Correlation of Perceived, Sleep Disturbance & Fatigue with Motivation & Pituitary Hormonal Deficiencies in Patients with Pituitary Tumors

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Background
Normal Pituitary Gland: sagittal section
Pituitary Adenomas

Classifications:

1. Size:
   - Microadenoma <1cm
   - Macroadenoma >1cm

2. Hormonal Secretion:
   - Excess: Growth Hormone, prolactin, ACTH/Cushing’s
   - Deficiency: Any pituitary hormone
Circadian Pituitary Hormone Production

- Melatonin
- Cortisol
- Growth hormone
Sleep Architecture

• Non-REM
  – 4 stages
    • theta waves
    • sporadic spindles and episodic rhythms from thalamus
    • 3 & 4 Slow wave sleep (SWS) with delta waves

• REM
  – motor activity is inhibited
  – most dreaming takes place
  – REM sleep deprivation disturbs normal body functions

Hypothalamus
(sleep-wake, neuroendocrine, temperature)

Paraventricular nucleus
Dorsomedial nucleus
Supraventricular nucleus
Medial preoptic area
Sympathetic ganglia
Circadian temperature control
Pineal gland (melatonin)
Brainstem (locus coeruleus)
Periphery
Sleep Disruption

- Hormonal /biochemical disturbance
- Age & gender
- Mediators internal /external
- Disruption of clock gene expression
- Modulation of sleep phases such as SWS, delta activity or REM depletion
Hypothalamic Pituitary Adrenal (HPA) Axis & Sleep

• HPA axis is affected by sleep-wake cycles via direct and indirect effects of the circadian and homeostatic mechanisms

• Conversely, the HPA axis function has well documented effects on sleep wake cycles.
HPA Axis/Cortisol

1. Low AM salivary cortisol levels have been correlated with patient perception of poor sleep quality, frequent waking, insomnia and sense of non-restorative sleep.

2. Depression - associated with high levels of nocturnal hypothalamic activity & CRH over secretion & HPA axis stimulation have been associated with depression. Studies contradictory
   - *Psychoneuroendocrinology* (2013) 38, 927—940
Cortisol

- When cortisol levels are elevated secondary to stressors, animal models have demonstrated resultant high melatonin levels - have a sedative effect during stress.

Follicle Stimulating Hormone (FSH) & Lutenizing Hormone (LH)

• Decreased SWS was noted in association with elevated FSH and LH levels in post menopausal woman with blunted FSH/LH response in depression.

Growth Hormone (GH)

- Levels decrease with age
- Preferentially secreted during deep, slow-wave sleep (SWS) associated with \( \uparrow \) Ghrelin
- GH deficiency associated with decreased total sleep time and increased sleep fragmentation compared to controls
- GH Deficiency associated with decreased energy and fatigue

Fatigue

• Defined in humans as self reported low levels of stress recovery associated with high allostatic stress load.

• Sleep deprivation = decreased time to task failure and cognitive performance and higher perceived exercise fatigue but no difference in muscle fatigue from non-deprived controls.


• Hypocretin-1 and melanin-concentrating hormone, measured in the human amygdala/hypothalamus shown to increase after eating and prior to sleep

More Fatigue

- Animal models have demonstrated structural neuronal changes with sleep deprivation and central fatigue that were reversible with sleep. The impact of chronicity is unknown.

Motivation

• Few studies have correlated sleep, fatigue and motivation
• 581 subject study of work stress - found a significant correlation between low AM cortisol levels, lack of energy, motivation ($r=0.11, p=0.036$)

AIM

For patients with pituitary adenomas:

• Assess patient perception of severity of sleep disturbance and fatigue

• Evaluate the relationship among sleep disturbance, fatigue & motivational disturbance.

• Assess the relationship to tumor size (macro or micro- adenoma) and/or hormonal dysfunction
Study Design/Methods

• Prospective
• Cross-sectional
• Single site
• Convenience sample
• 17 item questionnaire
• Likert scale of severity dysfunction (6 pt)
• Questions adapted from:
  – Epworth Sleepiness Scale
  – Fatigue Severity Scale (Krupp 1989)
  – Eysenck Personality Inventory.
## Questionnaire: Severity 0-6

<table>
<thead>
<tr>
<th>Fatigue</th>
<th>my fatigued interferes with my work life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I am fatigued during the day</td>
</tr>
<tr>
<td></td>
<td>my fatigue disrupts my family life</td>
</tr>
<tr>
<td></td>
<td>my exercise is limited by my fatigue</td>
</tr>
<tr>
<td></td>
<td>I lack energy to do social activities with friends</td>
</tr>
<tr>
<td>Sleep</td>
<td>I wake early morning &amp; can’t go back to sleep</td>
</tr>
<tr>
<td></td>
<td>I wake up tired</td>
</tr>
<tr>
<td></td>
<td>I fall asleep when I sit quietly/read</td>
</tr>
<tr>
<td></td>
<td>I sleep much of the day</td>
</tr>
<tr>
<td></td>
<td>I have trouble getting to sleep</td>
</tr>
<tr>
<td></td>
<td>I Wake frequently</td>
</tr>
<tr>
<td>Motivation</td>
<td>Others seem to get more done in a day than me</td>
</tr>
<tr>
<td></td>
<td>I lack motivation to do things.</td>
</tr>
<tr>
<td></td>
<td>I lack energy to do my household chores</td>
</tr>
<tr>
<td></td>
<td>motivated if my work is acknowledged/</td>
</tr>
<tr>
<td></td>
<td>I like seeing what I have accomplished myself</td>
</tr>
<tr>
<td></td>
<td>I feel like getting things done around the house</td>
</tr>
</tbody>
</table>
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Female n=47</th>
<th>Male n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=67</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MeanAge/yrs</strong></td>
<td>42.6</td>
<td>5</td>
</tr>
<tr>
<td><strong>Mean # Hormonal Def</strong></td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Micro &lt;1cm</strong></td>
<td>26 (55%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td><strong>Macro &gt;1cm</strong></td>
<td>18 (38%)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td><strong>Medical Hx</strong></td>
<td>12 (25%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td><strong>Non-Functioning</strong></td>
<td>19 (40%)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td><strong>Hyper-Functioning</strong></td>
<td>19 (40%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td><strong>other</strong></td>
<td>9 (20%)</td>
<td>4 (20%)</td>
</tr>
</tbody>
</table>
## Results: Spearman’s Correlations

<table>
<thead>
<tr>
<th>Categorical</th>
<th>Sleep</th>
<th>Fatigue</th>
<th>Motivation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gender</td>
<td>-</td>
<td>( r = -0.29, p = 0.015 )</td>
<td>-</td>
</tr>
<tr>
<td># deficiencies</td>
<td>( r = -0.35, p = 0.004 )</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Size of Tumor</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Med Hx</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>-</td>
<td>( r = -0.29, p = 0.016 )</td>
<td>( r = -0.25, p = 0.04 )</td>
</tr>
</tbody>
</table>
Mean Severity Scores: by Dysfunction & Item
Fatigue

<table>
<thead>
<tr>
<th>Item Responses</th>
<th>Mean Severity Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Micro</td>
</tr>
<tr>
<td>1</td>
<td>4.03</td>
</tr>
<tr>
<td>2</td>
<td>3.43</td>
</tr>
<tr>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>3.19</td>
</tr>
<tr>
<td>5</td>
<td>3.29</td>
</tr>
</tbody>
</table>
Motivation

Mean Severity Scores

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro</td>
<td>3.46</td>
<td>3.56</td>
<td>3.85</td>
<td>4.74</td>
<td>4.06</td>
<td>3.13</td>
</tr>
<tr>
<td>Macro</td>
<td>3.5</td>
<td>3.28</td>
<td>3.59</td>
<td>4.59</td>
<td>3.75</td>
<td>3.16</td>
</tr>
</tbody>
</table>
Conclusions

• Patients with pituitary adenomas experience a moderate level of sleep dysfunction.
• All patients reported similar and moderate levels of sleep dysfunction, fatigue and motivational disturbances.
• Larger tumor size was consistently, but not significantly, associated with worse dysfunction in sleep, fatigue and motivation.
• Female gender was only significant for increased fatigue.
• Numerically, more hormonal deficiencies correlated with greater sleep dysfunction.
• HF tumors correlated with worse fatigue and motivation.
Implications

• Treatment of sleep disturbance in patient’s with PA is multifaceted.
• More research is needed with respect to sleep phase dysfunction in PA in order to focus treatment.
• Further evaluation with differentiation of PA hormonal hyper-secretion and specific deficiencies is indicated.
Thank you.
Questions?
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