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REVIEW ARTICLE

Neuropathy in Chronic Renal Failure

MD MUNZUR ALAHI[1], MD PERVEZ AMIN[2], MD AHMED ALI1, MD KAFILUDDIN,[1]
QUAMRUDDIN AHMAD[3]

Abstract:

Peripheral neuropathy is common in chronic renal failure patients and it's early detection and treatment reduces the sufferings of these patients. Studies of neuropathy in ESKD have demonstrated prevalence rates which vary from 60 to 100%. The striking pathologic features of peripheral neuropathy in patients of CRF are axonal degeneration in the most distal nerve trunks with secondary segmental demyelination. The most frequent clinical features are those of large-fiber involvement, with paresthesias, reduction in deep tendon reflexes, impaired vibration sense, weakness and muscle wasting. Patients of CRF may present with mononeuropathies or autonomic failure also. The exact cause of nerve involvement has not been identified but the middle molecule hypothesis is widely accepted. Dialysis in any form fails to improve the neuropathy but renal transplantation does improve the neurological complications. This review details the various features of neuropathy in patients of chronic renal failure.

Keywords: *Neuropathy; Chronic renal failure, Middle molecule hypothesis.*

Abbreviations: *CRF – chronic renal failure; CTS – carpal tunnel syndrome; EMG – electromyography; EPO – erythropoietin; ESKD – End stage kidney disease; GFR – glomerular filtration rate; NSS – neuropathy symptom score; PTH – parathyroid hormone.*

Introduction:

Neuropathy is a common problem in patients of chronic renal failure (CRF). It increases the suffering of the patients who are already burdened by the renal problem. The increasing prevalence of CRF has also increased the load of patients with peripheral neuropathy. Early recognition of neuropathy in patients of CRF and appropriate treatment of the condition may decrease the suffering of these patients. Peripheral neuropathy in patients with CRF was suspected in the late 19th century. The possibility of peripheral neuropathy in patients treated with hemodialysis was first raised shortly after the introduction of the first formal hemodialysis program. Since the introduction of hemodialysis and renal transplantation in the early 1960s, uremic neuropathy had been investigated thoroughly.The first clinical documentation of neuropathy was provided in 1961 in two young male patients with hereditary interstitial nephritis and deafness[1]. Asbury, Victor and Adams published two articles titled 'Uremic polyneuropathy' in 1962[1] & 1963[2] in which they stated, "The fact that chronic renal failure may be associated with polyneuropathy is not generally appreciated and is practically undocumented in the medical literature." They extensively described clinical and pathological findings in four men who developed neuropathy as a consequence of CRF of varying etiologies. All four patients had clinical features of renal disease for many years before the development of neuropathy, which manifested as a symmetrical length dependent sensory motor neuropathy. Nerve biopsies established axonal degeneration, maximal distally, with sparing of the proximal nerve segments and nerve roots. Moreover, there was no evidence to suggest nerve compression, inflammation or superimposition of

1. Assistant Professor of Neurology, Rajshahi Medical College, Rajshahi.
2. Medical Officer, Dept. of Neurology, Rajshahi Medical College. Rajshahi.
3. Professor & Head, Department of Neurology, Rajshahi Medical College. Rajshahi.

a systemic disease process, such as diabetes or amyloid, leading to conclusion that the development of neuropathy was a consequence of the underlying renal disorder.

In 1964, Preswick & Jeremy[3] described presence of subclinical polyneuropathy in patients with renal insufficiency. In 1971, Dyck and colleagues[4] 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 study. Using quantitative histology, they demonstrated axonal shrinkage. The dysfunction of the neuron, rather than the schwann cells, resulted in a decrease in the diameter of the axon, rearrangement of myelin, and finally, complete degeneration of the axon. Nielsen published numerous papers from 1970-1974[5,6] on clinical and electrophysiological studies in patients of chronic renal failure

Early clinical neurophysiological investigations in CRF patient demonstrated reduction in motor nerve conduction velocity in symptomatic and asymptomatic patients[7]. In studies of the natural history of uremic neuropathy, clinical and nerve conduction findings were compared amongst patients treated conservatively and those receiving dialysis therapy. Whereas the development of neuropathy in conservatively treated group was related to deteriorating renal function, those patients treated with long term dialysis manifested improvement in both clinical and neurophysiological parameters. Following these early reports and in light of the increasing use of dialysis and renal transplantation therapies, greater attention was focused on uremic neuropathy, with numerous studies reporting high rates of neuropathy in CRF patients, generally relating the development of neuropathy to the severity of renal failure.Studies by Bolton[7,8] in 1970s demonstrated nerve conduction slowing in renal failure patients as well as improvement in neurophysiological parameters following renal transplantation.

Incidence and Clinical Features of Neuropathy in CRF

Peripheral neuropathy in end-stage kidney disease (ESKD) presents as a length-dependent, distal sensorymotor symmetrical polyneuropathy with greater lower limb than upper limb involvement[9]. Studies of neuropathy in ESKD have demonstrated prevalence rates which vary from 60 to 100%, depending on the choice of nerve segments, the indices measured and the number of nerves studied[10-21].

The condition is of insidious onset, progressing over months, and has been noted to have a male predominance. It generally only develops at a glomerular filtration rate of less than 12 ml/min[9].The neuropathy usually evolves over several months but rarely an acute or sub acute course is seen[10]. Although usually mixed motor and sensory in type, cases of either pure sensory or pure motor have been reported. The most frequent clinical features are those of large-fiber involvement, with paresthesias, reduction in deep tendon reflexes, impaired vibration sense, weakness and muscle wasting.

Laaksonen et al[18] staged the clinical severity of uremic neuropathy in 21 CRF patients. He used a modified version of neuropathy symptom score (NSS) and combined this assessment with results of nerve conduction studies. The NSS quantified symptoms that were grouped into three categories to reflect alteration in motor, sensory, and autonomic systems. Within each group, further subsets were used to group symptoms according to the region affected and the presence of positive or negative symptoms. Using the NSS and the staging procedure previously used in studies of diabetic patients, 81% of CRF patients received a diagnosis of neuropathy. Stage 1 neuropathy (asymptomatic neuropathy), was diagnosed in 19%, stage 2 neuropathy (symptoms non disabling) was present in 48% and stage 3 neuropathy (disabling symptoms) was noted in 14%. Krishnan et al[11] in another study showed that 93% of CRF patients had neuropathic changes on NSS testing, with 72% diagnosed with stage 2 neuropathy and 21% with stage 3 neuropathy, despite all patients meeting currently accepted guidelines of dialysis adequacy.

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 also seen in uremic patients without neuropathy. Patients report that crawling, prickling, and itching sensations are felt in their lower limbs which are partially relieved by movement of the affected limb.
- Autonomic dysfunction is present and usually manifest as postural hypotension.
- A Guillain-Barre type of presentation is rare, but rapidly progressive course with respiratory failure has been reported[18].
- Cranial nerve involvement is rare.

The vestibulocochlear nerve is the most commonly affected cranial nerve in uremia. Variable hearing loss and occasionally complete deafness are reported, which may reverse with dialysis or renal transplantation. Uremia related hearing deficit must be distinguished from the ototoxic effects of aminoglycoside antibiotics and other drugs, as well as conditions associated with hereditary hearing loss and nephropathy.

Impaired vibratory perception and absent deep tendon reflexes are the most common clinical signs reported by Lindbolm and Tegner[12]. Yosipovitch et al[13] found paradoxical heat sensation 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%.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. Abnormal valsalva maneuver and orthostatic hypotension may be noted in patients with autonomic neuropathy. Uremic pruritus has been shown to be associated with altered sympathetic innervations of the skin and this correlated with impaired peripheral somatosensory nerve conduction, suggesting that uremic pruritus is a manifestation of uremic neuropathy[14].

Mononeuropathies in CRF

Mononeuropathies are a frequent clinical complication in CRF patients and most typically occur in the median, ulnar, and femoral nerves. In uremia susceptibility of the peripheral nerves to compression and local ischemia is increased[15]. Carpal tunnel syndrome (CTS) is the most common mononeuropathy in CRF, with prevalence rates varying from 6% to 31%[16]. The carpal tunnel syndrome is caused by entrapment of the median nerve in the carpal tunnel, which is formed by the flexor retinaculum and the carpal bones. Symptoms include burning pain and paresthesias involving the ventral surface of the hand and fingers I-III and lateral half of finger IV. Thenar muscle atrophy may occur. Renal transplantation relieves the symptoms but does not reverse the atrophy[17]. B_2-microglobulin amyloidosis is a major factor underlying the development of CTS in CRF patients, a complication noted in patients on long term hemodialysis. Amyloid deposits have been identified in synovial specimens from dialysis patients with CTS and an increase in the rate of CTS has been demonstrated with increasing hemodialysis duration. Strategies geared at reducing the levels of B_2-microglobulin, such as the use of high-flux biocompatible membranes and B_2-microglobulin adsorption columns, have resulted in reduced rates of CTS development and ultimately improvement in symptoms.Other factors that may contribute to the increased incidence of CTS in CRF patients include uremic tumoral calcinosis and the placement of arteriovenous fistulas, inducing a “steal” of blood from the distal limb. This may also increase the venous pressure in the distal limb leading to nerve compression[18]. Damage to the ulnar nerve can occur by uremic tumoral calcinosis at the wrist, in Guyon’s canal. Depending on the site of compression in the canal, this may cause purely

motor dysfunction with paresis of intrinsic hand muscles, sensory loss to the hypothenar eminence, the small finger and the medial part of ring finger or mixed symptomatology. B_2 Amyloid deposition in the palm, can lead to local ulnar nerve compression with pain and paraesthesia over the fourth and fifth fingers.

Autonomic Neuropathy in CRF

Autonomic neuropathy may develop in CRF patients and can play a role in the pathogenesis of intradialytic and orthostatic hypotension, incontinence, diarrhoea, constipation, oesophageal dysfunction, hyperhydrosis and impotence[19,20]. In a study of 36 CRF patients, gastrointestinal autonomic symptoms were evident in 42% and impotence in 45%[21]. Although postural hypotension was an uncommon clinical finding, 36% of patients complained of episodes of postural dizziness, which was most prominent in elderly CRF patients.Some studies have suggested that autonomic neuropathy occurs as a manifestation of generalized polyneuropathy but others have shown no correlation between autonomic dysfunction and peripheral nervous system abnormalities[22].The mechanism underlying the development of uremic autonomic neuropathy remain unknown, although an association with hyperparathyroidism has been suggested.Studies utilizing objective measures of autonomic function, including R-R interval variation as a measure of parasympathetic function and sustained hand grip and sympathetic skin response as a measure of sympathetic function, have established abnormalities in upto 62% of CRF patients on dialysis treatment. However, these abnormalities frequently occur in the absence of clinical symptoms of autonomic dysfunction[23]. Parasympathetic dysfunction has been shown to occur with greater frequency them sympathetic dysfunction, which is generally more common in diabetic CRF patients[24-29]. Besides para-sympathetic vagal dysfunction neuropathy of other cranial nerves especially optic, trigeminal, facial and vestibulocochlear neuropathy have been described anecdotally[25]. The contribution of autonomic dysfunction to the development of intradialytic hypotension remains a matter of ongoing debate, with some studies suggesting a possible association and other suggesting no significant relationship[26]. A recent review of the literature on the use of the oral alpha-1-adrenoceptor agonist Midodrine in the treatment of intradialytic hypotension suggested a beneficial effect[27]. Autonomic neuropathy improves after institution of dialysis and resolves following successful renal transplantation. Although the etiology of hypotension during hemodialysis is multifactorial, one patient showed a paradoxical bradycardia in response to hypotension. Patients with autonomic dysfunction have been shown to have more cardiac arrhythmias during dialysis and are more prone to intradialytic hypotension.

Pathophysiology of Peripheral Neuropathy in CRF patients

The pathologic features of peripheral neuropathy in patients of CRF are striking axonal degeneration in the most distal nerve trunks with secondary segmental demyelination. The condition has a predilection for large diameter axons, with relative sparing of the unmyelinated and small myelinated afferent neurons. There is a marked loss of axons and fiber breakdown in the distal nerve trunks of the legs with less severe changes proximally, normal spinal roots and degeneration in the cervical portion of the dorsal column. Anterior horn cells are intact but may show chromatolytic changes. Paranodal demyelination and separation of the myelin sheath from the axolemma are also found, but are considered to be secondary to the primary axonal damage[28]. Although there may well be a defect in schwann cell function in uremia, the predominant defect is one of axonal loss with secondary demyelination. Following renal transplantation, early remyelination accounts for the initial rapid improvement in nerve conduction, whereas nerve regeneration is a slow process taking many months. Similarly, there is no significant improvement in nerve conduction studies following a single hemodialysis treatment[29]. In patients of chronic renal failure it was found that the number of myelinated fibers was approximately one half of normal at the mid calf level and only one third of normal at ankle level. In transverse electron microscope sections, most of the myelinated fibers of the uremic nerve had a normal appearance

except for irregularities of the myelin sheath, such as splitting of the myelin lamellae and separation of axolemma from compact myelin. Nerve biopsies also showed onion like structures due to several layers of schwann cell processes around myelinated nerve fibers, suggesting repeated episodes of demyelination followed by remyelination[30]. The precise cause of uremic neuropathy remain unknown although a number of potential neurotoxins accumulate in end stage renal disease. Functional and morphological alteration of peripheral nervous system in end stage renal disease predispose to the development of clinically manifest mono and polyneuropathies.

Mostly, the adverse effects on the peripheral nervous system are minimal as long as the glomerular filtration rate (GFR) exceeds roughly 12 ml/min., whereas the neuropathy is reversed, at least partially, by dialysis and dramatically by renal transplantation. At glomerular filtration rates below this value, nerve conduction studies become abnormal and patients begin to demonstrate clinical signs of peripheral nerve dysfunction when GFR of about 6 ml/min is reached[31]. The so called "middle molecule hypothesis" with accumulation of one (or several) neurotoxic molecules of molecular weight 300-2000 Daltons which are slowly dialyzable has been a popular explanation for the genesis of uremic neuropathy. But no one substance has yet been convincingly shown to have a close correlation among plasma and tissue concentrations and the severity of the polyneuropathy[32]. The observation that uremic neuropathy improves with hemodialysis has led most observers to conclude that neuropathy results from the accumulation of a dialyzable metabolite. It had been speculated that these substances might be in the middle-molecule range; compounds of this size cross most dialysis membranes much more slowly than smaller molecules such as creatinine and urea, which are the usual measures of chemical control of uremia. Thus, one might theoretically achieve chemical control of uremia, while failing to remove the putative toxins. Supporting this contention have been the observations that control of neuropathy may in some cases depend on increased hours of dialysis per week, beyond that which is necessary for chemical control of uremia; and that peritoneal dialysis appears to be associated with a lower incidence of neuropathy. These observations suggest that the peritoneal membrane may permit passage of some toxic molecules more readily and selectively than the cellophane membrane used in hemodialysis.

Because of the varying nutritional status of uremic patients, the possibility that vitamin deficiency is a mechanism of neuropathy should be considered. Massive doses of vitamins administered both orally and parenterally have failed to have any clear influence on the course of neuropathy in informal trials; this experience has led to the general agreement that uremic neuropathy is not a result of vitamin deficiency. However, patients who receive chronic hemodialyis require supplementation with at least the water-soluble vitamins to avoid depletion; failure to do so may lead to nutritional neuropathy, and occasionally to Wernicke's encephalopathy[33,34]. Many other factors, such as decreased transketolase activity, reduced circulating biotin concentration, increased concentration of phenols and myoenositol and hyperparathyroidism have been proposed in addition to thiamine deficiency. There may be an additional ischaemic component to uremic neuropathy as increasing the haematocrit with erythropoietin therapy improved nerve conduction studies.

Neuropathy is certainly multifactorial, in that it is exacerbated by hypermagnesaemia and hypercalcaemia. Nerve function and muscle strength improve following parathyroidectomy. However the most likely explanation is that retention of uremic toxins leads to a reduction in energy dependent processes, and failure to transport and assemble tubulin within the cell correctly. The ouabain sensitive calcium ATPase pump activity has been shown to be decreased in uremia, thereby affecting sodium-calcium exchanger.

Various 'uremic toxins' have been proposed, including guanidine compounds, particularly methylguanidine which can inhibit the sodium ATPase pump, polyamines, phenol metabolites, myoinositol, and 3-Carboxy-4-methyl-5-propyl-2-

fluranpropanoic acid, which inhibit organic acid transport. Other suggestions include toxin induced inhibition of other key enzymes, such as transketolase, and pyridoxal-phosphate kinase. But the nature of the uremic toxins remain obscure[35]. Fraser and Arieff[16] 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 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. It was 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 endoneurial space of either site and cause direct nerve damage and water and electrolyte shifts with expansion or retraction of space.

The Middle Molecule Hypothesis in CRF

It is postulated that uremic neuropathy occurred due to accumulation of a dialyzable substance on the basis of their observational studies that demonstrated improvement in neuropathy in two subjects with long standing CRF following commencement of dialysis therapy. Later studies demonstrated that patients treated with peritoneal dialysis had lower rates of uremic neuropathy despite the fact that these patients frequently had higher blood urea and creatinine concentration[36]. The lower neuropathy rate in the peritoneal dialysis group was thought to indicate that the substance responsible for neuropathy was better dialyzed by the peritoneum than by the cellophane membranes used in hemodialysis. On this basis, the most likely group of substances was thought to be the “middle molecules” substances with a molecular weight of 300-12000 Daltons given that such substances were known to be poorly cleared by hemodialysis membranes.Marked elevations in the concentrations of middle molecules have been demonstrated in CRF patients, a finding not observed in healthy controls. Examples of such molecules include parathyroid hormone (PTH) and B-2 microglobulin, the levels of which are elevated in patients with CRF. Further studies demonstrated that the use of thinner dialysis membranes and longer dialysis times, strategies that would have greater benefits for the clearance of middle molecules compared to small molecules, led to significant reductions in the rate of severe neuropathy. A study using a hemodialysis membrane highly permeable to middle molecules also demonstrated a dramatic reduction in the development of neuropathy[24].There is lack of conclusive evidence that any single molecule in the middle molecular range is actually neurotoxic. In a study of nerve conduction velocity following renal transplantation, correlation was noted between the postoperative concentration of myoinositol, a middle molecule, and median sensory conduction velocity. Although myoinositol levels are elevated in CRF patients, there is little convincing evidence for a neurotoxic effect.The only middle molecule for which some evidence of neurotoxicity exist is PTH, with some studies suggesting a link between PTH and the neurological complications of CRF. PTH has been shown to prolong motor nerve conduction velocities in animal studies, although human studies of the effect of PTH on peripheral nerves have yielded conflicting results, with variable changes in motor nerve conduction velocity in patients with CRF.

Despite the short comings of the middle molecule hypothesis, the hypothesis that a dialyzable toxin may be involved in the pathophysiology of this condition remains prevalent. More recently, it has been suggested that the following criteria should be met in order for a substance to be truly regarded as a uremic neurotoxin:

1. It must be an identifiable chemical;
2. It should be elevated in blood of uremic patients;
3. There should be direct positive relationship between blood level and neurological dysfunction;

4. It should cause neurological dysfunction in animals at appropriate blood levels; and
5. Its removal from the blood should abolish dysfunction.

The middle molecule hypothesis fails to satisfy a number of these criteria, most importantly criteria 3, as there is little evidence to suggest that such molecules are actually neurotoxic.Despite the evidence that a dialyzable toxin may underlie the development of uremic neuropathy the mechanism of this neurotoxicity remain unclear. The possibility that the neurotoxic effect may be due to alteration in membrane excitability was first proposed by Nielsen who, drawing on evidence from in vitro studies of muscles and red blood cells in CRF patients proposed that one or more of these toxins may cause neuropathy by inhibiting activity of axonal Na^+/K^+ pump. This energy dependent pump is electrogenic with three Na^+ ions being pumped out for every two K^+ ions pumped into the axon, leading to net deficit of positive charge on the inner aspect of axonal membrane. Paralysis of the Na^+/K^+ pump abolishes the direct contribution of the hyperpolarizing pump current to the membrane potential and leads to accumulation of extracellular K^+ that causes further depolarization. The Na^+/K^+ pump is therefore of critical importance in maintaining normal ionic gradients, which are essential for axonal survival. Disruption of these gradients may cause reverse operation of the Na^+/Ca^{2+} exchanger, leading to increased levels of intracellular Ca^{2+} and axonal loss.Although it is not possible to measure membrane potential directly in human axon in vivo, indirect information regarding membrane potential and axonal ion function may be gained from nerve excitability studies. Excitability techniques provide information regarding alteration in membrane potential and axonal ion channel function based on coherent changes in a number of different indices. Nerve excitability measures have been used to study peripheral nerves in patients with neuropathy and have provided information about disease pathophysiology.

Neurophysiological Findings in CRF

Early studies of uremic neuropathy utilizing nerve biopsy techniques revealed prominent axonal degeneration, most severe in the distal parts of nerve trunks. Although initial studies suggested that demyelination was a significant feature of uremic neuropathy, subsequent reviews demonstrated that demyelination was secondary to axonal loss and that proximal segments of the nerves were relatively spared[18].These findings supported the concept that uremic neuropathy was a dying back neuropathy, with metabolic failure of the neuron causing distal axonal degeneration. Numerous neurophysiological series have been under taken in patients with uremic neuropathy and have demonstrated findings consistent with a generalized neuropathy of axonal type[13]. Early studies focused on motor nerve conduction parameters and demonstrated slowing of conduction velocity in patients prior to the development of clinical neuropathy. Subsequent studies demonstrated abnormalities of nerve conduction with generalized slowing in both sensory and motor nerves, accompanied by reduction in sensory response amplitudes. Motor response amplitudes tend to remain relatively preserved, although abnormalities in lower-limb motor nerves were noted in some patients, accompanied by neurogenic changes in distal lower-limb muscles on electromyography.An abnormality of sural nerve conduction and/or late response latency was observed in 100% of 30 randomly selected patients with chronic renal failure (18 receiving hemodialysis), although five were without clinical signs or symptoms[38]. This confirms the importance of these studies in the early detection of peripheral nerve disorders in patients with chronic renal failure. Other groups have confirmed similar findings, demonstrating reduction in sensory and motor response amplitudes in addition to abnormalities of late responses[19,39]. Reduction in peroneal nerve motor conduction velocity and prolongation of tibial F-ware minimum latencies have been established as sensitive indicators of neuropathy in CRF patients. Prolongation of soleus H. reflexes has also been demonstrated in patients without clinical evidence of neuropathy, suggesting that this parameter may be more sensitive in detecting early neuropathy. Studies of quantitative sensory testing in CRF patients have demonstrated increased vibratory perception thresholds most marked in the

lower limbs. Somato-sensory evoked potentials in EKSD patients demonstrate abnormalities of conduction along both the distal and proximal segments of peripheral somesthetic pathways, but less commonly along intracranial sensory pathways.A study of single fiber electromyography demonstrated normal fiber densities in motor units of CRF patients[40]. These findings suggested that reinnervation, characterized by increased fiber density, had failed to occur. However, this was accompanied by increased jitter, possibly reflecting peripheral demyelination in the setting of axonal degeneration. A further single-fiber EMG study established that jitter abnormalities improved following a year of dialysis.Early studies of nerve excitability, utilizing a limited range of excitability parameters, demonstrated an elevated threshold for excitation even when nerve conduction values were normal, in addition to demonstrating prolongation of absolute and relative refractory periods[40]. As a consequence, it was concluded that the safety factor for neural transmission at the nodes of Ranvier would be lowered. Unexpectedly, uremic nerves retained vibratory perception and their, sensory response amplitudes for a longer period than control nerves when rendered ischemic. Uremic nerves also behaved differently when temperature was lowered, with a less rapid rise in response amplitude compared to controls.In addition to the slowly progressive sensorymotor axonal neuropathy, a more rapidly progressive motor neuropathy has also been described. A small number of CRF patients with diabetes have also been shown to develop a subacute neuropathy progressing over a few months, with severe muscle weakness. In this group of patients, nerve conduction studies may demonstrate features of either a demyelinating or axonal neuropathy. Although the presence of diabetes complicates assessment of nerve conduction data, the absence of pre existing neuropathic symptoms and the clinical improvement noted following dialysis or transplantation suggest a metabolic basis for the neuropathy related to underlying CRF. Analysis of cerebrospinal fluid (CSF) is rarely helpful, as CSF protein concentration is frequently elevated in CRF patients and may simulate the albumino-cytologic dissociation that is characteristic of Guillain-Barre Syndrome.

Small-fiber neuropathy many develop as a clinical entity in CRF patients. Lindblom and Tegner[25] demonstrated abnormalities of thermal sensation in 30% of CRF patients and concluded that small-fiber neuropathy may exist as a distinct entity in these patients. These results however, differed from those of other groups who demonstrated minimal impairment of thermal sensation in CRF. In a study of 20 CRF patients, abnormalities in standard nerve conduction studies were demonstrated in 16 patients, whereas abnormal thermal threshold were found in only 6 patients and, when present, did not correlate with clinical evidence of polyneuropathy. Such findings are consistent with those of pathological studies that demonstrated greater vulnerability of large-diameter fibers in CRF patients.

Pathophysiology of Nerve Excitability and Conduction Abnormalities

The chief role of the axon is that of impulse conduction, which depend on electrical cable structure and voltage dependent ion channels of the axonal membrane. In the myelinated axons from peripheral nerves, voltage sensitive Na^+ channels are clustered at high densities (upto 1000/µm) in the nodal region, compared to the internodal region (25/µm)[41]. The high density of Na^+ channels at the node reflects the need of saltatory conduction for a large inward current at the node. When nodal membrane is depolarized, an inward current is established, carried by Na^+ ions. The Na^+ conductance is voltage sensitive and regenerative: it increases with depolarization, and this in turn leads to greater depolarization as well as depolarization to the next node. Na^+ channels are membrane-spanning protein molecules, containing a pore unit (a-subunit) through which Na^+ ion can diffuse almost freely in the open state. A variety of toxins and drugs bind to the a-subunit of Na^+ channels. Nerve excitability studies in CRF patients have demonstrated significant alterations in membrane potential prior to haemodialysis, with recovery in the post dialysis period.

Measures of motor and sensory nerve excitability have been assessed in relation to changes in serum

levels of potential neurotoxins including K^+, Ca^{2+}, urea, uric acid and middle molecules such as PTH and B-2M. Predialysis excitability abnormalities were noted to be strongly correlated with serum K^+ in all studies, suggesting that hyperkalamic depolarization may underlie the development of uremic neuropathy. Furthermore, abnormalities of excitability become apparent with serum K^+ concentrations in the high normal range, well below the levels required to produce cardiac toxicity. The excitability abnormalities in CRF patients were also different from those noted in patients with diabetic neuropathy, another common metabolic neuropathy, suggesting that the abnormalities noted in CRF patients were not purely a consequence of structural change. K^+ satisfies criteria that have been suggested for a substance to be accepted as a uremic neurotoxin. It is an identifiable chemical that is elevated in the serum of CRF patients and causes neurological dysfunction in both humans and animals. A direct relationship exists between serum levels of K^+ and neurophysiological parameters, and its removal leads to considerable improvement in these indices[18]. Inhibition of the Na^+/K^+ pump by uremic neurotoxin, previously proposed as the mechanism underlying the development of uremic neuropathy, may induce membrane depolarization. On the other hand alteration in membrane potential and intra and extra cellular K^+ concentration have a direct effect on Na^+/K^+ pump function.

Effects of Dialysis and Transplantation on Neuropathy in CRF

Early reports investigating the effects of hemodialysis on uremic neuropathy suggested that some patients with mild neuropathy recovered completely with adequate dialysis. In fact, failure to improve was considered to be an indicator of insufficient dialysis. These reports, however, did emphasize that the extent of improvement was likely to be related to the severity of neuropathy and that patients with severe neuropathy were unlikely to experience any significant recovery. More recent studies, however, have demonstrated that improvement in neuropathy with dialysis is an uncommon event. Although these studies suggest that dialysis retards the progression of neuropathy in most patients, in some cases a gradual deterioration of neuropathy may occur.A comparison of hemodialysis and peritoneal dialysis with regard to neuropathy progression has demonstrated no significant difference between the two dialysis forms.

Renal transplantation remains the only known cure for uremic neuropathy with clinical improvement in sensory and, to a lesser extent, motor function occurring within a few days of transplantation[10]. Serial nerve conduction studies following transplantation demonstrated a correlation between the improvement in the nerve conduction and biochemical parameters, suggesting that metabolic phenomena may underlie the rapid improvement. Even with severe neuropathy, improvement in symptoms and signs may occur within one month of transplantation, although in some patients the recovery is prolonged or remain incomplete.

Dialysis and transplantation are less beneficial for patients with autonomic neuropathy compared to large-fiber neuropathy. An early study suggested that autonomic function may be improved with dialysis, but a later report failed to show any significant benefit[11]. Although renal transplantation may lead to improvement or normalization of autonomic function,[12] the time course of such improvement is often slow and may be incomplete, with significant change often occurring after 4-8 years[23]. Recent evidence suggests that the treatment with erythropoietin (EPO) may prove beneficial in CRF patients with neuropathy as well as for patients with neuropathy due to other etiologies[42]. Treatment with EPO improved motor nerve conduction velocity in CRF patients, but had no effect on sensory indices. In vitro studies have shown that EPO receptors are present on schwann cells and in dorsal root ganglion neurons[43]. Up regulation of EPO receptors occur after axonal injury, mediated by release of nitric oxide, and administration of exogenous EPO is associated with reduction in limb weakness and neuropathic pain behavior.

Conclusion:

Neuropathy occurs in 60 to 100% patients of ESKD. The first clinical documentation of neuropathy was

provided in the early 1960s. Peripheral neuropathy in end-stage kidney disease presents as a length-dependent, distal sensorymotor symmetrical polyneuropathy with greater lower limb than upper limb involvement. It generally develops at a glomerular filtration rate of less than 12 ml/min. The most frequent clinical features are those of large-fiber involvement, with paresthesias, reduction in deep tendon reflexes, impaired vibration sense, weakness and muscle wasting. Mononeuropathies are also a frequent clinical complication in CRF patients and most typically occur in the median, ulnar, and femoral nerves. In uremia susceptibility of the peripheral nerves to compression and local ischemia is increased. Autonomic neuropathy may develop in CRF patients and can play a role in the pathogenesis of intradialytic and orthostatic hypotension, in incontinence, diarrhoea, constipation, oesophageal dysfunction, hyperhydrosis and impotence. The pathologic features of peripheral neuropathy in patients of CRF are striking axonal degeneration in the most distal nerve trunks with secondary segmental demyelination. The condition has a predilection for large diameter axons, with relative sparing of the unmyelinated and small myelinated afferent neurons. The precise cause of uremic neuropathy remains unknown. One or several neurotoxic molecules of molecular weight 300-12000 Daltons called the “middle molecules” have been implicated in the pathogenesis of neuropathy of CRF. A comparison of hemodialysis and peritoneal dialysis with regard to neuropathy progression has demonstrated no significant difference between two dialysis forms. Renal transplantation remains the only known cure for uremic neuropathy with clinical improvement in sensory and, to a lesser extent, motor function occurring within a few days of transplantation.

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