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A neglected cause of uremic pruritus: Blastocystis hominis

Baloglu Ismail* and Turkmen Kultigin

Department of Nephrology, School of Medicine, Konya Necmettin Erbakan University, Meram School of Medicine, Konya, Turkey

Abstract

Uremic pruritus (UP) is one of the most bothersome side effect of uremia which can be seen in 50-90% of dialysis patients and about 25% of chronic kidney disease (CKD) patients. Despite the novel diagnostic tools and therapeutic approaches, appreciaply proportion of this population remains suffering from UP. *Blastocystis hominis* is one of the most common intestinal parasites encountered in human beings and various animals.

To date, in the literature, there has been no study investigating the relation between gastrointestinal colonization of *B. hominis* with UP in CKD population.

We hypothesized that colonization of *B. hominis* might be an important but neglected factor in the pathogenesis of UP especially in CKD patients who are resistant to treatment options mentioned above.

We suggest to examine fecal samples of CKD patients with intractable pruritus beside other biochemical test to determine the etiology of UP. If this hypothesis is proved, there will be no need to try much more expensive diagnostistic tools and drugs to treat UP.

Introduction

The high prevalance of uremic puriritus (UP) distress chronic kidney disease (CKD) and dialysis patients and negatively influence the quality of life and importantly mortality rates in this population [1]. Despite the improved diagnostic tools and therapeutic approaches, UP remains poorly characterized and treated. Common factors including uremic toxins, chronic ongoing inflammation, somatic neuropathy, skin dryness, high predialysis blood urea nitrogen, serum calcium, phosphorus and parathyroid hormone (PTH) levels, eleveted AGE levels in diabetic nephropathy were considered as triggers of UP in this population [2]. In this regard, antihistamines, erythropoietin, ultraviolet B (phototherapy), selective seratonin reuptake inhibitors, mast cell stabilizers, leukotriene receptor antagonists, nicotinamide, kappa opioid agonists including nalfurafine, tacrolimus ointment, gabapentin, topical capsaicin, thalidomide and even acupuncture were attempted to treat this unpleasent symptom [3]. However, the results of these studies were conflicting and most of these drugs failed to overcome UP.

Blastocystis spp. has been historically thought of as a commensal parasite with little potential for pathogenicity [4]. Recently, the clinical significance of this protozoa has been reexamined due to increased reports of symptomatic infection without other attributable etiologic agents, associations with other comorbid illness, and more frequent occurrences of invasive species in immuncompromised patients (5). Among them, *Blastocystis hominis (B. hominis)*, is one of oppurtunistic protozoa in the intestinal tract which can cause gastrointestinal symptoms including nause, vomiting, abdominal pain, and diarrhea and allergic skin diseases including urticaria, local and systemic pruritus [6]. Furthermore, treatment of B. hominis infestation with an aminoglycoside antibiotic, paramomycin, relieved palmoplantar pruritus effectively [7].

To date, in the literature, the data is scant in terms of investigating the gastrointestinal colonization of B. hominis. Recently, a case report demonstrated the co-infection of blastocystis and schistosomiasis in a patient with CKD [8]. However, there has been no data regarding the relationship between the colonization of B. hominis with UP in CKD population.

We hypothesized that colonization of *B. hominis* might be an important but neglected factor in the pathogenesis of UP especially in CKD patients who are resistant to treatment options mentioned above. To test this hypothesis, we suggest to examine fecal samples of CKD patients with intractable pruritus beside other biochemical test to determine the etiology of UP (Figure 1). If this hypothesis is proved, there will be no need to try much more expensive diagnostistic tools and drugs to treat UP.

Discussion

Blastocystis hominis was described by Alexeieff in 1911. In the following year, Brumpt demonstrated *B. hominis* among organisms found in human feces [9]. The prevalence of *B. hominis* is 1.5–10% in developed countries and a rate of up to 50% in less developed countries. Although the role of *B. hominis* in human disease is often referred to as controversial, the pathogenic features of this protozoa that impair health gained importance especially in immune-compromised patients. Most studies have reported that between 50% and 80% of individuals mono-infected with Blastocystis will show symptoms including nausea, vomiting, abdominal cramps, bloating, diarrhea and itching [10]. Main factors affecting the presentation of symptoms include patient's age, with younger patients less likely to show symptoms, and genetic factors that influence the production of cytokines [10]. Some studies

Correspondence to: Baloglu Ismail, Konya Necmettin Erbakan University, Meram School of Medicine Department of Nephrology, School of Medicine, Konya Necmettin Erbakan University, Meram School of Medicine, Konya, Turkey, E-mail: i_baloglu@hotmail.com

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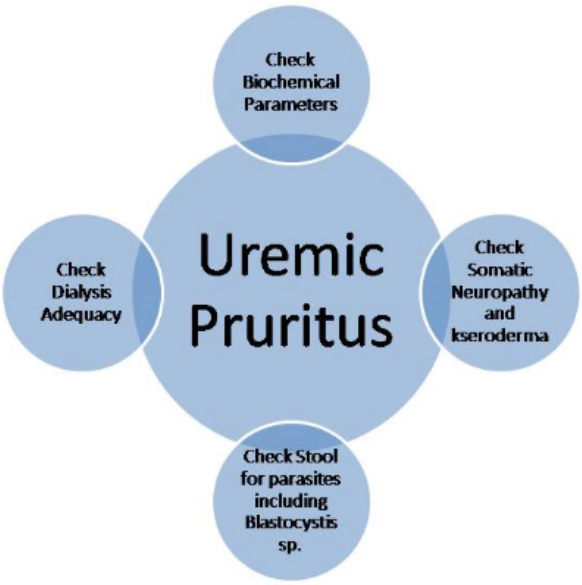

Figure 1. The Proposed Checklist of CKD Patients with Uremic Pruritus

have suggested that pathogenicity may be linked to specific subtypes and experimental studies have demonstrated that degrees of illness depend on the subtypes of *B. hominis*. At least 17 subtypes (STs) have been described, with ST1 to ST9 being recovered from human stool samples, the most common being ST3 [10]. The cyst form of *B. hominis*is transmitted via the fecal-oral route. After transmission, *B. hominis* might embedded itself in the intestinal mucosa, contributing to large ulcers in the gastrointestinal tract. The main diagnostic tests to determine the infection of *B. hominis*, include the direct examination of smears, in vitro culture of samples, and polymerase chain reaction (PCR) [10].

Recently, [6] showed that the amoeboid form was found in 60.6% of *Blastocystis*-positive patients with urticaria, but in none of the healthy controls. Subtype 3 was the only isolate found in both the patient and control groups. According to the results of this study, authors recommend to treat *B. hominis* especially in patients with urticaria. [7] also demonstrated that palmoplanter pruritus was disappeared after appropriate eradication of *B. hominis*.

The present work is the first to hypothesize that relationships among high colonization prevalance of *B. hominis* and uremic pruritus in chronic kidney disease. Previous studies have found evidence for both qualitative and quantitative chance in colonic microbiota in CKD patients. The numbers of anaerobic bacteria, including *Bifidobacterium*, *Lactobacillus* and *Prevotella* are decreased, and the numbers of *Clostridium perfringens*, aerobic enterococci and enterobacteria are increased in HD patients compared with healthy subjects. The primary reasons for these changes include chronic constipation, increased colonic transit times, decreased consumption of dietary fiber and impaired protein assimilation in the small intestine secondary to the uremic milieu that is present in the colon in CKD patients [11]. [12] found that Blastocystis sp. was one the most common protozoa in the hemodialysis patients when compared to healthy individuals. We also hypothesized that the colonization of *B. hominis* might be increased as a consequence of the composition of the colonic microbiota is altered. Uremic milue also deteriorate both colonic flora and immune system in CKD patients [11]. Accumulation of uremic toxins with altered T-cell and B-cell functions is thought to play a central role in the immune alterations that take place with progressive renal disease. Altered immunity in patients with CKD is associated with bacteremia, sepsis, and infections with severity not typically encountered in the general population [13]. According to our hypothesis, the release of antigens of *B. hominis* could trigger immunological mechanisms including activation of immunoglobulin E production that further activate mast cells releasing pruritogenic substances such as histamines.

To date, according to traditional stepwise approach, as first-line treatments emollients and gabapentin or phototherapy is suggested to treat UP. In refractory cases, more experimental options as μ-opioid-receptor—antagonists (i.e., naltrexone) or κ-opioid-receptor agonist (nalfurafine) and even kidney transplantation are applied (2). Both the diagnostic tools and therapeutic approachs are not cost-effective because appreciably proportion of CKD patients remain suffering from uremic pruritus. However, if our hypothesis is approved, CKD patients will be checked for *B. hominis* colonization via simple stool examination routinely before applying much more expensive tests and treatment options.

Conclusion

This report is the first to suggest the importance of colonization of *B. hominis* and the relation with intractable UP in CKD patients. There might be many pieces to the puzzle, however, in light of this hypothesis, a novel approach including examination of stool for *B. hominis* can be applied before more expensive tests are done. This approach will also much more cost effective in terms of both diagnosis and treatment.

Disclosure and conflict of interest

The authors of this manuscript have no relationship or financial interests with companies related to the findings of the study. The authors confirm that there are no known conflicts of interests.

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