

CASE REPORTS

A Case of Non-24-Hour Sleep-Wake Rhythm Disorder Treated With a Low Dose of Ramelteon and Behavioral Education

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Non-24-hour sleep-wake rhythm disorder (N24SWD) occurs when the intrinsic circadian pacemaker does not entrain (synchronize) to the 24-hour light/dark cycle. There is currently no established treatment for sighted patients with N24SWD. To the best of our knowledge, there have been very few reports on the efficacy of ramelteon administered to sighted patients with N24SWD. We report the case of a sighted patient with N24SWD whose free-running sleep-wake pattern recorded by actigraphy was stopped after the administration of a low dose of ramelteon combined with behavioral education.

Keywords: non-24-hour sleep-wake rhythm disorder, circadian rhythm sleep-wake disorders, ramelteon, behavioral education

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INTRODUCTION

Non-24-hour sleep-wake rhythm disorder (N24SWD) is one of circadian rhythm sleep-wake disorders that occurs when the intrinsic circadian pacemaker is not entrained (synchronized) to the 24-hour light/dark cycle.¹ The condition primarily occurs in blind individuals but can also occur in sighted individuals. Although several treatments (eg, blight light therapy, melatonin administration), have been reported to have succeeded in treating sighted patients with N24SWD, their efficacy has not yet been established.^{2,3}

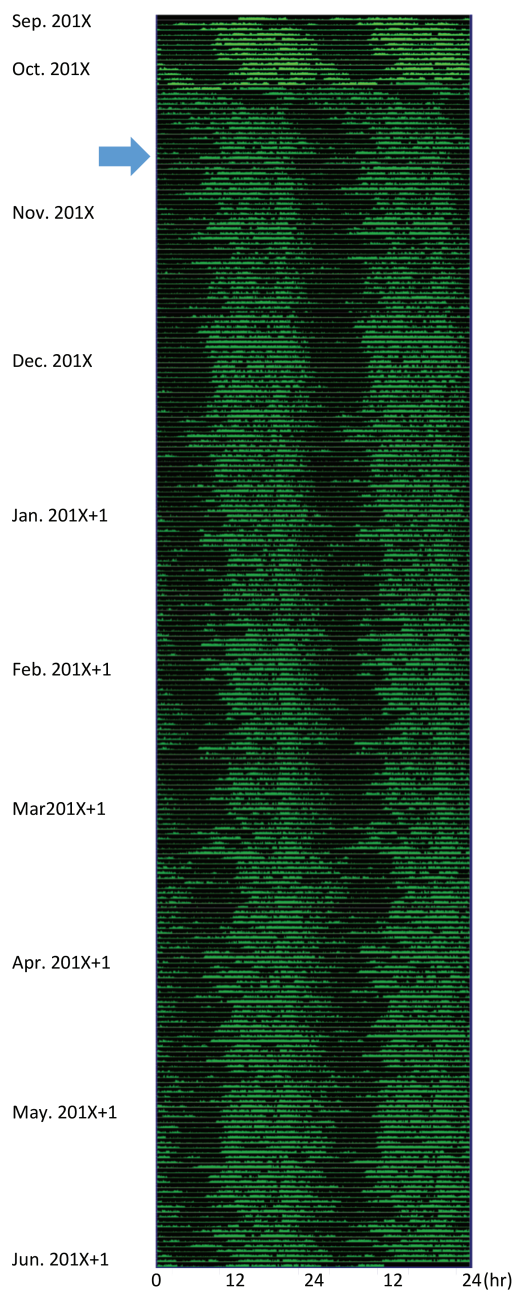
Here we report a case of a sighted N24SWD whose free-running sleep-wake pattern recorded by actigraphy was stopped after the administration of a low dose of ramelteon combined with behavioral education.

REPORT OF CASE

A 34-year-old female attended our clinic seeking treatment for a delayed sleep phase that progressed each day. There was no past history of physical disease or sight impairment, including color blindness. The patient lived with her parents. Since childhood, she tended to have difficulty awakening in the morning and was sometimes late for school. She was trying to go to bed at approximately midnight on weekdays, but she stayed up late at night on weekends and over vacation. After graduating from high school, she began working a day shift at a company. The patient reported a sleep-wake schedule with sleep onset at 11:00 PM to midnight and offset at 6:30 AM on work days, and onset at 1:00 AM–2:00 AM and offset at 8:00 AM during holidays. She was able to sleep at the desired time and did not experience drowsiness or any physical or mental symptoms during the day. Five years ago, she left the company in pursue of a new

job, although she considered her previous work to be fulfilling. Following this change, her sleep-wake schedule was substantially delayed, and she reported to go to sleep in the morning (eg, at 7:00 AM–8:00 AM) and waking in the afternoon or evening. There were no clear depressive symptoms. She attempted to adjust her sleep-wake schedule to make it compatible with a day job. Three years ago, she visited a psychiatric clinic for the first time. The attending physician prescribed a hypnotic (whose name the patient could not remember) for sleep-onset insomnia, but the patient's symptoms did not improve. Despite trying eagerly to adjust her sleep-wake schedule by herself, her forcible awakening in the morning was getting harder and her sleep-wake schedule exhibited progressive delay. She got information of circadian rhythm sleep-wake disorders on the internet and she came to our clinic seeking treatment. She reported us that her sleep onset and offset times were progressively delayed by approximately 2–3 hours each day, which had been ongoing for at least 1 year before the first visit. Based on the documentation of the progressively delayed sleep-wake pattern for 4 weeks with a daily sleep log and actigraph (MicroMini RC; Ambulatory Monitoring, Inc., Ardsley, New York, United States; worn by the patient on her non-dominant hand, with a preset of zero crossing mode, 16 Hz sampling frequency, and 1-minute recording epoch), she was diagnosed with N24SWD (**Figure 1**). Before the start of ramelteon treatment, the patient's average sleep duration was 7 hours 57 minutes and the length of her free-running cycle was 25.53 hours (automatically analyzed with the Action4 or AW2 software using a Cole-Kripke algorithm; Ambulatory Monitoring, Inc.). Her physical examination, blood test (including thyroid function), electroencephalogram, and head MRI revealed normal findings. There were no other sleep or primary psychiatric disorders. At the timing when her sleep phase matched the night time zone (her sleep-onset time was 12:30 AM and the offset

Figure 1—Actigraphic record of the patients' sleep-wake pattern (double plot).



This record was obtained from the first visit to our department. Free-running stopped immediately upon the commencement of ramelteon administration (indicated by the arrow). Areas with green spikes represent patient's movement and activity and are judged as wake; areas without spikes represent inactivity and are judged as asleep.

time was 6:30 AM, as recorded by the actigraph), we instructed her to start taking 1 mg of ramelteon at 7:00 PM. While receiving treatment with ramelteon, the patient also received sleep hygiene education, including instructions to avoid naps during the day, to turn lights off before midnight, and to refrain from use of IT devices after lights out. The free-running sleep-wake pattern stopped immediately upon ramelteon administration. One month after treatment initiation, her sleep-onset time was

changed to around 10:00 PM to midnight and the offset time to around 7:00 AM–9:00 AM, as recorded by the actigraph. As the patient became able to develop a routine schedule in the daytime, she began to seek work. Her sleep-wake schedule tended to be delayed; however, there was no relapse of the free-running sleep-wake pattern. After 8 months of sustained free-running cessation, the follow-up ended because she moved away for her new job. Average time of sleep onset, sleep offset, and sleep duration throughout ramelteon administration were 12:52 AM, 8:39 AM, and 7 hours 49 minutes, respectively (automatically analyzed with the Action4 or AW2 software; Ambulatory Monitoring, Inc.).

DISCUSSION

In this case, cessation of the free-running sleep-wake pattern following the administration of a low dose of ramelteon combined with behavioral education was objectively shown by actigraphy. No other major therapies, such as bright light therapy or other pharmacotherapies were administered. It can be considered that the cessation of the free-running sleep-wake pattern was attributable to the intervention because at the time of ramelteon initiation, the patient did not experience any environmental changes in terms of living place or social adaptation. This resulted in significant improvements in her social functioning, although her sleep-wake schedule still tended to be delayed.

The therapeutic target for N24SWD is the underlying non-entrained circadian pacemaker. Previous researches have been presented in the form of case series/reports of improvement following several treatments among sighted patients with N24SWD. Relevant studies include 3 case reports on light therapy, 3 case series/reports on melatonin, 4 case series/reports on combination of light therapy and melatonin, 1 case report on valproic acid, and one case report on aripiprazole.³⁻⁵ Although these may be strong therapeutic candidates, insufficient evidence has been provided to support the use of these treatments in sighted individuals with N24SWD, and there is no established recommendation.^{2,3}

Melatonin agonists may play an important role in resetting the circadian clock of the suprachiasmatic nucleus of the hypothalamus by endogenous melatonin receptor activation. Tasimelteon, a melatonin receptor agonist, was recently approved in the United States to treat N24SWD in blind patients. Yanagihara et al. reported 2 cases of free-running type N24SWD in sighted patients whose symptoms responded to the combined treatment with 8 mg of ramelteon, administered at 8:00 PM, and triazolam or methylcobalamin.⁶ To the best of our knowledge, our case report is the first to observe the cessation of the free-running sleep-wake pattern, as well as the maintenance of this state with a dosage as low as 1 mg of ramelteon combined with behavioral education. These circadian phase-shifting effects obtained with a small amount of ramelteon, such as 1 mg, have been reported in healthy adults.^{7,8} This case suggested that a small amount of ramelteon might also be beneficial for patients with N24SWD. Further accumulation of case reports is necessary to clarify the effectiveness of

ramelteon administration for N24SWD, as well as determining the appropriate timing of administration.

This case report includes the following limitations. Circadian markers such as endogenous melatonin rhythm and core body temperature rhythm were not studied. The patient's social function after finding employment is unknown, and evaluation of final improvement of social function remains lacking. The patient's exposure to light was not objectively measured; therefore, it is possible that changes in the light/dark exposure might have affected her circadian rhythm as a result of behavioral education. It is also possible that the behavioral changes introduced by the behavioral education (eg, avoidance of naps during the day, turning lights off by midnight, and avoidance of the use of IT devices after lights out) simultaneously with the initiation of ramelteon might have contributed to the change in her sleep-wake cycle. Taking these results together, it is difficult to totally exclude the possibility that factors other than ramelteon, including placebo effect, may have improved the patient's N24SWD; therefore, a randomized, double-blind, placebo-controlled study will also be necessary to confirm the efficacy of ramelteon alone. However, we consider that the relatively long maintenance of entrainment may be attributable to the combined intervention of low dose ramelteon and behavioral education. We believe that this report is valuable for future evaluation of treatment options for patients with N24SWD because in our clinical experience, this condition is rare and refractory.

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DISCLOSURE STATEMENT

Work for this study was performed at the Department of Psychiatry, Fujita Health University School of Medicine, Aichi, Japan. The patient provided written informed consent for this study. All authors have contributed to and have approved the final manuscript, and all agree with this submission to the *Journal of Clinical Sleep Medicine*. The use of ramelteon in this case is considered to be within the approved usage for insomnia in Japan, although the applied dosage of 1 mg in this case was lower than approved dosage (8 mg). Dr. Iwata has received research grants from Otsuka, GSK, Tanabe-Mitsubishi, Dainippon-Sumitomo, Eizai, Daiichisankyo, and has received personal fees from Eli Lilly, Janssen, Otsuka, Shionogi, GSK, Dainippon-Sumitomo, Astellas, Yoshitomi, Meiji, Novartis, and Pfizer. Dr. Kitajima has received research grants from Eizai, Takeda, MSD, and has received personal fees from Eizai, Tanabe-Mitsubishi, Otsuka, Takeda, Eli Lilly, MSD, Meiji, Yoshitomyakuhin, Dainippon-Suimitomo, Fukuda, Shionogi, and Novo Nordisk. The other authors report no conflicts of interest.