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Original Article

Factors associated with pruritus uremic in chronic kidney failure patients

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Abstract

Objective Uremic pruritus is one of the most distressing symptoms in patients with chronic renal failure. Interestingly, pruritus is not typically found in acute renal failure. Etiology and pathogenesis of uremic pruritus remain unclear. Several studies have demonstrated controversial results. Our study evaluated the frequency and intensity of uremic pruritus in patients with chronic renal failure (CRF) on hemodialysis including its associated factors. The aim of our study was to determine etiology and pathogenesis of uremic pruritus.

Methods The study was a cross-sectional study conducted at Dr. Kariadi Hospital in Semarang city involving 33 hemodialysis patients between June and November 2005. About 6 cc of blood volume was withdrawn from each patient before the patient undergoing hemodialysis. Laboratory findings including blood urea, parathyroid hormone, calcium, phosphate, magnesium, vitamin A, and interleukin 2 levels were evaluated. Patient were be interviewed and examined if they had other diseases that may also cause pruritus.

Results Uremic pruritus was found in 75.8% of the patients. Uremic pruritus had no correlation with urea level; secondary hyperparathyroidism, elevated divalent cations levels such as calcium, phosphate, magnesium levels as well as with hypervitaminosis A, interleukin-2 level or any group of those variables. On the other hand, uremic pruritus correlated to concomitant diseases. The intensity of uremic pruritus was related to the duration of hemodialysis.

Conclusion Multifactorial facets could be involved in the pathogenesis of uremic pruritus. Further experiments are required to reveal greater details regarding the pathogenesis of uremic pruritus.

Key words
Pruritus uremic, chronic kidney disease, acute kidney disease.

Introduction

Pruritus is an unpleasant skin sensation that induces a desire to scratch, which often occurs in patients with chronic renal failure (CRF).[1-3] Uremic pruritus is itching that has been frequently observed in patients with CRF who have high levels of urea.[1,2,4] According to some literatures, the prevalence of patients with CRF who had uremic pruritus may reach 90%.[5]

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Pruritus is a common problem in patients with CRF. Other studies have reported that the prevalence of uremic pruritus in CRF patients on hemodialysis is approximately 50% to 90%. Moreover, 65% of the patients complain about persistent pruritus.[1,6-10] Symptoms of uremic pruritus include paroxysmal pruritus, which is a sudden onset of excruciating itching that often wake the patients up from their sleep and relieves after scratching. Such symptom can be found in other diseases such as atopic dermatitis, nummular dermatitis, dermatitis herpetiformis, neurotic excoriation, eosinophilic folliculitis, subacute prurigo, prurigo nodularis and uremic pruritus.[10]

The skin of uremic patients would appear dry, atrophic and yellowish that occurs in approximately 67-93% cases and the skin condition does not respond to topical moisturizer treatments.[11]

A lot of studies have been performed to evaluate clinical characteristics and etiology of uremic pruritus; however, the certain cause and mechanism of CRF-associated pruritus is still poorly understood.[2,8,12,13]

Some factors are considered to have roles in the pathogenesis of uremic pruritus including dry skin, sebaceous and sweat gland atrophy, secondary hyperparathyroidism, hyperphosphatemia, hypermagnesemia, aluminum overload, iron deficiency anemia, hypervitaminosis A, peripheral neuropathy, opioid peptides, pruritus cytokines such as interleukin (IL)-2, inflammatory markers, and dialysis efficacy.[4,5,14,15] Hyperparathyroidism may cause increased levels of phosphate and calcium, which may have roles in soft-tissue calcification.[16]Hypervitaminosis A may cause dry skin, which will evoke pruritus.[11]However, other studies have demonstrated controversial results. The effect of urea on pruritus has not been extensively studied.[10,16,17] Magnesium is involved in modulated nerve conduction and histamine release from mast cells. It is excreted by the kidneys and therefore, any problem in the kidneys may cause hypermagnesemia.[19,20]

According to Yosipovitch et al, the criteria of uremic pruritus are complaints of itching in CRF patients that occur for at least 3 episodes within the last 2 weeks. The complaints come several times daily for at least several minutes and disturbing the patients; while the severity of itching in uremic pruritus is usually evaluated using visual analog scale.[1]

In patients with CRF, uremic syndrome occurs, in which biochemical and systemic dysfunction take place.[21] Common skin disorders include pallor, ecchymosis, hematoma, pruritus and uremic frost.[19]Xerosis, swelling, atrophy, and pigmentation disorder such as yellowish discoloration due to retained urochrome pigment and high levels of carotene in blood.[6,11] Brownish hyperpigmentation can be found due to increased melanin production resulting from poor dialysis of beta-melanocyte-stimulating hormone (beta-MSH).[6]

Methods

The study was a cross-sectional study with a population of CRF patients who underwent hemodialysis at Dr. Kariadi Semarang Hospital in 2005. The study was conducted between June and November 2005. The sample size was 33 patients. The independent variables were uremia, secondary hyperparathyroidism, hypercalcemia, hyperphosphatemia, hypermagnesemia, hypervitaminosis A and interleukin-2; while the dependent variable was uremic pruritus and the confounding variables were presence or absence of concomitant diseases that might also cause itching such as skin disease, systemic disease associated with CRF and idiopathic pruritus. Skin disease appeared as a lesion on itching skin. Systemic diseases, which were internal diseases associated with CRF that might cause itching included diabetes mellitus (DM), liver diseases (cholestasis, primary biliary cirrhosis, extrahepatic biliary tract obstruction, acute hepatitis). Laboratory tests such as gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), serum glutamic pyruvate transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT) and blood glucose evaluations were performed whenever there was any suspicion of the systemic diseases. The evaluation was performed when the patients underwent hemodialysis by the investigator and the results were cross-checked by another

examiner or doctor. The patients were assessed and categorized into 2 scales, i.e. patients with concomitant diseases and those without concomitant diseases.

In order to obtain data, 6cc of blood sample was withdrawn prior to the hemodialysis. The patients were then interviewed. History taking and physical examination were performed. The blood samples were assessed for serum levels of urea, parathyroid hormone, calcium, phosphate, magnesium, vitamin A and interleukin-2 as well as for other tests to detect other diseases that might cause itching such as random blood glucose test and liver function tests.

Inclusion criteria of our study were patients who underwent hemodialysis using recycled dialysis membrane at Dr. Kariadi Semarang Hospital. They were willing to participate in our study and had signed the informed consent form that they were agreed to be examined and to answer the questionnaire. The patients did not receive CAPD (Continuous Ambulatory Peritoneal Dialysis) treatment. They also did not receive treatment for pruritus and corticosteroid within the last one month. While the exclusion criteria were patients who had systemic diseases that might cause pruritus, but the diseases were not associated with kidney diseases.

Blood urea level was presented in mg/ dL and the blood samples were withdrawn prior to the hemodialysis. Evaluations on secondary hyperparathyroidism and IL-2 were performed using ELISA; while assessments to evaluate hypercalcemia, hyperphosphatemia and hypermagnesemia were carried out using Spectrophotometer 4010. Hypervitaminosis A was assessed using HPLC (High Performance Liquid Chromatography).

To analyze data on correlation between independent variables and uremic pruritus that had normal distribution, a student T-test was used; while for data with abnormal distribution such as IL-2, the Mann-Whitney test was used. ANOVA test was used to evaluate the difference between independent variables and the severity of uremic pruritus except for IL-2 by using Kruskall Wallis test. Chi-square test was used to evaluate the correlation between the levels of parathyroid hormone, blood urea, calcium, phosphate, magnesium, vitamin A as well as the presence/absence of concomitant diseases and the incidence of uremic pruritus.

Results

There were 35 subjects of CRF patients who participated in the study; unfortunately, 2 subjects died; therefore, the total sample size was 33 subjects including 25 men and 8 women. The youngest age was 19 years and the oldest was 73 years.

The severity of uremic pruritus was divided into 4 categories, which were: 1st degree: itching without scratch mark; 2nd degree: itching with scratch mark, but without excoriation; 3rd degree: continuous itching with scratch mark or excoriation; 4th degree: 2nd and 3rd degree and the itching caused the subject became extremely anxious.[7]

Based on the degree of severity, there were 10 subjects (40%) with 3rd degree; while there were 5 subjects (20%) with 4th degree. The frequency distribution of subjects with uremic pruritus based on the degree of severity can be seen in **Table 2**.

Most subjects reported that the itching was experienced on the back (51.5%); while others said that the itching was found on the abdomen (6.1%), feet (6.1%), face, shoulder, buttock, which were experienced by a subject,

Table 1 Frequency distribution of CRF patients experiencing uremic pruritus

Uremic pruritus	*n*	*%*
Present	25	75.8
Absent	8	24.2
Total	33	100.0

Table 2 Frequency distribution of subjects with uremic pruritus based on the degree of severity

Severity	*n*	*%*
1st degree	4	16
2nd degree	6	24
3rd degree	10	40
4th degree	5	20
Total	25	100.0

Table 3 Correlation between the severity of uremic pruritus and the onset of itching complaint

Onset of pruritus	*Severity*		*P value*
	Only complaint	*Complaint + skin disorder*	
	n (%)	*n (%)*	
Night-time	1 (25.0)	8 (38.1)	0.005
Daytime and night-time	0 (0)	11 (52.4)	
Hemodialysis	3 (75.0)	1 (4.8)	
Daytime	0 (0)	1 (4.8)	
Total	4 (100.0)	21(100.0)	

Table 4 Mean difference of independent variables in patients with uremic and non-uremic pruritus

Independent variables	*Mean ± SD in patients with UP complaints*	*Mean ± SD in patients without UP complaints*	*P-value*
Age (years)*	49 ± 12.2	49 ± 7.1	0.500
Duration of illness (months)	26 ± 33.9	18 ± 20.6	0.399
Numbers of hemodialysis (times)	84 ± 86.4	63 ± 100.9	0.205
Ureum level	170 ± 54.7	155 ± 38.2	0.688
PTH level	174 ± 209.7	208 ± 156.3	0.679
Calcium level	8.55 ± 0.79	9.05 ± 1.32	0.226
Phosphate level	3.85 ± 0.88	3.84 ± 1.18	0.875
Magnesium level	2.17 ± 0.22	2.30 ± 0.47	0.378
Vitamin A level	76.87 ± 34.00	77.30 ± 41.84	0.977
IL-2* level	0.2797 ± 0.225	0.1967 ± 0.191	0.366

Notes : * = were evaluated using Mann-Whitney test; UP = uremic pruritus

respectively. The results were consistent with those of other studies, i.e. the itching mostly was experienced on the back reaching to 70% of cases.[1,12] The second most frequent body location for pruritus was abdomen, which was found in 46% of cases. The back is more difficult to reach for scratching; therefore, the patients probably felt the itch to be more intense. About 33.3% of subjects with pruritus admitted that they often experience both daytime and night-time itching; while nine subjects (27.3%) experienced only night-time itching. There were four subjects (12.1%) who confessed experiencing the itch after hemodialysis procedure and there was only one subject (3%) who had the itch in the morning.

The result of our study showed that continuous daytime and night-time pruritus was the commonest finding and nocturnal pruritus was the second most. It probably occurred since at night-time, these subjects were at rest and had no further tasks; therefore, the itching was felt more intense and there was probably also psychogenic factors that might exist.[22,23] There was a significant correlation between the severity of uremic pruritus and the onset of itching complaint (P= 0.005) as can be seen in **Table 3**.

Analysis of results showed that the mean values of those independent variables were not significantly different between patients with and without uremic pruritus complaints. The mean difference of independent variables in **Table 4** was also tested whether there was a mean difference based on the severity of uremic pruritus. For the sake of the statistical test, we used categorization based on the four degree (the before-mentioned category). Two independent variables, which were age and the level of interleukin 2 in **Table 4** had abnormal distribution and therefore, they were analyzed

Table 5 Differences of independent variables based on the severity of uremic pruritus using ANOVA test

Variables	*Calculated F*	*P value*
Ln duration of illness	0.575	0.638
Ln duration of hemodialysis	3.552	0.032
Ln urea level	0.134	0.939
Ln parathyroid hormone level	0.260	0.854
Ln calcium level	0.916	0.450
Ln phosphate level	0.919	0.449
Ln magnesium level	0.349	0.790
Vitamin A level	2.470	0.090

Table 6 Differences of independent variable IL-2 based on the severity of uremic pruritus

	Interleukin 2 level	*Patients' age (yr)*
Chi-Square	.670	4.860
df	3	3
Asymp. Sig.	.880	.182

a. Kruskal Wallis Test
b. Grouping Variable: severity of uremic pruritus

using non-parametric method, i.e. by using Kruskal Wallis test. While the other independent variables were evaluated using the one-way ANOVA. Of all independent variables that had been analyzed, we found that only the number of hemodialysis had significant difference with the severity of uremic pruritus (P =0.32). Complete results can be seen on table 5. The Kruskal Wallis test showed that both age and interleukin 2 levels had no significant correlation with the severity of uremic pruritus **(Table 6)**.

Based on the results of ANOVA analysis, we found that the mean numbers of hemodialysis was significantly different from the severity of uremic pruritus (P =0.032). The mean number of hemodialysis in patients with 1st degree uremic pruritus was 100.5 times; while in the 2nd degree, the mean value decreased to only 24.3 times. In patients with the 3rd degree, the mean number of hemodialysis was the highest, i.e. 135.7 times. However, the mean decreased again to 39 times of hemodialysis in patients with 4th degree. The mean number of hemodialysis for each degree of severity of uremic pruritus can be seen in **Table 7**.

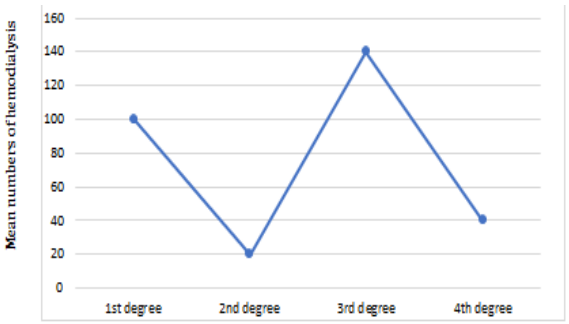

Figure 1 Graph of mean numbers of hemodialysis based on the severity of uremic pruritus in CRF patients

In further analysis, the investigator performed the post hoc test to evaluate mean difference of the number of hemodialysis for each degree of severity for uremic pruritus. Results of post hoc test LSD showed a significant difference of mean numbers of hemodialysis between patients with 4th degree and 3rd degree (P = 0.03). The mean difference between the 3rd and 4th degree was 96.7 times hemodialysis. Complete results of post hoc test LSD analysis can be seen in **Table 8**.

On the graph, there is a tendency of increased severity of uremic pruritus with increased mean numbers of hemodialysis, which is between the mean value of 24.3 and the 39 times of hemodialysis and such tendency can also be seen when the mean value is more than 100.5 times hemodialysis. It can be demonstrated based on the results of post-hoc test analysis, which showed significant results between the 2nd and the 3rd degree as well as between the 3rd and the 4th degree.On the history of hemodialysis procedure, i.e. between the mean value of 39 and 100.5 times hemodialysis, there was reduced severity of uremic pruritus complaint. It can be explained as there is an adaptation factor for the itching sensation. Another possibility is that the kidney function can still be maintained though using hemodialysis instrument; therefore, the

Table 7 Mean number of hemodialysis for each degree of severity of uremic pruritus

	N	*Mean*	*Std. Deviation*	*Std. Error*	*95% Confidence interval for Mean*		*Minimum*	*Maximum*
					Lower Bound	*Upper Bound*		
1st degree	4	100.50	111.60	55.80	-77.08	278.08	10	260
2nd degree	6	24.33	31.72	12.95	-8.96	57.62	3	87
3rd degree	10	135.70	89.10	28.18	71.96	199.44	5	244
4th degree	5	39.00	39.18	17.52	-9.65	87.65	6	98
Total	25	84.00	86.43	17.29	48.32	119.68	3	260

Table 8 Post hoc test: mean difference of the number of hemodialysis based on the severity of uremic pruritus

(I) the severity of uremic pruritus	*(J) the severity of uremic pruritus*	*Mean Difference (I-J)*	*Std. Error*	*Sig.*	*95% Confidence interval*	
					Lower Bound	*Upper Bound*
1st degree	2nd degree	76.17	48.79	.133	-25.30	177.64
	3rd degree	-35.20	44.72	.440	-128.20	57.80
	4th degree	61.50	50.71	.239	-43.95	166.95
2nd degree	1st degree	-76.17	48.79	.133	-177.64	25.30
	3rd degree	-111.37*	39.03	.010	-192.54	-30.19
	4th degree	-14.67	45.77	.752	-109.85	80.52
3rd degree	1th degree	35.20	44.72	.440	-57.80	128.20
	2nd degree	111.37*	39.03	.010	30.19	192.54
	4th degree	96.70*	41.40	.030	10.60	182.80
4th degree	1st degree	-61.50	50.71	.239	-166.95	43.95
	2nd degree	14.67	45.77	.752	-80.52	109.85
	3rd degree	-96.70*	41.40	.030	-182.80	-10.60

* The mean difference was considered significant at the .05 level.

Table 9 Frequency distribution of some factors affecting uremic pruritus

Affecting factors	*Categories*	*n*	*%*
Urea level (n = 33)	High	17	51.5
	Low	16	48.5
Parathyroid hormone (n = 33)	With secondary hyperparathyroidism	20	60.6
	Without secondary hyperparathyroidism	13	39.4
Calcium level (n = 33)	Hypercalcemia	1	3.0
	No hypercalcemia	32	97.0
Phosphate level (n = 33)	Hyperphosphatemia	12	36.4
	No hyperphosphatemia	21	63.6
Magnesium level (n = 33)	Hypermagnesemia	3	9.1
	No hypermagnesemia	30	90.9
Vitamin A level (n = 33)	Hypervitaminosis A	9	27.3
	No hypervitaminosis A	24	72.7
Interleukin 2 (n = 33)	High	16	48.5
	Moderate	17	51.5
Concomitant disease	Present	12	48.0
	Absent	13	52.0

pruritogenic substances can be excreted although the substances may not be fully removed. On further stage, i.e. more than 100.5 times hemodialysis, there was a tendency of greater uremic pruritus severity as the itching exacerbated in consistent with the severity of CRF, which had become more severe. Affected / dependent variables in our study were categorical data; therefore, some of laboratory results in **Table 4** should also be categorized.

Table 10 Correlation between the high or low urea level and the incidence of uremic pruritus

Urea level	*Uremic Pruritus*				*P value*
	Present		*Absent*		
	n	*%*	*n*	*%*	
High	12	48.0	5	62.5	0.688
Very high	13	52.0	3	37.5	
	25	100.0	8	100.0	

Table 11 Correlation between secondary hyperpara-thyroidism and the incidence of uremic pruritus

Secondary Hyperpara-thyroidism	*Uremic Pruritus*				*P value*
	Present		*Absent*		
	N	*%*	*N*	*%*	
Present	15	60.0	5	62.5	1.000
Absent	10	40.0	3	37.5	
	25	100.0	8	100.0	

Table 12 Correlation between hypercalcemia and the incidence of uremic pruritus

Calcium Level	*Uremic Pruritus*				*P value*
	Present		*Absent*		
	n	*%*	*n*	*%*	
Hypercalcemia	0	0	1	12.5	0.242
No hypercalcemia	25	100.0	7	87.5	
	25	100.0	8	100.0	

Table 13 Correlation between hyperphosphatemia and the incidence of uremic pruritus

Phosphate level	*Uremic Pruritus*				*P value*
	Present		*Absent*		
	n	*%*	*n*	*%*	
Hyperphosphatemia	9	36.0	3	37.5	
No hyperphos-phatemia	16	64.0	5	62.5	1.000
	25	100.0	8	100.0	

Table 14 Correlation between the presence or absence of hypermagnesemia and uremic pruritus

Magnesium level	*Uremic pruritus*				*P val ue*
	Present		*Absent*		
	n	*%*	*n*	*%*	
Hypermagnesemia	2	8.0	1	12.5	1.0
No hypermagnesemia	23	92.0	7	87.5	00
	25	100.0	8	100.0	

Table 15 Correlation between hypervitaminosis A and the incidence of uremic pruritus

Vitamin A level	*Uremic pruritus*				*P value*
	Present		*Absent*		
	n	%	n	%	
Normal	18	72.0	6	75.0	1.000
Above normal	7	28.0	2	25.0	
	25	100.0	8	100.0	

The result of categorization can be seen in **Table 9**.

Results of 2 x 2 cross tabulation showed that there was no correlation between urea level and the incidence of uremic pruritus **(Table 10)**. Moreover, an analysis was also performed to find any correlation between the high or low urea level and severity of uremic pruritus. The severity of uremic pruritus was categorized into two groups including those with complaintsalone ant those with complaints accompanied by skin disorders. The results of 2 x 2 cross tabulation also did not show any significant correlation between the severity of uremic pruritus and urea level (P = 1.000), which can be seen in **Table 18**.

Meanwhile, results of 2 x 2 cross tabulation between the incidence of uremic pruritus and the presence or absence of hyperparathyroidism can be seen in **Table 11**. Results in the **Table 11** also shows that there was no significant correlation between the incidence of uremic pruritus and hyperparathyroidism (P = 1.000).

Results in **Table 12** shows that there was no significant correlation between the incidence of uremic pruritus and hypercalcemia (P = 0.242).

Results in **Table 13** shows that there was no significant correlation between the incidence of uremic pruritus and hyperphosphatemia (P = 1.000).

Results in **Table 14** shows that there was no significant correlation between the incidence of uremic pruritus and hypermagnesemia (P = 1.000).

Results of Fisher's Exact test showed P = 1.000, which means that there was no significant correlation between the incidence of uremic pruritus and hypervitaminosis A. The correlation between hypervitaminosis A and the incidence of uremic pruritus can be seen in **Table 15**. Meanwhile, there was also no correlation between uremic pruritus and interleukin 2 (P = 0.688) as seen in **Table 16**.

Table 16 Correlation between interleukin 2 and the incidence of uremic pruritus

Interleukin-2 level	*Uremic pruritus*				*Pvalule*
	Present		*Absent*		
	n	*%*	*n*	*%*	
Moderate	12	48.0	5	62.5	0.688
High	13	52.0	3	37.5	
	25	100.0	8	100.0	

Table 17 Correlation between other diseases that may cause itching and uremic pruritus

Other diseases that may cause itching	*Uremic Pruritus*				*P value*
	Present		*Absent*		
	n	*%*	*n*	*%*	
Present	12	48.0	0	0	0.03
Absent	13	52.0	8	100.0	
	25	100.0	8	100.0	

Table 18 Correlation between the levels of urea, parathyroid hormone, phosphate, magnesium, vitamin A, interleukin 2 as well as concomitant disease and the severity of uremic pruritus

Severity of Uremic Pruritus	
Urea level	*P* : 1.000
Parathyroid hormone level	P : 1.000
Phosphate level	P : 0.602
Magnesium level	P : 0.300
Vitamin A level	P : 0.593
Interleukin 2 level	P : 1.000
Other diseases that cause itching	P : 0.593

Note: were tested using Chi square test

The variables of concomitant diseases in CRF patients were defined as other diseases that might cause itching including skin, systemic or idiopathic diseases. Laboratory tests were necessary for those with a suspicion of the concomitant diseases. The evaluation for detecting the concomitant diseases in CRF patients was performed using cross-checking method by another doctor, which provided a very good result, i.e. a kappa value of 1.00. The 2 x 2 cross tabulation in **Table 17** shows that there was a significant correlation (P = 0.03) between other diseases causing pruritus and the incidence of uremic pruritus.

To evaluate the correlation between the levels of urea, parathyroid hormone, phosphate, magnesium, vitamin A, interleukin 2 as well as other concomitant diseases and the severity of uremic pruritus, therefore, the severity of uremic pruritus was divided into 2 categories, i.e. the group with itching symptom alone and the other with itching symptom and skin disorder. Afterward, 2 x 2 tabulation was carried out. After the chi-square test was performed, we found that there was no significant correlation between the levels of urea, parathyroid hormone, phosphate, magnesium, vitamin A, interleukin 2 as well as concomitant disease and the severity of uremic pruritus **(Table 18)**. The correlation between calcium level and the severity of uremic pruritus could not be evaluated since all CRF patients with uremic pruritus did not have hypercalcemia.

Discussion

Uremic pruritus is a sensation that evokes the desire to scratch, which often occurs in patients with chronic renal failure undergoing hemodialysis. Uremic pruritus is often a major problem for patients with end-stage renal disease and it affects as many as 90% of HD patients.[5] Many studies have been done to evaluate the clinical characteristics and etiology of uremic pruritus, however, the certain etiology and mechanism of pruritus in chronic renal failure has been poorly understood.

The patient's age in our study had no significant correlation with uremic pruritus (P = 0.500) as seen on table 4. Other studies have suggested that the complaints of uremic pruritus are rarely found in children undergoing hemodialysis. Schwab M, Mikus G, Mettang T in 1999 reported that out of 199 children undergoing hemodialysis, there were only 9.1% who had complaints of pruritus with mild intensity or mild pruritus severity.[12] The study did not explain why it rarely occurred in children, but it mentioned that the pathogenesis of uremic pruritus in children still needs further studies. Another study has indicated that in elderly people, there is a greater tendency that T helper

cells may have differentiation into Th1 compared to children. Increased Th1 will produce greater interleukin 2, which will cause itching.[12] Our study did not include children as our subjects were generally older adults **(Table 4)**. This may explain why age did not have any significant correlation with uremic pruritus. There was no significant correlation between urea level and uremic pruritus and it may explain why uremic syndrome only occurs in CRF but it is not found in patients with acute renal failure (ARF). Chronic condition of high urea level induces the manifestation of uremic syndrome.

In patients undergoing hemodialysis who had high urea level, their blood urea level will rapidly decrease after the hemodialysis and it will increase quickly within sometime after the hemodialysis; therefore, the patients must have regular hemodialysis treatment. Unstable blood urea level has a tendency of high level and becomes chronic, which may occur with an assistance using hemodialysis instrument and it supports the CRF patients' survival. Therefore, it should be emphasized that temporary high blood urea level cannot be determined as a reference of developing uremic pruritus. In contrast, unstable and persistent high urea level may induce further problems including uremic pruritus. This notion is supported by evidences found in our study, i.e. there was a significant difference found between the severity of uremic pruritus and the mean numbers of hemodialysis (P = 0.032, ANOVA test **Table 5**) and such correlation was not found for blood urea level (P = 1.000**. Table 18**).

Some textbooks or journals of research reports have suggested that the pathogenesis of uremic pruritus is still vague.[7,10-12,24] Many theories have been proposed to explain the causes of uremic pruritus, but further studies have refuted the theories.

An older study, which was conducted by Massry S *et al* and published in the New England Med Journal in 1968, indicated that secondary hyperparathyroidism is the cause of uremic pruritus and in the same year, Hampers CL, Katz AI *et al* reported disappearance of uremic pruritus following parathyroidectomy;[12] however, the disappearance of itching in patients who had undergone parathyroidectomy was temporary.[24] It is consistent with results of our study, in which no significant correlation was found between secondary parathyroidism and uremic pruritus. In our study, we evaluated divalent cations, i.e. the blood levels of calcium, phosphate and magnesium and we found no significant correlation of them with uremic pruritus. The results are consistent with results of studies conducted by Hiroshige *et al* in 1995, Virga *et al* in 1998 and Merkus *et al* in 1999.[7] However, there is a report indicating that there is a correlation between uremic pruritus and hyperphosphatemia, hypercalcemia and hypermagnesemia.[14] It is said that divalent ions may cause nerve modulation and histamine release by mast cells, but recent studies have demonstrated that there is no correlation between the amount of histamine and uremic pruritus; therefore, it still requires further studies.[7,8,25]

Theories about divalent ions that can cause nerve modulation and histamine release by mast cells still need further investigation. A study conducted in hemodialysis patients has demonstrated that the skin mast cells in patients with uremic pruritus is not different from those in control group.[25] The most recent studies have also reported that the concentration of histamine does not correlate with uremic pruritus.[7,8,25]

Most of current literatures have excluded the divalent ions as the cause of uremic pruritus. In the Fitzparick's dermatology in general medicine 9th edition, it is said that the etiology of

uremic pruritus may comprise many factors including xerosis, peripheral neuropathy, mast cell hyperplasia, increased serum level of histamine, vitamin A, parathyroid hormone and inflammatory factors.[5] Multifactorial causes may also have role in the pathogenesis of developing uremic pruritus.

In our study, there was no correlation between hypervitaminosis A and uremic pruritus. Some literatures have reported that hypervitaminosis A does have role on the development of uremic pruritus.[6,7,11,26] Nevertheless, the pathogenesis of vitamin A causing pruritus has not been clear. It is assumed that vitamin A, which is fat soluble can not be excreted during dialysis and it causes hypervitaminosis A that may lead to dry and itchy skin.[11] Results of another study conducted by De Kroes S, Smeerk G in 1998 have indicated that there is no evidence that hypervitaminosis A may cause uremic pruritus.[7] Most recent literatures even have not mentioned vitamin A as one of causes for uremic pruritus.[24] Another study has reported that hypervitaminosis A at the epidermis of CRF patients does not have significant difference between CRF patients with and without dry skin. It is said that the dry skin does not occur due to hypervitaminosis A, but it occurs because there is some abnormalities in corneocyte maturity resulting from uremia.[6]

The theory that suggests the role of IL-2 on uremic pruritus has not been confirmed by our study, which did not find any significant difference of IL-2 levels in CRF patients between those with and without uremic pruritus. It may occur since uremic pruritus is not induced only by IL-2 cytokines and IL-2 is produced not only by Th1 but also by other T cells; while T lymphocytes also produce other cytokines such as IL-1, IL-2, IL-6, IL-10, IL-12, IL-14, IL-17, GM-CSF, TNF-α, IFN- β, INF- γ, and TGF-α-β.[27]

Other diseases that cause pruritus such as fungal disease, dermatitis or other skin diseases will exacerbate the existing pruritus. Uremic pruritus is often accompanied with other local skin disease due to weakened immune system. In our study, there was a significant correlation between uremic pruritus and other diseases that may cause itching. In this case, the other diseases include skin, systemic or idiopathic diseases. It can be easily understood as pruritus in other diseases is developed through the same impulse of itching in general, in which the free nerve endings interact with mast cells and the activated mast cells will release tryptase that will further activate receptors at nerve endings of type C nerve fibers; therefore, the itching sensation will be transmitted to central nervous system.[10,28] Neuropeptide release as neurogenic inflammatory mediator involves type 2 proteinase-activated receptors (PAR2) in sensory nerve. PAR 2 is broken down by tryptase from mast cells and neutrophils resulting in histamine release. PAR 2 produces calcitonin gene-related peptide (CGRP) and P substance (neurokinin 1) from nociceptors of type C nerve fibers.[16] CGRO and P substance will cause pruritus. In other diseases, similar mediator release occurs.

As the definition of pruritus is itching sensation that causes the desire to scratch[7,28] and the sensation occurs due to impulses from the central nerve system (CNS),[20,28,29] therefore, the itching sensation can also be felt as uremic pruritus. In this case, the development of pruritus can also due to the scratching itself as a result of complications accompanying CRF, which stimulates the release of mediators causing pruritus that will obviously induce the itching sensation.

Based on results of our study, most complaints were about persistent itching that had been experienced during daytime and night-time;

while the second most were complaints of night-time itching. It may occur since at night-time there was no more work and therefore, the itching sensation became more obvious and psychogenic factors may also have roles.[23] During their leisure time, patients are more likely to think about their kidney disease, considering their previous actions or other psychogenic issues.[22,23] It can be associated with reduced blood cortisol level at night-time, which is consistent with the circadian rhythm and therefore, it is more difficult to manage stress at night-time.[22] Meanwhile, daytime pruritus can be caused due to the severity of the existing complaints, which further analysis showed that it has significant correlation with the severity of pruritus (P =0.005) as seen on table 3.

It is necessary to have further studies on the role of psychogenic factors in the pathogenesis of uremic pruritus. Some studies have reported that depression and stress are often found in patients with terminal CRF as the patients are overwhelmed by their kidney diseases, which they think it is difficult to heal and they realize that their life merely depends on hemodialysis.[30,31] A study conducted by Koo et al has demonstrated that psychological stress in CRF patients on hemodialysis may reach 56.5%.[31]

There were some factors that had not been evaluated in our study such as sebaceous and sweat gland atrophy, plasma histamine level, cutaneous mast cell proliferation, iron deficiency anemia, peripheral neuropathy, opioid peptides, inflammatory markers, dialysis method and factors of daily activities. As we have known, dry skin may cause pruritus; however, in our study, we found no correlation between dry skin and uremic pruritus. Evaluations on plasma histamine and aluminum level were not performed due to our limitation on evaluation facilities; while cutaneous mast cells and sebaceous and sweat gland atrophy were not assessed as it required skin biopsy, which was not possible for our settings. Evaluation of blood iron level to assess iron deficiency anemia is not accurate since adequate iron level could not exclude the occurrence of iron deficiency.

Conclusion

The prevalence of pruritus of CRF patients at Dr. Kariadi Hospital is 75.8% and most patients (40%) have 3rd degree severity.

The investigators assume that multifactorial causes probably have roles in the pathogenesis of uremic pruritus. Further studies involving many multidisciplinary experts are required to reveal the pathogenesis of uremic pruritus.

References

1. Inbar Z, Yosipovitch G, David M, Uzi G. Prevalence and characterization of uremic pruritus is still a mayor problem for patients with end-stage renal disease. J Am Acad Dermatology 2003; 49; 5.
2. SzepietowskiJc, Sikora M, Krustal M. Uremic pruritus: A clinical study of maintenance hemodialysis patients. J Dermatol 2002; 29(10): 621-627.
3. Rayner HC, Larkina M, Wang M, et al. International comparisons of prevalence, awareness, and treatment of pruritus in people on hemodialysis. Clin J Am Soc Nephrol 2017; 18.
4. Germain MJ. Uremic pruritus: An itch with ominous consequences. Am J Nephrol 2017; 46; 448-9.
5. Forrestel AM, Micheletti RG. Skin manifestations of internal organ disorders. Fitzpatrick's Dermatology 9th Ed. New York:McGraw-Hill: 2019. p. 2436.
6. Nurley JR, Elston DM, Hogan DJ, et all. Dermatologic manifestation of renal disease. Update April 11th 2012. Available at: www.emedicine.com.
7. Virga G. Pruritus in Hemodialysis Patients 3rd Congress of nephrology in internet. CIN 2013.

8. Perhada V, Gruber F, Kastelan M, et al. Pruritus an important symptom of internal diseases. Dermatovenereologica 2000; 9: 3.
9. Ashmore SD. Ondestron therapy for uremic pruritus in hemodialysis pruritus. Am J Kidney Dis 2000; 35(5); 827-831.
10. Odom RB, James WD, Berger TG. Pruritus and neurocutaneous dermatosis. Andrew's Diseases of The Skin 9th ed. Philadelphia: WB Saunders Company 2000; p: 49-68.
11. Stahle-Backdah. Pruritus clinical aspects. The cause of uremic pruritus is unknown. Dermatol 2002; 14: 297-301. Available at www.cheus.ubc.ca/pruritus.pdf.
12. Mettang T, Magnus CP, Alscher DM. Uraemic pruritus new perspectives and insights from recent trials. European Renal Association Dialysis and Transplant Association. Nephrol Dial Transplant 2002; 17: p. 1558-63.
13. Aresi G, Hugh C, Hassan L, et all. Reasons for underreporting of uremic pruritus in people with chronic Kidney disease: A qualitative study. J Pain Symptom Manage 2019; 58; 578-86.
14. Aramwit P, Supasyndh O. Uremic pruritus; Its prevalence, pathophysiology and management. Intech Open Sci 2015; 19-41.
15. Swarna SS, Aziz K, Zubair T et all. Pruritus associated with chronic kidney disease: A comprehensive literature review. Cureus 11(7):e5256. DOI 10.7759/cureus.5256.
16. Twycross R, Greaves MW, Handwerker H, et all. Itch: Scarthing more than the surface. QJ Med 2003; 96; 7-26.
17. Scoot M. Renal Failure associated pruritus: Uremic pruritus. A family medicine resource. Update 5/10/2008. Available at: www.familypracticenotebook.com.
18. Nowak M, Tsoukas M, Deimus A. Generalized pruritus without primary lesions. Postgrad Med 2000; 107; 2.
19. Lupi O, Sessim M, Duarte DJ, et all. Cutaneous manifestations in end-stage renal disease. An Bras Dermatol 2011; 86(2); 319-26.
20. Blaine J, Chochol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol 2015; 10(7): 1257-72.
21. Nigam SK, Bush KT. Uraemic syndrome of chronic kidney disease: altered remote sensing and signaling. Nat Rev Nephrol 2019; 15(5):301-316.
22. Schmidt TJ. Physiological functions of corticosteroids. In: Lin AN, Paget SA eds. Principles of corticosteroid therapy. London: Arnold, 2002: 19-40.
23. Combs SA, Teixeira JP, Germain MJ. Pruritus in Kidney Disease. Semin Nephrol 2015; 35; 383-91.
24. Arnat K, Bowens KE. Pruritus. Manual of dermatologic therapeutics 6th Ed. Philadelphia: Lippincott Williams & Wilkins 2002; 166-72.
25. Filippi CD, Regazzini R, Piazza V, et all. Uremic pruritus is not related to plasma histamine concentrations. Clin Exp Dermatol 1995; 20; 294-6.
26. Henrich WL. Uremic pruritus. Up to date patient information. Society of General Internal Medicine. April 2005. Available at http://www.patients.update.com.topic.asp
27. Shaw DM, Merien F, Braakhuis A, Dulson D. T-cells and their cytokine production: The anti-inflammatory and immunosuppressive effects of strenuous exercise. Cytokine 2018; 104; 136-42.
28. Braun-Falco O, Plewig G, Wolf HN, Burdorf WHC. Pruritus, prurigo, self induced disease, psychiatric disease and neurologic disease. Dermatology second completely, revised edition. Berlin: Springer-Verlac 2000; 989-1012.
29. Scott M. Pruritus. Journal of American Family Physician 2003; 68; 1135-42.
30. Mollaoglu M. Depression and health-related quality of life in hemodialysis patients. J Dial & Trans 2004; 3; 9.
31. Koo JR, Yoon JW, Kim SG, et al. Association of depression with malnutrition in chronic hemodialysis patients. Am J Kidney Dis 2003; 41; 1037-42.