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CLINICAL REPORT

# Chronic Kidney Disease-associated Pruritus in Children

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**This study evaluated the frequency and severity of pruritus and dry skin in children with chronic kidney disease (CKD). A total of 103 children were included: 72 with CKD stage 3–5 (34 on dialysis and 38 treated conservatively without dialysis) and 31 as a reference group. Pruritus was assessed using the 4-item Itch Questionnaire and a visual analogue scale. Skin dryness was evaluated clinically, by non-invasive assessment of epidermal hydration and measurement of transepidermal water loss. Pruritus occurred in 20.8% of children with CKD, 18.4% on conservative treatment (receiving supportive care without dialysis) and 23.5% on dialysis. Xerosis was more common in children with pruritus (66.7%) than in those without pruritus (50.9%). Patients with pruritus had a significantly lower estimated glomerular filtration rate and a higher ratio of calcium × phosphate product (Ca × P). In conclusion, CKD-associated pruritus occurs not only in adults, but also in children, and it may already be present in the early stages of CKD.** ***Key words: pruritus; dry skin; chronic kidney disease; children*****.**

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Cutaneous lesions in patients with chronic kidney disease (CKD) are polymorphic and diverse. The most common skin symptom in adults with CKD is pruritus, termed "uraemic pruritus" or, more accurately, "chronic kidney disease-associated pruritus" (CKD-P). CKD-P affects 25% of patients on haemodialysis, according to a representative cross-sectional study, but may occur in up to 46% of patients depending on the country and haemodialysis unit in which they are treated (1, 2). Pruritus is less common in patients with less advanced stages of CKD (2). A recent study by Solak et al. (3) found that pruritus occurred in 18% of predialysis patients with CKD.

Our knowledge of the pathophysiological mechanism of CKD-P is incomplete. A number of hypotheses regarding its aetiopathogenesis have been put forward in the last 20–30 years, including: changes associated with dry skin, uraemic toxaemia, imbalance in divalent ions, proliferation of mast cells with a simultaneous increase in histamine levels, decreased levels of vitamin D, lipid dysregulation in the epidermis, hyperparathyroidism, abnormal tryptase and chymase activity, neurogenic disturbances, opioid receptor imbalance, and types of dialysis membranes (4–7).

Published data on pruritus in children with CKD are limited. There are few published papers on pruritus in paediatric patients, and these present the results of studies on a small number of patients who need chronic renal replacement therapy (8, 9). No studies of pruritus in children with CKD in earlier stages of the disease have been published recently. The burden of pruritus is often underestimated by nephrologists, particularly in this group of patients with CKD. However, itch is one of the most frustrating symptoms, significantly influencing daily activities, disrupting sleep and impairing health-related quality of life (10).

The aims of the current study were to evaluate pruritus in children with different stages of CKD, to determine the prevalence of CKD-P, its severity and characteristics in these patients, and to examine its link with dry skin and selected factors typical for CKD.

## MATERIALS AND METHODS

### *Patients*

A total of 103 children from 3 Polish paediatric nephrology centres located in Wroclaw, Krakow and Zabrze were included in the study. Among them, there were 72 patients with CKD stages 3–5 and 31 patients with primary monosymptomatic nocturnal enuresis (17 girls and 14 boys, mean age $10.7 \pm 3.9$ (range 4–17) years) who served as a reference group. A total of 38 patients with CKD were given conservative treatment (supportive care without dialysis) and 34 were given renal replacement therapy (20 haemodialysis subjects and 14 peritoneal dialysis subjects) (Table I). All dialysed patients were combined into a single group, as the numbers of patients on haemodialysis and peritoneal dialysis were low.

None of the children with CKD had had any dermatological treatment, infection, or other condition in at least the 4 weeks prior to enrolment in the study that might have significantly influenced skin function. Haemodialysis was performed 3 times a week for 4 h using polysulphone dialysers. Patients were dialysed using acetate and bicarbonate concentrate with standard



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Table I. *Characteristics of examined chronic kidney disease (CKD) groups*

| Characteristics | CKD on conservative treatment $n=38$ | CKD on dialysis $n=34$ | $p$-value |
|---|---|---|---|
| Age, years, mean ± SD | 11.0 ± 4.5 | 11.1 ± 4.2 | 0.95 |
| Sex, *n* (%) | | | < 0.001 |
| Male | 8 (21.1) | 22 (64.7) | |
| Female | 30 (78.9) | 12 (35.3) | |
| Cause of CKD, *n* (%) | | | |
| Urinary tract anomaly | 23 (60.5) | 13 (38.2) | 0.2 |
| Polycystic kidney disease | 7 (18.4) | 6 (17.6) | |
| Chronic glomerulonephritis | 3 (7.9) | 7 (20.6) | |
| Chronic interstitial nephropathy | 4 (10.5) | 4 (11.8) | |
| Other | 1 (2.6) | 4 (11.8) | |
| CKD duration, years, mean ± SD | 7.3 ± 4.9 | 7.4 ± 4.8 | 0.98 |
| CKD stage, *n* (%) | | | |
| 3 | 20 (52.6) | 0 | |
| 4 | 18 (47.4) | 0 | |
| 5 | 0 | 34 (100) | |

potassium and calcium concentrations. All assessments were conducted during hospitalization on days when haemodialysis was not performed, when patients stay in the hospital for check-ups. In the group of patients treated with automated peritoneal dialysis (APD) Baxter Peritoneal Dialysis Solutions (1.36% glucose) (Warsaw, Poland) were administered. Physioneal® and/or Extraneal® were used if required. APD lasted for 12 h on average. Examination was carried out during the patient's stay in the nephrology centre.

None of the children in the reference group had any chronic disease except primary monosymptomatic nocturnal enuresis. These children were not on any pharmacotherapy. Also, they had no acute infections or other acute conditions within the 4-week period prior to the study.

Before entering the study children and their carers gave their informed consent for participation in the study; they were also informed of their right to leave the study at any time. The study protocol was approved by Wroclaw Medical University bioethics committee (KB-751/2012).

### *Study design*

Each participant was assessed for pruritus and dryness of the skin. Patients with CKD also underwent blood tests. Data on the occurrence of pruritus, both at the time of the examination and previously, and its duration and location were collected. Pruritus intensity was assessed using a visual analogue scale (VAS) and a 4-item Itch Questionnaire to evaluate the extent, intensity, frequency of itch and sleep disturbances caused by pruritus (11, 12). The questionnaire scoring ranged from 3 (mildest itch) to 19 points (most severe itch) (12, 13). Patients used the VAS to report the maximal intensity of their pruritus within the previous 24 h. In children under the age of 7 years, a modified VAS scale, based on the Wong-Baker Faces Pain Rating Scale, was used (14).

General dryness of the skin was initially assessed as absent, mild, moderate, or severe by the study subjects themselves. If necessary, self-reported assessment of the severity of skin dryness was performed with the help of parents (especially in very young children). Skin dryness was then assessed by a dermatologist at 4 locations: forearm, lower leg, abdomen and chest, using the above-mentioned 4-point scale. Subsequently, non-invasive corneometric assessment of epidermal hydration, using a Corneometer CM825 (Courage+Khazaka Electronic GmbH, Köln Germany), and measurement of transepidermal water loss (TEWL), using a Tewameter TM300 (Courage+Khazaka Electronic GmbH), were carried out. Corneometer results were given in arbitrary units (AU), with a reduction in these values indicating a decrease in water content in the outer layers of the epidermis. TEWL values, reflecting skin barrier integrity, were given in g/h/m$^2$. All measurements were performed on 4 areas of the skin: forearm, lower leg, abdomen and chest, at stable room temperature (20–22°C) and air humidity (40–50%) after a 10-min rest in the sitting position.

### *Statistical analysis*

Microsoft Office Excel 2010 software (Microsoft Corporation, Warsaw, Poland) and Statistica 10.0 (Statsoft, Krakow, Poland) were used for statistical analysis of all data. Frequencies (percentage values) were calculated for qualitative parameters, while means and standard deviations were calculated for normally distributed quantitative variables, and medians and quartiles for skewed variables. The $\chi^2$ test, Student's $t$-test, Mann–Whitney $U$ test, analysis of variance (ANOVA) and Spearman's rank correlation test were used, where appropriate. Statistical significance level was set at 0.05.

## RESULTS

Pruritus occurred in 20.8% of the children with CKD. CKD-P was observed in 18.4% of the group of patients treated conservatively (without dialysis) and in 23.5% of those on dialysis (both on haemodialysis or APD). In all cases the pruritus was chronic (lasting longer than 6 weeks). Pruritus was not diagnosed in any child in the control group. The mean severity of pruritus in all patients with CKD-P was 6.9 points according to the 4-item Itch Questionnaire, and 3.5 points on the VAS. The characteristics of pruritus in CKD are shown in Table II. There was no difference between children treated conservatively and those dialysed with regard to the severity of itching according to the 4-item Itch Questionnaire and VAS, or the duration, or location of itching (Table II). Importantly, children on dialysis more often had generalized pruritus (87.5% of the children with pruritus) compared with 28.6% of pruritic subjects treated conservatively without dialysis. Among the children with CKD, the subgroups with

Table II. *Characteristics of chronic kidney disease (CKD) children with pruritus*

| | CKD children on conservative treatment $n=7$ | CKD children on dialysis $n=8$ | $p$-value |
|---|---|---|---|
| Duration of pruritus, years[a] | 2.5 (1.2–3) | 3 (2–4) | 0.38 |
| Intensity of pruritus (4-item Itch Questionnaire)[a] | 5 (5–8) | 7.5 (6.5–8.5) | 0.12 |
| Intensity of pruritus (VAS)[a] | 4.3 (0.8–4.4) | 3.8 (2.9–4.2) | 0.91 |
| Generalized pruritus, *n* (%) | 2 (28.6) | 7 (87.5) | 0.02 |

Multiple choice possible.
[a]Median and first and third quartile or number of patients and percentages.
VAS: visual analogue scale.

pruritus ($n=15$) and without pruritus ($n=57$) did not differ significantly with regard to age ($p=0.3$), sex ($p=0.77$), causes of CKD ($p=0.43$), stage of CKD ($p=0.65$) or duration of CKD ($p=0.43$). The group of patients with pruritus had a significantly lower estimated glomerular filtration rate (eGFR) compared with the group without pruritus; median 13.18 (range 7.7–23.4) ml/min vs. 21.04 (range 11.8–33.04) ml/min, $p=0.03$) and a statistically significant higher ratio of the calcium × phosphate product (Ca × P) (median 49.6 (range 44–66) $mg^2/dl^2$ vs. 40.6 (range 31.2–49.7) $mg^2/dl^2$, $p=0.015$) were noted.

Xerosis was more common in children with pruritus (66.7%) compared with those without pruritus (50.9%) ($p<0.01$). Dry skin was identified more frequently in patients on dialysis (67.6%) than in those on conservative treatment without dialysis (42.1%) ($p<0.01$). Patients with pruritus more frequently had signs of increased skin dryness on the forearms and lower legs, but there were no significant differences between the groups regarding skin dryness in other locations. Xerosis was also more severe in children with pruritus than in those without pruritus (Table III). In addition, there were no differences between the groups with and without pruritus with regard to the duration of dryness of the skin, the degree of skin hydration and TEWL values (Table III). No significant correlations were observed between the severity of pruritus, and the subjects' age, CKD duration, duration of skin dryness or results of laboratory examinations (serum creatinine, parathyroid hormone (PTH), calcium and phosphorus levels, and eGFR) (data not shown).

Table III. *Dry skin and pruritus in children with chronic kidney disease (CKD)*

| | CKD without pruritus $n=57$ | CKD with pruritus $n=15$ | $p$-value |
|---|---|---|---|
| Location of skin dryness, *n* (%) | | | |
| Forearm | 6 (10.5) | 5 (33.3) | 0.04 |
| Lower leg | 12 (21.1) | 9 (60.0) | <0.01 |
| Abdomen | 5 (8.8) | 3 (20.0) | 0.35 |
| Chest | 3 (5.3) | 2 (13.3) | 0.28 |
| Skin dryness self-assessment, *n* (%) | | | |
| Absent | 28 (49.1) | 5 (33.3) | 0.04 |
| Mild | 26 (45.6) | 6 (40.0) | |
| Moderate | 3 (5.3) | 4 (26.7) | |
| Duration of skin dryness, years, mean ± SD | 7.9 ± 4.8 | 7.7 ± 5.7 | 0.63 |
| Skin dryness assessed by dermatologist, mean ± SD | | | |
| Forearm | 0.1 ± 0.3 | 0.5 ± 0.6 | <0.01 |
| Lower leg | 0.2 ± 0.4 | 0.7 ± 0.6 | <0.01 |
| Abdomen | 0.1 ± 0.3 | 0.3 ± 0.6 | 0.06 |
| Chest | 0.1 ± 0.2 | 0.1 ± 0.4 | 0.28 |
| Epidermal hydration (AU), mean ± SD | | | |
| Forearm | 29.8 ± 8.6 | 28.3 ± 6.5 | 0.59 |
| Lower leg | 25.3 ± 6.8 | 24.9 ± 7.7 | 0.88 |
| Abdomen | 27.9 ± 9.5 | 25.7 ± 6.3 | 0.42 |
| Chest | 38.1 ± 12.1 | 34.2 ± 8.7 | 0.36 |
| Transepidermal water loss, $g/m^2/h$, mean ± SD | | | |
| Forearm | 8.3 ± 3.9 | 8.5 ± 2.8 | 0.45 |
| Lower leg | 8.3 ± 4.6 | 10.6 ± 6.8 | 0.17 |
| Abdomen | 9.4 ± 5.9 | 9.6 ± 6.4 | 0.97 |
| Chest | 8.9 ± 6.0 | 7.4 ± 2.4 | 0.66 |

SD: standard deviation; AU: aribtrary units.

## DISCUSSION

Pruritus occurred in approximately 20% of children with advanced CKD in this study. The proportion with pruritus was slightly higher in patients receiving dialysis than in those receiving conservative treatment (supportive care without dialysis) (23.5% vs. 18.4%). However, these results must be regarded with caution, due to the low number of analysed children, which is a major limitation of this study. Despite this, it is of interest that the described prevalence in children is close to that found in a cross-sectional representative study on chronic itch in haemodialysed patients (1). In the current study no itching was found in any child in the reference group. Thus, itching in children with CKD may be a symptom secondary to systemic disease, e.g. chronic renal failure. Attia et al. (15) made different observations, assessing skin lesions in 43 children treated with haemodialysis. They found pruritus in 18.6% of the children, but this proportion did not differ significantly from that of children without CKD (18.4% of 38 patients), which, according to the authors, indicates that itching in children cannot be regarded as a cutaneous manifestation of uraemia (15). It should be noted, however, that Attia et al. (15) did not specify whether other causes of itching, except for kidney disease, were excluded in the children from the reference group (e.g. eczema, urticaria, etc.). Another study, which included 27 children on peritoneal dialysis, noted pruritus in 22.2% (9), which is comparable to our observations of children on dialysis (23.5%). In contrast, in a German study of 199 paediatric patients on dialysis, pruritus was observed in only 9.1% (16). It should be noted that there are few epidemiological studies that assess the prevalence of chronic pruritus in children and adolescents. In only one cross-sectional study, which included 3,775 Norwegian adolescents, it was found that pruritus occurred in 8.8% (17), a much lower proportion than in the children with CKD.

No research on pruritus in children with CKD who do not require dialysis therapy has been published. Our findings show that itch occurs even in predialysis patients, but in a smaller proportion as compared with patients on dialysis. Similar observations apply to adults. In patients with lesser degrees of renal damage, itching has been reported half as often as in those who need dialysis. In the study by Balaskas et al. (18) of 189 dialysed patients, pruritus occurred in 62% of those on peritoneal dialysis and 54% of those on haemodialysis; while before dialysis it occurred in only 30% and 28%, respectively. In turn, Szepietowski et al.'s study (19)

of 130 patients on maintenance haemodialysis reported the presence of itching in almost 77%: 40.8% started to experience itching after starting haemodialysis, whereas in 36.2% pruritus was already present prior to haemodialysis. Amatya et al. (20) found an even greater disparity in the sensation of itching, depending on the stage of CKD; itching occurred in 87% of dialysed patients, but in only 12% of patients treated conservatively without dialysis.

The higher prevalence of CKD-P in adult patients compared with children may be caused by many factors, such as comorbidities, initial kidney disease leading to renal failure, or simply age. It should also be stressed that the sensation of pruritus is subjective. This is particularly relevant when trials are conducted with children, who may have difficulty describing sensations verbally.

What remains debatable is the severity of itching in people with CKD. We demonstrated rather low severity of pruritus in children with CKD. There was no difference in the severity of pruritus measured with the 4-item Itch Questionnaire and VAS scales between the groups treated conservatively and those on dialysis.

It has been suggested that dry skin can cause CKD-P. In our study, children with CKD-P assessed their skin as drier than did the children without itching. There was a significant relationship between the severity of dry skin and the occurrence of CKD-P. A number of other clinical studies have also found stronger itch in areas where dry skin has been diagnosed (17, 18). However, the relationship between dry skin and pruritus is not clear. In objective measurements of the barrier function of the skin, such as the assessment of the degree of hydration of the skin and TEWL, dryness of the skin does not always correlate with pruritus. The present study found no correlation between TEWL or hydration of the skin and pruritus, analogously to the other studies on adults (21–23). In addition, the study by Ostlere et al. (21) revealed normal TEWL even in patients on haemodialysis.

Dryness of the skin is not the only factor that may be associated with CKD-P. Laboratory tests of children with CKD show that disorders of calcium phosphate metabolism can contribute to the formation of CKD-P; patients with pruritus have been shown to have a significantly higher level of Ca × P than those without pruritus. These results are in agreement with the observations made by Senturk et al. (9) in their research on children on peritoneal dialysis. Patients with CKD treated conservatively without dialysis have less advanced stages of CKD (higher GFR), which could explain why Ca × P is higher in the dialysis group and that higher rates of CKD-P may be only an epiphenomenon. However, pruritus was found in more children with more advanced stages of CKD; therefore it is likely that the higher prevalence of dry skin in patients with pruritus is attributable to more advanced CKD. Furthermore, it has been shown that elevated levels of PTH and serum phosphorus are important parameters associated with pruritus in a given group (4, 21), although such a relationship was not observed in our study. It should be noted that many studies showed no effect of disorders of calcium phosphate metabolism on the occurrence of CKD-P, or that the itching was observed only at very high levels of calcium and phosphorus in the blood serum. These divergent results indicate the complexity of the pathogenesis of CKD-P. It cannot be ruled out that the accumulation of uraemic toxins may lead to activation of itch receptors in the skin. We found lower glomerular filtration rates in patients with pruritus than in those without pruritus.

In conclusion, CKD-P occurs not only in adults, but also in children with CKD. It is already present in the early stages of CKD, and there is a trend towards a higher incidence in children undergoing dialysis than in those treated conservatively without dialysis. In the aetiology of pruritus in children with CKD, dryness of the skin, eGFR and imbalance in divalent ions may play a role, as demonstrated by a higher incidence of dry skin and its higher severity, a higher ratio of Ca × P and decreased level of eGFR in children with pruritus compared with patients without itch. Further research on pruritus in children with CKD is necessary.

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