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Movement Disorders in Chronic Kidney Disease Patients on Hemodialysis in Mosul City

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Abstract

BACKGROUND: Movement disorders are not rare in patients with chronic kidney disease (CKD) on hemodialysis (HD). The prevalence and the exact mechanism of these disorders are unknown. Iron deficiency and dopamine dysregulation are implicated from one perspective, whereas chronic inflammation and calcium dysmetabolism may be involved from another perspective.

AIM: We studied the prevalence, delay in the diagnosis and the role of iron deficiency, inflammation, and bone abnormalities on some movement disorders in patients with CKD on HD.

METHODS: A cross-sectional study examined the prevalence, among patients with CKD on HD in Mosul city, of restless leg syndrome (RLS), periodic limb movement syndrome (PLMS), Parkinsonism, asterixis, and myoclonus. Delay in diagnosis of these disorders was also studied. Validated questionnaires and specified neurological examination were applied to define patients with these disorders. Using IBM® SPSS® v. 23 statistical software, we compared between the different groups of patients by different parameters (case–control design).

RESULTS: Among 281 enrolled CKD patients on HD in Mosul city, the prevalence of RLS, PLMS, Parkinsonism, asterixis, and myoclonus was 28.72%, 17.02%, 2.84%, 20.92%, and 24.11% respectively. Average delay in diagnoses was 2.6 (±3.09) years, 3.02 (±3.13) years, 1 (±0.78) year, 1.23 (±1.51) years, and 2.28 (±2.34) years, respectively. Median duration of dialysis in patients with PLMS and Parkinsonism tended to be higher than in those without PLMS or Parkinsonism. Neither inflammation, ferritin level nor bone dysmetabolism discriminated patients with CKD on HD with and without these movement disorders.

CONCLUSIONS: Movement disorders are prevalent in patients with CKD on HD. In Mosul city, there would be still delay in diagnosis and treatment of these movement disorders. The longer the duration on HD, the more frequent the PLMS and Parkinsonism cases.

Introduction

Chronic kidney disease (CKD) may disturb the nervous system by affecting cortical, subcortical, vascular, or peripheral structures [1], [2]. Diseases of subcortical gray matter can be divided into disorders affecting sleep like restless leg and periodic limb movement syndromes (PLMS), disorders happen in day time and affect quality of life like Parkinsonism, chorea, asterixis, or those have no specific diurnal variation like myoclonus [3], [4]. Mechanism underlying these movement disorders in patients undergoing dialysis is speculative. The main concept is that the depletion of brain iron with subsequent disruption of dopamine neurotransmission in hypothalamus and nigrostriatal system, aids in development of restless leg syndrome (RLS), PLMS, and Parkinsonism [3]. Other authors proclaimed chronic inflammation and oxidative stress for increasing the incidence of these disorders in CKD patients [5], [6], [7]. Still there is another group of authors supposed that high phosphorus and intact parathormone may have a role developing these dyskinetic movements [8], [9]. Uremic toxins have been proposed to cause myoclonus by affecting nucleus gigantocellularis in medulla oblongata [3].

In this work, we sought to define the prevalence and delay in diagnosis of some movement disorders in patients with CKD on HD in Mosul city. We also tried to elucidate the effect of demographic, physical, biochemical factors, and medical illnesses on these disorders. To the best of our knowledge, this is the first research dealt in detail with these disorders in this group of patients.

Methods

Study population

A cross-sectional study viewed the point prevalence and delay in diagnosis (the time period between the primary complaints and diagnosis of that

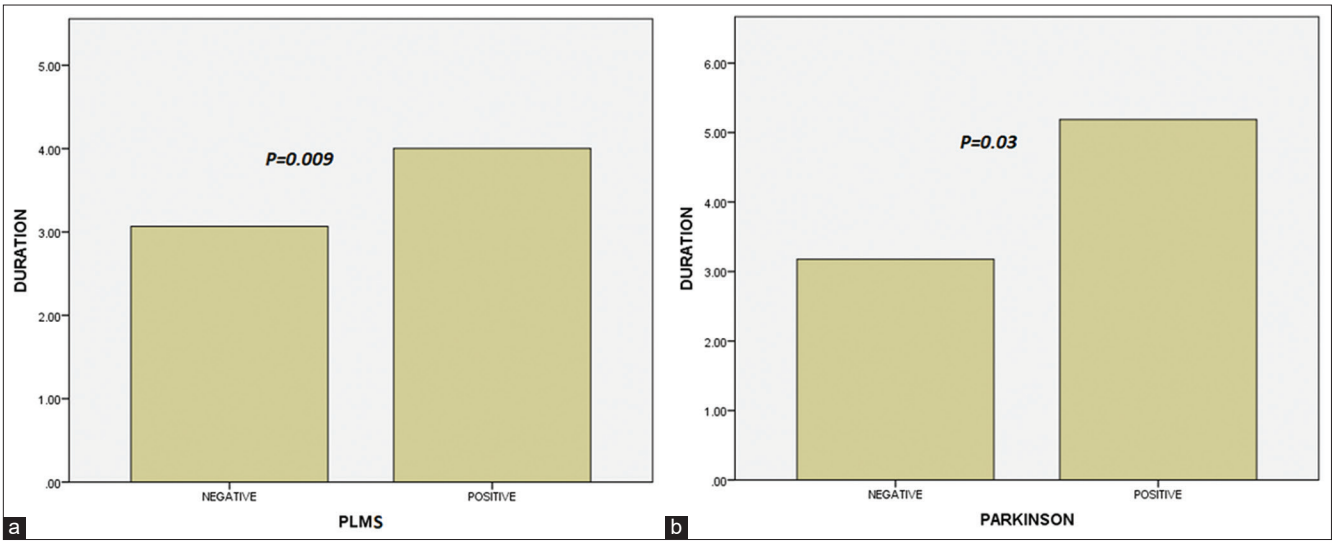

Figure 1: Differences between (a) periodic limb movement syndrome, (b) Parkinsonism positive and negative cases in terms of duration on hemodialysis measured by years

illness) of each of RLS, PLMS, Parkinsonism, asterixis, and myoclonus in adults with CKD from the hemodialysis (HD) units in Mosul city that includes Ibn –Sena Teaching Hospital and Mosul General Hospital (the only two hospitals in Mosul city that exclusively drain all dialysis patients from whole Ninevah governorate).

Patients were interviewed (based on specific questionnaire) and examined at dialysis sessions. Oral informed consent was obtained from all patients. The study was approved by the Ethical Committee in Medical College, University of Mosul.

Inclusion criteria were all patients who had initiated chronic dialysis more than 3 months' duration. Patients were excluded if they were deaf, mentally subnormal, or having cerebral palsy. RLS patients were diagnosed using a questionnaire based on 2012 IRLSSG, and patients with PLMS were diagnosed according to PLMS criteria published before [10], [11], [12]. Parkinsonism is considered in any patient having bradykinesia not attributed to musculosketal problem, resting tremor, rigidity, or postural instability on examination (3 of 4 features) [13]. All patients were examined for asterixis. Myoclonus was defined by sudden, brief, involuntary jerks of a muscle, or group of muscles, according to international Parkinson and movement disorder society [14].

The age, the gender of the patients, the causes of kidney disease, and the duration on HD all were studied. Any history of hypertension, diabetes, smoking, exercise, coffee consumption, and medications history including erythropoiesis stimulating agents was fixed. Of note, all of our patients took no antipsychotic, antiemetic, and antihistamine medications that may alter dopamine concentration in brain cells. Family history of movement disorders was considered (one patient has family history of essential tremor). Body mass index and dialysis efficacy using Kt/V formula were calculated (K' clearance multiplied by "t" time of dialysis session divided into volume of urea distribution which is approximately equal to total body water).

Laboratory tests

We measured serum creatinine as a marker of toxicity and severity of the disease. Serum albumin was calculated as an indicator of malnutrition. Serum calcium and serum phosphorus were considered as markers of bone metabolism; whereas iron reserves and inflammation were defined by hemoglobin level, serum ferritin, and C-reactive protein (CRP), respectively.

Statistical methods

Data were entered into Microsoft Office Excel v. 10, and statistical analyses were performed using IBM® SPSS® v. 23, SSPS Inc., Chicago, IL for windows statistical package. Statistical significance was demarcated as an alpha value of <0.05.

Total number of patients included in our study were 312. Thirty-one patients were excluded by the above criteria. The duration on dialysis and the duration of illnesses were calculated and the mean delay in diagnosis was measured.

Comparison between affected and non-affected patients (case–control study) in terms of RLS, PLMS, Parkinsonism, asterixis, and myoclonus was done using different types of parameters. Differences between groups in continuous data (the age of patients, the duration on dialysis, serum creatinine, albumin, calcium, phosphorus, ferritin, hemoglobin, and CRP) were measured using the two sample independent t-test or the Mann–Whitney U-test, depending on the pattern of distribution of the data, whereas Chi-square tests

were used to compare between categorical variables (the gender, hypertension, diabetes, smoking, coffee consumption, and exercise).

Results

A total number of 281 patients were enrolled by our inclusion criteria and their demographic characteristics are shown in Table 1.

Table 1: Patients characteristics

Demographic and historical features	Statistics
Age (years), average ± SD	48.1 ± 16.2
Duration on HD (year), average ± SD	3.2 ± 3.0
Male (%)	154 (54.8)
Hypertensives (%)	230 (81.9)
Diabetics (%)	67 (23.8)
Smokers (%)	28 (10)
Coffee consumers (%)	20 (7.1)
Exercise (%)	19 (6.8)

Table 2 clarified the prevalence of different movement disorders and mean delay in diagnosis calculated in year. RLS, myoclonus, and asterixis were having the highest prevalence in decreasing order of frequency.

Table 2: The prevalence and mean delay in diagnosis of different movement disorders in patients with CKD on HD

Movement disorders	Prevalence (%)	Mean delay by year ± SD
RLS*	28.72	2.60 ± 3.09
PLMS	17.02	3.02 ± 3.13
Parkinsonism	2.84	1.00 ± 0.78
Asterixis	20.92	1.23 ± 1.51
Myoclonus	24.11	2.28 ± 2.34

*RLS: Restless leg syndrome, PLMS: Periodic limb movement syndrome.

Using Chi-square tests, we found strong relationship between RLS and coffee consumption. Unfortunately, it was not statistically significant (p = 0.05) Table 3.

Table 3: Differences in categorical data between patients with and without movement disorders using Chi-square test

Patients	Gender (male)	HT	DM	Smoking	Coffee	Exercise
RLS*						
Positive cases	41/81	68/81	18/81	12/81	10/81	3/81
Negative cases	111/187	160/187	49/187	16/187	10/184	16/184
p-value	0.19	0.73	0.49	0.12	0.05	0.2
PLMS						
Positive cases	25/49	40/49	15/49	7/49	5/49	5/49
Negative cases	127/219	188/219	52/219	21/219	15/216	14/216
p-value	0.37	0.45	0.31	0.33	0.39	0.38
Parkinsonism						
Positive cases	3/8	5/8	0/8	0/8	0/8	1/8
Negative cases	149/260	223/260	67/260	28/260	20/257	18/257
p-value	0.30	0.10	0.21	0.18	0.26	0.45
Asterixis						
Positive cases	37/59	51/59	17/59	7/59	5/57	2/57
Negative cases	115/209	177/209	50/209	21/209	15/208	17/208
p-value	0.29	0.74	0.44	0.69	0.7	0.38
Myoclonus						
Positive cases	38/68	58/68	18/68	10/68	7/68	7/68
Negative cases	114/200	170/200	49/200	18/200	13/197	12/197
p-value	0.88	0.95	0.75	0.18	0.3	0.28

*HT: Hypertension, DM: Diabetes mellitus.

The duration on dialysis significantly increased the number of patients with PLMS (p = 0.009), and Parkinsonism (p = 0.03); as shown in Table 4 and Figure 1. See also supplementary Table 1.

Table 4: Differences in numerical data between patients with and without PLMS and Parkinsonism using Student's t-tests or Mann–Whitney tests

Parameter	With PLMS	Without PLMS	p-value	With Parkinsonism	Without Parkinsonism	p-value
S. Creatinin	905	917.7	0.58	980.8	913.6	0.87
S. Calcium	70.2	82.7	0.2	60.4	81.2	0.32
S. Phosphorus	87.6	76.5	0.24	107.2	77.6	0.15
S Albumin	69.3	80.0	0.25	84.6	77.8	0.74
Hb	82.2	91.4	0.37	48.5	91.2	0.07
CRP	8.9	15.3	0.07	21.7	31.5	0.38
S. Ferritin	34.2	33.9	0.95	45.8	33.5	0.3
BMI*	127.7	120.2	0.53	128.5	121.3	0.79
Kt/V	128.2	132.2	0.74	126.8	131.7	0.86
Age	125.9	134.6	0.48	112.6	133.6	0.44
Duration	160.6	128.7	0.009	191.9	132.7	0.03

*BMI: Body mass index, Kt/V: "K" clearance multiplied by "t" time of dialysis session divided into volume of urea distribution which is approximately equal to total body water. Duration=duration on hemodialysis.

Discussion

This is the first study in Iraq that was conducted to assess the prevalence of different movement disorders in patients on HD. The prevalence of RLS, PLMS, Parkinsonism, asterixis, and myoclonus was nearly 29%, 17%, 3%, 21%, and 24%. Certainly, few literatures reported the prevalence of these dyskinetic movements in this group of patients. Our statistics were slightly higher when compared with Western reported figures. This is explained in part by poverty of resources in Iraq as some patients are still undertreated and taking less recommended hours of HD. In their review of literatures, Novak *et al*. stated that RLS prevalence in patients on dialysis might be up to 25% [15]. According to Safarpour *et al*. myoclonus, RLS and asterixis were the most common disorders in dialysis patient [3]. In a largest Egyptian cohort study, Hamed *et al*. discovered movement disorders in about one fifth of uremic patients [16]. These results were roughly close to ours. The problem of underestimation of these disorders in patients undergoing dialysis was highlighted in medical writings [17]. To the best of our knowledge, no study before described the mean delay in diagnosis of these illnesses.

The pathophysiology of movement disorders in dialysis patients remains unclear. We found no correlation between these disorders and demographic, physical (age, gender, coffee consumption, smoking, exercise, etc.), biochemical parameters (serum creatinine, s. calcium, s. Phosphorus, s. Albumin, s. Ferritin, CRP, hemoglobin, etc.), medical illnesses (hypertension, DM, etc.), duration of dialysis or dialysis efficiency measured by Kt/V with the exception that PLMS and Parkinsonism cases were affected considerably by the duration of dialysis. As mentioned by Hamed *et al*., no clear border for kidney disease to result in movement disorders [16]. According to Wali and Alkhouli body mass index might have an effect on RLS frequencies, while saraji *et al.* described higher mean age and longer HD duration as risk factors for developing RLS [18], [19]. Low HDL-cholesterol and longer duration of dialysis were supposed to be risk factors for developing RLS according to Tsai *et al*. [8]. We thought that the

longer the dialysis duration, the more the trace metals disrupted in the basal ganglia including iron, cupper and manganese [3,14]. Important to mention is that regular coffee consumers may have an increased risk of developing RLS. Although these were inferentially insignificant as p = 0.05, these results were empowered by many documents across the world [20], [21]. These habits would be better emphasized to the dialysis patients complaining from RLS.

The disparities among different medical centers regarding the frequencies and risk factors contributing to these disorders may be explained by sample size, ethnic variation, and time point in which the study was performed.

In a whole Korean population cohort study, Nam *et al*. found a relation between severity of chronic kidney dysfunction and development of Parkinsonism [22]. Still we found no correlation between serum creatinine level (indirect measure of disease severity and estimated glomerular filtration rate) and Parkinsonism; their observations were in concord with ours that CKD independently affected the disease frequency in this group of patients. The notion that Parkinsonism only happens in diabetic patients has been refuted by our paper and others [23].

Myoclonus, when happens in CKD patients, it may be of cortical, subcortical, or reticular brain stem origin [14]. It may be due to metabolic disturbances or uremic toxins [24]. Although, we found no correlation between myoclonic jerks and severity of uremia.

Our work has some limitations. First, case–control studies do not usually permit cause – effect relationship as many confounding factors may not be apparent to authors. Second, polysmnographies were not performed to confirm RLS, PLMS, and myoclonus with gold standard tests. Third, magnetic resonance imaging was necessary to be done to recognize basal gangia signal intensity and morphology in this group of population. Unfortunately, financial limits compromised us doing such study. Fourth, small sample size confined duplication of results to all dialysis patients. Hence, multicenter and multidisciplinary studies should be conducted for longer duration with opened facilities to further explore pathophysiology of movement disorders in dialysis patients.

By raising alertness about these underreported and undertreated disorders in dialysis patients, we hope to reduce their complains, improve their sleep and quality of life and to offer them standards of care [4], [17].

Conclusions

In this communication, we described the frequency, delay in diagnosis, and effect of different risk factors on development of movement disorders in dialysis patients. Early diagnosis and effective treatment may relieve them from more suffering.

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Supplemetary Table

Supplemetary Table 1: Differences in numerical data between patients with and without movement disorders using Student's t-tests or Mann–Whitney tests

Patients*	S. Cr	S.Ca	S. Ph	S Alb	Hb	CRP	SFe	BMI	Kt/V	Age	Duration
W/RLS	903	73.1	79.4	72.1	90.9	28.9	34.5	113.4	136.7	128.6	145.9
W/OUT	920	83.5	78.1	80.4	89.7	33.9	33.4	124.9	129.2	134.9	129.5
p-value	0.69	0.19	0.88	0.29	0.89	0.27	0.83	0.24	0.47	0.54	0.11
W/Astr	997.0	93.2	83.9	75.2	8.8	33.5	34.2	112.2	121.8	130.0	132.7
W/OUT	898.4	78.1	77.4	78.6	9.1	29.4	33.9	124.1	134.2	134.0	135.0
p-value	0.65	0.13	0.51	0.72	0.25	0.47	0.95	0.28	0.28	0.72	0.84
W/Myo	998.5	71.7	81.1	74.5	89.8	29.2	35.0	131.2	125.2	132.1	143.7
W/OUT	892.1	83.0	77.8	79.0	90.1	31.8	33.6	118.4	133.7	133.3	131.3
p-value	0.59	0.2	0.7	0.6	0.98	0.6	0.79	0.43	0.22	0.91	0.24

*S. Cr: Serum creatinin. S.Ca: Serum calcium, S. Ph: Serum phosphorus, S. Alb: Serum albumin, Hb: Hemoglobin level, CRP: Serum reactive protein, S.Fe: Serum ferritin, BMI: Body mass index, Kt/V: 'K' clearance multiplied by 't' time of dialysis session divided into volume of urea distribution which is approximately equal to total body water. Duration: Duration on hemodialysis, Park: Parkinsonism, Myo: Myoclonus, astr: asterixis, W: With, W/OUT: Without.