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Pathogenesis and Treatment of Uremic Pruritus: Retrospect and Prospect

Xin Pan, Pan Xie, Yan Zhuo, Huan-na Li and Kan-fu Peng*

Department of kidney, Army Military Medical University, China

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Corresponding author:
Kan-fu Peng,
Department of kidney, Southwest Hospital, Army Military Medical University, Chongqing 400038, China,
Tel: 023-68754239;
Email: 392906786@qq.com

ABSTRACT

Uremic Pruritus (UP) is a tormenting symptom among patients with end-stage renal disease, which impacts seriously on life quality and increase the risk of the fatal rate. However, current studies indicate the pathogenesis of UP is complex and not fully clarified and therapeutic measures have provided only limited effectiveness. In this paper, factors involved in the deranged balance of T helper (TH) cell, opioid hypothesis and protein-bound uremic retention solutes are associated with UP and new treatment options. Metabolic disorders of phospholipid and glucose are worthy of further study. Finally, appropriate dialysis mode is also effective in reliving UP.

INTRODUCTION

In 1660, Samuel Hafenreffer, a German physician, proposed that itching has a physiological self-protective effect to prevent further contact between harmful components and the body. From an evolutionary point of view, itching, like pain, constitutes the first line of early warning for individual survival. In the past, electrophysiological and behavioral studies have suggested that the nerve conduction pathways of itching and pain are similar. However, in 2017, Sun Y G's team [1] further study the spinal cord-parabrachial tract pathway in itching-induced scratching behavior, Adeno-associated virus labeled with enhanced green fluorescent protein was injected into the dorsal cervical spinal nerve of mice and optical fibers were implanted into the bilateral parabrachial tract to selectively inhibit the activity of spinal axonal projection in the parabrachial tract. The scratching behavior induced by histamine and chloroquine was significantly reduced. The results show that PBN represents the primary transmission center of itching sensation, and its activity regulates scratching caused by acute and chronic itching. It is found that a class of itch cell neurons expressing Gastrin-Releasing Peptide Receptor (GRPR) in the spinal cord can activate PBN neurons through synaptic excitatory connections. In addition to the spinothalamic tract and the potential independent pathway of GRPR+ neurons, the parabrachial pathway plays an important role. Itching-related receptors are divided into histamine receptors, interleukin receptors, opioid receptors, and so on. Because itching is the subjective feeling of patients, there are individual differences. At present, the most commonly used method for evaluating the degree of itching, which is also recognized by most people, is the Visual Analog Score (VAS), which borrows the pain scoring method. The basic method is to use a swimming scale of about 10cm, with 10 scales on one side and two segments of "0" and "10" respectively. 0 means no itching. 10 points indicate unbearable itching, and the graduated side is turned back

to the patient during the evaluation. Patients mark their itching degree between 0 and 10 points according to their feelings. 0-2 points are excellent, 3-5 points are good, 6-8 points are medium, > 8 points are poor. By using this method many times, we can make a more objective evaluation.

However, VAS can only roughly estimate the severity of itching in patients. Different from ordinary pruritus, uremic pruritus has more complex factors, especially chronic lung disease, diabetes, and dryness, as well as higher blood phosphorus and lower hemoglobin (Hb) levels [2] are associated with a higher incidence of moderate to severe pruritus. Therefore, VAS is not comprehensive enough to uremic pruritus, at least limited in all-cause mortality and its correlation to prognosis.

UP'S HARM TO PATIENTS AND CHALLENGES TO PHYSICIANS

Uremic pruritus is quite common in patients with end-stage renal failure, including those on peritoneal dialysis and hemodialysis [3], 15% ~ 49% of pre-dialysis patients present with this symptom, 50% -90% of hemodialysis and peritoneum [4]. It seriously affected the physical and mental health of the patients.

Though uremic pruritus is not life-threatening, it increased the morbidity and mortality in patients with uremia, dialysis outcomes and practice research from 2006 (the dialysis outcomes and practice patterns study, DOPPS), about 42% of dialysis patients have severe skin pruritus, it not only seriously affects the patient's quality of life, some patients appear even anxiety, depression, sleep disorders and suicidal risk [5].

On the other hand, UP predicts the severe prognosis in CKD patients. Weng CH et al [6] conduct a retrospective study, recruiting Maintenance Hemodialysis (MHD) patients in 3 hemodialysis centers. They investigated the significance of UP as an independent predictor for 24-month cardiovascular mortality, in conclusion, nephrologists should pay more attention to UP for higher risk of cardiovascular complication, which is the major cause of mortality in hemodialysis patients.

Although various factors have been considered for the etiology of uremic pruritus, the pathophysiology of the symptom remains unclear. As a result, empiric treatment is often inadequate to relieve symptoms [7].

At present, the first-line drugs for chronic pruritus are moisturizers and external drugs such as glucocorticoids, menthol, capsaicin, local anesthetics, and so on. The system drugs are mainly antihistamine drugs, antidepressants (mirtazapine, paroxetine, doxepin), antiepileptic drugs (gabapentin, pregabalin), opioids, ultraviolet rays, and turmeric [8]. Antihistamine drugs are mainly effective against urticaria pruritus, and histamine independent pruritus is mainly based on its sedative effect, which usually can't relieve chronic pruritus in practical application, on the contrary. Omae et al [9]. investigated that antihistamine had a negative effect on eccentric cardiac hypertrophy, which improving cardiovascular mortality in HD patients. Most of the treatments are not firmly evidence-based, at the same time, the characteristic that drugs are eliminated by the kidney, shouldn't be ignored.

RETROSPECT THE PATHOGENESIS AND TREATMENT OF UREMIC PRURITUS

In the first longitudinal study of UP [10], it was pointed out that although the distribution of pruritus sites in patients was significantly different, there were bilateral symmetry similarities. This study indicates that UP has a significant central nervous origin. The pathophysiology of uremic pruritus is very complex, and the recognized factors include dermatitis [11], hyperparathyroidism [12], calcium and phosphorus deposition [13], histamine released by mast cells [14], opioid receptor imbalance caused by μ-opioid receptor over expression [15], and systemic inflammation, anemia, unreasonable dialysis, increased serum magnesium and aluminum levels, and HCV infection are also associated. However, not all of the findings have been confirmed in subsequent studies [16-18]. Different treatment modalities and medications such as phototherapy, thalidomide, calcineurin inhibitors, antihistamines and gabapentin have been used clinically, but the effects vary with each individual.

Imbalance of TH cell

Renal pruritus is considered to be an inflammatory systemic disease rather than a local skin disorder [19]. Based on several observations and results from various trials on UP, there are increasing evidences that an alteration of the immune system with an inflammatory pattern resulting in a deranged T helper cell (Th) differentiation may be involved in the pathogenesis of UP [20]. TH1 cells produce inflammatory cytokines such as IFN-γ, aggregating and activating cytokines, so excessive activation of TH1 cells leads to an inflammatory response. On

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the other hand, TH2 cells secrete anti-inflammatory cytokines, such as IL-4, associated with allergic reactions [21]. The Th1/Th2 cells can be discriminated by the cytokines they produce or the chemokine receptors they express. The balance of Th1/Th2 cells can be measured on a cellular level [22].

In order to elucidate the etiological role of TH1 overexpression in the etiology of UP, Mohammad Kazem Fallahzadeh et al [23]. compared the levels of IFN-γ, IL-2, and IL-4, in serum of HD patients with UP. IFN-γ and IL-2 represented TH1 factor , while IL-4 represented TH2 cytokines. a highly sensitive C-reactive protein (HSCRP), in the serum of the two groups, was used as an inflammatory marker. At the same time, serum PTH concentrations, calcium and phosphorus, and other blood indexes, including Hb, MCV, MCH, and MCHC. These were used to determine the possible role of secondary hyperparathyroidism, calcium-phosphorus metabolism, or anemia in the etiology of UP. It turns out the conclusion that except for the average serum concentration of IL-2, there was no significant difference in other factors.

Many studies have shown that cytokines play an important role in the relationship between the immune system and the central nervous system. IL-2 is not only an immune factor but also an important neuroregulatory molecule in the central nervous system. IL-2 can bind to receptors through the blood-brain barrier. Receptors are mainly distributed in neurons and glial cells in different regions of the central nervous system [24]. Moreover, due to structural similarity, IL-2 interacts with other molecules, such as opioid receptors, which have analgesic effects in the central and peripheral regions [25]. IL-2 can induce analgesic effects by activating opioid receptors in the dorsal root nerve of mice, and this analgesic effect can be blocked by naloxone, an opioid receptor antagonist [26]. Moreover, intramedullary injection of IL-2 could inhibit the withdrawal of morphine in mice. Increasing the input of pain stimulation can inhibit itching. Inhibition of pain can increase the feeling of itching [27]. To sum up, we guess, the symmetrical distribution of UP in patients with HD can be explained by stimulating the itching center of the central nervous system or activating the increase of IL-2 level in the central or peripheral opioid receptors. Therefore, the activation of central or peripheral itching receptors mediated by IL-2 is expected to explain the pathogenesis of UP. At the same time, we also look forward to future studies focusing on the potential contribution of IL-2 in patients with UP, such as experimental studies of anti-IL-2 receptor antibodies.

Opioid receptors

Biomarkers of inflammation are increased in patients with renal pruritus, and an imbalance of the endogenous opioid system might be involved in the complex pathogenesis of the disease.

Among many mechanisms of uremic pruritus, there is a great correlation in endogenous opioid peptides and the opioid system. The activation of the μ-opioid system has been confirmed to induce pruritus, which has been confirmed in the report of μ-receptor agonist morphine induced itching [14,28]. Intracerebroventricular injection of beta-funaltrexamine, a selective opioid μ-receptor blocker, can inhibit itching in animal experiments [18]. The overexpression of opioid μ-receptors in the central nervous system and skin is regarded as an important point in the etiology of UP [29,30]. Naltrexone (narcotic antagonists) A μ-opioid receptor antagonist can effectively reduce the severity of UP in a randomized controlled trial [14]. It has been reported that μ-receptor antagonists and kappa receptor agonists can inhibit substance P-induced pruritus in mouse models [31]. Kappa receptor agonists can inhibit the effect of μ-receptors from the central and peripheral regions [32]. Nalfurafine, a new type of kappa receptor agonist, can effectively reduce the scratching behavior of mice injected with substance P. We can assume that uremic pruritus can be stimulated and maintained by substance P release [33].

Therefore, the intervention targeting the opioid receptor itching pathway is expected to alleviate the severity of uremic pruritus. Deep Jaiswal et al carried out a systematic review and Meta-analysis of the therapeutic effects of μ-receptor and kappa-receptor on uremic pruritus patients. The results showed that nalfurafine, a kappa receptor agonist, significantly reduced the severity of pruritus during two weeks of treatment compared with placebo, although the treatment of uremic pruritus with μ receptor antagonist naltrexone was not recommended. But nalfurafine is expected to be a potential drug.

Indoxyl sulfate (IS) and P-cresyl sulfate (PCS)

P-Cresyl Sulfate (PCS) and Indoxyl Sulfate (IS) are major renal toxins, these protein-bound uremic retention solutes are derived from amino acids, which are absorbed from the gastrointestinal tract. Tryptophan is metabolized into indole, which further converted to indoxyl sulfate in the liver [34]. Similarly, tyrosine and phenylalanine turn to P -Cresyl Sulfate (PCS) after metabolization and conjugation. The serum levels of IS and PCS are elevated in advanced stages of Chronic Kidney Disease (CKD) and correlate with the glomerular filtration rate [35]. Because of their molecular weight and high binding affinity for albumin, they are difficult to be eliminated by hemodialysis. These protein-bound uremic retention solutes hurt the kidney, by inducing an inflammatory reaction, which is associated with uremic pruritus.

Chao-Ping Wang et al [36] enrolled CKD patients with and without uremic pruritus, measuring the serum levels of total IS and PCS concentrations. Their results indicate that PCS, a hampering removal protein-bound uremic toxin, has a pro-inflammatory effect and produces free radicals as evaluated by the increased oxidative burst activity of leucocytes at baseline. PCS may play a role in the pathogenesis of pruritus. The results support the idea that PCS may act through the inflammatory response to play an important role in the pathophysiology of renal pruritus in CKD patients [37]. Some studies indicate that patients given oral adsorbent (AST-120) showed significantly reduced serum concentration of IS, and it relieved itching in hemodialysis patients with generalized pruritus [38,39].

PROSPECT: METABOLIC DISORDER OF PHOSPHOLIPID AND GLUCOSE

Disorder of phospholipid metabolism

Wu Qiong et al. [40] analyzed the serum metabonomics and multivariate statistical analysis of uremic pruritus patients based on ultra-high pressure liquid chromatography-time-of-flight mass spectrometer. Among the 22 metabolites with mild pruritus and severe pruritus, nine of them were identified by stepwise regression analysis: LysoPE(20:3(5Z,11Z)/0:0), LysoPC(20:2(11Z,14Z), LysoPC(16:0), p-methyl phenol glucuronic acid, phenylacetic acid, taurine, 4- amino hippuric acid, kynurenine and androstenedione, respectively, belong to phospholipids, uremic toxins and steroids, and are identified as potential markers of uremic pruritus. Through binary logic analysis, the nine variables were combined into multivariate variables to distinguish severe pruritus from mild pruritus with high sensitivity and specificity. Therefore, these nine substances can be further explored to reveal the possible role in uremic pruritus, thus helping to diagnose uremic pruritus.

LysoPE (20:3 (5Z, 8Z, 11Z) / 0:0), LysoPC (20:2 (11Z, 14Z), and LysoPC(16:0) belong to phospholipid, so phospholipid metabolism disorder is one of the causes of UP. Previous studies have shown that LysoPCs can induce nephrotoxicity through oxidative stress [41], and it has been fully proved that LysoPCs can induce a variety of pro-inflammatory reactions, including stimulating monocytes and mastocytes to produce IL-1β, reactive oxygen species, and promoting cell growth and appreciation [42]. Other studies have shown that LysoPC is a chemical inducer of T lymphocytes and monocytes and plays an important role in skin inflammation [43]. At the same time, serum substance P, as a factor of UP, was reported to be related to the increase of LysoPC concentration [44]. Therefore, abnormal phospholipid metabolism may become the pathogenesis of UP by inducing inflammatory reaction and increasing substance concentration. Steroids such as male estrone are down-regulated in patients with UP, although there is no significant difference in the level of androstenedione in patients with severe and mild pruritus. Androstenedione is used as a precursor to testosterone in muscles and bones. It is closely related to the growth of hair. Both androstenedione and testosterone are aromatic compounds of estrogen, and estrogen is related to bone age maturation [45]. Therefore, the decrease of androstenedione may induce bone dysfunction in uremic patients, which is associated with UP.

Carbonyl stress

Insulin resistance and carbonyl stress are factors related to the pathogenesis of UP at present. The characteristic of IR is that although the level of insulin in plasma is high, insulin function is still defective, leading to a series of biochemical reactions [46], which is the known cause of advanced glycosylation end-products AGEs [47], which is an enzyme-free reaction in lipids containing sugar and lipid adducts with protein [48]. Oxidative stress also leads to the auto-oxidation of sugar and the formation of AGEs [49]. In addition, under the condition of renal insufficiency, the effect of glycosylation protein on

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glycosylated protein in the kidney is also caused by oxidative stress. The decrease of clearance rate also leads to the accumulation of AGEs. AGEs affect the skin barrier and function, and improving cytokines may become one of the mechanisms of UP.

Liao et al published a review on the mechanism of IR in CKD. They concluded that the etiology of IR in CKD patients was multifactorial and related to a complex network. It's not just chronic inflammation and oxidative stress, and vitamin D deficiency. Anemia is also associated with malnutrition. These factors are related to the increase of inflammatory cytokines and fat factors, which leads to the acquired defect of insulin receptor signaling pathway [50]. At the same time, IR is related to metabolism and cardiovascular complications [51]. Therefore, IR is a key therapeutic target to reduce mortality and incidence in patients with CKD.

PROGRESS ON THE EFFECT OF BLOOD PURIFICATION TECHNOLOGY FOR UP

Previous studies have shown that the accumulation of middle-molecule toxins such as b2-microglobulin (b2-MG) and intact parathyroid hormone (iPTH) is an important factor of UP. Hemodialysis (HD) is the most commonly used mode of renal replacement therapy, but this method can hardly remove the middle-molecule uremic toxins and provide relief from UP. Hemodiafiltration (HDF) can not only remove creatinine, urea nitrogen by diffusion, but also remove the toxic substances in macromolecules by convection, also can eliminate medium molecular substance which can induce mast cells releasing histamine to relieve pruritus. iPTH and b2-MG can be scavenged by HDF, however, when binding with retinol-binding protein, retinol, and prealbumin, the effect of HDF on high-molecular complexes is limited. Hemoperfusion (HP) can adsorb and remove molecules with a relative molecular weight larger than 300. Tang Qian et al. [52] compared hemodialysis combined with hemoperfusion and hemodialysis combined with hemodiafiltration. It synthesized 9 RCT, involving 405 UP patients. The meta-analysis illustrated that HD+HP had better remission rates than HD+HDF in treating UP and clearing blood BUN, while there's no significant difference in PTH decrease and Ca2+ influence.

Commonly used adsorbents in HP are activated carbon and adsorption resin, synthetic polymer adsorption materials have specific selectivity. HP Apparatus (RHA) RHA contains 5 different models: HA130, HA230, HA280, HA330, and HA330-II for various clinical targets. The Chinese authoritative guide recommends the combined treatment of HD and HP (HA130-RHA) as a relatively ideal blood purification method to treat UP [53]. HA130-RHA has structural characteristics mainly for the relative specific absorption of moderate and macromolecular weight toxins produced in uremia, and that the removal of PTH and b2-MG was the most prominent. However, the incidence of UP remains high.

In the clinical practice of using HP for the treatment of critically ill patients, Wen-Hong Li et found that HA330-RHA can significantly improve the itching symptom in patients. By comparing the structural and functional characteristics between HA130-RHA and HA330-RHA in 8 weeks of treatment, VAS scores, modified Duo scores, and CRP were significantly lower in HA330-RHA group than in HA130-RHA group. These revealed that HA330-RHA could safely and effectively improve refractory itching symptoms and the inflammation state in MHD patients.

DISCUSSION

With the continuous progress of medical research, the acquirement of the mechanism of uremic pruritus is being updated constantly. Unlike general topical skin problems, urinary pruritus has proved to be a multi-factor systemic problem. Histamine release by mast cells, opioid receptor imbalance caused by μ-opioid receptor overexpression, systemic inflammation and unreasonable dialysis are dominant mechanisms. However, in clinical applications, there are still number of complexities. For example, antihistamine had a negative effect on eccentric cardiac hypertrophy. After taking anti-epileptic drugs, patients observe the side effects to adjust the type and dose of drugs in time. At the same time, the effect of kappa receptor agonist and anti-IL-2 receptor antibody are also worth looking forward to. Blood phospholipid LysoPC, insulin resistance, and protein-bound uremic retention solutes are the bridge between end-stage kidney disease and inflammatory reaction. Therefore, connecting the bridge can further clarify the pathogenesis of uremic pruritus, so as to open a new door for new solutions.

Currently, we should pay more attention to the early detection of UP, classified severity of UP and analyzed poor prognosis

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of refractory uremic pruritis (RUP) in outpatients. For inpatients with different itching levels, psychological assessment and intervention are necessary. In addition to basic symptomatic treatment, oral medication and narrowband ultraviolet radiation needs to be specific and individual given to characteristics of patients as well as their compliance, relatively ideal blood purification requires further exploration for RUP with the progress of HP apparatus.

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