Exogenous Melatonin in Periodic Limb Movement Disorder: An Open Clinical Trial and a Hypothesis

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Study Objectives: The etiology of Periodic Limb Movement Disorder (PLMD) as well as the precise role of melatonin in human physiology remains poorly understood. Inspired by a single case observation we performed the presented study in order to obtain first evidence for the hypothesis that exogenous melatonin would decrease PLM’s and thereby improves symptoms of PLMD patients.

Design: N/A

Setting: N/A

Patients/Participants: Nine patients with first time diagnosis of PLMD without RLS were treated over a six-week period with 3 mg melatonin, taken between 10 and 11 p.m.

Interventions: N/A

Results: Melatonin improved well-being in 7 of the 9 patients. Polysomnography, performed prior and at the end of melatonin treatment, demonstrated a significant reduction of investigated movement parameters, such as PLMs, PLM index, PLMs with arousals and PLM-arousal index. Actigraphy, measured over 14 nights prior and during the last 14 days of melatonin treatment, showed a significant reduction in movement rate and minutes with movements during Time in Bed.

Conclusions: The temporal distribution of PLMs, as well as the coupling of PLMs with the phase position of circadian temperature curve, suggest an involvement of the circadian timing system in the pathophysiology of PLMD. Locomotor activity in animals clearly exhibits a circadian pattern and can be strongly influenced by exogenous melatonin. Results suggest a chronobiotic effect of exogenous melatonin in PLMD. More specifically, we hypothesize that the mode of action of melatonin in the presented PLMD patients might have been an increase of output-amplitude of the circadian timing system, thereby enhancing the circadian rhythmicity of locomotor activity with a reduction of sleep motor activity.

Key words: Circadian rhythms; locomotor activity; melatonin; PLMD; sleep

INTRODUCTION

SOME 35 YEARS AFTER THE FIRST COMPLETE DESCRIPTION OF PERIODIC LIMB MOVEMENT DISORDER (PLMD) BY LUGARESI,1 many drugs proved to be effective in improving symptoms,2,3,4 but the etiology of the disorder is still virtually unknown. PLMD may occur as a distinct disorder, in association with various drug treatments or other sleep disorders such as apnea5 or narcolepsy,6 and, very frequently, with restless legs syndrome (RLS).7 Together, PLMD and RLS represent the fourth most common cause of insomnia with frequent complaints of daytime disturbances.7

We previously reported a patient suffering from the symptoms of REM sleep behavior disorder (RBD), who responded to melatonin treatment with a clinical improvement, a reduction of motor activity during sleep, an increase of the percentage of REM sleep and a better preservation of REM sleep associated muscle atonia.8 As to the mode of action of melatonin in this patient we considered a specific effect on RBD, an effect on REM sleep regulation or the direct reduction of sleep motor activity. Thus, in order to create hypotheses, we treated in open-labeled trials: 1) patients with RBD;9 2) patients with a quantitative REM sleep deficit (yet unreported); and 3) patients suffering from symptoms of PLMD about whom we report here.

We chose PLMD, because it represents a well-operationalized motor disorder of sleep. PLMD is characterized by periodic episodes of repetitive and highly stereotyped limb movements which occur during sleep. The frequency of PLMs differs between individuals, but is intrindividually remarkably stable.10,11

The purpose of the presented pilot study was to obtain first evidence for the hypothesis that exogenous melatonin can reduce the number of PLM’s and thereby improves symptoms of PLMD.

METHODS

Patients, Treatment

Nine patients with first time diagnosis of PLMD without RLS (3 female, 6 male; mean age 57 years, range 40 through 71 years) were treated with 3 mg melatonin (Melatonin Quick-Sorb® - Great Earth) over a six-week period. Patients were instructed to take melatonin within 30 minutes prior to bedtime in the time interval of 10 to 11 p.m. Patients with RLS were excluded for two
reasons. Firstly, even though occurrence of PLMD and RLS seem to be closely linked, both of their pathologies are not yet known. Thus, a bias could have been introduced. Secondly, discomfort in RLS induces movements, which could never be differentiated in actigraphy from PLMs.

PLMD was diagnosed using the ICSD criteria (780.52-4). All nine diagnoses were considered as being chronic (duration six months or longer), four patients met the criteria for severe PLMD (PLM index > 50), three for moderate (PLM index 26 thru 50), and two for mild (PLM index 5 thru 25) PLMD. Five patients suffered from concomitant diseases, such as major depression (two patients, both recovered), idiopathic REM sleep behavior disorder (one patient), Parkinson’s disease (one patient) and sympathetic dysautonomia (one patient). Except for these disorders, neurologic and psychiatric examinations did not show any other neurologic and/or psychiatric disease. Whereas five patients were completely free of medication, comediations were: levodopa for Parkinson’s disease (one patient), nifedipine for hypertension (one patient), fludrocortisone for dysautonomia (one patient) and a combination of lithium and thyroxine for major depression (one patient). Prescriptive medication remained unchanged during all study procedures. Patients did not take any other medication that might interfere with melatonin production and/or secretion (e.g., benzodiazepines, antidepressants, beta-blockers, anti-inflammatory drugs etc.). Special care was taken with respect to sleep hygiene, which was controlled by continuous actigraphy and by keeping a sleep log. The 24-hour excretion of 6-sulfatoxymelatonin (aMT6s) in urine was measured under controlled conditions while patients were stationed on the ward for diagnostic polysomnography at baseline. All samples were analyzed in duplicate using a highly sensitive, competitive ELISA kit by IBL, Hamburg.

**Polysomnography**

Two nights of polysomnographic (PSG) recordings were performed in all patients with an adaptation and recording night, both at baseline (prior to melatonin treatment) and during the last week of a six-week period of melatonin treatment.

PSG included a standard, 19-channel montage for scoring sleep stages: horizontal and vertical EOG, central and occipital EEG (C3-A2; C4-A1; C3-C4; Oz-A1; Oz-A2) four EMG leads (mental, submental, tibiales left and right), EKG, snore microphone, bed actometry, and nasal/oral flow as well as thoracic respiratory effort.

Sleep stages were visually scored according to the method of Rechtschaffen and Kales (R&K), using 30-second epochs. PSG parameters as presented in Table 1 were: SPT (Sleep Period Time), defined as the interval between the first and last epoch stage NREM 2 or REM; TST (Total Sleep Time), defined as the sum of all epochs NREM 1, 2, 3, 4, REM and MT; SOL (Sleep Onset Latency), defined as the interval between lights off and the first epoch stage NREM 2; SE (Sleep Efficiency), defined as the percentage of TST on SPT; WASO (Wake After Sleep Onset); SWS (Slow Wave Sleep) NREM 3 + 4; MT (Movement Time); PLM index – the number of PLM’s per hour TST; PLM-arousal index—the number of PLM’s with arousals per hour TST. Values given as percentages are expressed as the percentage of SPT. Data were analyzed using the exact version of Wilcoxon matched-pairs signed-ranks test.

In the evening prior to each adaptation night and in the morning after each polysomnographic recording patients were asked to fill in a 24-item, validated well-being scale. Morning-score and evening-score were averaged. Results of well-being prior to and at the end of the six-week melatonin treatment were analyzed using the exact version of Wilcoxon matched-pairs signed-ranks test.

**Actigraphy and Sleep Diary**

Motoric activity during sleep was evaluated using a wrist-worn, solid-state actigraph (ZAK, Germany), first, during two weeks prior to melatonin treatment (baseline), and second, during the last 14 days of melatonin treatment. Activity data were recorded in two-minute intervals, always using the same actcometer for the same patient. Patients completed a sleep diary, indicating bed- and waketime. For the evaluation of the actigraphic data, we defined time in bed (TIB) as the interval from indicated “lights-off” until “lights on,” minus the first and the last 30 minutes. The actigraphic data were represented as movement rate (defined as movements per minute TIB), and the number of minutes with movements (expressed as percentage of TIB). Data of 14-day means were analyzed using the exact version of Wilcoxon matched-pairs signed-ranks Test.

**RESULTS**

Seven of the nine patients reported improvement of daytime symptoms within seven days after the beginning of melatonin treatment. Whereas two patients did not notice any change during the time of treatment, the seven responders reported a loss of prior fatigue (three patients) or excessive sleepiness (four patients). The two nonresponding patients were noncompliant with respect to the time of melatonin administration, changing several hours from day to day. Improvement was substantiated by a significant reduction (p<.046) of formerly impaired well-being at the end of treatment (given as the median and the inter-quartile-range (IQR): REM sleep percentage, which decreased as compared to agenorm, significantly tended towards normalization at the end of melatonin treatment (p=.039). Except for a tendency towards an increase in sleep efficiency (p=.059) due to a reduction of WASO (p=.055) and a tendency towards a decrease of epochs scored as MT per minute TST (p=.098), all other explorative tested PSG-parameters were not changed consistently. PLM index respectively PLM-arousal index at the end of treatment did not meet the criteria for severe
PLMD in any of the patients (prior treatment: four patients), for moderate PLMD in five patients (prior treatment: three patients), and in three patients there were no PLMs detectable in polysomnography at the end of the six-week treatment period.

Actimetry over 14 consecutive days confirmed PSG findings. Whereas the indicated TIB was unchanged, there was a significant reduction in movement rate—movements per minute TIB (1.28 IQR: 1.43 vs. 1.12 IQR: 1.25; p < .023)—as well as in the percentage of minutes TIB with movements (34.3 IQR: 16.5 vs. 29.9 IQR: 15.2; p < .039).

**DISCUSSION**

The presented data shows that melatonin, administered to PLMD patients over a six-week period, significantly improved clinical symptoms of PLMD. The improvement was polysomnographically and actigraphically substantiated by a significant reduction of measured movement parameters, such as PLMs, PLMs with arousal, PLM index, PLM-arousal index, movement rate, and the proportion of minutes TIB with movements.

The mode of action of melatonin on human sleep is still not fully elucidated. By virtue of the longlasting effect in our patients, with respect to melatonin discontinuation, we rule out a direct effect on temperature or sleep consolidation. The amount of 24-hour excretion of aMT6s in urine yielded a high interindividual variability; thus, the effect is unlikely to be due to replacement.

PLMD is characterized by periodic episodes of repetitive and highly stereotyped limb movements during sleep. The fact that many physiologic parameters during sleep, such as heart rate, respiration rate, blood pressure and EEG patterns, exert similar periodicity, points towards an involvement of the brainstem in the generation of the temporal pattern of PLMs. Brainstem output parameters are under strong circadian control. The time dependency of RLS symptoms, the temporal distribution of PLMs and the coupling of PLMs with the phase position of circadian temperature curve during nocturnal sleep suggest an involvement of the circadian timing system in the pathophysiology in RLS, although the phase position does not seem to be altered. Even though these results have been reported only in RLS, the similarity of PLMs in RLS, in PLMD and other disorders suggests a common pathomechanism. Of course, since we excluded patients with RLS from our study, results need to be confirmed in RLS as well. Locomotor activity in diurnal animals, such as sparrows or pigeons, and also nocturnal animals, such as rats, clearly exhibits a circadian pattern and can be strongly influenced by exogenous melatonin. There are similar results in humans and nonhuman primates for the influence of melatonin on locomotor activity during sleep. Many hints point to the assumption that melatonin exerts a chronobiotic action via the suprachiasmatic nucleus (SCN). The SCN transmits signals to the rest of the brain, organizing circadian rhythms throughout the body. A lesioning of the SCN abol-

<table>
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<th>(IQR)</th>
<th>post Median</th>
<th>(IQR)</th>
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<td>29.88</td>
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SPT1: Sleep Period Time; TST2: Total Sleep Time; SOL3: Sleep-Onset Latency; SE4: Sleep Efficiency; WASO5: Wake-After-Sleep-Onset; NREM6: Non-REM sleep; SWS7: Slow Wave Sleep; REM-∆-agennorm8: difference with respect to agennorm48; MT9: Movement Time; TIB10: Time In Bed; Movement rate11: amount of movements per minute TIB; p 13: data analysed by exact version of Wilcoxon matched-pairs sign-ranks Test (two-tailed)
ishes all circadian driven rhythms.35,36 Inversely, to animals whose own SCN have been ablated, transplants of the SCN restore circadian activity rhythms by means of a diffusible signal.37,38 The highest density of high affinity melatonin receptors has been shown to be located in the SCN.39 Within the SCN, melatonin reduces neuronal activity in a time-dependent manner.40,41 Entrainment of free-running circadian rhythms by melatonin depends on an intact SCN.42

Melatonin has been referred to as a chronobiotic,43 in particular by its well-known SCN mediated effect of shifting circadian rhythms.44 But, as expected by the phase-response curve of melatonin, there was no sign of a phase shift induced by melatonin treatment in the presented patients at the end of melatonin treatment. Besides its property of being able to shift circadian phase, a chronobiotic is defined as a substance capable of reentraining short-term dissociated or long-term desynchronized circadian rhythms.45 Melatonin, as a chronobiotic, has been suggested to increase the integrity of the individual’s circadian timing system, leading to resynchronization45 and thereby increasing overall output-amplitude.46 In animal studies, the amplitude of circadian driven parameters, such as temperature and locomotor activity, was increased during melatonin application in elderly rats,29 and of locomotor activity by bright light—the “counter-zeitgeber” to melatonin—in the Syrian hamster.47 We suggest that the resynchronization of circadian rhythms with an increase of output amplitude of the CTS might be the mode of action by which melatonin ameliorated symptoms in our PLMD patients.

In humans, only two preliminary studies deal with the influence of melatonin on output-amplitude of the circadian timing system.9,33 In the first study, melatonin enhanced the rest-activity rhythm in ten elderly individuals with self-reported sleep-wake disturbances.33 In the second study, exogenous melatonin led to a significant tendency towards normalization of REM sleep quantity and—quality in patients with REM sleep behavior disorder.9 It was hypothesized that a resynchronization of the circadian timing system by exogenous melatonin, including an enhancement of the circadian modulation of REM sleep, was responsible for this effect. We suggest the same mechanism for the effect of exogenous melatonin on locomotor activity in the currently presented PLMD patients. The similarity of results between the presented PLMD study and this earlier RBD study is corroborated by the facts that REM sleep percentage was significantly increased in the presented PLMD patients as well, and that the two nonresponders were the only patients who exercised bad sleep hygiene with changes in bedtimes and in the time of melatonin administration of several hours from day to day.

Since this was an open-labeled study, results need to be considered as preliminary. A confirmatory study will have to include the measurements of various circadian driven parameters. Nevertheless, because of low toxicity of melatonin, we suggest that melatonin might exert beneficial effects in PLMD patients. As to the pathophysiology of PLMD, we suggest that the mode of action of melatonin in the presented patients might have been an increase of output-amplitude of the circadian timing system, thereby enhancing the circadian rhythmicity of locomotor activity with a reduction of sleep motor activity.

REFERENCES

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