Case Report

Refractory Insomnia in an Adolescent with Total Blindness

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We present a totally blind adolescent with refractory insomnia due to a combination of Non-24 hour sleep-wake disorder and restless leg syndrome that was successfully treated with tasimelteon, iron replacement, and gabapentin. To our knowledge, this is the first published report of treatment of N24 with tasimelteon in an adolescent. In addition, this case highlights the importance of recognizing and treating multifactorial causes of insomnia.

INTRODUCTION

Humans follow a roughly 24-hour rhythm of sleep and wake. This rhythm is generated by a master pacemaker located in the suprachiasmatic nucleus of the hypothalamus. This internal clock maintains an intrinsic circadian rhythm of approximately, but not exactly, 24 hours. To ensure this internal circadian rhythm matches the 24-hour day, the internal circadian rhythm is entrained to 24 hours by external factors. These external factors are referred to as zeitgeibers (German for “time givers”). A variety of factors can serve as zeitgeibers such as social schedule or temperature. The most important zeitgeber is light. Photo-sensitive retinal ganglion cells provide direct input and regulation of the suprachiasmatic nucleus. Non-24 hour sleep-wake disorder (N24) is a rare circadian rhythm disorder in which circadian entrainment to the 24-hour day is lost [1]. This results in a progressive desynchrony between internal circadian rhythm and external clock time. Over time the circadian rhythm of sleep and wake drifts in and out of phase with the external environment. This results in nighttime awakenings and daytime sleepiness when the rhythm is out of phase and normal sleep when the rhythm is in phase, thus creating a pattern of cyclical insomnia. The most common cause of N24 is total blindness, as loss of visual input prevents entrainment to light [2].

Melatonin is capable of regulating the pacemaker by shifting the circadian rhythm to proper alignment with the rhythm of day and night. Melatonin receptor agonists have been used to re-entrain the pacemaker [2]. Tasimelteon, a dual MT1 and MT2 receptor agonist, is the only Food and Drug Administration approved treatment for N24 and has been shown to be effective in phase III clin-
The patient was diagnosed at one year of age with bilateral retinoblastoma, which was treated with bilateral enucleation. At age 13, patient underwent polysomnography, which showed wake time after sleep onset of 83 minutes and a sleep efficiency of 76 percent. Periodic limb movement index was elevated at 12/hour (normal is <5 in children). The periodic limb movement with associated arousal index was 8/hour and there was an association with nocturnal awakenings. Respiratory parameters were normal, with no evidence of central or obstructive sleep apnea.

Based on the history of cyclical insomnia and total blindness, the patient was evaluated for N24 using actigraphy. Example actigraphic data is presented in Figure 1. Over the 14-day recording period, the patient exhibited a pattern of progressively delayed bed time followed by a compensatory night of going to bed early, which is consistent with N24. This was initially managed with 5 mg continuous release melatonin nightly to treat her sleep maintenance insomnia based on previous studies in adolescents [4,5] as well as the reported previous lack of efficacy of immediate release melatonin. Given the patient’s elevated periodic limb movement index as well as reported restless leg syndrome symptoms, serum ferritin was checked and reported to be 19 ng/ml. She was started on 325 mg ferrous sulfate daily and continued on gabapentin.

At follow-up four months later, the patient reported improvement of her restless leg syndrome symptoms after iron replacement. However, for the past several weeks, she was taking 2 to 3 hours to fall asleep nightly, as well as falling asleep during the daytime. This was thought to be secondary to her N24 given she no longer reported symptoms of restless leg syndrome. Given her persistent symptoms on continuous release melatonin, and her previous lack of response to immediate release melatonin, tasimelteon 20 mg nightly was started for her N24.

Three months after starting tasimelteon, family reported that she was sleeping well and had no concerns at that time. She was able to reduce her gabapentin dose to 100 mg nightly. At her next follow-up two months later, patient reported tasimelteon made her sleepy in the evening without needing other medications or supplements. She was taking tasimelteon at 11 pm with sleep initiation waning and wane across months, such that there are periods of no disturbance alternating with periods of progressively worse sleep. The patient had tried melatonin (including immediate as well as sustained release formulations), eszopiclone, zolpidem, sublingual vitamin B12, clonidine, trazodone, valerian root, and gabapentin, all of which were either temporarily effective or completely ineffective. Her medications at the initial evaluation included naproxen, topiramate and magnesium for migraines, in addition to 5 mg immediate release melatonin and gabapentin 100 to 300 mg for insomnia. The patient’s social history was remarkable for attending high school full time and maintaining a consistent routine including a consistent bedtime of 10 PM and waketime of 6AM on weekdays and weekends. She was not employed outside of school.

She reported a history of multiple years of having an urge to move her legs that is worse at night, better with movement, and keeps her awake several nights out of the week. She was taking 100 to 300 mg gabapentin nightly for restless leg syndrome, which she reports has helped intermittently, but still complains of urge to move her legs some nights that awakens her at night after initially having fallen asleep. She was unable to tolerate gabapentin doses higher than 300 mg secondary to residual daytime sleepiness the following morning. She also tried magnesium for her restless leg syndrome, but it did not help. She did report a history of heavy menses which started at age 12 but denied a previous diagnosis of anemia.

The patient’s elevated periodic limb movement index was associated with nocturnal awakenings. Respiratory parameters were normal, with no evidence of central or obstructive sleep apnea.

We present an adolescent with multifactorial insomnia due to N24 and restless leg syndrome with symptom improvement after treatment for both underlying disorders. To our knowledge, this is the first published report of treatment of N24 with tasimelteon in an adolescent. In addition, this case highlights the importance of recognizing and treating multifactorial causes of insomnia. This is
particularly important in children, as insomnia in children is frequently multifactorial [6].

Tasimelteon is currently approved to treat N24 in adults. Using markers of melatonin production, two phase III clinical trials demonstrated that after 1 month of treatment, 20 percent of N24 patients receiving tasimelteon were entrained, while 3 percent of the patients receiving placebo were entrained. Moreover, continued administration of tasimelteon maintained entrainment in 90 percent of patients, compared to only 20 percent in the placebo group [3]. However, there are no current data to support the use of tasimelteon in children. This is problematic because the highest prevalence of N24 is in non-sighted teenagers and young adults, who often have rigid school or work schedules and who are the most vulnerable to the negative impact of disrupted sleep [1]. Effective treatment of N24 in children and adolescents is critical to prevent impaired daytime functioning, social distress, and psychiatric disorders [1].

It should be noted that tasimelteon is costly, with a retail price of over $100,000 per year, although this is subsidized by the manufacturer and the actual cost to patients may be much less than this. Prior studies have shown that immediate release melatonin at doses of 0.5 to 5 mg can be effective in phase-entraining the circadian rhythm in totally blind individuals, although it may take months to successfully entrain the patient as the effects of melatonin vary depending on administration time relative to an individual’s circadian rhythm [7,8]. Doses of 10 mg or higher may be ineffective [7], possibly due to a “washout” effect of the relatively high dose of melatonin preventing establishment of a normal increasing and decreasing level of endogenous melatonin. Given this, a trial of melatonin should be considered prior to use of tasimelteon. Unfortunately, no studies have performed a direct comparison of tasimelteon to melatonin to determine if tasimelteon is more effective than melatonin. In our case, the patient had used various doses of both immediate and continuous release melatonin without persistent improvement of her symptoms, therefore the family was very interested in use of tasimelteon.

This case also highlights the frequent multi-factorial nature of insomnia in children [6]. In this case, treatment of both her N24 as well as her restless leg syndrome was necessary to resolve the patient’s insomnia. Over the course of her treatment, adequate control of restless leg syndrome without control of N24 was associated with continued insomnia. Similarly, adequate control of her N24 with recurrence of her restless leg syndrome was associated with persistent insomnia. In this case, the
patient’s restless leg syndrome was associated with iron deficiency, a well-described association [9]. Given this association, for children with a serum ferritin <50, oral iron therapy (along with vitamin C to improve absorption) is the recommended first line therapy for restless leg syndrome [10]. In cases where additional pharmacotherapy for restless leg syndrome is indicated, gabapentin is typically used as a first line agent in children due to the potential risk of increased impulsive behaviors with dopamine agonists such as pramipexole or ropinirole [11,12]. The patient only had resolution of her insomnia when her N24 was treated with tasimelteon and her restless leg syndrome was treated with iron replacement and gabapentin.

CONCLUSION

This case of N24 in an adolescent demonstrates that tasimelteon was effective in a non-sighted adolescent, and additionally highlights the importance of recognizing and treating multiple underlying disorders in adolescents with insomnia.

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