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EDITORIAL COMMENTARY

A plea for more uremic toxin research in children with chronic kidney disease

Evelien Snauwaert[1] · Wim Van Biesen[2] · Ann Raes[3] · Griet Glorieux[2] · Raymond Vanholder[2] · Johan Vande Walle[3] · Sunny Eloot[2]

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Progressive loss of kidney function in childhood is paralleled by the development of a complex clinical picture, also referred to as the pediatric uremic syndrome. This syndrome, caused by chronic kidney disease or acute renal injury, is affecting nearly all organ systems (Table 1), and consequently, results in a significantly decreased quality of life and increased mortality during, and also beyond, childhood [1–3]. The complexity of the uremic syndrome is also related to its multifactorial character: due to (1) the deterioration of the renal endocrine function (e.g., erythropoietin and calcitriol deficiency), (2) the dysregulation of fluid and electrolyte homeostasis, (3) the development of specific symptoms related to kidney disease (hypertension, fluid overload) and its causes (e.g., diabetes, autoimmune disorders) or (4) treatment (e.g., reactions to bioincompatible dialysis materials), and (5) the accumulation of toxic organic metabolites (i.e., "uremic toxins") due to decreased renal excretion and/or accompanied by increased toxin generation (Fig. 1) [4, 5]. Without neglecting the multifactorial character of the uremic syndrome, this editorial commentary will focus mainly on the accumulation of uremic toxins and its impact within the pediatric uremic syndrome.

In recent decades, rapid progress in both identification of uremic retention solutes and evaluation of their toxicity has been accomplished. Currently, more than 140 uremic toxins are identified [6]. As proposed by the European Uremic Toxin Workgroup (EUTox), uremic toxins can be subdivided into three major classes based on their physicochemical properties that affect their removal during dialysis: (1) small water-soluble compounds (< 500 Da; e.g., urea) that are easily removed by diffusion, (2) middle molecules (≥ 500 Da; e.g., β2-microglobulin) that are most efficiently removed using large pore dialyzer membranes and by adding convective transport (hemodiafiltration), and (3) protein-bound compounds (e.g., indoxyl sulfate) that most often have a low molecular weight but are poorly removed by dialysis due to their protein binding [5, 7]. In experimental and clinical studies, many of these uremic toxins exert some degree of toxicity on one or more functional systems that contributes to the uremic syndrome and its complications [8]. In general, the cardiovascular, inflammatory, and fibrogenic system were most frequently affected by uremic toxins in experimental and clinical studies [8].

Nearly all these clinical studies on uremic solute retention were performed in adult chronic kidney disease (CKD) patients, and to the best of our knowledge, studies investigating the impact of uremic toxins on the growing child are virtually non-existent. Nevertheless, children, and the uremic syndrome they are suffering from, have particular characteristics that hamper the full translation of adult experience and knowledge in uremic toxicity into childhood (Fig. 2). First, children have physiological peculiarities that might affect the accumulation pattern of uremic toxins. For instance, children have proportionally larger body water volumes and lower circulating proteins than adults. Therefore, it is unlikely that the distribution, the inter-compartmental clearance, the removal pattern during dialysis, and the retention profile of uremic toxins would be identical to those in adults [9]. Also, the diet of children differs on several aspects from adults, e.g., relatively higher protein and caloric needs per kilogram body weight. As diet is one of the major determinants of intestinal microbiota, it is thus likely that the accumulation pattern of uremic toxins originating from microbial metabolism might be impacted, irrespectively of kidney function [10, 11].

✉ Evelien Snauwaert
Evelien.Snauwaert@UZGent.Be

[1] Department of Paediatrics and Medical Genetics, Faculty of Medicine and Health Sciences, Ghent University, Administratie Pediatrie 3K12D Corneel Heymanslaan 10, 9000 Ghent, Belgium

[2] Department of Nephrology, Ghent University Hospital, Ghent, Belgium

[3] Department of Paediatric Nephrology, Ghent University Hospital, Ghent, Belgium

Table 1 Symptoms, characteristics, and complications of the pediatric uremic syndrome. The symptoms, characteristics, and complications highlighted in bold with mark of (*) al features unique for the pediatric uremic syndrome

Fluid and electrolyte balance: polyuria, polydipsia, fluid overload, hypertension, oligo-anuria, metabolic acidosis, hyperkalemia, hyperphosphatemia, hypocalcemia
Endocrine and hormonal system: growth hormone resistance*, insulin resistance, thyroid dysfunction, hyperaldosteronism, adipokine dysbalance, pubertal delay*, anorexigenic hormones increase
Bone and soft tissue: disordered bone turnover and mineralization, bone pain, fractures, growth retardation*, vascular and soft tissue calcifications, rickets*, active vitamin D deficiency, hyperparathyroidism, FGF-23 excess, Klotho deficiency
Hematological system: anemia, erythrocyte fragility, susceptibility to infection, low response to vaccination, inflammation, hypercoagulability, bleeding tendency, bone marrow inhibition
Gastrointestinal system: anorexia, nausea, vomiting, gastropareses, slow gastrointestinal motility, altered taste
Neurological system: polyneuropathy, coordination disturbances, tremor, cognitive dysfunctions, decreased attention span, coma, lethargy, disturbed sleep pattern
Skin and mucosa: skin atrophy, pruritus, calciphylaxis, periodontitis, stomatitis
Cardiac system: left ventricle hypertrophy, cardiomyopathy, pericarditis, coronary calcifications
Psychosocial factors: school absenteeism*, low quality of life, parental stress and burn out*
Others: malnutrition, muscle weakness, changes in drug protein binding

FGF-23 fibroblast growth factor-23

Second, the impact of toxicity on maturational and developmental processes of nearly all organ systems, which represents a core aspect of the pediatric uremic syndrome, can by definition not be extrapolated from adults in whom maturation has come to an end (Fig. 2). Growth and puberty, which are unique pediatric features, are commonly affected in the pediatric uremic syndrome. The Annual Report of the North America Pediatric Renal Trials and Collaborative Studies (NAPRTCS) in 2011 demonstrated that still 32.8% of children initiated with dialysis between 2002 and 2011 had significant growth failure [12]. As growth failure in children with CKD impacts quality of life and is associated with an increased risk of hospitalization and death, it is considered as a relevant marker of the pediatric uremic syndrome [13, 14]. Multiple factors (e.g., nutritional, metabolic, and endocrine abnormalities) are identified in the pathophysiology of growth failure within the pediatric uremic syndrome. Although unexplored yet, it is very likely that uremic toxins directly affect growth since several studies demonstrated that enhanced removal, by applying intensified and daily hemodialysis, improved growth velocity compared to conventional hemodialysis [9, 15–18]. Although these studies were observational and uncontrolled, the catch-up growth achieved in these populations is striking, as standard treatment with adequate nutrition in children on maintenance hemodialysis remains associated with a mean loss in height SDS of −0.4 to −0.8 [19]. Beside growth, several other maturational processes occur in childhood. There is a maturational increase in organic solute transport in the proximal tubule up to the first 2 years of life [20, 21]. Since gut-derived, protein-bound uremic toxins, which are inadequately removed by current dialysis techniques, depend on these active transporters at the side of the tubules for their elimination; differences in their accumulation pattern and toxicity versus adulthood are very likely [22, 23]. Beside the maturational changes in excretion by organic solute transport, the accumulation pattern of gut-derived uremic toxins might also be influenced by the ongoing intestinal microbiota development which continues until the first 2–3 years of life [11].

Finally, several elements of the pediatric uremic syndrome differ from its adult counterpart. Whereas the pediatric uremic syndrome is mainly secondary to congenital anomalies of kidney and urinary tract (CAKUT) and hereditary renal diseases, the uremic syndrome in adulthood is predominately caused by glomerulopathies (e.g., diabetic nephropathy, hypertension)

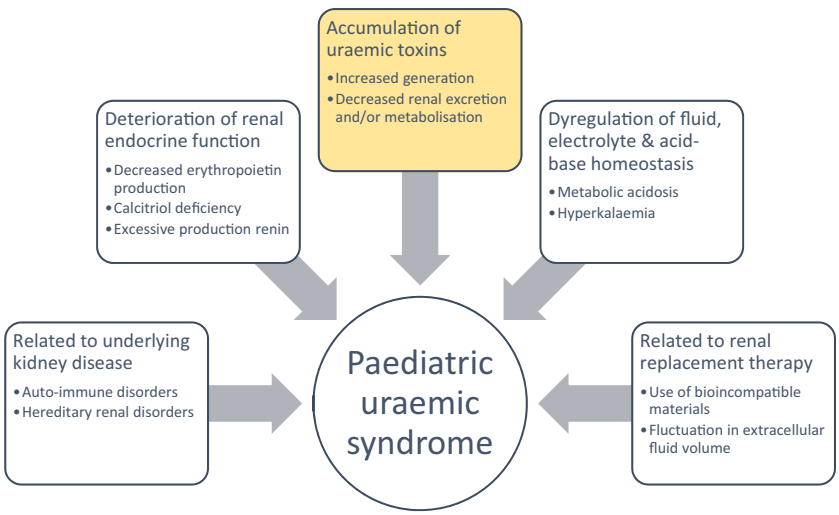

Fig. 1 Presentation of the multifactorial origin of the pediatric uremic syndrome

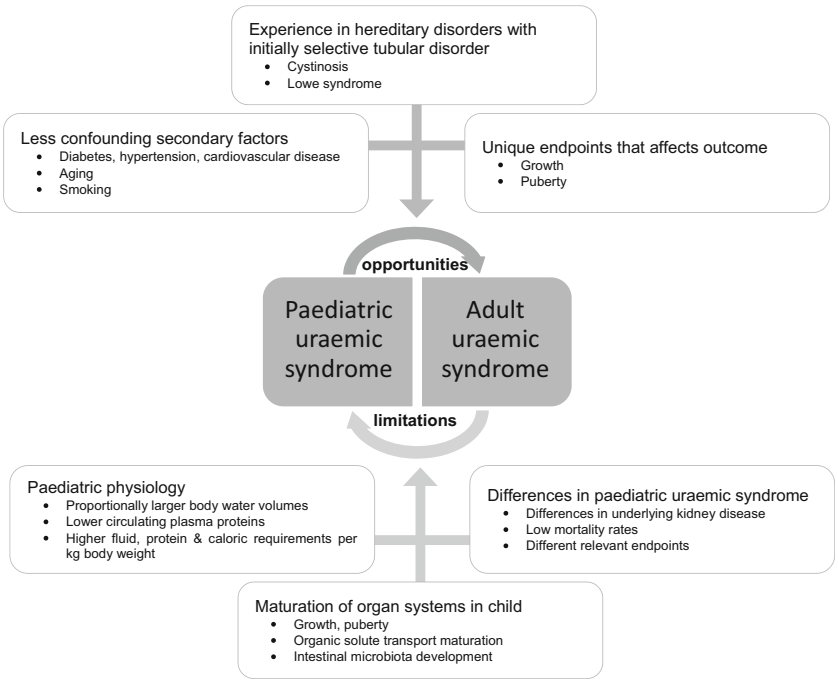

Fig. 2 Limitations and opportunities affecting respectively the translation and backtranslation of adult experience and knowledge to childhood uremic toxicity

and autosomal dominant polycystic kidney disease [24]. Moreover, the differences in survival are striking. While the 5-year survival probability is 89% for children initiating renal replacement therapy, adults have an expected survival of 10% after 10 years on dialysis [25]. These low-mortality rates in childhood make the use of mortality as primary endpoint in pediatric studies less relevant or at least insufficient. Therefore, clinical outcome studies in the pediatric uremic syndrome almost inevitably depend on consideration of other patient relevant outcomes, which may be both short term, e.g., growth, pubertal development, bone metabolism, cardiovascular risk factors, and schooling, as well as long term such as premature cardiovascular disease. Additionally, school absenteeism, education level, and parental stress and burnout are important and unique endpoints in the pediatric uremic syndrome [16]. Several of these parameters are patient-centered and relevant to social life (growth, pubertal development, school absenteeism, familial stress), which will allow to highlight novel and up to now often neglected aspects of uremia.

The limitations mentioned above with respect to translation of adult knowledge on uremic toxicity to childhood might be turned into an advantage, as research in the pediatric population might offer several opportunities to improve our understanding of uremic toxicity within both the adult and pediatric uremic syndrome (Fig. 2). For instance, the majority of adult CKD patients have confounding factors (e.g., diabetes, hypertension, smoking, and aging) that, like uremic toxins, impact the cardiovascular, inflammatory, and fibrogenic system. As these factors are less preponderant or even absent in the pediatric population, clinical outcome studies in the pediatric CKD population will probably be more suitable to elucidate the cardiovascular toxicity of uremic toxins per se in comparison to those in the adult CKD population. Additionally, unique for children is the early presentation of hereditary renal diseases with initially a selective tubular defect (e.g., cystinosis). Evaluating these renal diseases might improve our understanding of the role of tubular cells and their organic solute transporters in the clearance of uremic toxins, which are barely removed with current dialysis therapies. At last, the pediatric uremic syndrome has unique additional endpoints, e.g., growth, that might be helpful in the clinical study of the uremic toxicity since it can be evaluated in a relative short-term.

In conclusion, the pediatric uremic syndrome is a complex multisystem disorder caused and influenced by multiple factors, of which uremic toxin accumulation remained up till now unexplored. As children, and the pediatric uremic syndrome they are suffering from, have several peculiarities, the translation of adult knowledge on uremic toxicity to childhood might be skewed. On the other hand, we are convinced that uremic toxicity research in the pediatric population could have an added value in elucidating in a clinical setting the intrinsic toxicity of uremic toxins. Subsequently, better understanding of uremic toxicity might offer a solid pathophysiologic underpinning for the development of novel dietary and pharmacological interventions, with the ultimate goal not only of improving the health of patients with CKD but, hopefully, also of preventing its progression to end-stage kidney disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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