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NEUROLOGICAL COMPLICATIONS IN CHILDREN WITH CHRONIC KIDNEY DISEASE

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Background: This article presents an analysis of the prevalence and nature of peripheral neuropathy in children with chronic kidney disease (CKD). Methods: Nerve conduction studies (NCS) were conducted in accordance with standard protocols. Manifestations of electrophysiological disorders in the absence of clinical symptoms or signs were considered as subclinical neuropathy. Results: Almost 35 children were examined. The majority were men (n = 29, 85.7%). The average age was 8.9 ± 3 years (range from 2 to 14 years). The average estimated glomerular filtration rate (GFR) at admission was 23.4 ± 13.6 ml/min/1.73 m2 (range 5-67). Most of the children were at stage III (n = 18, 42%), followed by stages V (n = 14, 33%) and IV (n = 10, 25%). There were no signs of clinical neuropathy; 8 children (29%) had subclinical neuropathy. All nerves had an axonal pattern of involvement. Motor polyneuropathy was the most common type of peripheral neuropathy. The study showed that the most common affected nerves were the tibial and common fibular nerves. Conclusion: The prevalence of subclinical neuropathy is high in children with CKD stage III and higher. The predominant pattern is axonal motor polyneuropathy. Electrophysiological evaluation of nervous function should be performed regularly 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],[2],[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],[6],[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

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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 study was conducted for 3 months in the departments of pediatric nephrology of the National Children's Center. The inclusion criteria were children of any sex aged 2 to 14 years, diagnosed with stage III–V CKD in accordance with the standard definition [8]. The exclusion criteria were: children with concomitant diseases that can affect peripheral nerves (such as diabetes, connective tissue diseases, thyroid diseases, celiac disease, etc.), or taking medications predisposing to peripheral neuropathy (such as chemotherapy, antiretroviral therapy, tuberculosis therapy or antifungal drugs), or with a family history of diseases peripheral nerves (hereditary neuropathies).

At the time of the examination, all children were examined for signs and symptoms of neuropathy. Nerve conduction studies (NCS) were conducted in accordance with standard protocols using surface electrodes on muscles and supramaximal stimulation of the corresponding nerves. The values of distal latency, conduction velocities, and amplitudes of complex muscle action potential (CMAP) and sensory nerve action potential (SNAP) were recorded and interpreted using age-adjusted reference values [9],[10],[11] Peripheral neuropathy was considered when ≥2 abnormal signs with signs of muscle weakness, decreased reflexes of the ankle joint, changes in sensitivity or autonomic dysfunction. [12], [13]. For mononeuropathy, these features were taken into account in any motor or sensory nerve [13]. Subclinical neuropathy (as a sub-component of asymptomatic neuropathy) was defined as the presence of an NCS anomaly in the absence of an abnormal neurological examination or symptoms of neuropathy.[13] Neuropathy was evaluated according to the Dyck criteria originally proposed for diabetic neuropathy using a combination of neural studies, clinical examination, and neuropathy symptoms [14]. Statistical analysis was carried out using a statistical package for social sciences for Windows. Quantitative data is presented in the form of mean ± standard deviation (SD), while qualitative data is presented in the form of frequency and percentage. To compare the data between the groups, an independent T-test and a Chi-square test or Fisher's exact tests were used, depending on the circumstances. $P < 0.05$ was considered statistically significant.

Results. During the study period, almost 35 children were examined. The majority were men (n = 29, 86.7%). The average calculated GFR at admission was 23.4 ± 13.6 ml/min/1.73 m2 (range 5--67). Most of the children were at stage III (n = 18, 42%), followed by stages V (n = 14, 33%) and IV (n = 10, 25%). None of the children with CKD stage III and above had signs or symptoms of peripheral neuropathy. Of these, 8 children (29%) showed signs of subclinical or asymptomatic nephropathy (stage 1). All nerves had an axonal pattern. Motor polyneuropathy was

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the most common form of involvement. The most common affected nerves were the tibial and common fibular nerves [Fig. 1]. There were no clinical and biochemical predictors of peripheral neuropathy in the cohort [Table 3]. The stages of the disease (P = 0.8), the 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 observed in a third of children with CKD stage 3 and higher. Assessment of nervous status based on NCS should be carried out regularly in children with advanced stages of CKD, in our opinion, at least once a year to prevent chronic complications. Children who have electrophysiological disorders without any clinical signs or symptoms should undergo prospective screening to assess the progress of clinical uremic neuropathy. Despite the fact that peripheral neuropathy is often hidden, it is considered a cause of physical dysfunction and significantly reduces the quality of life in children with CKD [17], [18]. According to the results of various researchers, uremic neuropathy in pediatric cohorts varies from 0% to 52% [19]. Decreased motor activity. nerve conduction was noted in a single case in a small cohort of 11 children with CKD, although an electromyogram revealed increased polyphagia of motor unit potentials in four cases. [7] Higher prevalence of electrophysiologically determined peripheral neuropathy (52%) [5]. There is evidence of a higher prevalence of electrophysiologically determined polyneuropathy in children with more severe stages of CKD (stages IV and V). [7], [19]. About 19 children in our cohort were at stage III of CKD, followed by 15 at stage V of CKD. We did not find any effect of the CKD stage with signs of muscle weakness on the frequency of neuropathy. The presence of uremic neuropathy is an indication for renal replacement therapy, and the development of neuropathy in children already receiving renal replacement therapy should indicate the ineffectiveness and the need to adjust the dose and duration of dialysis [18]. Also, recent studies show that improvement of neuropathy, especially in severe cases and with predominance of motor activity, is rare in both hemo- and peritoneal dialysis [3]. In some cases, neuropathy can progress despite dialysis, and kidney transplantation is considered the only treatment for uremic nephropathy. Unfortunately, such extensive data are not available in children, and larger-scale studies are needed to study changes in nerve conduction in children with CKD and the effect of renal replacement therapy in them. 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

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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 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 atleast 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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