

Peripheral Neuropathy in Children With Chronic Kidney Disease: Are We Looking Enough?

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Abstract

Background: Peripheral neuropathy in chronic kidney disease (CKD) is the most common neurological complication. We aimed to look at the prevalence and patterns of neuropathy in children with CKD. **Methods:** This cross-sectional study was conducted over 1 year in children with CKD, stage III and above. Nerve conduction studies (NCS) were performed as per standard protocols using surface electrodes on the muscles and by supramaximal stimulation of the corresponding nerves. Presence of electrophysiological abnormalities in the absence of clinical symptoms or signs was considered as subclinical neuropathy. **Results:** Nearly 45 children were evaluated. The majority were males ($n = 39$, 86.7%). The mean age was 7.9 ± 3 years (range 2–14). The mean estimated glomerular filtration rate (GFR) at enrolment was 23.3 ± 14.6 mL/min/1.73 m² (range 5–67). The majority of children were in stage III ($n = 19$, 42%), followed by stages V ($n = 15$, 33%) and IV ($n = 11$, 25%). There was no evidence of clinical neuropathy; 13 children (29%) showed subclinical neuropathy. All the nerves had an axonal pattern of involvement. Motor polyneuropathy was most common type of peripheral neuropathy. The commonest nerves involved were tibial and common peroneal nerves. There were no biochemical or clinical predictors of neuropathy in our cohort. **Conclusion:** The prevalence of subclinical neuropathy is high in children with CKD, stage III and above. Axonal motor polyneuropathy is the predominant pattern. Electrophysiological assessment of nerve function should be routinely done in children with advanced stages of CKD to prevent chronic complications.

Keywords: Children, chronic kidney disease, peripheral neuropathy, renal disease, subclinical neuropathy, uremic neuropathy

INTRODUCTION

Peripheral neuropathy in chronic kidney disease (CKD), also known as uremic neuropathy, is one of the common neurological complication associated with a disorder. It affects up to 70% of pre-dialysis and 90% of dialysis patients.^[1-3] It usually occurs with a glomerular filtration rate (GRF) <12 mL/min/1.73 m².^[4] The pathogenesis is complex and multifactorial, including altered metabolic milieu. It affects both sensory and motor nerves. Neuropathy is considered an indication to initiate renal replacement therapy, especially when there is a loss of motor function. The neuropathy commonly begins as a distal, symmetrical, loss of sensation to pinprick and vibration in the lower limbs, with or without diminished reflexes, and may lead to motor weakness and muscle atrophy.^[3]

This comorbidity has received less attention in pediatric CKD compared to chronic diseases such as type 1 diabetes.^[5-7] In the absence of standardized guidelines and protocols for evaluation, peripheral neuropathy in children with CKD is probably under-recognized, especially in resource-constraint settings. Identification of peripheral neuropathy at an early stage of the disease and the factors predisposing to its development will help in risk stratification and selection of subjects for targeted interventions, thus preventing complications such as ulceration, infection, necrosis, and limb loss. Hence, looking at the burden of CKD in children and lack of studies on peripheral

neuropathy in this cohort, we looked at the prevalence and patterns of neuropathy in children with CKD.

METHODOLOGY

This cross-sectional study was conducted over 1 year in the Pediatric Nephrology and Pediatric Neurology units of the Department of Pediatrics at a tertiary care teaching hospital. Institute's ethics committee approved the study protocol and the departmental review board approved the manuscript. The inclusion criteria were (1) consecutive children of either sex between 2 and 14 years and (2) a diagnosis of CKD stage III–V as per the standard definition.^[8] Children with co-existing disorders that may affect the peripheral nerves (such as diabetes, connective tissue disorders, thyroid disorders, coeliac

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disease, etc.), or using medications predisposing to peripheral neuropathy (such as chemotherapy, antiretroviral therapy, antitubercular therapy, or antifungal drugs), or with a family history of peripheral nerve disorders (inherited neuropathies) were excluded. Informed consent was taken from the parents prior to enrollment.

All children were evaluated for the presence of signs and symptoms of neuropathy. Nerve conduction studies (NCS) were performed as per standard protocols using surface electrodes on the muscles and by supramaximal stimulation of the corresponding nerves. At least two motor (median and ulnar in the upper limb, common peroneal and tibial in the lower limbs), and one sensory (ulnar/median in the upper limb and sural in the lower limb) nerves in each of the four extremities were assessed. All four limbs were tested so that no cases of uremic mononeuropathies were missed. Motor conduction studies were measured with surface electrodes on the muscles by supramaximal stimulation of the corresponding nerves. Median and ulnar nerves were stimulated at the wrist and elbow, with motor action potential being recorded over the abductor pollicis brevis and abductor digiti minimi, respectively. Peroneal and tibial nerves were stimulated at the ankle and knee, with motor action potential being recorded over the extensor digitorum brevis and abductor hallucis, respectively. Sensory NCS was performed on the median, ulnar, and sural nerves, with orthodromic stimulation at finger II, finger V, and lateral malleolus, respectively. The sensory action potentials of the median and ulnar nerves was recorded at the wrist and at the lower leg for the sural nerve. Care was taken to keep the room temperature constant during the measurements by prewarming the extremities, if required by heat packs. The values of distal latency, conduction velocities, and amplitudes of compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) were recorded and interpreted using the age-adjusted reference values.^[9-11] Peripheral neuropathy was considered when ≥ 2 abnormal attributes were detected in NCS, with evidence of muscle weakness, diminished ankle reflexes, altered sensation, or autonomic dysfunction.^[12,13] For mononeuropathy, these features were considered in any motor or sensory nerve.^[13] The subclinical neuropathy (as a subcomponent of asymptomatic neuropathy) was defined as the presence of an NCS abnormality, in the absence of abnormal neurologic examination or symptoms of neuropathy.^[13] The neuropathy was graded according to Dyck's criteria originally proposed for diabetic neuropathy using a combination of nerve studies, clinical examination, and neuropathy symptoms [Table 1].^[14]

Statistical analysis was done using the Statistical Package for Social Sciences for Windows version 23 (SPSS Inc., Chicago, IL, USA). Quantitative data is depicted as mean \pm standard deviation (SD), while the qualitative data is depicted as demonstrated as frequency and percentage. Independent *T*-test and Chi-square test or Fisher's exact tests, as appropriate, were used to compare data between the groups. A $P < 0.05$ was considered statistically significant.

Table 1: NCS attributes considered in the study^[15,16]

Abnormal attributes for motor studies were:

- CMAP amplitude $< 80\%$ of 2.5 SD
- Conduction velocity $< 75\%$ of 2.5 SD below normal for age
- Distal latency $> 130\%$ of 2.5 above normal for age
- Proximal CMAP amplitude $< 50\%$ of distal CMAP amplitude, and
- F-wave latency $> 130\%$ of upper limit of normal for age

Abnormal attributes for sensory studies were:

- SNAP amplitude $< 80\%$ of 2.5 SD
- Conduction velocity $< 75\%$ of 2.5 SD below normal for age
- Distal latency $> 130\%$ of 2.5 above normal for age

Staging of neuropathy^[10]

- Stage 0 (no neuropathy): Absence of NCS abnormality, abnormal neurologic examination, and symptoms of neuropathy
- Stage 1 (asymptomatic neuropathy): Presence of NCS abnormality or abnormal neurologic examination or both plus no symptoms of neuropathy
- Stage 2 (symptomatic neuropathy): Presence of NCS abnormality or abnormal neurologic examination or both plus symptoms of neuropathy
- Stage 3 (disabling neuropathy): Presence of NCS abnormality or abnormal neurologic examination or both plus disabling symptoms of neuropathy

RESULTS

Nearly 45 children were evaluated during the study period. The majority were males ($n = 39$, 86.7%). The mean estimated GFR at enrolment was 23.3 ± 14.6 mL/min/1.73 m² (range 5–67). The majority of children were in stage III ($n = 19$, 42%), followed by stages V ($n = 15$, 33%) and IV ($n = 11$, 25%). The clinical and demographic characteristics are shown in Table 2.

None of the children with CKD stage III and above had signs or symptoms of peripheral neuropathy. Of these, 13 children (29%) showed signs of subclinical or asymptomatic neuropathy (stage 1). All the nerves had an axonal pattern. Motor polyneuropathy was the most common pattern of involvement. The commonest nerves involved were tibial and common peroneal nerves [Figure 1]. No clinical and biochemical predictors of peripheral neuropathy were identified in the cohort [Table 3]. The stages of disease ($P = 0.8$), presence of dialysis ($P = 0.7$), and gender ($P = 0.6$) did not predict the presence of neuropathy.

DISCUSSION

Our study shows that subclinical uremic polyneuropathy is seen in up to one-third of children with CKD stage 3 and above. Being subclinical, the entity is probably unrecognized in children. Hence, NCS-based assessment of nerve function should be routinely done in children with advanced stages of CKD, at least once a year to prevent chronic complications. Children who show electrophysiological abnormalities without any clinical signs or symptoms should undergo prospective screening to evaluate the evolution of clinical uremic neuropathy. Though often insidious, peripheral neuropathy has been considered a source of physical impairment and has reduced the quality of life in CKD secondary to progressive muscle atrophy, weakness, and gait abnormalities.^[17,18] Uremic neuropathy

Table 2: Clinical and demographic characteristics of enrolled children (N=45)

Characteristics	N (%)
Male gender	39 (86.7%)
Age at diagnosis of CKD (m)	51.1±43.7 (birth-132)
Age at enrolment (year)	7.9±3 (2-14)
Duration of CKD (year)	3.7±3.4 (0.5-12)
Estimated GFR at enrolment (mL/min/1.73 m ²)	23.3±14.6 (5-67)
Stage of disease	
Stage 3	19 (42%)
Stage 4	11 (25%)
Stage 5	15 (33%)
Weight at enrolment (kg)	19.5±7.8 (8.7-38.2)
Height at enrolment (cm)	113.6±16.7 (76-141.5)
Dialysis	20 (44%)
Clinical neuropathy	None
Subclinical peripheral neuropathy	13 (29%)
Motor polyneuropathy	7 (54%)
Motor mono-neuropathy	5 (38%)
Tibial nerve	4 (30%)
Peroneal nerve	1 (8%)
Motor and sensory neuropathy	1 (8%)
Sensory	None
Involvement of nerves	
Tibial	11/13 (84.6%)
Peroneal	3/13 (23%)
Sural	1/13 (7.6%)
Mean amplitude±SD (mV)	
Tibial	9.8±4.7
Common peroneal	3.4±1.2
Median	7.4±2.5
Ulnar	4.9±1.3
Type of subclinical neuropathy	
Axonal	13 (29%)
Mean amplitude±SD (mV)	
Tibial	4.9±1.3
Common peroneal	3.3±1.1
Median	7.8±2.4
Ulnar	4.5±1.3
Demyelinating	-

in pediatric cohorts varies from 0% to 52%.^[19] Diminished motor nerve conduction was seen in a single case in a small cohort of 11 children with CKD, although electromyogram revealed increased polyphagia of motor unit potentials in four cases.^[7] A higher prevalence of electrophysiologically defined peripheral neuropathy (52%) was seen in another North Indian cohort of 50 children with CKD.^[5] The study included children up to 18 years, thereby with prolonged duration of illness. A higher prevalence (0–59%) of electrophysiologically defined polyneuropathy has been reported in children with more severe stages of CKD (stage IV and V).^[7,19] About 19 children in our cohort were in CKD stage III, followed by 15 in CKD stage V. We did not find any effect of the with evidence of muscle weakness stage of CKD on the frequency of neuropathy. The presence of uremic neuropathy is an indication for renal replacement therapy and the development

Table 3: Association between probable risk factors and presence of subclinical neuropathy

	Subclinical neuropathy		Mean±SD	P
	Presence	N		
Age at enrolment (year)	Yes	13	8.5±2.7	0.4
	No	32	7.7±3.1	
Age at diagnosis of CKD (m)	Yes	13	50.8±50.5	0.9
	No	32	51.2±41.6	
Height (cm)	Yes	13	113.6±16.7	0.9
	No	32	113.1±17.8	
Weight (kg)	Yes	13	19.5±7.8	0.9
	No	32	19.5±7.1	
Head circumference (cm)	Yes	13	49.7±2	0.9
	No	32	49.6±2.3	
Body mass index (kg/m ²)	Yes	13	14.7±1.9	0.9
	No	32	14.7±1.7	
Height for age	Yes	13	-3.4±1.5	0.1
	No	32	-2.7±1.4	
Weight for age	Yes	13	-3.6±1.8	0.1
	No	32	-2.8±1.5	
Weight for height	Yes	7	-1.2±1.5	0.8
	No	21	-1.4±1.5	
Mid arm circumference (cm)	Yes	13	15.9±1.5	0.6
	No	32	16.2±2.2	
Serum Potassium (meq/L)	Yes	13	4.3±0.3	0.2
	No	32	4.4±0.4	
Serum sodium (meq/L)	Yes	13	137.6±3.9	0.6
	No	32	138.3±4.1	
Serum parathormone level	Yes	13	209.7±88.8	0.2
	No	32	179.6±67.1	
Serum vitamin D level	Yes	13	21.2±12	0.6
	No	32	19.8±9.8	
Serum phosphorus level	Yes	13	3.9±0.9	0.2
	No	32	3.7±0.6	
Creatinine	Yes	13	2.9±2.1	0.7
	No	32	2.8±1.7	
Urea	Yes	13	110.3±68.1	0.1
	No	32	87.6±38.7	
Estimated GFR	Yes	13	24.7±17.4	0.6
	No	32	22.7±13.5	

of neuropathy in children already on renal replacement therapy should hint toward ineffectiveness and need to adjust the dose and duration of dialysis.^[18] Although earlier reports suggested that some patients with CKD and mild neuropathy may recover completely with adequate dialysis, however, recent studies indicate that improvement in neuropathy, especially in severe cases and with motor-predominant pattern, is uncommon with both hemo- and peritoneal dialysis.^[3] In some cases, neuropathy may progress despite dialysis and renal transplantation is considered the only cure for uremic nephropathy. Such extensive data is lacking in children and larger studies are needed to study the serial changes in nerve conduction in children with CKD and the effect of renal replacement therapy in them.

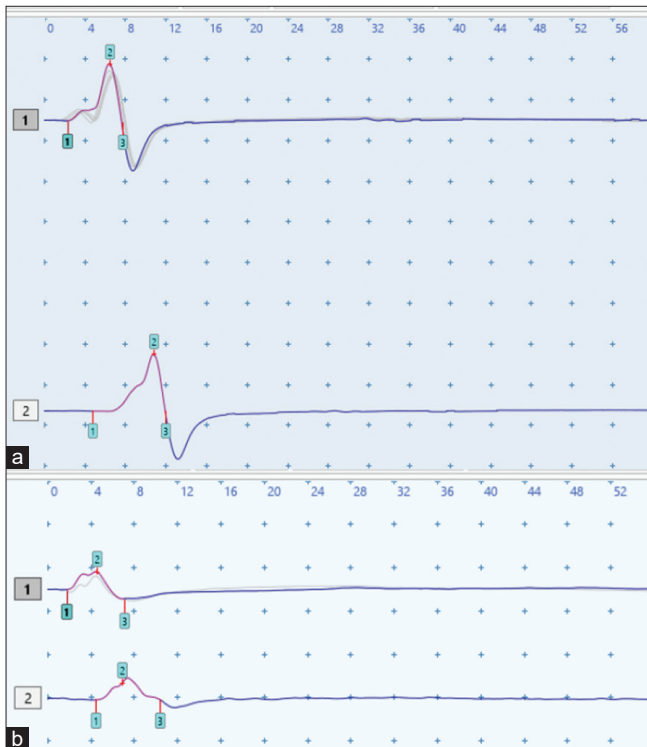


Figure 1: (a) Nerve conduction study of the left tibial nerve showing reduced CMAP amplitude 5.6 mV (2.5 SD = 10.3 mV) following supramaximal stimulation (100 mA) at both medial malleolus and popliteal fossa, with preserved distal latency (2.3 ms) and conduction velocity (43.8 m/s) suggestive of an axonal pattern. (b) Nerve conduction study of the left peroneal nerve showing reduced CMAP amplitude 1.7 mV (2.5 SD = 10 mV) following supramaximal stimulation (100 mA) at foot and head of fibula, with preserved distal latency (1.8 ms) and conduction velocity (46 m/s) suggestive of an axonal pattern

Peripheral neuropathy in CKD is classically considered a distal symmetrical, mixed sensorimotor neuropathy. The nerves show both demyelination and axonal degeneration. The subclinical neuropathy in our cohort was axonal motor type and it affected the tibial and peroneal nerves in the lower limbs. Motor-sensory neuropathy was seen in only a single case in our cohort while none had a pure sensory neuropathy. The pathogenesis of uremic neuropathy has been considered a primary axonal degeneration, resulting in secondary segmental demyelination.^[20] Understandably, these changes are most severe in the distal ends of the longer nerve fibers of the lower limbs, as also seen in our cohort. Motor NCS is commonly measured in the peroneal nerve. Similar to our study, majority of children with CKD have shown an axonal pattern (80.8%), followed by demyelinating (18.5%).^[5] Isolated motor involvement (92.3%) is more common followed by sensorimotor neuropathy (7.6%), as also seen in our cohort.^[5] It has been shown that the mean peroneal motor CV decreased significantly in children with mild renal failure, while ulnar motor CV was significantly reduced only when renal failure was advanced.^[15] The predominance of isolated motor neuropathy in our study and the one by Yoganathan *et al.*^[5] could be attributed to inclusion of children with

“non-diabetic” CKD, and an effect of the duration and severity of CKD in different cohorts.^[16]

The pathogenesis of peripheral neuropathy in children with CKD is complex. It has been attributed to the accumulation of uremic toxins such as parathyroid hormone, myoinositol, etc., oxidative free radical damage to the nerves, and electrolyte abnormalities.^[21] Specifically, hyperkalemia and hyperphosphatemia can cause chronic depolarization of nerves by disrupting the normal ionic gradient and activating the calcium-mediated processes leading to axonal death.^[18] Both these factors were not associated with development of subclinical neuropathy in our cohort. The effect of serum biochemical parameters has not been found significant on the causation of uremic neuropathy in other studies as well.^[5] A possible reason for this could be the rapid correction of transient hyperkalemia with dialysis, thus causing lesser disruption of normal ionic gradients and lesser activation of calcium-mediated neurotoxic processes.^[3] However, the effect of chronic hyperkalemia, especially if it persists between the periods of dialysis, on the nerve conduction needs to be seen in longitudinal studies with serial NCS in children. There was no significant association between vitamin D levels and uremic neuropathy in our cohort. However, the mean value of vitamin D was low and mean parathormone levels were high in our cohort, indicating an underlying deficiency in these patients requiring supplementation.

The subclinical electrophysiological abnormalities may be seen in 60–100% of patients undergoing dialysis for CKD.^[22] However, no association of dialysis was seen with subclinical neuropathy in our cohort. On the other hand, Yoganathan *et al.* reported a significant association between the two, although the duration of dialysis had no significant effect.^[5] A study of 100 non-dialysis CKD patients between 18 and 65 years who had serum creatinine >2 mg/dL, showed that 64% of patients had symptomatic polyneuropathy, and an additional 6% had subclinical polyneuropathy.^[2] The same study showed an increasing prevalence of neuropathy with worsening renal function [serum creatinine 2–3.4 (35%), 3.5–4.9 (89%), and >5 mg/dl (100%)].^[2] Studies in adults have also shown a strong correlation of declining eGFR and worsening stage of CKD with peripheral neuropathy.^[23] Although our study was cross-sectional, no significant association was noted with serum urea, creatinine, and GFR in our cohort. A probable reason for this could be the small sample size in our study. Hence, prospective studies with larger sample sizes are needed in children to ascertain the effects of worsening GFR on the prevalence of electrophysiological abnormalities and subsequent clinical neuropathy. Although uremic polyneuropathy has been noted to be more common in men, the same inference could not be drawn for children as they have lesser comorbidities and lesser duration of CKD or dialysis.

In conclusion, the prevalence of subclinical neuropathy in children with CKD stage III and above is high and needs attention. Children with CKD should be screened with NCS

at least once a year to detect subclinical electrophysiological abnormalities and to identify early electrophysiological markers of symptomatic peripheral neuropathy later on in these children. As disease related factors are not the major risk factors, nutritional factors such as micronutrients and vitamins should be evaluated for probable risk factors in our population. The small number of patients and limited biochemical parameters assessed limited our study. The late responses and an electromyography could not be tested in our cases due to the technical constraints. A prospective study should be conducted to study the effects of clinical and biochemical parameters in the causation of uremic neuropathy in children.

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Conflicts of interest

There are no conflicts of interest.

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