UREMIC PRURITUS AND ASSOCIATED FACTORS IN CHRONIC DIALYSIS PATIENTS: AN OBSERVATIONAL STUDY IN WESTERN NEPAL

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ABSTRACT

Introduction

Pruritus is one of the well-recognized major skin derangements in patients with advanced renal failure and are usually without visible skin lesions. Only few studies have addressed this issue in Nepalese population.

Objective

The present study aims to identify the prevalence and associated factors of uremic pruritus in chronic dialysis patients in western Nepal.

Methodology

A prospective observational study was conducted to include all chronic dialysis patients with uremic pruritus at the Manipal Teaching Hospital, Pokhara, Nepal over a period of one year (June 2018 and May 2019).

Result

During the study period, a total of 59 patients were included in the study with mean age of 55.8±15.8years,of which 37 (63%) patients developed uremic pruritus.

Statistically significant relationship between presence of pruritus and pruritus severity with frequency of itching grade and sleep disturbance score among elderly (p=0.001) were observed

The serum urea can predict uremic pruritus among elderly patients with a good diagnostic value. The multivariate analysis showed male gender, hypertension, elevated serum albumin and random blood sugar were independent predictors of pruritus in patients undergoing chronic dialysis.

Conclusions

Our findings demonstrate that higher proportion of patients undergoing chronic dialysis were diagnosed with uremic pruritus (63%) and occurrence of pruritus had association with frequency of itching grade and sleep disturbance score. The serum levels of urea may predict the occurrence of pruritus among elderly patients. Further more, a large multicenter study is warranted with longer follow up which may provide robust information on the burden of pruritus and its associated factors to guide appropriate management among elderly.

KEYWORDS

uremic pruritus, chronic kidney diseases, dialysis, risk factors

INTRODUCTION

Pruritus is one of the well-recognized major skin derangements in patients with advanced renal failure and is usually identified without visible skin lesions.[1,2] Other cutaneous manifestations of patients on dialysis are xerosis, hyper pigmentation, reactive perforating collagenosis, mucosal, hair and nail changes. An earlier study reported the global prevalence of uremic pruritus (moderate or extreme) to be 42%, and also suggested asignificant association of uremic pruritus with depression, sleeping disorders, impaired quality of life and death.[3] In Nepal, the prevalence of pruritus among chronic kidney disease patients undergoing dialysis was estimated to be 40-55%.[4,5]

Even though since long time evidence exists for the relationship between chronic renal failure and pruritus, its molecular basis remains controversial, considering the subjective nature and strong influence of psychological factors.[6] Also, there is paucity of information on the prevalence of uremic pruritus in chronic kidney disease patients from the western part of Nepal. Therefore, the present study aims to identify the prevalence and associated factors of uremic pruritus in chronic dialysis patients in western Nepal, with specific focus on the elderly population in Nepal.

METHODOLOGY

This prospective observational study was conducted to include all chronic dialysis patients with uremic pruritus at the Manipal Teaching Hospital, Pokhara, Nepal over a period of one year (June 2018 and May 2019). Patients with pruritus due to some other dermatological disorders and those who refused to participate in the study were excluded.

Uremic pruritus was considered, if it last for more than three months among dialysis patients, and was quantified with the help of visual analogue scale (VAS). It is a 10-point scale instrument in which 0 refers to no pruritus while 10 point is suggestive of very severe pruritus. The participants responded to the VAS questionnaire based on the previous four weeks status.

Study population included all chronic dialysis patients underwent peritoneal as well as hemodialysis. Ethical approval was obtained from the institutional review board before the study conduction. The purpose of the study was explained to the participants by study investigators and those who agreed for participation provided the written informed consent. Subjects who were not willing to participate in the study were excluded.

Data included patient characteristics (age, gender, body mass index), comorbidities (hypertension, diabetes mellitus), biochemical parameters (Hemoglobin, serum urea, creatinine, albumin, calcium, phosphate, and random glucose), type of dialysis (hemodialysis /peritoneal), pruritus status (present or absent, localized/generalized); Visual analog scale [no pruritus (VAS= 0), mild pruritus (VAS= 1-2), moderate pruritus (VAS= 3-6), severe pruritus (VAS= 7-8)]; Sleep Disturbance Score (sleep never disturbed due to pruritus, occasionally delays falling asleep, frequent delays in falling asleep, delayed falling asleep and occasionally awakes at night, and delayed falling asleep and frequently awakes at night); frequency of itching score [no pruritus, 4short episodes (less than 10 min), one long episode (more than 10 min) and persistent pruritus] and treatment (anti-pruritic treatments and other treatments/supplements).

Statistical analysis

Data were presented as proportions, medians (minimum–maximum range), or mean (±standard deviation; SD) as appropriate. Study variables were analyzed and compared according to pruritus status (Pruritus present vs. Pruritus not present) in the overall patients as well as among elderly patients. Differences between categorical variables were analyzed using the Chi-square or Fisher's exact test, whereas Student's t test was performed to compare continuous variables, whenever applicable. Receiver operating characteristic (ROC) curve was used to determine the cutoff value for serum urea for predicting the uremic pruritus in elderly patients. The area under the curve (AUC) was used to compare the discriminatory power of the serum urea with an AUC of 1.0 considered as perfect discrimination and 0.5 considered as equal to chance. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio and accuracy of the serum urea in predicting the uremic pruritus were determined. The multivariate logistic regression analysis was conducted to determine the factors associated with pruritus development in the overall patients as well as among elderly group. Two-tailed p value <0.05 was considered statistically significant. Data analysis was carried out using IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA.

RESULTS

During the study period, a total of 59 patients were included in the study. Table 1-3 presents descriptive characteristics, presence of pruritus in overall and elderly patients. Overall, 37 (62.7%)study participants were experiencing pruritus. The mean age of all the patients was 55.8±15.8years and those who developed pruritus were 54.6±16.9 years. In addition, the mean age of the elderly patients was 67.6±7.03 years and those with pruritus were 68.5±7. 5years. Table 3 shows that there was a significant relationship between presence of pruritus and the pruritus severity with the frequency of itching Grade and sleep disturbance Score among elderly (p=0.001).

Figure 1 demonstrates the sensitivity analysis for the serum urea to predict pruritus among elderly chronic dialysis patients. The ROC curve showed an area under the curve (AUC) for the serum urea to predict uremic pruritus among elderly patients to be 0.700 (95% CI: 0.505-0.895) which is considered to have a good diagnostic value. The optimal cutoff value of serum urea is 119 mg/dl based on the optimal sensitivity (72.2%) and specificity (78.6%). It had also a higher positive predictive value (81.2%), Negative Predictive Value (68.7%), Positive Likelihood Ratio (3.37), Negative Likelihood Ratio (0.35) and accuracy (75%).

Multivariate regression analysis was used to identify the factors independently associated with the development of pruritus in the overall patients as well as among elderly group (Table 4 & 5).Male gender, hypertension, elevated serum albumin and random blood sugar were independent predictors of pruritus in patients undergoing chronic dialysis.

Table 1: Uremic pruritus in chronic dialysis patient (n=59)

Variable	Value	Variable	Value
Age (mean±SD) years	55.8±15.8	**Intensity of pruritus (Visual Analogue Scale) Score**	
Sex		No pruritus (VAS= 0)	22 (37.3%)
Male	41 (69.5%)	Mild pruritus (VAS= 1-2)	7 (11.9%)
Female	18 (30.5%)	Moderate pruritus (VAS= 3-6)	23 (39.0%)
Body mass index	23.8±5.0	Severe pruritus (VAS= 7-8)	7 (11.9%)
Hypertension	52 (89.7%)	**Sleep disturbance score**	
Diabetes mellitus	34 (58.6%)	Sleep never disturbed due to pruritus	23 (39.0%)
Laboratory findings		Occasionally delays falling asleep	10 (16.9%)
Hemoglobin (g/dl)	9.1±1.8	Frequent delays in falling asleep	16 (27.1%)
Serum urea (mg/dl)	118.7±44.6	Delayed falling asleep and occasionally awakes at night	8 (13.6%)
Serum creatinine (mg/dl)	9.7±3.5	Delayed falling asleep and frequently awakes at night	2 (3.4%)
Serum albumin (g/dl)	3.9±0.5	**Frequency of itching score**	
Serum calcium (mg/dl)	7.8±1.4	No pruritus	23 (39.0%)
Serum phosphate(mg/dl)	6.5±2.1	Four short episodes (<10 min)	19 (32.2%)
Serum random glucose (mg/dl)	132.5±70.2	One long episode (>10 min)	15 (25.4%)
Dialysis type		Continuous pruritus	2 (3.4%)
Hemodialysis	47 (79.7%)	**Treatments**	
Peritoneal dialysis	12 (20.3%)	Anti-pruritic treatments	39 (66.1%)
No pruritus	22 (37.3%)	Other treatments/supplements	44 (74.6%)
Pruritus	37 (62.7%)		
Pruritus Localized/ Generalized			
Localized	18 (48.6%)		
Generalized	19 (51.4%)		

Table 2: Clinical characteristics, laboratory findings and treatment based on the presence of pruritus

	No Pruritus (n=22)	Pruritus (n=37)	P value
Age	57.8±13.9	54.6±16.9	0.46
Sex			
Males	15 (68.2%)	26 (70.3%)	0.86 for all
Females	7 (31.8%)	11 (29.7%)	
Body mass index	23.6±4.2	23.9±5.5	0.78
Hypertension	21 (95.5%)	31 (86.1%)	0.25
Diabetes mellitus	12 (54.5%)	22 (61.1%)	0.62
Laboratory findings			
Hemoglobin (g/dl)	9.2±2.1	8.9±1.6	0.64
Serum urea (mg/dl)	102.4±40.3	128.4±44.8	0.03
Serum creatinine (mg/dl)	9.6±4.3	9.9±2.9	0.76
Serum albumin (g/dl)	3.8±0.5	3.9±0.5	0.38
Serum calcium (mg/dl)	7.9±0.8	7.8±1.7	0.94

Serum phosphate(mg/dl)	6.3±1.8	6.7±2.2	0.52
Serum random glucose (mg/dl)	144.2±81.1	125.5±62.9	0.32
Dialysis type			
Hemodialysis	19 (86.4%)	28 (75.7%)	0.32 for all
Peritoneal dialysis	3 (13.6%)	9 (24.3%)	
Intensity of pruritus (VAS) Score			
No pruritus (VAS= 0)	22 (100%)	0 (0.0%)	0.001 for all
Mild pruritus (VAS= 1-2)	0 (0.0%)	7 (18.9%)	
Moderate pruritus (VAS= 3-6)	0 (0.0%)	23 (62.2%)	
Severe pruritus (VAS= 7-8)	0 (0.0%)	7 (18.9%)	
Frequency of itching Grade			
No pruritus	22 (100%)	1 (2.7%)	0.001 for all
Four short episodes (<10 min	0 (0.0%)	19 (51.4%)	
One long episode (>10 min)	0 (0.0%)	15 (40.5%)	
Continuous pruritus	0 (0.0%)	2 (5.4%)	
Sleep disturbance Score			
Sleep never disturbed due to pruritus	22 (100%)	1 (2.7%)	0.001 for all
Occasionally delays falling asleep	0 (0.0%)	10 (27.0%)	
Frequent delays in falling asleep	0 (0.0%)	16 (43.2%)	
Delayed falling asleep and occasionally awakes at night	0 (0.0%)	8 (21.6%)	
Delayed falling asleep and frequently awakes at night	0 (0.0%)	2 (5.4%)	
Treatments			
Anti-pruritic treatments	18 (81.8%)	21 (56.8%)	0.04
Other treatments/supplements	18 (81.8%)	26 (70.3%)	0.32

Table 3: Clinical characteristics, laboratory findings and treatment among elderly based on the presence of pruritus (n=32)

	No Pruritus (n=14)	Pruritus (n=18)	P value
Age	66.5±6.4	68.5±7.5	0.43
Sex			
Males	11 (78.6%)	10 (55.6%)	0.17 for all
Females	3 (21.4%)	8 (44.4%)	
Body mass index	24.1±3.3	24.9±4.2	0.56
Hypertension	1 (7.1%)	2 (11.8%)	0.66
Diabetes mellitus	5 (35.7%)	4 (23.5%)	0.45
Laboratory findings			
Hemoglobin (g/dl)	8.7±1.8	9.5±1.6	0.22
Serum urea (mg/dl)	96.4±35.8	122.4±36.1	0.05
Serum creatinine (mg/dl)	8.9±4.7	9.3±3.1	0.77
Serum albumin (g/dl)	3.7±0.4	3.9±0.5	0.12
Serum calcium (mg/dl)	7.9±0.9	7.6±1.7	0.57
Serum phosphate(mg/dl)	5.9±1.8	6.8±2.5	0.27
Serum random glucose (mg/dl)	165.4±94.6	142.4±86.1	0.48
Dialysis type			
Hemodialysis	13 (92.9%)	17 (94.4%)	0.85 for all
Peritoneal dialysis	1 (7.1%)	1 (5.6%)	

Intensity of pruritus (VAS) Score			
No pruritus (VAS= 0)	14 (100%)	0 (0.0%)	0.001 for all
Mild pruritus (VAS= 1-2)	0 (0.0%)	1 (5.6%)	
Moderate pruritus (VAS= 3-6)	0 (0.0%)	11 (61.1%)	
Severe pruritus (VAS= 7-8)	0 (0.0%)	6 (33.3%)	
Frequency of itching Grade			
No pruritus	14 (100%)	0 (0.0%)	0.001 for all
Four short episodes (<10 min	0 (0.0%)	9 (50.0%)	
One long episode (>10 min)	0 (0.0%)	8 (44.4%)	
Continuous pruritus	0 (0.0%)	1 (5.6%)	
Sleep disturbance Score			
Sleep never disturbed due to pruritus	14 (100%)	0 (0.0%)	0.001 for all
Occasionally delays falling asleep	0 (0.0%)	4 (22.2%)	
Frequent delays in falling asleep	0 (0.0%)	6 (33.3%)	
Delayed falling asleep and occasionally awakes at night	0 (0.0%)	6 (33.3%)	
Delayed falling asleep and frequently awakes at night	0 (0.0%)	2 (11.1%)	
Treatments			
Anti-pruritic treatments	11 (78.6%)	6 (33.3%)	0.01
Other treatments/supplements	11 (78.6%)	12 (66.7%)	0.45

Table 4: Severity of uremic pruritus by multivariate regression

Variable (reference value)	β	OR	95% CI		P value
Males	0.116	1.019	-1.957	2.189	0.911
Age	0.021	1.122	-0.051	0.093	0.558
Hemoglobin	-0.066	0.957	-0.582	0.451	0.799
Urea	0.013	1.243	-0.007	0.034	0.191
Creatinine	-0.070	0.912	-0.358	0.217	0.624
Albumin	1.426	1.290	-0.532	3.385	0.149
Calcium	-0.229	0.889	-0.820	0.362	0.439
Phosphorus	0.098	1.077	-0.347	0.544	0.659
Random blood sugar	0.005	1.130	-0.009	0.018	0.477
Hypertension	0.477	1.051	-2.803	3.758	0.771
Body Mass Index	0.017	1.031	-0.160	0.194	0.847

Table 5: Severity of uremic pruritus by multivariate regression among elderly

Variable (reference value)	β	OR	95% CI		P value
Males	1.139	1.193	-2.058	4.337	0.464
Hemoglobin	0.144	1.083	-0.818	1.107	0.756
Urea	0.004	1.045	-0.044	0.051	0.876
Creatinine	0.063	1.083	-0.370	0.496	0.763
Albumin	2.890	1.593	-1.958	7.737	0.226
Calcium	-0.234	0.899	-1.276	0.809	0.643
Phosphorus	-0.014	0.989	-0.944	0.916	0.976
Random blood sugar	0.005	1.165	-0.013	0.023	0.543
Hypertension	1.285	1.135	-4.156	6.726	0.626
Body Mass Index	0.038	1.047	-0.335	0.410	0.835

DISCUSSION

Pruritus in chronic kidney disease patients is characterized by itching that is directly associated with renal failure in absence of other co-morbidities.[7] It is one of the most frequent and distressing symptom in chronic kidney disease patients, which affects sleep, daily activities and impaired quality of life of the patients.[8,9] With the increase in ageing population even in developing country such as Nepal, the prevalence of pruritus is also on rise.

The diagnosis and burden of this nuisance and frustrating symptom are often remains undetermined and under reported by treating physician.[10] An international study by Rayner et al[11] on 35,452 hemodialysis patients reported underestimation of the prevalence of pruritus by two-third of the medical directors and that pruritus possess major impact on professional and social life of the patients. Previously, around 50–90% of the chronic dialysis patients were affected by pruritus, but the prevalence has declined over the past decades due to improved hemodialysis techniques. The symptoms of pruritus usually begins about couple of months after the initiation of dialysis which ranges from localized to generalized itching with different intensities (mild to severe).[12] The pathological mechanism of uremic pruritus is multifactorial which may involve xerosis, systemic micro inflammation, elevated Th1 to Th2 cell ratio, divalent ion abnormalities, hypervitaminosis A, secondary hyperparathyroidism, peripheral neuropathy, opiate receptorimbalance, neuropathic process, mastocytosis in skin either alone or in combination. Therefore, it is difficult to attribute a single factor in the pathogenesis of itching and hence the management is much challenging .[13]

An earlier study reported generalized pruritus in two-thirds of the hemodialysis patients and the remaining one-third had localized pruritus mainly confined to the back, face and arm with arteriovenous fistula.[3] This is in contrast with the present study in which localized and generalized pruritus were reported in almost equal proportions (48.6%Vs 51.4%). Moreover, our findings are in agreement with an earlier study by Narita et al[12] which reported generalized pruritus in up to 50% of patients with chronic kidney disease.

In case of generalized pruritus, various disorders related to hematology, dermatology, hepatic, endocrine, neuropsychiatry, drug allergies and other underlying malignancies should be ruled out. The severity of pruritus in chronic kidney disease patients varies from mild sporadic discomfort to severe persistent restlessness which strongly influence the quality of life of the patient. Interestingly, the skin of affected individuals remain unremarkable and often resembles with age related changes, like xerosis.[14]

Many larger studies have identified association of male gender with the chronic kidney disease-related pruritus. An international study on pruritus in hemodialysis patients showed higher association with males who had 1.1 times higher adjusted odds of developing pruritus.[3] Similarly, other studies have identified even higher risk of male gender (OR 1.5) for pruritus. Contrarily, unadjusted results based on smaller studies did not identify association of gender with more severe pruritus.[7] In line with these observation, there were no significant gender differences identified either in the overall cohort as well as in the subgroup analysis of elderly patients on dialysis (p value 0.86 and 0.17, respectively).

Uremic pruritus led to some sort of sleep disturbances in almost 61% of the patients, whereas another study by Ozen et al[15] reported sleep disturbances in only 33.8% patients. In the present study, a significant relationship was observed between presence of pruritus and the pruritus severity, frequency of itching grade and sleep disturbance score among elderly.

Moreover, blood urea level was significantly higher in patients with pruritus as compared to non-pruritus group among the overall cohort as well as in the elderly group (P=0.03 and P=0.05,respectively), which was consistent with the study by Hu et al.[16] However, there were no significant difference in the serum levels of hemoglobin, albumin, calcium and phosphorus between pruritus and non-pruritus group in both all chronic dialysis patients as well as elderly in our study. Serum phosphate level showed association with increase in pruritus in an earlier study from Nepal by Adhikari et al[4] and Dialysis Outcomes and Practice Patterns Study (DOPPS)[3] which was contrary to our findings where there was no association in all patients (P=0.52) as well as in elderly (P=0.27).

There was no association of uremic pruritus with the predisposing factors such as age, gender, ethnicity, duration of dialysis, and etiology of renal failure. The inconsistency for findings could be attributed to the smaller sample size and relatively short duration of study observation. Therefore, a large multicenter study is warranted to include more number of hemodialysis patients together with longer follow up that will provide substantial data on the burden of pruritus and its associated factors.

In the current study, 63% of the chronic kidney disease had associated pruritus. To date, there is advancement in the standard clinical approach for patients with uremic pruritus; but still further research is needed to understand the pathophysiology and develop more reliable treatment for pruritus.[17]

Improvement of symptomatic management in chronic kidney disease patients is the priority for establishing clinical practice guidelines and research. Notably, an earlier large cohort study showed that 20% of the severely affected chronic kidney disease patients did not receive treatment for pruritus which is consistent with lower treatment rates observed by other investigators. Patients with untreated pruritus were more likely to develop sleep disturbance, depression, and affect general health and impaired quality of life.[18] Health related quality of life of chronic dialysis patients is often compromised partially due to higher symptoms and significant impact on sleeping habit and socialization[19] which necessitates more attention and efforts to improve the holistic management approach which will be addressed in future research studies.

CONCLUSIONS

Our findings demonstrate that higher proportion of patients undergoing chronic dialysis were diagnosed with uremic pruritus (63%). The occurrence of pruritus showed association with frequency of itching grade and sleep disturbance score. The serum levels of urea may predict the occurrence of pruritus among elderly patients. In addition, male gender, hypertension, elevated serum albumin and random blood sugar were independent predictors of pruritus in patients undergoing chronic dialysis. Furthermore, a large multicenter study is warranted to include more number of hemodialysis patients together with long term follow-up which may provide robust information on the burden of pruritus and its associated factors to guide appropriate management among elderly.

LIMITATION OF THE STUDY

This is the unique study from western Nepal which assessed the prevalence of uremic pruritus and its associated factors in chronic dialysis patient and also focuses on elderly patients with chronic kidney disease associated pruritus. This study highlighted the patient characteristics, comorbidities, biochemical parameters, frequency of itching, sleep disturbance score and current care practice for pruritus at hospital settings.

The potential limitations of the present study include smaller sample size and single centre study which may influence the generalizability of our findings. Secondly, most of the patientsin our cohort were on polypharmacy, and so the role of medication in chronic kidney disease associated pruritus was not addressed in much detail. Third, various aggravating and relieving factors were not taken into consideration in the present study. Finally, WBC countand presence of dry skin as causes of pruritus were not assessed in the current study.

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CONFLICT OF INTEREST

No potential conflict of interest.

FINANCIAL DISCLOSURE

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