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High serum interleukin-2 levels are associated with pruritus in chronic kidney disease undergoing regular hemodialysis

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ABSTRACT

Background: Uremic pruritus or more accurately termed 'chronic kidney disease-associated pruritus' (CKD-aP) is chronic itch in patients with advanced or end-stage renal disease without evidence of any other active disease that could explain the pruritus. The pathogenesis of CKD-aP is complex and not fully clarified. Some preliminary studies indicate that CKD-aP is a systemic inflammatory disease with a deranged balance of T helper (TH) cell differentiation toward TH1 predominance especially IL-2. This study aimed to elucidate further the association of interleukin-2 serum levels with CKD-aP in patients undergoing regular hemodialysis (HD).

Methods: This was an analytical cross-sectional study. Sampling was taken with consecutive sampling technique. This study was carried out on 72 patients on regular HD consist of 36 patients

with CKD-aP and 36 patients without CKD-aP after meeting the inclusion and exclusion criteria. Blood samples were obtained at Hemodialysis Unit Sanglah General Hospital and IL-2 serum levels were measured at Clinical Pathology Laboratory Sanglah General Hospital Denpasar between July 2019 and August 2019. Mann-Whitney U Test was used to compare IL-2 serum between CKD-aP and non-CKD-aP group.

Results: Results in this study we found higher median IL-2 level (17.1 ng/l) on pruritus group versus those without pruritus (13 ng/mL) ($p < 0.05$).

Conclusion: IL-2 serum levels on CKD-aP patients are higher than those without CKD-aP in patients who undergo regular hemodialysis.

Keywords: chronic kidney disease-associated pruritus, interleukin-2 serum, hemodialysis

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INTRODUCTION

Uremic pruritus, or more correctly called "chronic kidney disease associated pruritus" (CKD-aP), is a chronic itching that occurs in patients with advanced or end-stage renal disease. Nearly 60% to 80% of patients on dialysis (either hemodialysis or peritoneal dialysis) complain of pruritus. Although several treatment options have been proposed to treat these symptoms, most had limited success. The complex and not yet fully understood pathophysiology of CKD-aP is a major obstacle in finding effective management for this problem.¹ Several factors are thought to have a role in the pathogenesis of CKD-aP. Metabolic disorders such as secondary hyperparathyroidism, hyperphosphatemia with increased calcium phosphate deposition in the skin and increased calcium/phosphate products, release of histamine by mast cells, changes in the endogenous opioid-ergic system with overexpression of opioid receptors and anemia (or possibly some other manifestation of erythropoietin deficiency) said to have contributed to the occurrence of CKD-aP. However, not all of these findings can be confirmed in subsequent studies.²

There is increasing evidence that CKD-aP is caused more by systemic disorders than skin disorders. A variety of evidence supports the immunological hypothesis. The disturbance of TH1-dominated T helper (TH) cell balance appears to be the main cause of this systemic inflammation.² TH1 cells produce inflammatory cytokines such as interferon (IFN)- γ which recruit and activate leukocytes, therefore, the overactivity of TH1 cells results in an inflammatory response. On the other hand, TH2 cells secrete anti-inflammatory cytokines such as interleukin IL-4 and are associated with an allergic response. Discrimination between TH1 and TH2 cells can be done by measuring the cytokines produced by these cells or the chemokine receptors they express.⁴

In order to explain the role of excessive TH1 activity in the pathogenesis of CKD-aP, in this study we measured serum IL-2 as a TH1 cytokine in HD patients with and without CKD-aP.

METHOD

Study design and population

This study used a cross sectional design. Seventy-two patients with end-stage kidney disease, aged

18 years to 75 years, who underwent regular hemodialysis at the hemodialysis unit in Sanglah General Hospital Denpasar, Bali-Indonesia between July 2019 to August 2019 were screened for CKD-aP. Patients were included in this study if they had undergone HD for at least 3 months and had CKD-aP (defined as having a total score on the five-dimensional itch scale questionnaire >8). A number of HD patients who met the same selection criteria but did not experience CKD-aP were also selected as the control group. All patients in the case and control groups underwent dialysis twice a week, for 4.5 hours each time, and had undergone hemodialysis for at least 3 months using high flux dialysers. Exclusion criteria in this study are patients with systemic diseases with other pruritus such as liver disease and allergies, patients with another skin diseases such as psoriasis, dermatitis, urticaria, and infections, patients with immunosuppressive diseases such as HIV infection and malignant diseases, receiving immunosuppressive therapy in the last 4 weeks prior to sampling, currently taking antihistamine drugs in the last 3 days prior to sampling.

Pruritus Assessment

CKD-aP can vary from generalized to localized itching to the back, face, and arms. After being selected as participants in the CKD-aP study, they were assessed using a five-dimensional (5-D) itch scale questionnaire before blood collection on the same day. The scores from each domain were obtained separately and added together to get a total 5-D score. Patients are said to have CKD-aP if they have a total score >8.

Preparation and blood sampling

Blood samples were collected from all HD patients at long dialysis-free week intervals prior to subsequent hemodialysis therapy. All study participants were tested for serum IL-2 levels using the Enzyme-Linked Immunosorbent Assay (ELISA) method.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA). Data were presented as median (IQR) for numerical value and categorical were presented in frequency and percentage. Kolmogorov Smirnov-Z test was used to assess normality distribution of the data. Independent t-test was used to evaluate differences between IL-2 in CKD-aP and non-CKD-aP group if data were normally distributed or Mann Whitney-U test if data were not normally distributed. All value considered significant if $p < 0.05$.

RESULT

The subjects of this study were 72 end-stage kidney disease patients who underwent regular hemodialysis at the Sanglah Hospital Hemodialysis Unit according to inclusion and exclusion criteria. Data on the basic characteristics of study participants including age, gender, duration of hemodialysis (in months), and the use of skin moisturizers are presented in table 1. Based on the data obtained, the youngest age of this study participant was 26 years, while the oldest age was 75 years. The mean age of the study participants was 51.9 ± 11.9 years, with more CKD-aP patients over 50 years of age (66.7%) compared to those aged ≤ 50 years (33.3%). There were no differences in characteristics based on age, gender, use of moisturizer, duration of HD between the CKD-aP and Non-CKD-aP groups ($p > 0.05$) (Table 1). Comparative analysis showed that the CKD-aP group had higher serum IL-2 than the non-CKD-aP group (17.1 ng / mL vs. 13.0 ng / mL; $p < 0.001$) (Table 2).

DISCUSSION

Based on this study, it was proven that the median IL-2 level in the pruritus group was higher than in the non-pruritic group. This result is supported by a previous study in Iran by Fallahzadeh et al.⁵ in 2009, which reported that the mean serum IL-2 levels in CKD-aP patients were significantly higher than those without CKD-aP. In this study, the mean serum IL-2 level in the pruritus group was 0.544 U/ mL while in the non-pruritic group it was 0.318 U/ mL ($p < 0.0001$). Based on research by Azim et al. in Cairo in 2011, it was reported that the mean serum IL-2 levels in CKD-aP patients were higher than those without CKD-aP.⁶ There are not many studies that analyze serum IL-2 levels in CKD-aP patients. The accumulated evidence including the results of this study indicates that CKD-aP is associated with TH1 overactivity. The exact pathogenesis of these symptoms is unclear, but is thought to be caused by IL-2-mediated central or peripheral itch receptor stimulation.⁵

Interleukin-2 was noted to have a role in pruritus.⁷ These cytokines are pruritogenic when injected into normal skin and skin of patients with atopic dermatitis.^{8,9} IL-2 infusion in cancer patients also causes itching and erythematous changes in the skin.¹⁰ In addition, there was an increase in the number of IL-2 immune reactive cells in pruritic psoriasis lesions compared with non-pruritic lesions of psoriasis.¹¹ IL-2 is not only an immunoregulatory cytokine but also an important neuroregulatory molecule in the central nervous system. Circulating IL-2 can enter the blood-brain

Table 1. Sample characteristics

Variable	Study group		p-value
	CKD-aP (n=36)	Non CKD-aP (n=36)	
Age (years) (mean ± SD)	54.3±9.5	49.6±13.6	0.094
≤ 50	12 (33.3%)	19 (52.8%)	
>50	24 (66.7%)	17 (47.2%)	
Sex			
Male	26 (72,2%)	20 (55,6%)	0.141
Female	10 (27,8%)	16 (44,4%)	
HD duration (months) (mean ± SD)	71.1±32.5	65.1±38.4	
≤ 60	14 (38.9%)	16 (44,4%)	0.470
> 60	22 (61.1%)	20 (55,6%)	
Moisturizer ointment			
Yes	20 (54.9%)	17 (47.4%)	0.479
No	16 (45.1%)	19 (52.6%)	

Table 2. Comparison of IL-2 levels between CKD-aP and non-CKD-aP groups

Variable	Study group		p-value
	Non CKD-aP (n=36)	Non CKD-aP (n=36)	
IL-2 (ng/mL), median (IQR) (min-max)	17.1 (359.1) 10.9-4564.2	13.0 6.8-1831.2	0.001

*significant (p<0.05)

barrier and have access to its receptors on nerve cells and glia in different regions of the CNS. These cytokines can affect the physiological function of nerve cells and regulate several neurotransmitter systems in the CNS. Therefore, IL-2 can result in changes in CNS function.¹²

Clinically, pruritus due to IL-2 resembles the histamine-independent pruritus that accompanies dry skin. Redness may be accompanied by secondary to severe dryness of the skin but the initial process does not appear histamine dependent.¹³ IL-2 induced pruritus can be explained by the interaction between IL-31 T cells in the epidermis, keratinocytes, and neurons. Keratinocytes can be the source and recipient of various transduction processes in inflammatory interactions. Classical signs of inflammation do not appear after release of inflammatory mediators from keratinocytes in the specialized environment of the epidermis without blood vessels. Conversely, inflammatory mediators interfere with the skin barrier function, making the skin dry, resulting in pruritus. This itching sensation

is further transmitted through C-fibers including mechanosensitive and mechanoinsensitive groups.¹⁴

IL-2 triggers a cytokine cascade that includes IL-4. TH2 cells are activated via IL-4 and IL-2 which play an important role in TH2 differentiation.¹⁵ T lymphocytes in the skin secrete IL-31 in response to activation of the TH2 cytokine. IL-31 acts via a heterodimeric receptor consisting of IL-31 Receptor A (IL-31A) and Oncostatin M receptor expressed on epithelial cells and keratinocytes.^{14,15} These cells respond to IL-31 stimulation and secrete inflammatory mediators that may be involved in pruritus. The histamine-independent itching mechanism may be the basis for IL-2-induced pruritus and thus may form the basis of the successful treatment of gabapentin in IL-2-induced pruritus.

Interleukin-2 through the activation of IL-4 and IL-10 activates the T helper 2 (TH2) pathway and because it is on the same pathway, IL-5 production and number of eosinophils in the peripheral blood.¹⁶ Eosinophils amplify the IL-2-induced inflammatory response by releasing TH2 cytokines and polarizing the immune response to the TH2 pathway.¹⁷ This TH2 shift can cause an increase in IL-31 secretion. However, the toxic effects of eosinophils can directly damage or interfere with the pruriceptive primary afferents, namely unmyelinated C fibers thus sensitizing the pruriceptive pathway.

This study has limitations such as a questionnaire is carried out when the subject is undergoing hemodialysis so that there is limited movement to read and write causing the researcher to read the questionnaire one by one to each respondent which causes perspective subjectivity.

CONCLUSION

IL-2 serum levels on CKD-aP patients is higher than those without CKD-aP in patients who undergo regular hemodialysis. There is association between IL-2 serum levels with development of CKD-aP in patients undergoing regular HD.

CONFLICT OF INTEREST

The author declare there is no conflict of interest regarding publication of this article.

FUNDING

This study doesn't receive any specific grant from government or any private sectors.

ETHICAL CONSIDERATION

Current study has been approved by Ethical

Committee Faculty of Medicine, Universitas Udayana/RSUP Sanglah Denpasar, and all study procedure in accordance with Helsinki Declaration of human rights.

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