Original Research Article

To study the spectrum of peripheral neuropathy in chronic kidney disease patients

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Abstract

Background: Chronic Kidney Disease (CKD) is a major public health problem in developed and developing countries, leading to decreased quality of life across the globe.

Aim: The clinical and electrophysiological features of peripheral neuropathy in patients with chronic renal failure. The correlation of various biochemical and hematological parameters to that of uremic peripheral neuropathy.

Materials and Methods: It was a prospective cross sectional study in 50 Patients admitted with advanced stages of chronic kidney disease.

Results: 50 CKD male patients were 30 (60%), female patients were 20 (40%). Among 20 females, 13 (65%) patients had ENMG evidence of polyneuropathy. Polyneuropathy was evident in 78%. Twenty one patients (42%) had clinical symptoms suggestive of polyneuropathy. In 8 patients (16%), it was only detected electrophysiologically. Motor conductions of the tibial, peroneal, median and ulnar nerves showed significant abnormalities in distal motor latency, compound motor action potential (CMAP) amplitude CV among the studied group. In patients with neuropathy there is predominant decrease in CMAP amplitudes with relatively decreased conduction velocity, and prolonged distal latency. Significant abnormalities were found in the peak latency, sensory nerve action potential (SNAP) amplitude and conduction velocity (CV) of the sural, median, ulnar nerves. In patients with neuropathy SNAP amplitudes were decreased significantly with relatively decreased conduction velocity. F wave parameters of peroneal, tibial nerves were abnormal in 30 (60%), and of

median 17 (34%), ulnar 16 (32%). We have observed that lower limb involvement is more common compared to upper limb. Sural nerve involvement is seen in all patients with electrophysiological evidence of neuropathy.

Conclusion: It can be concluded that axonopathic nature of polyneuropathy with predominant decrease in CMAP and SNAP was confirmed.

Key words

Spectrum, Peripheral neuropathy, Chronic kidney disease.

Introduction

Chronic Kidney Disease (CKD) is a major public health problem in developed and developing countries, leading to decreased quality of life across the globe. It is a well-known fact that patients of CKD are at increased risk of mortality as well as morbidity due to the myriad complications associated with this disease entity. Neurological complications, secondary to the uremic state, contribute largely to the morbidity and mortality in patients with renal failure. Despite continuous therapeutic advances, many neurological complications of uremia, like uremic encephalopathy, atherosclerosis, neuropathy, and myopathy fail to respond completely these treatment modalities. Although access to comprehensive dialysis programs and transplant facilities has become nothing short a routine protocol worldwide, the prevalence of neurological symptoms remains high in advanced renal dysfunction. Recent studies of neuropathy in the end stage renal disease (ESRD) have demonstrated that 70–100% of patients on dialysis experience neuropathic symptoms, despite attaining current targets of dialysis adequacy [1-3]. As almost all these patients will invariably develop neuromuscular disease, understanding the pathophysiological processes underlying neuropathic symptoms in ESRD patients is of highest priority for nephrologists dealing with this issue on routine basis. The most common neurological complication of CKD is peripheral neuropathy. The development of neuropathy has been widely attributed to the degree of renal impairment, with clinically significant neuropathy said to occur after the glomerular filtration rate drops to less than 12 mL/minute [4].

Recent advances in modalities of renal replacement have failed miserably to bring about any substantial reduction in the prevalence of neuropathy in this population. Although the prevalence of severe neuropathy may appear to have decreased to a certain extent, a significant cohort of ESRD patients still report symptoms which are considered functionally disabling, and even patients who meet accepted guidelines for dialysis adequacy may complain of neuropathic symptoms [5]. 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. Uremic neuropathy characteristically presents as a slowly progressive neuropathy which is symmetrical and length dependent, initially affecting the distal limbs, and gradually progressing more proximally [6]. The earliest symptoms usually reflect sensory dysfunction, resulting in paraesthesia, pain, and numbness mainly confined to the lower limbs, characteristically exhibiting a pattern of distal ‘‘stocking’’ sensory loss. With more severe disease, motor involvement develops, characterized by weakness, and muscle atrophy, again most prominent distally. Involvement of proximal regions of the lower limbs and upper limb develops in advanced disease. Peripheral neuropathy in CKD has been extensively studies since this condition was first described in ESRD patients on hemodialysis. Despite its significant contribution to morbidity in CKD patients,

clinicians in India tend to repetitively ignore the prevalence of this entity and the discomfort it causes to the patients, channelizing their treatment protocol toward managing the more severe and life threatening complications of CKD. Our hospital, a tertiary centre caterings to the needs of entire state, provides a significant platform to study this disease. We hereby have planned this study to assess the spectrum of peripheral neuropathy in patients of CKD, and correlate it with nerve conduction studies.

Materials and methods

50 Patients admitted to the Dept. of General Medicine, Neurology, Nephrology in Gandhi hospital between March 2015 - January 2017 and meeting the inclusion criteria and exclusion criteria were studied. It was a prospective cross sectional study.

Inclusion criteria were patients with advanced stages of chronic kidney disease.
Exclusion criteria were patients with diabetes, collagen vascular disease, amyloidosis, primary neurological disorder, patients receiving other drugs known to effect peripheral nerve function, alcoholics.

History taking with special emphasis on cause, onset, duration of kidney disease, duration of hemodialysis, detailed neurological history with particular reference to presence of risk factors for polyneuropathy and the occurrence of symptoms indicating peripheral neurological damage was done. Each patient was alert, fully oriented, cooperative and responsive during all phases of testing. Complete neurological examination was done with special emphasis on peripheral nerve examination. All patients in the study group were on weekly twice HCO3-based hemodialysis using BBRAUN HD machine. Mean kt/v in the study group was 1.2 ± 0.2. Hemodialysis was performed using appropriate sized hollow fibre for the duration of 4 hours with IJV catheter initially and later AV fistula as vascular access. Unfractionated heparin was used for systemic anticoagulation. Informed consent was taken from all subjects before inclusion in the study. The laboratory investigations were performed for every patient before electrophysiological examination. Median, ulnar, common peroneal and tibial nerves were tested bilaterally. The assessed parameters were distal latency (DL), amplitude and duration of the compound muscle action potential (CMAP), conduction velocity, F wave latency. Sensory nerve conduction studies, Ulnar, Median and Sural nerves were tested bilaterally. The Onset latency, amplitude of sensory nerve action potential (SNAP) and nerve conduction velocity (CV) were the recorded sensory parameters. For all patients, S. creatinine estimation was done based on modified Jaffe's method. Electrophysiological evaluation: were done by using RMS Machine. The electrophysiological study was done the day next to dialysis session. Various clinical parameters (age, sex, nature of CKD, duration of hemodialysis) and laboratory parameters including anemia, s. creatinine, s. potassium, s. calcium, s. phosphorous and s. PTH were analyzed in relation to peripheral neuropathy. Statistical analysis was performed by utilizing SPSS software. Initially frequency tables were made to estimate the frequency & percentage of each parameter analyzed. Descriptive statistics were expressed in terms of minimum, maximum, mean and standard deviation. Logistic regression was used for the prediction of occurrence of an event. The probability of association between two discrete attributes was made by chi square test. Means of the various parameters were compared by using student t- test (for 2 groups) or by ANOVA (for more than 2 groups).

Results

50 CKD patients who were on maintenance hemodialysis were included in this study. (Total 20 females and 30 males). Sex distribution of the study was that male patients were 30 (60%), female patients were 20 (40%). Among 20 females, 13 (65%) patients had ENMG evidence of polyneuropathy. Out of the total 30 males, 26

(86.7%) patients had ENMG evidence of polyneuropathy.

Table - 1 shows that no correlation was found between the sex distribution and presence or absence of neuropathy. The mean age was 34.5±13.5 years with minimum age in the study group being 11 years and maximum 58 years.

Table – 1: Neuropathy on NCS, age and sex distribution of the study group.

Neuropathy on NCS				
Sex			Absent	Present
	Female	Number (%)	7 (35%)	13 (65%)
	Male	Number (%)	4 (13.3%)	26 (86.7%)
	Total	Number (%)	11 (22.0%)	39 (78%)
Age groups (years)	Number of patients (50)			
	Male		Female	Total
11-20	8		2	10
21-30	5		6	11
31-40	7		5	12
41-50	4		7	11
51-60	6		0	6

Table - 2: Etiology of CKD in study.

Aetiology of CKD	**No. of patients with neuropathy**	**No. of patients without neuropathy**	**Total**
CGN	14	05	19
CIN	10	03	13
HTN	04	01	05
Obstructive CKD	04	01	05
Congenital	03	0	03
others	04	01	05

Table - 3: Neuropathy observed in study.

	Total No. of patients (%)		
		Present (%)	**Absent (%)**
Symptomatic	21(42%)	21 (100%)	0
No symptoms, only signs positive	10(20%)	10(100%)	0
No symptoms or signs	19(48%)	08(16%)	11(22)

Etiology of CKD was as per **Table – 2**. Neither patient's age, nor nature of underlying kidney disease was associated with occurrence of polyneuropathy. Out of the 50 CRF patients, polyneuropathy was evident in 78%. Twenty one patients (42%) had clinical symptoms suggestive of polyneuropathy. Another 10 patients (20%) had only objective evidence of neuropathy on examination without symptoms of polyneuropathy. In 8 patients (16%), it was only detected electrophysiologically (**Table – 3**).

Table - 3 shows that Tingling and numbness present in hands and feet in 21 (42%) patients. Weakness of hands and feet present in 12 (24%) loss of vibration sensation in lower limbs, loss of light touch, loss of pain and temperature sensation was seen in 31 (62%), 15 (30%), 14 (12%) of patients respectively. Restless leg

syndrome was present in 10(20%) patients. Autonomic dysfunction in the form of postural hypotension present in 9(18%) cases, Erectile dysfunction was seen in 6(12%). The mean duration of their kidney disease was 14.16 ± 19 months .The mean duration of hemodialysis were 19.18± 13 wks. The duration of dialysis in the polyneuropathy group didn't differ significantly from those without neuropathy.

Table - 4: Biochemical parameters.

Parameter	Neuropathy	Mean	Std. Deviation	Std. Error Mean	P value
Age	absent	33.727	14.9539	4.5088	0.714
	present	35.368	12.1864	1.9769	
Hb	absent	9.018	2.0252	0.6106	0.232
	present	8.654	1.4009	0.2243	
Na	absent	142.00	7.443	2.244	0.776
	present	140.18	6.529	1.045	
K	absent	4.691	0.6252	0.1885	0.007
	present	5.533	0.4619	0.0740	
cr	absent	7.518	2.5127	0.7576	0.298
	present	7.262	2.3671	0.3790	
Ca++	absent	8.564	0.8617	0.2598	0.081
	present	8.174	0.6828	0.1093	
Po4-	absent	5.082	1.2521	0.3775	0.198
	present	4.936	1.2315	0.1972	

Table - 5: Conduction velocity and prolonged distal latency in study

Nerve tested	Predominant Decrease in CMAP amplitude	Decrease Conduction velocity	Prolonged distal latency
Peroneal	38 (76%)	35(70%)	24(48%)
Tibial	34(68%)	33(66%)	21(42%)
Ulnar	18(36%)	18(36%)	3(6%)
Median	17(34%)	17(34%)	3(6%)

Table - 6: SNAP amplitude and conduction velocity in study.

Nerve tested	Decrease SNAP amplitude	Decreased Conduction velocity
Sural	39 (78%)	37(74%)
Median	22(44%)	24(48%)
Ulnar	20(40%)	23(46%)

In this study population we have observed that mean Hb were higher in patients without neuropathy compared to patients with neuropathy, but this association was not statistically significant (p value 0.23). A significant positive correlation was found between the level of serum potassium and presence of polyneuropathy (P value 0.007). No correlation was found between the hemoglobin concentration, other tested biochemical parameters (s. calcium, s. phosphorous) and the presence or absence of neuropathy. Conduction velocity and prolonged distal latency in study was as per **Table – 4**.

Table - 5 shows Motor conductions of the tibial, peroneal, median and ulnar nerves showed significant abnormalities in distal motor latency, compound motor action potential (CMAP) amplitude CV among the studied group. In

patients with neuropathy there is predominant decrease in CMAP amplitudes with relatively decreased conduction velocity, and prolonged distal latency.

Table - 6 shows significant abnormalities were found in the peak latency, sensory nerve action potential (SNAP) amplitude and conduction velocity (CV) of the sural, median, ulnar nerves. In patients with neuropathy SNAP amplitudes were decreased significantly with relatively decreased conduction velocity. F wave parameters of peroneal, tibial nerves were abnormal in 30 (60%), and of median 17 (34%), ulnar 16 (32%).We have observed that lower limb involvement is more common compared to upper limb. Sural nerve involvement is seen in all patients with electrophysiological evidence of neuropathy.

Discussion

Dysfunction of the peripheral nervous system induced by uremia commonly occurs in patients with end-stage renal disease [7]. Peripheral polyneuropathy generally develops only in advanced renal failure and is an indication to initiate dialysis. The development of uremic neuropathy is exceedingly common in CKD, with prevalence rates of 60-90% in the dialysis population [8]. Uremic neuropathy is a distal sensorimotor polyneuropathy 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. Rarely, patients undergoing maintenance dialysis develop a rapidly evolving polyneuropathy simulating the Guillain-Barre syndrome [9]. Several electrophysiological studies in adults demonstrated that almost 80% of CKD patients had electrophysiological signs of impaired nerve function, although only one half of these patients were symptomatic. Bolton, et al. [10] showed almost 80 percent of patients have electrophysiological signs of impaired nerve function, and only one-half of these patients were symptomatic. As Per the Study conducted by Arch Neurol, et al. [11], Studies of late responses and sural conduction, in addition to improving the diagnostic yield, provide a method whereby effects of dialysis and medical management can be followed quantitatively in patients whose neuropathy would otherwise be undetectable. Nielsen, et al. [12] showed that in patients with chronic kidney disease, 77% reported clinical symptoms and 51% had clinical signs of a neuropathy. In our study population of CKD, clinically evident neuropathy was present in 62% with symptomatic neuropathy in 42% and the remaining 20% were asymptomatic with only objective evidence of neuropathy. In only 16% of patients, neuropathy was demonstrated only on electrophysiological examination without clinical symptoms or signs. In majority of patients with NCS evidence of neuropathy, it was evident clinically, so patients with CKD should be clinically evaluated for neuropathy during routine examination.

The present study revealed that the prevalence of uremic neuropathy was not related to the patient's age, nature of underlying kidney disease or duration of dialysis treatment. These findings were consistent with Mendoza. Guevara, et al. [13], Ibrahim Sultan, et al. [14] showed that hyperkalemia even if moderate may contribute to uremic neurotoxicity. In the present study also significant correlation was found in the mean serum K+ between patients with and those without neuropathy. Moreover the serum K+ level was found to be positively correlated with the degree of polyneuropathy measured by Nerve conduction studies (NCS). Prolonged hyperkalemia may cause disruption of normal ionic gradient which are essential for axonal survival, thereby leading to accumulation of Ca+ [2] within the cell and subsequent axonal degeneration. Hyperkalaemia may present in dialysis patients with generalized muscle weakness in association with a reduction in peripheral sensation, in a stocking distribution

with loss of reflexes. Hypermagnesaemia can also cause muscle weakness and peripheral neuropathy. Profound hypocalcaemia following parathyroidectomy can lead to tetany, with carpopedal spasm, as can severe hypomagnesaemia. But, Apart from potassium, there was no evidence for an effect on the nerve conductivity of other biochemical parameters (Hb%, S. Creatinine, S. calcium, S. Phosphorous, S. PTH) in the present study, however the NCVs of all the tested nerves decreased significantly with increase in serum creatinine levels ($p < 0.01$): 70% of the patients had uremic polyneuropathy in the study conducted by Aggarwal HK, et al. [15], pub 2013 Aug 21, and some authors have reported that creatinine levels under 5 mg/dL are rarely associated with polyneuropathy, especially not alteration of conduction velocity, but that patients with levels above 7 mg/dL commonly develop these anomalies.

Patients with evidence of neuropathy were treated symptomatically with neurotropic drugs. But no significant symptomatic response was seen indicating that renal transplantation is the only definitive treatment of uremic neuropathy. Renal transplantation remains the only cure for uremic neuropathy and must be considered in any patient with progressive neuropathy. Following transplantation, clinical recovery typically occurs over a period of 3-6 months, although some patients continue to experience improvement for up to 2 years. Crucially, patients with severe neuropathy can fail to recover, emphasizing the need for preventive strategies. Standard three times per week dialysis regimens generally halt the progression of neuropathy, but such regimens rarely result in substantial clinical improvement. Progressive neuropathy, however, is both an indication for the commencement of dialysis therapy and an important indicator of insufficient dialysis. Patients with neuropathy must, therefore, meet the current guidelines of dialysis adequacy. In some cases, alterations to the dialysis regimen, such as a change to daily dialysis or high-flux dialysis will prevent clinical deterioration. In CKD patients with demyelinating neuropathy, standard immunomodulatory treatments such as intravenous immunoglobulin have been used with some success, although the potential benefits must be balanced against the small but well-documented risk of nephrotoxicity. This issue is particularly pertinent to patients who have some residual kidney function, and in whom nephrotoxic complications could precipitate the need for dialysis treatment. Accordingly, plasma exchange and steroid treatment should be considered as potential alternatives to intravenous immunoglobulin.

Patients with painful neuropathy benefit from treatment with tricyclic antidepressants, such as amitriptyline, or with anticonvulsant medications, such as sodium valproate or gabapentin. Vitamin supplementation with pyridoxine and methylcobalamin has also been shown to improve neuropathic pain in CKD, while exercise training programs might improve muscle strength, cardiorespiratory function and work capacity. Autonomic dysfunction is a common and potentially life-threatening complication of CKD, and can occur in the absence of length-dependent uremic neuropathy. Cardiovascular autonomic dysfunction in CKD is associated with an increased risk of cardiac arrhythmia and sudden cardiac death. Assessment of autonomic function has demonstrated abnormalities in 60% of patients with CKD, particularly relating to measures of parasympathetic function, such as heart rate response to deep breathing, induced hypotension, and the Valsalva maneuver. Impotence remains the most common symptom of autonomic dysfunction in CKD, and it develops in majority of male patients. Other common clinical features include bladder and bowel dysfunction, impaired sweating, and orthostatic intolerance. Arterial calcification might contribute to autonomic symptoms in CKD by reducing the sensitivity of baroreceptors in the arterial wall that mediate the short-term regulation of blood pressure. In addition to a potential role in sudden cardiac death, reduced baroreflex sensitivity can also contribute to intra

dialytic hypotension, a condition occurring during dialysis that is characterized by an abrupt reduction in blood pressure without a compensatory increase in heart rate. Management includes withdrawal of drugs, which block autonomic nerves and dialysing the patient in a chair, and maintaining an adequate hematocrit, more than 30 per cent. Hemodialysis patients should be dialysed with cooled dialysate and may benefit from blood volume and reverse sodium profiling. Sertraline, a selective serotonin reuptake inhibitor, and venlafaxine, which additionally reduces nor-adrenaline reuptake, reduces intra dialytic hypotension.

Conclusion

In the present study conducted on 50 patients with CKD, polyneuropathy was present in the 78% of patients. No correlation was found between age, sex distribution, duration of dialysis and presence or absence of neuropathy. Mean age was 34.5 to 13.5. Mean duration of kidney disease was 14.16 to19 months. It can be concluded that axonopathic nature of polyneuropathy with predominant decrease in CMAP and SNAP was confirmed.

References

1. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Bostock H,Kiernan MC. Altered motor nerve excitability in end-stage kidney disease. Brain, 2005; 128: 2164–2174.
2. Laaksonen S, Metsarinne K, Voipio-Pulkki LM, Falck B. Neurophysiologic parameters and symptoms in chronic renal failure. Muscle Nerve, 2002; 25: 884–890.
3. Tilki HE, Akpolat T, Coskun M, Stalberg E. Clinical and electrophysiologic findings in dialysis patients. J Electromyogr Kinesiol., 2009; 19(3): 500–508.
4. Brouns R, De Deyn PP. Neurological complications in renal failure: a review. Clin Neurol Neurosurg., 2004; 107: 1–16.
5. Ogura T, Makinodan A, Kubo T, Hayashida T, Hirasawa Y. Electrophysiological course of uraemic neuropathy in hemodialysis patients. Postgrad Med J., 2001; 77(909): 451–454.
6. Bolton CF, Baltzan MA, Baltzan RB. Effects of renal transplantation on uremic neuropathy. A clinical and electrophysiologic study. N Engl J Med., 1971; 284: 1170–1175.
7. Krishnan AV, Kiernan MC. Uremic neuropathy: clinical features and new pathophysiological insights. Muscle Nerve, 2007; 35: 273.
8. Krishnan A. V., Pussell B. A., Kiernan M. C. Neuromuscular disease in the dialysis patient: an update for the nephrologist. Semin. Dial., 2009; 22: 267- 278.
9. Ropper, AH. Accelerated neuropathy of renal failure. Arch Neurol., 1993; 50: 536.
10. Bolton CF, Young GB. Uremic neuropathy. In: Neurological Complications of Renal Disease. Butterworth, Boston, 1990, p. 76-107.
11. Ackil AA, Shahani BT, Young RR, Rubin NE Late response and sural conduction studies. Usefulness in patients with chronic renal failure. 1981 Aug; 38(8): 482-5.
12. Nielsen VK. Recovery from peripheral neuropathy after renal transplantation. Acta Neurol Scand., 1970; 46:Suppl 43: 207.
13. Lobna Ibrahim Sultan, et al. Evaluation of The Clinical and Neurophysiologic Parameters of Peripheral Nerve Functions in Uremic Egyptian Patients. Egypt J. Neurol. Psychiat. Neurosurg., 2007; 44(2): 473- 487.
14. Bostock H, Walter RJ, Andersen WK, Murray NM, Taube D, Kiernan MC. Has Potassium been prematurely discarded as a contributing factor to the development of uremic neuropathy.

Nephrol Dial Transplant., 2004; 19: 1054-7.

15. Aggarwal HK, Sood S, Jain D, Kaverappa V, Yadav S. Evaluation of spectrum of peripheral neuropathy in predialysis patients with chronic kidney disease. 2013; 35(10): 1323-9.