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Effect of Renal Transplantation in Restless Legs Syndrome

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Abstract

Objectives: **Restless legs syndrome is a disorder in which patients have irresistible urge to move legs during rest. Restless legs syndrome seems to be common in end-stage renal disease. After a successful renal transplant, symptoms ameliorate with renal function improvement and restless legs syndrome is seen less in this population. Here, we aimed to investigate restless legs syndrome frequency and associated factors in renal transplant patients.**

Materials and Methods: **In a cross-sectional study with 193 patients (116 hemodialysis patients, 45 transplant patients, and 32 controls), the presence of restless legs syndrome was assessed using the Restless Legs Syndrome Questionnaire. Medical history, demographic, and laboratory data were collected from the patients' medical records. Patients were questioned about the presence of restless legs syndrome using the Restless Legs Syndrome Questionnaire. Patients were evaluated with Beck Depression Scale for depression and Pittsburgh tests for sleep disturbances.**

Results: **While the rate of restless legs syndrome was similar between transplants and controls, it was significantly greater in hemodialysis patients. Hemodialysis patients and controls had similar depression scores that were higher compared with transplant patients. Pittsburgh score was similar in transplant patients and controls and significantly increased in the hemodialysis patients. The rate of insomnia was significantly higher in the hemodialysis patients compared with the other 2 groups. Logistic regression analysis revealed independent correlates of restless legs syndrome as insomnia, Beck depression score, and being on hemodialysis. Linear regression analysis showed that independent correlates of higher Pittsburgh score were higher depression score, higher age, and presence of restless legs syndrome.**

Conclusions: **The prevalence of restless legs syndrome is significantly lower in transplant patients than it is in patients on maintenance dialysis. In renal transplant patients, restless legs syndrome frequency was found to be lower because of improved renal functions (normalization of uremia), psychological symptoms, and sleep disturbances.**

Key words: *Kidney transplant, Restless legs syndrome, Insomnia, Dialysis*

Introduction

Restless legs syndrome (RLS) is a disorder characterized by unpleasant feeling in the legs, occurring at rest (particularly at bedtime), accompanied by an irresistible urge to move the limbs and thereby produce a temporary relief of symptoms.[1-3] It develops as idiopathic and is caused by genetic origin and also secondary to iron deficiency, neurologic lesions, uremia, rheumatoid arthritis, cigarette smoking, myelopathy or myelitis, hypothyroidism or hyperthyroidism, acute intermittent

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porphyria, diabetes, pregnancy, uremia, and use of certain medications (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors, lithium, dopamine antagonists, and caffeine).[3,4] The pathogenesis of the RLS disorder may involve disruption of dopaminergic function in the central nervous system, dysfunction of subcortical brain areas, and abnormal relation between brain iron metabolism.[3,5] Restless legs syndrome may be related to iron, folate, B12, or magnesium deficiency, and also caused by anemia.[6] We used International Restless Legs Syndrome Study Group diagnostic criteria, and RLS prevalence was recorded at 5% to 15% in the general population.[7]

Restless legs syndrome seems to be common in end-stage renal disease (range, 6.6%-62%).[8] In addition to the usual factors, hyperphosphatemia, poor sleep quality, anxiety, and stress are independently related to the presence of RLS in uremic patients under hemodialysis therapy. A paucity of publications show that reduced RLS and psychological disorders with disappearance of the uremic table after renal transplant, there has been recent interest in this topic. We aimed to investigate the effect of kidney transplant on RLS, insomnia, and psychological symptoms, and the factors that affect it.

Methods and Patients

One hundred ninety-three patients, aged 18 years and older, undergoing follow-up for more than 6 months after renal transplantation (transplant group, [TG]) or undergoing hemodialysis treatment (hemodialysis group, [HG]) in the nephrology outpatient clinic, and subjects with normal kidney functions (control group, [CG]) were enrolled in this cross-sectional study. Demographic data, medical history, smoking history, and coffee consumption were recorded (Table 1). All of the patients were questioned about the presence of RLS using the Restless Legs Syndrome Questionnaire.[9] Recent laboratory parameters were recorded from their files. Patients were questioned about active use of erythropoietin treatment. Patients were evaluated with Beck Depression Scale for depression and Pittsburgh tests for sleep disturbances.[10,11] Patients under treatment for RLS were excluded. Standard immunosuppressive therapy generally consisted of either tacrolimus (90%) or cyclosporine (10%) plus prednisolone and mycophenolate mofetil in TG. The present study was approved by Bursa Regional Ethics Committee, and all subjects gave written informed consent. All procedures were in accordance with the Second Declaration of Helsinki.

Statistical analyses

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 16.0, IBM Corporation, Armonk, NY, USA). While categorical data were presented with numbers and percentages, ordinal data were presented as median (interquartile range), and continuous data were presented as mean ± standard deviation. Categorical data were compared using chi-square test or the Fisher exact test. Ordinal variables were compared using the Mann-Whitney *U* and Kruskal-Wallis tests. Continuous data were compared using the *t* test and the 1-way analysis of variance test. Correlation analyses were performed using Spearman's rank correlation coefficient and the Pearson product moment correlation analysis, as needed. A correlation

Table 1. Comparison of the Groups

	TG (n = 45)	HG (n = 116)	CG (n = 32)	*P* Value
Age (y)	40.8 ± 13	44.8 ± 11.2	44 ± 10.5	.16
Sex (% males)	55.6	56	43.8	.45
Smoking (%)	11.6	28.9	40.6†	.02
Coffee consumption (%)	23.8	35.4	56.2†	.02
Diabetes mellitus (%)	9.8	18.8	9.4	.29
Hypertension (%)	45	34.5	18.8	.06
RLS (%)	15.6	45.6†	18.8	< .001
Erythropoietin treatment (%)	0	68.4	0	
Beck Depression score	4 (9)‡	8 (16)	7 (12)	.022
Pittsburgh score	4 (3)	7 (5) †	4 (3.25)	< .001
Insomnia*	45.5	71.2†	54.2	.009

Abbreviations: CG, control group; HG, hemodialysis group; RLS, restless leg syndrome; TG, transplant group

†Higher than other 2 groups.

‡Lower than other 2 groups.

*According to Pittsburgh score.

coefficient of 0.1 to 0.3 was accepted as slight correlation, > 0.3 to 0.5 as moderate correlation, and > 0.5 as a strong correlation. A logistic regression analysis was done to detect independent correlates of RLS and linear regression analysis was done to seek independent correlates of higher Pittsburgh scores. A 2-sided *P* value of < .05 was considered statistically significant.

Results

One hundred sixteen patients were enrolled in the HG, 45 patients in the TG, and 32 subjects comprised the CG. Comparison of the groups is given in Table 1. There was no significant sex or age difference between the groups. The rate of hypertension tended to be higher in the HG and the TG compared with the CG, and the rate of diabetes mellitus tended to be higher in the HG compared to the TG and the CG, but these differences were not statistically significant. While the rate of RLS was similar between the TG and the CG, it was significantly increased in the HG. The hemodialysis group and the CG had similar depression scores, which were significantly higher compared with the TG (*P* = .01 and *P* = .02). The Pittsburgh score was similar in the TG and the CG and significantly increased in the HG. The rate of insomnia was significantly higher in the HG compared with the other 2 groups.

Logistic regression analysis revealed independent correlates of RLS as insomnia (*P* = .01, Wald 6.7, 95% CI: [-2.1] to [-0.3]), Beck depression score (*P* = .04, Wald 4.2, 95% CI: (0.002-0.08), and being in HG (*P* = .07, Wald 3.2, 95% CI [-0.08] to [1.9]). Linear regression analyses showed that independent correlates of higher Pittsburgh score were higher depression score (*P* < .001, t 5.3, 95% CI: 0.1-0.2), higher age (*P* = .001, t 3.5, 95% CI: 0.03-0.12), and presence of RLS (*P* = .001, t 3.4, 95% CI: 0.77-2.9).

Table 2. Comparison of Laboratory Results in TG and HG

	TG (n=45)	HG (n=116)	*P* Value
Urea (mmol/L)	15.8 ± 6.3	36.8 ± 16.2	<0.001
Creatinine (μmol/L)	114.9 ± 44	822 ± 256	<0.001
Albumin (g/L)	38 ± 7	38 ± 4	0.98
Hemoglobin (g/L)	125 ± 24	113 ± 16	0.01
Ferritin (pmol/L)	912 ± 795	2577 ± 1316	<0.001
Parathyroid hormone (ng/L)	412 ± 505	375 ± 376	0.7
Calcium (mmol/L)	2.2 ± 0.4	2.1 ± 0.2	0.6
Phosphorus (mmol/L)	1.5 ± 0.3	1.6 ± 0.5	0.17
Calcium*Phosphorus	3.3 ± 0.1	3.3 ± 0.1	0.4

Abbreviations: HG, hemodialysis group; TG, transplant group

Discussion

Restless legs syndrome is a common disorder in hemodialysis patients. It has been reported in a case presentation that after a successful renal transplant procedure, symptoms of RLS were seemed to be relieved.[12] Studies after these observations showed that kidney transplant has a strong and positive influence on RLS symptoms in hemodialysis patients. In various studies, it has been found that 40% to 50% of patients had symptom improvement.[3,13] In our study, after a successful renal transplant, RLS frequency rates decreased to 66% because of lower uremia and normalization of other renal functions.

In case of renal failure or uremia, the brain has a decreased level of metabolic activity and oxygen consumption.[12,14] Balance of excitatory and inhibitory neurotransmitters seemed to be disrupted by guanidino compounds.[15-18] These organic compounds antagonize γ-aminobutyric acid receptors and have agonistic effects on N-methyl-D-aspartate glutamate receptors, which enhance cortical activity.[16-18] Restless legs syndrome symptoms may result from a decrease in dopaminergic modulation of intracortical excitability with reduced supraspinal inhibition and increased spinal excitability.[19-21] Iron deficiency or iron transport to the central nervous system play a central role in RLS. Iron is a cofactor for tyrosine hydroxylase, which has a role in dopamine synthesis at the rate-limiting step.[20-21] Even ferritin, or transferrin saturation index, are normal, cerebrospinal fluid ferritin levels may show CNS iron deficiency syndrome. Restless legs syndrome often persists with hemodialysis, but it improves after transplant, which may be associated with the normal calcium (Ca) and phosphorus (P) metabolism.[22]

Increased quality of life, psychological status, anemia parameters, normal Ca and *P* metabolism, a better sleep regularity can be counted as other factors affecting RLS symptoms except renal causes. In this study, renal transplant patients had decreased levels of uremia, reduced insomnia rates, and ameliorated psychological disorders.

The pathogenesis of the RLS disorder may also be related to abnormal relation between brain iron metabolism; serum iron, folate, B12, or magnesium deficiency as well as due to anemia.[3,5,23] Although anemia is a known etiological factor causing to RLS, hemoglobin levels were similar of guides'

recommended levels to hemodialysis patients. Even though hemoglobin levels were obtained lower than the renal transplant group, the lower frequency of RLS in transplant group shows other factors predisposing rather than the anemia. Also in our study, erythropoietin usage did not reveal any correlation with RLS frequency. There are controversial findings in literature, some of them shows erythropoietin usage caused to RLS and a part of the studies supports that erythropoietin deficiency increased RLS frequency.[24,25]

The better quality of life of transplant patients compared with hemodialyses patients, and the clinical improvement of some dangerous sleep-related problems (eg, sleep apnea or RLS) may erroneously suggest that sleep problems vanish after a successful transplant.[26-28] An association between RLS and insomnia in patients on maintenance dialysis has been suggested already by papers.[29-31] In our study, RLS and sleep disturbances were correlated. After renal transplant, one of the most important factors that effects improvement of sleep disturbances is the relieving of psychological disorders. Also, insomnia and psychological disorders showed a close relation in the present study.

Tobacco and coffee consumption were found to be associated with RLS in some clinical studies, but our study did not show any relation. These 2 factors were obtained more commonly in the HC group, but RLS frequency showed less than the other groups did. These results confirm that uremia, inflammatory factors, and psychological status are more relevant with RLS.

Besides having increased risk of mortality in hemodialysis patients who had RLS and sleep disorder clinically, renal transplant patients also carry with it and increased risk of mortality.[32-34] Several potential mechanisms may account for the association between RLS and mortality. Restless legs syndrome was associated with cardiovascular diseases. Both RLS and periodic limb movement in sleep cause chronic sleep loss and sleep fragmentation, which, in turn, lead to increased cardiovascular risk. Chronic sleep fragmentation is associated with an increased hypertensive burden that may result in left ventricular hypertrophy, which is an independent predictor of mortality in the transplant population.[32] Restless legs syndrome and sleep disorder treatment plays important role in modifying quality of life and decreasing mortality rates.

This study shows that half of the hemodialysis patients had RLS symptoms. After a successful renal transplant procedure, RLS rates were apparently decreased. As having a close relation with RLS in hemodialysis patients, improving sleep quality and psychological disorders increases not only quality of life but also survival of patients.

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