Uremic pruritus

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Uremic pruritus or chronic kidney disease-associated pruritus (CKD-aP) remains a frequent and compromising symptom in patients with advanced or end-stage renal disease, strongly reducing the patient's quality of life. More than 40% of patients undergoing hemodialysis suffer from chronic pruritus; half of them complain about generalized pruritus. The pathogenesis of CKD-aP remains obscure. Parathormone and histamine as well as calcium and magnesium salts have been suspected as pathogenetic factors. Newer hypotheses are focusing on opioid-receptor derangements and microinflammation as possible causes of CKD-aP, although until now this could not be proven. Pruritus may be extremely difficult to control, as therapeutic options are limited. The most consequential approaches to treatment are: topical treatment with or without anti-inflammatory compounds or systemic treatment with (a) gabapentin, (b) μ-opioid receptor antagonists and κ-agonists, (c) drugs with an anti-inflammatory action, (d) phototherapy, or (e) acupuncture. A stepwise approach is suggested starting with emollients and gabapentin or phototherapy as first-line treatments. In refractory cases, more experimental options as μ-opioid-receptor—antagonists (i.e., naltrexone) or κ-opioid-receptor agonist (nalfurafine) may be chosen. In desperate cases, patients suitable for transplantation might be set on 'high urgency'-status, as successful kidney transplantation will relieve patients from CKD-aP.

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Uremic pruritus or more accurately termed 'chronic kidney disease-associated pruritus' (CKD-aP) remains a frequent and compromising symptom in patients with advanced or end-stage renal disease.[1] The prevalence and the burden of this symptom are often underestimated by nephrologists.[2] Effective treatment options are limited because of a low number of randomized, placebo-controlled trials with most of them reporting only limited therapeutic success. In addition, several times in the past, reports on putative effective novel treatment options were followed by studies with contradictory results.[3–6] The lack of effective treatment modalities also results from a still incomplete knowledge of the underlying pathophysiological mechanisms. This review highlights the recent clinical and experimental findings focusing on the pathogenesis and current treatment options of CKD-aP.

CLINICAL FEATURES OF CKD-aP

Intensity and spatial distribution of pruritus in patients with chronic renal insufficiency may vary significantly over time. The degree of CKD-aP may range from sporadic discomfort to complete restlessness during day- and nighttime strongly reducing the patient's quality of life. The skin of affected patients is often unchanged, resembling that of patients without pruritus, which in most cases presents dry and scaly. In contrast to dermatological pruritus, primary skin lesions are not observed in patients with CKD-aP. However, excoriations with and without impetigo, linear crusts, papules, ulcerations, and less commonly prurigo nodularis may be seen as secondary skin changes due to intense scratching activity (Figure 1a–c). Up to 50% of patients with CKD-aP complain about generalized pruritus.[7,8] In the remaining patients, CKD-aP seems to affect predominantly back, face, and shunt arm, respectively.[9] Interestingly, in about 25% of patients pruritus is reported most severe during or immediately after dialysis. Once patients have developed CKD-aP, this symptom will in most cases last for month or years.[10] In patients with generalized pruritus, other causes such as dermatological, hepatobiliary, hematological, endocrinological, neurological and psychiatric disorders, drug intake as well as solid tumors need to be ruled out.

The diagnosis of CKD-aP may be challenging. Many patients with CKD in advanced stages (IV–V) are suffering from other diseases, such as cardiovascular diseases, diabetes mellitus, chronic liver or hematological diseases, which by itself or by medication given to treat these entities may provoke itch.

In some cases, the clinical appearance (localization, pattern, quality of itch, and so on) may be helpful to categorize the itch in these patients. Quite often, however, a definitive diagnosis cannot be established and treatment has to be initiated according to considerations of likelihood.

Epidemiology

Although in the early days of dialysis treatment, CKD-aP was a very common problem afflicting up to 85% of patients[11] its incidence declined to 50–60% in the late eighties.[12] However, numbers are difficult to compare as chronic itch has rarely been analyzed and instruments used to assess the intensity of itch diverge.

A recent large-scale investigation on several thousand patients reported that >40% of patients undergoing hemodialysis suffer from chronic pruritus[1] (Figure 2). This study uncovered a higher mortality of patients suffering from pruritus. However, when controlled for sleep disturbance this correlation did not remain statistically significant. Severe pruritus is, however, very rare in pediatric patients on dialysis (Figure 3).[13] Data on the prevalence of CKD-aP in patients undergoing peritoneal dialysis are rather scarce. The few reports available, however, permit the conclusion that patients undergoing peritoneal dialysis are similarly affected by pruritus as patients on hemodialysis.[12,14] Although prevalence of pruritus has declined during the last decades potentially by improved hemodialysis techniques, this symptom remains a major clinical symptom and in severe cases often a medical challenge.

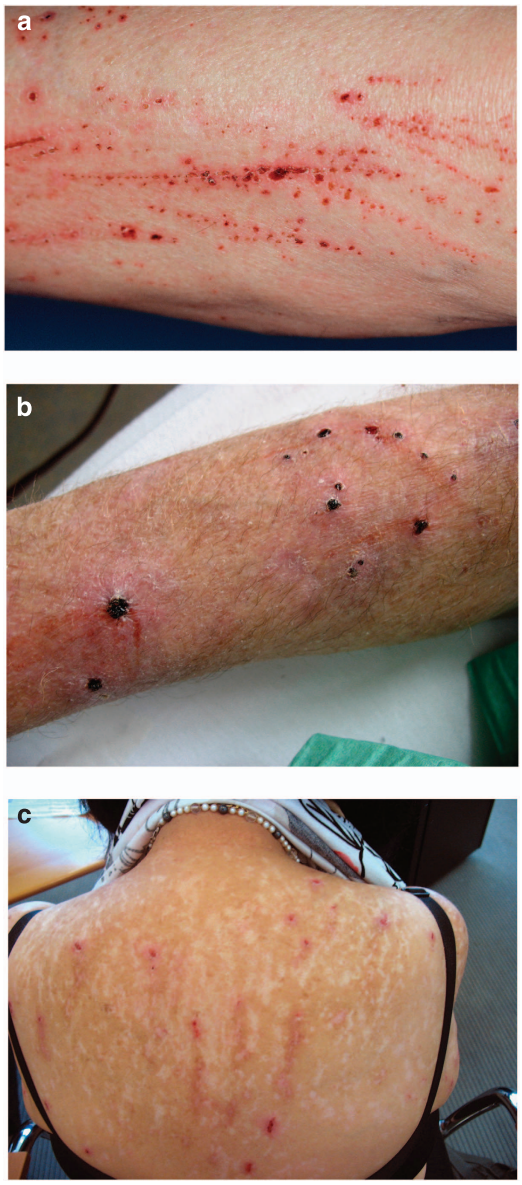

Figure 1 | Typical skin changes observed in patients suffering from chronic kidney disease-associated pruritus (CKD-aP). (**a**) Scratch marks with excoriations at the lower leg. (**b**) Typical hyperkeratotic partly excoriated nodules (prurigo nodularis) located on the forearm. (**c**) Deep scars and prurigo nodules at the shoulders and back of a female patient.

Etiopathology

The pathogenesis of CKD-aP remains obscure.[15] Various substances have been discussed as potential pruritogens in

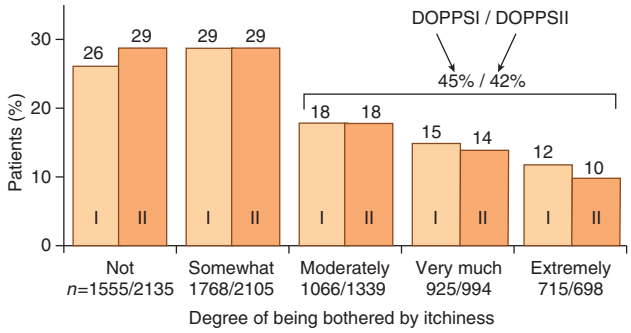

Figure 2 | Prevalence and intensity of uremic pruritus according to DOPPS-data from 1996 to 1999 (I) and 2002 to 2003 (II) (after Pisoni *et al.*[1]). DOPPS, Dialysis Outcome and Practice Patterns Study.

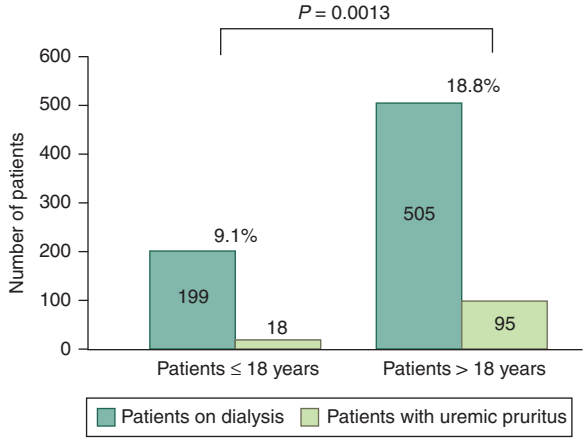

Figure 3 | Prevalence of uremic pruritus in children on dialysis (18 years or younger) and in adult dialysis patients (older than 18 years). Prevalence of uremic pruritus in children is significantly lower than in adult patients (χ^2 test according to Schwab *et al.*[13]).