CHRONIC KIDNEY DISEASE ASSOCIATED PRURITUS IN CHILDREN – DIAGNOSIS DILEMMA AND TREATMENT

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ABSTRACT

Pruritus represents a common and distressing feature of patients with chronic kidney disease (CKD). The severity of CKD associated pruritus (CKD-aP) can be assessed by using a visual analogue scale. Its presence is associated with a decreased quality of life, it contributes to the onset of other symptoms, it is correlated with depression, and represents an independent predictor of mortality. The aim of this article is to present the case of a 16 years old patient with end stage renal disease who developed CKD-aP in evolution, along with the apparition of other dermatological findings. Despite the adaptation of the dialysis prescription, the patient developed a severe uremic pruritus. Partial failure of numerous topical therapies associated with neuroleptics and sedatives was registered. The non-compliance to diet contributed to a slow amelioration of the symptoms. We highlight the importance of the correction of dialysis adequacy, phosphorus and calcium levels, along with skin hydration, nutrition, and patient education in an optimal outcome for pediatric patients with CKD-aP.

Key words: pruritus, chronic kidney disease, children

INTRODUCTION

According to Hill *et al.*, the worldwide prevalence of chronic kidney disease (CKD) in all stages was estimated at 13.4% [1]. In 2017, there were 697.5 million new cases of CKD, as well as 1.2 million deaths associated with CKD [2]. Unfortunately, the global the burden on health systems in CKD also stems from the presence of the disease in the pediatric population. The prevalence of CKD varies between 15-74.7 per million children in different geographical regions [3]. The etiological factors that contribute to the development of CKD are different in children compared to adults. While adults mostly develop CKD due to diabetic nephropathy, hypertension and autosomal dominant polycystic kidney disease (ADPKD), the main causes in children include congenital anomalies of the kidney and urinary tract (CAKUT), hereditary nephropathies and glomerulonephritis [4]. The major complications of CKD in children are represented by the cardiovascular disease, hypertension and/or dyslipidemia, impaired cognitive development, anemia, growth retardation, malnutrition, decreased appetite, or even death [5]. End stage renal disease (ESRD) is associated with a 30-fold higher probability of mortality than in healthy children. Moreover, children with CKD have a significantly reduced quality of life, due to reasons related to prolonged hospitalization, the impossibility of continuing the school

program, social disengagement, or complications of the disease [6]. More than that, the treatment with hemodialysis affects the patients' quality of life more intensely than heart failure, diabetes, chronic lung disease, arthritis and cancer. In their study, Tjaden *et al.* described how children undergoing dialysis experience have poor self-esteem and a pervasive sense of losing their identity, body integrity, control, independence and opportunity [7].

CASE PRESENTATION

We report the case of a 16 years old girl, diagnosed at 2,6 years old with stage 4 chronic kidney disease due to untreated reflux nephropathy. In evolution, the renal function deteriorated and the girl reached the age of 5 years in ESRD. Motivated by her young age, peritoneal dialysis (PD) was initiated. Consequently, she developed severe renal osteodystrophy refractory to standard phosphate binders. Then, she presented multiple episodes of peritonitis, with secondary sclerosing of peritoneum, necessitating conversion to hemodialysis on central venous catheter (CVC). In the context of a heterozygous profile for thrombophilia, the girl developed numerous episodes of CVC thrombosis, which is a dysfunction that prejudiced the dialysis sessions [8].

Physical examination revealed: irritability, purple subcutaneous hard nodules, dry skin, multiple excoriations, linear crusts, ulcerations, impetigo (Figures 1,2,3,4), respiratory rate 18 per minute, heart rate 80 per minute, blood pressure of 130/60 mmHg, with normal heart sounds, no murmurs.

Laboratory findings: Blood tests always revealed elevated calcium–phosphorus product, the highest being 123,76 mg^2/dL^2 with a corresponding PTH level of 1250 pg/mL (n=10–65 pg/mL). The serum chemistry revealed: before dialysis session blood urea nitrogen (BUN) of 277 mg/dL, creatinine of 10.84 mg/dL; normal electrolytes; serum albumin of 2.1 mg/dL; normal liver enzymes and cholesterol of 222 mg/dL (normal 100–200 mg/dL); calcium 11.71 mg/dL, phosphorus 10.98 mg/dL (calcium–phosphorus product corrected for low albumin = 128.57 mg^2/dL^2); magnesium 1.6 mg/dL; intact PTH 765 pg/mL (n=7–53 pm/mL). The hemoglobin was 8.9 g/dL, WBC= 10.550/mm^3 and platelets= 221.000/mm^3. The investigation of the cutaneous lesions and pruritus complaints included antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), *Mycoplasma pneumoniae* antibodies, and rheumatoid factor, which came all negative. Serum complement (C) C3 and C4, hepatitis serology, creatine phosphokinase (CPK), and serum immunoglobulins were all normal.

Subsequently, on the background of secondary hyperparathyroidism, she developed a brown tumor in the right mastoid and cervical region. She underwent parathyroid exeresis 1 year ago, with following regression of the mass. A parathyroid gland was preserved by reimplantation at the right deltoid level. Despite the adaptation of the dialysis prescription, with a good efficiency, Kt/V 1.2-1.5, the girl developed a severe uremic pruritus, with multiple lesions, some with impetigo, with the repeated compromise of the hemodialysis catheter. Numerous topical therapies were applied, associated with neuroleptics and sedatives, but the result was not the expected one. This is added to the background of non-compliance to diet (excessive consumption of dairy products rich in calcium and phosphorus).

DISCUSSION

The prevalence of CKD-associated pruritus (CKD-P) is highly variable in different studies. It has been reported to range from 20% to 90% [9]. Some studies state that the prevalence depends on the dialysis method and is therefore different in hemodialysis and peritoneal dialysis

patients. Thus, in a meta-analysis of cross-sectional studies, including 42 reports, the prevalence of CKD-P in each study varied between 18% and 97.8% with an overall prevalence of CKD-aP of 55%. The joint prevalence in men and women was similar (55%). The prevalence of pruritus in hemodialysis patients was similar to those undergoing peritoneal dialysis (55% vs. 56%) [10]. However, pediatric dialysis patients rarely experience severe pruritus. In a systematic review involving 199 children from different German pediatric dialysis centers, only 9.1% of children presented pruritus in a predominant mild form [11]. In a multicenter study from Poland, 20.8% of the pediatric population with CKD experienced pruritus. Dialysis children were noted to have higher rates of pruritus (23.5%) compared to those in conservative supportive care without dialysis (18.4%). Children with pruritus were more frequently associated with xerosis [12]. Some reviews of the literature on CKD-aP report that kidney transplantation appears to improve pruritus [13].

PTH is a crucial factor that regulates calcium and phosphate homeostasis in the body, influencing bones, kidneys, and the gastrointestinal tract [14]. PTH stimulates the release of Ca2+ into the extracellular fluid, influences osteoblasts and osteoclasts in bone, promotes renal calcium reabsorption, and inhibits phosphate reabsorption. It also stimulates the synthesis of α1-hydroxylase, which is an enzyme necessary in the synthesis of the biologically active form of vitamin D3. In CKD, decreased levels of activated vitamin D3, hyperphosphatemia, and hypocalcemia lead to chronic hyperstimulation of the parathyroid glands. This perpetuates the increased growth (initially diffuse, then glandular), secretion and release of PTH, with inevitable secondary hyperparathyroidism [15]. PTH and fibroblast growth factor 23 (FGF-23) are relevant compounds involved in the pathogenesis of CKD mineral and bone disorder (CKD-MBD) in children, influencing bone turnover, mineralization, volume, linear growth, structure and strength, as well as contributing to vascular calcification [16]. Literature data suggest that PTH is a factor that may contribute to the development of CKD-related pruritus. In 1968, Massry *et al.* reported the cases of 7 patients with ESRD, secondary hyperparathyroidism and severe intractable pruritus, which remitted consequent to subtotal parathyroidectomy [6]. Similar results were reported by Chou *et al.* [17], although the authors found no correlation between iPTH concentration and pruritus. Its postoperative severity rather correlated positively with calcium phosphorus (Ca × P) product. A study by Senturk *et al.* on 27 children with PD demonstrated higher serum concentrations of PTH in subjects with severe pruritus, correlated with increased values of phosphorus, C reactive protein and Ca × P product [18]. The exact pathogenetic mechanisms linking PTH and CKD-associated itch (CKD-aI) remain unknown. Several studies have shown that elevated serum calcium levels favored the occurrence of severe CKD-aI [19], while Momose *et al.* [20] observed an increased concentration of calcium in the deepest layers of the epidermis in patients with severe pruritus related to CKD. This may predispose to degranulation and release of various pruritogenic mediators from mast cells and other cells present in the skin. Higher levels of serum phosphorus (>5.5 md/dL) or serum calcium (>10.2 mg/dL), higher calcium phosphate (> 80 mg^2/dL^2), leukocytosis >6700/mL were also described as independent risk factors [9]. An increase in dialysis dose was also observed to improve pruritus [21]. Other studies have shown that higher PTH blood levels, higher dietary protein intake, long dialysis duration, weekly total Kt/V ≤ 1.88, and elevated CRP were independent determinants of higher pruritus intensity scores according to the Visual Analogue Scale [22].

Pruritus in patients with CKD may

embrace diverse clinical features. The clinical presentation of CKD-P is also variable; the onset of symptoms varies from one to another patient, while the intensity of itching can vary from mild to severe. However, the itching is daily, persistent and recurrent, bilaterally symmetrical, and it worsens at night. It occurs mainly over the trunk and limbs, with the dorsal region of the trunk most frequently affected. Heat and dryness seem to aggravate the itching. And in other diseases with chronic renal deterioration, such as Fabry's disease is the accentuation of heat symptoms. But in factory disease, clinical symptoms are first represented by gastrointestinal symptoms, neuropathic pain (pain attacks, chronic pain), acroparesthesia, angiokeratoma, hypohydrosis and corneal opacities (verticillalata cornea) [23]. The onset of symptoms occurs in childhood or adolescence with palmo-plantar burning pain, hypo-hidrosis, angiokeratomas and cornea deposits, which was also found in our patient [24]. In general, there are no primary skin lesions associated with pruritus, but secondary lesions due to scratching may be observed, such as: excoriations, linear crusts, ulcerations, impetigo or papules. [6]. In other studies, the itching associated with CKD is described as persistent, more severe at night than during the day, aggravated by showering, dialysis, heat, stress, cold, and physical activity [25]. Moreover, CKD-P is frequently associated with calcific uremic arteriolopathy (CUA). This is a rare disease, with an incidence that does not exceed 5% in the adult population with end stage renal disease. In the pediatric population, males with ESRD and secondary hyperparathyroidism present an increased risk for CUA with frequent distal extremity and visceral organ involvement [26]. Clinically, the lesions secondary to CKD-P can wear polymorphic aspects, predisposing to a differential diagnosis with ichthyosis, psoriasis, impetigo (the lesions created by itching can become superinfected), atopic dermatitis, polymorphous erythema. With the latter, the lesions usually appear symmetrically on the extensor surfaces of the distal extremities and progress proximally to the abdomen and back [27]. It may be generalized and can affect the palms, neck, and face, unlike CKD-P which, as a rule, respects the face, palms and soles. The hemorrhagic fever with renal syndrome associated with Hantavirus infection is also characterized by hematologic abnormalities, dermatological involvement and prominent renal involvement [28]. COVID-19 represents an infectious disease caused by the coronavirus SARS-CoV-2. The novel SARS-CoV-2 virus infection has an impact on our understanding of the previously unknown interactions between the immunological mechanism and the coagulation cascade [29]. Skin lesions were seen as COVID-19-associated papulovesicular exanthema scattered in the trunk and mild pruritus, like in our patient case [30].

CONCLUSION

Children with CKD have a significantly reduced quality of life, due to reasons related to prolonged hospitalization, social disengagement or complications of the disease. One of the most common complications is pruritus, which can take various forms and evolves chronically, being mainly related to secondary hyperparathyroidism, as well as uremic calcifying arteriopathy.

AUTHOR CONTRIBUTIONS

All authors have read and agreed to the published version of the manuscript. TIL, II, AMLB, ALC, GS, LSG, MAM contributed equally with RAB to this article.

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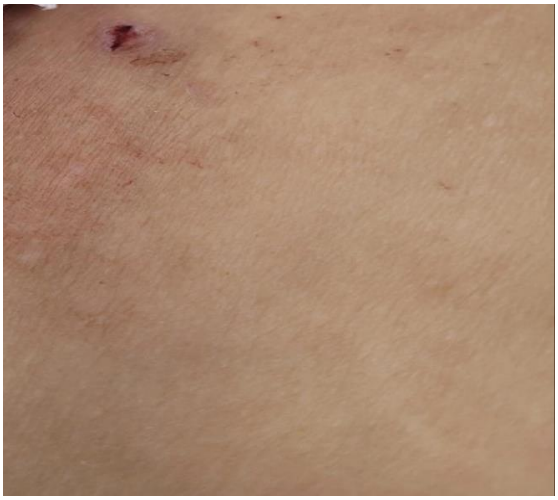

Figure 1. Skin disorders (multiple excoriations, linear crusts, ulcerations, impetigo) in a 16 years old girl with ESRD

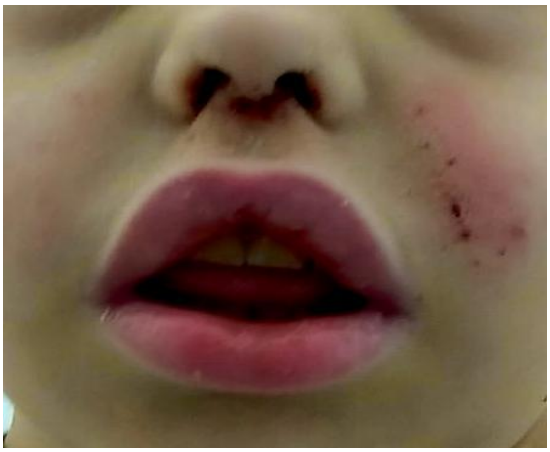

Figure 2. Skin disorders (multiple excoriations, linear crusts, ulcerations, impetigo) in a 16 years old girl with ESRD

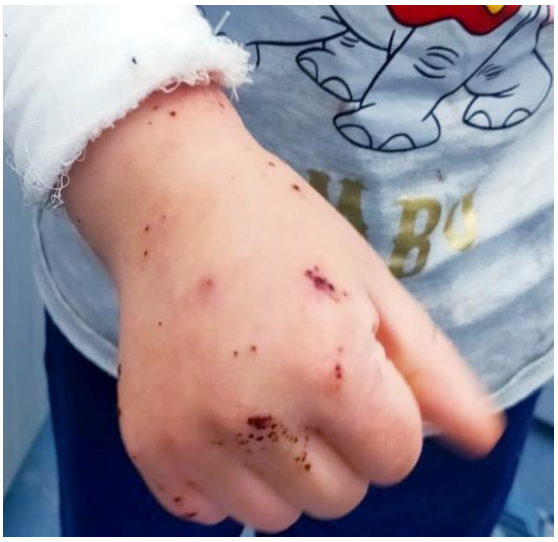

Figure 3. Skin disorders (multiple excoriations, linear crusts, ulcerations, impetigo) in a 16 years old girl with ESRD

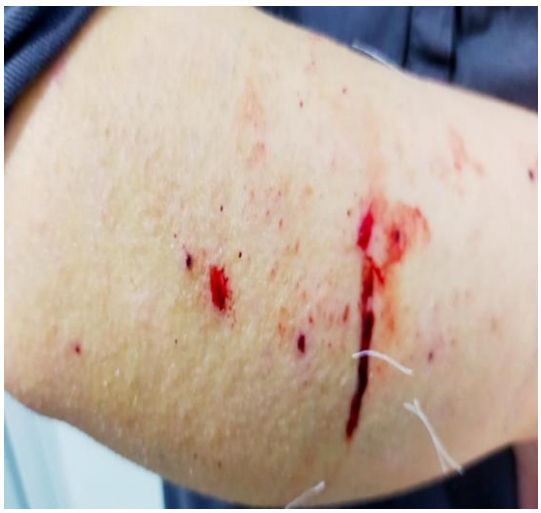

Figure 4. Skin disorders (multiple excoriations, linear crusts, ulcerations, impetigo) in a 16 years old girl with ESRD