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The correlation between uremic pruritus and blood lead levels in prevalent hemodialysis patients and its relation to the severity of pruritus using visual analog score

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Abstract

Background: Pruritus is a common and often distressing symptom in patients with chronic kidney disease. Though the pathogenesis of uremic pruritus remains poorly understood, systemic inflammation has presented itself as one of the possible explanations. High blood lead levels (BLLs) have been noted to be associated with inflammation and poor nutritional status in hemodialysis patients. Our aim is to study the relation between blood lead levels and uremic pruritus. This is a cross-sectional study that enrolled 50 patients; all were on regular hemodialysis 3 times per week for at least 6 months. Patients were divided into 2 groups, group 1 (n =10) with no pruritus and group 2 (n= 40) with varying degrees of pruritus. Group 2 was further divided according to intensity of pruritus by visual analog score (VAS) into mild (n=10), moderate (n=20), and severe pruritus (n=10).

Results: There was a significant difference in serum lead levels and ferritin levels between groups 1 and 2 (p value < 0.01 and < 0.05, respectively). There was a statistically significant difference in serum lead levels in the groups with varying intensity of pruritus, having higher serum lead levels in patients who exhibited severe pruritus (p value < 0.005) Moreover, a statistically significant relation between elevated blood lead levels and the duration of dialysis was observed in this study.

Conclusion: Uremic pruritus is a multi-factorial phenomenon, and our study showed that blood lead levels in hemodialysis patients might be associated with increased intensity of pruritus.

Keywords: Uremia, Pruritus, Hemodialysis, Blood lead levels

Background

Uremic pruritus is a common symptom of end-stage renal disease (ESRD) that affects up to 46% of hemodialysis (HD) patients. It is described as an itch that spans a large surface area of the skin, with a daily or near daily occurrence, without being associated with any primary skin lesion and without affecting certain dermatomes [1]. A higher mortality rate has been reported in dialysis patients with extreme pruritus. In addition, observational studies reported that these patients are more likely to suffer from sleep disturbances and depressive symptoms [2].

The pathogenesis of uremic pruritus is obscure and many studies have shown that several factors are implicated in its occurrence. In a review by Lugon in 2005, many factors were listed as possible contributing factors including xerosis, hypercalcemia, hyperphosphatemia, hypermagnesemia, disturbances in PTH (parathyroid hormone), the accumulation of aluminum and substance

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P, hypervitaminosis A, in addition to the presence of peripheral neuropathy and chronic inflammatory conditions [3]. Furthermore, it was observed in several studies that patients with secondary hyperparathyroidism exhibited an improvement in pruritus after parathyroidectomy [4–6]. However, there was no evidence that parathyroid hormone in itself elicits cutaneous reaction when injected intradermal [7].

Exposure to lead in the general population comes from different sources in the surrounding environment, including industrial pollutants, inhalation of fumes from burning lead batteries, lead-containing paints, contaminated water from old lead pipes, cosmetics, and some hair dyes [8].. Dongre et al. observed that workers with high lead exposure in the battery manufacturing factories had high blood pressure and complained of skin itching [9]. In Kerou and So-ava, where drinking water was polluted by lead, people who consumed drinking water had various symptoms including skin itching [10].

Studies have shown that blood lead levels in patients on maintenance hemodialysis are higher than in healthy adults [11, 12]. All this taken into consideration suggests a relation between lead contamination and pruritus. Moreover, an all-cause cardiovascular and infection-related 18-month mortality was higher in patients on dialysis with elevated blood lead level [13].

Methods

The aim of the study is to establish a correlation between blood lead levels and uremic pruritus.

This study is a cross-sectional study that included 50 patients with ESRD with age ranging from 18 to 65 years, who are on regular hemodialysis for at least 6 months in Al Agouza hospital and are receiving hemodialysis sessions three times per week, 4 h each session. Low flux membranes were used; dialysate was with bicarbonate-based buffer for all patients. Dialysate ionic composition (Na = 136–140 mEq/L, K= 0–4 mEq/L, Cl = 99–110 mEq/L, Ca = 1.5 mEq/L and HCO3 = 27–39 mEq/L). Patients with primary skin diseases, malignancies, end-stage liver disease (child C), hepatitis C virus infection, and those with serum PTH levels above 300 ng/l, total serum calcium levels above 10.2 mg/dl, and phosphorus levels above 5.5 mg/dl were all excluded from this study. We also excluded those with occupations related to lead exposure (e.g., batteries manufacture). To ensure that the patients were not exposed to lead contamination during hemodialysis, a sample from dialysis water was analyzed to ensure that lead level does not exceed the maximum allowed level of contaminants according to the ministry of health guidelines which is lead level < 0.005 mg/dl.

All samples were collected before the mid-week session (Tuesday or Wednesday), samples for lead were collected pre-dialysis session from arteriovenous fistula (AVF), they were collected in EDTA tubes, and lead was measured using atomic absorption spectrometry.

We divided the patients into 2 groups, group 1 (n =10) with no pruritus and group 2 (n=40) with varying degrees of pruritus. The severity of pruritus was measured by visual analog scale (VAS). Visual analog scale consists of a 10-cm horizontal line with 0 points (no pruritus) to 10 points (maximum intensity of pruritus). We used the categorization by Reich et al. [14] as a reference when classifying the VAS score. The severity of pruritus is as follows: < 4 points was considered mild, ≥ 4 points but < 7 points moderate; ≥ 7 points but < 9 points severe, and ≥ 9 points very severe pruritus.

Kt/v was calculated using the Daugirdes formula. Normalized protein catabolism ratio (NPCR) was calculated using the following formula = 0.22 + [0.864 × (intradialytic BUN rise in mg/dl)/intradialytic hours].

Statistical analysis and methods

IBM SPSS statistics (V. 25.0, IBM Corp., USA, 2017–2018) was used for data analysis. Data were expressed as median and percentiles for quantitative non-parametric measures.

The following tests were done:

1. Comparison between two independent groups for non-parametric data using Wilcoxon rank sum test.
2. Comparison between more than 2 patient groups for non-parametric data using Kruskal-Wallis test.
3. Ranked Spearman's correlation test to study the possible association between each two variables among each group for non-parametric data. The probability of error at 0.05 was considered sig., while at 0.01 and 0.001 are highly sig.
4. Diagnostic validity test: It includes:

a. The diagnostic sensitivity: It is the percentage of diseased cases truly diagnosed (TP) among total diseased cases (TP+FN).
b. The diagnostic specificity: It is the percentage of non-diseased truly excluded by the test (TN) among total non-diseased cases (TN+FP).
c. The predictive value for a +ve test: It is the percentage of cases truly diagnosed among total positive cases.
d. The predictive value for a −ve test: It is the percentage of cases truly negative among total negative cases.
e. The efficacy or the diagnostic accuracy of the test: It is the percentage of cases truly diseased plus truly non-diseased among total cases.

Results

The study population was divided into 2 groups. Group 1 included 10 patients without pruritus and group 2 40 patients with pruritus. Table 1 shows the demographic data of the 2 groups including original kidney disease and co-morbidities. In our study pruritus was symmetrical in 40% of patients, localized in 30% of patients in the back and limbs, generalized in 30% of patients. All patients reported that it occurred at any time during the day. All patients with pruritus reported occasional use of antihistaminic medication, 4 patients were using regular gabapentin 100–200 mg daily.

Table 2 shows a statistically significant difference in blood lead level between hemodialysis patients with uremic pruritus and those without uremic pruritus (7.5 and 18 μg/dl, respectively) with p value (< 0.003). Ferritin levels were higher among patients with pruritus (mean level 563.5 ng/ml) which was statistically significant with p value (< 0.05). Dialysis adequacy (Kt/v) is another parameter that was better in those with no uremic pruritus (p value < 0.05) than those with pruritus. No statistically significant difference as regards to serum albumin, normalized protein catabolism ratio (nPCR), creatinine, urea, hemoglobin (Hb) level, total leucocytic count (TLC), corrected serum calcium, phosphorus, and PTH. Although CRP levels were higher in group 2, this was not found to be statistically significant.

When comparing patients in group 2 according to their severity of pruritus using VAS, 10 patients described their pruritus as severe, 20 had moderate and 10 patients had mild pruritus, and none of the included patients in the study scored over 9.

Blood lead levels among patients with severe pruritus were significantly higher (p < 0.01) than those with mild and moderate pruritus. (10, 14.5, 26 μg/dl, respectively). Moreover, blood urea levels were higher in patients with severe pruritus (VAS score 10) more than those with mild and moderate pruritus (p < 0.05). Among the 3 groups, there were no significant differences as regards age, creatinine, hemoglobin, corrected calcium, phosphorus, PTH, albumin, nPCR, ferritin, dialysis adequacy, and duration of dialysis (p > 0.05).

Dialysis adequacy and duration were the 2 most important and statistically significant factors associated with increased levels of lead in our study population with p value < 0.05. Blood urea level was also associated with high blood lead level with p value < 0.01. However, blood lead levels were not significantly associated with age, hemoglobin levels, phosphorus, CRP, nPCR, and serum ferritin.

An association with higher blood lead levels and higher levels of PTH was found. However, it was not found to be statistically significant.

Table 1 Demographic data and original kidney disease for all study population (*N*=50)

	Min.	Max.	Mean
Age	21.00	65.00	45.6
		N	%
Gender	Female	28	56%
	Male	22	44%
		N	%
Causes of renal failure	Diabetes (DM)	16	32%
	Hypertension (HTN)	23	46%
	Unknown	3	6%
	Analgesic abuse	8	16%

Demographic data

Demographic data are shown in Tables 3 and 4 and Fig. 1.

Multi-regression analysis: A stepwise multi-regression analysis showing that blood lead levels together with lower Kt/V are the most sensitive predictors for pruritus (F-ratio = 6.2, P < 0.01).

Dependent variable: pruritus

Item	Regression coefficient	*T*	*p*	Significance.	*F*-ratio.	*P*	Significance
(Constant)	1.624	1.148	0.259				
Ferritin	0	1.928	0.062	NS			
Lead level	0.038	5.963	0	HS			
Kt/v	− 0.261	− 3.012	0.005	HS			
					6.396	0	HS

Cutoff point	AUC	Sensitivity	Specificity	+PV80%	−PV
> 11 *	0.811	72.50	80.00	93.5	42.1

The cutoff point of lead level for predicting pruritus in our study was 11 μg/dl with specificity and sensitivity 72.5%.

Discussion

Uremic pruritus or in other terms “chronic kidney disease-associated pruritus” (CKD-aP) remains a frequently bothersome symptom in patients with advanced CKD or end-stage renal disease. Our still incomplete knowledge of its underlying pathophysiological mechanisms result in a lack of effective treatment modalities [15]. The aim of our study was to find a possible correlation between blood lead level and the occurrence of uremic pruritus, in addition to a possible correlation with the severity of pruritus.

Table 2 A comparison between 2 groups (with and without uremic pruritus) as regards laboratory data where NS = non-significant, SS = statistically significant, and HS = highly significant

	Group 1	Group 2	*Z* test	*P* value	SS
Creatinine (mg/dl)	Median = 6.9	Median = 6.9	− 0.195	0.846	NS
Urea (mg/dl)	103.75	103	− 0.303	0.762	NS
Hemoglobin (g/dl)	10.25	9.7	− 1.834	0.067	NS
TLC	8.5	6.25	− 1.232	0.218	NS
Corrected calcium (mg/dl)	9.8	9.7	− 0.757	0.449	NS
PO4 (mg/dl)	3.45	3.75	− 1.021	0.307	NS
PTH (ng/l)	215	159.5	− 1.482	0.138	NS
Serum albumin (g/dl)	3.75	3.05	− 1.927	0.054	NS
Duration of dialysis (years)	4.5	5	− 0.356	0.722	NS
CRP	3	6	− 1.322	0.186	NS
nPCR mg/g/day	1	0.75	− 1.327	0.185	NS
Ferritin (ng/ml)	247.5	563.5	− 2.195	0.028	S
Blood lead level (μg/dl)	7.5	18	− 3.023	0.003	HS
Kt/v (Daugirdes)	1.28	1	− 2.007	0.045	S

A study by Palaneeswari et al. in 2012 concluded that blood lead levels were higher in hemodialysis patients than in the normal subjects, with a p value of 0.000 [11]. Furthermore, Chen et al., who studied Chinese stable chronic renal failure patients, hemodialysis patients, post-transplant patients, and subjects with normal renal functions, found that lead levels were elevated in the dialysis population [16].

It was evident in our study that patients who complained of pruritus had a higher blood lead level (mean lead level 17 μg/dl) than those who did not (mean lead level 8 μg/dl), with p value < 0.005). Similarly, Weng et al., in a study involving over 100 patients with uremic pruritus, showed that higher blood lead levels were significantly associated with uremic pruritus with a cutoff point of blood lead level of 12.77 μg/dl [13]. Our cutoff level for predicting pruritus in this study was above 11 μg/dl. However, we excluded from our study patients who would have had occupational lead exposure. Those patients were not excluded from the

Table 3 Correlation between patients with different degrees of pruritus and serum lead level for data using Kruskal-Wallis test

	Mild	Moderate	Severe	*p* value	Significance
Number	**10**	**20**	**10**		
Age	Median = 62.5	Median = 58.5	57	0.453	NS
Creatinine (mg/dl)	6.75	6.35	7.05	0.223	NS
Urea (mg/dl)	96.75	102.25	137.5	0.011	S
Hemoglobin (g/dl)	9.75	9.9	9.45	0.386	NS
TLC	5.25	6.25	8.5	0.476	NS
Corrected calcium (mg/dl)	9.7	9.65	9.75	0.977	NS
Phosphorus (mg /dl)	3.95	3.75	3.5	0.567	NS
PTH	159	154.5	164	0.43	NS
Albumin (g/dl)	3	3.05	3.35	0.435	NS
CRP	3.5	6	4.5	0.533	NS
nPCR (mg/g/day)	0.8	0.75	0.95	0.874	NS
Ferritin (ng/ml)	440	787.5	165.9	0.12	NS
Blood lead level (μg/dl)	10.5	14.5	26	0.005	HS
Kt/v (Daugirdes)	0.8	0,86	2	0.207	NS
Duration of dialysis (years)	4.5	5	6.5	0.144	NS

Table 4 The relation between blood lead level and other variables in cases, showing factors associated with high blood lead levels

	r (correlation coefficient)	*P* value	Statistical significance
Age	− 0.076	0.647	NS
Creatinine (mg/dl)	0.109	0.502	NS
Urea (mg/dl)	0.437	0.005	HS
Hb (g/dl)	− 0.264	0.009	NS
TLC	0.139	0.391	NS
Corrected calcium (mg/dl)	− 0.05	0.76	NS
Phosphorus (mg/dl)	− 0.108	0.507	NS
PTH (ng/l)	0.189	0.244	NS
Albumin (g/dl)	0.123	0.451	NS
CRP	− 0.117	0.471	NS
nPCR (mg/g/day)	− 0.017	0.916	NS
Ferritin (ng/ml)	− 0.089	0.584	NS
Kt/v (Daugirdes)	0.328	0.039	SS
Duration of dialysis (years)	0.38	0.016	SS

before mentioned study by Weng et al. which could contribute to the fact that our cutoff value for lead levels was lower.

In the current study, there was a significant difference in Kt/V between patients with no uremic pruritus and patients with uremic pruritus. It was apparent that patients with uremic pruritus had lower Kt/V values than those without, demonstrating that efficient and adequate dialysis might be associated with better clearance of pruritogens. These findings are in agreement with a study in 2013 which concluded that hemodialysis with the target of Kt/V ≥ 1.5 and the use of high-flux dialyzer may reduce the intensity of pruritus in patients on chronic hemodialysis [17]. Urea levels,

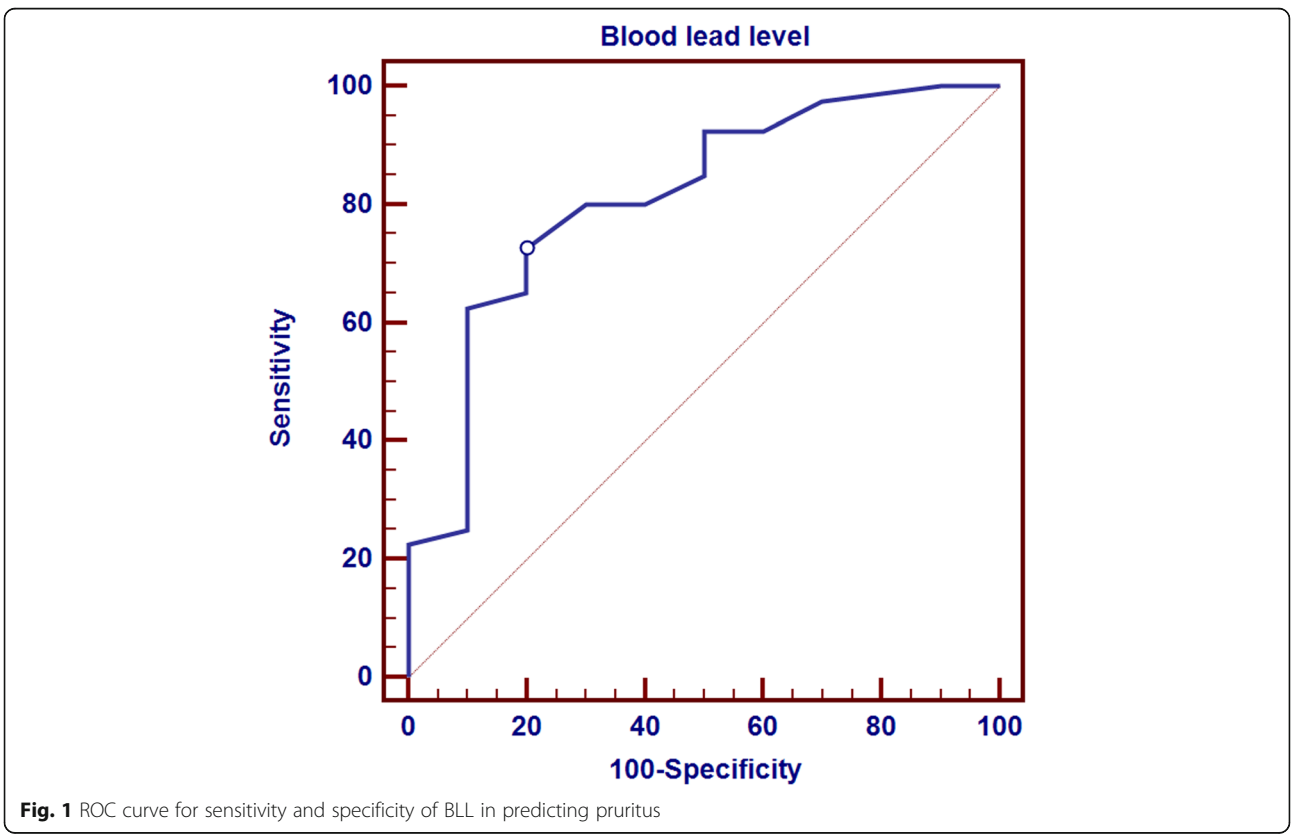

Fig. 1 ROC curve for sensitivity and specificity of BLL in predicting pruritus

however, showed no significant difference between group 1 and group 2 in our study, which could be related to the fact that several other factors (other than urea level pre-dialysis) contribute to dialysis adequacy by Kt/V formula, including volume of ultrafiltration and post-dialysis urea.

A study by Zucker et al. which included over 219 dialysis patients concluded that there was no relation between the occurrence of pruritus and demographic or medical parameters of the patients (including dialysis efficacy as expressed by Kt/V). In his study, however, patients used high flux dialyzers [18]. Similarly, in our study when comparing Kt/V for different levels of pruritus severity, dialysis adequacy seems to be higher in those with more severe pruritus by VAS score. This could be due to the fact that those patients with severe pruritus had higher pre-dialysis urea than those with milder symptoms and longer duration on hemodialysis which could be the contributing factor in the severity of their symptoms and not related to dialysis adequacy.

It was also observed in the current study that there are higher levels of ferritin among patients with pruritus in comparison to those without. Ferritin is a marker of systemic inflammation, and together with CRP, it was suggested in several studies that their levels can be higher in patients with pruritus [19]. Although CRP levels were higher in group 2 with pruritus than in group 1 without pruritus, this relation was not statistically significant. Lead exposure is thought to be associated with systemic inflammation, a study reported that serum CRP levels showed a fourfold increase in the lead-exposed occupational workers compared with the control group [20].

In this study, there was no association between anemia and n PCR and the occurrence of pruritus. Weng et al. reached the same conclusion in their study [13]. However, in our study, it was found that blood lead levels were negatively associated with hemoglobin and nPCR. Lead exposure can be involved in the pathogenesis of anemia. Chronic lead exposure causes damage to erythrocytes by lipid peroxidation and may interfere with iron absorption in the gastrointestinal tract and impair hemoglobin synthesis [21].

Patients with elevated PTH levels above 300 ng/dl, calcium over 10 mg/dl, and phosphorus over 5 mg/dl, were excluded from the study. The reasoning behind this was an attempt to neutralize the effects of hyperparathyroidism as an established cause of pruritus in patients on dialysis. This was evident when comparing control to cases of pruritus as PTH levels were found to be non-significant.

Moreover, we have found that the duration of dialysis and Kt/V were the two factors that are associated with increased BLLs. The elevated BLL in HD patients may be related to the incomplete removal of lead during HD. Therefore, environmental exposure to lead, even at low levels, may increase the BLL in these patients. These results are in agreement with other randomized studies on ESRD patients and blood lead levels [21, 22]. However, a study on aluminum and lead in ESRD showed that appropriate dialysis adequacy had no effect on serum metal levels before and after dialysis [22]. Another study in 2011 stated that patients with high blood lead levels have higher Kt/V and urea values that can be attributed to the higher blood flow rate and dialysate flow rate. However, higher Kt/V was not associated with higher blood lead levels in these patients after adjusting the related variables [23].

Weng et al. demonstrated that there was no difference in VAS score in patients with BLL < 12.77 μg/dl and BLL ≥ 12.77 μg/dl, respectively [13]. Higher blood lead levels were found in this study in patients who exhibited severe pruritus using VAS score than those who had mild and moderate pruritus which was found to be statistically significant and associated also with higher urea levels. This suggests that the level of lead in blood might affect the severity of itching in dialysis patients and could be a subject for further research on this point.

Conclusion

Uremic pruritus is a multi-factorial phenomenon; our study showed that blood lead levels in HD patients might increase the intensity and have an additive role in the pathogenesis of pruritus in dialysis patients. Hence, blood lead level is positively correlated with uremic pruritus with a cutoff lead level of 11 μg/dl for predicting pruritus. Further studies are needed to relate lead level to the severity of pruritus and demonstrate the effect of different dialysis techniques in improving blood lead levels and severity of pruritus.

Abbreviations

ERSD: End-stage renal disease; HD: Hemodialysis; PO4: Phosphorus; Ca: Calcium; VAS: Visual analog scale; BLL: Blood lead levels; PTH: Parathyroid hormone; Hb: Hemoglobin; nPCR : Normalized protein catabolism ratio; TLC: Total leucocytic count; HS : Highly significant; NS: Non significant

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Authors' contributions

All authors discussed the results and contributed in the final manuscript. Dr.S.S conceived the idea, Dr. R A collected the data, and Dr, LK analyzed data and wrote the paper. The authors read and approved the final manuscript.

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Availability of data and materials

The data sets used during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval and consent to participate was obtained from Ain Shams University Faculty of Medicine, reference number FWA 000017585, December 2018. Written consent to participate in this study was taken from all study participants.

Consent for publication

Consent for publication was taken from all participants.

Competing interests

The authors declare that they have no competing interests.

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