A STUDY OF PERIPHERAL NEUROPATHY IN CHRONIC KIDNEY DISEASE STAGE -5 AND IT'S OUTCOME AFTER KIDNEY TRANSPLANTATION

Dissertation submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the requirements
for the award of the degree of

DM (NEPHROLOGY) – BRANCH – III

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY
CHENNAI

AUGUST 2012

DECLARATION

I solemnly declare that this dissertation titled "A STUDY OF PERIPHERAL NEUROPATHY IN CHRONIC KIDNEY DISEASE STAGE-5 AND IT'S OUTCOME AFTER KIDNEY TRANSPLANTATION " is done by me in the Department of Nephrology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of Prof.N.Gopalakrishnan, MD., DM., FRCP., Professor & Head of the Department, Department of Nephrology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of DM.Nephrology.

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CERTIFICATE

This is to certify that the Dissertation entitled, **"**A STUDY OF PERIPHERAL NEUROPATHY IN CHRONIC KIDNEY DISEASE STAGE-5 AND IT'S OUTCOME AFTER KIDNEY TRANSPLANTATION**"** is the bonafide record work done by *Dr.S.Balamurugan,* under our guidance and supervision in the Department of Nephrology, Government General Hospital, Madras Medical College, Chennai, submitted as partial fulfillment for the requirements of D.M. Degree examination Branch III NEPHROLOGY, AUGUST 2012, under The Dr.M.G.R. Medical University, Chennai.

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ACKNOWLEDGEMENT

I sincerely thank the Dean, **Dr.V.KANAGASABAI M.D.,** for having permitted me to carry out this dissertation work at Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai.

I have great pleasure in expressing my gratitude and respect to ***PROF*. Dr.M.JAYAKUMAR, M.D., D.M.,** former Professor and Head, Department of Nephrology, Madras Medical College, Chennai, who allowed me to continue my dissertation, for his valuable suggestions, kind guidance, constant supervision and moral support without which this study would not have been possible.

I have great pleasure in expressing my gratitude and respect to ***PROF*. Dr.N.GOPALAKRISHNAN, M.D., D.M., FRCP.,** Professor and Head, Department of Nephrology, Madras Medical College, Chennai, who allowed me to continue my dissertation, for his valuable suggestions, kind guidance, constant supervision and moral support without which this study would not have been possible.

I also have immense pleasure in expressing my gratitude and respect to **PROF. Dr.R.LAKSHMI NARASIMHAN.,M.D,D.N.B., D.M,D.N.B.,** Professor, Department of Neurology, Madras Medical College, Chennai,

who allowed me to carry-out my dissertation with active help of his department, for his valuable suggestions, kind guidance, the support he had given to me.

I also thank **PROF.R.M.BHOOPATHI** ,**M.D,D.M,** Professor and Head, Department of Neurology, Madras Medical College, Chennai for giving me permission to carry out the nerve conduction studies in his department.

I am thankful to **DR.T.BALASUBRAMANIAN, M.D., D.M.,** Associate Professor, Department of Nephrology, Madras Medical College, Chennai, for his valuable suggestions and guidance in doing the study.

I am thankful to **DR.N.MALATHY, M.D.,D.M., DR.M.HARIS M.D., D.M.,DR.N.SRINIVASA PRASAD M.D., D.M.,**Assistant Professors, Department of Nephrology, Madras Medical College, Chennai, for their valuable suggestions and guidance.

I wish to thank **D.M Neurology postgraduates Dr.Sasi kumar, Dr.Jeyaraman, Dr.Valavan, Dr.Kannan & Dr.Venkatesan** for their immense help.

Last but not the least, my sincere thanks to the patients who co-operated for this study, without whom the study could not have been completed and to all my colleagues who shared their knowledge.

INDEX

INTRODUCTION

Neurological complications occur in approximately 60% of patients suffering from severe Chronic Kidney Disease (CKD), affecting the nervous system at all levels, central as well as peripheral, yielding weakness, prolonged disability and alteration of mental state.

Amongst the many manifestations of Uremia, the most common is uremic neuropathy and its prevalence increases as Glomerular filtration rate (GFR) decreases and also depends on the duration of the CKD and dialysis therapy[1,2]. Its prevalence is about 60- 100% in those on dialysis [6,7].Even though many patients may not have overt symptoms or signs, electro-physiological abnormalities in Nerve conduction studies may be detected in many patients indicating the presence of subclinical neuropathy. Uremic neuropathy characteristically progresses over the course of months, but can occasionally take a faster course, triggering a marked disability. It is believed that Uremic neuropathy is caused by the accumulation of medium-sized molecules that have not been adequately filtered.

Even though regular maintenance Hemodialysis (HD) slows the progression of neuropathy, the abnormalities rarely improve or sometimes they may worsen.

However renal transplantation is associated with rapid improvement in these neuro-physiological abnormalities within days and clinical improvement over months[11].

Aim of the study

This study aims to evaluate the prevalence of peripheral neuropathy(both overt and subclinical) in CKD stage -5 patients on HD (particularly those on transplant programme) through Nerve conduction studies and to assess the outcome of neuropathy after renal transplantation by follow-up nerve conduction studies at the end of first and third months.

REVIEW OF LITERATURE

History

The existence of uremic neuropathy was first suspected by Charcot (1880) and Osler (1892). Since the introduction of hemodialysis(HD) and kidney transplants in the early 1960s, uremic neuropathy has been studied in detail. Asbury et al[1,2] described the clinical and pathological characteristics in detail.

The current concept of uremic neuropathy was established in 1971 by Dyck[3] and colleagues in an extensive study of nerve conduction *in vivo* and *in vitro*, as well as in studies with light and electronic microscopy. Using quantitative histology, they demonstrated axonal retraction: neuronal dysfunction resulted in the decrease of axonal diameter, reorganization of myelin and ultimately, complete degeneration of the axon.

Peripheral neuropathy develops in 60%- 90% of patients with end-stage renal failure who require chronic dialysis [6, 7].

The development of neuropathy is determined by the degree of renal impairment, with clinically significant neuropathy generally only occurring after the glomerular filtration rate drops to less than 12 ml⁄minute.[8]

Severe uremic neuropathy has become less common as a result of earlier treatment with dialysis and renal transplantation. Uremic neuropathy is

more common in men than in women. The clinical features are those of a slowly progressive, predominantly sensory polyneuropathy.

The major feature of length-dependent neuropathies, such as uremic and diabetic neuropathies, is the greater involvement of those regions furthest from the spinal cord, resulting in greater distal disease than proximal disease and more severe involvement of lower limb nerves than upper limb nerves. Severe pains are unusual, but cramps, unpleasant dysesthesias, and restless legs are common symptoms. Muscle cramps of the distal limbs occur commonly in uremic patients and many of these patients lack evidence of neuropathy or tetany. Since cramps occur commonly in uremia. They probably represent either shifts of fluids into muscle or the effects of uremic toxins upon muscle or the neuromuscular junction[12].

Clinical examination in the initial stages reveals changes that are confined to the lower limbs, with reduction in ankle deep tendon reflexes and distal (‘‘stocking’’) sensory loss. With more severe disease, motor involvement develops, characterized by weakness and muscle atrophy, again most prominent distally. With further progression, proximal regions of the lower limbs are affected and upper limb involvement develops.[10]

Although the prevalence of severe neuropathy may appear to have lessened, a significant cohort of ESRD patients still report symptoms which are

functionally disabling, and even patients who meet accepted guidelines for dialysis adequacy may complain of neuropathic symptoms .

Acute Uremic Neuropathy[17]

In addition, there is a more rapid (accelerated) process that has not been widely appreciated as a cause of acute and subacute weakness. Most patients were diabetics with stable ESRD who had been treated by peritoneal dialysis for their long-standing kidney disease .In contrast to the better characterized and less severe chronic uremic neuropathy, generalized weakness and distal paresthesias progress over 1 or more weeks until a bedbound state is reached. The illness simulates subacute GBS. More aggressive dialysis or a change to hemodialysis has little immediate effect, although kidney transplantation is curative. Electrophysiologic studies show demyelinating features (slowing of conduction velocity), but usually not a conduction block. There is raised CSF protein concentration. A few reported cases have responded to plasma exchange or gamma globulin. The cause of the acute form is unknown.

Sub-acute progressive motor neuropathy in diabetic patients with CKD

There is also a subacute progressive motor neuropathy which can occur in diabetic patients with CKD. Nerve conduction studies in these patients may not demonstrate the features of a demyelinating neuropathy and improvement has been noted with a switch from conventional to high-flux dialysis, rather than with immunotherapy. The benefit of high flux dialysis in

these patients has been attributed to removal of advanced glycosylated end products which have been implicated in the pathogenesis of both diabetic neuropathy and nephropathy.

Small fiber neuropathy in CKD

While the clinical features of length-dependent uremic neuropathy reflect damage to large sensory and motor fibers, a small fiber neuropathy may also occur in CKD stage 5. Preferential damage to small fibers which carry pain and temperature sensation may induce sensory symptoms dominated by burning and painful dysaesthesiae. While objective changes in thermal sensation have been reported, small fiber neuropathy is a far less common presentation of uremic neuropathy and rarely occurs in the absence of large fiber involvement.

Restless legs syndrome (RLS).

Patients with RLS describe an urge to move their legs, typically with nocturnal exacerbation, due to the development of sensory symptoms which worsen during periods of inactivity. The dysaesthesiae are either partly or totally alleviated by the movements. Studies of RLS in ESRD patients have demonstrated significant disruption to sleep, with resultant reduction in quality of life. The distinction between RLS and neuropathy is critical to management, as patients with RLS may benefit from dopaminergic agents,

including levadopa or dopamine agonists. A favorable therapeutic response to these agents has led to the suggestion that central dopaminergic dysfunction may play a role in the development of RLS, although other processes such as hyperphosphatemia and iron deficiency have been linked to symptom development in ESRD[18] .

Diagnosis of Length-Dependent Uremic Neuropathy[10]

The initial step in the diagnosis of neuropathy in ESRD patients is to exclude other potential causes of neuropathy. Assessment for glucose dysmetabolism is essential, both in view of the high rates of diabetes in patients with ESRD and given that diabetic ESRD patients develop more severe neuropathy. Patients who have rapidly progressive neuropathy require further testing for connective tissue disorders which may be associated with vasculitic neuropathy. Testing should include inflammatory markers, antinuclear antibody, ANCA, Hepatitis antibodies (B and C),. Histological studies should be considered before immunosuppressive therapy is commenced, with combined nerve and muscle biopsies demonstrating abnormalities in 60%of such cases.

Nerve conduction studies remain the mainstay in the diagnosis of uremic peripheral neuropathy.

With long-term HD, the neuropathic symptoms and signs stabilize . In fact, rapid hemodialysis may worsen the polyneuropathy temporarily. Peritoneal dialysis appears to be more successful than hemodialysis in improving the neuropathy but this observation has not been firmly established. Complete recovery, occurring over a period of 6 to 12 months, usually follows successful renal transplantation

Pathology of Uremic neuropathy

Uremic neuropathy is one of a group of central-peripheral axonopathies, also known as dying-back polyneuropathies. The clinical characteristics of such distal axonopathies include the following:

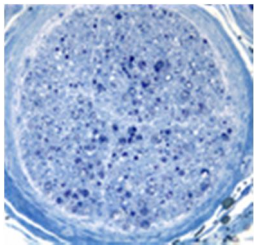
- Insidious onset. In most human toxic neuropathies, there is a steady low-level exposure. Because only the distal portion of selected, scattered fibers is affected, the patient may still function well despite the axonal degeneration.
- In all types of uremic polyneuropathies, pathologic changes are most intense in the distal segments of the nerves with the expected chromatolysis of their cell bodies.
- Onset in legs.

- Large and long axons are affected early, and fibers of the sciatic nerve are especially vulnerable
- Stocking-glove sensory loss. Degeneration in the distal axon proceeds toward the cell body, resulting in clinical signs in the feet and hands initially.
- Early loss of Achilles reflex. Fibers to the calf muscles are of large diameter and among the first affected by many toxins, even when longer, smaller-diameter axons in the feet are spared.
- Decrease of SNAP and CMAP amplitude with normal or mild slowing of motor nerve conduction
- Late responses (H-reflex and F-wave latencies) become abnormally prolonged early in the course of chronic renal failure
- Normal CSF protein content.
- Pathologic changes are usually distal and nerve roots are spared.
- Slow recovery. Axonal regeneration (in contrast to remyelination) is slow about 1 mm per day. Thus, after institution of dialysis or renal transplantation, recovery of nerve function may take months or years[19].

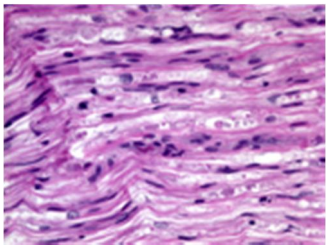
PATHOLOGICAL PATTERNS OF NEUROPATHY

The pathology of peripheral neuropathy follows three basic patterns: Wallerian degeneration, distal axonopathy, and segmental demyelination.

Wallerian degeneration. The neuronal cell body maintains the axon through the axoplasmic flow. When an axon is transected, its distal part, including the myelin sheath, undergoes a series of changes leading to its complete structural disintegration and chemical degradation.



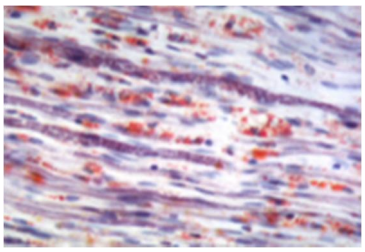
Acute neuropathy



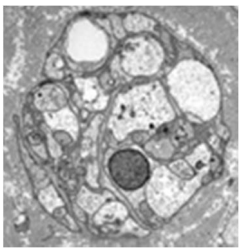
Wallerian degeneration

Changes also occur in the neuronal body. The RER disaggregates and the neuronal body balloons. The cytoplasm becomes smooth and the nucleus is displaced toward the periphery of the cell. This process is called ***central chromatolysis*** and reflects activation of protein synthesis in order to regenerate the axon. Cytoskeletal proteins and other materials flow down the axon.

In **distal axonopathy**, degeneration of axon and myelin develops first in the most distal parts of the axon and, if the abnormality persists, the axon "dies back". This causes a characteristic distal ("stocking-glove") sensory loss and weakness.



Lipid material in acute neuropathy



Axonal sprouts

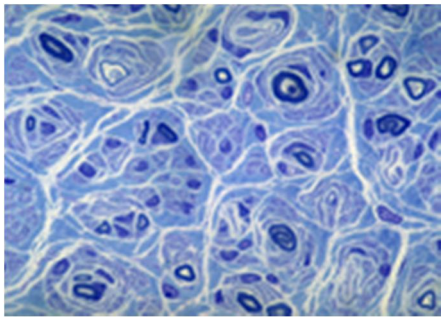
Neurofilaments and organelles accumulate in the degenerating axon (probably due to stagnation of axoplasmic flow). Eventually the axon becomes atrophic and breaks down. Severe distal axonopathy resembles Wallerian degeneration. At an advanced stage, there is loss of myelinated axons.

Distal axonopathy is thought to be caused by pathology of the neuronal body resulting in its inability to keep up with the metabolic demands of the axon. This explains why the disease begins in the most distal parts of nerves, and large axons that have the highest metabolic and nutritional demands are more severely affected.

Segmental demyelination

It is characterized by breakdown and loss of myelin over a few segments. The axon remains intact and there is no change in the neuronal body. The loss of saltatory conduction that results from segmental demyelination leads to decrease of conduction velocity and conduction block. Deficits

develop rapidly but are reversible because Schwann cells make new myelin. However, in many cases, demyelination leads to loss of axons and permanent deficits. The nerve, in segmental demyelination, shows demyelinated axons, thin-regenerating-myelin, "onion bulbs" and in severe cases, loss of axons. The status of myelin can be evaluated with teased fiber preparations of peripheral nerves and by electron microscopy. Neuropathies characterized by segmental demyelination include acute and chronic inflammatory demyelinative neuropathies, diphtheritic neuropathy metachromatic leuko-dystrophy and Charcot-Marie-Tooth disease.



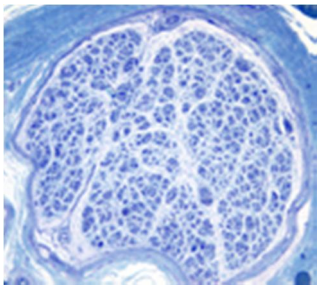
Hypertrophic neuropathy

"Onion bulb" formations are concentric layers of Schwann cell processes and collagen around an axon. This proliferation is caused by repetitive segmental demyelination and regeneration of myelin and can cause gross thickening of peripheral nerves (**hypertrophic neuropathy**). The central

axon is often demyelinated or has a thin layer of myelin. Onion bulb formations are the histological hallmark of **Charcot-Marie-Tooth disease**, but are also seen in other hereditary neuropathies (Dejerine-Sottas disease, Refsum disease), in diabetic neuropathy, and in chronic inflammatory demyelinative neuropathy.

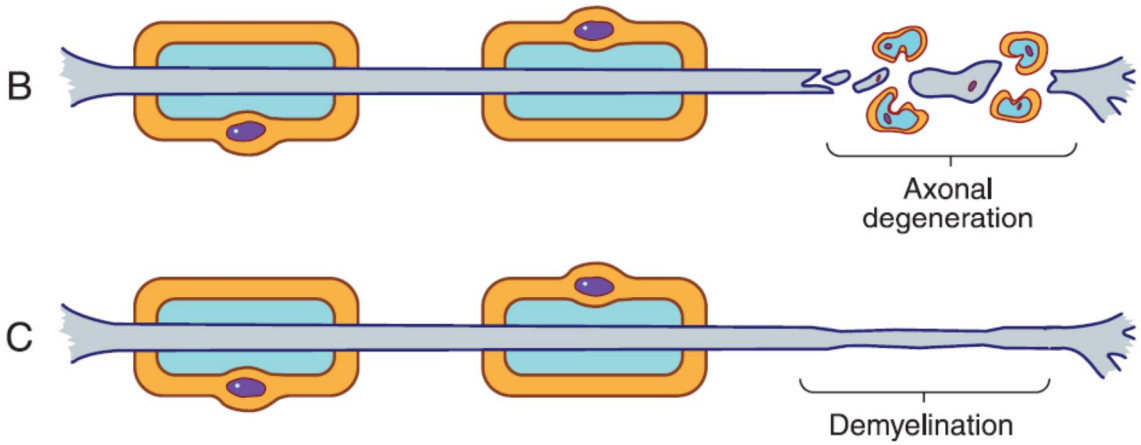
The pathology of peripheral neuropathy is reflected in the spinal cord. Acute axonal neuropathy causes cental chromatolysis. Axonal neuropathy and distal axonopathy involving the bipolar neurons of the dorsal root ganglia cause degeneration of the central axons of these neurons in the gracile and cuneate tracts of the spinal cord. This lesion is associated with loss of position and vibration sense and **sensory ataxia**.

Neuropathies can be classified on the basis of their pathological changes into **axonal** (Wallerian degeneration and distal axonopathy**), demyelinative, or mixed**.



End stage axonal neuropathy

The pathological changes of most peripheral neuropathies (axonal degeneration, segmental demyelination or a combination of these) are not specific. In any active neuropathy, there are macrophages removing myelin and axon debris.



In most neuropathies, the sural nerve biopsy can only establish the diagnosis of neuropathy and distinguish axonal from demyelinative and acute from chronic neuropathy, but cannot determine the cause of neuropathy. Only a few peripheral neuropathies show disease-specific pathological changes allowing a specific diagnosis. These neuropathies include acute and chronic inflammatory demyelinative neuropathies, hereditary motor and sensory neuropathies, vasculitis, sarcoid neuropathy, leprosy, amyloid neuropathy, neoplastic invasion of peripheral nerves, metachromatic leukodystrophy, adrenomyeloneuropathy, and giant axonal neuropathy.

Pathophysiology

The cellular basis for distal axonopathies, however, remains unclear. What has been called the "middle molecule" theory is possible[9]. The end stage of renal failure is associated with the accumulation of toxic substances in the range of 300 to 12,000 kDa molecular weight such as. such as, creatinine,

parathyroid hormone, myoinositol, and β2-microglobulin . As is the case with uremic encephalopathy, urea alone given to experimental animals and in controlled studies of humans, does not seem capable of inducing a metabolic neuropathy. Spencer et al[19]. have emphasized that a number of chemically unrelated neurotoxic compounds and several types of metabolic abnormalities can cause strikingly similar patterns of distal symmetric polyneuropathy in humans and animals. These authors suggest a possible common metabolic basis for many distal axonopathies. Neurotoxic compounds may deplete energy supplies in the axon by inhibiting nerve fiber enzymes required for the maintenance of energy synthesis. Resupply of enzymes from the neuronal soma may fail to meet the increased demand for enzyme replacement in the axon, causing the concentration of enzymes to decrease in distal regions. This could lead to a local blockade of energy-dependent axonal transport, which could then produce a series of pathologic changes culminating distal nerve fiber degeneration.

Studies investigating the pathophysiology of neurological disease in CKD have tended to focus largely on the hypothesis that one or more of these retained toxins is responsible for mediating the neurological dysfunction.

This hypothesis has been supported by studies that demonstrated conduction slowing in clinically unaffected nerve segments. These neuro-physiological changes correlated with severity of renal impairment, and the clinical symptoms and nerve conduction parameters were noted to improve rapidly

following renal transplantation, often within days of surgery. the rapidity of these changes suggests that toxin-mediated blockade of neural transmission has an important role in the neuro logical dysfunction associated with CKD[10]

Five criteria have been proposed that should be met for a substance to be considered as a uremic neurotoxin

Proposed criteria for a uremic neurotoxin

- Must be an identifiable chemical
- Should be elevated in the blood of patients with uremia
- A direct positive relationship should exist between blood level and neurological dysfunction
- Should cause neurological dysfunction in experimental animals at appropriate blood levels
- Removal from the blood should abolish the neurological dysfunction

on the basis of this framework.

Studies of uremic neuropathy have applied the rationale that bio chemical alterations in CKD will result in dysfunction of the axonal membrane that can be reversed with hemodialysis.

Several possible uremic toxins have been identified, which appear to be correlated with depression of MNCV in laboratory animals[23]. However, these studies do not take into account the fact that: (i) depressed MNCV is cyclical, with abnormal low values one day and normal values the next; (ii) there is a day-to-day variation in MNCV that approaches 20% [24] (iii) the

finding of depressed MNCV in laboratory animals associated with high plasma levels of potential uremic neurotoxins has generally not been confirmed in human subjects with renal failure. Although it is possible to relate impairment in MNCV with levels in blood of various substances, the best correlation was obtained between reduced MNCV versus a reduction in glomerular filtration rate.

Parathyroid Hormone[25.26]

Among the potential uremic neurotoxins is PTH, based on a possible correlation between plasma PTH levels and MNCV in patients with CRF. Although some earlier studies suggested a possible effect of PTH on MNCV in the dog, these impressions have not been confirmed In patients who have hyperparathyroidism without uremia, PTH has no observable effect on peripheral nerve function .

ROLE OF POTTASIUM AS A POTENTIAL NEUROTOXIN [10]

While nerve conduction studies remain the gold standard for the clinical assessment of neuropathy, they do not provide further insight into disease pathophysiology. Recently, novel ***nerve excitability techniques,*** which provide complementary information to nerve conduction studies, have been adapted for clinical use. These studies have examined changes in nerve function that occurred in ESRD patients before, during and after a single

session of hemodialysis. Measures of nerve function were also assessed in relation to changes in serum levels of potential neurotoxins, including potassium(K+), urea, and ‘‘middle-molecules" such as parathyroid hormone and b2-microglobulin.

Using these novel excitability techniques, predialysis excitability abnormalities were established to be strongly correlated with serum K+ in all studies.

Excitability studies also demonstrated that abnormalities of nerve function occurred at a level much lower than that required for cardiac toxicity, with patients manifesting axonal changes with serum K+ concentrations in the high normal range (i.e.,4.9–5.0 mmol ⁄ l). Following dialysis there was significant improvement although minor excitability abnormalities persisted, suggesting that dialysis alone is insufficient in normalizing nerve function. In contrast, the strong correlations noted with serum K+ were not demonstrated for any of the middle molecules. These findings are also supported by studies that investigated the causes of weakness and fatigue in ESRD, and demonstrated that abnormalities of K+ regulation may underlie muscle fatigue and thereby contribute to exercise limitation in ESRD.

Potassium satisfies all the criteria that have been recently proposed for a substance to be truly regarded as a uremic neurotoxin. It is an identifiable chemical that is elevated in the serum of ESRD patients and causes neurological dysfunction in both humans and experimental animals. It is also

a critical determinant of axonal resting membrane potential. Furthermore excitability studies have demonstrated that a direct relationship exists between serum levels of K+ and neurophysiological abnormalities and that removal of K+ leads to improvement in nerve function.

Such persistent elevation in serum K+ would lead to chronic membrane depolarization. It is well known that chronic changes in membrane potential are harmful to axons and may trigger reverse activation of the Na+/Ca2+ exchanger, leading to an influx of Ca2+.Such processes may initiate a cascade that eventually induces axonal death.

Role of Nerve Conduction Studies in diagnosing Uremic peripheral neuropathy[27]

Nerve conduction studies remain the mainstay in the diagnosis of uremic neuropathy. In length-dependent uremic neuropathy, nerve conduction studies demonstrate features of a generalized neuropathy of the axonal type, with reduction in sensory amplitudes and to lesser extent, motor amplitudes[15,16] . Sensory and motor conduction velocities are relatively preserved and needle electromyography may reveal changes in denervation in distal lower limb muscles. In patients who have a rapidly progressive course with significant weakness, the possibilities of demyelinating neuropathy and accelerated neuropathy of renal failure need to be considered [17,28]. Neurophysiological investigations in demyelinating

neuropathies demonstrate significant reduction in conduction velocities, often with preserved motor and sensory amplitudes .[29,30]

Management of Length-Dependent Uremic Neuropathy

Renal transplantation remains the only cure for uremic neuropathy and must be considered in any patient with progressive neuropathy[11]. Neurophysiological improvement following renal transplantation is rapid, often occurring within days[31]. Clinical recovery typically occurs over a period of months, with neurological improvement occurring within 3–6 months in patients with mild neuropathy. A more delayed and often incomplete improvement has been noted in patients with severe neuropathy, with some patients only manifesting improvement after 2 years . While modern dialysis regimens generally prevent progression of neuropathy, clinical reversibility is uncommon[11].

Rapidly progressive neuropathy, however, remains both an indication for the commencement of dialysis therapy and an important indicator of insufficient dialysis. It is also critical to ensure that patients with neuropathy meet current guidelines of dialysis adequacy and this may require an increased frequency of dialysis. In some cases, a change to daily dialysis or high-flux dialysis[3 2]may be beneficial as an interim measure in patients with severe progressive neuropathy who are awaiting transplantation. This may confer

symptomatic benefits even in patients who already meet conventional targets for dialysis adequacy.

In patients with painful neuropathy, options for symptomatic management include the use of tricyclic antidepressants, such as amitriptyline, which have proven efficacy in the treatment of neuropathic pain[33]. Of the anticonvulsant medications, while sodium valproate continues to be used widely, newer agents such as gabapentin are efficacious and well tolerated.

The potential role of hyperkalemia in uremic neuropathy raises the possibility that dialyzing against a lower K+ concentration and attempting to lower inter-dialytic K+ by ensuring strict dietary restriction of K+ may prove beneficial, and randomized studies exploring this hypothesis are currently underway. Certainly, the potential importance of K+ in length-dependent uremic neuropathy may question the suitability of urea-based measures of dialysis adequacy in determining the suitability of a dialysis regimen to prevent neurotoxicity.

More recent studies suggest that, at least from a neuropathy perspective, a better indication of adequate dialysis may relate to the maintenance of serum K+ within normal limits between periods of dialysis. Recent evidence suggests that treatment with erythropoietin (EPO) may be beneficial for ESD patients with neuropathy[34]. These studies have demonstrated neurophysiological improvement following EPO treatment. Such findings have been supported by studies which have demonstrated that EPO receptors

on neural cells are upregulated after nerve injury in animal models and that exogenous EPO administration is associated with reduction in limb weakness and neuropathic pain behavior.

Other Neuropathies in CKD

Autonomic Neuropathy[36]:

Autonomic dysfunction is a common and potentially life-threatening complication of CKD, and can occur in the absence of length-dependent uremic neuropathy. Cardiovascular autonomic dysfunction in CKD is associated with an increased risk of cardiac arrhythmia and sudden cardiac death.1Assessment of autonomic function has demonstrated abnormalities in 60% of patients with CKD, particularly relating to measures of parasympathetic function, such as heart rate response to deep breathing, induced hypotension, and the valsalva maneuver. Impotence remains the most common symptom of autonomic dysfunction in CKD, and it develops in the majority of male patients. Other common clinical features include bladder and bowel dysfunction, impaired sweating, and orthostatic intolerance. Arterial calcification might contribute to autonomic symptoms in CKD by reducing the sensitivity of baroreceptors in the arterial wall that mediate the short-term regulation of blood pressure. In addition to a potential role in sudden cardiac death, reduced baroreflex sensitivity can also contribute to intra dialytic hypotension. Intradialytic hypotension is an

independent risk factor for mortality in CKD, and its symptoms include dizziness, blurred vision, cramps, nausea and vomiting. renal transplantation leads to considerable improvement in autonomic function, whereas dialysis treatments do not result in a substantial change[37].

Compression neuropathies

Carpal tunnel syndrome may develop in more than 20% of patients on hemodialysis. Nerve compression from local edema secondary to the forearm arteriovenous shunts or ischemia from a fistula induced vascular steal syndrome are likely mechanisms in the early course of dialysis. Patients on long-term hemodialysis may develop carpal tunnel syndrome because of the deposition of β2-microglobulin-derived amyloid in the carpal ligament.

Ischemic monomelic neuropathy

It is an acute complication of the placement of a more proximal shunt between the cephalic vein and brachial artery; the monomelic neuropathy occurs mainly in diabetic patients with concomitant peripheral vascular disease. It is characterized by abrupt, painful sensory loss of the affected hand, and weakness of median, ulnar, and radial innervated distal muscles. Prompt surgical closure of the fistula is required to avoid permanent neurological deficits.

NERVE CONDUCTION STUDIES

Principles

Electrical stimulation of nerve fibers initiates impulses that travel along motor, sensory, or mixed nerves and evoke a compound action potential.

There are **three types** of Nerve conduction studies: **motor, sensory, and mixed**.

Conduction characteristics of **motor fibers** are assessed indirectly by studying the **compound muscle action potential (CMAP)** recorded from the muscle; **sensory fibers** are assessed by analyzing the **sensory nerve action potential (SNAP)** recorded from the nerve. **Mixed Nerve Conduction Studies** assess directly the sensory and motor fibers simultaneously by recording from **mixed nerve action potential (MNAP).**

The use of standard Nerve Conduction Studies allows precise lesion localization and accurate characterization of peripheral nerve function.

Supramaximal stimulation of a nerve that results in depolarization of all available axons is a paramount prerequisite to all NCS measurements. To achieve supramaximal stimulation, current (or voltage) intensity is slowly increased until it reaches a level at which the recorded potential docs not increase. Then, the current should be increased an additional 20-30% to ensure that the potential does not change further.

Recording Electrodes

- **Surface electrodes**
- **Needle electrodes**
- **Ring electrodes**

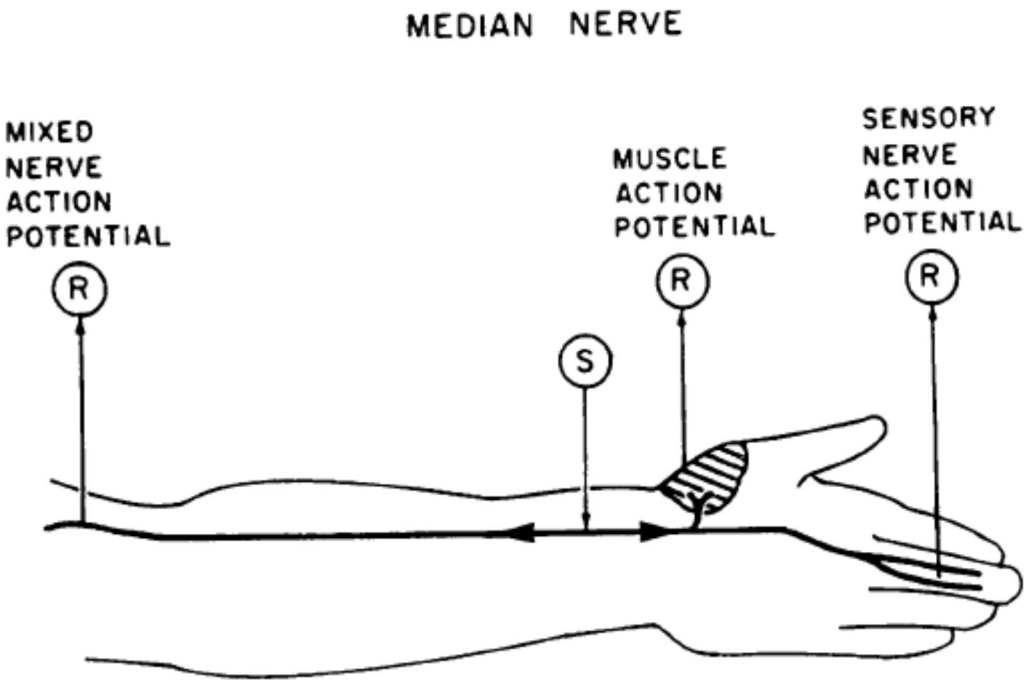
Recording Procedure

A pre-pulse preceding the stimulus triggers the sweep on a storage oscilloscope.

Motor Nerve Conduction Studies

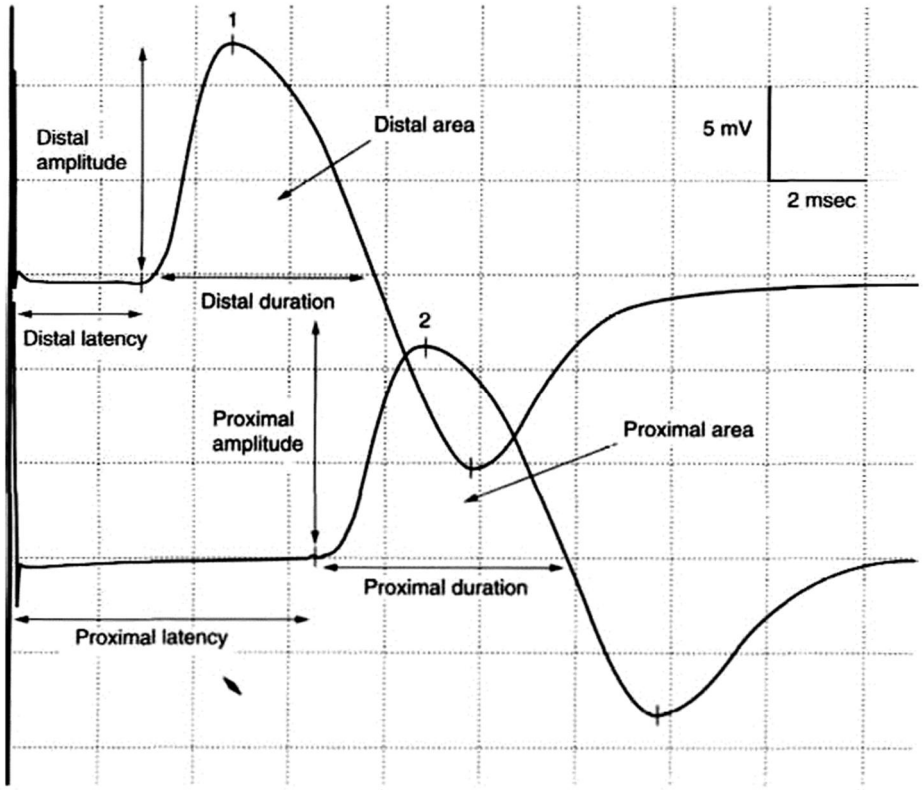
Motor Nerve Conduction Studies are performed by stimulating a motor or mixed peripheral nerve while recording the CMAP from a muscle innervated by that nerve. A pair of recording electrodes consists of an active lead (Gl) placed on the belly of the muscle and an indifferent lead (G2) on the tendon (belly-tendon recording). The propagating muscle action potential, originating under Gl located near the motor point, gives rise to a simple biphasic waveform with initial negativity. Initial positivity suggests incorrect positioning of the active electrode or a volume-conducted potential from distant muscles activated by anomalous innervation or by accidental spread of stimulation to other nerves. The nerve is stimulated at two or more points

along its course. Typically, it is stimulated distally near the recording electrode and more proximally to evaluate its proximal segment. Several measurements are evaluated with motor Nerve Conduction Studies.



CMAP amplitude.

This is usually measured from baseline to negative peak and expressed in millivolts. When recorded with surface electrodes, CMAP amplitude is a semi quantitative measure of the number of axons conducting between the stimulating and the recording points. CMAP amplitude also depends on the relative conduction speed of the axons, the integrity of the neuromuscular junctions, and the number of muscle fibers that are able to generate action potentials.



Motor nerve conduction study of the median nerve showing a typical compound muscle action potential (CMAP) with distal and proximal stimulations, showing the distal and proximal latencies and CMAP amplitudes, durations, and areas

CMAP duration.

This is usually measured as the duration of the negative phase of the evoked potential and is expressed in milliseconds. It is a function of the conduction rates of the various axons forming the examined nerve and the distance between the stimulation and recording electrodes.

Latencies:

This is the time interval between nerve stimulation (shock artifact) and the onset of the CMAP. It is expressed in milliseconds and reflects the conduction rate of the fastest-conducting axon. Whenever it is technically possible, the nerve is typically stimulated at two points: a distal point near the recording site **(distal latency**) and a more proximal point **(proximal latency**). Both latencies depend mostly on the length of the nerve segment and, to a much lesser extent, on neuromuscular transmission time and propagation time along the muscle membrane.

Conduction velocity:

This is a computed measurement of the speed of conduction and is expressed in meters per second. Measurement of conduction velocity allows the comparison of the speed of conduction of the fastest fibers between different nerves and subjects, irrespective of the length of the nerve. It is calculated after the length of the nerve segment is incorporated between distal and proximal stimulation sites. The nerve length is estimated by measuring the surface distance along the course of the nerve and should be more than 10 cm to improve the accuracy of surface measurement.

$$\textit{Motor conduction velocity} = \frac{\textit{Distance}}{\textit{Proximal onset latency} - \textit{Distal onset latency}}$$

Sensory Nerve Conduction Studies

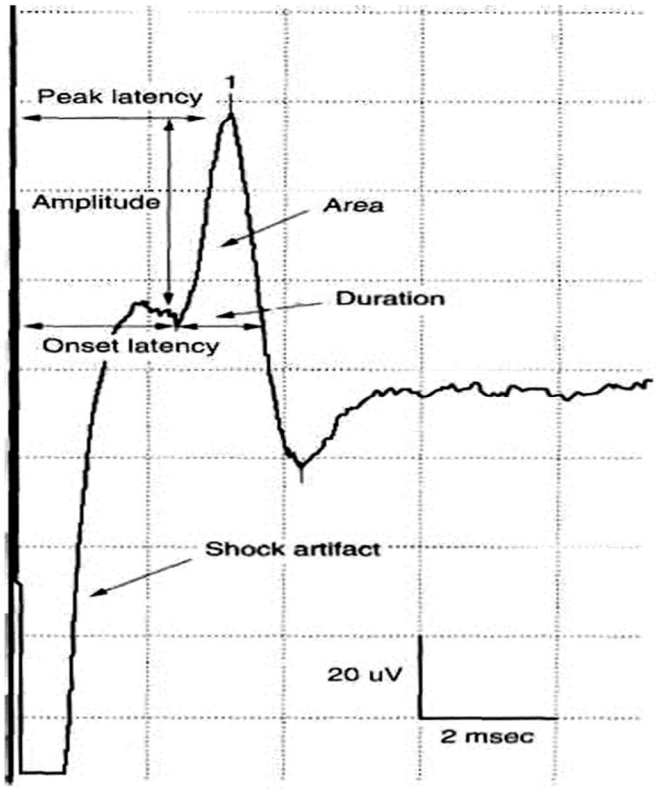
Sensory axons are evaluated by stimulating a nerve while recording the transmitted potential from the same nerve at a different site. Therefore, SNAPs arc true nerve action potentials. **Antidromic s**ensory Nerve Conduction Studies are performed by recording potentials directed toward the sensory receptors, whereas **orthodromic** studies arc obtained by recording potentials directed away from these receptors. Sensory latencies and conduction velocities are identical with either method, but SNAP amplitudes generally are higher in antidromic studies. Because the thresholds of some motor axons are similar to those of large myelinated sensory axons, superimposition of action potentials from distal muscles may obscure antidromically recorded SNAPs. Fortunately, latencies can still be measured accurately because the large-diameter sensory fibers conduct 5-10% faster than motor fibers. This relationship may change in disease states that selectively affect different fibers.

SNAPs may be obtained by stimulating and recording a pure sensory nerve (such as the sural and radial sensory nerves, stimulating a mixed nerve while recording distally over a cutaneous branch (such as the antidromic median and ulnar sensory responses), or stimulating a distal cutaneous branch while recording over a proximal mixed nerve (such as the orthodromic median and ulnar sensory studies). Similar to their motor counterparts, several

measurements are recorded with sensory NERVE CONDUCTION STUDIES.

SNAP amplitude:

This is a semi quantitative measure of the number of sensory axons that conduct between the stimulation and recording sites. It is calculated from the baseline to negative peak or from negative peak to positive peak and expressed in microvolts.



Antidromic median sensory nerve conduction study after stimulation at the wrist, revealing peak and onset latencies and sensory nerve action potential amplitude, duration, and area.

Sensory Latencies:

With sensory Nerve Conduction Studies, often only a single distal site is stimulated. Sensory distal latencies may be measured (in milliseconds) from the stimulus artifact to the peak of the negative phase (peak latency) or from the stimulus artifact to the onset of the SNAP (onset latency).

Conduction velocity:

This requires stimulation at a single site only because the latency consists of only the nerve conduction time from the stimulus point to the recording electrode. It may be also done with distal and proximal stimulation sites. Sensory conduction velocities are calculated similarly to their motor counterparts; only onset latencies (not peak latencies) are used to calculate the speed of the fastest conducting fibers.

$$\textit{Sensory conduction velocity} = \frac{\textit{Distance}}{\textit{Proximal onset latency} - \textit{Distal onset latency}}$$

The principal factors that influence the speed of NCV

- the integrity and degree of myelination of the largest diameter fibers;
- the mean cross sectional diameter of the responding axons;
- the representative intermodal distance in the segment under study;
- the micro environment at the nodes, including the distribution of ion channels

Physiological Variability and Common Sources of Error:

- Technical errors
- Temperature
- Age
- Height and Nerve Segment Lengths
- Anomalies

MATERIALS AND METHODS

This study was conducted from August 2010 to December 2011 at Department of Nephrology, Madras Medical college and Rajiv Gandhi Government General Hospital, Chennai with active support from Neurology Department. The study protocol was approved by the Ethics Committee of the Government General Hospital and all subjects gave their informed consent prior to the study.

Inclusion criteria

The study included 35 CKD stage V patients on Maintenance HD (polysulfone dialyser, low flux) who were on Kidney transplantation programme (Live related) in our department.

Exclusion criteria

- Diabetes mellitus
- small vessel vasculitis
- systemic lupus erythematosus
- chronic alcoholic

Methodology

All participants were assessed for the presence of peripheral neuropathy by eliciting detailed history regarding symptoms of neuropathy, co-morbid illness, history of alcohol intake, drug intake, duration of CKD and period of Hemodialysis(HD).

Detailed neurological examination was performed to assess presence of decreased touch, pain, temperature, vibration and position sensations and motor abnormalities like decreased power and deep tendon reflexes(DTR) in the extremities.

Routine investigation include urine analysis, complete hemogram, Blood Urea, serum creatinine, Electrolytes, Liver function tests,Viral Markers and Thyroid function tests.

All these patients were on supplemental doses of vitamin B complex during the period of study

All patients were subjected to Nerve conduction studies (motor and sensory of both upper and lower limbs). It was done immediately after a HD session so that patients were oedema free.

Electrodiagnostic Measures-Standardization

The Electro diagnostic protocol, as recommended by AAEM was used. Neuro-physiological studies were performed by RECORDERS and MEDICARE SYSTEMS EMG. EP MARK – II, EMG machine, a 4channel electrophysiological device.

Recommended filter settings (approximate values) were 20-3,000 Hz band-pass for sensory studies, 2-10,000 Hz band-pass for motor studies.

The temperature of the room was maintained at 22-24^{o}C during all processes

Standardized nerve conduction techniques were used. Conventional methods using surface electrodes for motor conduction and ring electrodes for sensory conduction were used

Nerve Conduction Studies in the lower limbs.

In the lower limbs sensory conduction in sural nerve (**SNAP**- ***sensory nerve action potential)*** and motor conductions in tibial nerves(**CMAP**-Compound Muscle action potential) were done bilaterally in all the patients.

Nerve Conduction Studies in upper limbs

Nerve conduction studies in the upper limbs included sensory (**SNAP**) and motor**(CMAP**) conductions of median nerve.

In the Median nerve Nerve conduction studies were done in the non AV fistula arm and in those patients who did not have an AVF it was done on the dominant arm (Right).

None of the patients had symptoms or signs of carpal tunnel syndrome.

COMPONENTS ASSESSED:

- ***Distal Latency (DL)***
- ***Proximal latency***
- ***Amplitude:***
- ***Nerve conduction velocity*** **(NCV)**

THE FOLLOWING PARAMETERS WERE MEASURED

- ***Sural nerve***- Amplitude, CV, DL of **SNAP**
- ***Tibial nerve***- Amplitude, CV, DL of ***CMAP***
- ***Median nerve -*** Amplitude, CV, DL of ***SNAP and CMAP***

Protocol for electro diagnostic test:

The normal values for representative nerve conduction values at various sites of stimulation were derived at after analyzing the nerve conduction studies of 20 age matched patients who came to Neurology OPD for complaints other than neuropathy.

Normal values

Sensory nerve conduction studies(SNAP)

Nerve	Amplitude(mv)	CV(m/s)	Distal Latency(ms)
Sural	**>6**	**>40**	**<4.4**
Median	**>5**	**>50**	**<3.5**

Motor nerve conduction studies(C MAP)

Nerve	Amplitude(mv)	CV(m/s)	Distal Latency(ms)	F wave latency(ms)
Median	**>4.2**	**>49**	**<4.2**	**<30**
Tibial	**>4.1**	**>41**	**<6**	**<56**

Based on the results the patients were divided into two groups

Group 1- patients who had clinical or electrophysiological evidence of neuropathy

Group 2- patients who had no clinical or electrophysiological evidence of neuropathy

The parameters (SNAP, CMAP) were analyzed to assess whether it's a **axonopathic** (↓ amplitude, ↔ conduction velocities , ↔ distal latency) or **demyelinating** (normal amplitude, ↓ CV ,↑ Latency).

They were further divided into predominantly ***sensory, motor or mixed sensorimotor*** involvement or predominant lowerlimb or upperlimb or involvement of both limbs.

Those patients in group 1 who had clinical or Neuro-physiological evidence of neuropathy underwent follow-up nerve conduction studies in Post renal transplant period at the end of 1^{st} and 3^{rd} months.

The parameters mentioned above were measured again and the results were compared with the pre-transplant values and analyzed for statitistical significance.

Statistical analysis was done using SPSS software using repeated measures ANOVA test.

OBSERVATION & RESULTS

The study included 35 participants (CKD Stage 5 patients) on Hemodialysis (HD) and on live related kidney transplantation programme. 30 patients (24 males; 6 females) completed the study. (5 people had either died or lost to follow up).

Native kidney disease among participants

	Male	Female
Chronic Glomerulonephritis	8	3
Chronic Interstitial nephritis	4	
CAKUT		1
Not known	12	1
Acute cortical necrosis		1

Pre-tranplant clinical examination:

Of the thirty patients, 8 (26.6%)(7M:1F) had clinical evidence of peripheral neuropathy. The main symptoms were paresthesiae or dysesthesiae of feet (burning sensation , tingling, pins and needles, or cramp-like sensations) and or numbness.

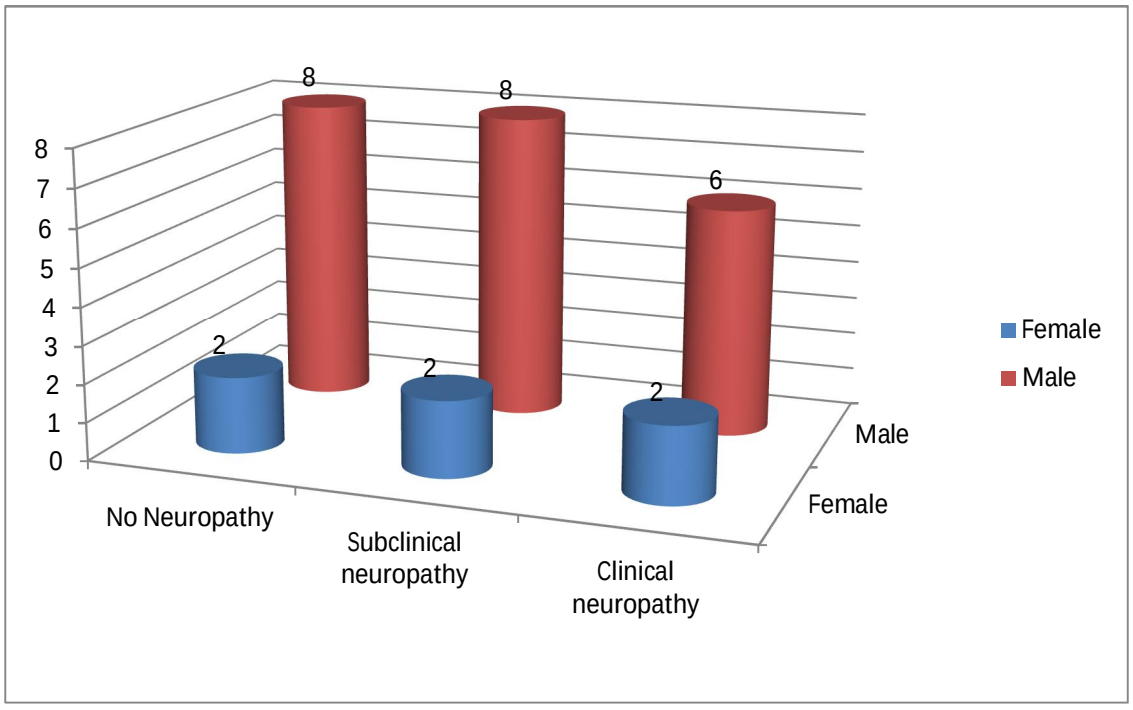
On neurologic examination these patients had symmetrical decreased vibration sense in the toes and ankle and also ↓temperature and superficial pain sensations in the feet. Six (20%) patients had decreased ankle jerk.

None of them had restless leg syndrome, weakness, wasting, spontaneous disabling pain in the limbs or sensory ataxia.

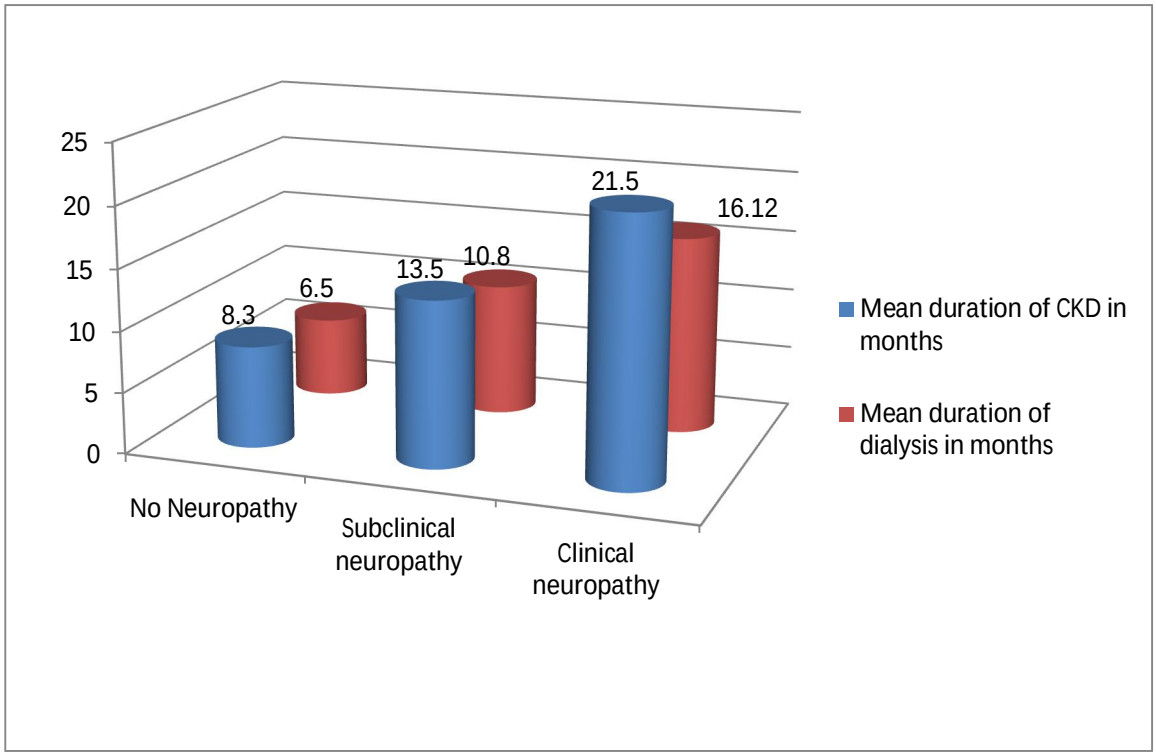
All 30 underwent nerve conduction studies in the pre- transplant period. On nerve conduction studies 20(66.7%) patients showed evidence of peripheral neuropathy.

{8 symptomatic and 12 asymptomatic patients(subclinical neuropathy)}.

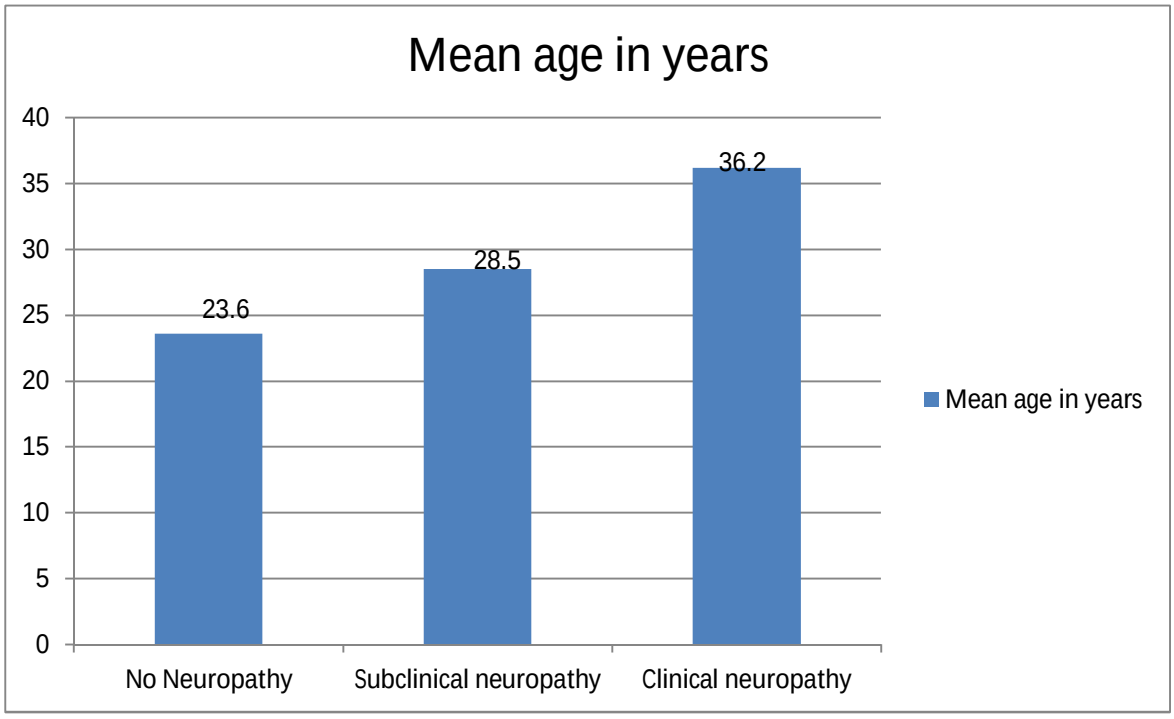
Sex ratio



Influence of duration of CKD and of dialysis on neuropathy



Mean age in years of patients & status of neuropathy



Clinical profile

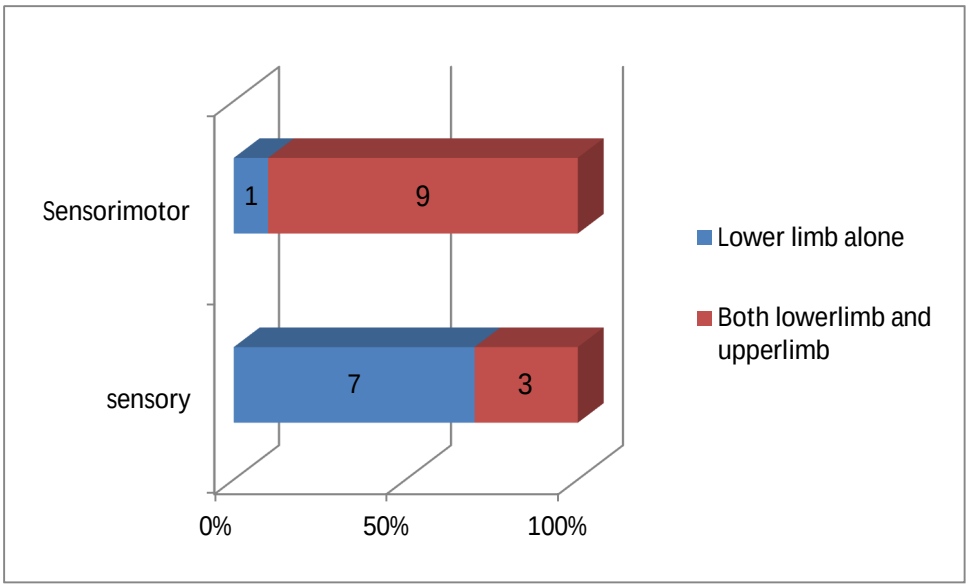
Parameter	No neuropathy	*Sub Clinical neuropathy*	Clinical neuropathy
No	10	12	8
M:F	8:2	10:2	6:2
Mean age in years	23.6	28.5	36.2
Mean duration of CKD in months	8.3	13.5	21.5
Mean duration of dialysis in months	6.5	10.8	16.12
HCV	2	1	

All 20 patients who had clinical or subclinical neuropathy underwent repeat nerve conduction studies after successful renal transplantation at the end of 1st and 3rd months.

Results of nerve conduction studies

Neuropathy	sensory	Sensorimotor
Lower limb alone	7	1
Both lowerlimb and upperlimb	3	9

Patterns of neuropathy



RIGHT SURAL NERVE (SENSORY NERVE ACTION POTENTIAL)

The sural nerve SNAP was obtained successfully in 26 subjects (86.6%). 16/26(61.53%) patients had abnormal SNAP in the pre-transplant period. Follow-up results of these 16 patients were analysed

Parameter	**PRE TX (A)**	***POST T X* 1 month *(B)***	***p value A vs B***	**POST TX 3 month(C)**	**p value A vs C**	**p value B vs C**	**n**
Distal latency ms mean(sd)	3.570 *(0.71)*	*2.963 (0.6562)*	*>.05*	2.527 (0.4776)	<.05	>.05	16
Amplitude in mv mean(sd)	4.831 (0.7846)	*5.913 (1.060)*	*<.05*	7.213 (1.244)	*<.05*	*>.05*	
conduction velocity mean(sd)	38.275 (1.541)	*46.758 (4.715)*	*<.05*	54.217 (8.220)	*<.05*	*>.05*	

In 4(13.3%) patients sural nerve SNAP was absent bilaterally in pretransplant period, but were included in the follow-up study

LEFT SURAL NERVE SNAP

Parameter	PRE TX (A)	POST T X 1 month (B)	p value A vs B	POST TX 3 months (C)	p value A vs C	p value B vs C	n
Distal latency in ms mean(SD)	3.606 (1.056)	*3.136 (1.470)*	*>.05*	2.528 (0.5468)	*<.05*	*>.05*	16
Amplitude in mv mean(SD)	5.188 (0.447)	*5.981 (0.7195)*	*<.05*	7.057 (1.058)	*<.05*	*<.05*	
conduction velocity mean(SD)	38.350 (1.637)	*46.874 (3.741)*	*<.05*	54.706 (4.820)	*<.05*	*>.05*	

In the pre-transplant nerve conduction studies 61.43% had involvement of sural nerve bilaterally. It was associated with ↓ amplitude of SNAP↓ or↔ Conduction velocity and a near normal distal latency (an axonopathic pattern).

The follow up study showed there is increase in SNAP conduction velocity, Amplitude of sural nerves bilaterally.

RIGHT TIBIAL NERVE CMAP

The tibial nerve CMAP was obtained successfully in all the patients. 10 patients had abnormalities in pre-transplant CMAP of tibial nerve bilaterally of axonopathic type. Follow-up data were analyzed for these ten patients and compared.

Parameter	**Pre tx (A)**	***Post t x 1 mon (B)***	***p value A vs B***	**Post tx 3 mon (C)**	**p value A vs C**	**p value B vs C**	**n**
Distal latency ms mean(sd)	4.050 (1.70)	*3.722 (0.5842)*	*>.05*	3.323 0.7278	*>.05*	*>.05*	10
Amplitude in mv mean(sd)	3.690 (0.3213)	*4.320 (0.6630)*	*>.05*	5.150 (0.9277)	<.05	<.05	
Conduction velocity m/s mean(sd)	42.344 (5.449)	*47.079 (5.605)*	*>.05*	48.890 (3.816)	<.05	*>.05*	

LEFT TIBIAL NERVE CMAP

The same 10 patients had abnormalities in pre-transplant CMAP of of left tibial nerve.

Parameter	**Pre tx (A)**	***Post tx 1 month (B)***	***p value A vs B***	**Post tx 3 months (C)**	**p value A vs C**	**p value B vs C**	**n**
Distal latency ms mean(sd)	3.689 (1.204)	*3.613 (0.5815)*	*>.05*	3.066 (0.6917)	*>.05*	*>.05*	10
Amplitude in mv mean(sd)	3.820 (0.1932)	*4.3 (0.6498)*	*>.05*	5.270 (1.197)	*<.05*	*<.05*	
conduction velocity mean(sd)	40.1 (1.897)	*47.938 (5.104)*	*<.05*	49.212 (4.955)	*<.05*	*>.05*	

These data show there is significant increase in CV and amplitude and a non-significant decrease in distal latency.

MEDIAN NERVE SNAP

11 patients had abnormal nerve conduction studies in median nerve SNAP values in the pre-transplant period. It showed ↓ amplitude, ↔ conduction velocities , ↔ distal latency. Follow-up data of these 11 patients analyzed. It was associated with improvement in electrophysiology (↑ in CV and amplitude).

Parameter	**Pre tx (A)**	***Post t x 1 month (B)***	***p value A vs B***	**Post tx 3 mon (C)**	**p value A vs C**	**p value B vs C**	**n**
Distal latency ms mean(sd)	2.073 (0.5176)	*1.994 (0.3525)*	*>.05*	2.132 (0.4039)	*>.05*	*>.05*	11
Amplitude in mv mean(sd)	4.636 (0.3802)	*5.318 (0.3430)*	*<.05*	6.264 (0.6562)	*<.05*	*>.05*	
Conduction velocity mean(sd)	48.351 (2.729)	*59.653 (5.051)*	*<.05*	64.784 (5.041)	*<.05*	*>.05*	

MEDIAN NERVE CMAP

6 patients had abnormal nerve conduction studies in Median nerve CMAP values in the pre-transplant period. Follow-up data of these 6patients analyzed. It also showed increased amplitude, CV & decreased latency in the post –transplant period .

Parameter	**pre tx (A)**	***post t x 1 mon (B)***	***p value A vs B***	**post tx 3 mon (C)**	**p value A vs C**	**p value B vs C**	**n**
Distal latency ms mean(sd)	3.098 (0.7223)	*2.915 (0.3122)*	*>.05*	2.892 (0.3158)	*>.05*	*>.05*	6
Amplitude in mv mean(sd)	4.0 (0.0894)	*4.383 (0.2483)*	*<.05*	5.833 (0.3724)	*<.05*	*>.05*	
conduction velocity m/s mean(sd)	51.605 (3.837)	*55.563 (5.169)*	*>.05*	61.358 (6.399)	*<.05*	*>.05*	

DISCUSSION

In this study of 30 patients, only 8 had symptoms / signs of peripheral neuropathy (overt) whereas another 12 had nerve conduction studies evidence of neuropathy (subclinical)

The clinical neuropathy group is associated with relatively older age(36.2 vs28.5y) longer period of CKD(21.5 vs 13.5 m) and dialysis(16.1vs 10.8m).

Those patients in group 1(neuropathic) had only relatively mild symptoms and signs when compared to earlier studies. This could be to initiation of Renal Replacement Therapy (RRT) earlier, shorter duration of dialysis and earlier kidney transplantation.

None of the patients in our cohort had restless leg syndrome. This is in discordance with earlier literature (Ekbom KA et al),which show it was very common in among dialysis patients. This may be due to shorter period of dialysis and CKD in our cohort which may account for the lower incidence.

One patient in group 1 had Hepatitis C infection in the pre-transplant period. However his Serum cryoglobulin was negative.

SENSORY NERVE CONDUCTION STUDIES

In the pre-transplant nerve conduction studies 61.43% had involvement of sural nerve bilaterally. It was associated with ↓ amplitude of SNAP,↓ or↔ Conduction velocity and a near normal distal latency (an axonopathic pattern).

In 4(13.3%) patients sural nerve SNAP was absent bilaterally in pre-transplant period. It is possible that the inability to record a distal sural SAP with surface electrodes may represent early changes of an as yet subclinical neuropathy, or it resulted from the difficulty in distinguishing a low amplitude SAP from noise.

However the nerves could be stimulated in the post transplant period and the neurophysiological parameters (↑amplitude, ↑Conduction velocity) improved between the two NCS done in the post-transplant period. Hence it was most likely due to neuropathic involvement. .

Of all lower limb sensory nerves only the sural provides such a ready index of lower limb sensory function. Sensory conduction studies in lower limb nerves have a higher percentage yield in polyneuropathy than such studies in upper limb nerves in concordance with David burke, et al[35].

Post-transplant studies in sural nerve SNAP showed increasing amplitudes and CV between pretransplant and post-transplant 3 months values($p < .05$)

In the upper limb SNAP of Median nerve showed axonal type of involvement in 11 (36.6%) patients. Its is associated with CMAP abnormalities in 6(20%) patients.

Following transplant there is there is an ↑ in amplitude and CV between 0 and 3 months ($p<.05$) .

MOTOR NERVE CONDUCTION STUDIES

Tibial and median nerves CMAP showed abnormalities of axonopathic type in 10(33.3%)and 6(20%) patients, respectively. These patients also had associated sensory nerve involvement. Post transplant there is an improvement in neuro-physiological parameters with increase in amplitude, CV and decrease in latency(ns).

None of the patients had motor nerve involvement without sensory involvement.

Our study correlates with earlier studies in that involvement in uremic neuropathy is a “dying back" axonal neuropathy with distal symmetrical involvement and length-dependent polyneuropathy, in which the it is that the neurons that have the longest axons appear to be the first to be affected similar to that what was observed. by Dyck PJ, et al[3]

It also concords that there is predominant sensory involvement, with lower limb involved much more than upper limb as have been described by Spencer and Schaumberg et al[26].

The earlier electrophysiological improvement seen in CV and amplitude (CV>Amplitude) may be due to segmental remyelination followed by axonal recovery as suggested as by Bolton, C. F., et al[11]

The almost invariable improvement of neuropathy after transplantation is due to clearance of "Middle molecules" such as methyl guanidine and myoinositol, which has been shown to correlate with the degree of neurotoxicity. These toxins (and the clinical signs of neuropathy) are not greatly reduced by hemodialysis.

The most commonly affected parameter in the present study was sural SNAP amplitude, which was abnormal in a higher percentage of patients than median SNAP amplitude, consistent with the lower limb predisposition of neuropathy similar to the study *by* Arun V. Krishnan, et al

Based on individual patients NCS in post –transplant period we divide them into two cohorts

- Cohort 1- Nerve conduction studies parameters improved
- Cohort 2- Nerve conduction studies parameters worsened or no change

Parameter	Cohort 1	Cohort 2	p value
No	17	3	ns
M:F	13:4	3:0	ns
Age in years	30.4	37.3	ns
Duration of CKD in months	16.3	18.6	ns
Duration of HD in months	11.4	18.5	P< .05

The only statistically significant association in cohort 2 is duration of HD. It probable that the axonapathy may take a longer time to recover. A follow-up study at 6,12 and 24 months would give a answer.

CONCLUSIONS

1. Peripheral neuropathy in CKD is common and its prevalence increases with duration of CKD and Hemodialysis.

2. Many patients may not have overt symptoms but nerve conduction studies can detect abnormalities.

3. It is a predominantly distal symmetrical sensory or sensorimotor neuropathy (sensory>motor) with lower limb involved more than upper limb.

4. Its predominantly axonal polyneuropathy with secondary demyelination.

5. Post renal transplantation there is improvement in conduction velocity and amplitudes earlier due to segmental remyelination.

6. In some patients recovery may take a longer time.

LIMITATIONS OF OUR STUDY

- Our cohort is small (30 patients)
- Male and females are not equally represented.
- NKD is not known in many patients.
- We have not ruled out ANCA negative vasculitis, heavy metal poisoning Amyloidosis as the cases of CKD (or) neuropathy.
- The follow up period is short (3 months post transplant)

The neurotoxic side effects of CNI s (Tacrolimus or Cyclosporine)on long term neurological recovery is not known

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APPENDIX 2- PROFORMA

A STUDY OF PERIPHERAL NEUROPATHY IN CHRONIC KIDNEY DISEASE STAGE -5 AND IT'S OUTCOME AFTER KIDNEY TRANSPLANTATION

NAME AGE

SEX NC

ADDRESS & CONTACT NO

NKD

CKD - DURATION

STAGE

DURATION OF DIALYSIS

COMORBID CONDITIONS:

DIABETES DURATION

HYPERTENSION DURATION

PERSONAL HISTORY:

ALCOHOLISM

SMOKING

DRUG HISTORY:

SYMPTOMS OF PARAESTHESIA

TINGLING

PINS & NEEDLES

HYPOESTHESIA (REDUCTION IN SENSE OF PRESSSURE, LIGHT TOUCH,WARMTH & COLD)

HYPERESTHESIA

HYPALGESIA

ALLODYNIA

GLOVE &STOCKING SENSORY LOSS

WEAKNESS

RESTLESS LEGS

EXAMINATION

PULSE

BLOOD PRESSURE

-SUPINE STANDING

HIGHER CEREBRAL FUNCTIONS

CONSCIOUSNESS

ORIENTATION

MEMORY

SENSORY SYSTEM:

LIGHT TOUCH

PRESSURE

TEMPERATURE

WARM

COLD

PAIN

VIBRATION

JOINT POSITION SENSE

MUSCULOSKELETAL SYSTEM

TONE

POWER

REFLEXES

SUPERFICIAL:

DTR -BICEPS

TRICEPS

SUPINATOR

KNEE

ANKLE

COORDINATION

GAIT

INVESTIGATIONS

INFORMATION SHEET

We are conducting a study, **"A study of Peripheral Neuropathy in CKD and its outcome after renal Transplantation"** among patients attending Government General Hospital, Chennai.

The purpose of this study is to analyse the prevalence, clinical presentation of Peripheral neuropathy in CKD stage V patients & to assess its outcome after renal transplantation .

When you are being evaluated for renal transplantation (with or without overt signs of peripheral neuropathy) we will include you in this study with your consent.

We may be using you to perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

NERVE CONDUCTION STUDY

CMAP

Nerve	Latency	Amplitude	Conduction Velocity

SNAP

Nerve	Latency	Amplitude	Conduction Velocity