

The significance of restless legs syndrome among patients with chronic kidney disease

Ph.D. thesis abstract

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Introduction

Patients with chronic somatic and psychiatric diseases frequently report sleep-related problems. Sleep disorders increase illness burden, deteriorate health-related quality of life and they are also associated with unfavorable clinical outcomes and the development of psychiatric co-morbidities. An increasing number of prospective studies indicates that the presence of sleep disorders is a risk factor of mortality.

The number of patients diagnosed with chronic kidney disease (CKD) is increasing steadily worldwide. Depression is a highly prevalent disorder in this patient population, and their health-related quality of life and life expectancy is considerably decreased compared to the level in the general population. Sleep-related complaints are very frequent among patients with chronic kidney disease, and these may also contribute to the impairment of these important clinical outcomes. However, the prevalence of sleep disorders, their correlates and consequences are still far from being well defined in this population.

Restless legs syndrome (RLS) is a group of sensomotor symptoms characterised by unpleasant feelings in the legs provoked by immobility during resting. The symptoms are accompanied by a strong urge to move the legs, which are relieved by the movement of the lower limbs. The symptoms are typically strongest during the first half of the night and cease in the morning hours.

RLS is one of the most frequent sleep disorder in dialysed patients, its prevalence is around 15-20%. RLS is strongly associated with insomnia and depression both in the general and in the dialysed population. The health-related quality of life of subjects with RLS was significantly worse than in those without RLS among dialysed patients. Several studies found that RLS is a risk factor of mortality in the dialysed population. RLS in kidney transplanted patients has not been described yet. Diagnosis and treatment of RLS and other sleep disorders may improve the quality of life and survival of patients with chronic kidney disease (CKD).

Objectives, hypotheses

Our aim was to describe the relationship of RLS with insomnia, depression, quality of life and mortality in kidney transplanted (Tx) patients. The following hypotheses were postulated:

1. The analysis of the relationship between restless legs syndrome and insomnia among Tx patients

- a) the prevalence of insomnia, independently of other co-variates, is significantly lower in the Tx group than in the waitlisted dialysed (WL) group
- b) RLS is a significant and independent predictor of the presence of insomnia

2. The analysis of the relationship between restless legs syndrome and quality of life among kidney transplant (Tx) patients

- a) Patients with RLS report significantly worse quality of life in most quality of life subscales, and this difference is clinically relevant
- b) The significant relationship between RLS and impaired quality of life is independent of other explanatory factors
- c) The association between RLS and insomnia weakens with the correction for insomnia, but it remains significant (i.e. the relationship between RLS and quality of life is not completely accounted for by insomnia)

3. The analysis of the relationship between restless legs syndrome and depression among waitlisted dialysed (WL) and Tx patients

- a) Patients with RLS report more depressive symptoms in the total CKD population than those without RLS
- b) The association between RLS and depressive symptoms remains significant following the correction for clinical and socio-demographic co-variates
- c) RLS is a significant predictor of depressive symptoms independent of insomnia in both WL and Tx patients

4. The prospective analysis of the relationship between restless legs syndrome and mortality in Tx patients

- a) The presence of RLS is significant, independent risk factor of the mortality of Tx patients

Methods

In the TransQOL-HU (Transplantation and Quality of Life-Hungary Study) cross-sectional study the sleep and mood disorders and health-related quality of life of renal transplant patients were investigated with questionnaires from 2002 to 2003. The Tx patients enrolled in the study were subsequently followed up to nearly four years during which mortality times were monthly registered.

Data collection

All the Tx patients above 18 years old regularly seen at the Transplantation and Surgery Clinic of the Semmelweis University (n=1067) and every dialysed patient on transplantation waiting list from the dialysis centres of Budapest (n=214) was approached to join the study. Exclusion criteria were dementia and or refusal to participate.

Socio-demographic data (gender, age, education) were collected from the patients' charts or directly from the participants at the enrollment. Anamnestic data of dialysis, transplantation and medications were also recorded.

Assessment of restless legs syndrome

RLS symptoms were assessed with the RLS questionnaire. This tool consists of eight questions incorporating all the four diagnostic criteria. The Hungarian version of the questionnaire had been utilised producing consistent results by our workgroup in different renal disease populations.

The respondent was considered to suffer from RLS only in case with positive answers to all the eight questions. If any answer was missing or the questionnaire was not completed according to the instructions, the result was skipped and was considered as missing data.

Assessment of depressive symptoms

Depressive symptoms were characterised with the Center for Epidemiologic Studies depression (CES-D) score. A cut-off score of 18 was applied in order to detect clinically meaningful depression as suggested for patients with chronic kidney disease. The Hungarian version of the scale is reliable in the assessment of depressive symptoms in different populations with chronic kidney disease.

Assessment of insomnia

The Athen Insomnia Scale (AIS) was applied to measure insomniac symptoms. AIS contains eight questions regarding nighttime symptoms (sleep onset and maintenance, early wake) and daytime consequences (sleepiness, fatigue and functioning) of insomnia. The original version was translated and validated by our workgroup.

Assessment of quality of life

Health-related quality of life (HRQoL) was assessed with the Kidney Disease Quality of Life (KDQoL) questionnaire. It is a modular tool, which incorporates the Medical Outcomes Study Short Form-36 (SF-36) general quality of life scale and a set of questions about focusing on the aspects influencing quality of life special to CKD. Validation of the Hungarian version of scale has been conducted in dialysed and Tx patients by our workgroup.

Assessment of the risk of sleep apnoea

Risk of obstructive sleep apnea (OSAS) was assessed with the Berlin sleep apnea questionnaire. The scale measures the most common symptoms, consequences of OSAS in addition to hypertension and high BMI. Analysis of the answers enlists the patient into a high or low risk group regarding OSAS. Validation of the Berlin questionnaire was conducted in the general population with reliable results.

Assessment of co-morbidity

The End Stage Renal Disease Severity Index (ESRD-SI) was utilised to gain information on co-occurring diseases. The magnitude of co-morbidity was indicated as the number of conditions based on patient reports.

Laboratory parameters

The following laboratory parameters were collected from patients' chart and the electronic databases of the hospitals: hemoglobin (Hb), serum albumin and creatinine, blood urea nitrogen, iron indicators (serum iron, serum transferrin, transferrin saturation) and serum C-reactive protein (CRP). Information of prescribed medications, height and weight for body mass index were also recorded from patients' charts.

In dialysed patients Kt/V values measuring dialysis doses was registered. Renal function of kidney transplanted patients was assessed with the estimated glomerular filtra-

tion rate (eGFR) calculated from the simplified MDRD formula (Modification of Diet in Renal Disease study):

$$\text{eGFR (ml/min per } 1.73\text{m}^2) = 186 \cdot S_{\text{Cr}}^{-1,154} \cdot \text{age}^{-0,203} (\cdot 0.742 \text{ for females}),$$
where S_{Cr} = serum creatinine.

Immunosuppressive medication

Time elapsed since transplantation and information about immunosuppressive medication were collected from patients' charts for Tx patients.

Representative sample from the general Hungarian population (Hungarostudy 2002)

An age and gender-matched sample (n=2034) was selected from the database of Hungarostudy 2002 in order to compare the prevalence of insomnia. Hungarostudy 2002 has a sample of 12 643 participants representative of the adult Hungarian population. The door-to-door survey was carried out with interviews. Besides socio-demographic and health risk behaviour data, the questionnaire included the Athens Insomnia Scale (AIS).

Statistical analyses

Data were registered in the computer database developed by our workgroup. Statistical analyses were run by SPSS 13.0 and SAS 9.1. Student's t or Mann-Whitney U tests were used to compare means of continuous variables, while correlations were analysed according to Spearman. Categorical variables were compared with chi square or Fisher's exact test.

Multivariate logistic regression models were applied to investigate the individual relationship between RLS and depression. Factors associated with AIS score were studied with multivariate binomial models. Multivariate ordinal regression models were used to detect individual associations between the scores within each quality of life subscales and RLS. In the prospective analyses of the relationship between RLS and mortality Kaplan-Meier survival curves, uni- and multivariate Cox proportional hazard models were utilised.

Ethical permission

The study protocol was approved by the Ethical Committee of the Semmelweis University. All patients had received detailed verbal and written about the objectives and protocol of the study before participation, and they signed an informed consent.

Results

Basic sample characteristics

The mean age of the total sample (WL and Tx groups combined) was 48 ± 13 years and 60% were male. There were no significant differences in gender, age, education, number of co-morbidities and in the majority of labor parameters between the two cohorts. Of the 1067 Tx patients 108 subjects refused to complete the RLS questionnaire and 143 had incomplete results. There were no statistically significant differences between those completing or not completing the RLS questionnaire with regard to socio-demographic parameters.

Prevalence and correlates of restless legs syndrome in the Tx group

RLS prevalence was significantly lower in the Tx group than in the WL group (Tx: 5% vs WL: 11%; $p=0.001$). Among kidney transplant patients iron deficiency was more prevalent, hemoglobin level was significantly lower and co-morbidity was higher in those with RLS than in those without the syndrome, while there was no significant difference in the frequency of diabetes between the two groups. Renal function of RLS patients was significantly worse compared to those with no RLS (RLS: $42 \text{ ml/min/1.73m}^2$ vs no RLS: $50 \text{ ml/min/1.73m}^2$, $p<0.05$). RLS prevalence was significantly higher in patients not taking steroids than in patients on steroid medication (9% vs 4%, $p<0.05$).

Insomnia prevalence and correlates

17% of the Tx patients, 14% of the WL group, and 6% of the matched sample from the Hungarostudy (HS) database refused or did not fill completely the Athens Insomnia Scale.

The prevalence of insomnia was 15% in the WL group in contrast to 8% in the Tx group ($p<0.01$), which was the same frequency as seen in the general population (8%). The median AIS (interquartile range: IQR) was significantly different across the three groups (WL: 4 (5) vs Tx: 3(4) vs HS: 1(5), $p<0.001$ in each comparison).

Insomniac patients were significantly elder than patients without insomnia (53 ± 10 vs 48 ± 13 years, $p<0.001$). In the Tx group the prevalence of insomnia was higher in women compared to men (6 vs 10%, $p<0.05$) as well as the median (IQR) AIS score (0

(4) vs 2 (6), $p=0.05$). Similar trend was observed in the HS sample too. Patients with insomnia reported more co-morbidities than normal sleepers. Kidney function correlated negatively with AIS score ($r=-0.15$, $p<0.001$).

The relationship between restless legs syndrome and insomnia

Prevalence of RLS was nearly four times higher in insomniac patients than in those without insomnia (15% vs 4%, $p<0.001$). RLS patients had significantly higher score on the AIS and the prevalence of insomnia was significantly greater among them than in participants without RLS both in the WL and Tx groups and in the total CKD population.

The relationship between insomnia and depressive symptoms

In the Tx population the median (IQR) CES-D score was 9 (11), while the prevalence of depression was 22%. There was a moderately strong positive correlation between AIS and CES-D scores in the total CKD population ($r=0.54$, $p<0.001$), and in both the WL and Tx groups. In Tx patients the presence of insomnia was associated with a significantly higher CES-D score than those without insomnia. The prevalence of depressive symptoms was 71% among insomniacs compared to 18% in patients without insomnia ($p<0.001$).

The relationship between RLS and insomnia in Tx patients in multivariate model

In multivariate negative binomial regression model the presence of RLS showed a significant relationship with higher AIS score after accounting for sex, age, hemoglobin, eGFR, co-morbidity, depressive symptoms and high risk of OSAS (OR=1.4, 95% CI: 1.07-1.83, $p<0.05$).

The relationship between insomnia and renal replacement modality

A similar multivariate model was built for the total CKD population with the additional introduction renal replacement modality (transplantation vs dialysis) in order to show if the modality is independently associated with insomnia. In this model transplantation was independently associated with significantly better sleep quality (OR=1.33, 95% CI: 1.16-1.53, $p<0.001$). The presence of RLS was a significant predictor of insomnia severity regardless of the patients' renal replacement therapy (OR=1.49, 95% CI: 1.21-1.84, 0.001).

The relationship between restless legs syndrome and quality of life in kidney transplant patients

Univariate analyses

Patients with RLS reached lower scores in every KDQoL scale, thus they reported worse quality of life than those without RLS. The difference was statistically significant and clinically relevant in the physical and mental domains of the general SF-36 scale. Similar differences were detected in the disease-specific domains.

Multivariate analyses

Multivariate models were applied to analyse the potential individual relationships between RLS and each of the quality of life domains. The dependent variables were the scores within the quality of life subscales, while the following explanatory variables were entered besides the presence of RLS: age, gender, eGFR, time elapsed since transplantation, time spent since the initiation of dialysis, serum albumin, hemoglobin, number of co-morbid conditions, education and CES-D score. RLS showed a significant association with the scores of all the analysed quality of life domains independently of these important factors. After the correction for insomnia, the relationship between RLS and lower quality of life scores remained significant in two domains. These were the ‘role physical’ (OR=6.67, 95%CI: 2.94-16.67, $p<0.001$) and ‘bodily pain’ subscales (OR=2.13, 95%CI: 1.08-4.17, $p<0.05$).

The relationship between restless legs syndrome and depressive symptoms in WL and Tx patients

The association between RLS and depression was analysed in the combined sample of WL and Tx groups. Of the 1281 patients 279 Tx and 53 WL subjects refused to participate or didn't fill completely either the RLS or CES-D questionnaire.

The prevalence and correlates of restless legs syndrome in the total kidney disease population

Prevalence of RLS was 11% in the WL and 5% in the Tx group ($p=0.001$). There were no significant differences in age, gender and education between patients with vs without RLS. The number of co-morbid conditions was higher and the total time spent

on dialysis was longer among patients with RLS (RLS (median(IQR): 30(44) vs no RLS: 24(31), $p=0.05$).

As seen in the Tx group, in the total CKD population the AIS score was significantly greater and the prevalence of insomnia was four times as high in patients with RLS compared to those without RLS (RLS: 31% vs no RLS: 7%, $p<0.001$). Use of hypnotics was more prevalent among patients with RLS than in those without symptoms (RLS: 15% vs no RLS: 6%, $p<0.05$).

The relationship between restless legs syndrome and depressive symptoms

The median (IQR) CES-D score was 10 (12). The prevalence of clinically meaningful depressive symptoms (CES-D score ≥ 18) was 24% in the total population ($n=248$), while it was 34% in the WL group and 22% in the Tx group ($p=0.001$). Prevalence of RLS was 4 times higher among depressed subjects than in those without depressive symptoms (14% vs 3%, $p<0.001$). Prevalence of RLS showed a significant association with higher CES-D score.

In patients with RLS depression was significantly more frequent than in those without RLS in the total CKD population (56 vs 22%, $p<0.001$), and also in the WL and Tx groups. The median CES-D score (IQR) was also higher in the RLS group than in patients with no RLS within the total sample (20 (15) vs 9 (11), $p<0.001$) and in both WL and Tx groups.

Multivariate analyses

In multivariate logistic regression model RLS was independently and significantly associated with depression (OR=4.05, 95%CI: 2.26-7.27, $p<0.001$) after correction for age, sex, education, serum albumin, renal replacement modality, cumulative dialysis time and number of co-morbidities. Presence of insomnia was entered into the model subsequently in order to see to what extent the relationship of RLS and depression is explained by the impaired quality of sleep. The magnitude of the independent association between RLS and depressive symptoms decreased, but remained significant even after accounting for insomnia (OR= 2.97, 95%CI: 1.59-5.58, $p<0.001$). The analyses were run for both WL and Tx groups separately, and similar results were gained.

The prospective analysis of the relationship between restless legs syndrome and mortality

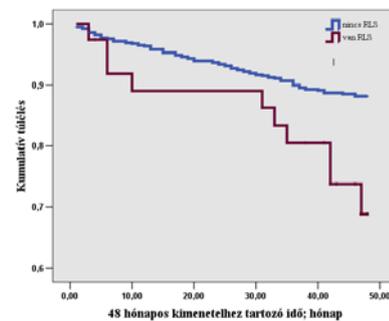
Follow-up data

The follow-up of the Tx cohort lasted for nearly four years (median 46 months), and 12 patients were lost during this period. In 2765 person-years 97 patients (12%) died (crude mortality rate=35/1000 person-year) and in 2595 person-years 63 patients (9%) returned to dialysis (crude graft loss rate=24/1000 person-year). Cardiovascular complications (24%) and infections (27%) were the most common causes of death.

Univariate analyses

Mortality of Tx patients was significantly greater in the RLS group than in patients without RLS: 26% vs 11%, $p < 0.05$. The cumulative survival of patients with no RLS was significantly better than those with RLS, as illustrated by the Kaplan-Meier curve.

In univariate Cox proportional hazard analysis the relationship between RLS and mortality was significant (HR = 2.53, 95% CI: 1.31-4.87, $p < 0.01$).



Multivariate analyses

The presence of RLS was an independent, significant predictor of mortality as suggested by multivariate Cox proportional hazard model (HR=2, 95%CI: 1-3.9, $p < 0.05$) in Tx patients after accounting for age, gender, eGFR, serum albumin, hemoglobin, serum CRP, time spent since transplantation, hypertension and diabetes.

Conclusions

The association between restless legs syndrome and insomnia

This is the first study to assess the prevalence of insomnia among kidney transplant recipients, and we showed that the presence of clinically relevant insomnia is significantly lower in this population than in waitlisted dialysis patients. The frequency of unique insomnia symptoms and the AIS score was significantly smaller in the Tx group than in the WL group. Compared to dialysis renal transplantation remained to be associated with decreased AIS score thus better sleep quality and lower insomnia prevalence

following statistical correction for several important factors. The correct explanation for these findings is not readily known, but the better metabolic state, the less invasive nature of the treatment as well as psychosocial factors might play a role.

The prevalence of insomnia in the Tx population did not differ from the occurrence found in a matched sample from the Hungarian general population. It is somewhat surprising, because Tx patients have a high co-morbidity and a lot of prescribed drugs that might potentially compromise sleep quality. However, the mean AIS score and the number of unique insomnia complaints were greater than the values found in the general population.

RLS was one of the strongest predictor of insomnia severity even after accounting for several co-variables in the Tx population. The relationship between RLS and insomnia had already been in waitlisted dialysed patients. RLS symptoms trigger difficulties in falling asleep and impair sleep quality, which is supported by former studies as well.

The relationship between restless legs syndrome and quality of life

This is the first study to analyse the association between RLS and health-related quality of life in kidney transplanted patients. Restless legs syndrome was related with a reduced quality of life, as indicated in every investigated quality of life domain following statistical correction for several relevant socio-demographic and clinical parameters. We had previously presented similar results in dialysed patients using the KDQoL questionnaire. More specifically, RLS was an independent predictor of worse quality of life in both the physical and mental subscales of the general SF-36 quality of life questionnaire and in the kidney-disease-specific domains as well. The relationship between RLS and impaired quality of life remained significant even after accounting for insomnia. This finding suggests that the association between RLS and some aspects of quality of life is not solely due to sleep problems. For example such explanatory factor could be the pain, which frequently accompanies the sensory symptoms of RLS.

The associations between restless legs syndrome, insomnia and depressive symptoms

The relationships between RLS, insomnia and depression are analysed in a large sample of dialysed and renal transplant patients for the first time in this study. The risk of depressive symptoms was higher in the presence of RLS than without RLS even with statistical correction of several important parameters. The association between RLS and

depression had been detected in the general population and in dialysed patients, however it has not been studied in kidney transplant patients.

This association was partially independent from insomnia, because the relationship between RLS and depression was not completely explained by sleep complaints, and other, sleep-independent mechanisms could also have an important contribution. Both psycho-social (anxiety, social isolation) and lifestyle factors (inactivity, inadequate diet) could provide such sleep-independent explanatory pathways.

The relationship between restless legs syndrome and mortality

According to our prospective studies, the presence of RLS is one of the a risk factors of mortality among renal transplant recipients. During the 4-year follow-up, the recorded rate of mortality in patients with RLS twice as high as those without RLS even accounting for several relevant socio-demographic and clinical explanatory factors. RLS was not associated with graft loss (returning to dialysis). This is the first study to investigate the relationship between RLS and survival in this patients group.

The association between RLS and mortality had been already found in dialysed patients, and a prospective study of the general population indicated similar findings among middle-aged women.

The mechanism of the relationship between RLS and mortality is not known. Cross-sectional studies suggest an independent, strong connection between the presence of RLS and cardiovascular diseases, which might be mediated by sleep deprivation and/or nocturnal blood pressure surges. Uremic factors and mechanisms related to reduced immune function could neither be excluded in the background.

Strengths and limitations of the study

The size of the cohort is outstanding compared to similar studies conducted on patients with chronic renal diseases. Standard and valid questionnaires were utilized to assess RLS, insomnia, depression and quality of life. The correction for socio-demographic and clinical parameters in multivariate models increase the reliability of the results. The socio-demographic characteristics were similar in the WL and Tx samples suggesting that the two groups can be combined for purposes of statistical analyses. In the last study the prospective design and long follow-up duration can also be highlighted as advantages.

An important limitation of the study that the cross-sectional design precludes the analysis of any temporal relationship. RLS is not diagnosed with questionnaires, though this method is inevitable in screening large samples. The applied RLS questionnaire had been found to be reliable during validation and its use in Hungarian chronic kidney disease populations.

In summary, restless legs syndrome was indicated to be a significant and independent predictor of insomnia, depression, impaired health-related quality of life and mortality. The relationships remained significant following the statistical correction for several relevant explanatory variables. RLS is easy to detect and diagnose in the routine clinical practice. The disease is usually treatable even when accompanied by chronic renal failure. The present results pose the notion that in renal transplant recipients the successful treatment of RLS may reduce the insomniac and depressive symptoms of patients with RLS, and their quality of life and survival may also improve. However, further studies are required to prove the suggestions.

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