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CLINICAL STUDY

Restless-legs syndrome and insomnia in hemodialysis patients

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Abstract

Aim/background: Restless legs syndrome (RLS) is a common neurological movement disorder which is commonly seen in hemodialysis (HD) patients. Insomnia, depression, and anxiety disorders frequently show concurrence. In this study, we aimed to investigate RLS and insomnia prevalence and related factors in HD patients. **Subjects and methods:** Patients who were under HD treatment and healthy controls with similar mean age, sex ratio, and hypertension and diabetes mellitus frequency were included in this study. Depression, insomnia, and daytime sleepiness assessments were performed by using Beck Depression Inventory, Insomnia Severity Index, and Epworth Sleepiness Scale. The diagnosis of RLS was made using the International RLS Study Group consensus criteria. **Results:** About 156 HD patients and 35 controls were enrolled. The mean age was 50.6 in the HD group and 49.7 in the control group. Female sex was 43.9% in the HD group and 57.1% in the control group. RLS was significantly more frequent in HD patients compared with controls. The rate of sub-threshold insomnia and insomnia with moderate severity was higher in HD patients. While insomnia severity score and diabetes mellitus were significantly associated with the presence of RLS, depression, RLS, older age, and being under HD treatment were independently associated with insomnia severity. **Conclusions:** HD patients commonly have RLS and insomnia. Insomnia and diabetes mellitus seem to be major factors underlying RLS in HD patients. Furthermore, depression and RLS seem to be closely related to insomnia in these patients. Treatment of depression, insomnia, and RLS may be beneficial to improve quality of life in HD patients.

Keywords

Anxiety, depression, hemodialysis, insomnia, restless legs syndrome

History

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Introduction

Restless legs syndrome (RLS) or Willis–Ekbom disease is a common sensory motor neurological disorder that is characterized by the need to move the legs due to uncomfortable or painful sensations in the legs.^{1,2} Symptoms have diurnal variation and diminish with movement.³ The diagnosis of RLS is based on the International RLS Study Group (IRLSSG) consensus which is depended on five essential diagnostic criteria.³ RLS prevalence is reported to be between 0.1 and 15% in the general population.^{4–8} RLS can be primary or secondary. Secondary RLS can occur due to iron or folate deficiency, pregnancy, chronic kidney disease (CKD), radiculopathy, polyneuropathy, and rheumatoid arthritis.⁹ RLS presence or clinical severity can be affected from accompanied insomnia, depression, or anxiety.^{10,11} Because of the several medical factors, quality of life and sleep quality are markedly reduced among HD patients. The neuropathic pain experienced by patients with RLS may lead to a noticeable

loss of sleep and decreased quality of life. In addition to the well-known factors underlying RLS in maintenance HD patients like iron deficiency, subclinical inflammation and oxidative stress may contribute to RLS.^{12,13} In this study, RLS prevalence and related factors were evaluated in a group of HD patients.

Subjects and methods

End stage renal disease (ESRD) patients who were under HD treatment for more than 6 months in the nephrology outpatient clinic and a control group with normal kidney functions were included in this study. Patients who were unable to answer the questionnaires were not included the study. One hundred and fifty-six HD patients and 35 controls were enrolled. The diagnosis of RLS was made using IRLSSG consensus criteria.³ All patients' neurological examinations were performed by neurologists for the presence of neuropathy and/or radiculopathy. Depressive symptoms were assessed using Beck Depression Inventory. A score of ≥ 9 over 63 was considered to indicate depressive state. Epworth Sleepiness Scale was used for daytime sleepiness (normal: 0–10, borderline: 10–12, and abnormal: 12–24 points). Insomnia was questioned and analyzed with Insomnia Severity Index.

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It was classified as no clinically significant insomnia (0–7), sub-threshold insomnia (8–14), moderate clinical insomnia (15–21), and severe clinical insomnia (22–28 points).

Demographic data, duration of HD treatment, presence of hypertension, and diabetes mellitus were recorded. The study was approved by Bursa Regional Ethics Committee, and all subjects gave written informed consent. All the procedures were conducted in accordance with the Second Declaration of Helsinki and its later amendments.

Statistical analysis

Statistical analyses were done using IBM SPSS version 21 for Windows (SPSS Inc., Chicago, IL). Categorical data were presented with numbers and percentages and continuous data were presented as mean \pm standard deviation or median (minimum–maximum) according to the distribution of the data. Categorical data were compared by Chi-square or Fisher's exact tests. Normality of the distribution of continuous data was assessed using the Kolmogorov–Smirnov test. Student's *t* or Mann–Whitney's *U* test was used to compare continuous variables between the groups. Pearson or Spearman test was used for correlation analyses. Multivariate logistic regression analysis was performed to determine factors independently associated with presence of RLS. A correlation coefficient of 0.1–0.3 was considered as weak, 0.3–0.5 as moderate, and >0.5 as strong correlation. A two-sided *p* value <0.05 was considered as statistically significant.

Results

Mean ages and sex ratios were similar between the groups (Table 1). Both the groups had similar rates of hypertension and diabetes mellitus. The frequency of RLS was significantly higher in HD patients compared with controls (47% versus 20%, $p=0.004$). When the whole study population was separated according to the presence and absence of diabetes, RLS was more common in diabetic subjects (55% versus 30%, $p=0.03$). However, while the frequency of RLS was similar in diabetic subjects in the control group (20% versus 20%, $p=1$), diabetic subjects in the HD group had a significantly

higher frequency of RLS compared with non-diabetic subjects in the HD group (66.7% versus 34.3%, $p=0.02$).

A significantly higher proportion of HD patients were taking sleep drugs (at least once a week) ($p=0.012$). The results of Insomnia Severity Index test indicated that the HD group showed a trend towards higher frequency of insomnia. When insomnia severity was further analyzed, sub-threshold insomnia and insomnia with moderate severity was significantly more frequent in the HD group (44% versus 22.9%, $p=0.03$). Insomnia Severity Index score was significantly higher in the HD group compared with the control group (median score 7 versus 3, $p=0.01$). Depression and Epworth sleepiness scores were similar in both groups.

The factors independently associated with the presence of RLS were higher insomnia severity score (OR = 1.1, 95% CI 1.03–1.2, $p=0.009$), diabetes mellitus (OR = 4.1 95% CI 1.2–13.7, $p=0.024$), and depression score (OR = 1.1, 95% CI 1.003–1.12, $p=0.04$).

Regression analysis revealed that depression score and older age were independently associated with having sub-threshold insomnia (OR = 1.08, 95% CI 1.02–1.14; $p=0.006$ and OR = 1.04, 95% CI 1.006–1.08, respectively). Being in the HD group showed a trend towards independent association with insomnia (OR = 2.6, 95% CI 0.8–6.6, $p=0.1$). Linear regression analysis showed that higher depression score, presence of RLS, older age, and HD treatment were independently associated with a higher insomnia severity score (OR = 0.22, 95% CI 0.09–0.4, $p=0.001$; OR = 3.3, 95% CI 0.7–5.8, $p=0.013$; OR = 0.09, 95% CI 0.008–0.17, $p=0.032$; and OR = 2.6, 95% CI 0.2–5, $p=0.033$, respectively).

Discussion

In this study, patients under HD treatment had significantly higher rates of RLS, depressive mood, and insomnia compared with controls. While insomnia, depression, and diabetes mellitus were independently associated with RLS, being in the HD group was not. Insomnia severity was independently associated with depression, RLS, older age, and being in the HD group.

Table 1. Comparison of hemodialysis patients and controls.

	Hemodialysis patients ($n=156$)	Controls ($n=35$)	<i>p</i> -Value
Age (years)	50.6 \pm 14.1	49.7 \pm 13.3	0.7 ^b
Gender (%females)	43.9	57.1	0.16 ^a
Smoking (%)	28.2	34.3	0.5 ^a
Hypertension (%)	33.3	28.6	0.6 ^a
Diabetes mellitus (%)	17.2	14.3	0.7 ^a
Restless leg syndrome (%)	47	20	0.004 ^a
Beck depression score	10.8 \pm 10	8.3 \pm 6.8	0.08 ^b
Epworth score	3 (0–15)	2 (0–21)	0.26 ^c
Daytime sleepiness (%)	7.5	11.4	0.4 ^a
Insomnia severity index score	7 (0–28)	3 (0–16)	0.01 ^c
At least sub-threshold insomnia (%)	44	22.9	0.03 ^a
At least moderate insomnia (%)	20.2	5.7	0.066 ^a
Sleep pill users (%)	32.9	11.4	0.012 ^a

^aChi-square test.

^bStudent's *t* test.

^cMann–Whitney's *U* test.

ESRD is commonly associated with severe distal motor and sensory deficits. RLS is reported in a rate of 6–50% in ESRD patients.^{14–22} RLS is associated with insomnia in HD patients.²³ It has been shown that RLS is associated with increased mortality and impaired quality of life in patients on maintenance dialysis.²⁴ In our study, diabetes mellitus was independently associated with the presence of RLS. Merlino et al.²⁵ reported that polyneuropathy was the main risk factor for RLS in diabetic patients. However, there are limited studies confirming these results.^{26,27} Besides from polyneuropathy, diabetes may affect central catecholaminergic systems by lowering dopaminergic content in midbrain and striatum where are crucial for RLS circuitry.²⁸ Despite sleep disorder treatment did not change in RLS-HD patients in a study consisting of RLS versus control subjects, a larger prevalence of sleep disorder was seen.¹⁸ A well-designed study has shown that RLS patients are suffering from disorders of onset and continuity of sleep.¹² Poor sleep quality has been shown to be associated with mortality risk and mental derangement in these patients.^{12,29} In a study from Japan, patient with RLS was associated with hyperphosphatemia and anxiety.³⁰ Collado-Seidel et al.²¹ compared stable HD patients according to the presence and absence of RLS and found no association among age, duration of uremia, anemia, or calcium levels and presence of RLS. Although its pathogenesis is unclear, uremic toxins, inflammation, vitamin deficiencies, and anemia may precipitate RLS symptoms in maintenance HD patients. When dialysis adequacy is increased by home dialysis, RLS symptoms have been shown to resolve.¹³ This finding supports the hypothesis of uremic toxins in the etiology. In another study in 227 HD/peritoneal dialysis patients, significant predictors of RLS were diabetes mellitus, coffee intake, afternoon dialysis, male sex, and peritoneal dialysis.²² In our study, independent factors associated with RLS were insomnia, depression, and diabetes mellitus.

Many patients undergoing dialysis therapy suffer from sleep disturbances. In a study, 65% of HD patients had sleep disorders, mainly insomnia.^{16,31} Patients in the HD group in our study had higher insomnia severity indices. Another large study consisting of 883 HD patients revealed a rate of insomnia and RLS of 69% and 18.4%, respectively.³² Nocturnal HD shift and home HD, where patients undergo HD treatment during their common sleeping time, may result in a decreased rate of excessive daytime sleepiness. However, none of our patients underwent HD treatment in these ways.

Depression is a very common psychological disorder in ESRD patients and the incidence rate is reported to be between 25 and 50%.³³ In our study, depression score was higher compared with controls and also seemed to be independently associated with insomnia severity and RLS. Depression may be an underdiagnosed and undertreated condition in these patients. Furthermore, there is insufficient body of evidence about the efficacy and the safety of various antidepressant treatment options in these patients.

Limitations of our study include the cross-sectional and observational design. Furthermore, the relatively small sample size of the control group may cause underestimation of the effect of being under HD treatment on RLS.

Conclusions

Depression, RLS, and insomnia are commonly found in HD patients. We found a close relationship among diabetes, depression, and insomnia and RLS. Independent factors associated with insomnia severity were depression, RLS, older age, and being under HD treatment. Interventional studies which focus on treatment of these factors on quality of life in these patients may give important information.

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Declaration of interest

The authors report that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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