Insomnia symptoms are associated with sleep architecture among kidney transplant recipients

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Sleep in chronic kidney disease

• 50-80% of patients with End-Stage Kidney Disease (ESKD) have sleep-related problems
  1. Insomnia
  2. Restless legs syndrome
  3. Periodic limb movement in sleep
  4. Obstructive sleep apnea
End-stage kidney disease

**TRANSPLANTATION:**

Better treatment modality compared to dialysis
- Lower morbidity and mortality
- Better quality of life

BUT!
Poor sleep is remarkably high, more than 50%!
Definition of insomnia disorder

- difficulty of falling asleep
- Frequent awakenings or early morning awakening
- poor subjective sleep quality
- impaired daytime functioning, tiredness, fatigue or sleepiness

• Diagnosis based on subjective complaints, Polysomnography is not necessary!
Sleep structure in insomnia

Sleep onset latency

- Higher wake after sleep onset time
- Beta activity increased
- Less slow wave sleep/delta activity
Kidney transplantation and insomnia

- Prevalence of insomnia is 8% among kTx vs vs 15% in dialyzed population.

- Symptoms of insomnia associated with:
  - Lower quality of life
  - Fatigue, depression
  - Pain, post-traumatic stress-symptoms
  - Higher number of comorbidities
Etiology of insomnia?

• Among kTx recipients lack of studies – multifactorial origin?
  • Anxiety, fear of rejection
  • Deteriorating graft function, altered metabolism of sleep-regulatory mediators
  • Ongoing subclinical inflammation
  • Other comorbid conditions
  • Immunosuppressant or other medications
Kidney transplantation and sleep architecture

- **PSG studies among kTx recipients:**

- Focusing on obstructive sleep apnea and not on sleep architecture!
  - Depressive Symptoms Are Associated With Objectively Measured Sleep Parameters in Kidney Transplant Recipients
  - Journal of Clinical Sleep Medicine
Hypothesis:

Symptoms of insomnia are associated with worse sleep architecture?

- Longer sleep onset latency
- Shorter sleep duration
- Less slow wave sleep and delta activity
- Higher wake time after sleep onset
- Higher wake-like (beta) EEG activity during sleep
Methods/II.

• **Selection of patients:**
  - Semmelweis University, Budapest, Hungary, Transplantation and Surgery Department, adult, kidney transplanted patients.
  
• **Random selection n= 100.** **Exclusion criteria:** previously diagnosed sleep apnea, transplantation earlier than 3 months, acute or active respiratory system illness, acute infection, hospitalization within 1 month, surgical procedure within 3 months.

Data collection:

• Demographic data
• Questionnaires: insomnia and depression
• Laboratory parameters
• Data about kidney disease and transplantation
• Comorbidity
• Sleep study

MINIT-HU study
N1= 1198

N2 = 100

Random sampling
Methods/II.

**Athens Insomnia Scale (AIS)**
- 8 items, 0-24 score range
- Subjective complaints of insomnia
  - sleep initiation
  - sleep maintenance
  - early morning awakening
  - non-restorative sleep and daytime symptoms

**Center for Epidemiologic Studies-Depression (CES-D) scale**
- 20 items, 0-60 score range
Methods/III.

Sleep Study:

- One-night Polysomnography (PSG) 1st Department of Internal Medicine, Sleep Laboratory, (SOMNOScreen PSG Tele, SOMNomedics GmbH, Germany, CBo494).

- 4 channel EEG, ECG, breathing movements, respiratory airflow, snoring, O₂ saturation, leg movements, muscle tone, eye movements.

- Parameters of sleep macroarchitecture were defined.
Methods IV.

Power Spectral Analysis of Sleep EEG

- Visual detection and elimination of artefacts
- Absolute spectral power on central derivations
  - Non-REM (stages 2., 3., 4.)
  - REM sleep.

MINIT-HU study
N1 = 1198

EEG analysis

N2 = 100

N3 = 56
## Demographics: kTx PSG sample

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (number)</td>
<td>57 males and 43 females</td>
</tr>
<tr>
<td>Age (year) (mean ± SD)</td>
<td>51±13</td>
</tr>
<tr>
<td>BMI (kg/m²) (mean ± SD)</td>
<td>27±5</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²) (mean ± SD)</td>
<td>54±19</td>
</tr>
<tr>
<td>AIS score (median;iqr)</td>
<td>4;6</td>
</tr>
<tr>
<td>Prevalence of insomnia %</td>
<td>16</td>
</tr>
<tr>
<td>CESD score (median;iqr)</td>
<td>9;11</td>
</tr>
<tr>
<td>Prevalence of depression %</td>
<td>21</td>
</tr>
</tbody>
</table>
# Sleep macrostructure

<table>
<thead>
<tr>
<th>PSG parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset latency (min) (median;iqr)</td>
<td>15;17</td>
</tr>
<tr>
<td>Total sleep time (h) (mean ± SD)</td>
<td>6±1.3</td>
</tr>
<tr>
<td>Slow wave sleep (%) (mean ± SD)</td>
<td>12±8</td>
</tr>
<tr>
<td>REM sleep (%) (mean ± SD)</td>
<td>13±6</td>
</tr>
<tr>
<td>REM latency (min) (median;iqr)</td>
<td>145;87</td>
</tr>
<tr>
<td>Wake after sleep onset time (min) (median;iqr)</td>
<td>61;47</td>
</tr>
</tbody>
</table>
Correlation of sleep macrostructure with insomnia symptoms

<table>
<thead>
<tr>
<th><strong>PSG parameters</strong></th>
<th>AIS score</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep onset latency</strong> <em>(min)</em></td>
<td>0.105</td>
<td>0.301</td>
</tr>
<tr>
<td><strong>Total sleep time</strong> <em>(h)</em></td>
<td>-0.127</td>
<td>0.214</td>
</tr>
<tr>
<td><strong>Slow wave sleep</strong> <em>(%)</em></td>
<td>0.060</td>
<td>0.557</td>
</tr>
<tr>
<td><strong>Wake after sleep onset time</strong> <em>(min)</em></td>
<td>0.088</td>
<td>0.392</td>
</tr>
</tbody>
</table>
Multivariable analysis of the association of sleep parameters with AIS score

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>β coefficient</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset latency (min)</td>
<td>-0.048</td>
<td>-0.285 – 0.188</td>
<td>0.686</td>
</tr>
<tr>
<td>Total sleep time (h)</td>
<td>-0.120</td>
<td>-0.374 – 0.134</td>
<td>0.350</td>
</tr>
<tr>
<td>Slow wave sleep (%)</td>
<td>0.263</td>
<td>0.026 – 0.500</td>
<td>0.030</td>
</tr>
<tr>
<td>Wake after sleep onset time (min)</td>
<td>0.088</td>
<td>-0.158 – 0.335</td>
<td>0.478</td>
</tr>
</tbody>
</table>

Adjusted for: age, sex, kidney function, CES-D score, sleep medication use
Correlation analysis of sleep microstructure in kTx EEG sample (n3=56)

<table>
<thead>
<tr>
<th>Frequency band</th>
<th>AIS score</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spearman’s rho</td>
<td></td>
</tr>
<tr>
<td><strong>NREM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta</td>
<td>0.194</td>
<td>0.152</td>
</tr>
<tr>
<td>Alpha</td>
<td>0.244</td>
<td>0.070</td>
</tr>
<tr>
<td>Delta</td>
<td>0.012</td>
<td>0.931</td>
</tr>
<tr>
<td><strong>REM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta</td>
<td>0.257</td>
<td>0.055</td>
</tr>
<tr>
<td>Sigma</td>
<td><strong>0.287</strong></td>
<td><strong>0.032</strong></td>
</tr>
<tr>
<td>Delta</td>
<td>0.197</td>
<td>0.145</td>
</tr>
</tbody>
</table>
Multivariable analysis of the association of sleep spectra with AIS score

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>$\beta$ coefficient</th>
<th>95% CI</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NREM Beta</td>
<td>0.160</td>
<td>-0.132 – 0.451</td>
<td>0.276</td>
</tr>
<tr>
<td>NREM Alpha</td>
<td>0.256</td>
<td>-0.050 – 0.563</td>
<td>0.099</td>
</tr>
<tr>
<td>NREM Delta</td>
<td>0.194</td>
<td>-0.064 – 0.452</td>
<td>0.138</td>
</tr>
<tr>
<td>REM Beta</td>
<td><strong>0.323</strong></td>
<td><strong>0.041 – 0.606</strong></td>
<td><strong>0.026</strong></td>
</tr>
<tr>
<td>REM Sigma</td>
<td>0.306</td>
<td>-0.005 – 0.616</td>
<td>0.054</td>
</tr>
<tr>
<td>REM Delta</td>
<td>0.273</td>
<td>-0.050 – 0.595</td>
<td>0.096</td>
</tr>
</tbody>
</table>

Adjusted for: age, sex, kidney function, CES-D score, sleep medication use
Conclusions

1. Despite poor sleep quality assessed by PSG insomnia symptoms were not associated with expected changes in sleep macrostructure.

2. However, more severe insomnia symptoms were associated with higher SWS and higher REM beta activity.

3. Impaired homeostatic sleep regulation and REM instability?
Clinical relevance?

• to draw attention to sleep complaints
• to highlight that insomnia symptoms are associated with different alterations in sleep architecture

**Future studies are needed:**

• higher homeostatic sleep pressure is due to some yet undefined factors? (p.e: fatigue, treatment modality, medications, subclinical inflammation).
• interventions to improve sleep would change these sleep parameters and improve sleep complaints?
Thank you for the attention.
Frekvenciahatárok:

- Gamma: 25.25-45 Hz
- Beta: 15.25-25 Hz
- Szigma: 11.25-15 Hz
- Alfa: 8.25-11 Hz
- Theta: 4.25-8 Hz
- Delta: 0.75-4 Hz

- (C₃, C₄) using Cz as reference
- Mintavételi frekvencia: 128Hz
- 0.2 Hz-es felül, ill. 60 Hz-es alul-áteresztő szűrők