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GROWTH AND NUTRITION IN CHILDREN ON PERITONEAL DIALYSIS

Croissance et nutrition de l'enfant en dialyse péritonéale

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Résumé

Le retard de croissance et la dénutrition sont fréquents chez l'enfant atteint de maladie rénale chronique et s'accroissent avec le degré de l'atteinte pour être maximaux chez l'enfant au stade de dialyse, conduisant à un risque de surmortalité. Malgré de nombreux progrès réalisés dans le domaine de la dialyse pédiatrique, la petite taille à l'âge adulte reste très commune dans cette population. L'origine de la dénutrition et du retard de croissance est complexe et multifactorielle. Chez le nourrisson en dialyse péritonéale, les apports nutritionnels insuffisants sont reconnus comme un frein majeur à la croissance adéquate. L'approche diagnostique de la dénutrition et du retard de croissance de l'enfant en dialyse péritonéale nécessite de s'appuyer sur plusieurs éléments : un interrogatoire, un examen clinique, et des examens complémentaires divers. En raison de l'aspect multifactoriel du statut nutritionnel et statural de l'enfant, plusieurs axes thérapeutiques sont à prendre en compte, à savoir un traitement nutritionnel adapté aux besoins de l'enfant, un traitement par hormone de croissance, et une optimisation de la dialyse pour permettre un contrôle métabolique optimal.

Mots clés : dialyse péritonéale, pédiatrie, retard croissance, nutrition

Abstract

Growth retardation and malnutrition are common in children with chronic kidney disease and increase with the degree of kidney failure to become maximal in children at the dialysis stage, leading to a risk of increasing mortality. Despite many advances in the field of pediatric dialysis, small size in adulthood remains very common in this population. The origin of malnutrition and growth retardation is complex and multifactorial. In infants on peritoneal dialysis, insufficient nutritional intake is recognized as a major barrier to adequate growth. The diagnostic approach to malnutrition and growth retardation in peritoneal dialysis requires the use of several elements: an evaluation of medical history, a clinical examination, and various complementary examinations. Due to the multifactorial aspects of the nutritional and statural status of the pediatric patients, several therapeutic axes have to be taken in account, mainly a nutritional treatment adapted to the needs of the child, a specific treatment by growth hormone, and an optimization of dialysis to allow optimal metabolic control.

Keywords : peritoneal dialysis, pediatric, malnutrition, stunting

INTRODUCTION

Children with stage 5 chronic kidney disease (CKD) have a mortality rate that is fifty-five times higher than that of the general pediatric population [1]. Stunting and undernutrition are correlated with a higher risk of mortality in children with CKD [2]. Despite the many advances in care for children with CKD on dialysis, stunting is a frequent complication in this population. According to studies, 30–60% of patients who have been on renal replacement therapy in childhood are small in adulthood [3–6].

Nutritional problems are extremely common in children on peritoneal dialysis (PD) and contribute to the genesis of stunting, but many other factors, such as hormonal resistance, inflammation, cachexia and uremic renal osteodystrophy also play a role. Achieving satisfactory growth and nutritional status is therefore an essential issue for pediatric nephrologist and is often a difficult challenge. The management of the child's growth while on PD must be comprehensive and must take into account three therapeutic areas: the nutritional aspect, treatment with growth hormone and optimized dialysis.

ANTHROPOMETRIC PARAMETERS AND CKD

Stunting increases along with the degree of renal failure and is greatest for dialysis patients and, for each standard deviation lost, there is a 14% increase in mortality [2, 7]. In the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) register, 36.6% of patients had, at baseline, severe growth retardation, defined as less than the 3rd percentile (i.e. >-1.88 SD).) [8]. 45% of patients included in the European Society for Pediatric Nephrology (ESPN/ERA-EDTA) register have a final size below the 3rd percentile [3]. Adequate growth of children with CKD may be considered one of the markers of appropriate management and, conversely, stunting may be a sign of deficient health and is thus correlated in children with CKD to an increased number of hospitalizations, increased days missed at school and a decreased quality of life on dialysis [4, 9]. Beyond the CKD, small size has been linked in the general population to poorer school performance and lower self-esteem [10, 11]. Children with CKD have complex abnormalities of the GH-IGF-1 axis causing a growth hormone (GH) defect, contributing to longitudinal growth retardation and to the risk of undernutrition of these patients [12]. In addition, it is clear that the rate of children born small for gestational age is higher in children with CKD (28% of children with CKD) and that only 1/3 of these children will have

catch-up growth [13, 14].

Size at the time of transplantation is a prognostic factor for height in adulthood since growth recovery is rare after transplantation, aggravated by corticosteroid treatment. This catch-up nevertheless remains more likely in the youngest children and those with a greater delay at baseline [9]. It is therefore very important to ensure that patients awaiting renal transplantation can have adequate growth.

The body mass index (BMI) is also an important prognostic factor for CKD, and a relationship with a U-shaped curve between mortality risk and standard BMI deviations for children with a deficiency has been shown. end-stage renal disease. Thus, if a low BMI (a state of malnutrition) increases the risk of death in these children, a high BMI (either overweight or obese) is also a recognized risk factor, as opposed to what could be found in some studies with adults. Similar to what is observed in the general population, an increase in the obesity rate is found in children with renal failure, with 13% of children in European registries and 21% of overweight children. The risk of being overweight/obese is higher in adolescents and has been linked to increased mortality in this population [3, 15]. In PD the IPPN register reports an obesity rate of 19.7% affecting all age groups associated with a risk of higher mortality in infants [15]. Particular vigilance must therefore be given to all children with an extreme BMI, and appropriate nutritional measures must be put in place.

CHILDREN ON PERITONEAL DIALYSIS

PD is the most widely used extrarenal treatment technique in children worldwide, especially for very young children since it is easy to use and is feasible from birth. Young children represent a population particularly at risk of undernutrition and growth disorders. While some studies have shown that dialysis sometimes allows a recovery of growth, it will nevertheless remain highly dependent on different treatments, nutrition and dialysis. The first two years of life are marked by rapid growth (little hormonodependante) with a size gain of 50 cm, and any loss of growth in this period will have a particularly significant impact on size in adulthood.

The NAPRTCS registry finds that children on dialysis tend to have greater stunting, the average height moving from -1.64 SD to -1.84 at two years of dialysis [6]. However, pediatric studies have shown contrary results, with growth recovery in both hemodialysis and PD, when optimized dialysis and/or adequate nutritional measures were applied [16–20].

Children on PD very often have nutritional difficulties with insufficient caloric intake [4, 6, 21] contributing to stunting.

These nutritional difficulties are multifactorial (Table 1) and more frequent in infants, with a decrease in nutritional intake or absorption. Anorexia and vomiting are common in patients with renal impairment, and children on PD often have gastroesophageal reflux secondary to increased abdominal pressure. In addition, these patients may experience a feeling of abdominal discomfort due to peritoneal filling, sometimes amplified by polydipsia in some kidney diseases. Taste is often altered in patients with CKD, and taking the many medications needed for children on PD adds to their nutritional challenges. The presence of a higher amount of certain toxins and cytokines, such as TNF- α , IL-1 or IL-6, impairs the patients' appetite [22]. The diet of children with CKD often has many restrictions, another barrier to food intake. The metabolic acidosis that may be present in these patients sometimes worsens the picture, along with the resistance to anabolic hormones such as insulin and growth hormone. These different parameters have an even greater impact if the child has a decrease in residual diuresis and inadequate dialysis [4, 6, 21, 23].

These difficulties of nutritional intake are accompanied by the protein losses in the dialysate, increased in the case of peritonitis, or in some cases in the urine. In addition, children on PD often have increased nutritional requirements due to recurrent inflammatory/infectious episodes and the need for catch-up growth when pre-existing growth was delayed during PD [21].

The challenge of managing child nutrition while on PD is ensuring adequate height-for-weight growth, and also maintaining verbal communication, sometimes impeded by the various elements mentioned above. Real work in partnership with the parents, the child, the dietician and the doctor is required, requiring a certain flexibility to

allow the child a caloric and protein intake sufficient for him or her its growth without endangering him or her it.

Children with CKD, especially when on dialysis, are at risk of protein-energy malnutrition (PEM) or cachexia. PEM/cachexia is a complex condition that leads to an inappropriate response with anorexia, increased metabolic expenditure, decreased protein stores, and decreased weight and muscle mass through activation of the ubiquitin-proteasome system, via the production of glucocorticoids, angiotensin II and IGF-1 [24-26]. Unlike malnutrition, which can be corrected by appropriate nutritional intake, the state of PEM requires the correction of many factors, such as acidosis, anemia, water-overload, inflammatory status and hormonal dysfunction. Optimizing dialysis and increasing nutritional intake is often required.

PEM has been linked to increased mortality in adults with CKD. In children, the prevalence of this condition remains poorly known, as the adult definition criteria cannot be used to report on the state of undernutrition in children. Pediatric criteria have been proposed including statural break in pediatric diagnostic criteria: a rate of 7 to 15% of children with CKD then presented with PEM, and this correlated with the risk of hospitalization of children [27-29]. For children on dialysis, according to studies and the criteria used, there is a rate of 15 to 68% of undernourished children [30-34]. The ESPN/ERA-EDTA register found that 3.5% of children and 16% of end-stage renal infants were underweight, while the International Pediatric PD Network (IPPN) register had a lower BMI in 8.9% of children at the start of dialysis [15, 34].

If nutritional status plays a key role in the child's growth while on PD, it should be remembered that renal osteodystrophy, hormonal resistance, inflammation, cachexia, acidosis, anemia, retardation pubertal and the uremic toxins present in children with CKD contribute

Tableau 1 : Factors causing child undernutrition in PD

Decrease in dietary intake and absorption	Protein losses increase	increased nutritional needs
Uremic toxins Hormonal abnormalities Inflammatory cytokines Metabolic acidosis Dietary restrictions and polydipsia Taking many medications Changes in taste Peritoneal filling Vomiting and gastro-oesophageal reflux Insufficient dialysis / loss of diuresis	Losses in dialysate Urinary losses peritonitis	Catch-up growth Inflammatory condition Intercurrent infectious episodes

to the lack of longitudinal growth.

NUTRITIONAL MANAGEMENT AND GROWTH OF CHILDREN ON PD

Clinical and paraclinical evaluation

The first step in this management is an assessment of the child's weight and nutritional state. Due to the rapid body changes of children, this assessment should be performed very regularly, as should the estimation of dry weight. The KDOQI's recommendations are to make at least a monthly estimate for children under two years old and every 3–4 months for older children, and up to once a week for newborns on dialysis. The complexity of the pathogenesis and clinical picture of PEM in children on PD requires both a clinical approach and different examinations, which are extensively detailed in the literature [21, 35].

In summary, this evaluation is based on interrogation (presence of nausea, vomiting, diarrhea, constipation, swallowing difficulties, etc.) and clinical examination (appearance of hair, nails, skin fold, etc.). Anthropometric parameters (weight, height, cranial perimeter, BMI) should be measured at each visit and placed on a curve to estimate standard deviations for the child's age. Another important parameter is the growth rate [21, 36–38].

More occasionally, anthropometric indices such as brachial circumference and triceps can be used, as in the case of adults, to estimate the muscle mass and body fat of the child, pediatric standards that have been validated in both sexes and in different age groups [39, 40]. These latter parameters, however, have some limitations with large inter-observer variability, and moderate sensitivity to detect early and mild stages of undernutrition [41].

A key element of nutritional assessment is the dietary survey with a calculation of ingestants, frequently based in pediatrics, on an estimate of ingestants over a period of 3 days. The main bias remains that the contributions are reported by the parents who can forget or omit to report certain contributions [21, 35].

Some biological parameters, such as albumin, can be used as markers of nutritional status in children and have been linked in pediatrics to the risk of mortality. The specificity of albuminemia as a nutritional marker is very limited because its rate is influenced by urinary and dialytic losses, by water-overload and by the inflammatory state of the child [29, 42].

Protein metabolism can be estimated at time *t* by the normalized protein catabolic rate (nPCR) which, in the case of clinical stability, is the equivalent of the dietary

protein intake between two dialysis sessions, and whose calculation takes into account urea in the dialysate and in the urine. In pediatrics, two formulas are proposed for this calculation: the modified Borah equation and the Mendley et al. equations [43, 44]. The KDOQI group recommends the use of these formulas only for adolescents on hemodialysis, but other indices derived from protein metabolism have shown reliability in assessing nutritional status in children with PD [45–47].

Single-frequency and multi-frequency bioimpedanceometry is a tool increasingly used by pediatric dialysis teams to estimate the body composition of children [31, 48, 49]. Several pediatric nutritional scores have been proposed, as well as pediatric scores for PEM. There is, however, no gold standard among these scores currently [21, 28, 33].

Prevention and treatment of undernutrition and stunting in children on PD

The origin of PEM and stunting in children on PD is often multifactorial. The correction of these states makes use of various measures that we will describe according to three therapeutic axes: nutritional management, pharmaceutical treatment with growth hormone, and optimized dialytic treatment with adequate medicinal support (Figure 1).

Nutrition

In children on PD, the nutritional aspect is recognized as one of the main obstacles to adequate growth. The work of the dietician in collaboration with family and doctors is essential for the management of kidney disease in children at all stages. The recommended energy intake corresponds to 100% of the recommended intake (RI) for the general population and varies with the age of the child (Table 2). An intake of less than 80% of the RI is associated with stunting. This energy intake will be provided by 45–50% of carbohydrates, 40–45% of lipids and 10% proteins. For the child on PD, the glucose uptake of the dialysate increases the calorie intake from 7 to 10 kcal/kg. This calorie intake must be based on an adequate amount of non-protein calories [4, 21, 45, 50].

The diet will be even less restrictive if the child has optimized dialysis and/or residual diuresis. Depending on the basic pathology, the recommended sodium intake varies and may not be adequately covered by the diet. Supplementation is therefore essential to allow adequate growth (for example in some tubulopathies), and a water-soluble restriction may be necessary in the absence of residual diuresis in the larger child. Phosphate restriction involves the removal of protein-rich foods. Phosphorous foods are usually those containing calcium, which

requires calcium supplementation [50, 51].

Regarding protein intake, the low protein diet is not recommended for children, since his growth is the main goal. The protein RI corresponds to 100% RI for healthy children of the same age and is secondarily adapted for growth and weight gain (Table 2). On DP, this contribution must take into account the protein losses in the dialysate of the patients. This loss is estimated at approximately 100 to 300 mg/kg and an increase in protein intake is therefore recommended (Table 2) [21, 45, 50].

Spontaneous oral intake is preferred in children when possible. However, the caloric intake is often insufficient, and food supplements or enriched/concentrated milk formulas can be proposed initially to increase caloric intake.

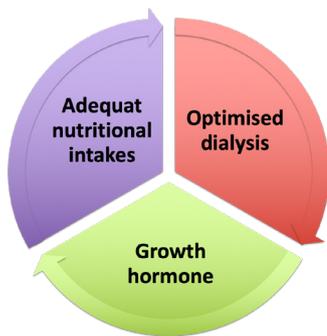


Fig 1 : Nutritional management and growth of the child in peritoneal dialysis and its three complementary therapeutic areas

If oral intake of caloric supplements is not sufficient, enteral nutrition should be considered promptly. This is very often required in infants on PD. The use of a nasogastric tube (NGT) or gastrostomy and, in rare cases, gastrojejunostomy varies from team to team. Growth and quality of life are likely better if enteral feeding is achieved through gastrostomy [Rees 2011]. NGT is easy to put in place, but is aesthetically visible and requires more frequent responses as the child is prone to vomiting. Gastrostomy is not very visible but can lead to complications such as infections, peritonitis and leaks [52]. Percutaneous insertion of a gastrostomy can only be performed before the start of PD, because according to some authors it entails a risk of fungal peritonitis and failure of PD if it was performed second. The surgical technique will then be with antibiotic therapy and preventive antifungal therapy [53]. This enteral feeding can be administered as a bolus or continuously at night, according to the «full stomach» tolerance [6, 21, 50]. Enteral feeding in infants is based on commercial milk formulas that can be enriched and concentrated. Breast milk, as for other children, is the most suitable milk for the child on dialysis and should be preferred and encouraged if possible. For larger children, different types of products may be used and have been reviewed in detail [51]. Some are specifically developed for children with renal impairment or on PD (Renastart®, Renacal®, Kindergen®, etc.), but their availability varies from country to country as well as their reimbursement. Many teams use traditional enteral nutrients for the child's age, given the lack of protein restriction in children on PD, choosing the formula best suited to the specific needs of the child [50, 51]. Several studies have shown a gain in height and weight during enteral nutrition in children on [19, 54]. The

Tableau 2 : Recommended energy and protein intake for children in PD [45] [50]

	Age	Energy intake recommendations	Protein intake recommendations (g/kg/days)
Girls and boys	0-3 months	115-150 kcal/kg	≥2,4
	4-6 months	95-150 kcal/kg	≥1,9
	7-12 months	95-150 kcal/kg	≥1,8
	1-3 years	95-125 kcal/kg	≥1,4
	4-6 years	90-110 kcal/kg	≥1,3
Girls	7-10 years	1740 kcal/j	≥1,2
	11-14 years	1845 kcal/j	≥1,4
	15-18 years	2110 kcal/j	≥1,3
Boys	7-10 years	1970 kcal/j	≥1,2
	11-14 years	2220 kcal/j	≥1,4
	15-18 years	2755 kcal/j	≥1,3

International Pediatric Dialysis Network's registry identifies gastrostomy feeding in children younger than 2 years as a positive predictor of longitudinal growth [55], and there was improvement in BMI for obese and malnourished patients during PD [15]. After two years, the results of studies on the possibility of catch-up growth when introducing enteral nutrition are more mixed, and some warn against the risk of obesity [15, 55–57]. The supply of amino acids via the dialysate has been described. Results regarding nutritional benefits are controversial and are only studied with a limited number of patients. If this type of dialysate is proposed, it does not appear to be a substitute for other dietary support measures [21, 58–61].

Growth hormone

Recombinant growth hormone is indicated in children with renal insufficiency and therefore a fortiori in children on PD. However, prescribing policies vary from country to country, possibly accounting for some of the variations in the final size of children with CKD which are observed between countries [62]. In France, it is prescribed after reaching bone age in the pre-pubescent child who is treated for at least one year for CKD with a clearance of <60 ml/min/m²73 and a slowing of the growth rate or a size <-2 DS. In children with CKD and a growth hormone resistance status, the prescribed doses are supra-physiological with initial doses of 0.045 to 0.050 mg/kg. At these doses, growth hormone treatment has been shown to be effective in longitudinal growth [62–65]. Several studies in adults suggest that growth hormone administration would have an anabolic benefit and improve nutritional status [45].

Dialysis and pharmacological treatment

Since growth and PEM are multifactorial, it is therefore best to correct, through adequate dialysis and pharmaceutical measures, anemia, acidosis and hyperparathyroidism, and to obtain a state of euvoemia, as well as correct hydro-electrolyte disorders to allow for proper growth and nutritional status.

A clear relationship has been established between dialysis dose and nutritional status [20, 21, 66, 67]. PD patients should be followed and monitored monthly to best adapt dialysis and treatment. Particular attention should be paid to the maintenance of residual diuresis, which is a strong prognostic factor for the nutritional status of these children.

While increasing the dialysis dose beyond KDOQI recommendations may or may not improve PD nutritional status, this is clearly open to debate [20, 66–68]. The adequacy of dialysis is not, however, reduced

to the dialysis dose, and the optimized PD improves all the parameters involved in the genesis of PEM and growth disorders [69]. Like the evidence-based results shown in HD on growth through intensive diets, it seems logical to propose optimized PD regimens in children to promote adequate nutritional status and growth [16, 17].

Conclusion

Despite numerous therapeutic advances in the care of children with CKD, these children are often small in adulthood. Nutritional management remains essential to enable them to grow, although it is only one link in their management. Children on PD often have inadequate nutritional intake and special attention should be paid to their dietary management. Adequate nutrition, growth hormone therapy and adequate dialysis are key elements in caring for these children.

CONFLICTS OF INTEREST

The authors declare no conflict of interest with this publication.

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