Association of Sleeping Disturbances and Environmental, Biological Factors

Thesis abstract

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INTRODUCTION

Sleep disorders have gained significant importance and attention in the medical literature during the last 10-15 years. Their importance and far-reaching impact is being increasingly appreciated. Therefore, it is important to understand factors that are associated with sleeping or sleep disorders.

Through the history of humanity, our celestial attendant has always played an important role in different cultures. The moon has always been the focus of attention. Starting from ancient times, people were trying to understand the mechanisms of its potential impacts on human life. Several studies tried to identify and document the effects of the moon on humans. Nevertheless, very few well-designed studies could find any association between moon phases and the aspects of human biology or behavior.

Patients suffering from insomnia frequently have a lot of sleeping-related anxiety. Moreover, insomnia is often associated with depression, exhaustion and physical discomfort, which significantly lead to an impaired life quality. Up to our best knowledge, no studies have looked specifically at the interaction between age and insomnia in their association with quality of life (QoL). In some studies it is suggested that insomnia may have a more profound impact on QoL among the elderly due to the overall greater comorbidity. On the other hand, insomnia may interfere more profoundly with the life and work of younger adults, contributing to more distress and more significant impact on QoL. In our analysis we intended to analyze these factors and the interaction between age and insomnia.

Only a few studies assessed the epidemiology and correlation of sleep disorders in kidney transplant recipients. According to the latest findings, the prevalence of insomnia is higher among patients with end-stage renal disease (ESRD) compared to the general population. Scientific evidence suggests that partial and total sleep deprivation results in elevation of proinflammatory markers like C-reactive protein (CRP), interleukine-6 (IL-6) and tumor-necrosis factor-α (TNF-α) in healthy individuals. It is also known that significantly higher concentrations of proinflammatory cytokines (IL-6, IL-1 and TNF-α) and acute phase proteins (like CRP) are detectable in patients with chronic kidney disease. Chronic inflammation was associated with worse quality of life, depressive symptoms, and risk of graft loss and mortality

in kidney transplant recipients. However, we do not know if there was any association between inflammation and the presence of insomnia in this patient population.

During the past years I have been actively participating in several studies carried out by the Sleep Medicine and Psychonephrology Working Groups. The current thesis is based on analysis of data obtained in those research projects, enrolling both patients referred to our sleep clinic for assessment of sleep problems and also kidney transplant recipients.

PURPOSE OF THE STUDY, HYPOTHESES

1. ASSOCIATION BETWEEN LUNAR PHASE AND SLEEP CHARACTERISTICS

The analysis of the impact of stars and planets on human beings goes back to ancient times. There are contradictory data concerning the influence of the Moon on human behavior and biology.

The following hypotheses were examined in my research:

- There is an association between lunar cycles and objective sleep parameters (sleep efficiency, sleep latency, superficial sleep, deep sleep, night cycles of waking, REM sleep, REM latency) among patients with/without insomnia and mild obstructive sleep apnea. We hypothesized that sleep efficiency is lower during full moon, deep sleep is shorter, light sleep is longer and there are more frequent awakenings in comparison to other lunar stages.
- The degree of this association is different among women and men.

2. FACTORS ASSOCIATED WITH QUALITY OF LIFE AMONG PATIENTS SUFFERING FROM INSOMNIA

With aging, the number of comorbidities increases. As a multifactorial disorder, insomnia can unfold differently across ages, changing the quality of life of the patients.

The following hypotheses were examined:

- The subjective and objective sleep time of adults, suffering from insomnia, shows differences according to the age of the patient. In comparison with younger adults, older ones estimate better their actual sleep time.
- The quality of life of patients suffering from insomnia shows significant differences between various age groups, regardless of the presence of depression; insomnia in young adults associates with emotional aspects, while in older individuals the sleep problem is more closely associated with somatic symptoms.

3. ASSOCIATION BETWEEN INSOMNIA AND INFLAMMATION IN KIDNEY TRANSPLANT PATIENTS

Insomnia is a common sleep disorder in patients with renal disease. Furthermore, insomnia reportedly contributes to higher morbidity, mortality and graft loss in these patients. Inflammation is an important predictor of mortality in hemodialyzed patients and kidney transplant recipients. In dialyzed patients there is few and controversial data available about the association of inflammation and sleep disorders, and there is no available information regarding kidney transplant recipients. The association of inflammation with sleep disorders has not been assessed in kidney transplant recipients until now. The aim of this cross-sectional study was to assess the association of different inflammatory markers with OSA insomnia in a random sample of kidney transplant recipients.

The following hypotheses were generated:

- There is an association between the presence of insomnia and proinflammatory markers (IL-6, TNF-α, CRP, white blood cell count) of the blood.
- This association is independent of renal function and other known factors.

METHODS

DATA COLLECTION

SAMPLE OF PATIENTS AND DATA COLLECTION IN THE FIRST TWO STUDIES

This retrospective, cross-sectional study was performed at the 1st Department of Internal Medicine, Semmelweis University, Budapest, Hungary. Data, obtained from 319 consecutive patients, referred to the sleep laboratory for sleep studies, were analyzed between January 2007 and November 2009.

Socio-demographic information (age, gender, level of education) and details of medical history were collected at enrollment. At the time of the sleep study, physical examination was performed, waist circumference, weight and height were measured and body mass index (BMI) was calculated (BMI=weight/height^2).

The dates of the lunar cycles were obtained from the yearbooks of the Hungarian Astronomical Association.

TRANSPLANT PATIENT GROUP

For this study ("Sleep Disorders Evaluation in Patients after Kidney Transplantation (SLEPT) Study"), potential eligible patients were selected from all prevalent adult transplant patients (n=1,214) who were regularly followed at a single outpatient transplant center on 31th December, 2006. After applying the exclusion criteria (transplant received within less than 3 months, active and acute respiratory disorder, acute infection, hospitalization within 1 month, surgery within 3 months) 1,198 patients have remained. From this base population 150 patients were randomly selected and approached from this base population, using the random sampling strategy offered by SPSS 15.0. Out of the 150 eligible patients 50 individuals (33%) refused to participate. Consequently, the final study population included 100 transplant patients. The basic characteristics (age, gender, eGFR, hemoglobin, serum albumin) of the 100 participating transplant patients were similar to the characteristics of the total clinic population.

Assessment of insomnia

The Athen Insomnia Scale (AIS) was applied to measure insomniac symptoms. The AIS consists of 8 items (score range 0-24, with higher scores indicating worse sleep). The first 5 items cover night-time symptoms of insomnia (difficulty initiating sleep; difficulty maintaining sleep; early morning awakening), and the last 3 items probe daytime consequences of disturbed sleep (well-being, functioning capacity and daytime sleepiness). Subjects were asked to grade the severity of these 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 providing acceptable sensitivity and specificity to detect clinically significant insomnia.

Assessment of depressive symptoms

Depressive symptoms were characterized with the Center for Epidemiologic Studies depression (CES-D) score. Scores range from 0 to 60, with high scores indicating greater depressive symptoms. A cut-off score of 16 was applied in order to detect clinically meaningful depression.

Polysomnography

Standard, attended overnight polysomnography was performed in four acoustically isolated and video-monitored units in our sleep laboratory (SOMNOscreen™ PSG Tele, SOMNOmedics GmBH, Germany, CE0494). Tests were always done on weekdays, "lights off" and "lights on" times were uniform and were set at 9 pm and 6 am, respectively. Sleep architecture was characterized by the following parameters: sleep efficiency is the ratio of time spent asleep over the time spent in bed; sleep onset latency: time from lights out until sleep onset (defined as first epoch of stage 2); number of awakenings; arousal index: number of arousals per hour. The amount of four different stages of non-rapid eye movement sleep and REM sleep were determined as percentages of sleep period time (time from sleep onset until final awakening). Light sleep is the sum of stage 1 and 2, slow wave sleep or deep sleep is the combination of stage 3 and 4. Wake percentage is defined as the percentage of wake period from lights out to lights on. All recordings were scored visually per 30 s epochs by experienced scorers according to the criteria of Rechtschaffen & Kales.

Definition and classification of obstructive sleep apnea

Apnea was defined as the absence of airflow for more than 10s; hypopnea was defined as a clearly discernible reduction in airflow for more than 10s, associated with an arousal and/or reduction in oxygen saturation >3%. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. "Average oxygen saturation" was calculated from the oxygen saturation values measured during sleep. Patients were defined apneic if: mild: 5≤AHI<15; moderate: 15≤AHI<30 and severe: AHI>30. Similarly to previous publications the term 'OSA' refers to moderate or severe apnea (AHI≥15) in this study.

Definition and classification of periodic limb movement in sleep

PLMS was defined by the following criteria: limb movement (LM) duration: 0.5-5s; inter-movement interval: 5-90s; and separation criteria for LMs occurring in both legs: more than 5s between onsets. A PLMS cycle consisted of at least four consecutive LMs. The periodic limb movement index (PLMI) was defined as the number of LMs per hours during sleep. We defined PLMS if PLMI>15.

Assessment of comorbidity

Patients were asked to report presence of comorbidity based on the Charlson Comorbidity Index (CCI). In addition, detailed medical history, physical examination and anthropometric parameters were obtained during a detailed interview and assessment performed by a physician of our working group.

Assessment of quality of life

Health-related quality of life was assessed with the 36-item short form health survey. It contains 36 items and measures 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The SF-36 yields a score for each of these domains, as well as summary scores both for physical and mental health, and a single health utility index. The questionnaire is self-administered, either via pen-and-pencil or computer, or given by a trained interviewer to persons older than 14 years. It takes five to ten minutes to complete.

Assessment of daytime sleepiness

Daytime sleepiness was measured with the Epworth Sleepiness Scale (ESS). The questionnaire asks the subject to rate, his or her probability of falling asleep, on a scale of increasing probability from 0 to 3, for eight different situations that most people engage in during their daily lives, though, not necessarily every day.

Specific procedures to test the association between insomnia and inflammation in kidney transplant patients

Serum samples were collected at the time of the baseline assessment and stored at -70 Co for future use. From these samples high sensitivity interleukine-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels were measured using immunoassay kits based on solid-phase sandwich enzyme linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN).

Statistical analysis

Statistical analysis was carried out, using the SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Data were summarized using proportions, mean±standard deviation, or median (interquartile range – IQR), as appropriate.

Multivariate analysis for association between lunar phase and sleep characteristics

Data were analyzed using ANCOVA or Kruskal-Wallis test, as appropriate. Sidac post hoc analyses or Mann-Whitney test with Bonfferoni correction were conducted to explore the differences of the sleep parameters between moon phase groups. Tests for interaction (ANCOVA) between gender and lunar phases were used to examine whether the association between sleep parameters and moon cycle is different between men and women. We investigated the association of lunar phases and objective sleep efficiency, light sleep%, deep sleep%, wake%, REM%, sleep latency and REM latency. Skewed variables were square root- or rank- transformed, as appropriate. We adjusted our analyses for several co-variables,

reportedly associated with sleep characteristics: age, gender, smoking, coffee consumption, use of sleeping pills, regular exercise, Charlson Comorbidity Index and CES-D score.

Moon phase was determined using information from the Hungarian Astronomical Association sidereal calendar. We analyzed our data in three different ways: first, we categorized lunar phases into three groups: new moon, full moon and alternate moon (Waxing Crescent, Waxing Gibbous, Waning Gibbous and Waning Crescent). For sensitivity analysis we repeated our analysis using three different cut-off points: 1) New/Full moon and one day before and one day after; 2: New/Full moon and two days before and after; 3: New/Full moon and three days before and after.

Exclusion criteria were technical failure of polysomnography and/or refusal to participate and/or moderate and sever (AHI ≥15) and/or sleep efficiency under 20%.

MULTIVARIATE ANALYSIS FOR FACTORS ASSOCIATED WITH QUALITY OF LIFE AMONG PATIENTS SUFFERING FROM INSOMNIA

Exclusion criteria were technical failure of polysomnography and/or refusal to participate and/or moderate and sever (AHI ≥15) and/or who had incomplete AIS questionnaires.

The patients were divided into three age groups: 18-39 year, 40-59 year, and above 60 year (young adults, middle-older adults and older adults, respectively).

Patients suffering from insomnia typically underestimate their actual sleep time. A misperception index was computed using the following formula: misperception index (MI) = (objective total sleep time -subjective total sleep time)/ objective total sleep time.

MULTIVARIATE ANALYSIS FOR ASSOCIATION BETWEEN INSOMNIA AND PROINFLAMMATION CYTOKINES

Continuous variables were compared using Student's t test or the Mann–Whitney U test, and categorical variables were analyzed withchi-square test. Kruskal–Wallis test was used to analyze the relationship between continuous and categorical variables. As many of our results are negative, we had to make sure to avoid the type II error. Consequently, based on our clinical experience, we have defined the clinically minimally important difference in inflammatory markers: CRP at least 5 mg/l; IL-6 at least 1 ng/l; at least 0.5 ng/l; serum albumin at least 1

g/l;and white blood cell count at least 1 9 10 3 /l. We have performed sample-size estimation to assess the number of patients needed to detect these minimally importantdifferences. All of these numbers are less than our sample size.

The significance level was defined as $p<0.05$.

ETHICAL APPROVAL

The ethics committee of the Semmelweis University had approved the study. Before enrollment, patients received detailed written and verbal information regarding the aims and protocol of the study and signed informed consent.

RESULTS

1. ASSOCIATION BETWEEN LUNAR PHASE AND SLEEP CHARACTERISTICS

Five hundred and twenty-two consecutive patients' data were enrolled. Two patients had a sleeping efficiency under 20%, four recordings were excluded due to technical limitations and 197 patients had mild/severe obstructive sleep apnea. Thus, 319 patients were included in the final analysis. The mean (±SD) age of the study participants was 45±14 years for men and 52±12 years for women. The mean BMI was 28.2±5.4 kg/m2. Twenty three individuals used sleeping pills. Mean sleep efficiency was 78.2%. The median [interquartile range] Charlson Comorbidity Index was 1.0 [2.0].

One hundred and seventeen patients (36%) had mild obstructive sleep apnea, their mean AHI was 9.3±2.2, one hundred and fourteen (35%) had PLMS, their mean PLMI was 42.0±28.4, while ninety-five (29.7%) of our patients reported insomnia symptoms, their mean Athens score was 13.5±3.5. There were no significant differences regarding age, gender, BMI, use of sleeping pills, coffee consumption, shift work, Charlson Comorbidity Index, CESD score and sleep disorders in the study sub-groups.

Objective sleep parameters, recorded with polysomnography, showed significant associations with lunar phases. Deep sleep ($p<0.001$), wake ($p<0.001$) and REM ($p=0.002$) percentages were significantly different between the three groups. Post hoc analyses revealed less deep sleep percentage (6.1[4] vs. 10.9[9], $p<0.05$) and REM percentage (10.1±6.6 vs. 13.9±6.6, $p<0.05$),

higher wake percentage (28.7±12.3 vs. 20.2±12, $p<0.05$) at full moon compared to alternate moon phases. Sleep efficiency was significantly shorter ($p<0.001$), while sleep latency ($p=0.001$) and REM latency ($p<0.001$) was longer at full moon compared to the other two moon phases. The results were similar in our sensitivity analyses using the three cut off points to define "full moon" specified in the methods section.

These associations remained significant after adjusting for age, gender, smoking, coffee consumption, use of sleeping pills, and regular exercise. Most of these associations remained significant after adjustment for the Charlson Comorbidity Index. Finally, adjustment for the Center for Epidemiologic Studies Depression Scale score in the final model did not abrogate the significant associations for deep sleep, wake percentage, sleep efficiency, and REM latency.

The interaction between gender and lunar phases was significant for deep sleep ($p=0.01$) and sleep latency ($p=0.01$), and in general, the observed differences for the variables of interest were consistently more pronounced in women. Interestingly, none of the assessed sleeping parameters (neither subjective nor objective) were associated with pre- or postmenopausal status in this sample.

Subjective sleeping-related parameters were not significantly different between the three groups. Within gender strata, however, the self-reported sleep onset latency was longer at full moon in women (median[IQR]: new moon 30.0[25] min, full moon 52.5[66] min, alternate moon 25.0[50], $p=0.04$), and the difference was nearly significant among men (median[IQR]: new moon 30.0[45] min, full moon 60.0[76] min, alternate moon 30.0[45] min, $p=0.06$).

2. FACTORS ASSOCIATED WITH QUALITY OF LIFE AMONG PATIENTS SUFFERING FROM INSOMNIA

Ninety four percent of the 319 participants completed out the AIS questionnaire. Therefore, the data of three hundred people have been analyzed. Based on the AIS criteria 95 individuals were classified as high risk for insomnia. There were no statistically significant differences between the patients who filled out the questionnaire and those who did not (age, sex, sleep parameters).

Those who scored 10 or above on the AIS questionnaire have showed significant differences on the basis of age groups. The average BMI level of the older adults patients was significantly

higher, while the AIS score lower compared to young adults. Similarly, the medium score of Charlson Comorbidity Index was higher in the case of older adults in comparison to the other two groups (median;IQR young adults 0;0, middle-aged 1;1, older adults 2;1.7, $p<0.001$). Thirty-one percent of the young adults, 29% of the middle-older adults and 13% ($p=0.4$) of the older adults patients were taking antidepressants, hypnotics or anxiolytics.

By comparing the polysomnographic results of the patients divided into two groups according to AIS, it has been found out that participants with high risk for insomnia had lower sleep efficiency and higher wake percentage.

Surprisingly, their REM sleep percentage was also higher (mean ±SD AIS<10 12.2±6.2 vs. AIS>10 13.7±6.6, $p=0.01$). Sleep latency also tended to be higher, but this difference was not statistically significant (median; IQ: AIS<10 11.6;19 vs. AIS>10 15.8;22, $p>0.05$). Furthermore, REM latency (median; IQ: AIS<10 90.7;65.2 vs. AIS>10 126.0;105, $p<0.01$) was also significantly different between the two groups.

Although sleep parameters are usually associated with age (deep sleep, REM sleep and REM latency are shorter, while sleep latency and light sleep become significantly higher with age), in our sample only the rate of wakefulness and sleep efficiency (post-hoc Sidac $p<0.05$ young adults vs. older adults adults) followed this pattern.

Each group has significantly underestimated their actual sleeping time (young adults: subjective sleeping time (SST) 5.46 hours, objective sleeping time (OST) 7 hours, middle-aged: SST 5.39 h, OST 6.9, older adults: SST 5.31 h, OST 6.7 h, $p<0.001$). The misperception index (MI) of the groups were as follows: young adults MI 0.22, middle-aged MI 0.21, older adults MI 0.02. The group which did not have the risk of insomnia has shown the following results: (AIS<10) young adults MI 0.08, middle-aged MI 0.05, age MI -0.07 ($p=0.02$).

The young age group suffering from insomnia demonstrated a better level of 'physical activity', 'physical pain', and 'general health' life quality dimensions in comparison to the other groups. The 'social function' dimension, however, was lower in the younger than the older adults group, even after adjustment for several covariables. There were no significant differences, in the case of patients suffering from other sleep disorders.

3. ASSOCIATION BETWEEN INSOMNIA AND INFLAMMATION IN KIDNEY TRANSPLANT PATIENTS

Of the 150 eligible patients, 50 individuals (33%) refused to participate. Consequently, the final study population included 100 Tx patients (participants) (Figure S1). There were no significant differences regarding age and gender between participants and those who refused to participate. The basic characteristics (age, gender, eGFR, hemoglobin, serum albumin) of the 100 participating Tx patients were similar to the characteristics of the total clinic population.

The mean age was 51 ± 13 years, 43% were women, and the prevalence of diabetes was 19%. The mean ± standard deviation (SD) or median (inter- quartilerange (IQR)) of serum albumin and white blood cell count and the median and IQR of serum IL-6, serum CRP and TNF-a were 40.2 ± 3.4 g/l,8.2 ± 2.4 9 10 3 / l,2.0(1.2–3.2) ng/l, 3.5(1.5–5.9)mg/l and 1.9(1.4–2.7) ng/l, respectively. Eighty-five percent of the Tx patients were taking steroids, 43% were administered CsA, 71% were on MMF, 46% of the patients were administered tacrolimus, and 5% were on azathioprine. Only 1 and 12% of the patients took everolimus and sirolimus, respectively. Six percent of Tx patients had at least one previous transplantation.

Sixteen percent of our patients suffered from insomnia symptoms. The serum IL-6 level was significantly higher in patients with insomnia (AIS < 10 than in non-insomniacs [median (IQR): 3.2 (2.6–5.1) vs. 1.7 (1.2–2.9) ng/l; p=0.009]. The levels of other inflammatory markers were similar in the two groups. Insomniacs were older and had significantly higher CCI compared with patients without insomnia. The usage of sleeping pills was significantly higher in insomniacs than patients without insomnia. All other parameters were similar between the two groups. AIS showed a weak (rho<|0.20|), non-significant correlation with all inflammatory markers. Gender differences were examined, and IL-6 levels were higher [median (IQR): 4.3 (2.7–6.3) vs. 1.4(1.0–2.4) ng/l; p=0.02] and serum albumin levels (mean ± SD: 38.4 ± 3.1 vs. 40.8 ± 2.7 g/l; p=0.03) were lower in women with insomnia versus without insomnia. Among men, we observed no such differences.

CONCLUSIONS

To summarize our new results and conclusions:

1. In our sample of individuals with insomnia and mild obstructive sleep apnea participants had less deep sleep percentage and REM percentage, higher wake percentage at full moon compared to alternate moon phases. Sleep efficiency was lower, while sleep latency and REM latency was longer, superficial sleep was more common during full moon in comparison to other moon phases, even after controlling for several potentially important covariables.

2. These differences were more pronounced among females compared to males.

3. In the group of patients suffering from insomnia, older individuals estimated their actual sleeping time more accurately compared to younger adults.

4. Insomnia among young adults was associated with emotional aspects, while insomnia among older adults was more consistently associated with somatic symptoms.

5. There was significant association between serum IL - 6 levels and insomnia. This association was not significant in case of other inflammatory markers (TNF-α, CRP, white blood cell count).

6. The association between presence of insomnia and serum IL-6 level disappeared after adjusting for renal function and age, gender, hemoglobin and comorbidity in the multivariate model.

We suggest that further research is needed to confirm the association between sleep parameters and lunar phases and to also elucidate any potential mechanisms.

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PUBLICATIONS RELATED TO THESIS

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