Psycho-social aspects of chronic kidney disease – Restless Legs Syndrome and Periodic Limb Movements in Sleep

Doctoral thesis

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INTRODUCTION

In developed countries aging of the society poses a significant challenge for medicine: the increasing prevalence of chronic diseases contributes to the continuous increase of healthcare costs. Sleep disorders also belong to the group of chronic diseases and recently it became obvious that they also bear substantial physiological and psycho-social consequences. In the last 20 years more and more studies reported high prevalence of sleep-related complaints among patients with chronic kidney disease, mainly in dialyzed patients. Furthermore, sleep disorders are related to somatic and psychiatric comorbidities, that aggravate the condition of these patients.

Restless legs syndrome (RLS) and Periodic Limb Movements in Sleep (PLMS) are sleep disorders which may be associated with sensomotor symptoms. Restless legs syndrome is 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 show circadian rhythm: they appear or escalate during the first half of the night.

RLS is not a well known phenomenon among doctors: despite the fact that RLS is a common sleep disorder, only a small percentage of the patients receive a proper diagnosis and treatment. According to epidemiological studies the prevalence of RLS is 5-10%. Although RLS is considered to be a sleep disorder, not only sleep quality is influenced by its presence. Patients also have to live with the unpleasant sensory symptoms that contribute to an increased prevalence of depression and anxiety, as well as impaired quality of life. Besides the psycho-social consequences of RLS, several studies also report an association with cardiovascular diseases, a leading cause of mortality.

RLS is strongly associated with chronic kidney disease. In dialyzed population RLS is associated with insomnia, depression and anxiety, as well as decreased quality of life. RLS patients tend to have less compliance, they spend less time on dialysis treatment, that may contribute to the higher mortality rate among these patients. Additionally, patients with RLS have an increased risk to develop cardiovascular diseases, that are also associated with an increased mortality risk. However, there is only limited data about the

occurrence of RLS after renal transplantation and its consequences in this patient population.

Periodic Limb Movements in Sleep (PLMS) is closely related to RLS. In contrast to RLS, PLMS occurs only during sleep, and its direct effects on the everyday life of the patients is yet unknown. Additionally, patients are not always aware of the limb movements during night. Although during a polysomnographic measurement the objective signs of this sleep disorder are usually registered, they are not necessarily associated with worse subjective sleep quality and daytime sleepiness. To date it is unclear whether PLMS is only a polysomnographic finding or it has substantial clinical concequences. Nevertheless, more and more studies report that PLMS may have clinical significance through its cardiovascular effects.

It is well known that sleep disorders are highly prevalent among patients with chronic kidney disease (CKD), while sleep disorders of patients after renal transplantation (Tx) are less known. Several studies in the general population found relationship between sleep disorders and cardiovascular morbidity and mortality. As cardiovascular diseases are the leading cause of mortality in transplanted patients, exploring the associations between sleep disorders, mortality and cardio-cerebrovascular risk factors may have clinical significance.

In my thesis I present the results of three studies, in which I was involved as member of the Psychonefrology Study Group. We studied the relationship of RLS with important clinical outcomes as quality of life, mortality, and analyzed the prevalence of PLMS and its association with cardio-cerebro-vascular disease in waitlisted dialyzed (WL) and Tx patients.

AIMS

1. THE ANALYSIS OF THE RELATIONSHIP BETWEEN RESTLESS LEGS SYNDROME AND QUALITY OF LIFE AMONG KIDNEY TRANSPLANT (TX) RECIPIENTS

Increasing evidence support that restless leg syndrome is associated with impaired quality of life. In kidney transplant recipients no data have been published about the association of these two factors. We investigated the association between RLS and quality of life and assessed the influence of insomnia on this association. Our hypotheses were:

- Patients with RLS report significantly worse quality of life in most quality of life dimensions, and this difference is clinically relevant
- The association between RLS and quality of life is weaker when the confounding effect of insomnia is taken into account, but it still remains significant (i.e. the relationship between RLS and quality of life is not completely explained by insomnia)

2. The prospective analysis of the relationship between restless legs syndrome and mortality in Tx recipients

Several studies reported that the presence of RLS and PLMS predict mortality in dialyzed patients, suggesting a role of cardiovascular factors in the association. We examined the relationship between RLS and mortality in a four-year cohort study. Our hypothesis was the following:

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

3. The analysis of the relationship between periodic limb movements in sleep and cardio-cerebrovascular risk in patients with renal failure

PLMS is common in dialyzed patients. The only published paper, that assessed periodic limb movement before and after transplantation in 18 Tx patients, reported that the PLM-index (PLMI) was significantly reduced after kidney transplantation. It has been suggested that PLMS is associated with increased cardiovascular risk in the general population. A recent cohort study reported that higher PLMI predicted mortality among elderly men. The primary aim of our study was to assess the association between the prevalence of severe PLMS, cardiovascular and stroke risk in our waitlisted dialyzed and Tx patients. Our secondary aim was to assess whether the type of renal replacement therapy was associated with the presence of severe PLMS in our ESRD population. We hypothesized, that:

- Higher PLMI is related to increased cardio-cerebrovascular risk in ESRD patients
- Prevalence of PLMS is higher among waitlisted dialyzed patients than in renal

transplant recipients.

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 recipients were investigated with questionnaires between 2002 and 2003. Socio-demographic data (gender, age, education) were collected from the patients' charts or directly from the participants at enrollment. Anamnestic data of dialysis, transplantation and medications were also recorded. The Tx patients enrolled in the study were subsequently followed for nearly four years. During follow-up the time of death and graft failure were monthly registered. Patients with renal transplant and waitlisted patients of four dialysis centers were randomly selected for polysomnography.

SAMPLE OF PATIENTS FOR RLS ANALYSIS

All Tx patients of 18 years of age or older regularly followed at the Transplantation and Surgery Clinic of the Semmelweis University (n=1067) were approached to participate in the study between August 2002 and February 2003. Exclusion criteria were dementia and/or refusal to participate.

COHORT PHASE

Patients were followed for four years from initial data collection. The possible outcomes were: death with functioning graft, return to dialysis therapy, and a combined outcome (mortality with working graft or return to dialysis). Analysis of the relationship between RLS and mortality among transplant recipients is based on data of the abovementioned cross-sectional study and cohort phase.

SAMPLE OF PATIENTS FOR POLYSOMNOGRAPHY

For this study ("SLeep disorders Evaluation in Patients after kidney Transplantation (SLEPT) Study") potentially eligible patients were selected from all prevalent adult Tx

patients (“total clinic population”; n=1214) who were regularly followed at a single outpatient transplant center on December 31, 2006. After applying exclusion criteria (previous diagnosis of OSA or PLMS, recent (less than 3 months) start of dialysis or transplantation, active and acute respiratory disorder, acute infection, hospitalization within 1 month, surgery within 3 months) 1198 patients remained eligible for enrollment. From this “base population” we randomly selected and approached 150 patients using the simple random sampling strategy. We asked all (n=100) eligible waitlisted (WL) dialysis patients who were treated at the four largest dialysis centers in Budapest to participate. Prevalence of PLMS and its association with cerebro-cardiovascular risk was investigated in this sample.

ASSESSMENT OF COMORBIDITY

Patients were asked to report presence of comorbidity based on the End Stage Renal Disease Severity Index (ESRD-SI): heart disease, vascular disorder, bone disease, lung disorder, eye disorder, paresthesias, diabetes mellitus, or other conditions. Furthermore, Comorbidity was assessed by the modified Charlson Comorbidity Index (CCI) completed by the most responsible transplant physician. We also collected data about coronary disease and hypertension from the medical records. For patients participating in polysomnography we measured blood pressure and recorded antropometric paremeters and data about smoking. Atrial fibrillation was diagnosed from the ECG recorded during polysomnography.

ASSESSMENT OF RESTLESS LEGS SYNDROME

RLS symptoms were assessed with the RLS questionnaire. This tool consists of eight questions incorporating all four diagnostic criteria. The Hungarian version of the questionnaire was validated by our workgroup on dialyzed sample. Sensitivity was 75%, specificity was 86% of the Hungarian version of this questionnaire.

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

relevant 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 Athens Insomnia Scale (AIS) was used to measure symptoms of insomnia. AIS consists of eight questions regarding nighttime symptoms (sleep onset and maintenance, early waking up) and daytime consequences (sleepiness, fatigue and functioning) of insomnia. The original version was translated and validated by our workgroup and it showed good psychometric parameters.

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 specially related 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 syndrome (OSAS) was assessed with the Berlin sleep apnea questionnaire. Ten questions of the scale measure the most common symptoms, consequences of OSAS in addition to hypertension and high BMI. Analysis of the answers renders the patient to a high or low risk group regarding OSAS. Validation of the Berlin questionnaire was conducted in the general population with reliable results.

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) serum triglyceride, serum HDL and LDL cholesterol, as well as 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 were registered. Renal function of kidney transplant patients was assessed with the estimated glomerular filtration rate (eGFR) calculated from the simplified MDRD formula (Modification of Diet in Renal Disease study).

IMMUNSUPPRESSIVE MEDICATION

Transplantation related information included current medications, transplant and dialysis "vintage" (i.e. time elapsed since transplantation or since the initiation of dialysis treatment), time spent on dialysis prior to transplantation, type of transplantation (deceased or living donor), history of acute rejection, HLA mismatch, pretransplant panel reactive antibodies titer (PRA), cold ischemic time (CIT), age and gender of donor and history of delayed graft function. Time elapsed since the initiation of the first treatment for End Stage Renal Disease (ESRD) (cumulative ESRD time) was also calculated.

ASSESSMENT OF CARDIOVASCULAR AND CEREBROVASCULAR RISK

The ten-year coronary heart disease risk was estimated for all patients using the Framingham score (calculated with LDL- cholesterol). Similarly, the ten-year estimated risk of stroke was calculated according to the modified version of the Framingham Stroke Risk Profile.

STATISTICAL ANALYSES

Data were registered in the computer database developed by our workgroup. Statistical analyses were carried out using SPSS 15.0 and STATA 11.1 software. Student's t or Mann-Whitney U tests were used to compare continuous variables, while correlations were analysed according to Spearman. Cathegorical variables were compared with khi-square or Fisher's exact test.

Multivariate ordinal regression models were used to detect individual associations between the scores within each quality of life dimensions and RLS. In the prospective analyses of the relationship between RLS and mortality Kaplan-Meyer survival curves,

uni- and multivariate Cox proportional hazard models were utilised. Spearman's correlation was used to assess the association between PLMI versus continuous variables. Linear associations between PLMI and the Framingham risk score were assessed using fractional polynomials and restricted cubic splines. To assess wether PLMI is independently associated with the Framingham risk scores multivariable linear regression models were built. The variables entered in the multivariable-adjusted models were selected by theoretical considerations. The risk scores were logarithmically transformed to obtain normal distribution. Only two-sided p values were computed and the results were considered statistically significant if p was less than 0.05.

ETHICAL PERMISSION

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

RESULTS

BASIC CHARACTERISTICS OF TRANSPLANT RECIPIENTS FOR RLS ANALYSIS

The mean age of the sample was 48±13 years and 60% were male. Iron defficiency occured in 12% of patients and 17% had diabetes. 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 and not completing the RLS questionnaire with regard to socio- demographic parameters. Prevalence of RLS was 5%.

THE RELATIONSHIP BETWEEN RESTLESS LEGS SYNDROME AND QUALITY OF LIFE IN KIDNEY TRANSPLANT RECIPIENTS

Patients with RLS reached lower scores in every KDQoL dimensions, thus they reported

worse quality of life than those without RLS. Multivariate models were applied to analyse the potential individual relationships between RLS and each of the quality of life domains. RLS showed a significant association with the scores of all the analysed quality of life domains independently of important co-variates. As the quality of sleep is related to both RLS and quality of life, we repeated the analysis with insomnia entered into the model. 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' and 'bodily pain' dimensions.

THE PROSPECTIVE ANALYSIS OF THE RELATIONSHIP BETWEEN RESTLESS LEGS SYNDROME AND MORTALITY

Data of 804 patients were analysed. There were no significant differences regarding baseline characteristics (age, gender, presence of diabetes, hemoglobin and albumin level) between participants and those who refused to participate. 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.

Mortality of Tx patients was significantly higher 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 of those with RLS.

The presence of RLS was significant predictor of mortality as suggested by multivariate Cox proportional hazard model (HR=2.02; 95%CI: 1.03-3.95, $p<0.05$) in Tx recipients, and this association was independent of age, gender, eGFR, serum albumin, hemoglobin, serum CRP, time elapsed since transplantation, hypertension and diabetes. However, RLS did not show association with graft-failure.

PERIODIC LIMB MOVEMENTS IN SLEEP ARE ASSOCIATED WITH STROKE AND CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH RENAL FAILURE

Demographic data and baseline characteristics of the sample

Of the 250 eligible patients 100 individuals, including 50 Tx (33%) and 50 WL (50%) subjects refused to participate. Consequently, the "final study sample" included 100 Tx and 50 WL patients (participants). Three WL patients were treated with continuous ambulatory peritoneal dialysis and 47 WL patients with intermittent in centre hemodialysis. There were no significant differences regarding age and gender between participants and those who refused to participate.

The WL and Tx group did not differ regarding socio-demographic parameters. In WL group mean age was 50±13 years and 54% was male, in Tx group mean age was 51±13 years and the proportion of men was 57%. Dialyzed patients had lower hemoglobin level, more comorbidities, but hypertension occured more frequently in the Tx group.

Prevalence and severity of periodic limb movements in sleep in Tx vs. WL dialysis patients

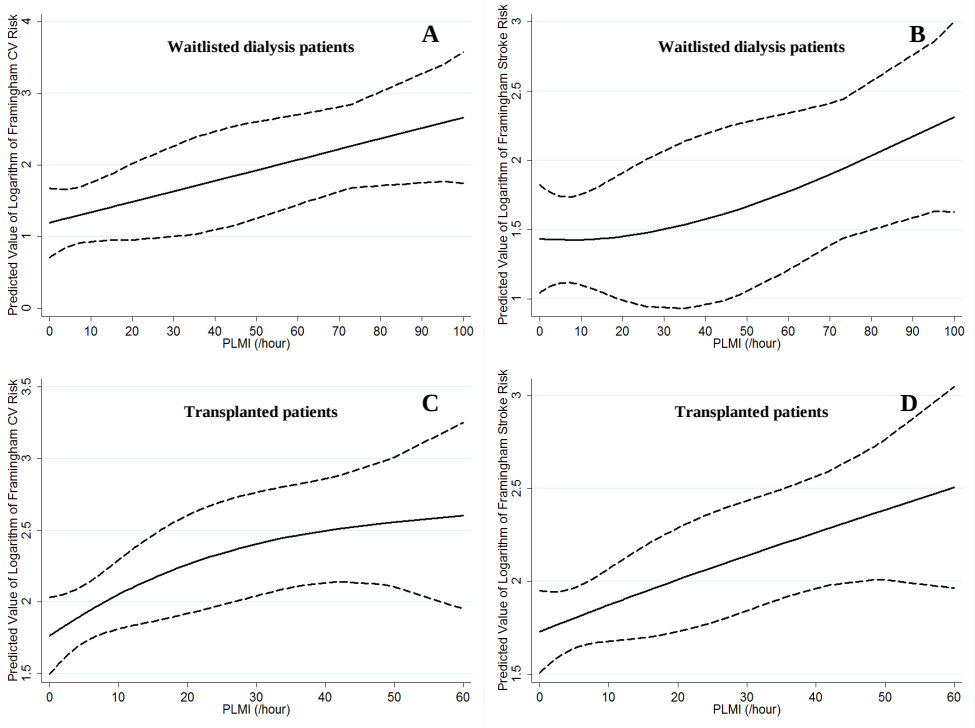
The PLMI was similar in the Tx and WL groups (median; IQR: 6.2 (0.7-16) vs. 6.2 (0.8-45.1); p= 0.23). According to the previously defined criteria 27% of the Tx and 42% of WL patients had PLMS (PLMI$\geq$15) (p=0.094). The prevalence of moderate PLMS was 11% in the Tx group and 10% in the WL group. The prevalence of severe PLMS, however, was significantly higher among WL (32%) versus Tx (16%) patients (p=0.034)

Estimated coronary heart disease risk and estimated stroke risk

The ten-year estimated coronary heart disease risk (based on the Framingham score) and the ten-year estimated stroke risk (based on the modified Framingham stroke risk profile) were two-fold higher in the severe PLMS group compared to patients without severe PLMS in the Tx group. Both the estimated coronary heart disease (CHD) risk and the estimated stroke risk showed a moderate positive correlation with PLMI (Spearman's rho=0.265; p=0.009 for CHD and rho=0.274; p=0.006 for stroke).

Similarly, the estimated ten-year CHD risk was higher in patients with severe PLMS and it correlated significantly with the PLMI (Spearman's rho =0.409; p=0.022) in the WL group. The estimated stroke risk, however, was not associated with the PLMI in this group.

We assessed the association between Framingham scores and PLMI using restricted cubic splines which disclose very close similarity between the Tx and the HD groups regarding the association of logarithm of Framingham cardio-cerebrovascular risk scores versus PLMI. These analyses reveal similar, linearly increasing, "dose-response" relationship between the PLMI and the risk scores in both groups.



Association between PLMI and logarithm of Framingham cardio-cerebrovascular risk scores

To assess the independent association between the PLMI versus the Framingham CHD score a linear regression model was built for the total sample (Tx+WL) and in the Tx as well as in the WL group separately. In the total sample the PLMI was independently associated with the log-transformed Framingham CHD score (Beta=0.222; p=0.004). In the WL group PLMI showed a similarly strong relationship with the

Framingham CHD score (Beta=0.357; p=0.015), while in the Tx group a clear trend was seen between the two variables (Beta=0.157; p=0.090).

In the linear regression model in the total sample the PLMI was also significantly associated with the log-transformed Framingham stroke risk score even after adjusting for the abovementioned co-variables (Beta=0.154; p=0.031). In WL patients PLMI was related to Framingham stroke risk score (Beta=0.312; p=0.033) but in the Tx group this association did not reach statistical significance (Beta=0.098; p=0.234).

CONCLUSION

Our study examined the relationship of RLS with important clinical outcomes, such as quality of life and mortality among Tx patients. Moreover, we presented new results regarding the prevalence of PLMS and its association with cardio-cerebro-vascular disease in waitlisted dialyzed (WL) and Tx patients.

Hereinafter I summarize our new results and answers to our hypothesis:

- Patients with RLS had significantly worse quality of life regarding both common SF-36 and kidney disease specific domains.
- RLS was an independent, significant predictor of QoL scores in different dimensions.
- In some QoL dimensions (namely pain and physical role) RLS remained significant predictor after adjusting for insomnia.
- Presence of RLS was an independent, significant risk factor for mortality.
- Severe PLMS was more frequent in dialyzed patients than in patients after transplantation.
- Increasing severity of PLMS showed a significant and independent association with higher cardio- and cerebrovascular risk in patients with CKD.

The three studies described in my thesis analyzed the prevalence and significance of periodic limb movements in sleep and restless legs syndrome. Both RLS and PLMS are associated with important clinical outcomes, which are related to the patients' survival and quality of life. These syndromes are treatable and their diagnosis and therapy does not require special qualification from doctors. Hopefully, our findings might open up the way for therapy and further studies.

PUBLICATIONS

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