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Prevalence of Restless Legs Syndrome in Patients with Chronic Renal Failure undergoing Hemodialysis

Running Title: Prevalence of Restless Legs Syndrome in Patients with Chronic Renal Failure

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ABSTRACT

Introduction:Sleep disorders like restless legs syndrome (RLS) are common in hemodialysis (HD) patients and associated with reduced quality of life in them. In this study, we evaluated the frequency of RLS in HD patients for diagnosis and control the signs of RLS to increase the quality of life in them. **Materials/Methods**: The Society who had been studied was 118 Chronic Renal Failure (CRF) patients who were under dialysis treatment in dialysis units of the west of Mazandaran. Register of information was done by a questionnaire that completed with interview and laboratory measurements. The data recorded and analyzed by the Chi-Square test. **Results**: In this study, 118 HD patients were evaluated. 16.1% of patients affected by RLS. Most patients (65.61%) were more than 60 years old. There was no correlation between sex and age with RLS. There was no correlation between laboratory findings including hemoglobin, Calcium, Ferritin, and creatinine with suffering by RLS. There was a correlation between blood urea nitrogen (BUN) and suffering from RLS. There was no correlation between body mass index(BMI), family history, the cause of CRF, the period of CRF diagnosis, the period of dependency to dialysis, weekly frequency of dialysis, ferritin, and Erythropoietin (EPO) intake, drug history of patients and suffering by RLS. **Conclusion**: According to this study, we found that RLS is a common problem in HD patients and there is no correlation between affected by RLS and laboratory findings except BUN.

INTRODUCTION

Restless legs syndrome (RLS) is a neurological sensory-motor disease. It has been defined by the irresistible urge to move limbs that could happen in each of legs, especially at the lower parts, or in both legs or in arms. This symptom often appears with unpleasant, creeping or crawling sensations through inside the legs. These symptoms become more severe when the patients rest or sleep and could cause sleep disorders (1). Different reasons had been expressed for RLS. It could be idiopathic or because of some conditions such as pregnancy, iron deficiency, anemia, neurological disease, and Kidney disease (2, 3). Smoking and caffeine intake are considered as risk factors for this syndrome in a healthy population (4). Patients with kidney disease and renal failures especially the ones who are under hemodialysis treatments present a high prevalence of sleep disorders such as RLS (5). Different prevalence of RLS in patients with chronic renal failure (CRF) undergoing hemodialysis has been reported all over the world. Prevalence range through conducted research differ from 1.5% to 69.8%(6). Also this prevalence will be increased with the progression of renal dysfunction (7). Hemodialysis patients have a heavy symptom burden that was correlated to a reduction in quality of life and sleep (8). Having a high risk of RLS and sleep disorders are significant causes of poor quality of life (9). There is a strong relationship between quality of life and morbidity and mortality of end stage renal disease (ESRD) patient (10).

Also, some researchers believed that RLS could lead patients to other problems such as cardiovascular disease that make the quality of life worse (11). Inattention to research on RLS, especially among patients with ESRD or renal failure, is a complication, and conflicting results therefore, fur-

ther studies on these patients are needed so the aim of this study is Prevalence of restless legs syndrome in patients with Chronic Renal Failure undergoing hemodialysis.

MATERIALS AND METHODS

This cross-sectional study was performed on one hundred and eighteen patients undergoing hemodialysis who were referred to Rajaee hospital in Tonekabon, Imam Sajjad hospital in Ramsar, and Taleghani hospital in Chalus, Mazandaran, Iran for their dialysis therapy.

An interview was performed and demographic data including age, gender, the duration of CRF, frequency of dialysis per week, duration of dialysis, family history, and received treatment were recorded. Subjects with dementia, patients with incomplete data, and the ones who died in last year were excluded from the study. The information related to this syndrome was assessed by a questionnaire based on international restless legs syndrome group (IRLSSG) criteria which consist of RLS diagnostic criteria (2). In addition "Restless leg syndrome rating scale" questionnaire in patients who certainly have diagnosed with RLS have been done and duration of RLS symptoms, received treatment, and medication doses were recorded.

Inclusion criteria: The patient is suffering from chronic renal failure or end stage renal disease

That has been treated for dialysis for at least one month 2. The patient has the full consent to participate in study 3. The disease has the ability and consciousness necessary to participate in study 4. During the study, the patient has a stable condition and does not have an acute cardiovascular or brain disorder, such as heart failure and stroke.

In this 10-point scale: score 0 = patient had no pain; score 1 = discomfort severity was mild; score 2 = discomfort severity was moderate; score 3 = discomfort severity was extreme; score 4 = discomfort severity was very extreme.

Eventually, if patients total score was 0 patients doesn't suffer syndrome; 1-10, RLS severity was mild; 11-20, RLS severity was moderate; 21-30, RLS severity was extreme; 31-40, RLS severity was very extreme. Anthropometry data like/such as height in cm, weight in kg, and body mass index (BMI) in kg/cm^2 also were measured.

Laboratory tests including the level of hemoglobin, calcium, ferritin, blood urea nitrogen (BUN) in post dialysis, and alkaline were carried out every 3 months for all hemodialysis patients in these centers.

Chi-square test was used to prove a significant connection between qualitative variables. The statistical analysis has been done using statistical package for the social sciences (SPSS) software, version 23 and all output results will be presented at following tables.

RESULTS

A group of one hundred and eighteen patients with chronic renal failure on regular hemodialysis with the mean age of 59.83 years (range 15-92 years) was included in the study. Based on the IRLSSG criteria, 19 patients (16.1%) were diagnosed with RLS. The average RLS severity score based on the IRLSSG (severity scale) was 23.5.

The demographic pattern and physical examination of the patients are shown in Table 1. There was no significant correlation between RLS and age, gender, BMI.

No significant difference was observed between RLS-positive and RLS-negative patients regarding the hemoglobin level, the serum level of ferritin, calcium, and creatinine. However, there is a relation between RLS and BUN level ($p < 0.03$)) Table 2).

There was just one (5.26%) patient with RLS which has a positive family history and there is no correlation between RLS and family history ($p=0.58$).

The average daily use of iron supplements was 55.26 mg and the average Weekly received Erythropoietin was 9473.68 units. There was no correlation between receiving iron supplements and Erythropoietin and drug history of patients and suffering by RLS. Details of drug usage were shown in Table 3.

In this research According to data obtained from patients with RLS; CRF etiology 26.31% caused by Diabetes mellitus, 52.63% by hypertension and 15.78% by other reasons. None of them was because of Glomerulonephritis and Polycystic kidney disease (PKD). There was no correlation between CRF etiology and RLS ($P=0.57$). In addition, there was no correlation between the period of CRF diagnosis, the period of dependency to dialysis, weekly frequency of dialysis and RLS (Table 4).

DISCUSSION

Our result showed that from 118 patients under hemodialysis treatment, 19 patients (16.1%) according to IRLSSG criteria have RLS. The prevalence of RLS in HD patients is very different. In IRAN it differs from 37.4% to 55% (12-14). Generally, in the Middle East, the prevalence was reported 47 % (15). Also, it has been reported 12% in Turkey (16), 18% in Egypt(17), 50.22% in Saudi Arabia (17) and 20.3%in Syria (4). Almost all of this prevalence is higher than our study. It can be explained by the lower proportion of patients in our work.

Studies that performed in other countries for example in Canada (18), Italy (19), China (20) and India (21, 22) showed a prevalence between 1.5 and 62% in HD patients. This different prevalence in countries could be because of geographical regions and genetic factors (21) but this opinion needs more studies and researchers to be proved. The prevalence of our study is near Merlino work (18.4%)(19) and Mucsi I et al. (14%) (18). At all, the prevalence of RLS patients among hemodialysis ones is higher than the general population (8.00 %).

In This study, there is no relation between the prevalence of RLS and gender, family history, the period of CRF diagnosis, dialysis duration, and frequency. These are as same as Mohammad Rohani et al. work (12) but in al-jahdali work (17), the prevalence of RLS in women was higher than men. In our study, there is no relation between age, BMI, and RLS. It is as same as al-jahdali et al. (17) research but in Zadeh saraji et al. study the age and BMI of RLS-positive group were significantly higher than the RLS-negative group. They agree that weight loss may be able to help to relieve the symptom

of RLS. Also in this research, unlike our work, there is a relation between duration of dialysis, BMI, and RLS (13).
In addition, there is no association between RLS prevalence and laboratory data like hemoglobin level, the serum level of Ferritin, Calcium, Erythropoietin, and Creatinine. The research of Yazdi Z et al. confirm these findings (14). Chen Yu and colleagues comment that HD patients' laboratory data were usually reported abnormal in BUN, Cr, potassium, and HGB level (23). In Zadeh saraji, et al. study Erythropoietin dosage was significantly lower in the RLS group and significant relation between serum hemoglobin level, serum calcium, and RLS reported (13).
Likewise, there is a correlation between BUN level and suffering RLS. In Kim JM et al. investigation The relationship between BUN levels and severity of RLS was found, but the BUN level did not differ between individuals with and without RLS, while in our article the BUN level was different (24). Mao S et al. (25) and Hasheminasab Zaware R et al. (26) found no correlation as well as other biochemical factors such as iron, creatinine, and calcium.
According to H. Khan et al. study in primary RLS patients Whereas, iron in the serum is often normal , but the density of iron in the brain significantly decreased in substantia nigra and other regions of the brain such as thalamus, caudate, putamen, and white matter and these decreases were correlated with RLS symptom severity. In addition, ferritin in the cerebrospinal fluid decreases in the RLS-positive group. In this study, there is no relation between serum level of ferritin and Daily received iron supplements (mg) with RLS (27).
In the RLS patients, the density of DAT (dopamine transporter) was higher in the caudate, the posterior putamen and the entire striatum compared with the RLS-negative group (28). However, the numbers of dopamine D2 receptors in the striatum and putamen decreased (1, 2). In the brain, iron and dopamine are related to one another. Iron is needed for the synthesis of L-DOPA so it suggested that in iron deficiency synthesis of L-DOPA decreased but in opposite the rate-limiting enzyme of L-DOPA in the substantia nigra of RLS patients increased and RLS patients have hyperdopaminergic state (27).
According to some studies, a specific neuroprotective effect of vitamin D on dopaminergic neurons reported (8). Cakır et al. found that in RLS patients the amount of vitamin D decreases and because of this fall in the level of vitamin D, the neuroprotective effect on the dopaminergic neurons would be decreased and with a drop in dopamine level, the risk of RLS might be increased (29).
Recent studies suggest that in pregnant women who are under hemodialysis it's better to keep the BUN level low. Because they believe that blood urea nitrogen (BUN) level and the neonatal birth weight have a negative relation (30). On the other hand, pregnancy is one of the reasons that cause RLS symptoms but the main reason for this association was not well known(1). In this study, we found a lower level of BUN in RLS-positive patients. Maybe lowering the BUN level in hemodialysis pregnant women makes them show RLS symptoms. More researchers should be conducted to clarify this issue.
RLS patients should be checked regularly to measure the change of signs and complications and be trained to have a better lifestyle and dealing with illness. Iron treatment in iron deficiency patients can help to improve RLS. However, in patients with kidney disease, there is almost no improvement of RLS under hemodialysis .pharmacological treatment such as dopamine agonist and kidney transplanta-

Table 1. Demographic data in RLS-positive and RLS-negative CRF patient.

Variable	**RLS+**		**RLS-**		
	Number of patients	percentage	Number of patients	percentage	*p*-value
age					0.591
<30	1	5.26	3	3.03	
30-60	5	26.31	38	38.38	
>60	13	68.42	58	58.58	
BMI					0.351
<18.4	1	5.26	5	5.05	
18.5-24.9	6	31.57	41	41.41	
25-29.9	8	42.1	41	41.41	
>30	4	21.05	12	12.12	
Sex					0.22
male	7	36.84	49	49.49	
female	12	63.15	50	50.50	

Table 2. Laboratory data in RLS-positive and RLS-negative CRF patient.

Variable	**RLS+**		**RLS-**		
	Number of patients	percentage	Number of patients	percentage	*p*-value
Hemoglobin					0.227
7<	1	5.26	3	3.03	
7-12	16	84.21	74	74.74	
12>	2	10.52	22	22.22	
calcium					0.223
8<	2	52.10	22	22.22	
8-10	11	89.57	15	15.15	
10>	6	57.31	66	66.66	
BUN					0.03
50<	9	36.47	23	23.23	
50>	10	63.52	76	76.76	
creatinine					0.663
5.1<	0	0	1	1.01	
5.1>	19	100	98	98.98	
ferritin					0.273
150<	2	52.10	16	16.16	
150-300	0	0	9	9.09	
300>	17	47.89	16	16.16	

Table 3. Drug usage

Variable	**RLS+**		**RLS-**		
	Number of patients	percentage	Number of patients	percentage	*p*-value
drug history of patients					
Not taking psychotropic drugs	15	78.94	85	85.85	
taking psychotropic drugs	4	21.05	14	14.14	
Daily iron supplements(mg)					0.30
0	7	36.84	44	44.44	
50	5	26.31	32	32.32	
100	5	26.31	16	16.16	
150	2	10.52	7	7.07	
Weekly received Erythropoietin (unit)					0.071
4000	3	15.78	27	27.27	
8000	3	15.78	26	26.26	
10000	0	0	3	3.03	
12000	13	68.42	43	43.43	

Table 4. Dialysis information

Variable	**RLS+**		**RLS-**		
	Number of patients	percentage	Number of patients	percentage	*p*-value
period of CRF diagnosis(year)					
<1	1	5.26	10	10.10	
1-4	6	31.57	45	45.45	
5-9	6	31.57	27	27.27	
>10	6	31.57	17	17.17	
period of dependency to dialysis(year)					0.58
<1	1	5.26	21	21.21	
1-4	16	84.21	65	65.65	
5-9	2	10.52	9	9.09	
>10	0	0	4	4.04	
weekly frequency of dialysis					0.75
1	1	5.26	4	4.04	
2	5	26.31	33	33.33	
3	13	68.42	62	62.62	

tion may help. In primary RLS patients nonpharmacological treatment for example exercises may be effective but in patients with moderate or severe symptom of RLS use of drugs is needed (1).

CONCLUSION

The aim of the current study was to determine the frequency of RLS in hemodialysis patients for diagnosis and control the signs of RLS to increase the quality of life in them. According to this study, we found that RLS is a common problem in hemodialysis patients and there is no correlation between affected by RLS and laboratory findings except BUN. Our study merely refers to the prevalence of factors in patients and, due to the type of method and type of study and the type of data collection, this study can not reveal the risk factors of the disease. Other studies are required to validate these results in different settings. We suggest a multicenter, multinational, prospective study involving both RLS and ESRD patients with the same indication for a renal problem to obtain a homogeneous and highly accurate result. A systematic review and meta-analysis of the literature are also beneficial to evaluate the predictive value of different factors found in different studies.

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AUTHOR CONTRIBUTION

All authors contributed.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL STANDARDS

Informed consent was obtained from all individual participants included in the study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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