INCIDENCE AND CORRELATION BETWEEN PERIPHERAL NEUROPATHY AND ESRD IN PEDIATRIC PATIENTS

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ABSTRACT

Background: Chronic kidney disease (CKD) is a major health problem worldwide with increasing incidence and prevalence that is threatening to bring on the onset of a real ‘epidemic’. According to the KDIGO guidelines, CKD is identified by the presence of kidney damage, either structural or functional, or by a decline in glomerular filtration rate (GFR) below 60 mL/min/1.73 m² of body surface area for more than 3 months. Neurological complications frequently affect patients with chronic kidney disease (CKD) and are an important cause of morbidity and mortality. Some of these complications are related to the underlying renal disease, or to the CKD itself, whereas others are secondary to dialysis. They affect both the central and peripheral nervous systems. Uremic neuropathy in end-stage kidney disease is classically a distal symmetrical length dependent, sensorimotor polyneuropathy which is more common in lower limbs than in upper extremities with an unexplained male predominance. The systemic effects of uremia on peripheral nerves is emphasized by the generalized nature of nerve conduction slowing which has been demonstrated in upper and lower extremities, and in both sensory and motor nerves.

Keywords: Peripheral Neuropathy, Chronic Kidney Disease (CKD), End Stage Renal Disease (ESRD).

End stage renal disease in pediatrics

I. INTRODUCTION:

The economic and societal burden of diagnosing, treating and preventing chronic kidney disease (CKD) in children and adults remains substantial. In the US, the incidence of end stage renal disease (ESRD) in children age 0-19 years was 12.9 per million/year in 2012 compared to 352.6 per million/year in all age groups. Efforts are ongoing to improve early diagnosis, intervention and long term outcome (Pirojsakul et al., 2015). Prevalence has increased along with incidence of dialysis and renal transplant recipients. The median incidence of RRT in children less than 20 years old worldwide was approximately 9 per million of the age-related population (pmarp) in 2008, with the United States median higher at 15.5 pmarp. The prevalence of RRT was also higher in the United States compared to that in developed countries with 85 vs. 65 pmarp, respectively. Race is differentially affected by region, with black children having 2-fold greater incidence of ESRD vs. white children in the United States (Harambat J et al., 2012).

Because children with risk factors for CKD, such as prematurity and low birth weight, are increasing in number, we need to launch a concerted national effort to systematically track these children. With convincing adult data showing the effectiveness of angiotensin converting enzyme inhibitors in slowing the progression of CKD (Jafar TH et al., 2011).

In children, peritoneal dialysis (PD) is preferred over hemodialysis (HD) in terms of quality of life, growth, and preservation of residual renal function. Hemodialysis poses greater risks of access failure, vascular thrombosis, and obliteration of the great veins, which can be compromised for life (Warady A et al., 2014).
In addition, multisystem involvement in ESRD in this population can lead to growth retardation, cardiovascular complications, and hematological complications. The life span of children with ESRD is significantly lower than that of the age- and gender-matched general population (Duzalka A et al., 2013).

According to the most recent North American Pediatric Renal Trials and Collaborative Studies Dialysis Report (NAPRTCS), the youngest pediatric patients have the worst survival at 12, 24, and 36 months following dialysis initiation. Five-year survival probability is 89% for patients initiating ESRD treatment according to US Renal Data Surveillance Report, and mortality rate is 30 times higher than healthy children (Saran R et al., 2015).

Definitions and Classification:

In 2003, National Kidney Foundation proposed the new definition and staging for CKD in children. Patient with CKD defines as functional or structural damage of the kidney or decrease in glomerular filtration rate (GFR) to less than 60 ml/min/1.73m² for more than 3 months. Damage to the kidney can be manifested by abnormalities in blood, urine, imaging test or pathology on the kidney biopsy (Hogg RJ et al., 2003)

Stage 1: normal eGFR R 90 mL/min per 1.73 m2 and persistent albuminuria

Stage 2: eGFR between 60 to 89 mL/min per 1.73 m2

Stage 3: eGFR between 30 to 59 mL/min per 1.73 m2

Stage 4: eGFR between 15 to 29 mL/min per 1.73 m2

Stage 5: eGFR  15 mL/min per 1.73 m2 or end-stage renal disease (Coresh J et al., 2013).

KDIGO (Kidney Disease - Improving Global Outcomes):

In 2013, KDIGO published new definition and classification of CKD. CKD is defined as presence of abnormalities of kidney structure or function for more than 3 months. Abnormalities consist of either of albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, or history of kidney transplantation (KDIGO, 2013).

North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS):

NAPRTCS was initiated in 1987 aimed to collect retrospective data from pediatric renal transplant and dialysis patients. It has expanded to include pediatric CKD patients since 1992. Recent data from NAPRTCS about anemia and growth in pediatric CKD patients will be discussed

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/min/1.73m2)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>3 a</td>
<td>45-59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>3 b</td>
<td>30-44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Kidney failure</td>
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FACTORS THAT PREDICT DEVELOPMENT OF CKD:

Hypertension:

Hypertension is one of the modifiable co-morbid variables that should be evaluated and managed properly in children with CKD. An increase in blood pressure (BP) causes increase intra-glomerular pressure and hyper-
filtration that leads to progressive deterioration of renal function. The CKiD study has shown that as high as 64% of pediatric CKD patients required anti-hypertensive medications to control their BP (Flynn JT et al., 2008).

Samuels et al. conducted a cross sectional study about ambulatory blood pressure monitoring (ABPM) pattern in children with CKD. Interestingly, among 332 CKD patients, 35% of patients were found to have masked HT diagnosed by ABPM. Moreover, patients who were on ACE-inhibitor also were 89% more likely to have normal ABPM than those who did not. These patients with masked HT were also found to have left ventricular hypertrophy as much as the patients with confirmed HT (Samuels J et al., 2012).

The optimal target of BP in pediatric CKD patient has also been studied in the randomized control study “Effect of strict BP control and ACE inhibition on progression of CKD in pediatric patients” also known as “ESCAPE trial” (Wuhl E et al., 2009).

Proteinuria:
Proteinuria has been shown to be associated with progression of CKD in adult population. In the pediatric population, there was a randomized control trial of low protein diet on the progression of CKD. There was no benefit of low protein diet to slow progression of CKD course. In multivariate analysis, proteinuria was one of the predictor of CKD progression. As in the adult study, pediatric patients who had glomerular cause of CKD were found to have lower proteinuria associated with treatment of renin-angiotensin antagonist (Wong CS et al., 2009).

Omoloja et al. recently reported effect of secondhand smoke exposure in the CKiD study. Investigators found that patients who reported secondhand smoke exposure had higher urine protein/creatinine ratio compared to the group without smoke exposure (0.6 vs 0.4, p<0.01). Smoke exposure in this study was confirmed by higher urinary cotinine level (metabolite of nicotine) in the group with smoke exposure. The pathogenesis of smoke exposure and deterioration of renal function remains unclear (Omoloja A et al., 2013).

Oxidative Stress:
Oxidative stress is an imbalance in the reactive oxygen species (ROS) production/degradation ratio. Under normal conditions, ROS (which include various compounds such as superoxide anions, hydrogen peroxide, and hydroxyl radical) can accelerate renal injury progression. Inflammatory markers such as C-reactive protein and cytokines increase with renal function deterioration suggesting that CKD is a low-grade inflammatory process. In fact, inflammation facilitates renal function deterioration. Several factors can be involved in triggering the inflammatory process including oxidative stress (Cachofeiro V et al., 2008).

Low Birth Weight, Prematurity and Risk for Progression of CKD:
The metanephrons gives rise to definitive kidneys which continue to develop until 36 weeks of gestation. Although glomerulogenesis still occurs in premature infant, many of the glomeruli are abnormal such as cystic dilatation (Abitbol CL et al., 2012).

Another study by Mañalich et al. showed that low nephron number was directly correlated with birth weight and inversely correlated with glomerular size. These infants have low nephron number and abnormal glomeruli leading to hyper-filtration of the remaining glomeruli, proteinuria and CKD later in life (Carmody J et al., 2013).

Genetic factors:
Genetic abnormalities can cause CKD either by fostering nephrocalcinosis, cystic degeneration, weakening epithelial integrity or abnormal processing or storage of metabolites or glycoproteins (Oliveira B et al., 2016).

Genetic testing has revealed that~20% of early-onset CKD (defined as CKD manifesting before 25 years of age) can be attributed to a monogenic cause (Vivante A et al., 2016).

Until recently, monogenic causes of CKD were mostly reported in children or adolescents, but genetic variants also contribute as co-factors to CKD progression in adults.UMOD gene variant, present on 17% of the alleles in the general population, is associated with developing CKD (Kottgen A. et al., 2009).
Hemodialysis in children

The history of dialysis treatment for children is closely related to the development of pediatric nephrology and to renal replacement therapy (RRT) in general, which both started soon after World War II (Schärer and Fine, 2004). The practice of pediatric hemodialysis (HD) was first restricted to a few pediatric centers, mainly for the treatment of acute intoxication although the application of peritoneal dialysis (PD) in acute kidney injury (AKI) has been institutionalized in many children’s hospitals since the 1950s. The first use of maintenance pediatric hemodialysis was reported in 1968 by Fine et al. Until recently, PD was the preferred mode of RRT in infants with end-stage renal disease (ESRD), and HD is seldom used in neonates and infants due to the risk of major complications in the very young. Nevertheless, there are clinical situations where hemodialysis is needed and may be helpful in small children. Previously, it was difficult to implement in children due to their small weight and difficulty in vascular access, but recently, with the development of HD equipment, it has become possible to implement in children up to 2 kg (Heeyeon Cho, 2020).

Traditionally peritoneal dialysis (PD) has been the preferred modality of dialysis in children. However with advances in technology, hemodialysis (HD) has rapidly gained popularity. During the past two decades there have been many improvements in the technology: bicarbonate used as buffer in the dialysis solution, volumetrically controlled ultra filtration, smaller dialysis lines and synthetic membranes useful even for babies, modeling of ultra filtration rate and dialysate composition, on line hemodiafiltration and the concept of ultrapure dialysate, i.e. sterile and pyrogen free (Gulati et al., 2012).

Specific to the needs of infants and children, extracorporeal volume during HD should be maintained at .10% of the patient’s blood volume to minimize excessive blood loss, hemodynamic instability, and/ or the need for a blood prime (Muller D et al., 2011).

Conventionally, HD has been provided 3 times a week; however, intensified HD for children and adolescents, including short daily HD, intermittent nocturnal HD, and daily nocturnal HD, increasingly is recognized as an important strategy to optimize care. Compared to conventional thrice-weekly HD, intensified programs have demonstrated improved control of phosphate levels, anemia, blood pressure, and fluid status and have provided unique benefits for children and adolescents in terms of improved growth and nutrition (Chertow GM et al., 2010).

As with PD, the efficiency of HD typically is measured in terms of urea clearance. Current guidelines recommend that the delivered dialysis dose be measured monthly in children and adolescents, with a minimum single-pool Kt/V target of 1.2 (Warady BA et al., 2014).

For patients receiving intensified HD, standard Kt/V should be measured that combines an estimated double-pool Kt/V calculation normalized over any weekly schedule to provide the same pretreatment serum urea nitrogen concentration. A recent study assessed the validity of this concept in children demonstrated that a standard Kt/V of at least 2.0 was equivalent to a thrice-weekly single-pool Kt/V of 1.2 (Mammen C et al., 2010).

Peripheral Neuropathy in CKD children

Neurological complications frequently affect patients with chronic kidney disease (CKD) and are an important cause of morbidity and mortality. Some of these complications are related to the underlying renal disease, or to the CKD itself, whereas others are secondary to dialysis. They affect both the central and peripheral nervous systems. There is scarce data on neurological complications in children. These complications include: dialysis disequilibrium, uremic encephalopathy, intracranial hemorrhage, brain infarction, white matter disease, posterior reversible encephalopathy syndrome (PRES), peripheral neuropathy, cerebral atrophy, and restless leg syndrome. Other neurological problems encountered in CKD include neurocognitive dysfunction with defects in attention, language, and memory (Moodalbail DG et al., 2013).

Peripheral neuropathy in CKD, also known as uremic neuropathy, is the most common neurological complication of CKD, in children it had shown a prevalence ranging from 0-59% while in adult studies, the prevalence of neuropathy varied from 37.5-90%. Diabetes being the commonest cause of CKD in adults might explain the higher prevalence and severity of neuropathy in adults (Chao CC et al., 2011).
Uremic neuropathy in end-stage kidney disease is classically a distal symmetrical length dependent, sensorimotor polyneuropathy which is more common in lower limbs than in upper extremities with an unexplained male predominance (Pan Y et al., 2011).

Pathophysiology:

Despite the huge effort developed in this area, the pathophysiology of uremic neuropathy has not been established yet. Nevertheless, there are two main postulated hypotheses. First, with the ‘Middle Molecule Hypothesis’ it was postulated that uremic neuropathy occurred as consequence of retention of neurotoxic molecules in the middle molecular range of 300-12000 Da, given that such molecules were slowly dialyzable by hemodialysis membrane. However, there is little evidence that such molecules are actually neurotoxic (Ondina et al., 2012).

Second, recent nerve excitability studies, undertaken over the course of a dialysis session, demonstrated that patients with uremic neuropathy had motor and sensory axonal changes before dialysis suggesting that hyperkalaemia could be a contributing factor to the development of neuropathy (Krishnan AV et al., 2006).

As such, it is possible that while structural changes occur in a length-dependent manner, uraemia may have a universal neurotoxic effect caused by an unknown uraemic toxin. While many substrates have been investigated as a potential uraemic neurotoxin including; urea, creatinine, guanidine, methylguanidine, guanidinosuccinic acid, uric acid, oxalic acid, phenols, aromatic hydroxyacids, indican, amines, myo-inositol, ‘middle molecules’, b-2-microglobulin, PTH, amino acids and neurotransmitters, none of these have yielded evidence of causality (Watanabe K et al., 2014).

In contrast, a substantial body of research has recently demonstrated that hyperkalaemia has a pivotal role in uremic neuropathy. These studies provided evidence that hyperkalaemia impairs nerve function in a dose-dependent manner and this dysfunction can be normalized with the removal of excess serum potassium (Pussell BA et al., 2014).

These studies also suggest that maintaining normal levels of potassium in CKD patients may prevent peripheral nerve injury and established a causal association between hyperkalemia and axonal dysfunction in patients with end stage renal disease (Arnold R et al., 2014).

The prevalence of neuropathy with normal vitamin E levels in patients with CKD may be explained by the fact that carboxyethylhydroxychromans, a metabolite of vitamin E, increases in serum with declining renal function and carboxyethylhydroxychromans could interfere with the functions of vitamin E (Galli F et al., 2004).

Low or low normal vitamin B12 values were found in 16% of the total patients with CKD in our study, but there was no significant association of vitamin B12 with neuropathy (Yoganathan S et al., 2014).

Copper deficiency can predispose to polyneuropathy, myeloneuropathy or optic neuropathy (Rowin J et al., 2005).

Low levels of antioxidants such as erythrocyte copper, zinc and selenium and correspondingly high levels of oxidative stress markers such as plasma malondialdehyde and asymmetric dimethyl arginine have been reported in CKD patients as compared to controls (Yilmaz MI et al., 2006).

It has been postulated that mononeuropathies in CKD patients might result from compression susceptibility, beta-2-microglobulin related amyloidosis, local ischemia, uremic tumour calcinosis, and haemodialysis (Krishnan AV et al., 2009).

It was speculated that the neurological complications in patients with CKD might improve by dialysis. Patients on peritoneal dialysis have a lower incidence of peripheral neuropathy than patients on hemodialysis and this observation has been cited to possibly support the ‘middle molecule hypothesis’. However, the duration of dialysis therapy did not have a significant association with neuropathy. Exposure to neurotoxins during dialysis and also the severity of CKD could possibly attribute to the neuropathy (Babb AL et al., 1981) (Yoganathan S et al., 2014).

An increase in nerve conduction velocity was detected with magnesium-free dialysate and a decrease was observed on switching to magnesium-containing dialysate in patients on regular dialysis treatment (Bagga A et al., 2014).
In another study, correlation between serum magnesium and nerve conduction velocity was not detected in chronic renal failure patients on chronic hemodialysis (Laaksonen S et al., 2012).

The systemic effects of uremia on peripheral nerves is emphasized by the generalized nature of nerve conduction slowing which has been demonstrated in upper and lower extremities, and in both sensory and motor nerves (Arnold et al., 2016).

Diabetic neuropathy is also length dependent and of greater severity than other neuropathies with different aetiologies (Krishnan AV et al., 2009).

The pathophysiology of diabetic neuropathy has not been established but it seems to be related with metabolic disturbances, such as hyperglycaemia, dyslipidaemia, oxidative and nitrosative stress and growth factor deficiencies, microvascular insufficiency and autoimmune damage to nerve fibres (Vinik A et al., 2010).

Both axonal and demyelinating polyneuropathy have been described in CKD patients with underlying diabetes (Yoganathan S et al., 2014).

Clinical picture:
Clinically, patients with either uremic neuropathy or diabetic neuropathy can be asymptomatic. When symptomatic they can present with increased vibratory thresholds, loss of deep tendon reflexes, paraesthesias, hyperesthesia or hypoesthesia, cramps, restless legs, muscle weakness and atrophy. Patients typically experience functionally disabling symptoms as pain, loss of sensation and weakness. Neuropathy is also a significant contributor to ulceration and amputation (Krishnan AV et al., 2009).

Signs and symptoms in the initial stages of uraemic neuropathy include distal sensory loss to pinprick and vibration as well as reduced or absent tendon reflexes in the lower limbs. With disease progression, sensory loss extends proximally in the lower limb and similar signs and symptoms may manifest in the distal upper limb. In advanced cases, motor nerves can be affected resulting in weakness and atrophy in distal muscles of the lower limb (Krishnan AV et al., 2009).

This should be differentiated from the pattern of weakness in myopathy in uraemic myopathy, in which weakness is maximal proximally with muscles of the hip girdle particularly affected. The presence of sensory symptoms could be related to the severity of the underlying neuropathy (Laaksonen S et al., 2012).

In addition to the damage of large motor and sensory fibers in uremic neuropathy, small fiber neuropathy may also occur. In diabetic CKD patients, small fiber neuropathy may result in burning and sharp pain as well as altered perception of temperature. Traditionally, uremic neuropathy was thought to only become clinically apparent when GFRs fell below 12 mL/min. However, studies in contemporary cohorts have demonstrated that neuropathy is apparent in up to 70% of pre-dialysis patients (Kwai N et al., 2014).

Diagnosis:
Diagnosis of peripheral neuropathy is complex. For its early detection and appropriate intervention, it is required careful clinical assessment with history and physical examination including neurological examination, laboratory testing and electro diagnostic studies or nerve biopsy, if the diagnosis remains unclear. The gold standard for diagnosis of neuropathy is clinical neurological examination including nerve conduction studies, which examine conduction velocity and amplitude (Arnold et al., 2016).

Nerve conduction studies in patients with uremic neuropathy typically demonstrate changes of an axonal neuropathy, with reduced sensory amplitudes initially and reduced motor amplitudes in later disease stages while conduction velocities are only minimally affected. Electrodiagnostic tests, namely electromyography and nerve conduction studies are reliable and sensitive methods to access peripheral nerve function (Krishnan AV et al., 2008).

They can support the clinical diagnosis and provide information about the type of fibers involved – motor, sensory or both -, the pathophysiology – axonal loss versus demyelination - and the pattern of involvement – symmetric or asymmetric (Azhary H et al., 2010).
Clinical diagnosis of neuropathy in CKD requires eliminating other causes of neuropathy such as glucose dysmetabolism and connective tissue disease. The presence of glucose dysmetabolism is significant in diabetic CKD patients who may have pre-existing neuropathy. Connective tissue disorders such as peripheral nerve vasculitis may be associated with a rapid progression of neuropathy (Arnold et al., 2016).

Other causes of rapidly progressive neuropathy in CKD patients include inflammatory demyelinating neuropathies, such as chronic inflammatory demyelinating polyneuropathy, which may occur in the context of glomerulonephritis (Arnold et al., 2016).

In a review of pediatric neuroimaging studies in children with CKD, it was found that signs of cerebrovascular disease including deep white matter hyper-intensities, white matter lesions, cerebralmicrobleeds, and silent cerebral infarction were present (Albaramki J et al., 2016).

Hurkx et al. evaluated 22 children with chronic renal insufficiency (CRI) and dialysis dependence using somatosensory evoked potential of the right median nerve. They reported an increased interpeak latency (N13–N20) suggesting a delayed thalamocortical conduction. No differences in CRI versus dialysis subgroups were found (Hurkx W et al., 1995) (Gipson D et al., 2004).

**Treatment:**
Renal transplantation has previously been recognized as the most effective treatment to improve clinical outcomes. However, some immunosuppressive medications such as calcineurin inhibitors may hinder neurological improvements (Issar et al., 2016).

For dialysis patients there is some evidence for enhanced dialysis strategies such as haemodiafiltration may improve nerve function (Issar et al., 2016).

Research on the subjects is contradictory. Recent investigation reports demonstrated that improvement of uremic neuropathy with dialysis is uncommon. Some authors suggested that dialysis retards the progression of neuropathy in most patients, while others suggested that in patients on dialysis there is a gradual worsening of the neuropathy (Kiernan MC et al., 2007).

Recent evidence suggests that maintaining normal levels of potassium in CKD patients may prevent peripheral nerve injury. Lowering serum potassium levels may be a potential strategy to prevent or treat neuropathy in CKD. A Phase 2 clinical trial has recently been completed which will provide information on the potential benefits of dietary potassium restriction on neuropathy progression in stage 3-4 CKD (Issar et al., 2016).

Neuropathic pain can be managed pharmacologically with membrane-stabilizing treatments such as tricyclic antidepressants and anticonvulsants. However, these drugs have many potential side effects and dosing restrictions (Busui R et al., 2010).

Anticonvulsants such as pregabalin or gabapentin provide an alternative although both have dosing restrictions in patients according to creatinine clearance (Issar et al., 2016).

**REFERENCES**