Melatonin and REM Behavior Disorder

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Abstract

REM Sleep Behavior Disorder (RBD) is commonly associated with neurodegenerative diseases and leads to abnormal and often aggressive behavior during sleep, often causing injury to self or bed partner. Clonazepam and melatonin have been considered as treatments of RBD, but the underlying mechanism of action is unknown. Melatonin may restore the presence of physiological REM sleep muscle atonia. A clinical protocol was established to follow patients with RBD with clinical evaluation and polysomnography (PSG). A retrospective analysis was then performed on data from 28 RBD patients. From the obtained data, melatonin 6 mg has a positive effect on both clinical manifestation and PSG findings. Most subjects responded to melatonin 6 mg with a significant decrease or absence of abnormal behavior, and less than 20% of EMG bursts during total REM time during PSG, but one patient never responded to the drug even at up to 12 mg of melatonin and 3 mg of clonazepam. Depending on the patient, more disturbed sleep was noted with melatonin alone than with the combination of both melatonin and clonazepam, and a further decrease of “wake after sleep onset” was noted at polysomnography.

Keywords: Melatonin; REM behavior disorder; Treatment; Poor nocturnal sleep; Response to treatment

Introduction

Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD) is a syndrome that was recognized many years ago by Japanese researchers in association with alcoholic delirium [1,2]. Jouvet and Delorme in Lyon, France lesioned the region of the peri-coeruleus in the upper brainstem in cats that was responsible for the initiation of the active inhibition of muscle tone during REM sleep, inducing a syndrome where cats were “acting out” their dreams with behavior similar to a cat trying to catch an invisible mouse or other oniroid behaviors [3]. More recently, this descending pathway involving glycinergic and glutaminergic neurotransmitters has also been well mapped in rats by the Lyon school, as the rat anatomy of this descending pathway [4] is closer to the human anatomy than the one noted in cats. The syndrome called “REM without atonia” was also observed in olivo-ponto-cerebellar degeneration, a neuro-degenerative disorder, by Quer-Salva and Guilleminault in 1986 [5]. Then Schenck et al. noted the presence of REM without atonia in subjects who appeared to have no other neurological symptoms and the syndrome was called “RBD” [6]. Since then, RBD has been noted in Parkinson’s patients and in patients with other neuro-degenerative disorders. Furthermore, the long-term follow-up of “idiopathic RBD cases” performed predominantly by Schenck et al. [6] has demonstrated the evolution of these idiopathic RBD patients toward the development of neuro-degenerative diseases, particularly Parkinson’s, Multiple System Atrophy, or Dementia [7]. The histologic investigation of the brain of these patients revealed the presence of Lewy bodies and these different neuro-degenerative disorders with Lewy bodies at histology are classified today as “synucleinopathies” [8,9]. The aim of RBD treatment has been to eliminate the dangerous behavior associated with the abnormal persistence of muscle tone during REM sleep, leading to the acting out of dreams, and also to provide quiet and uninterrupted sleep.

Two drugs have been advocated as treatment: a benzodiazepine (clonazepam) and melatonin. Both drugs are given orally in the evening and have been reported to decrease or eliminate the violent behavior associated with RBD. However, the degree of response (complete vs. partial or incomplete), the dosages required, and the potential side effects remain unclear.

During 5 years (July 2007 to July 2011) we used a clinical protocol to treat patients recognized with RBD. This clinical protocol covered the first 7 months following diagnosis of RBD and involved repeated polysomnography tests. Following the initial 7 months, patients may have been followed by neurologists or other specialists and/or may have been intermittently seen by the sleep medicine service (particularly when patients did not respond to treatment).

We retrospectively looked at the data obtained using our clinical protocol, and in specific cases we added follow-up information past the initial 7 months (these subjects were usually non-responders). The retrospective analysis of anonymous data was approved by the hospital IRB.

Clinical Protocol

Interview

There was a systematic interview of all patients seen in the sleep clinic on the presence of abnormal behavior during sleep. The interview was conducted not only with the patient but also with the bed partner or caregiver in elderly subjects. All symptoms associated with sleep disorders were explored and documented.

Most commonly, patients were referred for evaluation of snoring and the question of sleep-disordered breathing, but when symptoms of another sleep disorder were uncovered, further questions were asked to characterize the syndrome and its severity. If any reports of abnormal
behaviors or vocalizations during sleep were elicited, further questions on dream enactment, degree of awareness, and bruises and trauma to self or bed partners were collected in a pre-established standardized grid covering the major sleep disorders.

Evaluation of co-morbidities and associated diseases was also systematically tabulated, including evaluation of any current medical treatment. Based on the results of the interview, the decision to perform a nocturnal polysomnographic (PSG) evaluation was made.

Polysomnography (PSG)

The following variables were systematically monitored: 4 EEG (including central, frontal, and occipital derivation), 2 electro-oculogram, EMG leads including chin and legs, and 1 ECG lead. Respiration was monitored with nasal cannula pressure transducer, oral thermistor, chest and abdomen respiratory plethysmography bands, respiratory EMG leads, pulse oximetry, neck microphone, and position sensor. Patients were continuously video recorded during the nocturnal PSG.

Based on the results of the clinical interview and PSG, patients were labeled differently. If patients presented with Sleep-Disordered Breathing (SDB), they were first treated with nasal CPAP and the monitored nasal flow was derived from a Respironics PR1™ nasal CPAP machine replacing nasal cannula recording. Presence of abnormal EMG elevation during REM sleep was determined either at initial recording or during nasal CPAP recording.

Scoring of abnormal amount of EMG activity during REM sleep

At the time of initiation of the clinical protocol, monitoring of extra EMG leads involving legs and arms had been recommended to make a valid diagnosis, but the International Classification of Sleep Disorders2 (ICSD-2) [10] did not provide cut off values for the definition of “excessive amount of phasic or tonic EMG activity,” nor did they indicate which muscle should be investigated in patients suspected of RBD. As a result, the same montage for PSG was used with the addition of flexor and extensor muscle monitoring at the wrist. The EMGs were recorded with surface electrodes placed about 2 cm apart and recorded with the low frequency filter set at 10 Hz and high frequency filter set at 100 Hz.

Scoring of the abnormal EMG activity was systematically undertaken. When low EMG activity allowed the identification of a clear onset of REM sleep, a REM sleep segment was scored. Rechtschaffen and Kales criteria [11] were used for further delineation of the onset and offset of REM and to identify NREM sleep, including the presence of K complexes and sleep spindles. When there was a large increase in the chin EMG, the REM sleep segment was defined based on the presence of a phasic event (i.e., rapid eye movement and abrupt burst of EMG activity in chin EMG) and on analysis of the EEG, using sleep spindles and K complexes to delineate the REM sleep segment. Once a sleep segment had been identified as REM, each 30-second period was sub-scored looking at all EMG bursts. Each muscle burst could last up to 5 seconds, independently of the involved muscle. If two muscles presented overlapping EMG bursts, the total time spent with high EMG activity extended from the beginning of the increase EMG activity of the first muscle to the end of the EMG activity of the second muscle. In these cases, the total segment of “high EMG activity” may have been longer than 5 seconds. The percentage of time spent with “high EMG” during REM sleep was calculated.

Follow-up procedures

Once the presence of abnormal behavior and EMG activity were confirmed, and any SDB had been controlled, patients were placed on the clinical protocol. The first two patients were initially treated differently but ultimately had similar treatment to the 26 other patients at 4-month follow-up (section below). During the first 4 weeks, bed partners were asked to keep a log of the number of nights with the presence of abnormal behavior and PSG with video recording was obtained at the end of this period. Follow-up was performed the following month and every other month thereafter up to the beginning of the 7th month. At each follow-up appointment, there was an interview with the patient and bed partner, collection of 4 weeks of sleep logs, and PSG with scoring of EMG in REM. Thus, three PSGs preceded by 4 weeks of sleep logs were obtained: at baseline, at the end of the 4th month, and at the end of the 6th month. With the exception of one patient who failed to respond to treatment, further follow-up after 7 months was performed by their neurologists with only intermittent referral back to the sleep clinic.

Melatonin prescription

Initial and follow-up treatment: In the 2 initial patients seen early in our treatment investigation, melatonin was started at a dosage of 3 mg given near bedtime. After 4 weeks of drug administration, bed partners reported no clear change in behavior confirmed by sleep logs. A follow-up PSG indicated the continued presence of an abnormal amount of leg movements, muscle twitches, and EMG bursts. The impression was that melatonin at the dosage used gave no significant clinical response. These 2 patients were then placed on clonazepam 0.5 mg at bedtime and this was increased to 1 mg after 1 month. At the 2-month follow-up, bed partners reported much quieter sleep and the absence of abnormal behavior. As behavioral symptoms were again noted at 4 months after treatment onset, these 2 patients received melatonin at a dose of 6 mg in addition to the clonazepam, and are included in the 6 months of investigation (n=28). Thereafter, oral melatonin was always prescribed at a dose of 6 mg in all patients as the initial treatment dose (n=26). The drug was administered orally, about 30 minutes before usual bedtime.

After 4 months of treatment and the results of 4 weeks of sleep logs and one PSG, clonazepam 0.5 to 1 mg was added to the melatonin 6 mg prescription to all (n=28) subjects and the treatment was maintained until the end of the clinical protocol (i.e., at the beginning of the 7th month).

Past 7th month follow-up: After the end of the clinical protocol, as mentioned, one patient who had failed to respond to the medications continued with the same follow-up regimen consisting of 4 weeks of sleep logs and a PSG. Concomitantly, the dose of melatonin was increased at 9 months and at 12 months to 12 mg and the dose of clonazepam was increased to 3 mg.

Statistical Analysis

Statistical computations were performed using the SPSS 19.0. P values were one-sided with a significance level of 0.05. Data on demographic and disease characteristics were analyzed by descriptive statistics. For descriptive purposes, mean and standard deviation were used to address changes in dream-acting-out, percent of WASO, and percent of EMG during REM phase for three times: at Base Line (BL), at the end of the 4th month, and at the end of the 6th month. The Generalized Estimating Equation (GEE) was used to identify the changes in dream-acting-out, percent of WASO, and percent of
EMG after receiving melatonin treatment. The GEE, an extension of the generalized linear model, was developed by Zeger and Liang and is commonly used to analyze longitudinal data [12,13]. The unequal number of follow-up assessments among study subjects (26 and 2) was taken into consideration in the GEE analysis because the GEE model used the information obtained from each assessment as the analytical unit.

Results

Patients

The 28 patients presented in this retrospective report are listed in table 1. All patients were collected during the 5 years when the clinical protocol was applied. The suspicion of OSA was the cause of referral to the sleep clinic in 14 of the 16 patients diagnosed with OSA. Abnormal behavior during sleep was mentioned in only two of the referral letters for the patients. Patients were also referred for insomnia associated with neurological diseases, but all had family member reports of abnormal behavior during sleep. These were associated with dream enactment, patient unawareness, and some had injury with bruises and trauma to themselves and/or bed partners. The mean age of the group was 66.46 ± 9.1 years and the mean Body-Mass-Index (BMI) was 26.6 ± 2.3 kg/m². Twenty-eight percent were women.

Co-morbidities

Initial PSG showed that 16 patients (57%) presented with Obstructive Sleep Apnea (OSA) with a mean baseline Apnea-Hypopnea Index (AHI) of 29.5 ± 8 events/hour and a mean lowest oxygen saturation of 86 ± 3%. As severe OSAS may be associated with pseudo-RBD, all patients with OSAS were first treated with nasal Continuous Positive Airway Pressure (CPAP) with demonstration of complete resolution of this sleep-disordered breathing. With CPAP treatment, the minimum oxygen saturation was 93.3 ± 2.4%, but there was still a persistence of abnormal elevations of EMG tone during REM sleep and abnormal behavior related to dreaming. Ten patients had clinical signs of Parkinson’s disease with 4 of them receiving dopamine agonists for their syndrome (pramipexole 2 to 4 mg/day) and 4 other patients exhibiting cognitive decline. Six of these patients were reported to have poor nocturnal sleep labeled as “insomnia”. When performing investigations for RBD, the drugs prescribed for treatment of the associated neurological disorders were kept unchanged at the prescribed dosages. The dopamine agonist was at similar dosage from entry until the end of the 7th month.

Baseline

At entry, all bed partners reported the presence of vocalization and abnormal behavior during sleep. When awakened, these behaviors were associated with dream mentation, usually of a violent nature. The history of abnormal behavior during sleep had been present for a mean of 2.5 ± 3.2 years when patients were seen. All patients had experienced arm and leg movements during sleep, leading to mild trauma to bed partners in 23 out of 28 cases and bruises in all patients.

Sleep log investigation

Tables 1 and 2 show the results of the number of nights that abnormal behavior was observed during sleep during the 4 initial weeks of sleep logs. Abnormal behavior was often associated with some type of vocalization, but of variable intensity and duration, and there were some nights with movement but no vocalization. All patients with OSAS had nasal CPAP during sleep during this baseline data collection.

PSG investigation

The first PSG at the end of the 4 weeks of sleep logs showed an abnormal presence of chin and limb EMG tone during REM sleep with a variable presence of leg movements, small arm movements, and vocalization (Figures 1 and 2). Using the criteria outlined for the scoring of high EMG during REM sleep, all patients spent more than 20% of the total REM sleep time with elevated EMG, with the inclusion of the EMG bursts tabulated from all recorded muscles. However, only 14 subjects spent 50% or more of the total REM sleep time with elevated EMG. These 14 subjects included all patients with associated neurological disorders.

During this baseline nocturnal PSG, vocalization with or without abnormal behavior was observed in only 10 of the 28 patients.

### Table 1: Number of Nights with Abnormal Behavior at home.

<table>
<thead>
<tr>
<th>Case #</th>
<th>Baseline No Drug</th>
<th>Melatonin 6mg at 4 months</th>
<th>Clonazepam 0.5-1mg &amp; Melatonin 6mg at 7 months</th>
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<tr>
<td>1</td>
<td>5</td>
<td>1</td>
<td>0</td>
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<tr>
<td>28</td>
<td>10</td>
<td>1</td>
<td>0</td>
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</table>

Abbreviations: RBD= Rapid Eye Movement Sleep Behavior Disorder. SD= standard deviation.

### Table 2: Summary of distributions of frequencies of dream-acting-out, and nights of vocalizations after the treatment of melatonin (6 mg) or/and clonazepam (.5 to 1 mg) in RBD subjects.
Treatment and clinical response

All patients were treated with medication. The first 2 patients received melatonin 2 and 3 mg given near bedtime. After 8 weeks of drug administration, bed partners reported no change in the frequency of abnormal behavior and a follow-up PSG indicated the persistence of an abnormal amount of leg movements, muscle twitches, and EMG bursts. The percentages of total REM sleep time spent with elevated EMG were, respectively, 28 and 33%. With treatment, this improved to 26 and 25.4%. These patients were then treated with clonazepam 1 mg given at bedtime.

The next 26 patients received melatonin at a dose of 6 mg taken before bedtime. Table 2 shows the results obtained from the bed partner logs. Compared to baseline, there was a clear and significant improvement in all patients with treatment even though complete control of the abnormal behavior was not present in all cases. There was a significant decrease in the number of nights with reported clinical manifestations (Table 2). As can be seen in table 1, patients with a greater frequency of abnormal behavior at baseline were those, in general, who did not reach complete behavioral control during sleep with melatonin 6 mg.

Despite decreased abnormal behavior and vocalization, bed partners reported an impression that there were frequent short awakenings with the use of melatonin 6 mg. Therefore, “Wake After Sleep Onset” (WASO) was tabulated. Overall, there was a significant decrease in WASO compared to baseline. The percent of WASO during total sleep time decreased from 11.37 (SD=3.25) at baseline to 8.11 (2.48) (p=0.001Chi-square statistics) at the 4th month, but the standard deviation indicates that some subjects did not respond as well.

As clonazepam is considered to have hypnotic effects, clonazepam was also paired with melatonin in all patients. The addition of clonazepam further decreased the WASO compared to melatonin 6 mg taken in isolation, and at the end of the 6th month there was a significant reduction in the percent of time spent awake after sleep onset to 5.53 (SD=2.38) (Table 3 and Figure 3).

Evolution of the presence of high EMG during REM sleep

Repetitive PSG studies overtime indicated variable amounts of change in the percentage of elevated EMG tone during REM sleep (Table 4 and Figure 4). Compared to baseline, at the 4th month recording there were clear changes in the EMG pattern during REM sleep (Figures 5 and 6). However, as shown in figure 4, despite the fact that good control of abnormal behavior is reported by bed partners and demonstrated with sleep logs, there is actually a small, non-significant increase in the amount of time spent with high EMG at the 6-7th month recording compared to the previous recording. This is noted despite the administration of clonazepam and melatonin. There are no systematic follow-up PSG recordings after the end of the 6th month to demonstrate if this trend evolves. Only subjective reports were obtained at irregular intervals after the end of the systematic clinical protocol.
Failure

One subject diagnosed with "idiopathic RBD" and with no evidence of any other neurological disorder was never controlled by melatonin during the systematic clinical protocol. After an initial and short-lived decrease in the frequency of the events, the bed partner log indicates the recurrence of events despite subsequent dose increase. This subject was followed beyond the clinical protocol with additional month-long sleep logs and PSGs at the 9th and 12 months with increased medication doses, reaching 12 mg of melatonin and 3 mg of clonazepam near bedtime at the 12th month of evaluation. Despite these increased doses, the patient was never controlled. He slept on the floor in a sleeping bag and used arm and abdominal restraints to avoid injury from the persistent abnormal behavior.

Discussion

Our report is based on a clinical investigation and it is a retrospective study, with all the attendant limitations of this type of study. When we created our clinical protocol, there was no clear indication on the most appropriate treatment for RBD available, and both clonazepam and melatonin were used clinically as treatments. Long-term responses to treatment were not well described. Even today, when more information is available, systematic recordings are not necessarily repeated and many studies are based on sleep logs and bed partner reports. McCarter et al. [14] surveyed 45 patients seen at the Mayo clinic between 2008 and 2010 treated either with melatonin 6 mg or clonazepam 0.5 mg, and only 2 subjects received both treatments simultaneously. These authors found significant improvement in the RBD Visual Analogue Scale (VAS) with each treatment, but indicated that the patients receiving melatonin 6 mg had significantly reduced injuries and less frequent adverse effects. As this study is based on VAS, the issues of WASO and the impact on EMG augmentation in REM sleep cannot be addressed. Ferri et al. [15] also addressed the use of clonazepam in RBD, but these authors focused on the effects of the pharmaceutical agent on NREM sleep. They looked at the sleep recordings of drug-free idiopathic RBD patients and the changes observed following the administration of clonazepam on the REM sleep behavior disorder severity scale (RBDSS) [16] and on the NREM

Table 3: Percent of wake after sleep onset-WASO- during total sleep time at different time-points.

<table>
<thead>
<tr>
<th></th>
<th>BL (n=28)</th>
<th>4th month (n=26)</th>
<th>6th month (n=28)</th>
</tr>
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<tbody>
<tr>
<td>WASO (%)</td>
<td>Mean</td>
<td>(SD)</td>
<td>Mean</td>
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<tr>
<td></td>
<td>11.37</td>
<td>(3.25)</td>
<td>8.11</td>
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<td>5.53</td>
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BL; baseline (no treatment but with nasal CPAP if with OSA), 4th month: melatonin 6 mg, 6th month melatonin 6 mg and clonazepam 5 to 1 mg SD; standard deviation.
Legend: ** indicates p value <0.001. Abbreviations: WASO= wake after sleep onset. BL= baseline. 4M= 4th month. 6M= 6th month.

**Figure 3:** Comparison of percent of wake-after-sleep-onset-WASO- in RBD patients over time.

<table>
<thead>
<tr>
<th></th>
<th>BL (n=28)</th>
<th>4th month (n=26)</th>
<th>6th month (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High EMG during REM (%)</td>
<td>46.98 (16.66)</td>
<td>1.37 (2.47)</td>
<td>2.55 (9.34)</td>
</tr>
</tbody>
</table>

At 4 months there were only 26 subjects taking melatonin 5 mg, but at end of 6th months the 28 subjects received both melatonin 6 mg and clonazepam (see text)

**Table 4:** Percentage of time spent with high EMG during total REM sleep time in different conditions (n=28).

**Figure 4:** Percentage of time spent with high EMG during total REM sleep time in different conditions. The calculation of "high EMG activity" took into consideration all monitored muscles and the percentage of time with high EMG activity spent during the total scored REM sleep period was calculated. The different REM sleep periods were then collapsed in a total REM sleep time, and a percentage of "high EMG activity" during total calculated REM sleep time was derived. There was a non-significant change between 4th and 6th months with increase in REM EMG at 6th month.
sleep recordings. These authors found that WASO was significantly decreased with clonazepam with an increase in stage 2 NREM sleep. The change in WASO is consistent with our finding that clonazepam decreased WASO further than melatonin alone. Our study included patients with neurological disorders, including those with Parkinson’s disease, who usually have more disturbed sleep than what is usually noted in idiopathic RBD patients.

Scales have been validated since we established our clinical protocol and several could now be used. As recently reviewed by Lam et al. [17], the most attractive option to perform future follow-up studies on the treatment and evolution of RBD may be the RBD Questionnaire Hong Kong (RBDQ-HK) [18]. The most effective way to score the REM sleep EMG bursts has also been reviewed and improved in the recent past. Frauscher et al. [19] highlighted that until recently there was no consensus on how muscle activity during REM sleep should be scored. In 2012, the “Sleep Innsbruck-Barcelona Group” [19] proposed a way to monitor EMG activity during REM sleep and Frauscher et al. [20] also reviewed the different means of monitoring and scoring abnormal EMG activity (including computer-assisted methods). Our method of scoring was in line with what was suggested by Frauscher et al. in 2012 [19], but admittedly these methods were not exactly the same.

In our group of subjects, the diagnosis of REM behavior disorder was well established by patient history, 4 weeks of sleep logs, and repetitive PSG with video recordings. We found with our approach that at baseline there was a minimum of 20% of abnormal EMG activity during REM sleep. Moreover, melatonin at a dose of 6 mg always significantly decreased this percentage. This did not necessarily lead to a complete control of the abnormal behavior, however. In the future, one of the challenges related to follow-up of REM behavior disorder will be to establish the cut-off points based on PSGs that indicate the elimination of the risk of abnormal behavior during sleep.

Many of our patients had co-morbidities. The association of RBD with Parkinson’s disease and with the presence of other neurodegenerative diseases is well investigated. It is also known that OSA may be associated with RBD. The need to clearly control OSA before affirming the presence of RBD has been previously emphasized, and all our cases were first appropriately treated with nasal CPAP with demonstrated compliance. A fair number of subjects presented with both syndromes. The relationship between RBD and OSA has not been explored much. More than 50% of our patients had OSA and this was much more recognized than RBD in the letters of referral for sleep investigation. Except for the abnormal behavior during sleep, none of the OSA patients had any neurological symptoms and the RBD would commonly be called “idiopathic” in these subjects. They all demonstrated narrow naso-maxillary-mandibular complexes and secondary narrow upper airways, consistent with OSA. As mentioned, very little is known of the role of OSA in RBD. It is clear that both syndromes are seen in an aging population, and systematic questioning on dream-enactment behavior in OSA patients is justified. Such questioning is particularly important in patients investigated only for sleep-disordered breathing with the use of type III portable equipment.
that will miss the presence of the associated patterns of elevated EMG during REM sleep.

Finally further investigation is needed to understand the underlying problems in patients that are non-responders to the usual treatments considered for RBD.

Acknowledgement

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