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Prevalence, Risk Factors And Relationship Of Pruritus With Blood Lead Level In Chronic Kidney Disease On Maintenance Hemodialysis

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ABSTRACT

Background: one of the most nearly daily compromising symptoms in hemodialysis patients is skin itching. Blood lead level (BLLs) may have a risk factor that increase the intensity of hemodialysis pruritus .

Objective: To evaluate the prevalence of pruritus and its relationship with blood lead level in renal patients maintained on hemodialysis .

Patients and Method: Cross -sectional Study carried on100 patients with End stage renal disease (ESRD) divided into Group I; low BLLs (<15 µg/dl) included 56 patients, Group II; High normal BLLs (15 ≤ BLL< 25 µg/dl) included 32 patients and Group III; High BLLs (≥ 25 µg/dl) included 12 patients. All subjects were evaluated for kidney and liver function, electrolytes, CBC, estimation of GFR by MDRD equation, and Lead level in serum and dialysis water.

Results: we found in this study that prevalence of pruritus was (19%), BLLs have a high statistically significant positive relation to HD duration (P<0.001) & I-PTH(P<0.001) & pruritus (P< 0.001) & visual analogue scale (VAS) (P<0.044) and high significant negative relation to serum albumin (P< 0.015) & hemoglobin(P<0.001). Also, Serum Lead (µg/dL) is an independent predictor for incidence of uremic pruritus [odds ratio (OR) =1.207; 95% by Multiple logistic regression analysis

Conclusions: pruritus prevalence was (19%), blood lead level is highly related to pruritus and independent risk factor with HD duration for early onset and progression of itching in chronic haemodialysis patients. So we recommend serum lead investigation in these patients for early detection and reduction of its dermatological and psychological morbidity.

Keywords: blood lead level, Hemodialysis, pruritus, Zagazig University, Egypt

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INTRODUCTION

Uremic pruritus (UP) remains one of the most tormenting, frequent and potentially disabling problem in CKD patients ***Mettang et al. [1].***

Social relation and sleep habit may have affected by pruritus in patients mentained on hemodialysis if leaved without management for long time, which can lead to impaired quality of life & depression development and higher mortality rates. ***Pisoni et al. [2]; Chen et al. [3].***

The kidneys constitute the main route of lead excretion and one of the soft tissues with the highest concentrations of lead ***Fischbein and Hu. [4].***

Aim of the work

To evaluate the prevalence and relationship between pruritus and blood lead level in chronic kidney disease (CKD) on hemodialysis.

SUBJECTS AND METHODS

In Hemodialysis Unit of Al-Agoura hospital in Giza we carried out Cross-sectional study on 100 patients on chronic hemodialysis during the period from November 2018 to the end of April 2019, in Egypt. Patients of this study were divided according to blood lead level into **group I;** Including 56 HD patients with low BLLs (<15 µg/dl), (35 males and 21 females) 4 of them with uremic pruritus, with median age 50. and **Group II;** Including 32 HD patients with high normal BLLs (15 ≤ BLL< 25 µg/dl), (15 males and 17 females) 8 of them with uremic pruritus, with median age 49. and **Group III** Including 12 HD patients with high BLLs (≥ 25 µg/dl), (8 males and 4 females) 7 patients of them with uremic pruritus with median age 44.

Inclusion criteria: Age between 18 to 60 years old, all patients on dialysis had been dry weight stable for at least 2 months before the study and had been achieved normotensive edema free state, with a kt/v of more than 1.2. All hemodialysis treatments were performed with a polysulfone dialyzer (Fresenius, Bad Homburg, Germany), three sessions per week, 4 hs for each for at least 6 months and ultrapure water for dialysis was prepared in the Gambro system WRO ROHH (Gambro, Lund AB, Land, Sweden). **Exclusion criteria including**: Age < 18 or >60 years, patients refusing to enter the study, any associated primary skin lesion, malignancies, infectious diseases, pregnancy, Patients with cholestasis and immune diseases and those who had been admitted or received surgery within 3 months of the study.

consent had taken from all persons shared in this study after complete explanation of the procedure steps and nature of the research.

All persons included in this study were subjected to the following:

- complete clinical history and physical examination, lab investigation: like complete blood count, serum Na, K, Ca Ph. and I-PTH, liver and kidney function, blood and dialysis water lead level measured by Atomic Absorption Spectrometry, eGFR calculated by MDRD4 equation,
- All blood samples withdrawals were performed by dialysis unit nursing staff on day of dialysis session before the intervention when they were fasting.

Data management: Collected data revised, verified, edited on P.C, and then analyzed statistical using SPSS statistical package for the social science under windows version 20.

The following statistical tests were used: Qualitative variables was descripting by frequency and percentage. Description of quantitative variables in the form of mean and standard deviation, (mean ± SD), Median and inter-quartile range (IQR). Chi-square (x2) test was used for comparison of qualitative variables with each other. Comparison between quantitative variables was carried out using Student t-test of two independent samples. For comparison of more than two quantitative groups one-way ANOVA F- test and Kruskal-Wallis test was used for categorical data. Logistic regression analysis is used when we want to predict the value of a variable based on the value of two or more other variables. Significance level (p) was expressed as following: P- Value >0.05 is not significant. P - Value < 0.05 is significant. P- Value < 0.001 is highly significant.

RESULTS

Table (1): demographo- Clinical data of the studied population and its Comparison among different groups.

Demographic data	Low normal BLL N=56	High normal BLL N=32	High BLL N=12	Test	P-value (Sig.)
Male	35 (62.5%)	15 (46.9%)	8 (66.7%)	2.461 [C]	0.292 (NS)
Female	21 (37.5%)	17 (53.1%)	4 (33.3%)		
Age	50 (43.25 – 54)	49 (48 – 55)	44 (40 – 53.75)	4.307 [K]	0.116 (NS)
HD duration	12 (8.5 – 36)	24 (13.5 – 48)	66 (48 – 81)	23.119 [K]	<0.001 (HS)
HTN	21 (37.5%)	10 (31.3%)	4 (33.3%)	0.366 [C]	(0.833 (NS)
DM	12 (21.4%)	7 (21.9%)	5 (41.7%)	2.336 [C]	0.311 (NS)
Smoking	20 (35.7%)	9 (28.1%)	5 (41.7%)	0.880 [C]	0.644 (NS)
Pruritus	4 (7.1%)	8 (25%)	7 (58.3%)	17.928 [C]	<0.001 (HS)

[K] Kruskal Wallis test. [C] Chi-square test p< 0.05 is significant

Table (2): kidney functions& electrolytes data of the studied population and its Comparison among different groups according to BLLs.

ALT; alanine transferase AST; aspartate transferase ALP; alkaline phosphatase

Lab. Variable	Low normal BLL N=56	High normal BLL N=32	High BLL N=12	Test	P-value
Blood urea(mg/dl)	110 (104.25 – 117.25)	115 (103.5 – 135)	108 (103 – 113)	3.781 [K]	0.151 (NS)
S. Creatinine(mg/dl)	4.45 (4.03 – 5.08)	4.5 (4 – 4.98)	4.9 (4.3 – 5.22)	1.064 [K]	0.587 (NS)
***S. Sodium* (meq/L)**	134 (132.25 – 136.75)	133 (130.25 – 136)	133.5 (132 – 138)	1.175 [K]	0.556 (NS)
***S. potassium* (meql/L)**	4 (3.83 – 4.5)	4 (3.8 – 4.2)	4 (3.8 – 4.3)	1.761 [K]	0.415 (NS)
Ionized CA(mmol/L)	4.9 (4.08 – 5)	4.5 (4 – 4.95)	4.55 (4.35 – 4.88)	2.686 [K]	0.261 (NS)
Phosphorus(mmol/L)	4.2 (4 – 4.9)	4.55 (4 – 4.9)	4.5 (4.05 – 5)	1.679 [K]	0.432 (NS)

Hb; hemoglobin I-PTH; intact

Table (3): laboratory data of the studied population and its Comparison among different groups according to BLLs.

PTH: parathormone hormone TLC; total leukocytes count

	Low normal BLL N=56	High normal BLL N=32	High BLL N=12	Test	P-value
***ALT* (IU/L)**	30.9 (28 – 34)	37 (33.25 – 43.5)	38.5 (30 – 47.75)	2.011 [K]	0.366 (NS)
***AST* (IU/L**	31.1 (28 – 34)	40 (33.25 – 43.5)	38.5 (30 – 47.75)	2.011 [K]	0.366 (NS)
***ALP* (IU/L)**	70 (65 – 77.75)	76.5 (65 – 88)	69.5 (66 – 83.5)	2.813 [K]	0.245 (NS)
Albumin (mg/dl)	4.2 (3.9 – 4.5)	4 (3.8 – 4.2)	3.7 (3.25 – 3.9)	8.400 [K]	0.015 (S)
T.bilirubin *(mg/dl)*	1 (1 – 1.1)	1.05 (1 – 1.1)	1 (1 – 1)	4.682 [K]	0.096 (NS)
D.bilirubin *(mg/dl)*	0.1 (0.1 – 0.175)	0.1 (0.1 – 0.2)	0.1 (0.1 – 0.275)	2.566 [K]	0.277 (NS)
Hb (gm/dL)	11 (10.3 – 11.9)	10.5 (10 – 11)	10.1 (9.9 – 11)	13.135 [K]	0.001 (S)
TLC (*1000/µL)	7.64 (6.1 – 8.98)	7.76 (6 – 9)	7.95 (5.25 – 8.88)	0.273 [K]	0.873 (NS)
I-PTH (pg/mL)	103 (91.25 – 119.75)	116.5 (109.25 – 132)	154.5 (128.5 – 170.25)	29.519 [K]	<0.001 (HS)
Serum lead (µg/dL)	9.5 (8.25 – 12)	20.5 (15.75 – 23)	29 (27.25 – 30)	78.031 [K]	<0.001 (HS)

Table (4): pruritus data Comparison among the studied groups.

Variable	*Pruritus data*	Low normal BLL N=4	High normal BLL N=8	High BLL N=7	Test	P-value (Sig.)
Onset	*Acute*	2 (50%)	7 (87.5%)	3 (42.8%)	6.192 [C]	0.185 (NS)
	Subacute	2 (50%)	0 (0%)	2 (28.6%)		
	Gradual	0 (0%)	1 (12.5%)	2 (28.6%)		
Course	*Progressive*	2 (50%)	7 (87.5%)	4 (57.2%)	2.388 [C]	0.303 (NS)
	Stationary	2 (50%)	1 (12.5%)	3 (42.8%)		
Duration	*Recent*	2 (50%)	8 (100%)	5 (71.4%)	4.388 [C]	0.11 (NS)
	Chronic	2 (50%)	0 (0%)	2 (28.6%)		
Location	*Trunk*	4 (100%)	8 (100%)	7 (100%)	-	-
	Upper limb	2 (50%)	0 (0%)	2 (28.6%)	4.388 [C]	0.111 (NS)
	Lower limb	2 (50%)	3 (37.5%)	4 (57.2%)	0.592 [C]	0.744 (NS)
Drug history	*Negative*	0 (0%)	1 (12.5%)	1 (14.3%)	0.609 [C]	0.738 (NS)
	Positive	4 (100%)	7 (87.5%)	6 (85.7%)		
VAS	*Mean ± SD*	4.5 ± 0.58	6.63 ± 2.50	7.57 ± 0.98	3.819 [A]	0.044 (S)

[A] One-way Anova test. VAS - visual analog scale

Table (5): Univariate logistic regression analysis between pruritus and clinical variables.

Variable	Unadjusted OR	95% Confidence Interval for OR		-value Sig.)
		Lower Bound	Upper Bound	
Male gender	1.304	0.465	3.656	0.613
Age (years)	1.034	0.961	1.114	0.368
Hemodialysis (months)	1.054	1.029	1.080	<0.001
HTN	0.828	0.284	2.410	0.729
DM	1.615	0.538	4.853	0.393
Smoking	1.538	0.553	4.280	0.409
B.Urea (mg/dL)	1.055	1.024	1.087	<0.001
S.Creatinine (mg/dL)	1.552	0.720	3.345	0.262
S.Sodium (mmol/L)	1.152	0.968	1.371	0.111
S.Potassium (mmol/L)	1.136	0.303	4.265	0.850
Ionized Ca (mg/dL)	0.388	0.136	1.105	0.076
Phosphorus (mg/dL)	1.638	0.690	3.890	0.263
AST (IU/L)	1.048	0.992	1.108	0.094
ALT (IU/L)	1.035	0.981	1.092	0.209
ALP (IU/L)	1.001	0.963	1.041	0.960
Albumin (gm/dL)	0.183	0.046	0.735	0.017
T. Bilirubin (mg/dL)	142.595	0.667	30483.610	0.070
D. Bilirubin (mg/dL)	372.156	0.113	1222395.273	0.152
Hb (gm/dL)	0.730	0.385	1.385	0.335
TLC (*1000/µL)	1.208	0.883	1.653	0.237
I-PTH (pg/mL)	0.001	1.041	1.017	0.001
Serum Lead (µg/dL)	1.207	1.107	1.315	<0.001

Table (6): Multivariate logistic regression analysis between pruritus and clinical variables.

Variable	Adjusted OR	95% Confidence Interval for OR	-value (Sig.)

		Lower Bound	Upper Bound	
HD duration (months)	1.052	1.016	1.089	0.004 (S)
Urea (mg/dL)	1.124	0.986	1.281	0.081
Albumin (gm/dL)	0.354	0.048	2.625	0.310
I-PTH (pg/mL)	1.019	0.986	1.053	0.269
Serum Lead (µg/dL)	1.070	1.030	1.113	0.001 (HS)

Table (7): Comparison between pruritus grades and HD duration and laboratory data.

		Mild&mod. Pruritus N=8	Sever pruritus N=11	T test	P value
HD duration	*Mean ± SD*	60.0 ± 9.1	58.9 ± 31.0	0.096 [c]	0.925 (NS)
I-PTH(pg/ml)	*Mean ± SD*	116.1 ± 27.8	146.6 ± 31.2	-2.201[c]	0.042 (S)
S. lead (mg/dl)	*Mean ± SD*	17.5 ± 5.0	26.7 ± 4.0	-4.479 [c]	<0.001 (HS)

Table (1) showed that there were high statistical significant differences between different groups as regarding HD duration and pruritus. while there were no statistical significance differences as regarding age and gender, DM, HTN and smoking.

Table (2) showed that there were no statistical significant differences between different groups as regarding blood urea, S. creatinine, S. Na, S. K, I. Ca and phosphorus.

Table (3) showed that there were statistical significant differences between different groups as regarding S. albumin, hemoglobin and high statistical significant differences between different groups as regarding I-PTH and S. lead level. while there were no statistical significance differences as regarding ALT, AST, ALP and TLC.

Table (4) showed that HD pruritus mostly acute onset progressive course, recent, affecting trunk, lower and upper limbs respectively and high statistical significant differences between different groups as regarding VAS.

Table (5): univariate logistic regression analysis between pruritus and many lab and clinical variables showed that there was high significant effect of dialysis duration, blood urea, S. albumin, I-PTH and serum Lead on incidence of pruritus

Table (6): Multiple logistic regression analysis between pruritus and many clinical variables showed that there was high significant effect of Serum Lead and HD duration on uremic pruritus. where Serum Lead (≥14µg/dL µg/dL) is a cut of value.

Table (7): grades of pruritus have a statistical significant difference with serum lead and serum I- PTH, but not with hemodialysis duration where Serum Lead (≥14µg/dL µg/dL) is a cut of value.

DISCUSSION

Xerosis and hyperpigmentation may be existed in sever chronic renal failure patients, also uremic roseola, calcinosis cutis, acquired perforating dermatosis, bullous dermatosis of hemodialysis, and pruritus **Levillard and Kambil. [5].** Although late stages of chronic kidney diseases commonly complaining of annoying uremic pruritus (UP) as same as hemodialysis and peritoneal dialysis patients, no one can clarify its pathogenesis. **Patel et al. [6]**. Level of blood level has been observed to be changed in patients maintained on hemodialysis it is contributing to nutrition and inflammation state. **Szeto et al. [7]**. BLLs changes may have additive role or increasing effect on pruritus intensity caused by other risk factors **Weng et al. [8].** So this push us to evaluate the possible relationship between BLL and UP in chronic HD patients.

Prevalence of skin itching in dialytic patients found to be (19%) 19 out of 100 in our study, it is low in comparable to **Davison et al. [9]** who conclude that 46% of hemodialysis patients was affected by pruritus. this is due to efficient dialysis, good education of the patients and small size of study.

Multiple logistic regression analysis of our results showed that high significant effect of serum Lead (p<0.001) and HD duration (p<0.004) on uremic pruritus and they were independent risk factors for UP. In agreement with our study **Weng et al., [8]** study included 866 patients on regular dialysis, Multivariate logistic regression demonstrated that HD duration, ferritin level and BLL were associated with UP.

Also we found that, blood Lead ≥ 14µg/dl is a cut of value predictor for pruritus in HD patients with sensitivity 89.5%, specificity of 64.2% and accuracy of 69%.

In present study univariate logistic regression analysis showed that there was high significant effect of I-PTH and S.albumin on incidence of pruritus, also there were high statistical significant differences between different groups as regarding I-PTH(p <0.001) and S. albumin (p <0.015). which was concordant with **Weng et al. [8]** study who stated that the difference among the groups was highly significant regarding serum PTH (p <0.001), this was Contradictory with **Ko et al. [10] and Lin et al. [11]** studies that found a non-significant difference regarding serum albumin (p<0.930) in three groups of hemodialysis patients with different BLL, these is due to long term follow up in the previous study 5-Year for **Ko et al. [10]** study and 18 months for **Lin et al. [11]** study.

According to Pruritus criteria in our study, there was a non-statistically significant difference among the studied groups, this is may be due to short time and small size of the study, Contradictory with us, **Dyachenko et al. [12]** studied Hemodialysis related pruritus and associated cutaneous manifestations and found that there was a statistically significant difference regarding pruritus onset, course, duration and location.

Regarding the pruritus data, the mean value of Visual Analog Scale (VAS) was 6.53 ± 2.04 with a statistical significant difference (P value <0.044) this was concordant with **Chiu et al. [13]** study which included 321 HD patients for >3 months HD duration followed up using A visual analogue scale (VAS) to measure the severity of itching.

According to Risk factors, there was a non-statistical significant difference regarding hypertension and diabetes (p < 0.833, P< 0.311) respectively. This was concordant with **Min et al. [14]** study severity of pruritus in 1773 adult hemodialysis patients and found that there was a non-statistical significant difference regarding hypertension and diabetes (p value 0.7235 and 0.4052 respectively).

Blood Hb and serum albumin founded to be significant difference among the studied groups, it is similar to **Yang et al., [15]** who said that up grading BLL lead to acute tubular injury complicated by albuminuria and increase urine NAG then chronic interstitial nephritis leading to anemia

In our study, there was a statistical non-significant difference among the studied groups regarding the renal function tests and serum electrolytes this was harmony with **Mei-Ju et al. [16]** which conducted a 5-year prospective cohort study on patients with maintenance hemodialysis and found non-significant difference regarding the renal functions and pruritus intensity. While **Harari et al. [17]** Mack a prospective cohort study on 6,790 indeveduals and declare that decreased kidney functions (decrease eGFR, increase urea and creatinine) in follow up of patients with high blood lead level, also

In our study, there was a statistical non-significant difference in different studied groups regarding some liver function tests (aspartate aminotransferase and alanine aminotransferase) (P<0.366 and P< 0.157)

respectively. In agreement with our study, **Ko et al. [10]** found that there was statistical non-significant difference regarding aspartate aminotransferase and alanine aminotransferase (p<1.0 and p< 0.07 respectively).

CONCLUSION AND RECOMMENDATION

Blood Serum Lead is independent predictor of pruritus in patients with End stage renal disease maintained on Hemodialysis. So Larger sample size studies and longer follow up periods in multicenters are recommended to consolidate our finding.

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