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ORIGINAL RESEARCH

Blood lead level is a positive predictor of uremic pruritus in patients undergoing hemodialysis

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Abstract: Although uremic pruritus (UP) is a common and annoying symptom for end-stage renal disease patients on hemodialysis (HD) and peritoneal dialysis, its pathogenesis is poorly understood. However, systemic inflammation is one of the possible pathogenesis of UP, and blood lead level (BLL) has been noted to be associated with inflammation and nutritional status in long-term HD patients. There might be an interaction or association, therefore, between BLL and UP through systemic inflammation. We analyzed cross-sectional data among 866 participants. All of the 866 patients in this study were stratified into groups with low-normal (<10 μg/dL), high-normal (10–20 μg/dL), and abnormal BLLs (>20 μg/dL). The associations between UP and BLL and the clinical data were analyzed. Multivariate logistic regression demonstrated that HD duration, non-anuria, log ferritin, serum low-density lipoprotein, log BLL, high-normal BLL, and high BLL were associated with UP. In conclusion, BLL was positively associated with UP.

Keywords: blood lead levels, uremic pruritus, hemodialysis

Introduction

Uremic pruritus (UP) is a common and annoying symptom for end-stage renal disease (ESRD) patients on hemodialysis (HD) and peritoneal dialysis (PD). The prevalence of UP varies from 22% to 57%[1–3] with a prevalence in Taiwan of 28.6%–62.6% in ESRD patients on HD or PD.[4–6] Unfortunately, the pathogenesis of UP remains poorly understood. Proposed hypotheses include systemic inflammation,[7] imbalance between the expression of opioid receptors,[8] and other risk factors. Blood lead level (BLL) has been reportedly associated with inflammation and nutritional status in long-term HD patients with diabetes and might contribute to 1-year mortality in these patients.[9] All-cause, cardiovascular, and infection-related 18-month mortality in patients on maintenance HD were positively associated with high BLL.[10] Taking these findings into consideration, there might be an interaction or association between BLL and UP through systemic inflammation. The purpose of this study, therefore, was to find the possible association between BLL and UP.

Materials and methods

Methods

Chang Gung Memorial Hospital's Institutional Review Board (IRB) Committee approved the study protocol (Code of IRB: 98–1937B). The methods in the study were performed in accordance with the approved guidelines. Because this was a cross-sectional retrospective-designed study, informed consent was not required, and this was approved by our IRB committee. We collected all primary data in accordance with

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the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Data was de-identified to ensure patient confidentiality.

Patients

All patients were enrolled from three HD centers of Chang Gung Memorial Hospital, Lin-Kou Medical Center, including both the Taipei and Taoyuan branches. Maintenance hemodialysis (MHD) patients who were equal to or older than 18 years old and had undergone HD for at least 6 months were recruited in this study. Exclusion criteria were patients with malignancies, infectious diseases, and those who had been admitted or received surgery within 3 months of the study. Most patients received 4 hours of HD per session and HD 3 times a week. Dialysate with standard ionic composition and bicarbonate-based buffer was used for all patients. Cardiovascular diseases were recorded in these patients. Smoking behavior was also noted in this study. Diagnosis of pruritus was as follows: pruritus appearing after HD with/without antipruritics as visualized by trained dermatologists or nephrologists. The severity of pruritus was measured by visual analog scale (VAS), which consisted of a 10-cm horizontal line with 0 point (no pruritus) to 10 points (maximum intensity of pruritus).

Measurement of BLL

We measure BLLs at the end of the run-in phase using a previously described method.[11,12] BLLs were measured by electrothermal atomic-absorption spectrometry (SpectrAA-200Z; Agilent Technologies, www.agilent.com) with Zeeman background correction and an L'vov platform.

Definition of low-normal, high-normal, and high blood lead levels

All of the studied patients were stratified into groups with low-normal (<10 μg/dL), high-normal (10–20 μg/dL), and abnormal BLLs (>20 μg/dL).[9]

Laboratory parameters

We drew blood samples from the arterial end of the vascular access immediately after the initial 2-day interval of HD. Nutritional markers were recorded as serum creatinine levels, normalized protein catabolism rate (nPCR), and serum albumin levels. High-sensitivity C-reactive protein levels were used as marker of inflammation. Dialysis adequacy, Kt/V_{urea}, of HD patients was calculated by Daugirdas method. The nPCR of HD patients was calculated by validated equations.[13] The definition of anuria was a daily urine amount <100 mL.

Statistical analysis

Normal distribution was tested by the Kolmogorov–Smirnov test. Mean ± SD/median (interquartile range) was expressed for continuous variables, and numbers or percentages were expressed for categorical variables. The correlation between categorical variables was analyzed by chi-square or Fisher's exact test. Mann–Whitney *U*-test or Student's *t*-test was used to compare two groups. Univariate and multivariate logistic regression analyses were performed to evaluate the variables related to UP. Area under the receiver operating characteristic (AUROC) analysis was used to assess the discrimination. The best Youden index (sensitivity + specificity – 1) was used to calculate the cutoff points. Data were analyzed using SPSS, version 12.0 for Windows 95 (SPSS Inc, Chicago, IL, USA). The level of significance was set at $P<0.05$.

Results

Study population characteristics

The flow chart of HD patient recruitment was demonstrated in Figure 1. Eight hundred and sixty-six patients were included (Table 1). They received an average HD duration of 6.96±5.35 years. Patients with high BLLs had a higher incidence of hepatitis C infection, UP, and hemodiafiltration, and higher HD durations, Kt/V_{urea} Daugirdes, levels of hemoglobin, and intact parathyroid hormone. There were 189 patients with UP. There was a significant difference in BLLs between HD patients with UP and HD patients without UP, (13.9 μg/dL [interquartile range: 10.45, 19.26] vs 9.48 μg/dL [interquartile range: 6.94, 12.76], respectively, $P<0.001$). The severity of UP was evaluated by VAS.[14,15] The median of VAS was 6 (interquartile range: 4, 6.5). The correlation between log Pb and VAS was not significant with $r=0.012$ and $P=0.869$. The median VAS of patients with UP and BLL <10 μg/dL, 20> BLL ≥10 μg/dL, and BLL ≥20 μg/dL were 6.0 (interquartile range: 4, 7), 6.0 (interquartile range: 5, 6), and 6.0 (interquartile range: 4, 7), respectively. There was no difference of VAS between these three groups ($P=0.681$).

Predictors of uremic pruritus

Univariate logistic regression showed that 13 variables were associated with UP (Table 2). Multivariate logistic regression demonstrated that the following were associated with UP: HD duration (odds ratio [OR]: 1.092, 95% confidence interval [CI]: 1.056–1.130, $P<0.001$), non-anuria (OR: 0.557, 95% CI: 0.340–0.979, $P=0.041$), log ferritin (OR: 2.086, 95% CI: 1.388–3.134, $P<0.001$), serum low-density lipoprotein (LDL) (OR: 1.009, 95% CI: 1.003–1.015, $P=0.002$), and log BLL (OR: 29.230, 95% CI: 11.512–574.214, $P<0.001$)

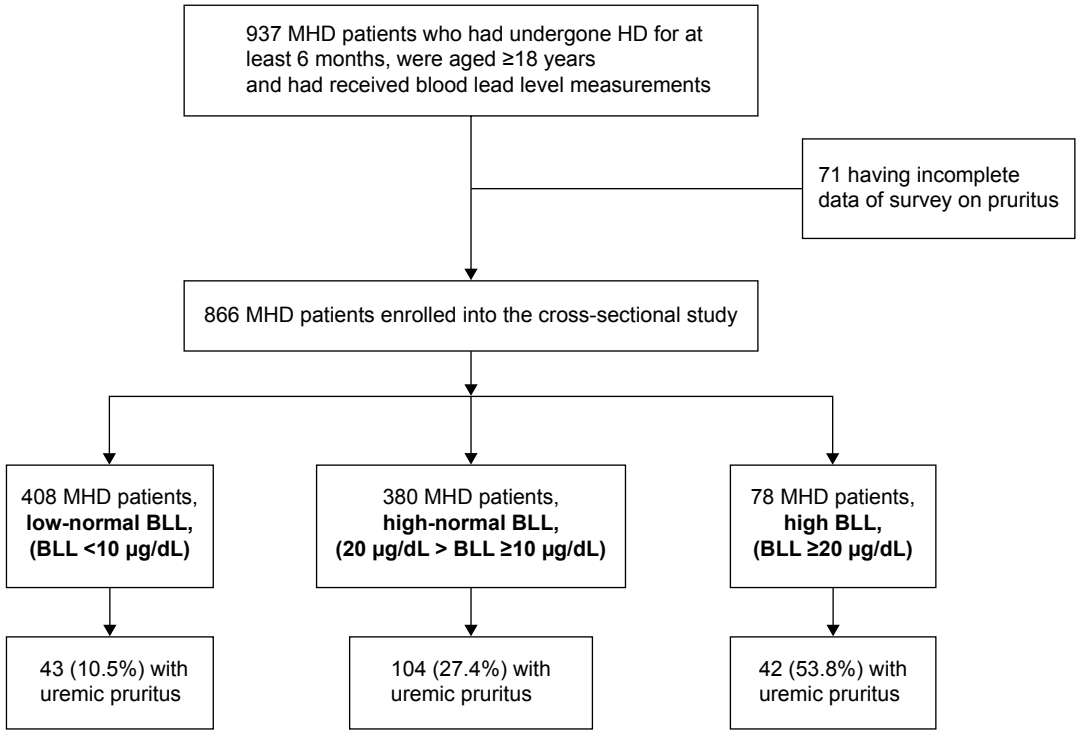

Figure 1 Flow chart of patient recruitment.
Abbreviations: BLL, blood lead level; HD, hemodialysis; MHD, maintenance hemodialysis.

(Table 3). After we divided BLLs into low-normal BLL, high-normal BLL, and high BLL, multivariate logistic regression showed that HD duration (OR: 1.088, 95% CI: 1.051–1.126, $P<0.001$), non-anuria (OR: 0.565, 95% CI: 0.333–0.960, $P=0.035$), log ferritin (OR: 2.153, 95% CI: 1.428–3.248, $P<0.001$), serum LDL (OR: 1.009, 95% CI: 1.003–1.015, $P=0.003$), high-normal BLL (low-normal BLL as reference) (OR: 3.286, 95% CI: 2.174–4.967, $P<0.001$), and high BLL (low-normal BLL as reference) (OR: 8.938, 95% CI: 4.942–16.166, $P<0.001$) were associated with UP (Table 4).

Calibration, discrimination, and correlation for the BLLs

Calibration of BLL was carried out as follows: Hosmer–Lemeshow; $X^2=12.77$, $P=0.12$. The BLLs had good calibration, as estimated by the Hosmer–Lemeshow goodness-of-fit test. The cutoff point calculated by obtaining the best Youden index (0.375) of BLLs to predict UP was 12.77 μg/dL (AUROC =0.792±0.023, 95% CI: 0.74–0.83, $P<0.001$, Figure 2) with a sensitivity of 78%, specificity of 66%, and overall correctness of 71.8%. Multivariate logistic regression showed that BLL ≥12.77 μg/dL (OR: 4.511, 95% CI: 3.128–6.505, $P<0.001$) was one of the predictors of UP (Table 5). The median VAS of patients with UP and BLL <12.77 μg/dL and BLL ≥12.77 μg/dL were 6.0 (interquartile range: 4, 6) and 6.0 (interquartile range: 4, 7), respectively. There was no difference of VAS between these two groups ($P=0.279$).

Discussion

UP has been proposed to be the result of systemic inflammation.[7,16] BLLs have been previously shown to be associated with inflammation and poor nutrition in long-term HD patients.[9] Al Momen demonstrated a case of chronic lead exposure with the symptoms of hyperpigmentation of the skin, severe itching, muscle weakness, and thrombocytosis. After chelation therapy with dimercaptosuccinic acid, complete recovery of hyperpigmentation, itching, and thrombocytosis was noted.[17] Dongre et al showed that in the battery manufacture, workers with lead exposure had high blood pressure, disturbed calcium and phosphorous metabolism, and skin itching.[18] In the surveys of drinking water polluted by lead in Kerou and So-ava, people who consumed lead-polluted water had various symptoms including skin itching.[19,20] Therefore, there was significant correlation between BLL and the occurrence of skin pruritus. There was no significant correlation between Log (Pb) and severity of UP in our study, but we showed that BLL ≥12.77 μg/dL was a cut-off point to predict UP. This may suggest that BLL ≥12.77 μg/dL may be a point to trigger pruritus

Table 1 Characteristics of studied MHD patients and comparison of patients with different blood lead levels

Characteristics	Total (N=866)	Low-normal BLL, BLL <10 μg/dL (n=408)	High-normal BLL, 20 μg/dL > BLL ≥10 μg/dL (n=380)	High BLL, BLL ≥20 μg/dL (n=78)	*P*-value
Demographics					
Age (years)	56.18±13.59	56.22±13.89	55.87±13.26	57.53±13.66	0.72
Male gender (yes)	440 (50.8%)	197 (48.3%)	198 (52.1%)	45 (57.7%)	0.099
Body mass index (kg/m^2)	22.19±3.18	22.21±3.27	22.22±3.13	21.94±3.01	0.64
Smoking (yes)	150 (17.3%)	64 (15.7%)	69 (18.2%)	17 (21.8%)	0.37
Comorbidity					
Diabetes mellitus (yes)	192 (22.2%)	112 (27.5%)	73 (19.2%)	7 (9.0%)	<0.001
Hypertension (yes)	339 (39.1%)	159 (39.0%)	149 (39.2%)	31 (39.7%)	0.89
Previous CVD (yes)	41 (4.7%)	17 (4.2%)	23 (6.1%)	1 (1.3%)	0.92
HBV (yes)	98 (11.3%)	41 (10.0%)	46 (12.1%)	11 (14.1%)	0.22
HCV (yes)	168 (19.4%)	60 (14.7%)	84 (22.1%)	24 (30.8%)	<0.001
Uremic pruritus (yes)	189 (21.8%)	43 (10.5%)	104 (27.4%)	42 (53.8%)	<0.001
Dialysis-related data					
Hemodialysis duration (years)	6.96±5.35	5.74±4.75	7.59±5.39	10.28±6.18	<0.001
Erythropoietin (U/kg/week)	73.62±47.37	79.58±46.34	69.57±47.73	62.27±47.33	<0.001
Fistula as blood access (yes)	689 (79.6%)	321 (78.7%)	303 (79.7%)	65 (83.3%)	0.39
Hemodiafiltration (yes)	187 (21.6%)	61 (15.0%)	94 (24.7%)	32 (41.0%)	<0.001
Kt/V_{urea} Daugirdes	1.79±0.32	1.75±0.30	1.82±0.32	1.90±0.39	<0.001
nPCR (g/kg/day)	1.18±0.26	1.18±0.26	1.19±0.27	1.16±0.27	0.97
Residual daily urine of >100 mL	178 (20.6%)	96 (23.5%)	70 (18.4%)	12 (15.4%)	0.035
Biochemical data					
Hemoglobin (g/dL)	10.51±1.36	10.33±1.31	10.63±1.34	10.88±1.57	<0.001
Albumin (g/dL)	4.06±0.34	4.08±0.33	4.05±0.35	3.98±0.36	0.018
Creatinine (mg/dL)	10.88±2.39	10.88±2.46	10.90±2.29	10.79±2.47	0.88
Ferritin (μg/L)*	305.0 (129.57, 504.45)	359.9 (165.1, 569.8)	272.4 (111.2, 445.5)	283.5 (156.3, 420.4)	0.001
Corrected calcium (mg/dL)	9.94±0.93	9.89±0.9	9.96±0.94	10.06±0.99	0.11
Phosphate (mg/dL)	4.84±1.35	4.84±1.35	4.87±1.37	4.72±1.26	0.76
Intact parathyroid hormone (pg/mL)*	130.1 (52.52, 319.2)	112.4 (41.5, 249.1)	144.2 (55.6, 365.4)	195.8 (82.6, 435.2)	<0.001
hsCRP (mg/L)*	2.95 (1.4, 7.01)	2.87 (1.34, 7.51)	2.98 (1.54, 6.49)	3.36 (1.4, 7.38)	0.6
Cardiovascular risks					
Cholesterol (mg/dL)	171.3±37.66	170.0±36.7	172.7±39.2	170.7±34.5	0.52
Triglyceride (mg/dL)	164.33±115.8	160.6±106.7	163.8±122.3	185.6±127.3	0.15
LDL (mg/dL)	94.83±30.59	93.96±30.63	95.95±30.58	93.91±30.69	0.62
BLL (μg/dL)*	10.39 (7.26, 14.19)	7.12 (5.53, 8.59)	13.02 (11.34, 15.31)	23.03 (21.19, 26.93)	<0.001

Note: *Non-normal distribution data are presented as median (interquartile range). Data throughout the rest of the table are presented as n (%) or mean ± SD.
Abbreviations: BLL, blood lead level; CVD, cardiovascular disease; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; hsCRP, high-sensitivity C-reactive protein; Kt/V_{urea}, dialysis clearance of urea; LDL, low-density lipoprotein; MHD, maintenance hemodialysis; nPCR, normalized protein catabolic rate; VAS, visual analog scale.

symptom, and BLL above this point is not correlated with the severity of UP. And the severity sensation of UP is different in every patient and this may explain that the quantitative measure of pruritus did not correlate with BLLs.

Imbalances in the expression between mu and kappa opioid receptors, which will cause pruritus, have also been proposed as a hypothesis of UP.[21,22] Lead treatment by using rat models has shown that lead alters the development of mu and delta receptors and biological responses to opioids.[23] Other studies have also shown that the dynorphin/kappa opioid system is less affected by lead than the mu and delta systems.[24] Therefore, it is reasonable to postulate that lead can cause UP via the opioid systems.

Animal studies have also demonstrated that chronic exposure to low-dose lead results in reactive oxygen species (ROS) generation.[25] ROS has also been noted to play a role in atopic dermatitis, which is a noncontagious, relapsing inflammatory skin disease characterized by eczema and pruritus.[26] Lead may thus cause UP through the induction of ROS. Exposure to low levels of lead could also induce lipid peroxidation.[27] Yago et al demonstrated that neurotropin significantly suppressed the C3a level and improved the condition of pruritic HD patients. They also found that neurotropin could lower the level of lipid peroxidase in plasma of HD patients.[28] Secondary hyperparathyroidism (SHPT) was also associated with UP.[29,30] Chu et al showed

Table 2 Univariate logistic regression analysis between uremic pruritus and clinical variables

Characteristics	Univariate logistic regression	
Variables	**Odds ratio (95% confidence interval)**	***P*-value**
Age (years)	1.011 (0.994–1.029)	0.188
Male gender	1.218 (0.709–2.093)	0.476
Body mass index (kg/m^2)	1.078 (1.005–1.157)	0.036
Smoking (yes)	1.327 (0.777–2.266)	0.300
Diabetes mellitus (yes)	0.46 (0.29–0.73)	0.001
Hypertension (yes)	1.164 (0.804–1.683)	0.422
Previous CVD (yes)	0.860 (0.338–2.186)	0.752
HBV (yes)	0.56 (0.31–1.01)	0.058
HCV (yes)	1.52 (1.03–2.23)	0.032
Hemodialysis duration (years)	1.105 (1.058–1.155)	<0.001
Fistula as blood access (yes)	1.216 (0.750–1.969)	0.428
Hemodiafiltration (yes)	1.524 (1.05–2.20)	0.026
Kt/V_{urea} (Daugirdes)	2.943 (1.8–4.79)	<0.001
nPCR (g/kg/day)	1.934 (1.06–3.51)	0.03
Non-anuria	0.44 (0.27–0.71)	0.001
Hemoglobin (g/dL)	1.118 (0.957–1.305)	0.160
Serum albumin (g/dL)	0.57 (0.36–0.91)	0.02
Creatinine (mg/dL)	1.087 (0.955–1.238)	0.205
Corrected calcium (mg/dL)	1.18 (0.99–1.40)	0.056
Phosphate (mg/dL)	0.986 (0.840–1.157)	0.860
Log ferritin	1.37 (0.96–1.95)	0.079
Log iPTH	1.518 (1.14–2.02)	0.004
Log hsCRP	0.779 (0.518–1.172)	0.231
Cholesterol (mg/dL)	1.005 (1.001–1.009)	0.021
Triglyceride (mg/dL)	0.998 (0.996–1.001)	0.215
LDL (mg/dL)	1.008 (1.002–1.013)	0.005
Log Pb	32.782 (13.73–78.22)	<0.001
Blood lead levels		<0.001
Low-normal BLL, BLL <10 μg/dL (reference)		
High-normal BLL, 20 μg/dL > BLL ≥10 μg/dL	3.19 (2.16–4.71)	<0.001
High BLL, BLL ≥20 μg/dL	9.9 (5.73–17.09)	<0.001

Abbreviations: BLL, blood lead level; CVD, cardiovascular disease; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; Kt/V_{urea}, dialysis clearance of urea; LDL, low-density lipoprotein; nPCR, normalized protein catabolic rate; Pb, blood lead.

Table 3 Multivariate logistic regression analysis (forward method) between uremic pruritus and clinical variables

*Variables	Multivariate logistic regression	
	Odds ratio (95% confidence interval)	***P*-value**
Hemodialysis duration (years)	1.088 (1.052, 1.126)	<0.001
Non-anuria	0.577 (0.340, 0.979)	0.041
Log ferritin	2.086 (1.388, 3.134)	<0.001
LDL (mg/dL)	1.009 (1.003, 1.015)	0.002
Log Pb	29.230 (11.512, 74.214)	<0.001

Note: *After adjustment for body mass index, DM, HBV, HCV, hemodiafiltration, Kt/V_{urea}, nPCR, serum albumin, corrected calcium, and log iPTH.
Abbreviations: DM, diabetes mellitus; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; iPTH, intact parathyroid hormone; Kt/V_{urea}, dialysis clearance of urea; LDL, low-density lipoprotein; nPCR, normalized protein catabolic rate; Pb, blood lead.

Table 4 Multivariate logistic regression analysis (forward method) between uremic pruritus, and clinical variables

*Variables	Multivariate logistic regression	
	Odds ratio (95% confidence interval)	***P*-value**
Hemodialysis duration (years)	1.088 (1.051, 1.126)	<0.001
Non-anuria	0.565 (0.333, 0.960)	0.035
Log ferritin	2.153 (1.428, 3.248)	<0.001
LDL (mg/dL)	1.009 (1.003, 1.015)	0.003
BLLs		<0.001
Low-normal BLL, BLL <10 μg/dL (reference)		
High-normal BLL, 20 μg/dL > BLL ≥10 μg/dL	3.286 (2.174, 4.967)	<0.001
High BLL, BLL ≥20 μg/dL	8.938 (4.942, 16.166)	<0.001

Note: *After adjustment for body mass index, DM, HBV, HCV, hemodiafiltration, Kt/V_{urea}, nPCR, serum albumin, corrected calcium, and log iPTH.
Abbreviations: BLL, blood lead level; DM, diabetes mellitus; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; nPCR, normalized protein catabolic rate; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein; Kt/V_{urea}, dialysis clearance of urea.

that SHPT might result in an increased release of lead from bone stores because of high bone turn over; they found that parathyroidectomy effectively suppressed the elevated levels of blood lead.[31] Some evidence also indicates an association between beta-2 microglobulin levels and UP in HD patients,[32–34] and rats given lead acetate in drinking water experienced an increase of beta-2 microglobulin excretion.[35] The association between BLLs and UP might occur through the effect of beta-2 microglobulin. However, we cannot confirm this because we did not regularly measure beta-2 microglobulin in our HD patients. According to the above discussion, BLLs in HD patients might increase the intensity of or have an addictive role of pruritus caused by other more common risk factors.

Lead compound can also cause crystallization of calcium phosphate in the body like bone and skin.[36] Elevated skin

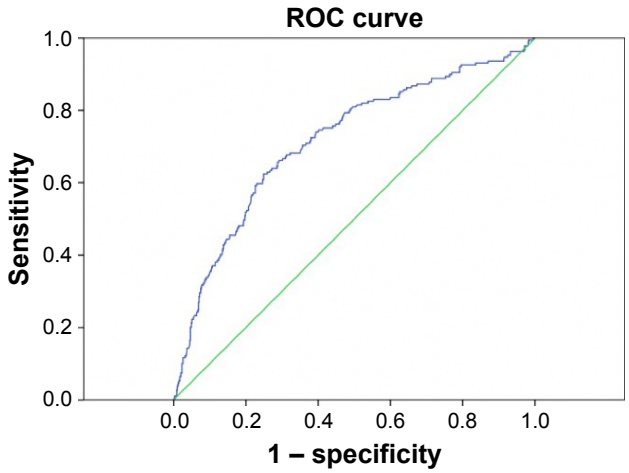

Figure 2 ROC curve of blood lead levels to predict uremic pruritus.
Abbreviation: ROC, receiver operating characteristics.

Table 5 Multivariate logistic regression analysis (forward method) between uremic pruritus and clinical variables

*Variables	Multivariate logistic regression	
	Odds ratio (95% confidence intervals)	*P*-value
Hemodialysis duration (years)	1.092 (1.056, 1.130)	<0.001
Non-anuria	0.555 (0.327, 0.943)	0.030
Log ferritin	2.099 (1.392, 3.166)	<0.001
LDL (mg/dL)	1.010 (1.004, 1.016)	0.001
BLL		<0.001
BLL <12.77 μg/dL (reference)		
BLL ≥12.77 μg/dL	4.511 (3.128, 6.505)	<0.001

Note: *After adjustment for body mass index, DM, HBV, HCV, hemodiafiltration, Kt/V_{urea}, nPCR, serum albumin, corrected calcium, and log iPTH.
Abbreviations: BLL, blood lead level; DM, diabetes mellitus; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; nPCR, normalized protein catabolic rate; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein; Kt/V_{urea}, dialysis clearance of urea.

calcium phosphate content was associated with skin inflammation and UP in HD patients.[3,37]

In this study, we showed that even BLLs in the high normal range[38] were significantly associated with UP. The cutoff point of BLLs to predict UP in our study was 12.77 μg/dL, which had a high sensitivity, specificity, and overall correctness. A previous study also revealed that high BLL was associated with increased hazards for all-cause, cardiovascular-related, and infection-related 18-month mortality in patients on MHD.[39] The definition of high BLL was BLL >12.64 μg/dL in this study. Chronic low-level environmental lead exposure might inhibit urate excretion in the general population,[12] and accelerate progressive renal insufficiency in patients without diabetes who have chronic renal disease.[11] These patients all had normal lead burden, and chelation therapy could improve renal function and slow the progression of renal insufficiency. According to our findings and those from the abovementioned studies, the normal range of BLL in HD patients needs to be revised or there are no normal BLLs in HD patients.

Ferritin had a positive correlation with UP in our study, which was consistent with previous research.[40] BLLs have been noted to be negatively associated with serum ferritin levels.[10,41,42] In our study, both serum ferritin and BLL were two independent factors positively associated with UP. Blood lead-related systemic inflammation, therefore, appears to play an important role in the elevation of serum ferritin in our studied HD patients.

More than half (52.9%) of our recruited HD patients were in the high-normal or high BLL categories, which was higher than the average BLL in general Taiwanese adults (7.7 μg/dL).[43] The elevated BLL in patients on maintenance HD might have been due to a complete loss of renal function, which is a main route to excrete lead from the body, and the difficulty in removing lead through HD.[9] Our present study also showed that anuria was also a positive predictor of UP. Anuria definitely caused a decreased excretion of blood lead in HD patients compared to those with residual urine output. Therefore, lead from environmental lead exposure in maintenance HD patients cannot be excreted efficiently.

Conclusion

Our study is the first to show that BLL is positively correlated with UP and can predict it, and there may actually be no normal blood lead level in maintenance HD patients. Further randomized controlled study to use chelation therapy for lead removal is needed for the definite causal relationship between blood lead and UP.

Limitations

This is a cross-sectional study and further randomized controlled studies using chelation therapy to reduce BLL should be performed to confirm the relation between causal and effect of BLL and UP in HD patients.

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Author contributions

CH W and WH H wrote the main manuscript text. CW H and CC H prepared figures and tables. CH W, TH Y, and MJ C collected the data. All authors reviewed the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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