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# *Uremic pruritus in the chronic renal failure patients*

Chronic renal failure, particularly the end-stage renal disease (ESRD) is connected with a number of cutaneous symptoms. Some of them can be a consequence of the disease that caused the renal failure (e.g. systemic sclerosis, systemic lupus erythematosus) and other may be themselves the ESRD manifestation. Among these skin disorders occurring in ESRD patients, pruritus (itch) is recognized as the most distressing (3, 8-13, 15). The data of NECOSAD study concerning the quality of life in patients on chronic dialysis, indicate that pruritus and fatigue were the most common symptoms experienced by both hemodialysis and peritoneal dialysis patients (6). Other authors confirm the uremic pruritus as a common complaint among these patients and it is being significantly associated with the poor prognosis (9, 13). Pruritus is especially distressing and troublesome skin sensation inducing the compulsive need to scratch. Scratching of skin, although temporarily decreases itching, but continually damages skin integrity, decreases resistance to infections, affects sleeping and in consequence impairs the quality of life (1, 2, 6, 14, 15). Some patients feel oppressed to such a degree that they even decide to try the topical application of pesticides to relieve the skin sensation (9). The prevalence of pruritus ranges widely between 25 and 90% among the chronic dialysis patients (8, 9, 11, 15). Recent few years, however, bring still decreasing prevalence of uremic itch. Nowadays, extremely intensive itch is reported by about 10–25% of ESDR dialysed patients (8, 11), which may be explained by the constant improvement in dialysis techniques (11). The intensity of the reported uremic itch varies from mild and infrequent to continual severe itching (9). There are no significant differences in pruritus prevalence between the patients undergoing hemodialysis and peritoneal dialysis (8). Renal pruritus is not related to age, sex, race, duration of dialysis, or etiology of the renal failure and method of dialysis (8, 13). Itch in uremic patients can be generalized or can be limited to the back and to the forearm in which the hemodialysis arteriovenous shunt is localized (8, 11). The uremic itch may be constant or epizodic and frequently paroxysmal in its nature (9, 13). It is relatively high during treatment and lowest during the day following dialysis (8, 13). After two days without dialysis, the pruritus quickly increases and peaks at night (13). Although for some patients this skin symptom can be relieved with the initiation of dialysis, the data of Yosipovich et al. (14) indicate that pruritus in hemodialysed patients tends to be prolonged, frequently intense and not influenced by dialysis.

## PATHOPHYSIOLOGY OF UREMIC PRURITUS

The pathophysiology of uremic pruritus remains still poorly understood. Mechanisms of uremia--induced itching are believed to result from metabolic disequilibrium and probably from dialysis

techniques as well (2, 4, 7, 8, 9, 11, 12, 13, 15). These include inadequate dialysis/ accumulation of poorly dialysed compounds, decreased transepidermal elimination of pruritogenic factors, dry skin, decrease of sweating, secondary hyperparathyroidism, hypercalcemia, hyperphosphatemia, hypermagnesemia, increased vitamin A level, changed dermal mast cell function, increased plasma histamine levels, increased plasma serotonine levels, altered balance between opioid receptors, elevated release of substance P, uremic sensory neuropathy, aluminium toxicity, altered immune function and others (5, 7, 8, 9, 11, 13, 15). It is also believed that the proinflammatory pruritogenic cytokines (including IL-1) can be released locally close to the itch receptors in the dermis (11, 13). What is interesting, correcting levels of some of these potential factors does not improve skin symptoms, on the other hand, pruritus usually decreases or even disappears after renal transplantation, with the restoration of renal function (4, 7, 8). Since pruritus is not observed with acute renal failure, abnormalities in blood urea nitrogen and creatinine cannot be solely responsible for this phenomenon.

Studying the renal failure-related pruritus, neural mediators of pruritus has been carefully considered. The neural transmission of itch follows the same pathway as pain (2, 11). Data of many authors indicate that pruritus is initiated by stimulation of unmyelinated C-fibres in the dermal-epidermal junction (2, 11). Mediators of pruritus include histamine through H1 receptors, and serotonin through 5HT2 and 5HT3 receptors (2, 11). The perception of itch leads to motor response of scratch which stimulates myelinated A delta sensory fibers and temporarily block the sensation (2).

Since histamine is a well known mediator of itch, the attention of researchers has been especially directed to this agent released from the degranulated mast cells. However, opinions on the role of the mast cells and histamine in uremic itch are controversial. Some authors observed the increased number of mast cells in the skin of uremic patients suffering from itch in comparison with normal ones and uremic patients without itch (10, 11). There was no relationship between the number of mast cells found in the dermis of ESRD patients and the prevalence of pruritus (5, 13). The increased number of mast cells may be possibly connected with the elevated parathyroid hormon plasma concentrations often observed in uremic patients with secondary hyperparathyroidism (11). It has been observed that the majority of mast cells diffusely spread in the dermis appeared to be degranulated (11, 13). Some authors present opinions that it could be due to skin damage caused by scratching (11). Moreover, plasma histamine levels are found to be considerably elevated in uremic patients with pruritus when compared to those without or nonuremic (11, 13). There was no relationship between plasma histamine concentrations and severity of pruritus (11, 13). Weisshaar et al. failed to detect the elevated plasma histamine levels in the examined group of patients with uremia-related pruritus (13). Although plasma histamine concentrations are often found raised in uremia, the importance of this agent in inducing the uremic itch remains uncertain and what is more, H1-antihistamines are often ineffective in the itch controlling (11).

Apart from histamine, another potent pruritus mediator possibly involved is serotonin. It is well known that the injected or iontophoresed serotonin causes itch in humans (7), but its role in uremic pruritus is not clearly elucidated yet. Serotonin (5-hydroxytryptamine, 5HT) can induce itch by both peripheral and central mechanisms (11). Peripherally, it acts indirectly through the release of histamine from dermal mast cells (11). The central mechanism probably involves the opioid neurotransmitter system (11). Elevated plasma serotonin levels are assumed to be responsible for pruritus in both renal and liver failure patients (2). Increased levels of serotonin have not only been observed in dialysed patients but also have been found higher in those with pruritus than in those without it (7, 13). There was no significant correlation however, between age or intensity of pruritus and serotonin levels (13). It is possible that the imbalance in the expression of the opioid receptor subtypes may contribute to the pathogenesis of uremic itch mediated by serotonin (11). Some researchers not only could not find any alterations either in histamine or serotonin levels in their uremic patients in comparison to controls,

but what is more, no significant differences were seen before and after hemodialysis (13). Furthermore, the treatment with neither antihistamines nor antiserotonines did influence plasma histamine and serotonin levels (13).

Among the other possible itch mediators the neuropeptides are being taken into consideration. Some of them, including calcytonin-gene related peptide (CGRP) and substance P are known to enhance itch (11). Observation that topically applied capsaicin, which depletes substance P from cutaneous nerve terminals, can relieve localized chronic itch in some patients, supports the role of neuropeptides (11). Additionally, beneficial effects of capsaicin can be also due to its ability to destroy about 80% of C-fibres in the superficial layers of the skin (11).

It is believed that disturbance in some ion concentrations may also contribute to induction of itching in the chronic renal failure patients. It has appeared that skin of uremic patients suffering from pruritus contains elevated concentrations of calcium, magnesium and phosphate (11). The increased cutaneous concentrations of these divalent ions can lead to microprecipitation of calcium or magnesium phosphate, which in turn may cause itching (11). Moreover, magnesium can be involved not only in the modulation of nerve transmission but also in the release of histamine from mast cells as well (11). It is also suggested that calcium affects itching by influencing the mast cell degranulation (11). Marked improvement of uremic itch due to the low dialysate calcium and magnesium, which has been evidenced in dialysed patients, is consistent with the supposed role of these ions in inducing pruritus (11). Apart from this, the possible association between the uremic itch and elevated plasma aluminium concentrations in patients undergoing long-term hemodialysis has also been suggested (8, 9, 11).

Among various pathologic phenomena occurring in the chronic renal failure, the bile acid imbalance has been reported (4). What is specially interesting, pruritus was more frequently observed when the impaired renal function in uremic patients was accompanied by hypercholanemia (4). However, despite hypercholanemia, when renal function has been restored by kidney transplantation, none of patient suffered from pruritus anymore (4).

In summary, it should be considered that many patients suffering from the uremic pruritus have no detectable metabolic abnormalities (13). It supports the belief that induction and severity of uremic pruritus depends on the interaction of various mechanisms involved in its complex pathophysiology, some of them probably not clearly elucidated yet.

## MANAGEMENT OF UREMIC PRURITUS

Persistent pruritus being a tormenting skin sensation deserves the same degree of attention as pain. Many therapeutic options, both pharmacologic and nonpharmacologic have been suggested, unfortunately, up till now, none of them sufficiently effective. Uremic pruritus is usually associated with dry skin, thus it seems reasonable that emolients to alleviate xerosis should be tried first (11). Due to observation that the intensity of pruritus decreases with the augmentation of dialysis adequacy, enhancing the dialysis regimen is regarded as the standard response when uremic patient experiences severe itch (8, 11). In order to diminish the electrolytic and metabolic disturbances as much as possible the magnesium-free dialysis is proposed accompanied by low-protein diet (8, 15). Moreover, some data indicate that normalization of serum calcium and phosphate levels, due to pharmacologic treatment or using parathyroidectomy, may result in remission of itch in patients with secondary hyperparathyr--oidism (9, 11, 15).

The most commonly used class of medications in the treatment of itching are antihistamines. The opinions about usefulness of this therapy in uremic pruritus are divergent. Anihistamines frequently are not helpful with various secondary itches, like pruritus associated with renal failure and cholestic or paraneoplastic pruritus (2). Although some authors believe that antihistaminic therapy in uremic

pruritus does not have satisfactory results, this option is often tried as relatively safe for at least psychological reason (8, 9). However, some beneficial results have been reported with azelastine and ketotifen treatment (8, 15). For some patients sedating antihistamines may provide temporary relief, but nonsedating antihistamines usually are not helpful. Doubtful effects of antihistaminic agents directed attention of clinicists to the possibility of blocking other pruritus mediators.

Observations that dialysis patiens have elevated plasma serotonin levels assumed to be responsible for pruritus, have been the rationale for trying the serotonin antagonists (2). So, selective inhibitors of serotonin receptors were introduced to itch treatment. Good effects were observed due to ondansetron – 5-HT3 inhibitor, which can decrease concentration of both serotonin and histamine (8, 7). It appeared that ondansetron can relieve not only uremic but also cholestatic associated pruritus (2). Some authors, however, have found this agent no better than placebo in controlling renal itch (7), and they cannot recommend the medicine for this indication. Recently, there have been suggestions that some other serotonin receptor blockers: naloxone, naltrexone can alleviate uremic pruritus but results are often conflicting (11). Twycross et al. (11) believe that in the uremic patients with severe uncontrolled pruritus naltrexone therapy should be tried, despite the confusing reports of its usefulness. When other antiserotonin agents prove to be ineffective, alternatively mirtazapine should be considered (5, 11). Mirtazapine is one of the new antidepressants which are selective noradrenergic and specific serotonin receptor antagonists (2). Mirtazapine blocks most of the major receptors associated with pruritus (i.e. H, 5HT2 and 5HT3 receptors) (2). Mirtazapine may be an effective drug for pruritus associated with renal failure but also with advanced cancer, cholestasis, and hepatic failure (2). Therapeutic activity is believed to be related to binding cutaneous serotonin and histamine receptors, and probably to central receptor blockage as well (2). Another new serotonine antagonist – the selective serotonin reuptake inhibitor (SSRI) paroxetine is recently introduced in the management of pruritus but futher clinical observations are needed to confirm its usefulness and efficacy (2).

Various other pharmacologic regimens have been proposed to alleviate pruritus in patients with chronic renal failure, including venous injection of lidocaine or heparin, oral administration of cholestyramine, nicergoline, erythropoietin, thalidomide, activated charcoal (8, 9, 15). However, treatments for renal pruritus have shown limited success (15) and what is more, some options such as cholestyramine and activated charcoal may decrease absorption of essential nutriens, perhaps making them more detrimental than beneficial. In some patients, erythropoietin was tried to control severe pruritus, due to clinical observation of decreased histamine level during treatment of uremic anemia with erythropoietin (8). It is suggested that thalidomide can be effective in more than 50% of patients but because of its serious side-effects it should be used only when other options have failed (11).

Beneficial effects of topically applied capsaicin have been also reported (8). It seems that they are be probably associated with decrease of substance P in peripheral sensory nerves which can result in blocking sensory stimuli trasmission to the central nerve system (8).

UVB phototherapy is regarded as one of the most effective therapeutic regimens (8, 9, 11, 15). It is believed to be in some cases even superior to drug therapy and may have prolonged benefit in controlling uremic pruritus. This method of releasing itch is not commonly used at present but may be helpful in uremic patients because of its advantages, lack of serious side-effects and drug-interactions (11).

Various nonpharmacologic therapies that have been considered, including sauna therapy, electric needle stimulation, aromatherapy (9, 15). These therapies are often of limited usefulness due to poor efficacy (9). Among these nonpharmacologic options, aromatherapy was proposed as a noninvasive nursing intervention to alleviate pruritus in patients with chronic renal failure (15). Various therapeutic effects of essential oils have been previously reported in animal studies, including sedative, antiseptic, antiinflammatory and analgesic effects (15). Although there has been growing interest in aromatherapy, its actual effect on uremic pruritus has been insufficiently documented (15). Some observations suggest

that aromatherapy is effective in decreasing the severity of pruritus and can be at least partially comforting for those patients (15).

All the therapy regiments proposed to provide relief of uremic pruritus are unsatisfactory, probably progress in understanding the complex pathophysiology of this distressing cutaneous sensation enable to find some new more effective options.

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## SUMMARY

Chronic renal failure is connected with various cutaneous symptoms, of which the persistent pruritus is regarded as the most distressing and severily affecting the quality of life. The pathophysiology of uremic pruritus is poorly understood but believed to result from metabolic disequilibrium, increased release of pruritogenic mediators and altered balance between the opioid receptors. Several methods of controlling pruritus are considered, including pharmacologic and nonpharmacologic options, but their efficacy is still unsatisfactory.

## Świąd skóry u pacjentów z przewlekłą niewydolnością nerek

Wiele różnorodnych objawów skórnych może towarzyć przewlekłej niewydolności nerek. Wśród nich uporczywy świąd skóry jest uważany za najbardziej dokuczliwy i znacznie pogarszający jakość życia chorych. Chociaż patofizjologia świądu mocznicowego nie jest całkowicie wyjaśniona, uważa się, że największe znaczenie w jego powstawaniu mają zaburzenia metaboliczne, zwiększone uwalnianie mediatorów świądowych oraz zaburzona równowaga pomiędzy receptorami serotoninowymi. Próby zmniejszenia nasilenia świądu mocznicowego poprzez zastosowanie wielu metod leczenia zarówno farmakologicznego, jak i niefarmakologicznego nie okazały się dotychczas wystarczająco skuteczne.