History of Medicine, 2023, 9(1): 1775–1781
DOI: 10.17720/2409-5834.v9.1.2023.227

Uremic polyneuropathy: Correlation with parathyroid hormone levels, cross-sectional study among hemodialyzed patients

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Received: 20 January 2023 **Accepted:** 15 April 2023

Citation: Abdul- Aa'ama TK, Al- Saegh RMA, Dleikh FS, Ajeena IM (2023) Uremic polyneuropathy: Correlation with parathyroid hormone levels, cross-sectional study among hemodialyzed patients. History of Medicine 9(1): 1775–1781. https://doi.org/10.17720/2409-5834.v9.1.2023.227

Abstract

Background: One of the common endocrine sequelae of chronic kidney disease (CKD) is secondary hyperparathyroidism, which increases morbidity and mortality among uremic cases. How CKD triggers the parathyroid gland to secrets parathyroid hormone (PTH) is still an open question. Another common sequel of CKD is peripheral neuropathy (PNP), which involves around 60-100% of dialysis-dependent patients. Nevertheless, the precise pathophysiology of PNP among CKD subjects required additional investigation, particularly in our country. Objectives: To evaluate the correlation of uremic polyneuropathy with PTH levels among patients undergoing hemodialysis. Materials and Methods: 215 patients were recruited in this cross-sectional study (99 women and 116 men). All applicants had ESRD and were assessed by expert physicians, average ages of 17-80 years, on regular visits for hemodialysis unit, receiving standard follow-up hemodialysis regimen. All patients had completed neurophysiological assessments. Biochemical tests of serum levels of Calcium, phosphorus, and PTH were completed according to the manufacturer's instructions. SPSS software was utilized to inspect the statistical investigations. A p-value of 5% had considered significant. Results: Mean age of patients was (48.2±13.4) years. The mean duration of dialysis was 4.7±1.4 years. There were significant differences in the mean levels of serum PTH with the incidence and severity of UPNP (P-0.001 and 0.003), respectively. The prevalence of UPNP was 63.7% among the involved candidates. Of total patients, (51.8%) exhibited moderate UPPN, (29.2%) mild, and (19. 0%) severe type (P<0.05). There were significant differences in the means of age (p-0.001), PTH (p-0.001), Ca++ (p-0.003), and PO4 levels (p-0.001) between patients with UPNP and patients without UPNP. Conclusion: The main outcomes of this study were the significant correlation of hyperparathyroidism with incidence and with worsening severity of UPNP (P-0.001) and (P-0.013), respectively. Neuropathy is a common sequel in patients with uremia undergoing hemodialysis.

Keywords

PTH, uremia, polyneuropathy, CKD, chronic kidney diseases, dialysis, ESRD, neurotoxin, phosphorus, calcium.

Parathyroid hormone (PTH) normalizes circulatory calcium (Ca), phosphorus (Ph) levels, and bone mineral metabolism [1, 2]. A reduction in serum Ca stimulates PTH secretion and, when sustained, parathyroid gland proliferation. The active biological form of PTH has a half-life < 3-minutes in the blood and is cleared mostly by the liver (60−70%) and kidney (20−30%) [3]. Once PTH release is triggered by hypocalcemia, plasma Ca increases vis stimulating renal tubular

reabsorption, bony resorption, and intestinal Ca uptake indirectly through the renal activation of vitamin D [1].

The secretion of PTH is controlled by fluctuations of extracellular Ca. Reduced ionized Ca activates the PTH release, while raised levels decrease the PTH secretion and increase calcitonin release. In the kidney proximal tubules, PTH reduces phosphate reabsorption. As well, it rises Ca reabsorption by activating "basolateral Na^{+}-Ca^{++} transporters" and inserting Ca-channels in the apical membrane of renal distal tubules [4]. Abnormal mineral metabolism can occur initially or recurrently in the course of chronic kidney disease (CKD). Progressive deterioration of kidney functions can cause the decreased renal synthesis of calcitriol (an active form of vitamin D), hypocalcemia, phosphorus retention, and secondary increased PTH [5]. Calcitriol indirectly enhances PTH release due to reduced intestinal Ca-absorption [6].

Secondary hyperparathyroidism is frequently found in "end-stage renal disease (ESRD)", mostly in patients on dialysis regimens. PTH starts to increase when the "estimated glomerular filtration rate" reaches around 50ml/min/1.73 m^2 [7].

Neuropathy (NP) is neuropathology affecting sensory-motor neurons, which might involve different parts of the neurons, in an acquired or hereditary, autonomic or somatic fashion [8]. The etiopathology of NP is a wide spectrum involving metabolic, inflammatory, inherited, dietetic, poisons, uremic, or others [9].

Increased circulating PTH levels have been proposed to contribute pathogenesis of PNP. Nonetheless, there is inadequate clinical data to support this impression. For instance, PTH may increase the neural content of Ca and convince defects in nerve conduction velocity [10].

Peripheral NP (PNP) is among the most common neural conditions with a rate of 77/100,000/year and a frequency of 2.4%, although this rate increases critically with specific age intervals since traumas are not merged in this frequency [9, 11]. Around 60-100% of PNP impacts subjects admitted for hemodialysis units caused by CKD. Uremic PNP (UPNP) develops when kidney dysfunction involves glomerular filtration, initiating the accumulation of organic wastes. Generally, UPNP affects lower limbs in a distal symmetric manner [12, 13], and is caused by "length-dependent axonal degradation" and secondary local demyelination [12]. In ESRD and hemodialysis-dependent cases, a progressing uremic sensory-motor axonal PNP is a recognized sequel [14]. Nonetheless, the exact PNP among CKD patients has to be thoroughly inspected exclusively in Iraq.

This cross-sectional research aimed to evaluate the correlation of uremic PNP with PTH levels, among Iraqi patients undergoing hemodialysis.

Materials and Methods

This was a cross-sectional observational study, conducted on 215 patients (116 males and 99 females) registered in the dialysis unit of Al-Husseiny Teaching Hospital at Karbala City, through the period of January-April 2021. All members who had ESRD were assessed by professional physicians, 17-80 years old, on a classical hemodialysis program comprising 2-4 weekly sessions, for 3-4 hours/session for exceeding 3-months. All members were exposed to thorough clinical history, general medical, and nervous examination before dialysis.

Venous sampling from the candidates was taken for biochemical analysis of serum Ca (mg/dl), Ph (mg/dl), and PTH levels (pg/ml). The tests were completed according to the standard techniques used in the local hospital laboratories using commercially existing immunoassay approaches by Abbott automated analyzers.

Informed written permission from each candidate was taken. The whole study was approved and permitted by the Karbala health institution.

All cases had accomplished neurological examination in the hospital for the sensory and motor nerves that included: tibial, peroneal, sural median, and ulnar nerves, irrespective of whether they had neurological findings of PNP or not.

Patients with preexistent NP before the diagnosis of CKD were excepted. In addition, those with NP diseases like inherited or autoimmune, collagen vascular disorders, amyloidosis, any primary neurologic disorder, and immunosuppressed subjects all were excluded from the study. The presence and severity of NP were assessed using "Baba's classification" [15].

Continuous parameters were stated as means(±SD), while the categorical parameters were stated as numbers/percentages. The independent-samples t-test was applied for the continuous parameters and the Mann-Whitney test was used to compare two groups when the variable was non-normally distributed. ANOVA test was used to compare means between three groups or more. Kruskal-Wallis test was used to compare three groups or more when the variable was non-normally distributed. Pearson chi-square and Fisher's exact test were used to finding the association between categorical variables A p-value of ≤ 0.05 was considered as significant. In addition, correlation analyses were done between all the continuous data to report the strength of the relationship between them. SPSS (V-25) software was used for statistical analysis.

Results

Table-1 shows the descriptive statistics of uremic patients according to study variables. The mean age of patients was (48.2 ± 13.4) years, min-max. age was 18-80 years. The mean weight of patients was (66.9 ± 12.9) kg, min-max. weight was 32-102 kg. 54% (116) of the patients were males. The mean duration of hemodialysis/years was 4.7±1.4, min-max. the duration was 1-6.5 years. Around 2/3rd of them were dialyzed for 1-5 years. Mean serum levels of PTH were 411.2±9370.1 (pg/ml), Ca^{++} were 9.2±0.8 (mg/ml), and PO4 were 5.4±1.3 (mg/ml). The majority of the patients (85.1%, n=183) were thrice weekly.

Table 1: The Descriptive statistics of uremic patients according to study variables (N=215)

Study variables	Descriptive Statistics	
Age/years	Mean (SD) 48.2 ± (13.4)	Min − max (18.0 - 80.0)
Weight/kg	Mean (SD) 66.9 ± (12.9)	Min − max (32.0 - 102.0)
Gender/Male	No=116	54.0%
Duration of hemodialysis/years	Mean (SD) 4.7 ± (1.4)	Min − max (1.0 − 6.5)
< 1	N=36	16.7%
1 − 3	N=59	27.5%
3 − 5	N=76	35.3%
> 5	N=44	20.5%
PTH (pg/ml)	Mean (SD) 411.2 ± (9370.1)	Min − max (23.1 − 1500.0)
Ca^{++} (mg/dl)	Mean (SD) 9.2 ± (0.8)	Min − max (7.0 − 12.0)
PO4 (mg/dl)	Mean (SD) 5.4 ± (1.3)	Min − max (3.1 − 8.9)
Frequency of hemodialysis/week		
Two times	N=27	12.6%
Three times	N=183	85.1%
Four times	N=5	2.3%

Figure-2 shows the distribution of patients according to the incidence of uremic PNP. Of the total of 215 patients, uremic PNP was present in (63.7%), N= 137.

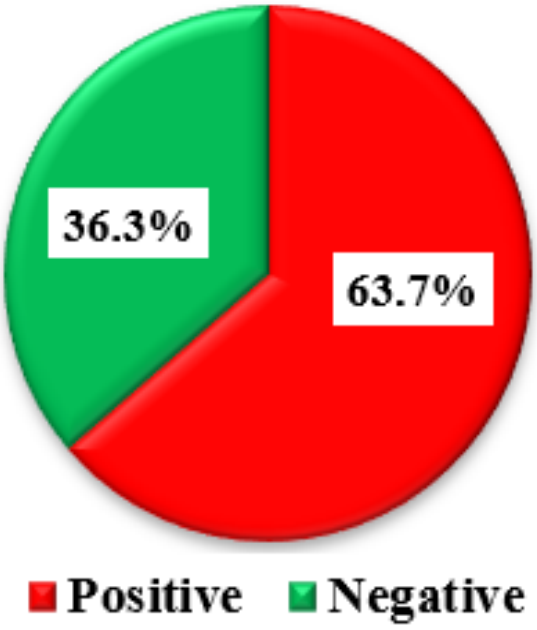

Figure-4: Distribution of patients according to uremic polyneuropathy (N=215)

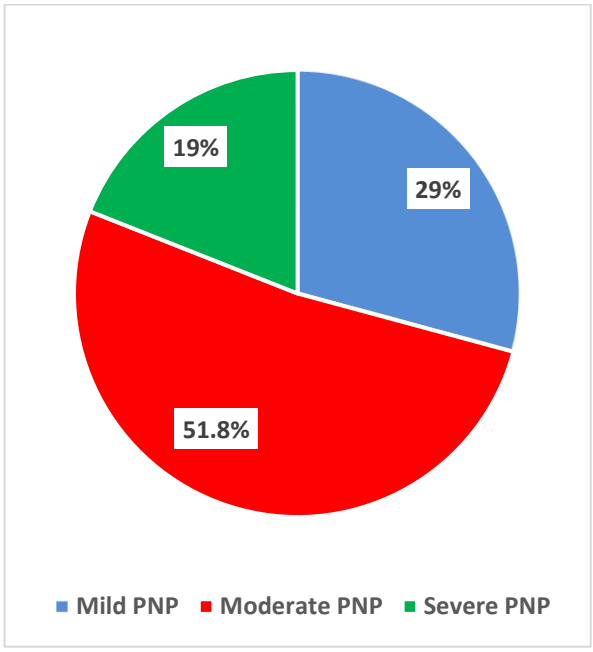

Figure-3: Distribution of patients with uremic polyneuropathy according to severity (N=137)

Figure-3 shows the distribution of patients with uremic PNP according to their severity. More than half of patients (N=71, 51.8%) had moderate neuropathy, (N=40, 29.2%) revealed mild type, and (N=26, 19.0%) of patients exhibited severe nerve involvement.

The mean differences of study variables according to the presence of PNP were revealed in table-2. There were significant differences between means of age (p-0.001), PTH (p-0.001), Ca^{++} (p-0.003), and PO4 levels (p-0.001) in patients with uremic PNP.

Table 2: The mean differences of study variables according to the presence of uremic polyneuropathy

Study variables	Uremic polyneuropathy	Mean	SD	P-value
Age (years)	Positive	52.8	12.4	<0.001
	Negative	40.0	11.1	
Weight (Kg)	Positive	67.6	12.3	> 0.05
	Negative	65.9	13.9	
Gender/male	Positive	58.4%		0.08
	Negative	46.2%		
PTH (pg/ml)	Positive	468.8	360.0	0.001
	Negative	307.5	207.2	
Ca (mg/dl)	Positive	9.1	0.8	0.003
	Negative	9.4	0.9	
PO4 (mg/dl)	Positive	5.7	1.3	<0.001
	Negative	4.9	1.1	
Frequency of hemodialysis/week				
Twice	Positive	17	12.4	> 0.05
	Negative	10	12.8	
Three times	Positive	117	85.4	
	Negative	66	84.6	
Four times	Positive	3	2.2	
	Negative	2	2.6	
Duration of hemodialysis/years				
< 1	Positive	17	12.4	> 0.05
	Negative	19	24.4	
1 – 3	Positive	48	35.1	
	Negative	28	35.9	
3 – 5	Positive	38	27.7	
	Negative	21	26.9	
> 5	Positive	34	24.8	
	Negative	10	12.8	

Table-3 showed the mean differences of study variables based on the severity of uremic PNP. There were significant differences between means of age (p-0.001), and PTH levels (p-0.014), with worsening of severity of neuropathy.

Table-3: The mean differences of study variables according to the severity of uremic polyneuropathy

Study variables	Uremic polyneuropathy	N	Mean	SD	P-value
Age (years)	Mild	40	45.2	12.1	<0.001
	Moderate	71	55.4	10.8	
	Severe	26	57.6	11.9	
Weight (kg)	Mild	40	70.4	15.5	> 0.05
	Moderate	71	67.2	9.5	
	Severe	26	64.2	12.9	
Serum Ca (mg/dl)	Mild	40	9.1	0.7	> 0.05
	Moderate	71	9.1	0.9	
	Severe	26	8.8	0.8	
Serum PO4 (mg/dl)	Mild	40	5.9	1.3	> 0.05
	Moderate	71	5.5	1.2	
	Severe	26	5.8	1.4	
PTH (pg/ml)	Mild	40	432.7	352.3	0.014
	Moderate	71	418.8	321.6	
	Severe	26	660.9	489.1	

Discussion

This observational study was preset to estimate the correlation of PNP with PTH levels among uremic patients submitted to the dialysis unit. The main outcomes were a significant correlation of hyperparathyroidism with incidence and with worsening severity of UPNP (P-0.001) and (P-0.013), respectively.

In the pathogenesis of secondary uremic hyperparathyroidism, many systemic and local factors are possibly intricate. Reduced serum Ca and calcitriol in initial renal impairment and higher phosphate in advanced stages; induce a continual

PTH synthesis [16]. Furthermore, overexpression of vitamin D receptor [17] and Ca-sensing receptor [18] in the parathyroid gland, practically subsidizes escape of secretory control of parathormone [16]. Transforming Growth Factor (TGF) is a cytokine with multidisciplinary cell activities [19-22] -in particular- the abnormality of TGF-α de novo expression may induce the parathyroid hyperplasia in KCD [18].

In this study, UPNP was very common, experienced by about 2/3rd (137) of the studied cases, exceeding half (71) presented with moderate NP, and < 1/5th (26) patients revealed severe NP ($P<0.05$). A comparable outcome was described by a Turkey survey comprising 36 peritoneal dialysis subjects [23]. As well, contemporary research conducted on thirty uremic teenagers from Egypt exposed similar findings [24]. Despite lower frequency rates of UPNP unveiled by another Egyptian scholar involved 60 uremic adults. Clinically their NP was described in 55% of the patients and manifested electrophysiologically by an entire clinically apparent group compared to 92.5% of the clinically unapparent patients [25]. Additionally, a larger USA cohort comprised 1121 elders with KCD displayed only15.6% of the candidates had 2.37 times more chance to have new motor NP. In addition, KCD had 2.02 times more chance of deterioration of -but not- with the evolution of new monofilament insensitivity [26]. On the same channel, other contemporary Indian studies of 200 cases with KCD on hemodialysis, showing that frequency and severity of PNP upswing as deteriorating renal Functions [27].

Generally, it is challenging to clarify the neuromuscular syndrome in UPNP by the action of hyperparathyroidism only. Hence, the impression arose that some diverse target tissues interactions must exist like endocrine, skeletal, gastrointestinal, and renal systems too.

Disturbed metabolism of body minerals is common in the early stages of ESRD [9]. Progressive loss of kidney function results in reduced secretion of calcitriol and phosphorus retention causing hypocalcemia, as well as increased PTH release [28].

Even though intact and/ or carboxy-terminal molecules of PTH do not cross the blood-brain barrier (BBB), a prolonged increase of serum PTH levels rises the resting concentrations of intracellular Ca in synaptosomes of the brain [29]. For decades Evanson et al displayed that the calcemic body response to PTH was weakened in ESRD [30]. This might clarify, at least to some extent, one very remarkable opinion. For any given serum level of PTH, bone turnover in uremic cases is lower than that of healthy. Overactive parathyroid is an essential long-term problem of KCD that remains a risk factor in the health rehabilitation of patients on dialysis. A point proved by the fact that after two decades of continuous dialysis, around 20% of cases necessitate parathyroidectomy [29].

The pathogenesis of neuronal injury uremia is expected to be multifactorial. Nevertheless, the predicted mechanisms may be divided into two evolving premises, specifically neurodegenerative and vascular postulates [31].

Many possible deleterious uremic neurotoxins have been inspected in the milieu of CKD. Neurovascular interactions have been anticipated for numerous molecules for instance uric acid [31, 32], p-cresyl sulfate, as well as indoxyl sulfate [33]. IL-1β and TNF-α are vital multifaceted cytokines largely incorporated in inflammatory responses [21, 34, 35] and both related to various pathologies like ESRD [31]. Cystatin-C is a novel biomarker of kidney function [36, 37], the scientists lately have proved that high levels of cystatin-C are linked with lower intellectual scores and neuronal degeneration through amyloid plaque formation although many studies are necessary [38].

Alternatively, vascular hypothesis assumes that the uremia may present with a high frequency of non-classical cardiovascular risk factors like metabolic derangements, mostly related to phosphate and calcium, hypercoagulability, and oxidative stress [39], and urate levels that are believed to aggravate endothelial dysfunction and worsen atherosclerosis [40-42].

In this study, the candidates' age exhibited a significant impact on the rate of UPNP (P-0.001), this view was supported by several researchers [26]. Some previous reviews have revealed a higher incidence of vascular dysfunctions [43], neuropathies, and nephropathy with higher ages [44]. In the interim, other researchers fail to show such a link [45].

There was no sex dominance among the study patients similar to other readings [26, 46]. Most of the applicants were on hemodialysis for > 1 year (83.7%) and had dialysis thrice weekly (85.3%). Nevertheless, the dialysis mean duration generally was shorter than that reported by other studies that may be resulted from poor compliance or missed patients. There was a significantly high rate of UPNP with increased duration of dialysis, but no detected variations in the rate of UPNP with the frequency of dialysis per week. Egyptian adults also revealed a common manifestation of UPNP and its frequency increases with the duration of dialysis among uremic patients on hemodialysis [25]. However, the duration and effectiveness of hemodialysis were not linked with the rate of UPNP in other research [45].

Consequently, early identification of neuropathy and PTH assessment, in mild KCD is believable

and may denote a window of a vision to reduce its effect in advanced stages. Upcoming works should support this interrelation precise pathophysiology of hyperthyroidism and delineate if early recognition of neural impairments may initiate preventive measures to improve quality of life in uremic patients.

Conclusion

The main outcomes of this study were the significant correlation of hyperparathyroidism with incidence and with worsening severity of UPNP (P-0.001) and (P-0.013), respectively. Neuropathy is a common sequel in patients with uremia undergoing hemodialysis.

Funding: Self-funding

Declaration of interest: The authors did not report any conflicts of interest, and they are alone responsible for its content and writing.

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