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Association of symptoms of insomnia and sleep parameters among kidney transplant recipients

Katalin Z. Ronai[a], Andras Szentkiralyi[a,b], Alpar S. Lazar[a,c], Zsolt I. Lazar[d], Istvan Papp[d], Ferenc Gombos[e], Rezso Zoller[f], Maria E. Czira[b], Anett V. Lindner[g], Istvan Mucsi [a,h], Robert Bodizs[a], Miklos Z. Molnar[i,j], Marta Novak[a,k,*]

[a] Inst. of Behavioural Sciences, Semmelweis University, Budapest, Hungary
[b] Inst. of Epidemiology and Social Medicine, University of Muenster, Muenster, Germany
[c] Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, UK
[d] Dept. of Physics, Babes-Bolyai University, Cluj-Napoca, Romania
[e] Dept. of General Psychology, Pázmány Péter Catholic University, Budapest, Hungary
[f] 1st Dept. of Internal Medicine, Semmelweis University, Budapest, Hungary
[g] Klinikum Landkreis Erding, Interdisciplinary Pain Center, Erding, Germany
[h] Dept. of Medicine, Division of Nephrology, University Health Network, University of Toronto, Toronto, Canada
[i] Dept. Transplantation and Surgery, Semmelweis University, Budapest, Hungary
[j] Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, TN, USA
[k] Centre for Mental Health, University Health Network and Dept. of Psychiatry, University of Toronto, Toronto, Canada

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ABSTRACT

Objective: Insomnia complaints are frequent among kidney transplant (kTx) recipients and are associated with fatigue, depression, lower quality of life and increased morbidity. However, it is not known if subjective insomnia symptoms are associated with objective parameters of sleep architecture. Thus, we analyze the association between sleep macrostructure and EEG activity versus insomnia symptoms among kTx recipients.
Methods: Participants (n_1 = 100) were selected from prevalent adult transplant recipients (n_0 = 1214) followed at a single institution. Insomnia symptoms were assessed by the Athens Insomnia Scale (AIS) and standard overnight polysomnography was performed. In a subgroup of patients (n_2 = 56) sleep microstructure was also analyzed with power spectral analysis.
Results: In univariable analysis AIS score was not associated with sleep macrostructure parameters (sleep latency, total sleep time, slow wave sleep, wake after sleep onset), nor with NREM and REM beta or delta activity in sleep microstructure. In multivariable analysis after controlling for covariables AIS score was independently associated with the proportion of slow wave sleep (β = 0.263; CI: 0.026–0.500) and REM beta activity (β = 0.323; CI = 0.041–0.606) ($p < 0.05$ for both associations).
Conclusions: Among kTx recipients the severity of insomnia symptoms is independently associated with higher proportion of slow wave sleep and increased beta activity during REM sleep but not with other parameters sleep architecture. The results suggest a potential compensatory sleep protective mechanism and a sign of REM sleep instability associated with insomnia symptoms among this population.

1. Introduction

Several studies suggest that 50–80% of patients with end-stage kidney disease (ESKD) may have sleep-related problems, including insomnia [1–4], restless legs syndrome [5–7], periodic limb movements in sleep [2,5–7] and obstructive sleep apnea [8–10]. Successful kidney transplantation might alleviate some sleep problems [3,11], but the prevalence of poor sleep remains remarkably high among these patients: 52.5% among kidney transplant (kTx) recipients were poor sleeper in a cohort study [12]. We previously showed the percentage of kTx recipients who had at least one insomnia complaint was nearly 1.5 times higher compared to the general population [3].

Insomnia and poor sleep are frequent complaints in kTx recipients and they are associated with fatigue [13], depression [3,4], pain [4], post-traumatic stress-symptoms [4] and lower quality of life [3,12,14]. Surprisingly, there is almost a complete lack of information regarding

* Corresponding author at: Toronto General Hospital; University Health Network, EN8-212 200 Elizabeth street, Toronto, Ontario M5G 2C4, Canada.
E-mail address: marta@nefros.net (M. Novak).

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objectively measured sleep parameters in kTx recipients. Altough there are a few published articles that report polysomnographic assessment of sleep in kTx recipients [15–19] most reports focus on obstructive sleep apnea and do not analyze sleep structure in details [16–19].

Insomnia disorder is characterized by difficulty falling asleep, difficulty staying asleep or poor sleep quality, and it leads to impaired daytime functioning, tiredness, fatigue and sleepiness according to the International Classification of Sleep Disorders III and Diagnostic and Statistical Manual of Mental Disorders V criteria [20,21]. These complaints can be of multi-factorial origin among kTx recipients. Anxiety, fear of rejection, deteriorating graft function, altered metabolism of sleep-regulatory mediators, ongoing subclinical inflammation, the presence of other comorbid conditions, immunosuppressant (IS) or other medications and hospitalization may all influence a preexisting sleep disorder or contribute to de novo emergence of sleep problems [22,23].

Diagnosis of insomnia in CKD is similar to the diagnosis among the general population and it is based on clinical interview [23]. The assessment of polysomnography (PSG) is required only when a comorbid sleep-disorder is suspected. However, studies using PSG and detailed EEG analysis contributed important information about the pathophysiology of insomnia among non-kidney disease patients and helped to develop better therapies to improve the subjective symptoms. Patients with insomnia disorder often have longer sleep onset latency (SOL) [24,25], lower total sleep time (TST) [24–27], dysregulated sleep homeostasis (less slow wave sleep [SWS] or delta activity) [24,26,28,29] or higher wake time after sleep onset (WASO) [24,25,27,30]. Moreover, increased wake-like (beta) EEG activity during sleep is also characteristic for patients with insomnia [27,31,32].

The association of subjective insomnia complaints with objectively assessed sleep architecture and EEG activity (microstructure) have not been investigated before among kTx recipients. However, gaining insight into the objective structure of sleep behind the subjective symptoms might help to treat patients with insomnia more properly among this patients population. Thus, in this study we hypothesized that, similarly to patients with insomnia but no kidney disease, insomnia symptoms are associated with altered sleep macro- and microstructure paramateres (longer SOL, shorter TST, less SWS and delta activity, higher WASO and beta activity).

2. Methods

2.1. Sample of patients and data collection

Data for this analysis are obtained from the "SLeep disorders Evaluation in Patients after kidney Transplantation (SLEPT) study" [15,19,33–40]. Potentially eligible patients were selected from all prevalent adult transplant recipients ("total clinic population"; $n = 1214$) who were regularly followed at a single outpatient academic transplant center, the kidney transplant clinic of the Dept. of Transplantation and Surgery at Semmelweis University, Budapest, Hungary (Fig. 1).

All patients followed at the clinic on December 31, 2006 were considered for enrollment in the Malnutrition and inflammation in transplant (MINIT-HU) study. After applying exclusion criteria (transplant received within < 3 months, presence of active and acute respiratory disorder, acute infection or hospitalization within 1 month, surgery within 3 months), 1198 patients remained ("base population"). From this "base population" we randomly selected and approached 150 patients ("kTx study sample") using the simple random sampling strategy offered by SPSS 15.0 (IBM Corporation, Armonk, New York, USA).

From these 150 eligible patients ("kTx study sample"), 50 individuals (33%) refused to participate. Consequently, the "kTx PSG sample" who underwent PSG included 100 kTx patients (Fig. 1). There were no significant differences regarding age and sex between the "kTx PSG sample" and those who refused to participate (data not shown). The basic characteristics (age, sex, eGFR, hemoglobin, serum albumin) of the "kTx PSG sample" were similar to the characteristics of the "total clinic population" (data not shown).

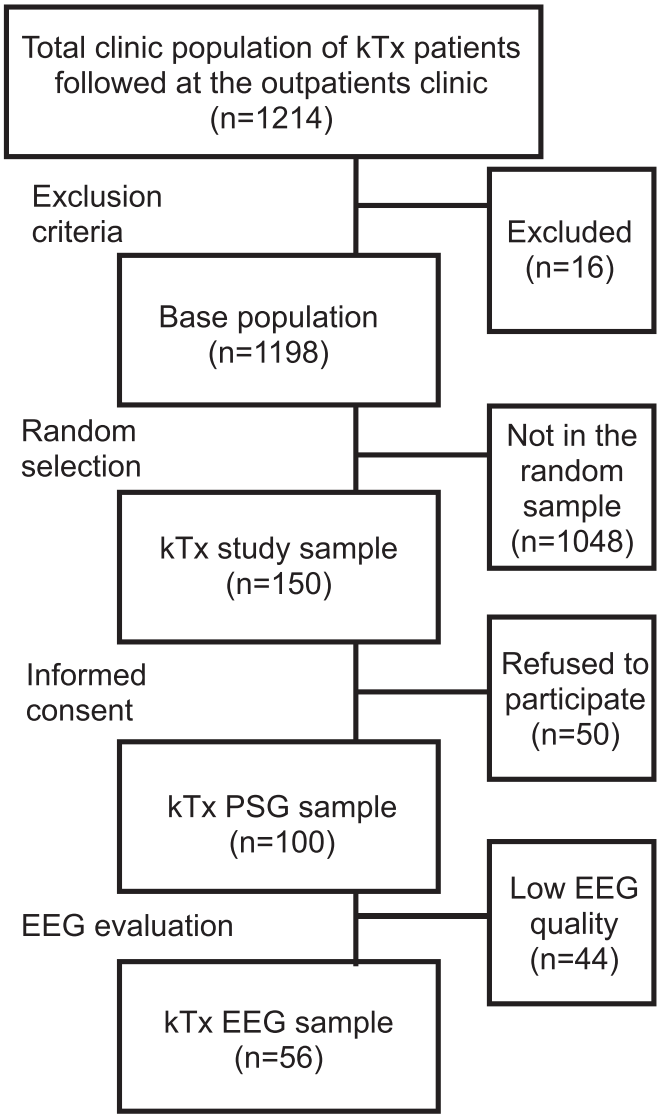

Fig. 1. Selection of patients.
EEG: electroencephalography; kTx: kidney transplant; PSG: polysomnography.

Of all PSG recordings in the "kTx PSG sample" 56 had sufficient quality to allow sleep microstruture analysis ("kTx EEG sample") (Fig. 1). There were no significant differences in the baseline characteristics between the "kTx EEG sample" and the 44 participants excluded from the EEG analysis, except for significantly lower serum albumin in the "kTx EEG sample" (Table A.1).

2.2. Assessment of insomnia

The Athens Insomnia Scale (AIS) was used to assess sleep complaints and to identify possible cases of insomnia [41,42]. The AIS consists of eight items, with score range 0–24, with higher scores indicating worse sleep. Subjects are asked to grade the severity of the sleep complaints (absent, mild, severe, very severe) only if the particular complaint occurred at least three times per week during the last month. A cut-off score of 10 has been suggested for epidemiological studies to detect clinically significant insomnia [42]. The English version of the AIS had