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CASE REPORTS

Sleep deprivation therapy to reset the circadian pacemaker in a non-24-hour sleep-wake disorder: a case report

Kelly Guichard, MD, MS[1,2,3]; Jean-Arthur Micoulaud-Franchi, MD, PhD[1,2,4]; Pierre Philip, MD, PhD[1,2,4]; Jacques Taillard, PhD[2,4]

[1]Clinique du Sommeil, Bordeaux University Hospital, Bordeaux, France; [2]Université de Bordeaux, Sommeil - addiction - neuropsychiatrie SANPSY, Bordeaux, France; [3]Nouvelle Clinique Bel Air, Bordeaux, France; [4]Centre National de la Recherche Scientific (CNRS), unité de service et de recherche 3413, SANPSY, Bordeaux, France

Non-24-hour sleep-wake disorder is 1 of several chronic circadian rhythm sleep-wake disorders. It is defined as progressive daily shifts in sleep onset and wake times. It mainly affects patients who are sight-impaired, is relatively rare in sighted patients, and is difficult to treat, with no guidelines. This case report discusses non-24-hour sleep-wake disorder in a sighted young man who complained of alternating severe insomnia and excessive sleepiness, with a sleep agenda and actigraphic data showing a daily delay of approximately 2 hours. A novel therapy by total sleep deprivation followed by a combination of morning light therapy and nocturnal melatonin administration was efficient in stopping his free-running sleep-wake pattern both immediately and in the long term. The treatment combination for 6 months resulted in stable circadian entrainment to a 24-hour cycle. Compliance with chronotherapy was maintained over the course of follow-up.

Keywords: N24SWD, circadian rhythm sleep disorders, wake therapy, total sleep deprivation

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INTRODUCTION

Non-24-hour sleep-wake disorder (N24SWD) is 1 of several chronic circadian rhythm sleep-wake disorders. It is defined as a "chronic steady pattern comprising one- to two-hour daily delays in sleep onset and wake times in an individual living in society," according to the *International Classification of Sleep Disorders,* third edition.[1]

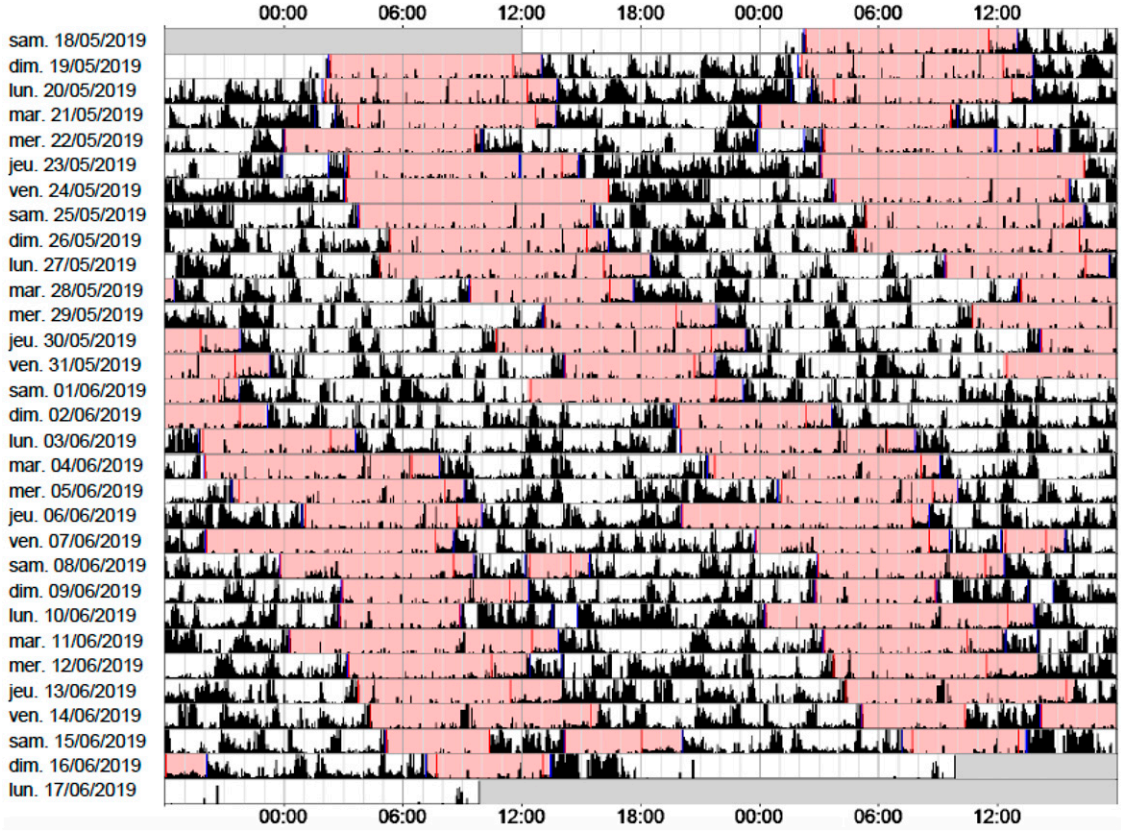
N24SWD mainly affects patients who are sight-impaired in whom the endogenous circadian pacemaker is not synchronized with the 24-hour day and exhibits a free-running period (generally longer than 24 hours). The inability to maintain stable entrainment is explained by the loss of photic synchronization, which resets (entrains) the circadian endogenous pacemaker each day to the 24-hour day. N24SWD is relatively rare in sighted patients, although the number of patients with reported cases is constantly increasing. Although it seems to be more prevalent in males (4:1 ratio) and with onset preferentially in the teens or twenties, its pathophysiology is less well understood. Several hypotheses may explain the pathophysiology of N24SWD. The first is that these patients have reduced sensitivity to the daily phase-resetting effect of light and inappropriate social time cues often caused by psychiatric conditions.[2] A second hypothesis is that their free-running period is longer than 24.5 hours, so their capacity for entrainment by a photic or nonphotic synchronizer is impaired.[3] The third is that the endogenous circadian pacemaker functions normally but may be systematically phase-delayed every day by inappropriate nocturnal exposure to light, particularly short-wavelength blue light, before sleep onset and during the phase-delay portion of the phase response curve, resulting in an approximately 25-hour sleep-wake cycle.[4]

The condition has dramatic consequences for patients because of their severe circadian misalignment. Because of periods of sleeping during the day (symptomatic periods) that alternate with periods of sleeping during normal nighttime hours (asymptomatic periods), patients are unable to work at regular times and are prone to social isolation. Although the health consequences of N24SWD remain unclear, in general, circadian misalignment may increase the risk of physical and psychiatric disorders, such as cardiovascular disease and mood disturbances. Therefore, appropriate alignment of the endogenous circadian phase with the external, 24-hour day should be pursued.

All these consequences require that this condition should be treated rigorously. Nevertheless, there are no specific treatment guidelines for sighted patients with N24SWD. The most suitable treatment to date has been the use of a powerful zeitgeber, which resets the phase of endogenous circadian pacemakers. Light therapy, melatonin, or a combination of both are alternative strategies recommended by the American Academy of Sleep Medicine.[1] Morning bright-light therapy normally (if light exposure is applied after core body temperature minimum) induces a phase advance by shifting the circadian phase earlier and, if repeated daily, prevents a further shift to later hours and stabilizes circadian pacemaker entrainment to the 24-hour day. Melatonin is given before sleep time to promote sleep onset and entrain the circadian pacemakers, if it is administered at the same time each day.

Circadian rhythm resynchronization by chronotherapy is not always achieved in sighted patients with N24SWD.[5] Wake therapy by total sleep deprivation (TSD), in conjunction with other chronotherapies, helps reset and maintain stable entrainment of the circadian pacemaker.[6] In addition, sleep

Figure 1—Actigraphic assessment of N24SWD. Bed and wake times delayed each day.



deprivation increases homeostatic sleep pressure and facilitates subsequent nocturnal sleep onset, thereby making it easier to anchor sleep at adequate and proper clock times. Appropriately timed bright-light therapy and melatonin administration can entrain the endogenous circadian pacemaker; however, the addition of TSD (ie, triple chronotherapy) to these interventions has not been described. In this case report, we present the effect of triple chronotherapy in a young sighted man with N24SWD.

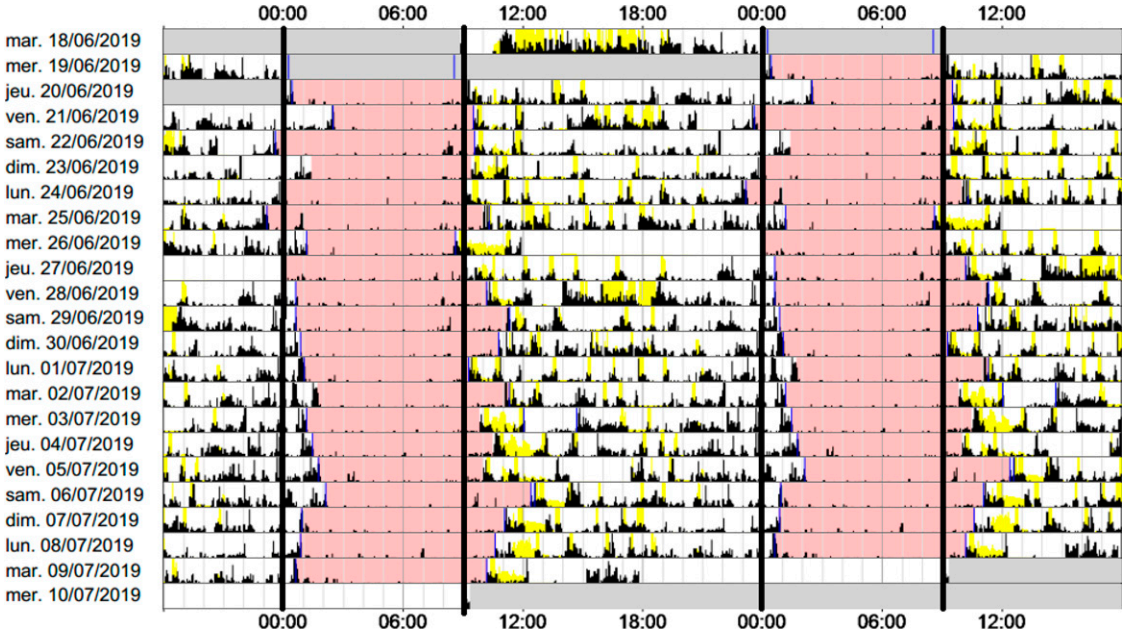
REPORT OF CASE

A 25-year-old man presented to the sleep clinic at Bordeaux University Hospital with difficulty falling asleep followed by sleepiness. He lived at his mother's house, was currently without a job, had a diagnosis of mood disorder that had been stabilized with outpatient treatment and only psychiatric consultations, was a smoker, and had no other medical history. The patient was referred by his psychiatrist for a better evaluation of sleep complaints in the context of another specified bipolar and related disorder, with "hypomanic episode without prior major depressive episode". The sleep disorders interview was conducted by a psychiatrist in sleep medicine from the Sleep Unit at Bordeaux University Hospital in Bordeaux, France.

The patient's sleep diary over 30 days showed a daily sleep phase delay of 1 hour per day on average (**Figure 1**). This circadian rhythm had appeared 6 years earlier without any apparent trigger, but he had previously experienced insomnia as a teenager. No visual problems or ophthalmology history were discussed during the medical interview. The patient underwent 30 days of actigraphic monitoring (Motion Watch 8, CamNtech, Fenstanton, UK), initialized to store data in 1-minute epochs. Actigraphy assessment revealed an objective daily sleep phase delay (**Figure 1**). The period length of actimetry, as assessed by the CamNtech software (version 7.27), was 25 hours and 46 minutes. The diagnosis of N24SWD was made on the basis of the patient's clinical history and these actigraphy data. No sleep disorder was found on polysomnography recording. Blood melatonin levels were not measured. Sleep hygiene education and the adoption of appropriate sleep behavior helped him for a few days, but the daily phase delay returned.

After this short sleep hygiene recommendation period, the sleep specialist decided to implement a combined circadian therapy during a 48-hour hospitalization. First, a TSD program was carried out over 36 hours under electroencephalogram recording and nurse supervision. The night after this sleep deprivation, the patient was allowed to sleep from 00:00 PM until 09:00 AM in accordance with his preferred sleep timing, with the introduction of a 2 mg melatonin intake between 09:00 and 10:00 PM and morning bright-light therapy (10,000 lux) for 45 minutes after wake time. The patient left the sleep clinic after the 48-hour hospitalization with recommendations to follow the

Figure 2—Actigraphic assessment after sleep deprivation.



predefined sleep times, avoid light at night, and continue daily melatonin intake and light exposure for 6 months. A bright-light box was bought independently by the patient, with a recommendation of 10,000 lux intensity, an ultraviolet light filter, and european conformity (CE) marking for standard safety and protection for an exposure of at least 45 minutes.

During the first month after hospitalization, actigraphic and light recordings were carried out (**Figure 2**). As shown in **Figure 2,** the free-running sleep-wake pattern stopped immediately upon administration of the triple chronotherapy and a 24-hour sleep-wake cycle was established. The period length assessed by actimetry was 24 hours and 4 minutes, confirming resynchronization of the 24-hour sleep-wake cycle by combined circadian therapy. The first weeks of treatment led to stabilization of bedtime in the evening and wake time in the morning. His sleep windows coincided with his target time, with a slight delay in sleep times, especially a delayed wake time. Treatment efficiency and compliance were assessed by a medical interview with a sleep specialist during consultation follow-up (at 40 days and at 6 months posttreatment). The patient found it difficult to adhere to the predefined sleep times and morning light therapy. However, he was still compliant with the chronotherapy (melatonin and light) and sleep hygiene recommendations after several months. **Figure 2** shows that the patient was exposed to light every morning and during the middle of the day, but not in the evening, suggesting good compliance with light exposure recommendations. After 6 months of chronotherapy, he maintained circadian entrainment, although his sleep-wake timing was still relatively delayed.

The patient remained adherent to therapy and his N24SWD had not relapsed after more than 6 months of follow-up. His complaints about sleepiness and the need to sleep during the day have also abated fully, as has his insomnia. Furthermore, he has not experienced any mood decompensation and was able to live in his own flat 1 year later.

DISCUSSION

This case report adds to the literature on the rare occurrence of N24SWD in sighted people and is the first to suggest the efficacy of triple chronotherapy (TSD followed by nocturnal melatonin administration and morning light therapy), leading to cessation of the free-running pattern and entrainment on a stable 24-hour cycle. The small number of recent publications about N24SWD in sighted persons shows the extent to which this disease has been overlooked, the lack of specific treatment guidelines, and the therapeutic challenge it represents.[5,7] Although melatonin is recommended in adults who are sight-impaired, no recommendations exist for sighted persons because of the lack of data.[8] In some patients, hygiene education, light therapy, and melatonin (0.5–14 mg), or a combination of both, even with the melatonin agonist hypnotics aripiprazole or valproic acid, has proved effective, although rhythm resynchronization has not always been achieved.[5,9–12]

TSD has been proposed as an alternative treatment in line with the pathophysiological underpinnings of N24SWD. TSD not only improves symptoms in mood disorders but also aligns core body temperature, sleep, and cortisol timing, suggesting that the circadian endogenous pacemaker may be reset in this way.[13] The second advantage of 36-hour sleep deprivation is the soporific effect induced by the greater homeostatic sleep pressure when the patient is asked to fall asleep. This pressure also facilitates the anchoring of sleep at adequate and appropriate times.

Before the initiation of light therapy, the circadian phase should be estimated to guide the timing of therapy. Ideally, the intervention should start after the patient's sleep has drifted to normal alignment with the solar light-dark cycle so that morning light therapy can begin.[4] Another approach is to wait until sleep timing aligns with the target time to initiate chronotherapy.[5] When circadian phase information is not available in N24SWD, wake therapy makes it possible to start light therapy immediately after the first normal nighttime sleep. This is not the recommended approach, but the present case report suggests that triple chronotherapy is of practical value when circadian phase information is not available.

In the present case report, the improvement was very quick and efficient without any adverse effects, and the combined therapy had a lasting beneficial effect. Triple chronotherapy is probably superior to double chronotherapy, as suggested by the speed of action in this case report. Moreover, sleep deprivation can easily be overcome during a hospitalization.

In addition to benefiting sighted individuals with N24SWD, the nonphotic components of therapy (melatonin and sleep deprivation) make this intervention adaptable to blind individuals with N24SWD. However, blind individuals with remaining light perception are likely to benefit from all 3 components. This case report has some limitations. First, circadian markers such as endogenous melatonin or body temperature measures were absent; therefore, the precise circadian phase before and after the intervention was unknown. Second, we used 2 mg of melatonin as compared to a lower dose (eg, 0.5 mg) that may be more effective for circadian entrainment. Third, light exposure and melatonin intake were not supervised at home. However, given the efficacy of the treatment, we assume that compliance was good. Fourth, it would have been useful to try a combination of light therapy and melatonin alone before using TSD therapy, to compare the efficacy of the treatments. However, given the severity of the patient's symptoms, rapid initiation of treatment was required. It was not possible to know whether behavioral therapy or melatonin alone may have been sufficient to treat this patient, because no comparison with the literature is possible. This case report suggests the need for clinical research to better understand the effect of TSD on the circadian pacemaker (and clock genes) and the potential efficacy of TSD to reset the circadian pacemaker in treatment of some circadian rhythm sleep-wake disorders. Of course, the greatest limitation of a case report is its lack of empirical control. Randomized trials are now needed to probe this issue.

CONCLUSIONS

This report describes a new therapeutic alternative for N24SWD in sighted people to reset their abnormal circadian rhythm, followed by daily circadian pacemaker entrainment with light therapy combined with melatonin. The patient was relapse-free 6 months later. The effectiveness of this triple therapy now needs to be verified in a larger sample of patients.

ABBREVIATIONS

N24SWD, non-24-hour sleep-wake disorder
TSD, total sleep deprivation

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Address correspondence to: Kelly Guichard, MD, MS, Clinique du Sommeil, Bordeaux University Hospital, Hôpital Pellegrin, Place Amélie Raba-Léon, 33000 Bordeaux, France; Email: kelly.guichard@gmail.com

DISCLOSURE STATEMENT

All the authors have seen and approved the manuscript. The authors report no conflicts of interest.