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Original Research Article

Electrophysiological study of peripheral neuropathies in chronic kidney disease patients and relation of severity of peripheral neuropathy with degree of renal failure

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ABSTRACT

Background: Patients with chronic kidney disease (CKD) are frequently afflicted with neurological complications. Peripheral neuropathy occurs in 60-100% patients of CKD. Nerve conduction study is the gold standard method to diagnose uremic neuropathy. In this study we have examined the correlation of nerve conduction latency, amplitude and nerve conduction velocity with serum creatinine, blood urea, serum uric acid levels and compared these parameters among dialysis and non-dialysis dependent CKD patients.
Methods: The present cross-sectional study was conducted on 100 adult patients diagnosed to have and treated for CKD. All cases were subjected to nerve conduction study (NCS) which was performed on median nerve, ulnar nerve, common peroneal nerve, tibial nerve and sural nerve.
Results: The prevalence of neuropathy was 68% in both dialysis and non-dialysis dependent groups. The most involved nerve was sural nerve. On NCS, there was prolongation of nerve latency, decrease in nerve amplitude and nerve conduction velocity with rising blood urea and serum creatinine levels. All these abnormalities were more evident in dialysis dependent patients as compared to non-dialysis dependent patients. Depressed amplitude was the most common abnormality in all the tested nerves.
Conclusions: The nerve latency, amplitude and nerve conduction velocity worsened with rise in blood urea, serum creatinine and decrease in eGFR suggesting that neuropathy progress with increased severity of renal failure. Nerve conduction abnormalities were more prominent in dialysis dependent patients and therefore was associated with more advanced stage of CKD.

Keywords: Chronic kidney disease, Nerve conduction study, Neuropathy

INTRODUCTION

Chronic kidney disease (CKD) is one of the leading causes of chronic disease with 8-16% worldwide prevalence. The number of CKD patients is increasing day by day, reflecting the growing elderly population and increasing numbers of patients with diabetes and hypertension. Diabetes mellitus, along with hypertension, is now the major cause of end-stage renal failure worldwide.[1] CKD is usually asymptomatic until late stages and is commonly detected by routine blood testing during the evaluation of comorbid conditions. Symptoms are usually due to complications of decreased kidney function and when severe, they can be treated only by dialysis or transplantation. Approximately 60% of the population with CKD encounters neurological complications which affect at all the levels of nervous system, including stroke, cognitive dysfunction, encephalopathy, peripheral and autonomic neuropathies, resulting in altered mental state, continued disability, and weakness.[2,3] Uremic neuropathy

is one of the most common neurological complications of uremia. Uremic polyneuropathy is a distal, symmetrical, mixed sensorimotor neuropathy which usually affects large diameter axons.[4] It is often multifactorial and is exacerbated by nutritional deficiency, hypocalcemia, and hypomagnesemia. Uremic toxins such as guanidine compounds, polyamines, phenols, indican, myo-inositol, 'middle molecules', advanced glycation end products, β-2 microglobulin, PTH, were proposed as causative agents of uremic neuropathy.[5,6] However, none of these have yielded evidence of causality.[7]

The occurrence of neuropathy is highly correlated with the severity and duration of renal failure. Chronic dialysis may prevent neuropathy in some patients, especially if begun early. Renal transplantation is generally the most successful method to prevent neuropathy.[8] Uremic neuropathy is usually asymptomatic until renal function is under 15%, and glomerular filtration is lower than 10–12 ml/min.[9] Early symptoms are paresthesia, paradoxical heat sensation, restless leg syndrome, increased pain sensation, and cramps. Long-term symptoms include weakness, impaired deep tendon reflexes, imbalance, numbness, and atrophy of the lower limbs.[4]

Neuropathy can be diagnosed by various methods like medical history, neurologic examination, and electrophysiological studies. Nerve conduction study is the gold standard method for diagnosis of neuropathy and for establishing the type of peripheral neuropathy.[10] The measurements for nerve conduction study include onset latency, duration, amplitude and nerve conduction velocity. Median nerve, ulnar nerve, common peroneal nerve, tibial nerve and sural nerve are the commonly tested nerves for nerve conduction study.

Although the prevalence of neuropathy and its clinical signs and symptoms have been classically described in various studies, the data about electrophysiological features in CKD patients is very sparse in Indian literature. The correlation of neuropathy with individual serological, biochemical abnormalities (urea, creatinine, uric acid, calcium, magnesium, phosphate) is also not well established in previous studies. Due to this lack of knowledge the present study was undertaken to compare the nerve conduction parameters (nerve latency, amplitude, nerve conduction velocity) among both dialysis dependent and non-dialysis dependent CKD patients, and their correlation with serum creatinine, blood urea and serum uric acid levels.

METHODS

The study was a cross sectional, observational hospital-based study. The study was conducted on 100 adult patients diagnosed to have CKD and treated for it in Emergency, Medicine and Nephrology OPD and inpatient wards at Jawaharlal Nehru Medical College (JNMC) and Hospital, Aligarh from December 2018 to December 2020.

Inclusion criteria

All patients of age ≥18 years with CKD on drug therapy. All patients of age ≥18 years with CKD on regular hemodialysis.

Exclusion criteria

Age less than 18 years. Patients with other known cause of peripheral neuropathy. Patients on drug therapy known to cause peripheral neuropathy as side effect. Electrically sensitive patients. Allergy to electrode or contact material (tape/gel). Subjects with reduced levels of consciousness or impaired understanding.

Methodology

The 100 consecutive CKD patients were divided into two groups as shown in Table 1. Group 1 included 50 dialysis-dependent CKD patients while Group 2 included 50 non-dialysis dependent CKD patients. Each group was further divided into two subgroups which included diabetic patients and non-diabetic patients.

Table 1: Distribution of patients among groups.

S. No.	Group	DM/NDM		
		DM	NDM	Total
1	Dialysis	24	26	50
2	Non-dialysis	31	19	50
3	Total	55	45	100

All patients were subjected to detailed history, general physical examination, and neurological examination. The routine renal and other biochemical investigations including blood urea (mg/dl), serum creatinine (mg/dl), serum uric acid (mg/dl), Hemogram, blood sugar (mg/dl), arterial blood gas analysis, serum sodium, serum potassium, serum corrected calcium, serum phosphorus, serum protein (g/dl), iPTH levels (pg/ml), serum vitamin D, urine routine and microscopy were done as per the standard methods in JNMCH, Aligarh. eGFR was estimated using Cockcroft-Gault equation.

All cases were subjected to nerve conduction studies (NCS) using Nicolet EDX NCS/ EMG/ EP/ IOM system in the clinical neurophysiology unit, Department of Medicine. The nerve conduction studies were performed in all patients on all 4 limbs. Median nerve, ulnar nerve, common peroneal nerve and tibial nerve were assessed for motor conductions. Median nerve, ulnar nerve and sural nerve were assessed for sensory conduction. The latency, CMAP amplitude and conduction velocity were derived for each nerve.

Statistical analysis

The data was collected and tabulated using Microsoft Excel 365 and analyzed using Statistical package for social

science (SPSS) version 25.0. Results were expressed as mean+SD. All the qualitative variables were analyzed using Pearson chi square test. The variables were compared in two groups using independent sample t test. Pearson product moment correlation analysis was used to study the correlation between the variables. For all analysis, p-value less than 0.05 was considered as statistically significant.

RESULTS

The mean age of patients in the present study was 55.45±15.95 years. Majority of patients were of age group 31-60 years in both dialysis and non-dialysis dependent groups. Males (n=59) outnumbered females (n=41).

Table 2: Prevalence of neuropathy.

	No. of patient	Patients with peripheral neuropathy	%	P value
Dialysis	50	34	68	<0.01
Non-dialysis	50	34	68	<0.01
Total	100	68	68	<0.05

The mean blood urea, serum creatinine, mean uric acid and mean eGFR were 76.10±36.27, 5.14±3.07, 6.59±1.65 and 17.64±9.46 respectively. The mean blood urea was higher in dialysis dependent group (89.38±38.59) as compared to non-dialysis dependent group (62.82±28.44).

Table 3: Nerve conduction abnormalities in 100 CKD patients.

Nerves		No. of cases	Dialysis	Non-dialysis	Ch^2-value	P value
Median nerve (motor)						
Latency	Normal	80/100	38/50	42/50	36	<0.001
	Increased	20/100	12/50	8/50		
Amplitude	Normal	57/100	26/50	31/50	1.96	<0.05
	Decreased	43/100	24/50	19/50		
Velocity	Normal	87/100	41/50	46/50	54.76	<0.001
	Decreased	13/100	9/50	4/50		
Ulnar nerve (motor)						
Latency	Normal	87/100	44/50	43/50	54.76	<0.001
	Increased	13/100	6/50	7/50		
Amplitude	Normal	47/100	21/50	24/50	0.36	>0.05
	Decreased	53/100	29/50	24/50		
Velocity	Normal	74/100	33/50	41/50	23.04	<0.001
	Decreased	26/100	17/50	9/50		
Peroneal nerve						
Latency	Normal	67/100	36/50	31/50	11.56	<0.01
	Increased	33/100	14/50	19/50		
Amplitude	Normal	31/100	14/50	17/50	14.44	<0.001
	Decreased	69/100	36/50	33/50		
Velocity	Normal	60/100	32/50	28/50	4	<0.05
	Decreased	40/100	18/50	22/50		
Tibial nerve						
Latency	Normal	79/100	41/50	38/50	33.64	<0.001
	Increased	21/100	9/50	12/50		
Amplitude	Normal	47/100	23/50	24/50	0.36	>0.05
	Decreased	53/100	27/50	26/50		
Velocity	Normal	57/100	31/50	26/50	1.96	>0.05
	Decreased	43/100	19/50	24/50		
Median nerve (sensory)						
Latency	Normal	45/100	22/50	23/50	1	>0.05
	Increased	55/100	28/50	27/50		
Amplitude	Normal	75/100	36/50	39/50	25	<0.001
	Decreased	25/100	14/50	11/50		
Velocity	Normal	46/100	27/50	19/50	0.64	>0.05
	Decreased	54/100	23/50	31/50		
Ulnar nerve (Sensory)						
Latency	Normal	83/100	45/50	38/50	43.56	<0.001

Continued.

Nerves		No. of cases	Dialysis	Non-dialysis	Ch^2-value	P value
	Increased	17/100	5/50	12/50		
Amplitude	Normal	71/100	37/50	34/50	17.64	<0.001
	Decreased	29/100	13/50	16/50		
Velocity	Normal	56/100	31/50	25/50	1.44	>0.05
	Decreased	44/100	19/50	25/50		
Sural nerve						
Latency	Normal	33/100	15/50	18/50	11.56	<0.01
	Increased	67/100	35/50	32/50		
Amplitude	Normal	34/100	15	19/50	10.24	<0.01
	Decreased	66/100	35/50	31/50		
Velocity	Normal	34/100	15/50	19/50	10.24	<0.01
	Decreased	66/100	35/50	31/50		

Table 4: Comparison of nerve conduction parameters of 100 CKD patients.

Median nerve (motor)	Mean ± SD		
	Latency	**Amplitude**	**Velocity**
Dialysis	3.57 ± 0.85	6.47±1.99	50.75±5.10
Non-dialysis	3.44±0.71	6.78±2.06	53.92±4.42
Total	3.51±0.79	6.63±2.02	52.34±5.01
Ulnar nerve (motor)			
Dialysis	2.55±0.49	6.86±2.82	46.39±8.20
Non-dialysis	2.64±0.51	7.37±2.18	50.24±5.39
Total	2.60±0.50	7.12±2.52	48.32±7.17
Peroneal nerve			
Dialysis	3.78±0.91	2.74±2.16	46.26±5.81
Non-dialysis	3.73±0.91	3.31±2.40	46.60±5.45
Total	3.76±0.91	3.02±2.28	46.43±5.61
Tibial nerve			
Dialysis	4.13±0.99	5.90±3.80	42.86±8.54
Non-dialysis	4.01±1.23	6.52±3.81	43.07±8.53
Total	4.07±1.11	6.19±3.80	42.97±8.49
Median nerve (sensory)			
Dialysis	4.12±0.56	34.96±19.57	49.02±11.17
Non-dialysis	4.22±0.84	36.09±20.95	46.76±11.60
Total	4.18±0.71	35.51±20.15	47.93±11.38
Ulnar nerve (sensory)			
Dialysis	3.42±0.41	29.87±20.20	53.07±10.54
Non-dialysis	3.41±0.60	26.67±13.78	48.72±10.16
Total	3.42±0.51	28.29±17.30	50.93±10.53
Sural nerve			
Dialysis	4.84±0.58	17.81±2.63	58.16±4.32
Non-dialysis	4.79±0.65	25.61±12.63	54.97±4.99
Total	4.82±0.62	22.18±10.27	56.38±4.91

The mean serum creatinine was higher in dialysis dependent group (7.19±2.94) as compared to non-dialysis dependent group (3.09±1.31). The mean serum uric acid was comparable in both groups. The mean eGFR was 10.82±4.03 in dialysis dependent patients and 24.46±8.34 in non-dialysis dependent patients. The prevalence of neuropathy was 68% in both dialysis and non-dialysis dependent groups (Table 2).

Comparison of nerve conduction parameters of dialysis dependent and non-dialysis dependent CKD patients is shown in Table 4.

From correlation of median nerve (motor) graph (Figure 1), it was found that as the blood urea and serum creatinine levels rise, the peripheral nerve dysfunction increase i.e. nerve latency prolongs while nerve amplitude and nerve conduction velocity decreases.

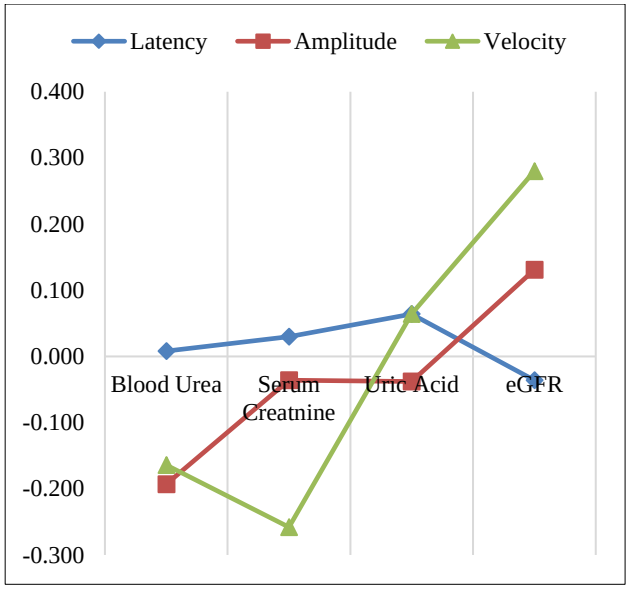

Figure 1: Correlation of median nerve (motor).

DISCUSSION

CKD is characterized by irreversible and gradually progressive decline of renal function. Patients of CKD are at increased risk for mortality as well as morbidity due to the myriad complications associated with this disease. Neurological complications, secondary to the uremic state, contribute largely to the morbidity and mortality in patients with renal failure. Uremic neuropathy is the most common neurological complication seen in CKD. There is segmental demyelination and axonal degeneration in peripheral nerves. 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. In studies it was found that signs of neuropathy are generally lacking if the creatinine clearance exceeds 60 mL/min.[11] Thus, the chronicity and severity of kidney disease appear to be an important cause related to the development of neuropathy.

Most patients having features of peripheral neuropathy do not come out with complaints of it unless specifically asked or looked for. Thus, a clinician faces a problem in diagnosing the presence of peripheral neuropathy. Nerve conduction studies are the most sensitive detector of neuropathy and are the most used diagnostic procedure for establishing the presence and type of peripheral neuropathy.

The prevalence of neuropathy in the present study was almost similar to that of previous studies which have established that 60 to 100% of patients with ESRD suffer from peripheral neuropathy.[12]

In contrast to previous Indian studies where nerve conduction studies were done on pre-dialysis CKD patients while those on hemodialysis were excluded, this study was conducted on both dialysis-dependent and non-dialysis dependent CKD patients.[13,14] Dialysis dependent patients had more advanced stage of CKD as compared to non-dialysis dependent patients. Thus, the nerve conduction parameters were compared in both the groups to correlate the extent of nerve damage to different stages of renal disease.

On comparing nerve conduction parameters, it was found that there was significant decrease in SNAP amplitude of sural nerve in dialysis dependent patients (17.81±2.63) as compared to non-dialysis dependent patients (25.61±12.63) (Table 4). In a study by Krishnan et al it was stated that sural sensory nerve action potential is the most sensitive indicator of uremic neuropathy.[15] The most commonly involved nerve is sural nerve as sural sensory nerve latency was increased in 67% patients, SNAP amplitude was depressed in 66% patients and nerve conduction velocity was depressed in 66% patients (Table 3). Other commonly involved nerves were common peroneal nerve, tibial nerve, median nerve (motor) and ulnar nerve (motor).

The most common nerve conduction abnormality was depressed nerve amplitude, both in dialysis and non-dialysis dependent groups (table 3), suggesting axonal neuropathy as the most common pattern found in CKD patients.

All the abnormalities were more in dialysis dependent patients than non-dialysis dependent patients suggesting that neuropathy tends to worsen with advanced stage of CKD. Thus, patients who are on maintenance dialysis have more prevalence of peripheral neuropathy when compared to predialysis patients. Previous studies by Jasti et al and Aggarwal et al compared the abnormalities among patients of mild and severe renal failure and found worsening of neuropathy with advancement of CKD stage.[13,14]

There was significant correlation between nerve latency, amplitude and conduction velocity and serum creatinine and blood urea. However, there is no specific correlation of nerve latency amplitude and velocity with serum uric acid. This correlation may be due to deterioration of renal disease with rise in blood urea and serum creatinine. Also there was significant correlation of nerve latency, amplitude and velocity with eGFR.

The occurrence of neuropathy is highly correlated with the severity and duration of renal failure. Nerve conduction studies play a major role in detecting subclinical neuropathy. It can also help in monitoring the progress of neuropathy during a long period, particularly if the patient is asymptomatic. Chronic dialysis may prevent neuropathy in some patients if begun early. Chronic hemodialysis may stabilize neuropathy in most patients. However, the course of neuropathy cannot be improved with certainty simply by manipulating the hemodialysis schedule. Peritoneal dialysis is associated with a lower incidence of uremic neuropathy than hemodialysis because peritoneal dialysis

is often characterized by better removal of mid-weight molecules. 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.

CONCLUSION

Peripheral neuropathy is a common neurological complication in CKD patients. Pure axonal neuropathy is the most common pattern and sural nerve is the most common nerve involved. Nerve conduction abnormalities were more prominent in dialysis dependent than in non-dialysis dependent patients suggesting increased prevalence of neuropathy with advancement of CKD stage. The nerve latency, amplitude and nerve conduction velocity worsen with rise in blood urea, serum creatinine and decrease in eGFR suggesting that neuropathy progresses with increased severity of renal failure.

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