement of these nerves produces enlargement, with or without tenderness, and standard regional patterns of sensory and motor loss.

Small dermal sensory and autonomic nerves are affected producing hypoaesthesia and anhidrosis within borderline tuberculoid and tuberculoid lesions and glove and stocking sensory loss in lepromatous disease. Sensation on the hands and feet can be assessed and monitored by use of Semmes-Weins monofilaments.[47]

NERVE CONDUCTION STUDIES

Problems associated with leprosy neuropathy include loss of sensory and autonomic nerve functions and muscle strength. In practice, touch/pressure and muscle strength are the modalities tested in leprosy patients.[48,49]. However, the issue of importance lies in the sensitivity, reliability and reproducibility of any standard assessment method.

The Semmes–Weinstein monofilaments (MF), used for assessing sensory nerve function are advocated on the grounds that the results are reliable, since the force required to bend the accurately manufactured monofilaments is relatively constant and repeatable when used by skilled examiners, and since they are graded (1–5), they provide a quasi-quantitative estimate of sensory loss.[50,51].

The utility of electrophysiological methods particularly nerve conduction studies (NCS) in the detection and monitoring of nerve abnormalities in leprosy and other neuropathies have been well established.[52-54] Though not specific to leprosy neuropathy, NCS is by far more reliable, reproducible and has proved a sensitive measure of nerve damage, since it defines small late components originating from demyelinated, remyelimated or regenerated fibres. [55-59.] The large diameter sensory fibres have lower thresholds and conduct faster than motor fibres by about 5 to 10% and fastest sensory conduction velocity is particularly observed amongst mixed nerves.[60] Studies correlating the nerve conduction test findings with the

clinical tests are few and far between. Studies by van Brakel, et al. (2005), as well as Kaplan and Gelber (1985) have reported a good concordance between Mono Filament (MF) testing and sensory nerve conduction (SNC) studies, supporting the validity of monofilaments as standard screening test of sensory function and the usefulness of clinical testing modalities for assessing nerve function impairment (NFI). Since NCS is a more sensitive technique for assessing nerve damage, it is considered as gold standard for assessing functional nerve impairment.

MECHANISM OF NERVE DAMAGE

The mechanism of nerve damage remains diverse and unclarified.[61] It may be intrafascicular, intraneural, extrafascicular or extraneural lesions.[62] Peripheral nerve involvement is usually more and appears earlier in TT than in LL and also certain nerves are affected more than others in HD. Croft et al. found that the most commonly affected nerve by function impairment was the posterior tibial (sensory) followed by the ulnar nerve. [63,64]

Although the route of entry of M. leprae into the body and the method of its migration to the peripheral nervous system are unknown, it is known that M. leprae preferentially invade Schwann cells, and that this represents the early crucial step that leads to sensorimotor loss. [65-68] Although M. leprae has no locomotory ability, the bacilli can move across endothelium and through

connective tissue to reach Schwann cells. It is possible that they are conveyed to the nerve cells by macrophages.[69] Another possibility is that that the bacilli could be transported to nerve cells via intraneural capillaries.

Recent studies have provided an insight into the molecular basis of the neural tropism of M. leprae, and have identified the Schwann cell receptors involved in M. leprae infection.[30,31]

The peripheral nerve comprises myelinated and non-myelinated Schwann-cell–axon units. In both cases, the Schwann-cell–axon unit is completely surrounded by the basal lamina, a characteristic feature that distinguishes Schwann cells from fibroblasts and macrophages. As such, it is reasonable to assume that the tropism for Schwann cells, and perhaps cellular entry, might involve components of the Schwann cell basal lamina. The major components of the basal lamina are laminin-2, collagen IV, heparan sulfate proteoglycan and entactin/ nidogen[70-73]. By in vitro analysis of purified native components of the Schwann cell basal lamina, it was found that M. leprae preferentially bind to laminin-2. Laminin forms major basement membrane networks and interacts with various extracellular ligands and cellular receptors.[74-76]. Such interactions are required for the differentiation and survival of cells. Laminin has striking effects on Schwann cell behavior (changes in Schwann cell morphology and proliferation have been observed when these cells are cultured on laminin substrates), and has also been implicated in the ensheathment and myelination of axons.

M. leprae invasion of the Schwann cell represents a crucial early step that leads to nerve damage in leprosy patients. The deformities resulting from this nerve damage are largely responsible for the horror and dread of the disease. Currently, more than onequarter of all reported leprosy patients worldwide have disabilities, with ~50% being severely disabled.[77] Therapeutic intervention has prevented only one-third of infected individuals from suffering further nerve damage. Many investigators believe that the best strategy for overcoming neurological damage in leprosy depends on detecting and preventing the disease at an early stage.

RECOMMENDATIONS ON DIAGNOSIS OF PURE NEURITIC LEPROSY:

Recent epidemiological data reinforces the need for all clinicians to maintain a high index of suspicion for possible leprosy in patients with unclear peripheral neuropathy.[79] The presence of mononeuritis multiplex, tender and enlarged nerves should always raise suspicion towards possible underlying leprosy.[80] Sensory nerve biopsy, which is usually performed at the superficial sensory radial nerve branch at the wrist or the sural nerve is useful when there are no skin lesions.

In the case of negative or non-specific nerve biopsy findings, the most useful additional tissue samples are from skin with sensory changes and the nasal mucosa.[81,82]. In the case of diffuse sensory changes, multiple small skin punch biopsies (3 mm diameter) will increase the likelihood of picking up specific changes. Needle aspiration of the nerve is a relatively “nerve sparing” procedure, this may allow examination of motor nerves when sensory nerves are not involved or cannot be sampled. In the face of clinical non-specific features with negative histological findings, the physician will be placed in the difficult position on whether to treat with prednisolone or wait-and-see. For this situation there are no clear guidelines. In either case, initial close follow up (monthly) of the peripheral nerve status is mandatory as new clinical signs may provide diagnostic clarification.

NERVE BIOPSY:

Usually a sensory nerve is selected. Most commonly selected nerves are sural and superficial radial nerves. A small length of the nerve of approximately 2-4 cms is biopsied and stained with hemotoxylin and eosin and Fite-Faraco. Both low power and high power microscopy is used to evaluate and classify the disease.

Nerve fragments comprising of Schwann cells cytologically simulate epithelioid cell granuloma in low-power screening. It can be differentiated by morphological details made in high power. The Schwann cells are spindle-shaped cells of varying sizes with abundant, pale-staining cytoplasm with pulled out ends, and have oval, centrally or eccentrically, placed vesicular nuclei with ill-defined nucleoli [83]. Epithelioid cell granuloma is comprised by the collection of epithelioid cells. The epithelioid cells can be differentiated from Schwann cells by the presence of pale cytoplasm and vesicular elongated, drawn out, indented or folded nucleus, producing a shape reminiscent of a footprint. The nuclear chromatin is fine, and nucleoli are usually inconspicuous. The cytoplasmic margins are indistinct [83].

If the nerve involvement is solitary, the differential diagnosis includes tumors of the nerve sheath (neurofibromas and schwannomas), sarcoidosis, and sporotrichosis. In sarcoidosis, the granulomas may be randomly dispersed from the roots to the distal nerve trunks and branches. In these cases, involvement of neural tissue occurs after the expansion of a

neighboring granuloma, while in leprosy the granulomas occur primarily in the nerve. Moreover, sarcoidosis usually presents as a multifocal disease with multiple granulomas in several organs, mainly in the lung tissue. The diagnosis of sporotrichosis can be suggested by the occurrence of several abscesses distributed along the lymphatic chains, but with no relation to the neural tissue. In endemic area of leprosy, pure neuritic leprosy should always be considered in the investigation of a peripheral neuropathy. Sarcoidosis shows open granulomas with the absence of necrosis, acute, and chronic inflammatory cells and rarely the presence of asteroid bodies or Schaumann bodies in histiocytes and giant cells. Sporotrichosis shows suppurative granuloma with surrounding plasma cells and demonstration of fungal elements.

DIFFERENTIAL DIAGNOSIS

The manifestations of leprosy are protean, and the differential diagnosis is therefore wide. The consideration of leprosy as a diagnosis and adherence to the clinical criteria for diagnosing leprosy will facilitate a correct diagnosis. It can be difficult to diagnose leprosy especially in nonendemic regions or where the prevalence is very low. Congenital lesions such as nevus depigmentosus have normal sensation and are present at birth. Vitiligo is depigmented rather than hypopigmented. Pityriasis alba can be difficult to distinguish from early disease. Pityriasis versicolor and dermatophyte

infection may cause diagnostic difficulty. A history of preceding trauma or inflammation should be sought to rule out postinflammatory hypopigmentation. The importance of differentiating relatively benign hypopigmented skin changes from leprosy was emphasized by a recent study from Mali.[84]. In some parts of the world, leprosy is a more common cause of granulomatous lesions than sarcoid, granuloma multiforme, cutaneous tuberculosis, and granuloma annulare. Cutaneous leishmaniasis does not usually produce as many nodules as lepromatous leprosy, and the lesions usually crust and ulcerate after weeks or months. Post kala-azar dermal leishmaniasis may present with papules and hypopigmented macules and nodules, which may mimic lepromatous leprosy.

Nerve thickening is a feature of hereditary sensory motor neuropathy type III and Refsum's disease. Amyloid, which itself can complicate leprosy, can cause nerve thickening, and nerve enlargement due to neurofibromatosis mimicking leprosy has been reported.[85]

MATERIALS AND METHODS

STUDY DESIGN

A cross-sectional Study was conducted during the period of January 2010 to January 2012. Ethical Committee Approval was taken prior to the commencement of the study.

STUSY SAMPLE:

Seventy patients with clinical signs and symptoms suggestive of pure neuritic leprosy attending the Neurology clinic and dermatology clinic of Rajiv Gandhi Government General Hospital, Chennai.

SUBJECTS

INCLUSION CRITERIA

Newly diagnosed patients with clinical suspicion of pure neuritic hansen's disease without any leprosy skin lesions.

All patients with sensory loss of an area or part of the body.

Patients with loss of power or motor weakness in peripheral nerve distribution pattern.

Patients with nerve thickening, Nerve tenderness, Nerve swelling or Abcess.

Patients with deformities like Wrist drop, Foot drop, Claw hand, Facial palsy, lagophthalmos without any skin lesions or history of previous cutaneous Leprosy.

Patients with Trophic ulcer.

Patients who gave written Consent for the Study

EXCLUSION CRITERIA

Patients with skin lesions of leprosy.

Patients with previous history of leprosy skin lesions.

Patients with history of treatment for Leprosy.

Patients who have known comorbid illnesses such as Diabetes, connective tissue disorders, nutritional deficiencies, malignancies etc are excluded

Patients who refused written Consent.

METHODOLOGY

This study was done over a period of two years between January 2010 and 2012.

A detailed history with screening for nerve thickening and skin hypo or hyperpigmentation was done.

Clinical examination included assessment of power and sensory distribution areas.

SLIT SKIN SMEAR

Skin Smears from both ear lobes were taken for Acid Fast bacilli demonstration.

OTHER INVESTIGATIONS

Routine investigations like Complete Blood Count, Random Blood Sugar, Liver Function Test, Renal Function Test, VDRL, HIV-ELISA, Chest X Ray, ECG were taken. Appropriate investigations for connective tissue disorders for suspected cases were done.

ELECTRO DIAGNOSIS

Nerve conduction studies were done using the RMS system with the recommended filter settings under room temperature.

MOTOR NERVE CONDUCTION STUDIES

Median and ulnar nerves in both upper limbs

Tibial and peroneal nerves in both lower limbs.

Distal latencies, amplitudes and conduction velocities were assessed in all stimulated nerves.

F wave analysis was done in all nerves.

Sensory nerve conduction studies:

Median, ulnar and superficial radial nerves in both upper limbs

Sural nerve in lower limbs

Amplitude and conduction velocity were estimated.

Sympathetic skin response in both upper and lower limbs.

The normal values are taken from standard electrodiagnosis text books and articles.

The cut off values for abnormal conduction study is as follows.

CMAPS	DL(mS)	AMP(mV)	CV(mS)	Fmin LAT(Ms)
Median	>4	<4	<50	>31
Ulnar	>3.5	<4	<50	>31
Tibial	>6	<4	<40	>56
Peroneal	>6	<2	<40	>56

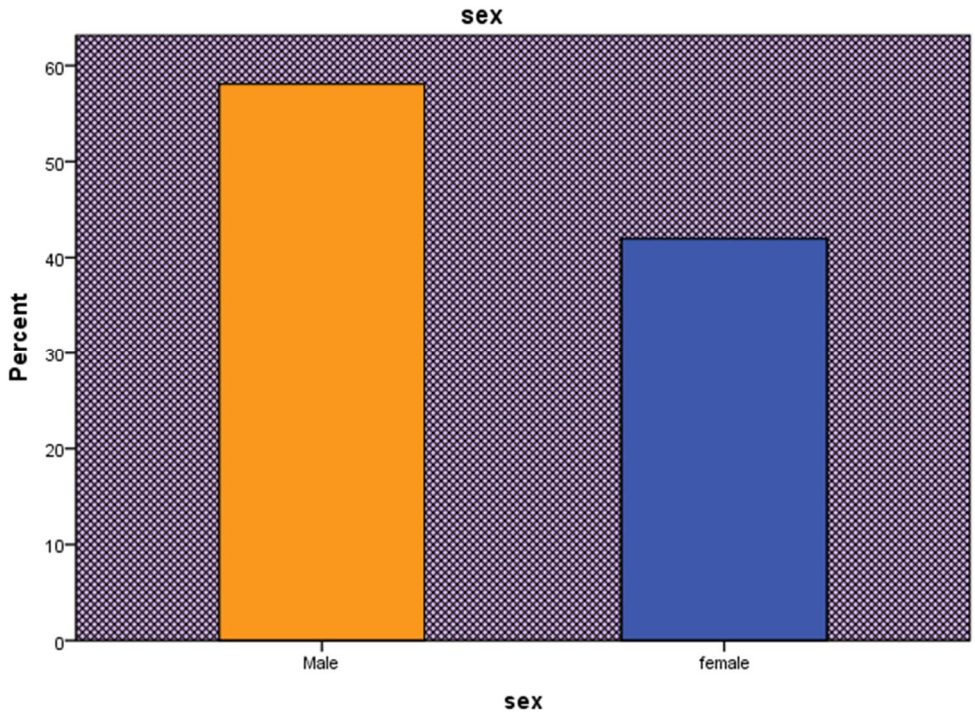
SNAPS	AMP (µV)	CV(mS)
Median	<10	<50
Ulnar	<10	<50
Sural	<6	<40

HISTO PATHOLOGICAL EXAMINATION

After taking a written consent from the patients, left Sural Nerve Biopsy was done under aseptic precautions under local anaesthesia. Hematoxyllin & Eosinophil stain and modified Fite Faraco Stains were used to assess the histopathology and visualization of m.leprae. The histopatological changes were studied with respect to Nerve tissue damage (Fibre/Axon loss or Degeneration, Perineural thickening and Fibrosis), Cellular component (Epitheloid Cells, Giant Cells and Foam Cells), Pattern of inflammation (Granuloma, Diffuse infiltrates, focal or Sparse infiltrates, Perivascular infiltrates and Necrosis) and Acid Fast Bacilli demonstration by Fite Faraco.

RESULTS

CHART 1. BAR CHART AGE VS SEX



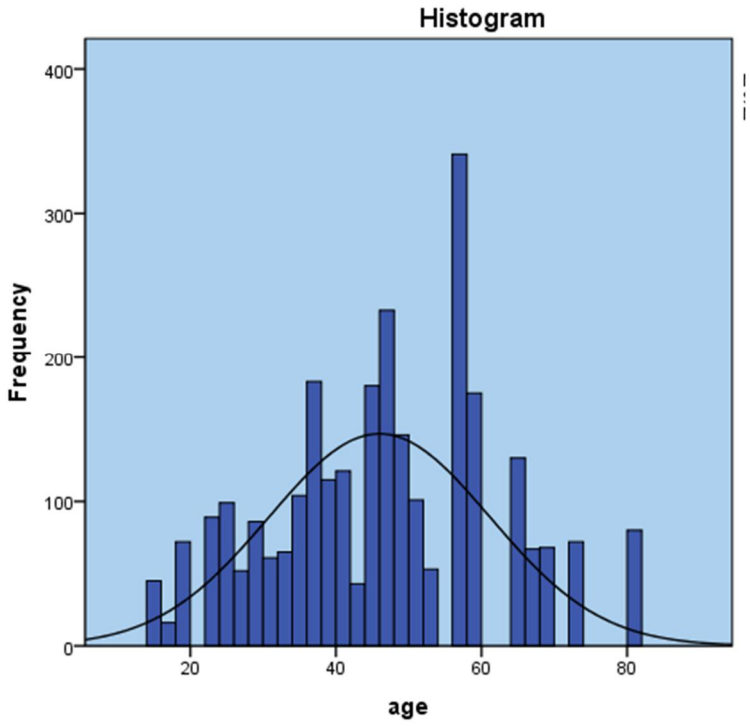
Among the 70 patients, 40(58%) were males and 30(42%) were females.

TABLE AGE DISTRIBUTION

MEAN	45.98
MEDIAN	46
RANGE	65
MINIMUM	15
MAXIMUM	80

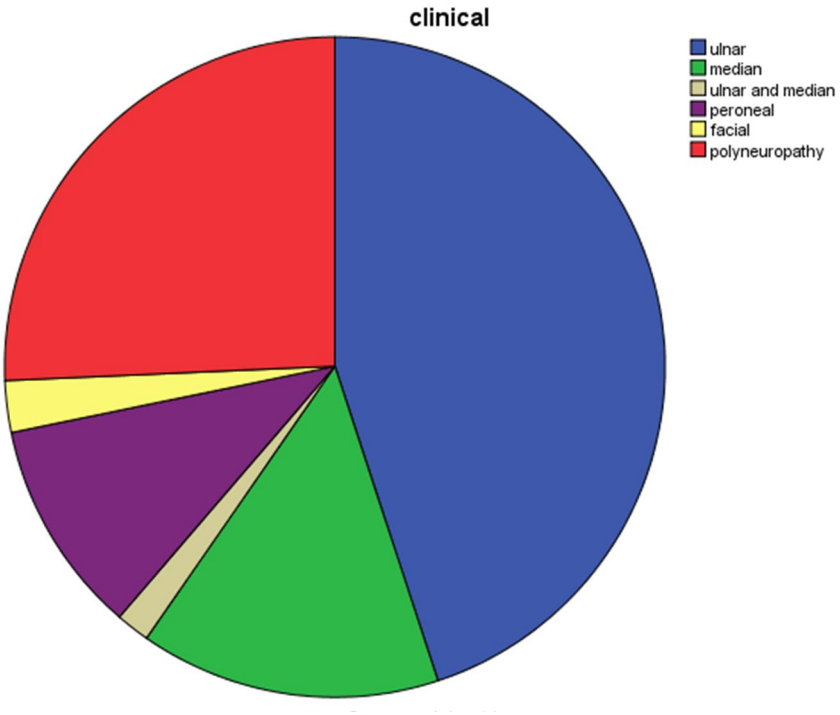
The minimum and maximum age in this study is 15 and 80 yrs and the mean age is 46 yrs. The range of age is 65 yrs.

CHART 2: AGE FREQUENCY HISTOGRAM



The age frequency histogram depicts the average age group in this study is 45 to 53 yrs.

CHART 3 : CLINICAL PRESENTATION

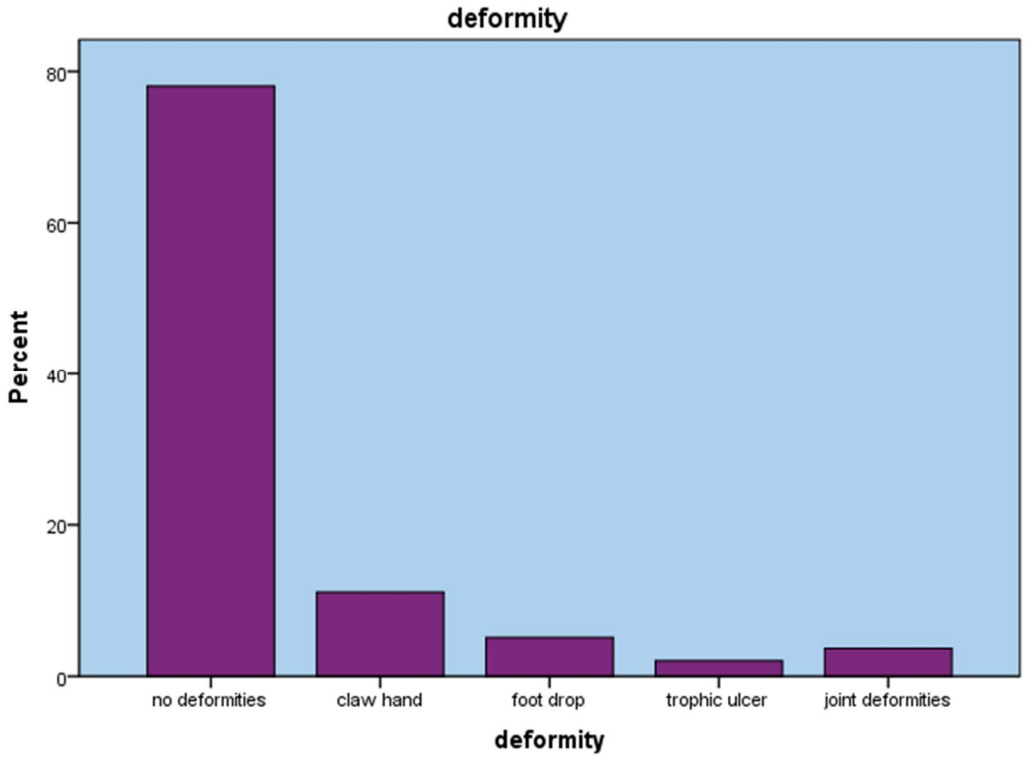


CLINICAL PRESENTATION

ULNAR	44.7%
MEDIAN	14.7%
ULNAR AND MEDIAN	1.7%
PERONEAL	10.5%
FACIAL	2.5%
POLYNEUROPATHY	25.5%

Ulnar nerve is the most commonly involved nerve (44.7%) followed by polyneuropathy like pattern 25.5%

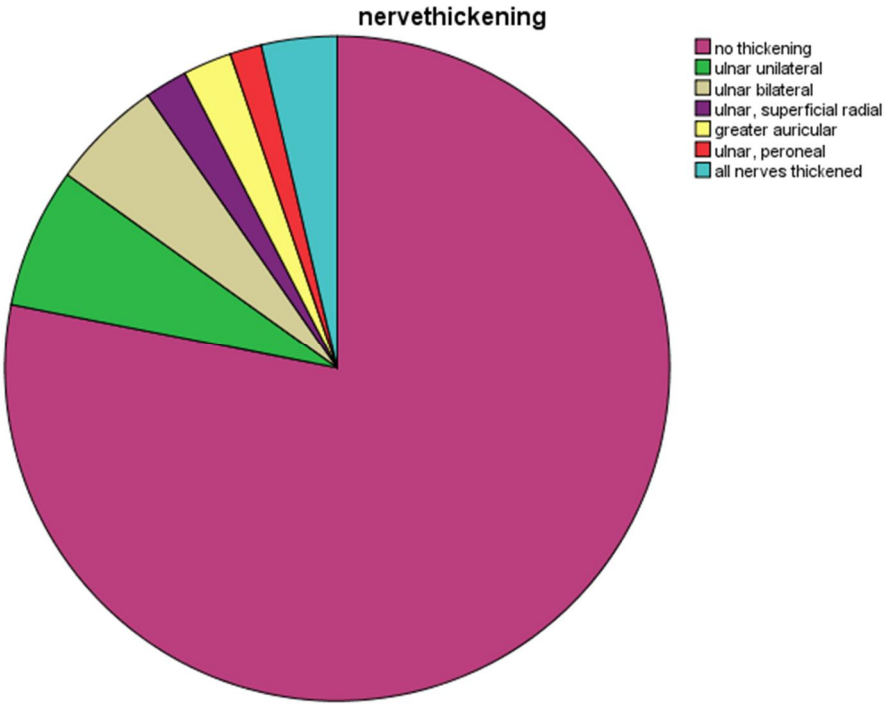
CHART 4: DEFORMITIES (OVERALL)



NO DEFORMITIES	78%
CLAW HAND	11.1%
FOOT DROP	5.1%
TROPHIC ULCER	2.0%
JOINT DEFORMITIES	3.7%

Most of the patients didn't have any deformities at the time of presentation(78%). Claw hand is the most common deformity observed (11.1%)

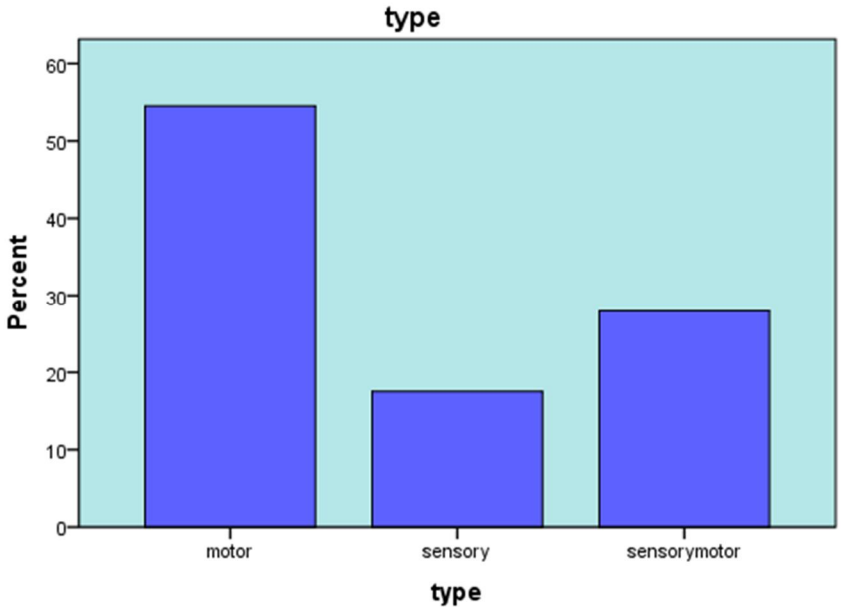
CHART 5: NERVE THICKENING



NO THICKENING	78.1%
ULNAR UNILATERAL	6.8%
ULNAR BILATERAL	5.4%
ULNAR AND SUPL. RADIAL	2.1%
GREATER AURICULAR	2.4%
ULNAR AND PERONEAL	1.5%
ALL NERVES	3.7%

78.1% of the patients didn't have nerve thickening. Unilateral ulnar nerve thickening is the most common nerve thickening observed.

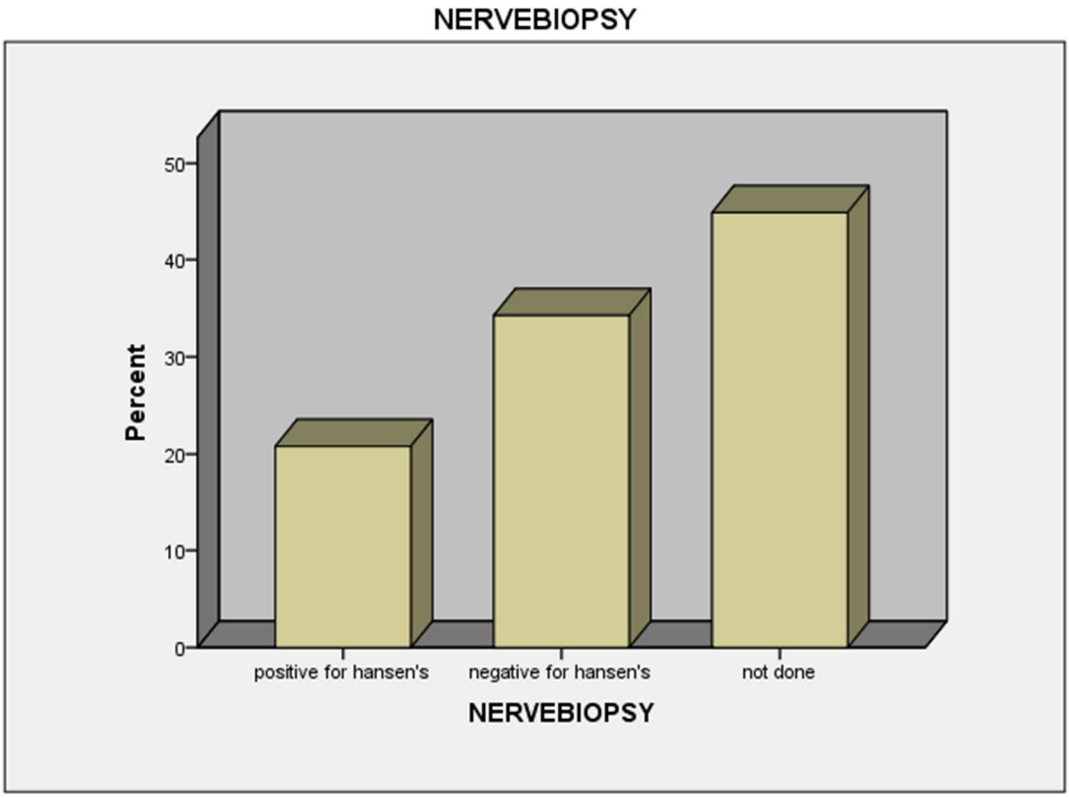
CHART 6: CATEGORY OF NERVES INVOLVED



MOTOR	54.5%
SENSORY	17.5%
SENSORY MOTOR	28%

Most of the patients presented with motor symptoms such as weakness and wasting (54.5%) followed by isolated sensory symptoms and mixed motor and sensory symptoms.

CHART 7: NERVE BIOPSY

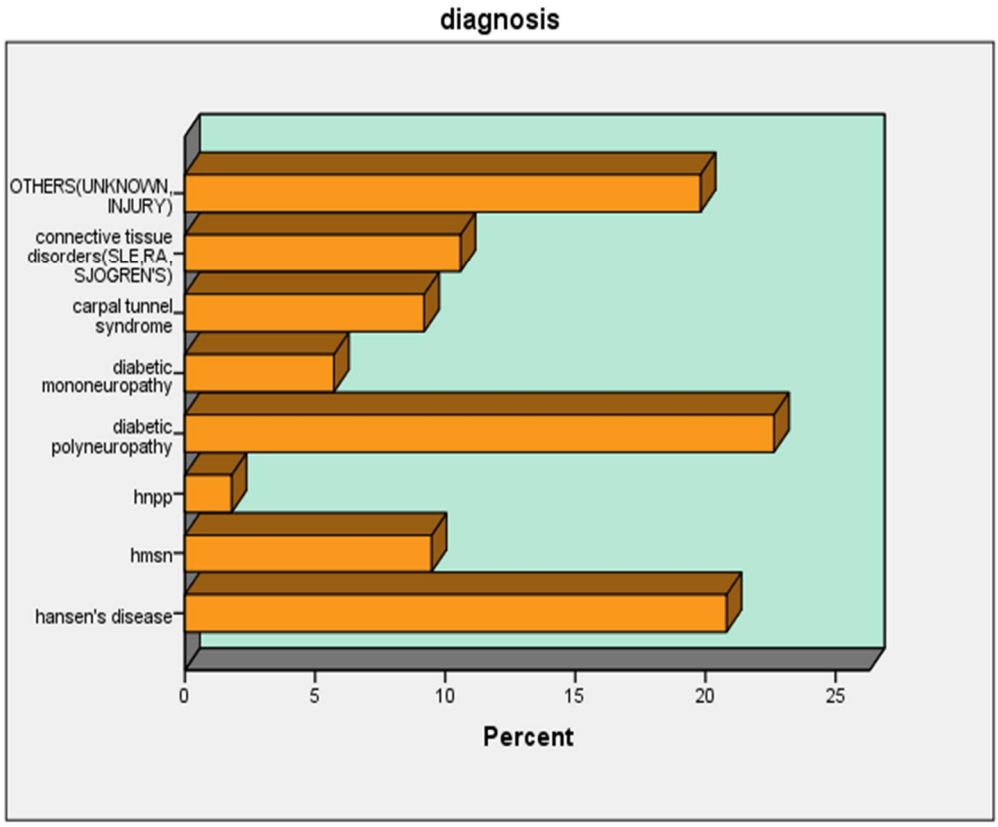


POSITIVE FOR HANSEN'S	20.8%
NEGATIVE FOR HANSEN'S	34.3%
NOT DONE	44.9%

Among the 70 patients, nerve biopsy was not done for 44.9% of the patients.

Biopsy proved hansen's positive in 20.8% .

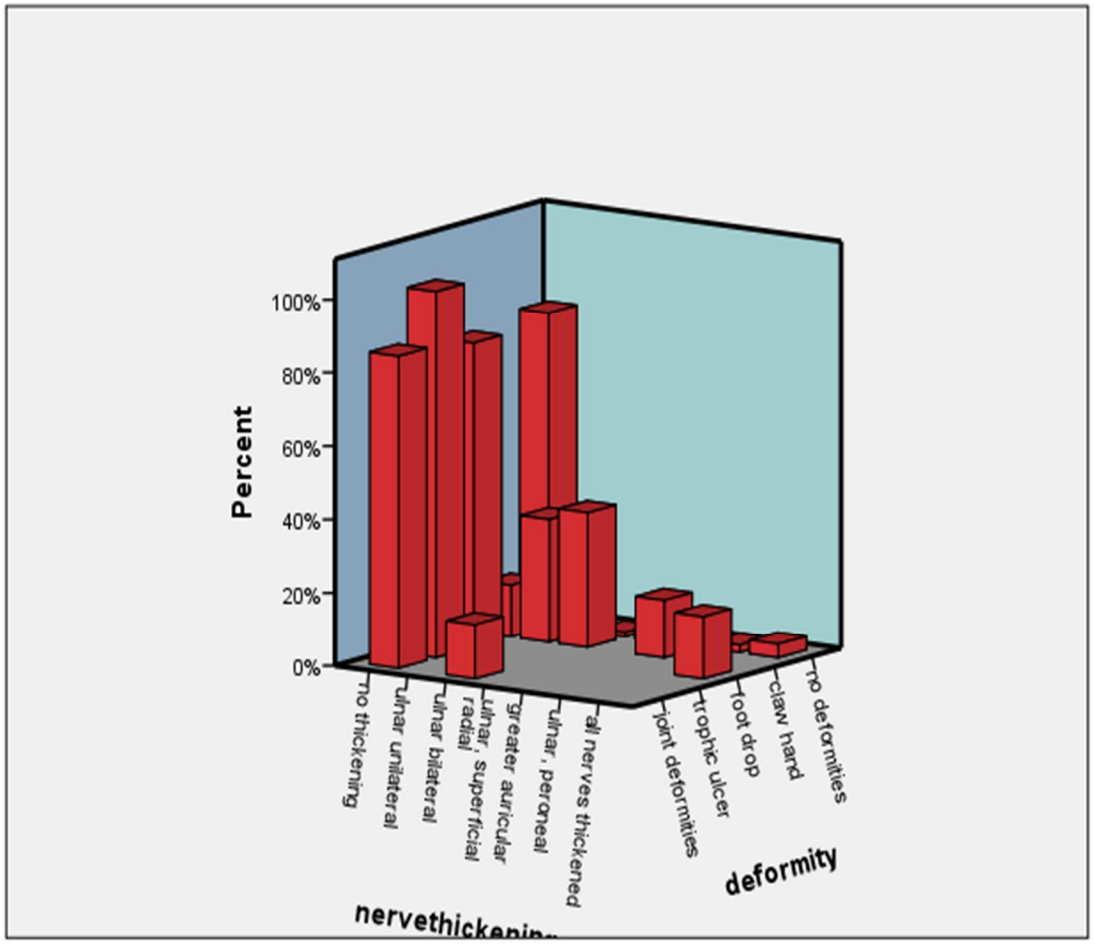
CHART 8 : DIAGNOSIS



HANSEN'S DISEASE	20.8%
DIABETIC POLYNEUROPATHY	22.6%
DIABETIC MONONEUROPATHY	5.7%
CONNECTIVE TISSUE DISORDERS	10.6%
HMSN	9.5%
HNPP	1.8%
CARPAL TUNNEL SYNDROME	9.2
OTHERS	19.8%

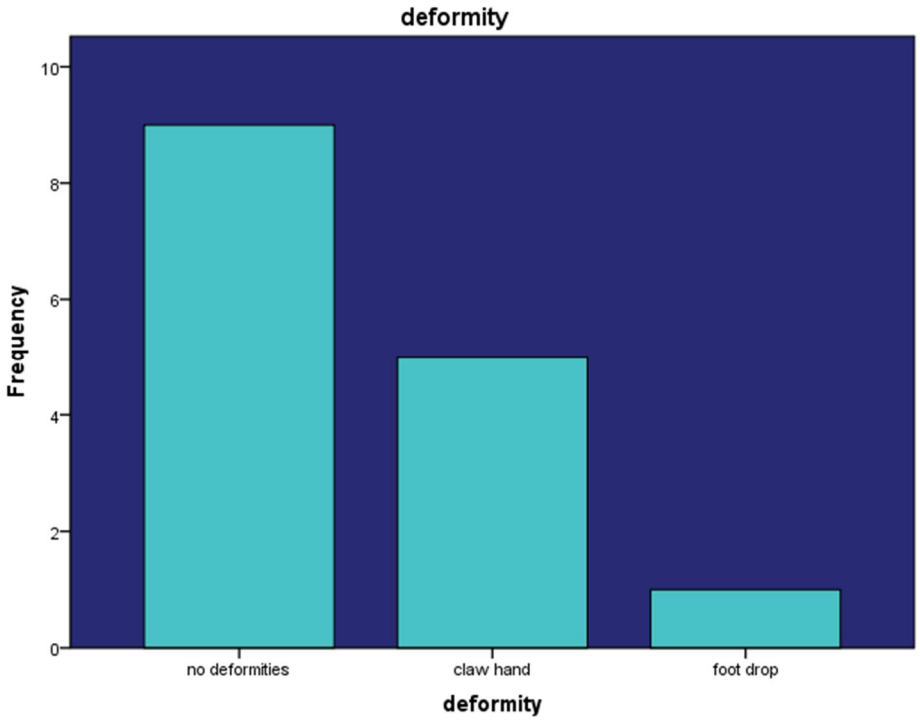
The most common disease mimicking hansen’s is diabetic polyneuropathy in previously undiagnosed diabetics, 22.6%. others(19.8%) include mononeuropathy following injury and in whom biopsy was negative and was advised follow up.

CHART 9: ULNAR MOTOR CONDUCTION VELOCITY IN PATIENTS WITH DEFORMITIES



Ulnar nerve motor conduction velocities are abnormal in 100% of patients with trophic ulcer and ulnar nerve thickening

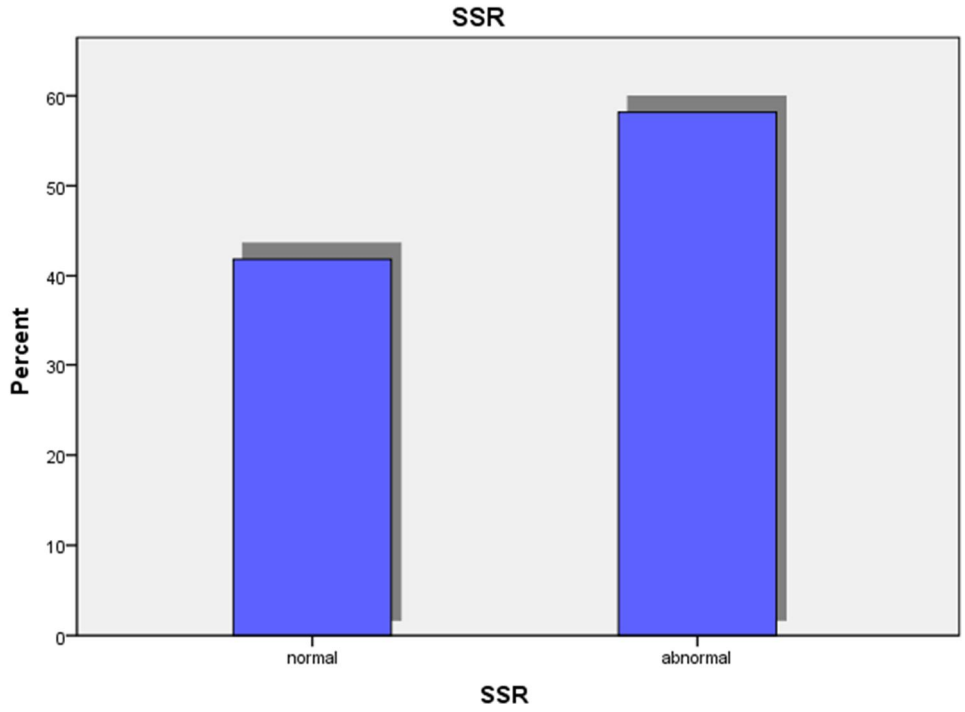
CHART 9: DEFORMITIES IN HANSEN'S DISEASE:



NO DEFORMITIES	60%
CLAW HAND	33.3%
FOOT DROP	6.7%

60% of the patients didn't have any deformities at the time of presentation who later tested positive for hansen's by nerve biopsy

CHART 10: ABNORMAL SYMPATHETIC SKIN RESPONSE:



SYMPATHETIC SKIN RESPONSE

NORMAL	41.8%
ABNORMAL	58.2%

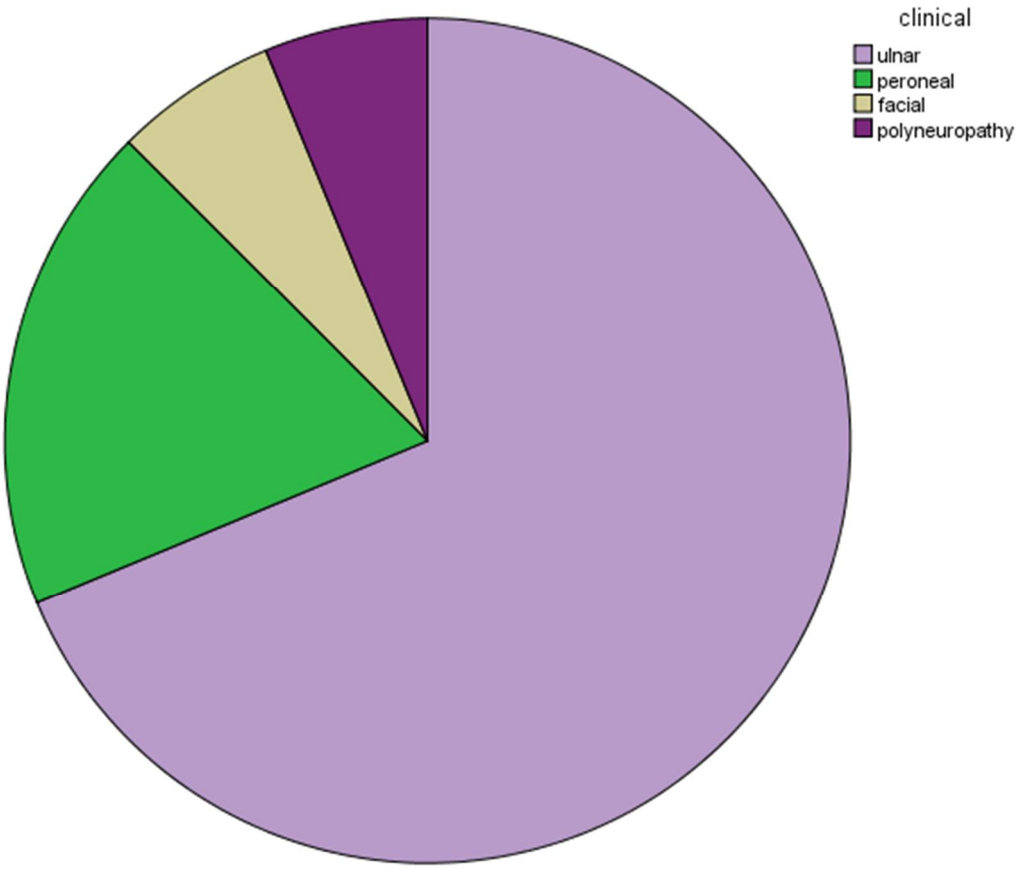
Of the total number of 70 patients, 58.2%, nearly more than half, had abnormal sympathetic skin response.

TABLE 11. ABNORMALITIES IN ULNAR AND MEDIAN NERVES IN HANSEN'S AND OTHER DISEASES

	ULNAR NERVE				**MEDIAN NERVE**				**SSR**
	AMP	LAT	CV	SNAP AMP	AMP	LAT	CV	SNAP AMP	
NORMAL(%)	31.5	56	48.9	34.3	50.7	65.2	64.8	50.1	41.8
ABNORMAL(%)	68.5	44	51.1	63.7	49.3	34.8	35.2	49.9	58.2
NORMAL IN HANSEN'S (%)	43.8	52	56	31.3	87.5	93.8	98.0	93	31.3
ABNORMAL IN HANSEN'S (%)	56.2	48	44	68.8	12.5	6.2	2.0	7	68.8

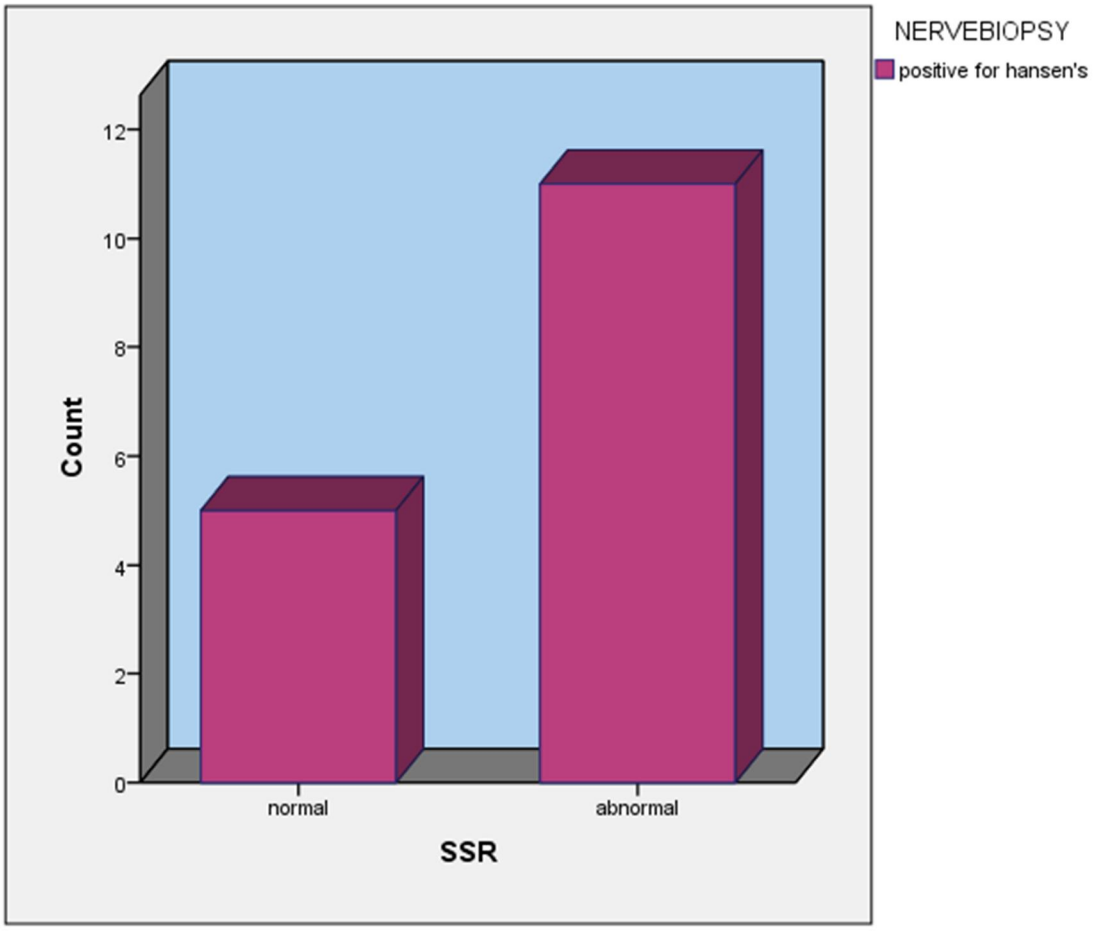
Ulnar nerve showed significant abnormalities in biopsy proven Hansen's disease. 70% abnormalities are seen in SNAPs and 56.2% in motor amplitudes.

CHART 12: CLINICAL PRESENTATION IN HANSEN'S DISEASE



ULNAR	68.8%
PERONEAL	18.8%
FACIAL	6.3%
POLYNEUROPATHY	6.1%

CHART 13: SYMPATHETIC SKIN RESPONSE IN HANSEN'S DISEASE



SSR	NO OF PATIENTS WITH BIOPSY POSITIVE
NORMAL	5 (45%)
ABNORMAL	11 (55%)

CHART 14: SURAL NERVE SNAPS IN HANSEN'S DISEASE

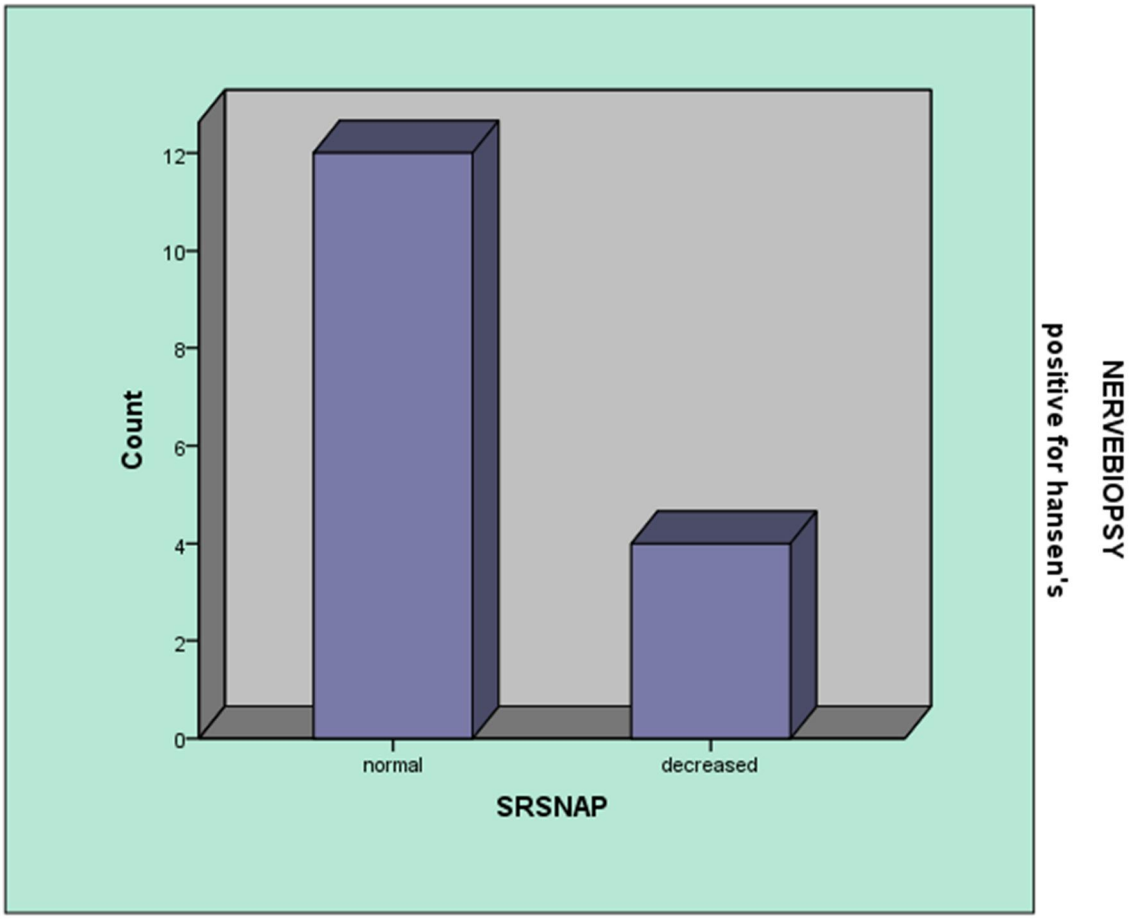


CHART 15: SPLIT SKIN SMEAR AND SYMPATHETIC SKIN RESPONSE CORRELATION

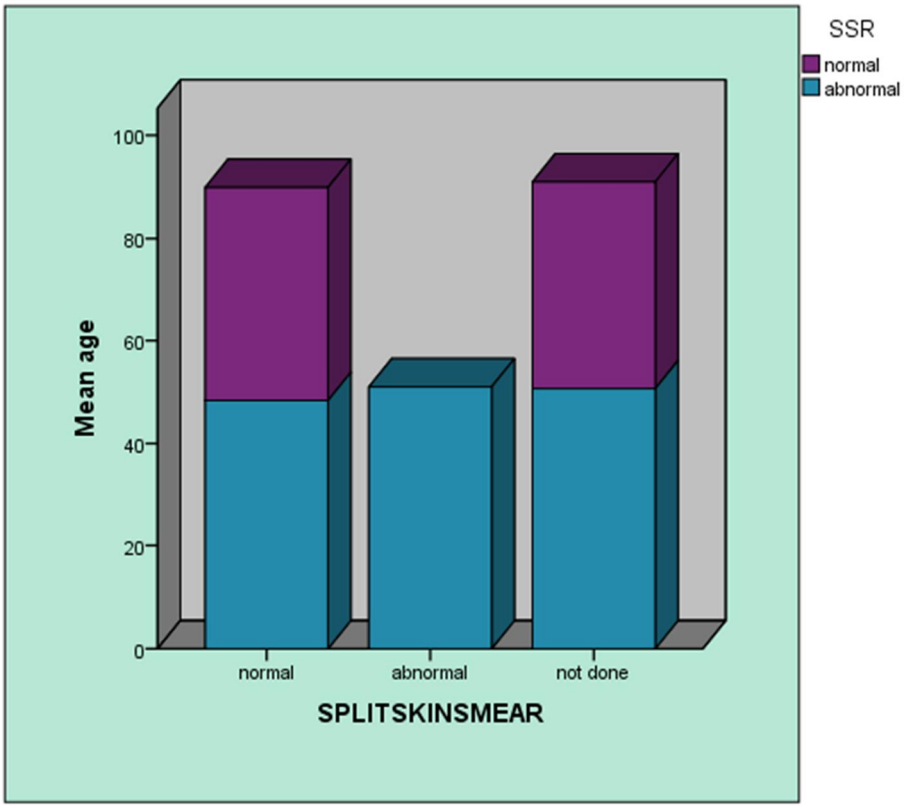
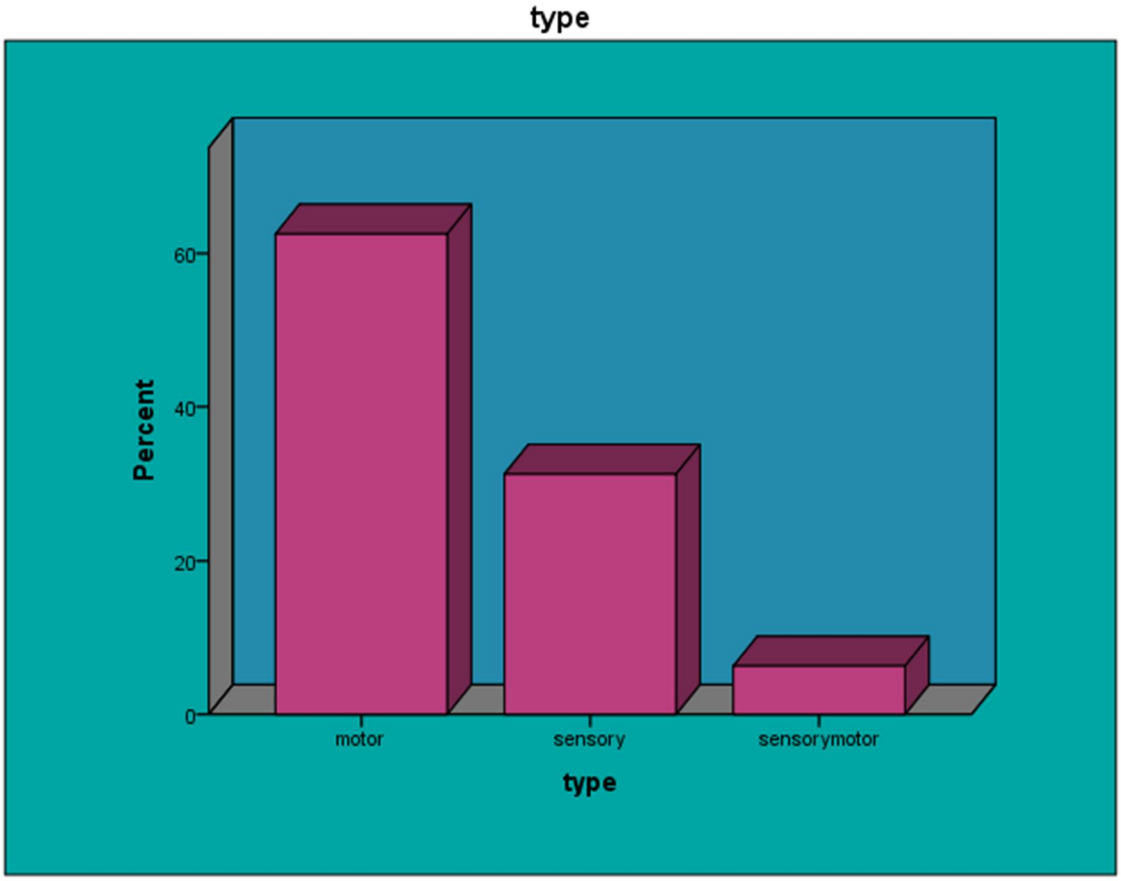


CHART 16: CLINICAL TYPES IN HANSEN'S DISEASE



MOTOR	62.5%(10)
SENSORY	31.3%(5)
SENSORYMOTOR	6.2%(1)

DISCUSSION

Of the 70 patients who were clinically suspected to have leprosy, 16 were later proven by nerve biopsy to have hansen’s disease.

Kumar et al[78] has reported a male: female sex ratio of 2.6:1 with male predominance. In our study, 81%(13) were males and 19%(3) were females.

Though multiple symptoms have been observed at the time of presentation, sensory deficit was most common, followed by motor symptoms and Trophic changes, according to Kumar et al. However in this study, motor symptoms were the predominant presenting symptom followed by sensory and trophic ulcers. Probable reason may be that motor symptoms are noted earlier by the patients and they are disabling which makes the patients to sought medical attention in case of pure neuritic hansen’s disease.

Almost all the patients diagnosed with hansen’s disease showed abnormal nerve conduction studies. Patients with suspected clinical features of hansen’s were later subjected to nerve biopsy. Nerve conduction studies were also abnormal in many other diseases such as rheumatoid arthritis, diabetes and carpal tunnel syndromes. In case of diabetes with mono neuropathy, NCS was abnormal in non-involved nerves also.

In a study of “Clinical, electrophysiological, and immunopathological study of peripheral nerves in Hansen's disease” by Ramadan et al claw hand was the most common disability among their patients which indicates that ulnar

nerve is the most affected nerve in leprosy patients. Similarly in this study also claw hand was the most common deformity and ulnar nerve is most commonly involved. Antia et al has shown that the motor nerve conduction studies of ulnar nerves are more frequently abnormal than that of median nerve. This study also showed the same pattern with ulnar nerve distal latencies, amplitudes and F waves being more abnormal than the other nerves examined.

Ramadan et al in his study has found that ulnar nerve sensory nerve action potentials(SNAP) were more affected than that of the compound muscle action potentials (CMAPs). In this study both sensory and motor potentials were equally affected in patients with clinical involvement of ulnar nerve. The reason for this could be that most of the patients in his study by Ramadan et al had sensory disturbances in the ulnar nerve distribution whereas in this study the most common presenting symptom was motor and hence both sensory and motor component of ulnar nerve were equally affected.

Mshana et al. mentioned that some nerves that appeared to be clinically normal have been shown to have pathological changes. In this study, patients who presented with symptoms of mononeuritis multiplex didn’t show any evidence for involvement of other nerves electrophysiologically. However, those patients who didn’t have sural nerve involvement clinically and electrophysiologically, later underwent sural nerve biopsies which

revealed findings conforming with hansen's disease. These indicate that the earlier pathologic changes that can occur in non-involved nerves in hansen's are not detected in routine nerve conduction studies.

Leprosy is a disease predominantly early involvement of small fibres. These routine nerve conduction studies may not detect the abnormalities of the small fibres. However, sympathetic skin response is a measure of the small fibre intactness. Sympathetic skin response can be abnormal earlier in many other neuropathies caused by systemic illnesses namely diabetes, alcohol etc. In this study sympathetic skin response was abnormal in all of the patients with biopsy positive for Hansens disease. But sympathetic skin response was also abnormal in some other diseases which comes under the differential diagnosis for Hansen's disease such as diabetes, connective tissue disorders, HIV neuropathy etc. Hence sympathetic skin response, even if abnormal, cannot detect or suspect hansen's disease with high specificity.

Split skin smear studies didn't show any abnormality in any of the cases. This could be because of the pauci bacillary nature of the disease and low sensitivity index of the test.

With respect to the histo pathological results most of the patients diagnosed as Hansen's disease showed chronic granulomatous infiltrate with foamy macrophages with minimal or no fibrosis. This was in contrast to the study by Van Brakel and Khawas, in which fibrosis was the predominant finding in nerve biopsy with little or no inflammation. This could be due to the

duration of the disease. In this study most of the patient presented within 1 year of the onset of illness. In his study most of the patients had disease for more than two to four years thereby chronic inflammation which might have progressed to fibrosis.

Though the incidence of leprosy is decreasing, this study has found that incidence of pure neuritic hansen's is still may be the same with detection of 16 new cases in 2 years. However, this institute being a tertiary care centre catering the needs of most of south India, the incidence may look abnormally high. It may need a broad cross sectional study including the primary and secondary care centres to assess the true incidence of pure neuritic hansen's. The most common cause for this is the delay in detection and treatment. The delay is primarily because of the absent skin manifestations. Pure neuritic hansen's needs a high index of suspicion for an earlier diagnosis.

CONCLUSION

- Nerve conduction studies including sympathetic skin response are abnormal in all patients with pure neuritic hansen's disease.
- Abnormalities in motor or sensory nerve conduction studies or sympathetic skin responses alone cannot predict the possibility of Hansen's disease.
- Nerve biopsy clinches the diagnosis.
- There is a high degree of electrophysiological and nerve biopsy correlation for Pure Neuritic Hansen's disease, though it is not specific.

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DIAGNOSTIC SIGNIFICANCE OF NERVE CONDUCTION STUDIES IN EARLY DETECTION OF PURE NEURITIC HANSEN'S DISEASE

Name of the Participant :

Name of the Institution :

Name and address of the sponsor/

agency (ies) (if any) :

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.

5. I have been informed the investigator of all the treatments I am taking or have taken in the past _____ months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.
8. I have not participated in any research study within the past _____month(s).
9. I have not donated blood within the past _____ months—Add if the study involves extensive blood sampling.
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
13. I have understand that my identity will be kept confidential if my data are publicly presented

14.I have had my questions answered to my satisfaction.

15.I have decided to be in the research study. I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name **:** Signature **:** Date **:**

Name and Signature of impartial witness (required for illiterate patients):

Name **:** Signature **:** Date **:**

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name **:** Signature **:** Date **:**

PROFORMA

A STUDY OF DIAGNOSTIC VALUE OF NERVE CONDUCTION STUDIES IN PURE NEURITIC HANSEN'S NEUROPATHY

Name	:	MIN No. :
Age	:	IP No :
Sex	:	Duration of DM :
Address	:	
Contact Number	:	
Occupation	:	

HISTORY

1. Motor Symptoms : Thinning, flailness, weakness (D,P), gait disturbance

2. Sensory Symptoms : Burning / tingling / cramps/ pins and needles, pricking / aching / numbness / Loss of touch, pain and temperature sensations.

3. SKIN CHANGES: Hypo or hyperpigmentation

4. Previous H/O hansen's treatment

   H/o PTB, ATT

   H/o STD

   H/o Hypothyroidism, polyarthritis

Personal History

Contact with Hansen's patient

Smoking

Drug Abuse

Diet

Family History

Hypertension

Diabetes Mellitus

Chronic Kidney Disease

Neuropathy

Connective tissue disorders

Treatment History

EXAMINATION

Signs of Hyperlipidemia

BP

HR

Pallor

Pedal Edema

Peripheral pulses

RS

CVS

P/A

CNS :

Motor system -

Bulk

Tone

Power

DTR

Gait

Sensory system -

Pin Prick

Touch

Temperature

Timed Vibration

Position sense

Romberg's Test

Autonomic nervous system -

Sweating abnormalities

Trophic changes

HRV

SSR

Investigations

CBC

Urine RE

FBS

PPBS

HbA1c

Serum Lipids

Urea, Creatinine

LFT

Connective tissue disorders screening

NERVE CONDUCTION STUDY

Motor	:	Distal Latency
		Amplitude
		Conduction Velocity
Sensory	:	Latency
		Amplitude
		Conduction Velocity

F Wave Studies:

F mean

H - Reflex

INSTITUTE OF NEUROLOGY
MADRAS MEDICAL COLLEGE, CHENNAI - 3
NERVE CONDUCTION STUDY

Name : Age / Sex : Date:

MIN No. : Unit :

MOTOR NERVE CONDUCTION STUDY

Nerve	Distal Latency (ms)	Amplitude (mv)	CV (m/s)	F-Wave Latency (ms)
R. Median				
L. Median				
R. Ulnar				
L. Ulnar				
R. Tibial				
L. Tibial				
R. Peroneal				
L. Peroneal				

SENSORY NERVE CONDUCTION STUDY

Nerve	Latency (ms)	Amplitude (µv)	CV (m/s)
R.Median			
L.Median			
R. Ulnar			
L. Ulnar			
R. Sural			
L. Sural			

Sympathetic skin response:

Slit skin smear:

Nerve biopsy:

age	sex	nerve thickening	type	clinical	side	deformity	duration	MDL	UDL	TDL	PDL	MDA	UDA	TDA	PDA	MCV	UCV	TCV	PCV	MF	UF	TF
31	2	2	1	1	1	2	6	1	2	1	1	1	2	1	1	1	2	1	1	1	2	1
25	1	3	2	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
46	1	1	2	3	2	3	8	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
18	1	6	1	4	2	1	5	1	1	1	2	1	1	1	2	1	1	1	1	1	1	1
51	1	1	1	2	3	1	4	1	2	1	1	1	2	1	1	1	2	1	1	1	2	1
18	1	5				1	7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
26	1	1	2	1	2	1	10	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
56	2	1	3	2	2	4	5	2	1	1	1	2	1	1	1	1	1	1	1	2	1	1
15	1	1	1	4	3	1	24	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
45	2	1	1	2	3	1	6	2	1	1	1	2	1	1	1	2	1	1	1	2	1	1
37	1	1	1	1	1	1	7	1	2	1	1	1	2	1	1	1	2	1	1	1	2	1
28	2	1	1	2	3	1	8	2	1	1	1	2	1	1	1	2	1	1	1	2	1	1
34	1	1	2	1	2	1	1	1	2	1	1	1	2	1	1	1	2	1	1	1	2	1
57	2	1	3	1	1	1	9	1	1	1	1	2	2	2	2	2	1	1	1	1	1	1
30	2	1	1	2	3	1	5	2	1	1	1	2	1	1	1	2	1	1	1	2	1	1
45	1	2	2	1	2	1	6	1	2	1	1	1	2	1	1	1	2	1	1	1	2	1
65	2	1	3	1	3	1	12	1	1	1	1	2	2	2	2	1	1	1	1	1	1	1
32	1	3	1	1	3	2	12	1	2	1	1	2	2	1	2	1	2	1	1	1	2	1
47	1	1	1	1	3	1	11	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
24	1	7	3	6	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
22	1	7	3	6	3	1	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
57	2	7	3	6	3	1	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
18	2	1	2	1	1	1	7	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1
39	1	1	2	1	2	1	2	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1
45	1	1	1	2	3	1	8	2	2	2	2	2	2	1	2	1	1	1	2	1	1	1
22	1	2	1	1	1	2	2	1	2	1	1	1	2	1	1	1	2	1	1	1	2	1
57	2	1	3	4	3	1	10	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
59	1	1	1	1	1	1	12	1	2	1	1	1	2	2	1	1	2	1	1	1	2	1
29	2	1	1	2	3	1	7	2	1	1	1	2	1	1	1	2	1	1	1	2	1	1
45	1	1	3	6	3	1	12	2	1	1	2	2	1	1	2	1	1	1	1	2	1	1
15	1	3	1	1	3	5	24	1	2	1	1	1	2	1	1	1	2	1	1	1	2	1
38	2	1	1	2	1	1	9	2	1	1	1	2	1	1	1	2	1	1	1	2	1	1
49	1	2	1	1	1	2	8	1	1	1	1	1	2	1	1	1	2	1	1	1	2	1
58	2	1	1	4	1	1	12	1	1	1	2	1	1	1	1	1	1	1	2	1	1	1

PF	MSNAP	USNAP	SURSNAP	SRSNAP	SSR	SSS	BIOPSY	DIAGNOSIS
1	1	2	1	1	2	1	1	1
1	1	2	1	1	2	1	1	1
1	1	1	1	1	1	1	3	8
1	1	1	1	1	1	1	1	1
1	1	2	1	1	2	2	3	8
1	1	1	1	1	1	1	3	8
1	1	2	2	2	1	1	1	1
1	2	1	1	1	1	3	3	8
2	2	2	2	2	2	3	2	2
1	2	1	1	1	1	3	3	6
1	1	1	1	1	1	1	2	8
1	2	1	1	1	1	3	3	6
1	1	2	1	1	2	3	3	8
1	2	2	2	1	2	3	3	4
1	2	1	1	1	1	3	3	6
1	1	2	2	2	1	1	1	1
1	2	2	2	1	2	3	3	4
2	1	2	2	1	2	1	1	1
2	2	2	2	2	2	3	3	4
2	2	2	2	2	2	3	3	2
2	2	2	2	2	2	3	3	2
2	2	2	2	2	2	3	3	2
1	1	2	2	1	2	1	1	1
1	1	2	1	1	2	1	1	1
1	2	2	2	1	2	3	3	4
1	1	2	1	1	2	1	1	1
2	2	2	2	2	2	3	3	4
1	1	1	1	1	1	1	2	4
1	2	1	1	1	2	3	3	6
2	2	1	1	2	2	1	1	1
1	1	2	1	1	2	1	2	7
1	2	1	1	1	1	3	3	6
1	1	2	1	1	2	1	1	1
2	1	1	1	2	1	3	3	8

25	1	6	1	6	3	1	36	2	2	1	2	2	2	1	2	1	1	1	2	2	2	1
36	2	1	1	1	1	1	8	1	2	1	1	1	2	1	1	1	2	1	1	1	1	1
48	1	5	1	5	1	2	7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
50	1	1	1	1	1		3	1	2	1	1	1	2	1	1	1	2	1	1	1	1	1
36	1	1	1	4	1	3	6	1	1	1	2	1	1	1	2	1	1	1	2	1	1	1
26	2	2	1	1	1	1	8	1	2	1	1	1	2	1	1	1	2	1	1	1	2	1
16	1	1	3	6	3	1	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
57	2	1	3	6	3	1	12	1	1	1	1	2	2	2	2	1	1	1	1	1	1	1
72	1	1	1	4	1	1	5	1	1	1	2	1	1	1	2	1	1	1	2	1	1	1
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53	2	1	3	6	3	1	15	1	1	1	1	2	2	2	2	1	1	1	1	1	1	1
58	1	1	3	6	3	1	6	1	1	1	1	1	2	2	2	1	2	2	2	1	2	2
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38	2	1	3	6	3	1	5	1	1	1	1	2	2	2	2	1	1	1	1	1	1	1
35	1	1	1	6	3	3	36	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
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35	2	1	2	4	3	1	8	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
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15	1	1	2	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
57	1	1	1	1	2	1	6	1	1	1	1	1	2	1	1	1	2	1	1	1	2	1

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1		1	1	1	1	1	2	8
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2	1	1	2	2	2	1	1	1
1	1	1	1	1	1	1	2	8
1	2	2	2	2	2	1	2	4
2	2	2	2	2	2	1	2	7
2	1	1	1	1	1	1	2	5
2	2	2	2	2	2	1	3	5
	2	2	2	2	2	1	2	8
1	1	2	1	1	1	1	2	3
	1	2	1	1	1	3	3	8
1	1	2	1	1	1	3	3	7
1	2	2	2	2	2	3	3	4
2	1	2	2	2	1	1	2	4
2	2	2	2	2	2	3	3	4
1	1	2	1	1	1	3	3	8
1	1	2	1	1	1	1	3	8
1	2	1	1	1	1	3	3	6
1	1	1	1	1	1	1	2	8
1	1	1	1	1	1	3	2	7
1	1	2	1	1	2	1	2	5
1	2	2	1	1	2	1	2	7
1	2	2	2	2	2	3	3	7
2	2	2	2	2	2	3	2	2
2	2	2	2	2	2	3	2	2
2	2	2	2	2	2	3	2	2
1	1	1	2	1	1	3	2	7
1	2	1	1	1	1	3	3	6
1	1	2	1	1	2	1	2	8
1	1		1	1	1	1	2	5

MASTER CHART REFERENCE

SEX	1. MALE
	2. FEMALE
NERVE THICKENING	1. NO THICKENING
	2. ULNAR UNILATERAL
	3. ULNAR BILATERAL
	4. ULNAR AND SUPL. RADIAL
	5. GREATER AURICULAR
	6. PERONEAL
	7. ALL NERVES
TYPE	1. MOTOR
	2. SENSORY
	3. SENSORYMOTOR
CLINICAL	1. ULNAR
	2. MEDIAN
	3. ULNAR AND MEDIAN
	4. PERONEAL
	5. FACIAL
	6. POLYNEUROPATHY
SIDE	1. LEFT
	2. RIGHT
	3. BILATERAL
DEFORMITY	1. NO DEFORMITY
	2. CLAW HAND
	3. FOOT DROP
	4. TROPHIC ULCER
	5. JOINT DEFORMITIES

MEDIAN DISTAL LATENCY (MDL)
ULNAR DISTAL LATENCY (UDL)
TIBIAL DISTAL LATENCY (TDL)
PERONEAL DISTAL LAT (PDL)
MEDIAN DISTAL AMPLITUDE (MDA)
ULNAR DISTAL AMPLITUDE (UDA)
TIBIAL DISTAL AMPLITUDE (TDA)
PERONEAL DISTAL AMPLITUDE (PDA)
MCV, UCV, TCV, PCV – MEDIAN, ULNAR, TIBIAL AND PERONEAL CONDUCTION VELOCITIES
MF, UF,TF.PF – MEDIAN, ULNAR, TIBIAL AND PERONEAL F WAVE LATENCIES
MSSNAP, USSNAP, SURSNAP, SRSNAP – MEDIAN, ULNAR, SURAL AND SUPERFICIAL RADIAL SENSORY NERVE ACTION POTENTIALS

1. NORMAL
2. ABNORMAL

SSS – SPLIT SKIN SMEAR

1. NORMAL
2. ABNORMAL

SSR – SYMPATHETIC SKIN RESPONSE

1. NORMAL
2.ABNORMAL

NERVE BIOPSY

1. POSITIVE FOR HANSEN'S
2.NEGATIVE FOR HANSEN'S
3.NOT DONE

DIAGNOSIS

1. HANSEN'S DISEASE
2. HMSN
3. HNPP
4. DIABETIC POLYNEUROPATHY
5. DIABETIC MONONEUROPATHY
6. CARPAL TUNNEL SYNDROME
7. CONNECTIVE TISSUE DISORDERS
8. OTHERS(INJURY, FOLLOW UP)