PERIPHERAL NEUROPATHY IN CHRONIC UREMIA – A STUDY OF CLINICAL AND ELECTROPHYSIOLOGICAL FEATURES AND CHANGES IN PATIENTS ON INTERMITTENT PERITONEAL DIALYSIS

Dissertation submitted in partial fulfillment of regulation for the award of

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CERTIFICATE

*This is to certify that the dissertation entitled "**PERIPHERAL NEUROPATHY IN CHRONIC UREMIA – A STUDY OF CLINICAL AND ELECTROPHYSIOLOGICAL FEATURES AND CHANGES IN PATIENTS ON INTERMITTENT PERITONEAL DIALYSIS"** , herewith submitted by **Dr. BIDHUN KURIAKOSE PAULOSE**, post graduate in General Medicine Coimbatore Medical College Hospital is the record of a bonafide research work carried out by him under our guidance and supervision from July 2007 to June 2009.*

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DECLARATION

I solemnly declare that the dissertation titled **"PERIPHERAL NEUROPATHY IN CHRONIC UREMIA – A STUDY OF CLINICAL AND ELECTROPHYSIOLOGICAL FEATURES AND CHANGES IN PATIENTS ON INTERMITTENT PERITONEAL DIALYSIS"** was done by me at Coimbatore Medical College hospital from July 2007 to June 2009 under the guidance and supervision of **Prof Dr. S USHA M.D.**, Unit Chief, Medical Unit VI.

This dissertation is submitted to the Tamilnadu Dr. MGR Medical University towards the partial fulfillment of the requirement for the award of MD Degree in General Medicine (Branch I).

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CONTENTS

INTRODUCTION

Chronic Kidney Disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate.[1] The prevalence of CKD in India is 0.78% -0.8% [2]. The crude and age adjusted incidence rates of stage 5 CKD or End Stage Renal Disease (ESRD) is 151 and 232 per million population repectively.[3] Uremia is defined as a clinical syndrome associated with fluid, electrolyte, and hormone imbalances and metabolic abnormalities, which develop in parallel with deterioration of renal function.

Peripheral neuropathy is a severe, disabling complication of uremia. Uremic neuropathy is a distal sensorimotor polyneuropathy supposedly caused by uremic toxins. The severity of neuropathy is correlated strongly with the severity of the renal insufficiency. Uremic neuropathy is considered a dying-back neuropathy or central-peripheral axonopathy associated with secondary demyelination. However, uremia and its treatment can also be associated with mononeuropathy at compression sites.

Charcot suspected the existence of uremic neuropathy in 1880.[4] Since the introduction of haemodialysis and renal transplantation in the early 1960s, uremic neuropathy has been investigated thoroughly. Asbury, Victor, and

Adams[5] described the clinical and pathologic features of uremic peripheral neuropathy in detail in 1962.

In 1971, Dyck and colleagues[6] established the current concept of uremic neuropathy based on their extensive nerve conduction studies in vivo and in vitro and on light and electron microscopy studies. Using quantitative histology, they demonstrated axonal shrinkage. Myelin sheaths appeared to be affected out of proportion to axons. The dysfunction of the neuron, rather than the Schwann cell, resulted in a decrease in the diameter of the axon, rearrangement of myelin, and finally, complete degeneration of the axon.

The peripheral neuropathies have been variably described by the patients as paraesthesias, pain, weakness and atrophy of lower limbs, muscle cramps, restless legs and sometimes presents like Guillain-Barre like features. Various modalities of renal replacement have restored the peripheral nerve functions or sometimes halt its progression. The rate of reversibility depends on various parameters such as duration symptoms, modality of renal replacement, adequacy of dialysis and so on. Of all the modalities, a matched renal transplant offers the best results for the improvement of symptoms.

This study is targeted to highlight the presence and various attributes of clinical as well as subclinical peripheral neuropathy in patients who are undergoing intermittent peritoneal dialysis programme in our hospital.

AIMS AND OBJECTIVES

The present project was undertaken to study

1. The clinical and electrophysiological features of peripheral neuropathy in patients with chronic renal failure.

2. Variations in clinical and electrophysiological features of peripheral neuropathy during the course Intermittent Peritoneal Dialysis.

3. The correlation of various serological, hematological parameters to that of uremic peripheral neuropathy.

REVIEW OF LITERATURE

1) Incidence:

Peripheral neuropathy in patients with renal failure has been recognized for over 100 years. This disorder, however, was not fully appreciated until the early 1960s. Prior to the institution of chronic dialysis therapy, majority of patients with end-stage renal disease probably did not live long enough to develop clinically apparent neuropathy. Peripheral neuropathy occurs in upto 65% of patients prior to or shortly after starting upon dialysis for CRF [7]. According to Nielsen, of 109 patients in Denmark with chronic renal failure, 77% reported clinical symptoms, and 51% had clinical signs of a neuropathy.[8] Bolton and Young claimed the incidence of clinical uremic neuropathy to be 10-83% in patients with renal failure.[9] Males develop peripheral neuropathy several times frequently than females. The basis of this interesting observation remains unexplained. Nielsen reported the male-to-female ratio as 60:49 in his 109 patients.[8] Individual serologic and biochemical abnormalities (calcium, magnesium, phosphate, urea, creatinine etc) do not correlate well with the incidence of neuropathy. The chronicity and severity of renal failure appear to be more important to the development of neuropathy. [7, 8, 10] No reported study has examined the role of race in uremic neuropathy. Uremic polyneuropathy

may occur at any age once the degree of renal failure is sufficient. Apart from the various aspects of peripheral neuropathy, uremia causes various autonomic as well as central nervous system manifestations.

2) Etiology of uremic peripheral neuropathy:

Although, the metabolic derangements responsible for uremic neuropathy have not been identified, a number of observations have been made with regard to potential urotoxins that might lead to the uremic neuropathy. These include guanidine compounds, parathyroid hormone, middle molecules, myoinositol and so on. Although any or all of these agents may play a role in the development of uremic neuropathy, the actual evidence that they are bonafide neurotoxins is scant.

Numerous studies have been carried out in order to identify which of the many compounds that are elevated in uremic subjects is truly a uremic toxin. In the early days of dialysis, so-called “middle molecules” were said to be likely candidates as uremic toxins.[11] Although evidence was mainly observational, the concept lasted a long time.[12] The observation that uremic neuropathy improves with dialysis has led most observers to conclude that neuropathy results from accumulation of a dialyzable metabolite. Schribner has speculated that these substances might be in the middle molecule range (compounds with molecular

weights of 500-2,500 Da); compounds of this size cross most dialysis membranes much more slowly than smaller molecules like creatinine and urea, which are the usual measure of biochemical control of uremia.[10] Thus, one might theoretically achieve chemical control of uremia, while failing to remove the offending toxins of the middle-molecular range. Observations supporting this point of view have been (1) that control of neuropathy may, depend on increased hours of dialysis per week, beyond that which is necessary for the control of uremia and (2)that peritoneal dialysis appears to be associated with a lower incidence of neuropathy, inspite of persisting high levels of urea and creatinine, suggesting that peritoneal membrane passes toxic molecules more readily and selectively than cellophane membranes used in haemodialysis machines.[10] In one study by Raskin et al however, which included 5 uremic patients with neuropathy and 25 without neuropathy, the correlation between a calculated middle molecule concentration and the presence of neuropathy was poor.[10] Also, maneuvers that might be expected to increase the removal of middle molecule have had little demonstrable effect in peripheral nerve function. The ‘middle-molecule’ hypothesis is thus attractive, but there is as yet little rigorous evidence to support it.

A decade later, criteria were established by Bergstom and Furst for uremic toxins. The criteria are as follows[13] (1) the compound should be

chemically identified and quantifiable in biologic fluids, (2) the concentration of the substance in plasma from uremic subjects should be higher than that found in subjects who do not have renal insufficiency, (3) the concentration of the substance in plasma should somehow correlate with specific uremic symptoms, and these should be alleviated with reduction of the substance to normal, (4) the toxic effects of the substance should be demonstrable at concentrations found in plasma from uremic patients.

Uremic neurotoxins would imply retention of solutes that have specific detrimental effects upon nervous system function, whether peripheral nervous system or central nervous system. [14, 15]

There are at least three different types of uremic solutes that are potentially toxic and that can be characterized.[16] These include (1) small water soluble compounds[14] (2) middle molecules, (3) protein-bound compounds. Most of the small water soluble compounds, such as urea and creatinine, are not particularly toxic and are easily removed with dialysis. A low molecular weight compound for which there is increasing evidence for a role in the pathogenesis of stroke, atherosclerosis, and cardiovascular disease is asymmetric dimethylarginine (ADMA). [17, 18]

Presently no single uremic toxin has been shown to affect peripheral nerve function. Most of the evidence suggests that uremic neuropathy may be related

to anatomical nerve damage and also to cumulative effects of multiple toxic agents.[19, 20] Possible uremic toxins are listed here, but most remain unproven.

- **Small water-soluble compounds**
    - Guanidines
    - Asymmetric dimethylarginine
    - Creatinine
    - Purines
    - Oxalate
    - Phosphorus
    - Urea
- **Middle, large molecules**
    - Advanced glycosylated end products
    - Parathyroid hormone
    - Oxidation products
    - Peptides (beta-endorphin, methionine-enkephalin, beta-lipotropin, granulocyte inhibiting proteins I and II, degranulation-inhibiting protein, adrenomedullin)
    - Beta 2-microglobulin
    - Complement factor D

- **Protein-bound compounds**
    - Indoles
    - 3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid
    - Hippuric acid
    - Homocysteine
    - Indoxyl sulfate
    - P-cresol
    - Polyamines

Guanidine Compounds

Guanidine compounds have been postulated to be “uremic toxins” for many years, [21] based on possible detrimental effects on the central nervous system. Recent studies have demonstrated that several guanidino compounds are present in uremic brain [22] and may be important in the etiology of uremic encephalopathy.[23] There are at least four guanidino compounds that are experimental convulsants. These guanidino compounds appear to work by activation of N-methyl-D-aspartate (NMDA) receptors by guanidino-succinic acid (GSA). Activation of the NMDA receptor is a major pathologic mechanism in the etiology of several types of brain damage, including head trauma [24] and stroke. [25, 26]

In addition, guanidine compounds have a depressant effect on mitochondrial function.[27] In brain of uremic patients, guanidino compounds were measured in 28 different regions.[28] Guanidinosuccinic acid levels were elevated by up to 100-fold in uremic brain versus control brain, and levels increased with increasing extent of uremia. The brain levels of guanidinosuccinic acid in uremic brain were similar to those observed in normal animal brain following injection to blood levels, which cause convulsions.[28]

Guanidines inhibit neutrophil superoxide production, can induce seizures, and suppress natural killer cell response to interleukin-2.[29] Other guanidines, which are arginine analogues, are competitive inhibitors of nitric oxide (NO) synthetase, which impairs removal of AGEs[30] and can lead to vasoconstriction, hypertension, ischemic glomerular injury, immune dysfunction, and neurological changes.[29] Two other low molecular weight compounds that have been recently studied appear to be important uremic toxins are diotyrosine-containing cross-linked protein products (designated AOPPs) and asymmetric dimethylarginine (AMDA). [17, 18] The AOPPs behave as do mediators of inflammation and are found in very high concentration in the plasma of dialysis patients. ADMA is an inhibitor of nitric oxide and is associated with high plasma levels of homocysteine.[18]

With established renal insufficiency, guanidines, which are competitive inhibitors of nitric oxide (NO) synthetase, will rapidly accumulate in blood, and their presence will impair removal of AGEs[30] and can lead to worsening hypertension, immune dysfunction,[31] and neurological changes,[32] such as stroke.[33]

Advanced Glycation End Products

Advanced glycosylation (glycation) end products (AGEs) can modify tissues, enzymes, and proteins and may play a role in the pathogenesis of dialysis-associated amyloidosis.[34] Advanced glycosylation end products may also play a role in the pathogenesis of diabetic nephropathy.[35] Advanced glycosylation end products are markedly elevated in plasma of patients with ESRD.[36] The AGEs react with vascular cells to inactivate endothelial nitric oxide and may increase the propensity of ESRD patients to develop hypertension. Current dialysis therapy is relatively ineffective in removal of AGEs, so that there is accumulation of AGEs in patients with ESRD, particularly those with diabetes mellitus. The AGEs are “middle molecules” and have the potential to cause tissue damage and lead to hypertension. Thus, at least some “middle molecules” may actually be deleterious in patients with ESRD, and they are poorly removed with conventional dialysis.[36] There is evidence that angiotensin converting enzyme antagonists decrease the

formation of AGEs[37] Protein-bound compounds (toxins) are not substantially removed by dialysis, and almost all are lipophilic. Such compounds include polyamines such as spermine.[38] Spermine is postulated to be a uremic toxin and appears to react with the N-methyl-D-aspirate (NMDA) receptor, which affects calcium and sodium permeability in brain cells.[38] Stimulation of the NMDA receptor in brain is the final common pathway for brain cell death in a number of pathological pathways. [39, 40] The uremic state is associated with increased oxidative stress, resulting in protein oxidation products in plasma and cell membranes. There is eventual alteration of proteins with formation of oxidized amino acids, including glutamine and glutamate.[34] Such reactions may eventually lead to stimulation of the NMDA receptor in brain, with brain cell damage or death.

Parathyroid Hormone

In patients dying with acute or chronic renal failure, the calcium content in brain cerebral cortex is significantly elevated. [41, 42, 43] Dogs with acute or chronic renal failure show increases of brain gray matter calcium and have EEG changes similar to those seen in humans with acute renal failure. [44, 45] In dogs, both the EEG and brain calcium abnormalities can be prevented by parathyroidectomy. Conversely, these abnormalities can be reproduced by administration of parathyroid hormone to normal animals while maintaining

serum calcium and phosphate in the normal range. Thus, parathyroid hormone is essential to produce some of the central nervous system manifestations in the canine model of uremia. [43, 46] In addition, hyperparathyroidism in subjects with chronic renal failure is strongly associated with multiple types of cardiovascular disease, including myocardial infarction, congestive heart failure, [47] and stroke.[48]

Parathyroid hormone is known to have central nervous system effects in humans even in the absence of impaired renal function. Neuropsychiatric symptoms have been reported to be among the most common manifestations of primary hyperparathyroidism.[49-52] Patients with primary hyperparathyroidism also have EEG changes similar to those observed in patients with acute renal failure. [41, 53] The common denominator appears to be elevated plasma levels of parathyroid hormone. [41, 45] In patients with acute renal failure the EEG is abnormal within 18 hours of the onset of renal failure and is generally not affected by dialysis for periods of up to 8 weeks.[41] In patients with either primary or secondary hyperparathyroidism, parathyroidectomy results in an improvement of both EEG and psychological testing, suggesting a direct effect of parathyroid hormone on the central nervous system. Similarly, dialysis results in a decrement of brain (cerebral cortex) calcium toward normal in both patients and laboratory animals with renal failure concomitant with

improvement of the EEG. [41,42,43,45] In uremic patients, both EEG changes and psychological abnormalities are improved by parathyroidectomy or medical suppression of parathyroid hormone.[42] Parathyroid hormone, a high brain calcium content, and abnormal calcium transport are probably responsible, at least in part, for some of the encephalopathic manifestations of renal failure.

The mechanisms by which parathyroid hormone might impair central nervous system function are now better understood but far from complete. The increased calcium content in such diverse tissues as skin, cornea, blood vessels, brain, and heart in patients with hyperparathyroidism suggests that parathyroid hormone may somehow facilitate the entry of Ca^{2+} into such tissues.

The finding of increased calcium in the brains of both dogs and humans with either acute or chronic renal disease and secondary hyperparathyroidism is consistent with the conception that part of the central nervous system dysfunction and EEG abnormalities found in acute renal failure or chronic renal failure may be due in part to a parathyroid hormone mediated increase in brain calcium. Calcium is essential for the function of neurotransmission in the central nervous system as well as a number of intracellular enzyme systems. Increased brain calcium content could disrupt cerebral function by interfering with either of these processes. [54,55]

Transketolase

. It has been suggested that transketolase, a thiamine dependent enzyme in the pentose phosphate pathway found in the erythrocytes and neural tissues, is inhibited by the accumulation of low molecular weight toxins in uremia, which might lead to subsequent neuropathy.[10] It has been demonstrated that erythrocyte transketolase activity was frequently inhibited in pre-dialysis blood samples of patients on long term haemodialysis, but rose sharply in the post-dialysis blood samples; but its relationship to neuropathy or uremia is yet to be settled. In addition, it is not known whether other important enzyme systems are equally or more affected by the accumulation of uremic toxins, nor is known whether transketolase plays a critical role in the maintenance of normal peripheral nerve function.[56,57,58]

Myoinositol

Elevated plasma levels of myoinositol in patients with chronic renal failure have been suggested as a factor in the development of uremic neuropathy. Myoinositol is a water soluble, cyclic hexitol, with a molecular weight of 180 Daltons. It is a precursor of phosphoinositides, a class of phospholipids, whose rapid turnover in neural tissues has resulted in speculation linking their metabolism to the functional activity of the nerve. The kidney probably plays an important part in both myoinositol metabolism and excretion.

Investigators have shown a linear relationship between urea nitrogen retention and myoinositol levels. Hypermyoinositolemia has been produced in rats with a diet that contains 35% myoinositol; slowed motor nerve conduction velocities were induced in sciatic nerve of these animals. Conduction velocities became normal after a normal diet was instituted. In brief, myoinositol accumulation in progressive uremia, along with accumulation of many other metabolites, may correlate with nerve conduction decrement, but its role if any, in precipitating neuropathy, remains unclear.[6, 9, 10]

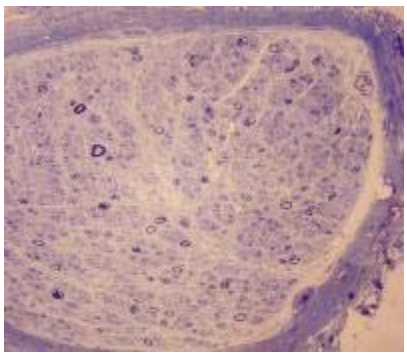
3) Pathologic features:

Although clinical studies of uremic polyneuropathy have been numerous, pathologic studies have been relatively few. Most of these are sural nerve biopsy studies. Some confusion regarding the essential morbid anatomy of uremic neuropathy appears to have been created by several studies; in which demyelinative aspects of the neuropathy were emphasized. The disorder was widely assumed to be caused by metabolic dysfunction of the Schwann cells. However, in the original clinical and pathological description of this disorder by Asbury *et al*,[5] the pathological findings were typical of those that may be seen in any neuropathy involving axonal degeneration. Myelin sheaths appeared to be affected out of proportion to axons, although a critical judgment about the

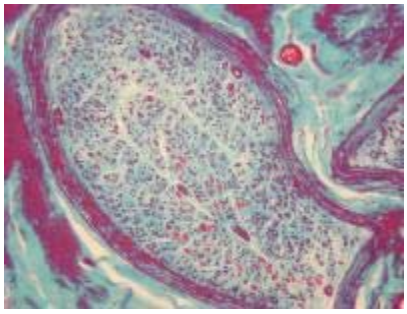
presence of segmental demyelination could not be made because teased nerve fiber preparations were not carried properly. Fraser and Arieff [59] postulated that neurotoxic compounds deplete energy supplies in the axon by inhibiting nerve fiber enzymes required for maintenance of energy production. Although all neuronal perikarya would be affected similarly by the toxic assault, the long axons would be the first to degenerate since the longer the axon, the greater the metabolic load that the perikaryon would bear. In toxic neuropathy, dying back of axons is more severe in the distal aspect of the neuron and may result from a metabolic failure of the perikaryon. Energy deprivation within the axon may be especially critical at nodes of Ranvier, since these nodes demand more energy for impulse conduction and axonal transport.

Nielsen[8] theorized that peripheral nerve dysfunction was related to an interference with the nerve axon membrane function and inhibition of Na^+/K^+ - activated ATPase by toxic factors in uremic serum. Bolton [9] postulated that membrane dysfunction was occurring at the perineurium, which functioned as a diffusion barrier between interstitial fluid and nerve, or within the endoneurium, which acted as a barrier between blood and nerve. As a result, uremic toxins may enter the endoneural space at either site and cause direct nerve damage and water and electrolyte shifts with expansion or retraction of the space.

Dyck *et al* [6] in their study of two patients with uremic peripheral neuropathy, concluded that it is a primary axonal degeneration. All fiber sizes, both myelinated and unmyelinated are affected, although the largest and the most distal fibers are selectively vulnerable. Segmental demyelination occurs in the fibers about to undergo breakdown, although nerve fibers degenerating rapidly probably bypass the demyelinating phase. Qualitative changes seen on electro microscopy include splitting of the myelin lamellae, and their separation from the subjacent axolemma and minor mitochondrial abnormalities. No consistent abnormalities of neurofilaments or neurotubules are recognized. These changes are abnormal, but not distinctive for uremic neuropathy.[7]



Semithin transverse section of biopsied sural nerve in uremic neuropathy. The nerve shows severe axonal loss of large and small fibers. Toluidine blue stain, 200X.

 Modified trichrome-stained sural nerve in uremic neuropathy. The same nerve exhibited marked loss of myelinated fibers. 200X.

4) Clinical features:

Uremic neuropathy was described by Asbury and colleagues[5] as a distal, symmetrical, mixed motor and sensory polyneuropathy that affects legs more than arm. There is considerable clinical variation in the severity, tempo of progression, presence of dysesthesias and ratio of motor to sensory signs, but pattern of distribution (i.e., distal, graded, symmetrical, feet more than arms) seems to be inviolate.[7]

The restless leg syndrome occurs frequently in uremic patients and probably heralds peripheral nerve involvement by the uremic process.[10, 59] The syndrome consists of creeping, crawling, prickling pruritic sensations deep with in the lower limbs, which almost always are worse in the evening and are relieved by the movements of the limbs. Nielsen [60] found these symptoms in over 40% of 109 patients with varying degrees of renal failure. These symptoms were reported by an equal number of patients with and without clinical neuropathy (56% and 44% respectively), raising doubts about the significance

of ‘restless legs’. Whereas some authors (Callaghan as quoted by Asbury[5] and Thomas[61]) consider them to be important and early sign of peripheral nerve damage.

Muscle cramps of the distal extremities occur commonly in uremic patients, many of whom lack evidence of neuropathy. Since cramps often occur in acute uremia, they probably represent shifts of fluids into muscle or the effects of uremic toxins upon the muscle or the neuromuscular junction.[10]

‘Burning feet’ identical to those encountered in alcoholic are according to Tytler[62], a frequent early manifestation of neuropathy, but Neilson[60] found that only 7 of 109 patients complained of such symptoms, although 40% of his patients had some sensory symptoms. Most patients with uremic neuropathy have distal dysesthesias, often as an early symptom, described in a variety of ways such as painful tingling or electric feelings, unpleasant raw sensations resulting from mild cutaneous stimulation of fingers or toes, band like constrictive feelings around the feet and ankles or aberrant sensations of swelling and turgidity of the fingers or toes or the distal extremities being twisted into bizarre positions.[7]

Impaired vibratory sense in the lower limbs and loss of deep tendon reflexes, first ankle jerks and then knee jerks, are the usual first signs of peripheral neuropathy.[7.10, 60] The rate of progression of the neuropathy varies

widely among patients, in general it evolves slowly over several months, plateau and then remain stationary despite worsening renal failure.[7]

Uremic neuropathy is one type of central-peripheral axonopathies, also known as dying-back polyneuropathies, which have been described by Spencer and Schaumberg.[63] The causes of such central-peripheral axonopathies include many types of toxic compounds. These include neuropathies associated with diabetes, multiple myeloma, amyloidosis, certain hereditary polyneuropathies, and uremia.[63] There is also an associated degeneration of the spinal cord, particularly involving posterior columns, as well as other portions of the central nervous system. Such findings are usually attributed either to local central nervous system disease or to damage of spinal ganglion cells secondary to ascending peripheral nervous system damage. It is likely, however, that the central nervous system components of distal axonopathies. The clinical characteristics of such distal axonopathies as described by Schaumberg and Spencer include the following [63,64]:

1. Insidious onset. In most human toxic neuropathies, there is a steady low-level exposure. Because only the distal portion of selected, scattered fibers are affected, the patient may still function well despite the axonal degeneration.

2. Onset in legs. Large and long axons are affected early, and fibers of the sciatic nerve are especially vulnerable.

3. Stocking-glove sensory loss. Degeneration in the distal axon proceeds toward the cell body, resulting in clinical signs in the feet and hands initially.

4. 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.

5. Moderate slowing of motor nerve conduction. In demyelinating neuropathies, motor nerves or roots are diffusely affected; in axonal neuropathies, scattered motor fibers are often intact and motor nerve conduction velocity may appear normal or only slightly slow despite severe paresis.

6. Normal cerebrospinal fluid protein content. Pathologic changes are usually distal and nerve roots are spared.

7. 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.

8. Residual disability. Most toxic axonopathies are characterized by tract degeneration of long, large-diameter fibers in the central nervous system concomitant with changes in the peripheral nervous system. Signs of lesions in the corticospinal and spinocerebellar pathways may not be clinically apparent if there is severe peripheral neuropathy. However, on recovery from the neuropathy, there may be spasticity or ataxia.

It can readily be recognized that these features are similar to many descriptions of uremic neuropathy. [64, 65] The cellular basis for distal axonopathies, however, remains unclear. Spencer and associates [66] 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. Among uremic patients who also have diabetes mellitus, oxidative stress, including superoxide accumulation, and accumulation of advanced glycation end products (AGEs) appear to be major contributors to the development of uremic neuropathy. [8,16] In experimental diabetic neuropathy, there was a significant reduction in desert hedgehog mRNA,[67] which was substantially improved by treatment with sonic hedgehog-IgG fusion protein.[67] Such an approach may be promising in the management of uremic neuropathy as well.

In addition to uremic neuropathy, uremic myopathy is a frequent cause of weakness, exercise limitation, and rapid onset tiredness in dialysis patients. [68, 69] Later on, muscle wasting occurs, particularly in the limb muscles

In general, there are two broad categories of peripheral neuropathy. These are described in terms of the pattern of involvement of the peripheral nervous system. First, there are processes that result in a bilaterally symmetric disturbance of function that can be designated as polyneuropathies. Polyneuropathy tends to be associated with agents such as toxic substances, metabolic disorders (uremia, diabetes, deficiency states), and certain examples of immune reaction that act diffusely on the peripheral nervous system. The second category comprises isolated lesions of peripheral nerves (mononeuropathy) or multiple isolated lesions (multiple mononeuropathy). In

severe symmetric polyneuropathies, a generalized loss of peripheral nerve function may occur, and the impairment is usually maximal distally in the limbs. A mixed motor and sensory polyneuropathy with a distal distribution results in weakness and wasting that is most frequently observed peripherally in the arms and legs. There are also distal sensory changes of “glove and stocking” distribution. In those neuropathies that involve “dying back” of the axons from the periphery,[64] it is possible that the neurons that have the longest axons to maintain appear to be the first to suffer.

Clinically, uremic polyneuropathy cannot be distinguished from the neuropathies associated with certain other metabolic disorders such as diabetes mellitus, chronic alcoholism, and various deficiency states. The occurrence of neuropathy bears no relationship to the type of underlying disease process (i.e., glomerulonephritis or pyelonephritis). However, certain diseases that can lead to renal failure may simultaneously affect peripheral nerve function in a manner separate from the manifestations of uremia. Such diseases include amyloidosis, multiple myeloma, systemic lupus erythematosus, polyarteritis, nodosa, diabetes mellitus, and hepatic failure [5]The clinical manifestations of uremic neuropathy are characterized by several different stages. It appears that when glomerular filtration rate exceeds 12 ml per minute, clinical evidence of neuropathy is generally absent.

Many patients with chronic renal failure who are neurologically asymptomatic may exhibit abnormalities on physical examination. They may also have evidence of autonomic neuropathy such as impotence and postural hypotension. Moreover, in patients who have renal insufficiency, abnormal nerve conduction may be present in the absence of symptoms or abnormal findings on physical examination. Additionally, alternations in nerve conduction do not necessarily indicate structural changes in the peripheral nerves. It is often overlooked that many patients with ESRD have autonomic dysfunction, which in turn results in impaired baroreceptor sensitivity, which can impair blood pressure regulation.[70]

To summarize,

- Typical uremic neuropathy symptoms are insidious in onset and consist of a tingling and prickling sensation in the lower extremities.
    - Paresthesia is the most common and usually the earliest symptom.
    - Increased pain sensation is a prominent symptom.
    - Weakness of lower extremities and atrophy follow the sensory symptoms. As disease progresses, symptoms move proximally and involve the upper extremities.

    - Muscle cramps and restless legs syndrome were reported by 67% of uremic patients. These symptoms also can be seen in uremic patients without neuropathy.
    - Patients report that crawling, prickling, and itching sensations in their lower extremities are relieved partially by movement of the affected limb.
- A Guillain-Barré type of presentation is rare, but a rapidly progressive course with respiratory failure has been reported. Generalized limb weakness develops over days or weeks with imbalance, numbness, and diminished reflexes.
- Mononeuropathies in the form of compressive neuropathy can occur in the median nerve at the wrist, in the ulnar nerve at the elbow, or in the peroneal nerve at the fibular head.
    - Already partially dysfunctional peripheral nerves may be more susceptible to local compression.
    - Connective tissues and tendons are found to have amyloid deposits surrounding the carpal tunnel.
    - Multiple distal mononeuropathies present in an extremity following the construction of arteriovenous fistulas because of distal ischemia.

Summary of physical examination findings

- Impaired vibratory perception and absent deep tendon reflexes are the most common clinical signs, noted in 93% of patients. 16% had sensory loss to pinprick in a glove and stocking distribution.
- Paradoxical heat sensation was found in the feet of 42% of patients with chronic renal failure, as compared to less than 10% of healthy controls.
- Muscular weakness and wasting were observed in 14%.
- Cranial nerve involvement is rare; transient nystagmus, miosis, impairment of extraocular movement, and facial asymmetry may be found rarely on physical examination.
- Focal weakness, sensory loss, and positive Tinel sign at compression sites can be observed in the median, ulnar, or peroneal nerve distribution if compressive mononeuropathy is present.

5) Effect of Dialysis on peripheral neuropathy:

In most patients with end stage renal disease and neuropathy, the neuropathy will either stabilize or improve with regular dialysis therapy.[10, 71,72,73,74] In Patients with mild neuropathy dialysis may result in apparent recovery. When patients have severe neuropathy before the dialysis is begun, recovery may be only partial, even after several years of dialysis.[10] The most

important variable that determines the effects of dialysis on the nerve function seems to be the GFR of the patient before onset of dialysis. Peritoneal dialysis seems to be associated with lower incidence of peripheral neuropathy.

6) Intermittent Peritoneal Dialysis:

It typically involves 12-24 hours of frequent peritoneal dialysis exchanges, usually delivered by a cycler in a hospital or in-center setting, two to three times weekly. The procedure is not the favored modality because of the inadequate clearances due to its intermittent nature, requirement to be in hospital and time consuming nature. However, IPD might be the only option for elderly dialysis patients with significant co-morbidities, unable to undergo haemodialysis (HD) or PD at home without any assistance, for various reasons.[10] Recent studies prove that IPD is associated with fewer episodes of peritonitis, fewer admissions, and longer survival than is often believed.[75] Suitable patients in whom palliative care alone seems inappropriate should not be denied a trial of IPD if they choose.[76]

7) Hemodialysis:

A great number of patients on long-term haemodialysis have different forms of clinically manifested uremic neuropathy (60–75%). Paresthesias is an early symptom of uremic neuropathy in patients on haemodialysis. The prevalence of these symptoms in different studies varies from 6% to 32%

Prolonged hemodialytic treatment does not influence the clinical course of uremic neuropathy but leads to evident deterioration of electrophysiological findings.[77-81]

8) Renal transplantation:

Renal transplantation offers the best modality for restoring the peripheral nerve functions in patients with ESRD. Most of the studies have proved the restoration of clinical and electrophysiological features to near normalcy by the normally functioning nephrons in the transplant kidney. Nielson *et al* [62] measured sensory and motor nerve conduction in 22 patients after successful renal transplantation. In this longitudinal study electrophysiological signs of peripheral nerve dysfunction in uremia resolved after successful renal transplantation in most patients, in keeping with the remission of clinical neurological manifestations. The remission was in two phases; an early, rapid phase was followed by a late, slow phase. The recovery was more rapid and complete in distal than in proximal segments. The rapid improvement in the nerve conduction velocity within weeks demonstrates the superiority of a successful renal transplant over hemodialysis in relieving uremic manifestation, Bolton *et al* [82] also emphasized this point. In some series, the disability persists in those on long tern dialysis in whom permanent damage has occurred.[82,83]

9) Electrodiagnosis:

The most widely used measure of disordered functioning of peripheral nerve has been the determination of motor nerve conduction velocities.[7] Preswick in 1964 [84] has shown that slowing of nerve conduction is frequent occurrence in uremic patients with no other symptoms or signs of neuropathy. Jebsen [85] showed that in patients with moderate renal failure not requiring dialysis, severe creatinine elevation correlated with decreased velocity of motor nerve conduction.

Several possible uremic toxins have been identified that appear to be correlated with depression of motor nerve conduction velocity (MNCV) in laboratory animals. [86, 87] The MNCV has become a standard test for assessment of nerve function, although it has many flaws. Most studies do not take into account the fact that (1) depressed MNCV is cyclical, with abnormal low values one day and normal values the next,[88] (2) there is a day-to-day variation in MNCV that approaches 20%, and (3) 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. [89-92] 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. The motor nerve conduction velocity (MNCV) is a test that is frequently used to assess peripheral neuropathy. The test, however, is somewhat unreliable because there is a large normal variation in MNCV[93] and the test has very limited utility in detecting moderate impairment of peripheral nerve function. Sensory nerve conduction velocity (SNCV) is more sensitive than MNCV, but the test is quite painful and most patients do not permit repeated tests.

Clinical neuropathy appeared generally in patients whose renal function deteriorated most markedly and whose conduction velocities slowed the most. Neilson[19] further pointed out the high degree of correlation between diminishing creatinine clearance and reduction of conduction velocities. He also demonstrated that the slowing was generalized, motor and sensory, proximal and distal, and in arms as well as legs. Later several investigators[94] have demonstrated that late responses, utilizing the H-reflex and F-wave studies, became abnormally slowed early in the course of chronic renal failure at a time when standard motor nerve conduction velocities are still normal. The electrophysiological deterioration during long term haemodialysis is best seen through worsening of the H-wave of tibial and F-waves of peroneal and tibial nerves [95,96]

MATERIAL AND METHODS

This study was done in thirty adult patients attending Intermittent Peritoneal Dialysis program of the Nephrology Department in Coimbatore Medical College and Hospital, Coimbatore.

Inclusion Criteria :- All patients had advanced stages of chronic kidney disease, defined as kidney adamage for 3 months or longer, manifested as either pathologic abnormalities or mrkers of kidney damage, including abnormalities in composition of blood or urine, abnormality renal imaging findings, and a glomerular filtration rate (GFR) of 15-29 ml/min/1.73m^2 (Stage IV) and GFR <15ml/min/1.73m^2 (Stage V or End Stage Renal Disease). All patients at the time of evaluation were on intermittent peritoneal dialysis, 18-24 hr per sitting, 2-3 times a week. All the patients were having intermittent peritoneal dialysis as the sole mode of renal replacement therapy.

Exclusion Criteria :- Those who had evidence of diabetes, collagen vascular disorders, amyloidosis, or any primary neurologic disorder and those receiving medications known to affect peripheral nerve function were excluded from the study. Alcoholics were also excluded.

The eligible patients were enrolled for the study by simple random sampling, after obtaining informed consent. GFR was estimated by calculating creatinine clearance, as per Cockroft-Gault formula.

Clinical evaluation:- The history comprised of a through inquiry into all symptoms related to peripheral neuromuscular symptoms. The patients were requested to give a detailed description of the character and localization of sensory symptoms, the time of onset, changes in intensity and their significance for their normal activity. The extend of muscular weakness was also inquired into. Each patient was subjected to a detailed physical examination which included testing of cutaneous sensitivity to (1) light touch and pin prick, (2) vibration sense,(3) bulk and tone of muscles, strength of muscles (Grading of weakness was done as per Medical Research Council Scale) and (5) deep tendon reflexes. The results were entered in a standard proforma.

Technique of Nerve Conduction Velocity determination: - a) Motor conduction velocity: - In tests on median motor nerve, a surface electrode was attached to the skin over the abductor pollicis brevis muscles. A reference electrode was attached to the distal phalanx of the thumb and a ground electrode placed on the dorsum of the hand. The median nerve was supramaximally stimulated first at the wrist and then at the elbow. The

stimulus artifact and the muscle action potential were displayed on the oscilloscope and then recorded. The time latency in milliseconds from stimulus at the wrist to onset of muscle response was subtracted from the latency after stimulation at the elbow. The lateral popliteal nerve was stimulated at the ankle and the knee and the muscle response recorded from the extensor digitorum brevis. The posterior tibial nerve was stimulated at the ankle and knee, and the muscle response recorded from abductor pollicis.

.

b) Sensory conduction velocities were determined orthodromically for median nerve and antidromically for sural nerve. The digital branches of the median nerve was stimulated at the base of the index finger using ring electrodes and evoked potentials recorded from the median nerve at the wrist, using need electrodes. The sural nerve was stimulated on the posterior aspect of the distal third of the leg, at a point slightly lateral to the midline. The evoked potentials were recorded using needle electrodes, from below the lateral malleolus.

RMS EMG EP MARK-II electromyograph was used for recording the nerve conduction velocities.

Statistical methods:

Conduction velocities were expressed as standard deviation from the arithmetic mean. The student‘t’ test was employed as the test of significance when comparing the samples.

Ten normal healthy controls were drawn from hospital staff and relatives of the patients to generate the normal values of the nerve conduction studies.

Peripheral neuropathy was classified into mild, moderate and severe according to the following criteria[85].

i) Mild neuropathy:

Sensory - absent vibratory sense in feet.

Motor - Grade 4 strength distally in hands or feet.

ii) Moderate neuropathy:

Sensory - absent vibratory sense below knee or decreased pain or touch distally.

Motor - Grade 3 strength distally.

iii) Severe neuropathy:

Sensory - absent pain or touch distally

Motor - grade 0-1 strength distally.

RESULTS AND ANALYSIS

Over a period of one and half years thirty patients diagnosed to have chronic renal failure were selected for the study, based on the defined criteria.

The mean duration of uremic symptoms was 19.33 $\pm$ 12.5 months (range 7-52 months). All the patients were undergoing intermittent peritoneal dialysis at the time of evaluation, the mean duration after starting dialysis being 6.33 $\pm$ 3.14 months (range 1- 14 months).

Age and sex distribution

The mean age was 35.6 $\pm$ 10.6 years (range 18-60 years). There were 19 males and 11 females.

Table 1
AGE DISTRIBUTION

Age (years)	No. of Patients	Percentage of total (%)
< 20	2	07
21-30	9	30
31-40	10	33
41-50	5	17
51-60	4	13
Total	30	100

Graph 1

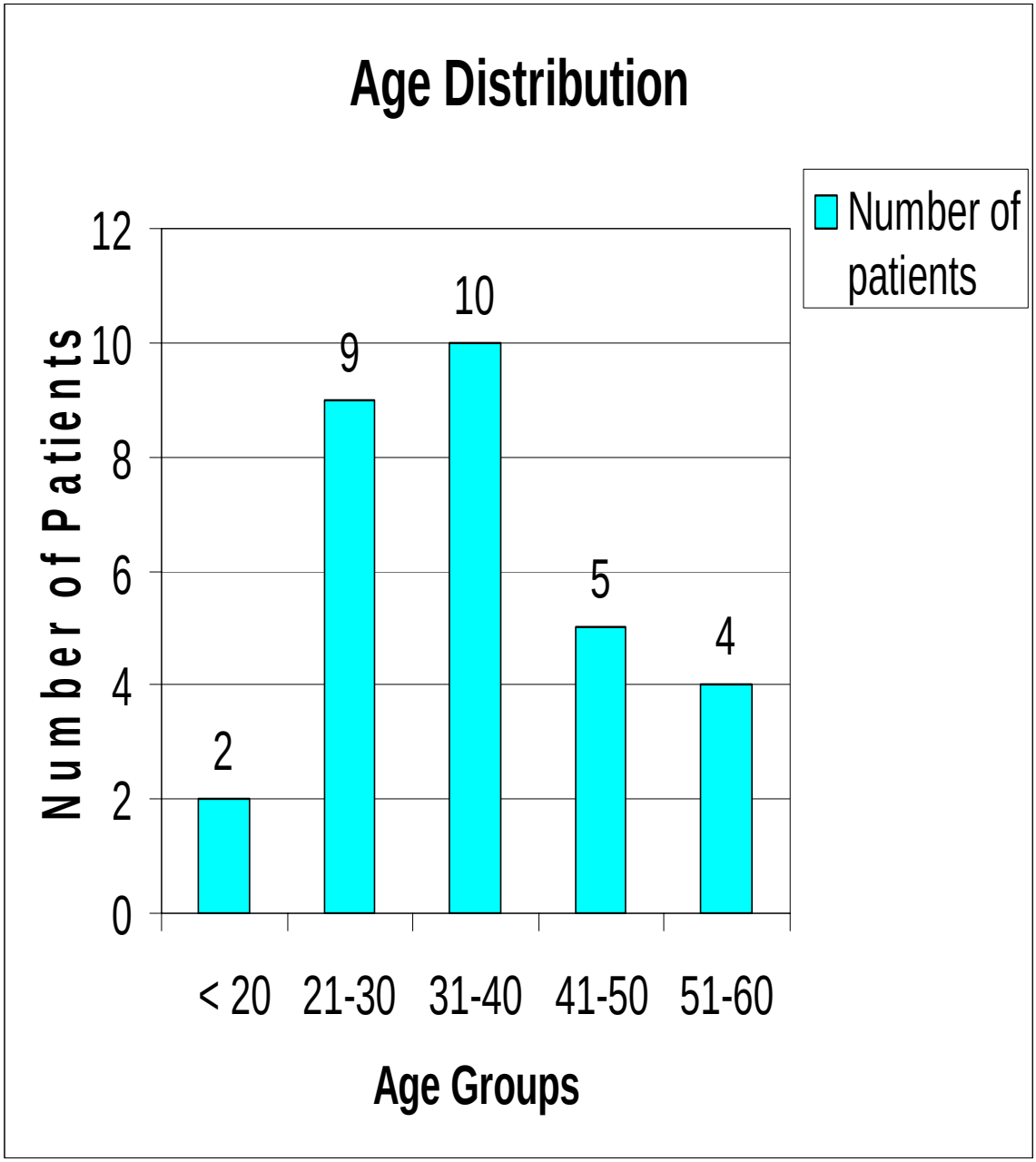

Age Distribution
Number of patients
Number of Patients
12
10
8
6
4
2
0
2
9
10
5
4
< 20
21-30
31-40
41-50
51-60
Age Groups

Table 2
SEX DISTRIBUTION

Sex	No. of Patients	Percentage
Male	19	63.33 %
Female	11	36.67 %
Total	30	100 %

Graph 2

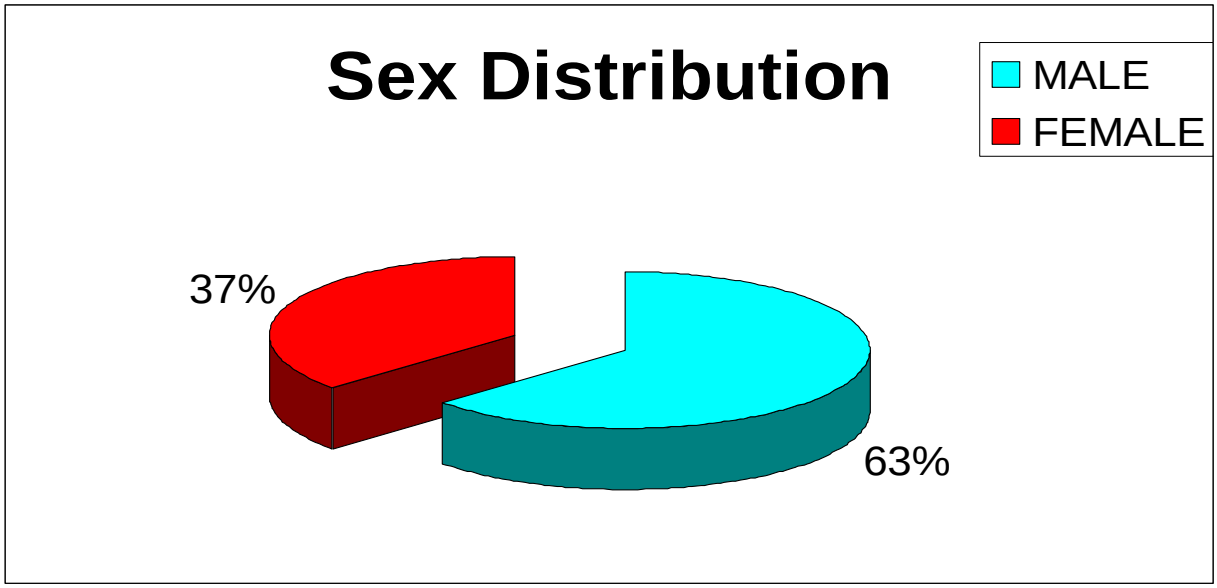


Table 3
DISTRIBUTION OF DISEASES

Disease	No. of Patients
Chronic glomerulonephritis	10
Hypertension	6
Chronic Interstitial nephritis	3
ADPKD (misc)	2
RPGN (misc)	2
Chronic Pyelonephritis (misc)	1
Urate Nephropathy (misc)	1
Unknown	5
TOTAL	30

Graph 3

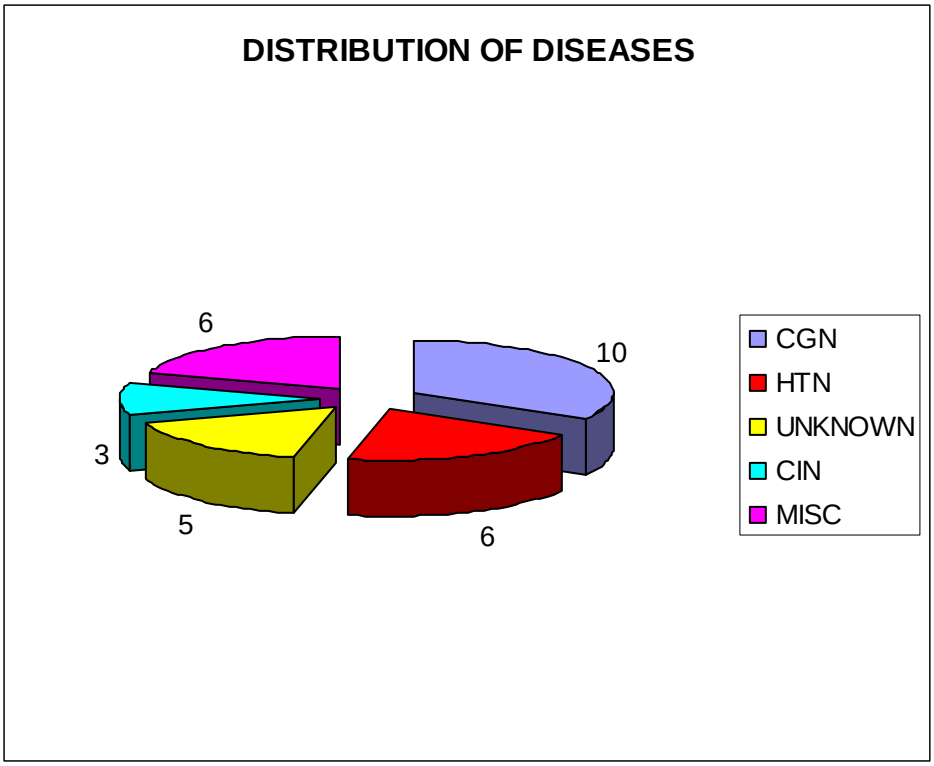


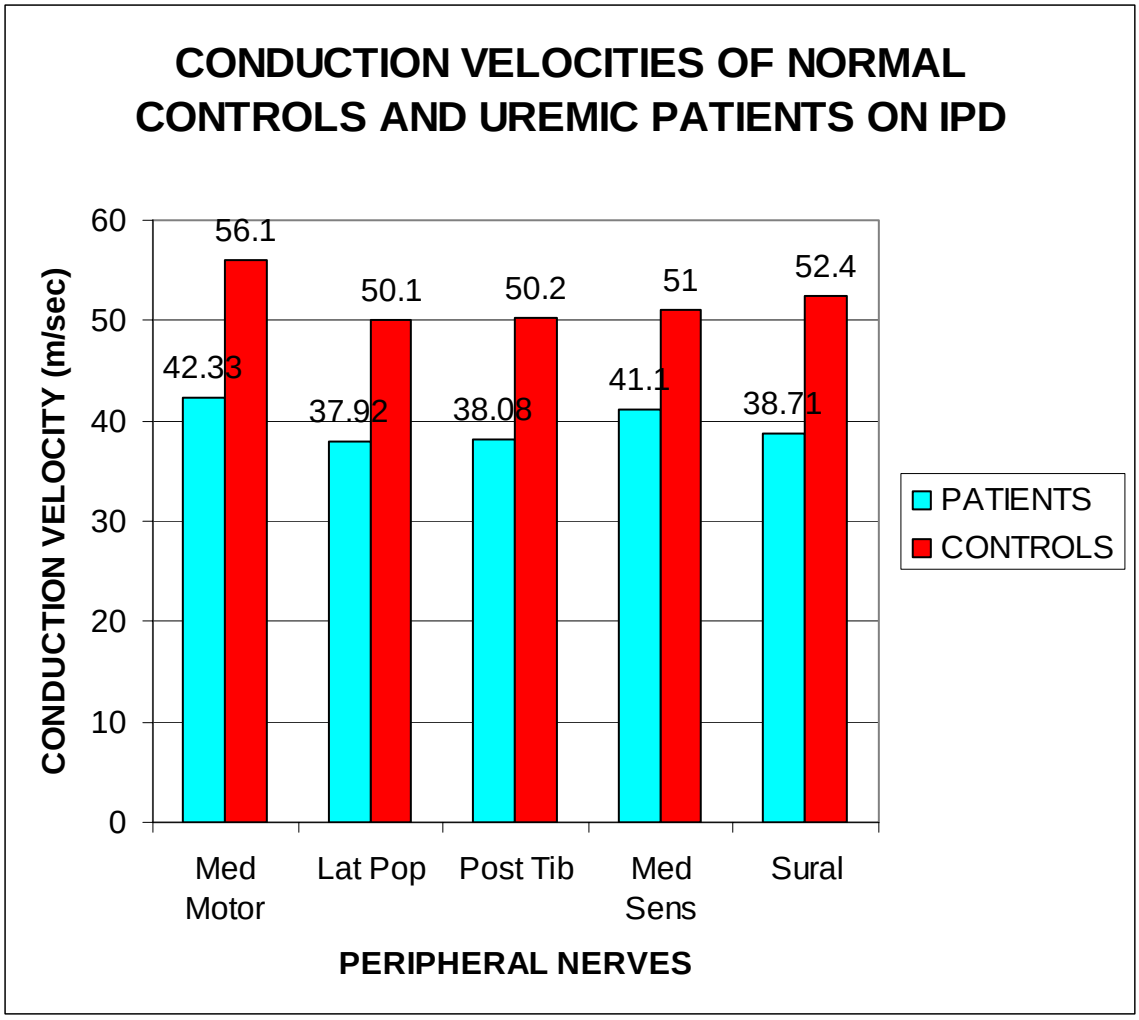
Table 4
DISTRIBUTION OF NERVE CONDUCTION VELOCITIES

NCV m/sec	Mean Velocity (m/sec)									
	Med. Mot		Lat. Pop		Post. Tib		Med. Sen		Sural	
	No.	NCV	No.	NCV	No.	NCV	No.	NCV	No.	NCV
30-34.9	0	_	5	33.4 ± 1.29	8	33.65 ± 1.38	0	_	0	_
35-39.9	10	38.18 ± 1.74	17	37.54 ± 1.46	12	37.55 ± 1.55	9	38.48 ± 0.99	20	37.63 ± 1.46
40-44.9	12	42.7 ± 1.30	8	41.55 ± 0.90	8	41.21 ± 1.22	19	41.87 ± 1.32	10	40.88 ± 0.63
45-49.9	08	46.96 ± 1.10	0	_	2	46.45 ± 0.78	2	45.5 ± 1.14	0	_
Total	30	42.33 ± 3.71	30	37.92 ± 2.96	30	38.08 ± 3.85	30	41.10 ± 2.27	30	38.71 ± 2.00
Normal	10	56.10 ± 5.40	10	50.10 ± 7.2	10	50.2 ± 9.3	10	51.0 ± 3.8	10	52.4 ± 4.4

Table 5
CONDUCTION VELOCITIES OF NORMAL CONTROLS AND UREMIC PATIENTS ON IPD

Peripheral Nerves	MEAN VELOCTIY (m/sec)		P Value
	Controls	Patients	
Median Motor	42.33 ± 3.71	56.1 ± 5.4	**< 0.0001**
Lateral Popliteal	37.92 ± 2.96	50.1 ± 7.2	**< 0.0001**
Posterior Tibial	38.08 ± 3.85	50.2 ± 9.3	**< 0.0001**
Median Sensory	41.10 ± 2.27	51.0 ± 3.8	**< 0.0001**
Sural	38.71 ± 2.00	52.4 ± 4.4	**< 0.0001**

Graph 4



Clinical Neuropathy

Six patients (20%) complained of burning sensation in the feet. Eleven patients (36 %) had clinical neuropathy- mild, as defined earlier (Patient Nos. 1, 2, 4, 5, 7, 12, 13, 21, 22, 24, 28, and 30). Four patients (13.3 %) also had absent ankle jerks bilaterally (Patient Nos. 2, 5, 7 and 13). None of the patients had any muscle wasting, weakness, trophic changes or sensory ataxia. The duration of uremic symptoms in patients with clinical neuropathy was 29 $\pm$ 13.49 months as against 12.89 $\pm$ 6.27 months in those without clinical neuropathy (P Value < 0.0001). The duration of IPD in patients with clinical neuropathy was 7.5 $\pm$ 3.8 months and that of those without clinical peripheral neuropathy was 5.56 $\pm$ 2.43 months (P Value = Not Significant).

The mean serum Creatinine in those with clinical peripheral neuropathy was 5.03 $\pm$ 2.60 mg% whereas, that in those without peripheral neuropathy was 4.16 $\pm$ 1.29mg% (P Value = Not Significant)

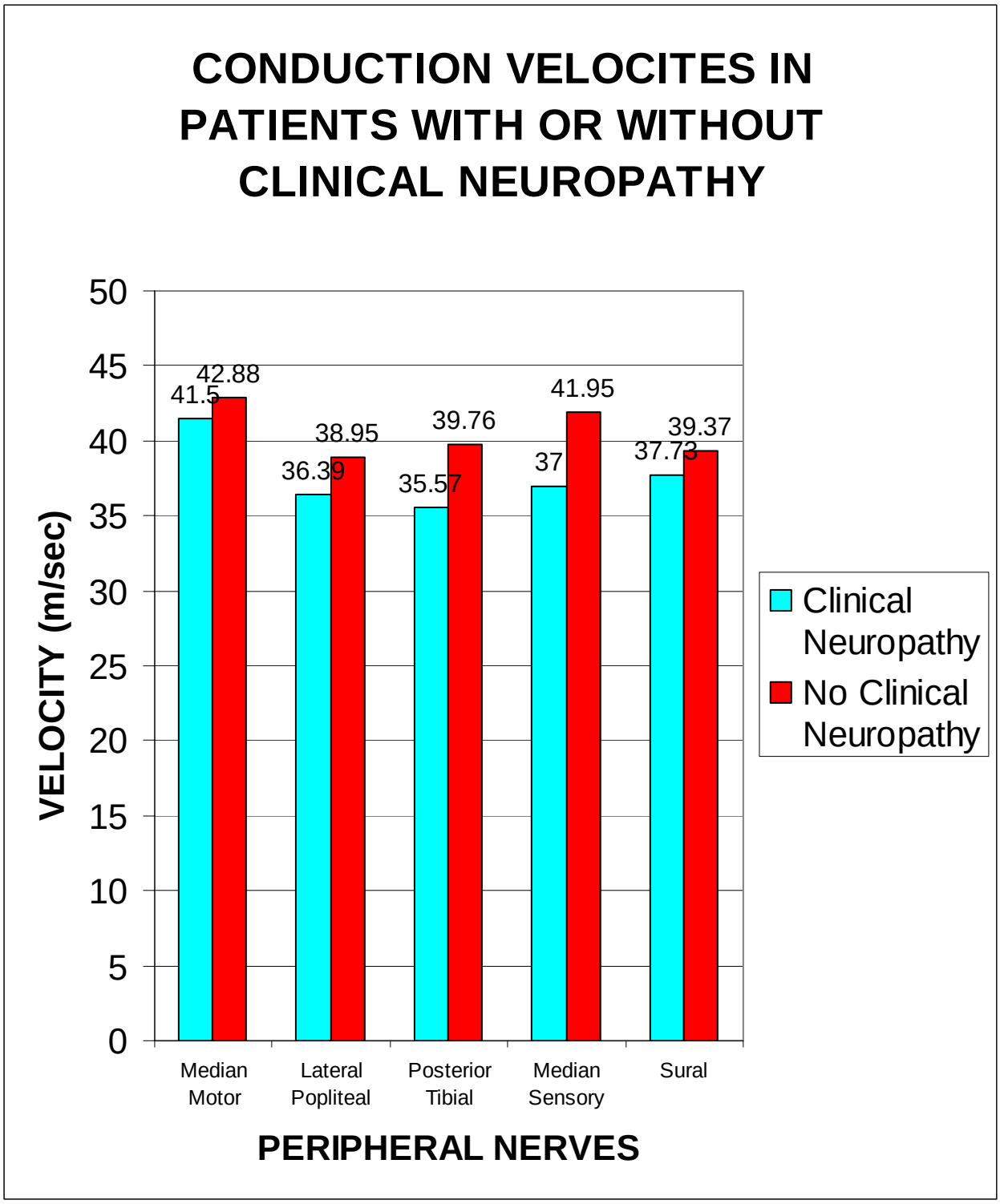
Table 6
CONDUCTION VELOCITIES IN PATIENTS WITH AND WITHOUT CLINICAL NEUROPATHY

Peripheral Nerves	MEAN VELOCTIY (m/sec)		P Value
	Clinical Neuropathy	No Clinical Neuropathy	
Median Motor	41.5 ± 3.64	42.88 ± 3.76	**0.3356**
Lateral Popliteal	36.39 ± 2.38	38.95 ± 2.93	**0.0203**
Posterior Tibial	35.57 ± 2.59	39.76 ± 3.57	**0.0020**
Median Sensory	37.00 ± 2.76	41.95 ± 2.03	**0.0000**
Sural	37.73 ± 1.67	39.37 ± 1.96	**0.0275**

Table 7
VARIOUS PARAMETERS IN CLINICAL PERIPHERAL NEUROPATHY VS NO CLINICAL PERIPHERAL NEUROPATHY

	Clinical Neuropathy	No Clinical Neuropathy	P Value
Duration of Uremic symptoms (months)	29 ± 13.49	12.89 ± 6.27	**0.0001**
Duration of IPD (months)	7.5 ± 3.8	5.56 ± 2.43	**0.0981**
S. Creatinine (mg %)	5.03 ± 2.60	4.16 ± 1.29	**0.2288**

Graph 5


CONDUCTION VELOCITES IN PATIENTS WITH OR WITHOUT CLINICAL NEUROPATHY
VELOCITY (m/sec)
50
45
40
35
30
25
20
15
10
5
0
41.5
42.88
36.39
38.95
35.57
39.76
37
41.95
37.73
39.37
Median Motor
Lateral Popliteal
Posterior Tibial
Median Sensory
Sural
PERIPHERAL NERVES
Clinical Neuropathy
No Clinical Neuropathy

The mean conduction velocity for posterior tibial nerve in patients whose ankle jerks was absent was 34.22 $\pm$ 3.29 and that of those with preserved ankle jerk was 38.67 $\pm$ 3.63. (P value < 0.0001).

DISCUSSION

Thirty adult patients with end stage renal disease enrolled in an Intermittent Peritoneal Dialysis programme for varied indications were studied for clinical and electrophysiological evidence of peripheral neuropathy. The age and sex distribution of the present group (mean age 35.6 $\pm$ 10.6 years and male to female ratio of 1.72:1) may not reflect the true prevalence figure in chronic renal failure, as the patients were exclusively drawn from those attending IPD programme in our institution.

The mean duration of uremic symptoms in the groups of patients studied was 19.33 $\pm$ 12.50 months. The relatively short duration of symptoms could have been an artifact, due to the patient selection criteria. The short duration of uremia is probably the reason for the low prevalence of **clinical neuropathy (36%)** in our patients. The mean serum creatinine level in our patients at the time of study was only 4.51 $\pm$ 1.94 mg%, which is a reflection of the fact that the patients were on Intermittent Peritoneal Dialysis for a mean period of 6.33 $\pm$ 3.15 months.

In a study of 14 patients treated conservatively for end-stage renal disease, Jebsen *et al* [97] *showed* a correlation between increasing serum creatinine and decreasing motor nerve conduction velocities. On the strength of this study, they defined adequate dialysis as the amount necessary

to arrest, or prevent the development of peripheral neuropathy [98].In patients with chronic renal disease, Blagg *et at* [99] described slowing of nerve conduction with increasing levels of urea and creatinine. Jennekens *et al* [100] studied 83 patients with severe renal insufficiency who were being treated conservatively for uremia, in order to establish the relationship between uremic polyneuropathy and impairment of renal function. They found signs of neuropathy only when the creatinine clearance was less than 5 ml/min. Polyneuropathy was most frequent in patients with the highest levels of blood urea and creatinine, and the lowest creatinine clearances. However the duration of severe renal insufficiency also appeared to influence the onset of polyneuropathy.

In our study clinical evidence of neuropathy was present in 36% of our patients, whereas statistically significant slowing of nerve conduction velocities was noted in all our patients (Table 5). With a mean creatinine value of 4.51 $\pm$ 1.94 mg% all our patients (100%) had subclinical neuropathy. There were no significant association between the level of serum creatinine in those with and those without clinical neuropathy. The association between the severity of neuropathy and raising creatinine was also not observed. Larger studies are required to delineate the actual association in patients on IPD.

Six patients (20 %) complained of 'burning feet'. Tyler [69] quotes it to be a frequent early manifestation of clinical neuropathy, while others [5, 7, 60] found it to be an uncommon symptom. This is probably because, although most patients with uremic neuropathy have distal dysesthesias, these are not frequently described as 'burning' in character, but a variety of unpleasant sensations.

In our study impaired vibratory sense in the feet was the commonest physical sign in the present group of patients, being present in 9/30 patients **(30%)**. Loss of ankle jerks was seen in 4 patients **(13.33%).** The duration of uremia was significantly longer in patients with clinical neuropathy (29 $\pm$ 13.49 months vs. 12.89 $\pm$ 6.27 months). The mean serum creatinine values were not significantly different in those with and without clinical neuropathy, as everybody were receiving intermittent peritoneal dialysis. These observations confirm the fact that development of neuropathy depends on the duration and severity of renal failure. [6] Impaired vibratory senses in the lower limbs and loss of deep tendon reflexes, especially the ankle jerks, are the first sign of uremic neuropathy [7, 9, 60] This has been noticed in our study also.

The course of neuropathy is variable in patients undergoing dialysis. Nielson *et at*[101] showed that, on regular haemodialysis,

there was no further slowing of nerve conduction, nor any significant improvement. Many workers have confirmed the lack of improvement in neuropathy, on haemodialysis [102,103]. Hemodialysis may reduce serum urea and creatinine concentrations without any improvement in neuropathy. The absence of improvement in nerve conduction has suggested that impulse propagation is impaired by toxic substance(s) of a higher molecular weight, and with a considerably lower clearance through the artificial kidney than urea and creatinine[11]. Evidence favoring a toxic role for larger retained solutes (500-5000 daltons) is based on two observations: first, anecdotal comparisons of patients on chronic haemodialysis and chronic intermittent peritoneal dialysis show that patients on the latter mode of therapy may remain well and free of uremic neuropathy despite higher BUN and creatinine levels; second, lengthening the time on dialysis/week (more "square meter hours" i.e. , membrane area multiplied by dialysis time) prevents neuropathy [104, 105]. CAPD gives relatively high clearances of middle molecules [106-108]

So it has been hypothesized that peripheral neuropathy should not develop on this mode of therapy and, if it already exists, should improve. Few studies of nerve conduction velocities have been done in patients undergoing CAPD. Lindholm *et al* [109] reported the appearance of neuropathy and deterioration in 11 patients during CAPD, but could not

exclude the influence of poor nutrition. Pierratos *et at* [110] found no significant change in nerve conduction velocity in 18 patients followed for two years on CAPD treatment.

The most widely used measure of disordered functions of peripheral nerve has been the determination of motor nerve conduction velocities. The pathology of uremic neuropathy is focused upon destruction of the axon, with only secondary demyelination.[6, 7, 10] In this type of neuropathy, motor nerve conduction velocity would not be expected to be a guide to the severity of the underlying neuropathy.[10] also Kominami *etal* [111] found that conduction velocities were unreliable because they varied as much as 9.6 m/sec from day to day. Sensory nerve conduction velocity probably is more sensitive than motor nerve conduction velocity.[8,59] Inspite of these drawbacks, determination of nerve conduction velocity has been used as objective measure of peripheral nerve function by many authors. [60, 84, 85] Slowing of nerve conduction is a frequent occurrence in the uremic patients with no other symptoms or signs of neuropathy[84] which is confirmed in our study also. In the present study, we found that all the [112] patients had statistically significant slowing of both motor and sensory conduction velocities, while **64%** of them had no symptoms or signs of peripheral neuropathy. Symptomatic patients had

significant longer duration of chronic renal failure, when compared to the rest. Also, conduction velocities were slower in patients with clinical neuropathy.

These findings correlate with the observations of Asbury [7], that, in the past decades, the occurrence of clinically evident neuropathy in patients on chronic dialysis programme (both haemodialysis and peritoneal dialysis) has become rare, as a result of earlier institution of treatment, frequent dialysis scheduling and improvement in dialysis techniques.[113] In contrast, nerve conduction velocity abnormalities, indicative of subclinical neuropathy tend to persist unchanged regardless of the type of dialysis programme used.[101]

Further studies of this nature should try to use conduction velocities to assess the adequacy of peritoneal dialysis programme and should evaluate the long term prognosis of the patients on peritoneal dialysis based on the conduction velocities. Studies have claimed the usefulness of nerve conduction studies for prediction of mortality in patients on haemodialysis[114]. Similar studies can be done on peritoneal dialysis patients as well.

CONCLUSIONS

1) The prevalence of clinical neuropathy in a series of 30 patients with end stage chronic kidney disease attending an Intermittent Peritoneal Dialysis (IPD) Programme was 36%. Clinical neuropathy occurred in those with longer duration of uremic symptoms.
2) Clinical neuropathy though less observed than sub clinical neuropathy, indicative severe axonal damage and worse prognosis.
3) Slowing of nerve conduction velocities were a universal phenomenon in the patients on IPD programme, even in the absence of clinical evidence of neuropathy.
4) Serial electro physiological monitoring may be used to monitor adequacy of dialysis schedules.

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APPENDIX 1 (PROFORMA)

NAME : AGE: SEX: I.P.No:

OCCUPATION: ADDRESS:

Past history:

	Yes	No
Diabetes Mellitus		
Thyroid dysfunction		
Joint pains, chronic skin changes		
Photosensitivity		
Medication		
Other systemic illnesses, if any.		

General examination:

	Yes	No
Pallor		
Hyper pigmentation		
Facial puffiness		
Pedal edema		
Thyroid swelling		
Angular stomatitis, cheilosis		
Skin texture		
Others, specify		

Pulse: B.P:

Respiratory rate: Temperature:

Nutritional status assessment for adequacy of Peritoneal dialysis:

C.V.S:

R.S.:

Abdomen:

C.N.S.:

Spinomotor system- Bulk, tone and power of the Upper and Lower limbs.

Deep and superficial reflexes-

Sensory system- Posterior column and spinothalamic tracts.

Investigations

1. Urine complete examination:
2. 24 hr Urine Protein:
3. Blood:

    Hb: gm/dl

    TC: cells/cu.mm

    DC:

    RBC:

    Peripheral smear:

4. ESR:

5. Blood Urea: 6.Serum Creatinine:

7. Serum Na+: 8. Serum K+:

9. Calcium: 10.Total protein and albumin

11.ECG:

12.USG abdomen:

NERVE CONDUSTION STUDIES:

1. Sural nerve Sensory Conduction Velocity.

2. Peroneal nerve Maximum Motor Conduction Velocity.

APPENDIX 2 (INFORMED CONSENT)

DEPARTMENT OF GENERAL MEDICINE , COIMBATORE MEDICAL COLLEGE HOSPITAL.

PERIPHERAL NEUROPATHY IN CHRONIC UREMIA – A STUDY OF CLINICAL AND ELECTROPHYSIOLOGICAL FEATURES AND CHANGES IN PATIENTS ON INTERMITTENT PERITONEAL DIALYSIS.

Informed consent form for prospective participants

Principal Investigator: Dr Bidhun Kuriakose Paulose, Junior Resident.

Research Guide: Prof. Dr S.Veerakesari.MD Chief, Medical Unit – VI.

Organization: Department of Medicine, Coimbatore Medical College Hospital.

This informed consent form has two parts

PART – I INFORMATION SHEET(to share the information about the research with you)

PART – II CERTIFICATE OF CONSENT (for signatures if you agree to take part)

(You will be given a copy of the full informed consent form.)

PART – I INFORMATION SHEET

I , Dr. Bidhun Kuriakose Paulose, Junior resident in Dept of Medicine invites you to join as participant in my research on peripheral neuropathy in chronic uremia, which is a very common problem in our country. I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with, about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.

Chronic Kidney disease is common disease caused by the irreversible loss of nephron function which is the functional unit of kidney. This result in accumulation of toxic waste materials normally removed by the kidneys, resulting in a condition called Uremia, causing a variety of clinical manifestations including damage to the peripheral nerves, called peripheral neuropathy. We are doing this research to learn the prevalence of peripheral neuropathy in patients with chronic kidney disease who are undergoing intermittent peritoneal dialysis which is one of the modalities of treatment of

Uremia and also to see the correlations with the various clinical and biochemical parameters.

In this study you will have to answer questions regarding your illness, undergo a physical examination, give urine, blood for tests, and undergo nerve conduction studies. You are being selected because we are inviting all adults with chronic kidney disease who is receiving intermittent peritoneal dialysis in the nephrology department/medicine department to enroll in the study.

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at the department will continue and nothing will change. You may change your mind later and stop participating even if you agreed earlier. You will have to give details regarding your age, duration of disease, family history of the disease, any symptoms you are having at present, your past medical problems, and current medications. A doctor will examine you to look for any problems. All the data will be recorded in a proforma. Ten ml of blood will be drawn for doing various laboratory tests to know about the status of your disease. Any excess sample will be destroyed immediately after the laboratory tests are completed. Taking the blood sample will produce some pain and there may be slight redness at the

site of puncture for a day or two. Also you will have to provide 3 ml or urine for tests. You will be subjected to a nerve conduction study and ultrasound scan of your abdomen, all of which cause only minimal discomfort.

On the first day you will be asked about your problems, a doctor will check you up and a proforma will be filled. And necessary blood and urine samples will be collected. You will be given a date to return which may be up to a week later Ultrasound scan, if not already done. If you participate in this research you will be having a thorough check up of your peripheral nervous system, This may reveal some unidentified problems in you. We will promptly start the treatment for them. Also by participating you are providing valuable data that will help doctors understand this disease better and ultimately serve the patients in a better way. We will not be providing any money for participating in this research; you may incur more expense since you will have to visit the hospital more frequently, if situation arise.

It is possible that if others in the community are aware that you are participating in this research, they may ask you questions. We will not be sharing the identity of those participating in the research with anyone. The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will not be identified by your name but by a number. Only the researchers

will know what your number is and they will lock that information up with a lock and key. It will not be shared with or given to anyone except my research guide.

The knowledge that we get from doing this research will be shared with you before it is made widely available to the public. Confidential information will not be shared. There will be small meetings in the community and these will be announced. After these meetings, we will publish the results in order that other interested people may learn from our research

You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected. If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact

Dr Bidhun Kuriakose Paulose,
Junior Resident,
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Coimbatore Medical College Hospital
Coimbatore – 18.
Phone – 9788580225.

Prof .Dr.S Veerakesari,
Chief, Medical Unit – VI,
Dept Of Medicine,
Coimbatore Medical College Hospital
Coimbatore- 18.
Phone – 9442589517.

This proposal has been reviewed and approved by the Ethics Committee of Coimbatore Medical College Hospital which is a committee whose task it is to make sure that research participants are protected from harm.

CERTIFICATE OF CONSENT

I have been invited to participate in research on peripheral neuropathy in patients with chronic kidney disease. I understand that it will involve answering a detailed questionnaire, undergoing a thorough physical exam, giving blood urine samples and undergoing nerve conduction studies. I have been informed that the risks are minimal and may include only slight pain and redness at sight of needle prick. I am aware that there may be no benefit to me personally and that I will not be compensated monetarily. I have been provided with the name of a researcher who can be easily contacted using the number and address I was given for that person.. I have had the opportunity to ask questions about it and any questions I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research and understand that I have the right to withdraw from the research at anytime without in anyway affecting my medical care.

Name of the participant: _____

Signature of the participant: _____

Date: _____

(DD/MM/YY)

If illiterate

A literate witness must sign (if possible , this person should be selected by the participant and must have no connection to the research team)

I have witnessed the accurate reading of the consent form to the potential participant , translated to his mother tongue, and the individual has had opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness: _____ ANDThumb print of participant

Signature of witness:_____

Date : _____

(Day/Month/Year)

I have accurately read or witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of the researcher: _____

Signature of the researcher:_____

Date: (Day/Month/Year) _____

APPENDIX 3 (MASTER CHARTS)

Sl.No	Name	Age (years)	Sex	Duration of uremic symptoms (m	Duration of IPD (months)	Serum Creatinine (mg%)	Diagnosis	Clinical Neuropthy	Motor Weakness	Ankle Jerk	Burning sensation of feet	Impaired vibration sense	Median Nerve **Motor** (m/sec)	Lateral Popolit-**Motor** Nerve (m/s	Posterior Tibial Nerve **Motor** (m/s	Median Nerve **Sensory** (m/sec)	Sural Nerve **Sensory** (m/sec)	Weight (kg)	Height (m)	e GFR (ml/min/1.73m2
1	Muthu kum	35	M	52	6	5.1	CGN	P	A	P	P	P	44.2	31.3	34.3	42	39	55	1.68	1.62
2	Lakshmi	42	F	24	12	2.7	UNKNOWN	P	A	A	A	P	46.6	33.8	31	43	38	48	1.6	22.2
3	Mylathal	34	F	10	8	3.6	HTN	A	A	P	A	A	48.1	36.2	33.9	41	35	50	1.49	20.17
4	Fathima	23	F	42	5	4.8	HTN	P	A	A	A	A	47.6	36.7	35.2	37	35	62	1.58	19.54
5	Selva raj	43	M	24	5	4.1	RPGN	P	A	P	P	P	43	35.7	33.3	41	35	80	1.84	24.71
6	Pandian	32	M	10	5	6.2	PYE NEPH	A	A	A	A	A	44.4	42.2	32.3	42	38	64	1.72	15.4
7	James	36	M	52	8	4.3	HTN	P	A	P	P	P	44	34.8	45.9	43	40	71	1.8	23.24
8	Eswari	35	F	10	4	3.1	RPGN	A	A	P	A	A	42	33.5	37.2	45.4	39.6	50	1.5	23.05
9	Rajendran	27	M	9	8	5.8	UNKNOWN	A	A	P	A	A	35	39.6	38	45.6	40.8	72	1.68	6.7
10	Ganesan	27	M	10	5	2.8	CGN	A	A	P	A	A	40.3	36	35.6	42	38	78	1.88	29.3
11	Tamil selvi	48	F	24	7	5.2	CGN	A	A	P	A	A	39.8	33.8	36.3	41	36.8	56	1.48	13.67
12	Elangovan	28	M	24	1	11.5	CGN	P	A	A	P	P	41.6	38.4	38.4	40	39.8	90	1.6	13.16
13	Murugan	43	M	18	10	4.4	CIN	P	A	P	A	P	39.6	36	34.8	39	37.5	73	1.64	25.65
14	Asiz	18	M	24	6	5.7	ADPKD	A	A	P	A	A	45.6	41.4	39.6	41.8	40.4	70	1.69	21
15	M.Raja	35	M	9	3	5.9	CGN	A	A	P	A	A	46.4	38.6	41.6	44.9	41.6	76	1.79	18.5
16	Kuppamma	37	F	12	4	6	UNKNOWN	A	A	P	A	A	42.5	38.5	40.8	39.4	38.5	63	1.58	13.97
17	Chinnakan	29	M	9	3	4.6	UNKNOWN	A	A	P	A	A	37.5	36.4	34.8	38.5	36.5	78	1.65	23
18	Moorthy	40	M	9	8	3.6	HTN	A	A	P	A	A	47.5	42.5	40.6	44.5	40.9	80	1.7	29.9
19	Vasan	26	M	11	6	4.2	CGN	A	A	P	A	A	48.4	41.5	47	42.5	42	56	1.79	20.4
20	Arulmozhi	54	M	10	10	2.8	URATE	A	A	P	A	A	43.4	40	40	39.5	38.5	63	1.69	27.5

Sl.No	Name	Age (years)	Sex	Duration of anemic symptoms (months)	Duration of IPD (months)	Serum Creatinine (mg%)	Diagnosis	Clinical Neuropathy	Motor Weakness	Ankle Jerk	Burning sensation of feet		Impaired vibration sense		Median Nerve Motor (m/Sec)	Lateral Popolit- Motor Nerve (m/Sec)	Posterior Tibial Nerve Motor (m/Sec)	Median Nerve Sensory (m/Sec)	Sural Nerve Sensory (m/Sec)	Weight (kg)	Height (m)	eGFR (ml/min/1.73m2)
19	Vasan	26	M	11	6	4.2	CGN	A	A	P	A		A		48.4	41.5	47	42.5	42	56	1.79	20.4
20	Arulmozhi	54	M	10	10	2.8	URATE	A	A	P	A		A		43.4	40	40	39.5	38.5	63	1.69	27.5
21	Parthasara	44	M	16	3	1.9	CGN	P	A	P	A		A		35.2	36.8	34.8	37.5	36.5	59	1.88	28.1
22	Jaffer	26	M	11	8	3.4	CGN	P	A	P	P		P		38.9	39.6	35.8	38.8	37.6	70	1.66	39
23	Kala	27	F	18	7	3	CIN	A	A	P	A		A		42.6	40.5	39.8	41.2	40.8	58	1.56	28.6
24	Veeran	54	M	31	11	5.8	ADPKD	P	A	P	P		P		39.1	38.6	38	37.5	39	60	1.61	13.27
25	Chempaka	28	F	7	2	3.1	HTN	A	A	P	A		A		43.4	42	40.5	41	40.1	61	1.59	28.3
26	Priya	19	F	14	1	2.2	HTN	A	A	P	A		A		40.9	39.5	41	42	41.2	48	1.67	29.9
27	Tamarai	50	F	28	8	3.3	CIN	A	A	P	A		A		38.5	36.5	39	40.5	38.9	57	1.46	21.7
28	Selvi	34	F	33	14	4	CGN	P	A	P	A		P		39	36	37.7	39.1	36.8	53	1.51	18.6
29	Ayyavu	45	M	8	5	3.9	UNKNOWN	A	A	P	A		A		45.5	42.3	44	42.2	41	60	1.71	20.2
30	Mahali	51	M	21	7	8.4	CGN	A	A	P	A		A		39.2	39	41.2	40	38.5	70	1.69	10.5

Sl.No	Name	Age (years)	Sex	Duration of uremic symptoms (mo	Duration of IPD (months)	Serum Creatinine (mg%)	Diagnosis	Clinical Neuropthy	Motor Weakness	Ankle Jerk	Burning sensation of feet	Impaired vibration sense	Median Nerve **Motor** (m/sec)	Lateral Popolit-**Motor** Nerve (m/se	Posterior Tibial Nerve **Motor** (m/s	Median Nerve **Sensory** (m/sec)	Sural Nerve **Sensory** (m/sec)	Weight (kg)	Height (m)	e GFR (ml/min/1.73m2
1	Muthu kum	35	M	52	6	5.1	CGN	P	A	P	P	P	44.2	31.3	34.3	42	39	55	1.68	1.62
2	Lakshmi	42	F	24	12	2.7	UNKNOWN	P	A	A	A	P	46.6	33.8	31	43	38	48	1.6	22.2
3	Mylathal	34	F	10	8	3.6	HTN	A	A	P	A	A	48.1	36.2	33.9	41	35	50	1.49	20.17
4	Fathima	23	F	42	5	4.8	HTN	P	A	A	A	A	47.6	36.7	35.2	37	35	62	1.58	19.54
5	Selva raj	43	M	24	5	4.1	RPGN	P	A	P	P	P	43	35.7	33.3	41	35	80	1.84	24.71
6	Pandian	32	M	10	5	6.2	PYE NEPH	A	A	A	A	A	44.4	42.2	32.3	42	38	64	1.72	15.4
7	James	36	M	52	8	4.3	HTN	P	A	P	P	P	44	34.8	45.9	43	40	71	1.8	23.24
8	Eswari	35	F	10	4	3.1	RPGN	A	A	P	A	A	42	33.5	37.2	45.4	39.6	50	1.5	23.05
9	Rajendran	27	M	9	8	5.8	UNKNOWN	A	A	P	A	A	35	39.6	38	45.6	40.8	72	1.68	6.7
10	Ganesan	27	M	10	5	2.8	CGN	A	A	P	A	A	40.3	36	35.6	42	38	78	1.88	29.3
11	Tamil selvi	48	F	24	7	5.2	CGN	A	A	P	A	A	39.8	33.8	36.3	41	36.8	56	1.48	13.67
12	Elangovan	28	M	24	1	11.5	CGN	P	A	A	P	P	41.6	38.4	38.4	40	39.8	90	1.6	13.16
13	Murugan	43	M	18	10	4.4	CIN	P	A	P	A	P	39.6	36	34.8	39	37.5	73	1.64	25.65
14	Asiz	18	M	24	6	5.7	ADPKD	A	A	P	A	A	45.6	41.4	39.6	41.8	40.4	70	1.69	21
15	M.Raja	35	M	9	3	5.9	CGN	A	A	P	A	A	46.4	38.6	41.6	44.9	41.6	76	1.79	18.5
16	Kuppamma	37	F	12	4	6	UNKNOWN	A	A	P	A	A	42.5	38.5	40.8	39.4	38.5	63	1.58	13.97
17	Chinnakan	29	M	9	3	4.6	UNKNOWN	A	A	P	A	A	37.5	36.4	34.8	38.5	36.5	78	1.65	23
18	Moorthy	40	M	9	8	3.6	HTN	A	A	P	A	A	47.5	42.5	40.6	44.5	40.9	80	1.7	29.9
19	Vasan	26	M	11	6	4.2	CGN	A	A	P	A	A	48.4	41.5	47	42.5	42	56	1.79	20.4
20	Arulmozhi	54	M	10	10	2.8	URATE	A	A	P	A	A	43.4	40	40	39.5	38.5	63	1.69	27.5
21	Parthasara	44	M	16	3	1.9	CGN	P	A	P	A	A	35.2	36.8	34.8	37.5	36.5	59	1.88	28.1
22	Jaffer	26	M	11	8	3.4	CGN	P	A	P	P	P	38.9	39.6	35.8	38.8	37.6	70	1.66	39
23	Kala	27	F	18	7	3	CIN	A	A	P	A	A	42.6	40.5	39.8	41.2	40.8	58	1.56	28.6
24	Veeran	54	M	31	11	5.8	ADPKD	P	A	P	P	P	39.1	38.6	38	37.5	39	60	1.61	13.27
25	Chempaka	28	F	7	2	3.1	HTN	A	A	P	A	A	43.4	42	40.5	41	40.1	61	1.59	28.3
26	Priya	19	F	14	1	2.2	HTN	A	A	P	A	A	40.9	39.5	41	42	41.2	48	1.67	29.9
27	Tamarai	50	F	28	8	3.3	CIN	A	A	P	A	A	38.5	36.5	39	40.5	38.9	57	1.46	21.7
28	Selvi	34	F	33	14	4	CGN	P	A	P	A	P	39	36	37.7	39.1	36.8	53	1.51	18.6
29	Ayyavu	45	M	8	5	3.9	UNKNOWN	A	A	P	A	A	45.5	42.3	44	42.2	41	60	1.71	20.2
30	Mahali	51	M	21	7	8.4	CGN	A	A	P	A	A	39.2	39	41.2	40	38.5	70	1.69	10.5