Periodic leg movement, sleep fragmentation and central sleep apnoea in two cases: reduction with Clonazepam

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Periodic leg movement (PLM) syndrome during sleep was first described in 1953 by Symonds [11], who called it "nocturnal myoclonus" and distinguished it from the jerks occasionally experienced by normal individuals upon falling asleep. The phenomenon is a sleep-related problem involving repetitive, stereotypic discharges of varying intensity in the anterior tibialis muscles, leading to the extension of the big toe. The ankle, knee, and sometimes the hip may flex after the toe has been extended. The phenomenon presents itself as the classic abnormal plantar response or Babinski sign that is present and sometimes the hip may flex after the toe has been extended. The phenomenon presents itself as the classic abnormal plantar response or Babinski sign that is present and[/ldots]

Patients and methods

Case reports

Two patients, a 42-year-old man (patient 1) and a 48-year-old woman (patient 2), with body mass index (BMI) of 25 and 23, respectively, were referred with marked insomnia. Past medical history was non-significant: patient 2 had a tonsillectomy in childhood and smoked for three years in her early twenties. Neither patient used alcohol regularly, having at most one glass of wine every 15-30 days. Both complained of no apirsty sleep disturbances consisting of short sleep latencies at sleep onset, frequent awakenings during sleep, and a feeling of daytime fatigue for a minimum of five and eight years, respectively. Each had previously received hypnotic medications with transient improvements, but neither had taken any drug during the four months prior to consultation. Spouses confirmed that the patients manifested frequent leg jerks, very restless sleep, and the presence of apnoea without snoring. Clinical evaluation had been non-contributive; chest roentgenograms, 12-lead ECG, supine, awake blood gases, and blood tests (electrolytes, glucose, etc.) were within the normal laboratory limits. A clinical neurological evaluation was negative, and 4-limb electromyogram and nerve conduction studies were normal. Cephalometric roentgenograms showed no abnormal cranio-mandibular features.

Protocol

Each patient underwent three nights of baseline polygraphic monitoring. The monitored variables included electroencephalogram (EEG) (C3/A2 - C4/A1 derivations from the 10-20 international placement system), electro-oculogram (EOG), chin electromyogram (EMG), electrocardiogram (ECG with modified V2 lead), left and right anterior tibialis EMG. Respiration was monitored by non-calibrated inductive respiratory plethysmography, nasal and buccal thermistors and ear oximetry (Biox III). An oesophageal balloon was also used on the third baseline night. Polygraphic monitoring started between 22.00 and 22.30 h. Monitoring ended when patients decided to get up, although they were encouraged to stay in bed for as long as possible. On the two nights following completion of the nocturnal baseline monitoring, patients received 0.5 mg of Clonazepam at bedtime and were again monitored. Patients were then sent home for 1 week and instructed to take one mg of Clonazepam each night at bedtime. After the week of increased dosage, patients returned to the clinic for a final night of monitoring. All procedures conformed to guidelines established by the university’s committee on ethics.

Analysis

Records were scored following the international manual of RECHTSCHAFEN and KALES [8]. Each periodic leg movement was identified and any alpha EEG arousal was noted [9]. If apnoea was present, its type was defined. We calculated an apnoea index (apnoeas per hour of sleep), defined as number of apnoeas x 60 per total sleep time (TST) in min, and a PLM index (PLMs per hour of sleep), defined as number of PLMs x 60 per TST in min.

Results

The very significant sleep disruption and fragmentation coincided with a combination of leg movements and central apnoeas (table 1). Since missed breaths of <10 s duration were not considered “apnoeas,” there were actually more than were tabulated. Apnoeas tended to be short, with mean duration of 13 and 15 s, respectively, for patients 1 and 2 on baseline nights 1 and 2. The lowest oxygen saturation (Sao2) drop was 92% in both cases. On baseline night 3, placement of the oesophageal balloon caused a significant increase in long awakenings after onset of sleep and led patients with significant sleep disturbance to complain of nose and throat irritation. During night 3, however, sleep segments demonstrated the central apnoeas noted during monitoring the two previous nights.

Our small sample did not permit valid statistical analysis, but 0.5 mg of Clonazepam at bedtime and, more importantly, 1 mg dosages allowed maintenance of sleep associated with significant decrease in arousals, PLM, and central sleep apnoeas (table 1). The apnoea index (AI) dropped from a mean of 60 and 36 (patients 1 and 2) on baseline nights 1 and 2 to 13 and 8 with

Table 1. - Patient data from nocturnal monitoring

<table>
<thead>
<tr>
<th></th>
<th>XTRT (%)</th>
<th>X%TST (%)</th>
<th>REMS (%)</th>
<th>PLM</th>
<th>PLM w/alpha (%)</th>
<th>AI % central apnoea</th>
<th>PLM Index</th>
<th>PLMw/alpha Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline X nights 1 and 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>patient 1</td>
<td>465</td>
<td>178</td>
<td>4</td>
<td>220</td>
<td>100</td>
<td>60</td>
<td>&gt;95</td>
<td>74</td>
</tr>
<tr>
<td>patient 2</td>
<td>481</td>
<td>235</td>
<td>7</td>
<td>450</td>
<td>215</td>
<td>36</td>
<td>&gt;95</td>
<td>114.9</td>
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<tr>
<td>Baseline night 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>patient 1</td>
<td>361</td>
<td>65</td>
<td>1.2</td>
<td>40</td>
<td>37</td>
<td>20</td>
<td>&gt;95</td>
<td>36.9</td>
</tr>
<tr>
<td>patient 2</td>
<td>350</td>
<td>100</td>
<td>3</td>
<td>79</td>
<td>59</td>
<td>39</td>
<td>&gt;95</td>
<td>47.4</td>
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<td>Clonazepam 0.5 mg X nights 4 and 5</td>
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<td></td>
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<tr>
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<td>309</td>
<td>12</td>
<td>85</td>
<td>41</td>
<td>13</td>
<td>&gt;95</td>
<td>13.8</td>
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<tr>
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<td>486</td>
<td>371</td>
<td>14</td>
<td>76</td>
<td>20</td>
<td>8</td>
<td>&gt;95</td>
<td>12.3</td>
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<td>Clonazepam 1 mg X night 14</td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>patient 1</td>
<td>439</td>
<td>351</td>
<td>13</td>
<td>20</td>
<td>7</td>
<td>9</td>
<td>&gt;95</td>
<td>3.4</td>
</tr>
<tr>
<td>patient 2</td>
<td>462</td>
<td>379</td>
<td>14.5</td>
<td>42</td>
<td>11</td>
<td>4</td>
<td>&gt;95</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Baseline night 3: As mentioned in the text, patients were monitored with oesophageal balloon, which greatly disturbed the already existing poor sleep. This added sleep disturbance explains the differences noted between baseline nights 1 and 2 and night 3. TST is greatly reduced, and sleep-related parameters are thus artificially low. X: mean; XTRT: total recording time; TRT: total sleep time; TST: total sleep time; PLM: periodic leg movement; AI: apnoea index; S-1: stage 1 NREM sleep; S-2: stage 2 NREM sleep; REMS: percentage of REM sleep during TST.
0.5 mg Clonazepam. The PLM index dropped from 74 and 114.9 on baseline nights to 13.8 and 12.8, respectively. The improvement was even more pronounced with 1 mg clonazepam, with an apnoea index of 9 and 4 and a PLM index of 3.4 and 6.6, respectively, for patients 1 and 2. These changes in apnoea index and PLM index were associated with a decrease in the percentage of stage 1 NREM sleep and an increase in the percentage of stage 2 NREM and REM sleep during TST.

Discussion

The two patients studied were of interest, presenting with significant sleep reduction, marked sleep fragmentation, and a combination of PLM and multiple repetitive central breathing irregularities. It is unclear from the baseline recordings whether PLM syndrome or breathing irregularities was primarily responsible for the significant sleep disturbance. Considering the normal daytime clinical evaluation and test results, the very limited and rare \( \text{SaO}_2 \) drops seen with the central apnoeas, and the importance of PLM associated with alpha arousal and awakenings, we hypothesized after the first recording that the significant sleep fragmentation with continuous wake-sleep-wake shift was responsible for the breathing irregularities. Because PLM syndrome contributed significantly to the sleep fragmentation, we selected a hypnotic drug (despite its depressant effects on the central nervous system) previously used in the treatment of PLM syndrome. The resulting marked reduction in PLM and sleep fragmentation led to a near-normal breathing pattern during sleep and normal passage to deeper stages of sleep. These observations have to be related to the recently published abstract by Bonnet et al. [10] on the effect of Triazolam in increasing sleep continuity and decreasing the number of central sleep apnoeas in healthy elderly subjects. Onal et al. [11] have hypothesized that obstructive sleep apnoea may develop in patients presenting marked respiratory oscillations during sleep. Our observations, and those of Bonnet et al. [10] indicate that sleep fragmentation will lead to "missed breath" (central apnoeas), and that better maintenance of sleep, related here to a decrease in the number of PLMs, will eliminate these apnoeas. The drop from AIs of 60 and 36 to 9 and 6, respectively, with 1 mg of Clonazepam was striking. This reduction in apnoea frequency was obtained despite the fact that stages 1 and 2 NREM sleep still represented 87 and 85% of TST respectively. Stages 1 and 2 NREM sleep are the two stages during which both respiratory oscillations and PLM are normally observed.

Very little data are currently available on the development of repetitive sleep apnoeas. Recently, Issa and Sullivan [12], Guilleminault et al. [13], and Hoffstein et al. [14] reported on the impact of nasal continuous positive airway pressure (CPAP) on central sleep apnoea, and the association of upper airway anatomical abnormalities. We have also reported observations in children [15] and adults [16], with anatomical abnormalities of the upper airway, where central apnoeas preceded by months or years the monitoring of mixed and obstructive apnoeas. The two cases reported clearly demonstrate that elimination of sleep fragmentation induced by PLM greatly improves the maintenance of normal air exchange during sleep despite the added effect of a benzodiazepine. Models considering onset of "respiratory oscillations" during sleep give the primary role to ventilatory variables, particularly changes in blood gases as seen in sleep-related periodic breathing at high altitude [17], or cluster of hyperventilatory breaths at time of arousal (which decrease carbon dioxide tension \( P_{\text{CO}_2} \) and drive it below the "apnoeic threshold" during sleep) in some mixed sleep apnoeas [18]. But no cluster of hyperventilatory breaths at time of arousal, or significant increase in positive and negative pressure measurement with an oesophageal balloon was noted here.

Our two case reports indicate that non-ventilatory variables, in this case sleep fragmentation, can be the primary element in repetitive abnormal breathing patterns during sleep. A systematic evaluation of one hundred successive male obstructive sleep apnoeic patients has shown that 39 presented with PLM not influenced by nasal CPAP [19]. Another study, performed on a smaller group of subjects, produced similar findings [20]. The role of sleep fragmentation in disturbing hypoxic and hypercapnic responses has been well demonstrated in animal studies [21]. However, its potential role in induction of periodic ventilatory problems in humans and the development of central sleep apnoea is difficult to demonstrate. The two subjects reported were rare, but observation of them gave us insight into the different mechanisms, ventilatory and non-ventilatory, that can be involved in the development and maintenance of sleep apnoea.

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