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PII: S1389-9457(21)00470-6

DOI: https://doi.org/10.1016/j.sleep.2021.08.026

Reference: SLEEP 5076

To appear in: *Sleep Medicine*

Received Date: 21 June 2021

Revised Date: 21 August 2021

Accepted Date: 26 August 2021

Please cite this article as: Kimura S, Takaoka Y, Toyoura M, Kohira S, Ohta M, Core body temperature changes in school-age children with circadian rhythm sleep–wake disorder, *Sleep Medicine*, https://doi.org/10.1016/j.sleep.2021.08.026.

Core body temperature changes in school-age children with circadian rhythm sleep–wake disorder

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Abbreviations: Apnea-hypopnea index (AHI), attention deficit–hyperactivity disorder (ADHD), autism spectrum disorder (ASD), central sleep apnea syndrome (CSAS), circadian rhythm sleep–wake disorder (CRSWD), core body temperature (CBT), delayed sleep–wake phase disorder (DSPD), insulin-like growth factor 1 (IGF-1), obstructive sleep apnea syndrome (OSAS), polysomnography (PSG), standard deviations (SDs).

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Abstract

Objective/Background: Core body temperature (CBT) is considered a valuable marker for circadian rhythm. This study aimed to investigate the changes in CBT that are associated with the symptoms of circadian rhythm sleep–wake disorder (CRSWD) post-treatment in children.

Patients/Methods: Twenty-eight school-age children [10 boys and 18 girls; mean age (±standard deviation), 13.68±0.93 years] who were admitted to our hospital with CRSWD underwent treatment for 6–8 weeks according to the following protocol: lights-out for sleep at 21:00; phototherapy for waking at 6:00 or 7:00; light exercise everyday (e.g., a 20- to 30-min walk). CBT was continuously measured for 24 hours on the first day of admission and on the first day after treatment.

Results: The mean time of sleep onset/offset (±standard deviation; in hours:minutes) 1 week before admission and 1 week after treatment were 23:53±2:26/9:58±2:15 and 21:17±0:19/6:46±0:32, respectively. The mean times of sleep onset and offset measured post-treatment were significantly earlier than those measured pre-treatment (p<0.001). The mean CBT and mean minimum CBT during sleep were significantly lower on the first day post-treatment than on the first day of admission (p=0.011 and p<0.001, respectively).

Conclusions: Symptom improvements in patients with CRSWD were associated with a decrease in CBT during sleep, suggesting that CBT may be a biomarker for improvements in CRSWD. These results help elucidate the cause of this sleep disorder.

Keywords: Body core temperature, circadian rhythm sleep–wake disorder, therapeutic effect, biomarker, school-age children, developmental disorders

1 Introduction

Core body temperature (CBT) has been considered a valuable marker for circadian rhythm, medical evaluations, and research studies, as it is the most relevant indicator of the body's thermal status [1]. However, CBT assessments have some disadvantages such as being invasive and often uncomfortable, difficulty in safely maintaining the instruments once they are inserted, and associated hygiene issues because CBT reflects the temperature of the related anatomic region's internal location (i.e., intracranial, deep thoracic, esophageal, intra-abdominal, and rectal) [2,3]. Although skin temperature can be measured in a less invasive manner, this measurement is influenced by the surrounding temperature. The zero-heat-flux sensor (Bair Hugger™ Temperature Monitoring System; 3M Corporation, St. Paul, MN, USA), which is placed on the forehead, measures CBT in a non-invasive manner [4]. It has demonstrated clinically acceptable accuracy and precision for CBT monitoring during elective major surgery [5].

In circadian rhythm sleep–wake disorders (CRSWDs), there is a desynchronization between one's internal sleep–wake rhythms and the light–dark cycle [6]. Individuals with CRSWDs cannot sleep or wake up naturally at the time necessary for their work, school, or social obligations. In delayed sleep–wake phase disorder (DSPD), a person remains asleep several hours beyond intended, whereas advanced sleep–wake phase disorder shifts sleep and waking times to be several hours earlier than the desired or customary time. The other types of

CRSWDs include the following: irregular sleep–wake rhythm, wherein a person does not have a clear circadian rhythm; non-24-hour sleep–wake rhythm, wherein a person's natural circadian rhythm does not align with the 24-hour day; circadian rhythm sleep disorder not otherwise specified, which is a disorder that is difficult to categorize into any of the aforementioned classifications [7].

Carpenter et al. studied 50 young people with affective disorders and 19 control participants (aged 16–31 years) who underwent continuous overnight CBT measurement in three patient groups ("delayed sleep–wake," "disrupted sleep," and "long sleep"). Notably, the "delayed sleep–wake" group displayed a significant difference in both delayed melatonin onset and core temperature nadir [8]. Narita et al. reported that the CBT in two patients (irregular sleep–wake type) lacked circadian rhythmicity, but their rhythm normalized after treatment [9]. They concluded that the continuous measurement of CBT is effective in diagnosing CRSWD and evaluating its treatment.

Sleep problems are common among patients with autism spectrum disorder (ASD) and attention deficit–hyperactivity disorder (ADHD) [10]. Patients with these conditions experience sleep problems that are classified as CRSWDs. Bijlenga et al. reported that the CBT of patients with ADHD, irregular sleep–wake cycles, and delayed sleep tended to be lower than that of the controls [11].

We recently reported that the serum insulin-like growth factor 1 (IGF-1) concentration in patients with CRSWD (including both ASD or/and ADHD) significantly increased after treatment for sleep disorders [12]. These results suggest that serum IGF-1 levels could be a biomarker for improvements following CRSWD treatment.

In this study, we hypothesized that improving CRSWD would be associated with changes in CBT. This study aimed to determine whether continuous CBT measurement for 24 hours is useful as a biomarker for CRSWD in school-age children.

2 Material and Methods

2.1 Patients and study design

In total, 1,705 patients (ages 6 months to 18 years) visited the pediatric department of the hospital for sleep disorder treatment from June 2019 to May 2020. Eighty-nine patients were voluntarily admitted to our hospital for therapy and examination. Of these patients, 54 were admitted for further examination [i.e., polysomnography (PSG) and multiple sleep latency tests] and received treatment for <6 weeks, as they did not stay for the full recommended 6- to 8-week treatment protocol [12]. An additional 35 patients with CRSWD were admitted, who subsequently participated in a 6- to 8-week treatment program designed specifically for patients with CRSWD. Seven of these patients did not undergo CBT assessments on the first day of admission or the first day after treatment. Therefore, a total of 28 patients completed the 6- to

8-week treatment protocol for CRSWD, all of whom were truant children (Table 1). Patients who received the 6- to 8-week treatment protocol had more severe CRSWD than those who received treatment for <6 weeks.

A retrospective study design was used to analyze the medical records of patients diagnosed with CRSWD who were admitted to and treated at our hospital. The study was approved by the Independent Ethics Committee of our hospital and conformed to the principles of the Declaration of Helsinki. Informed consent was obtained in the form of an opt-out sheet posted on the bulletin board in our hospital, and comprehensive informed consent was obtained from the participants' families. The 28 patients who completed the treatment protocol participated in this study. All patients were surveyed and classified as having one of the CRSWDs upon hospital admission, using the International Classification of Sleep Disorders—Third Edition [6]. Patients' sex is shown in Table 1. The numbers of patients with DSPD, non-24-hour sleep–wake rhythm disorder, irregular sleep–wake phase disorder, and circadian sleep–wake disorder not otherwise specified were 21, 1, 1, and 5, respectively. The circadian sleep–wake disorder not otherwise specified could not be classified because some patients had two or more of the following symptoms: DSPD, non-24-hour sleep–wake rhythm disorder, irregular sleep–wake phase disorder, or long sleep. Similarly, information regarding existing ASD or ADHD diagnoses was collected upon admission. The numbers of patients diagnosed with ASD, ADHD, and ASD with ADHD were 2, 7, and 5, respectively. However, almost all

patients had comments in their medical records noting behaviors characteristic of ASD, such as impaired social interactions, limited and repetitive interests and behavior, irritability, and aggression. They did not have any mental illness such as depression. The numbers of patients who were truant for 1 month to 6 months, 7 to 12 months, and >13 months were 10, 10, and 8, respectively. The shortest duration was 1 month, and the longest was 72 months, with a mean truancy duration of 14.07±16.53 months. The numbers of patients who received melatonin on the first day of admission and on the first day after treatment were 15 and 22, respectively. The numbers of patients who received risperidone on the first day of admission and on the first day after treatment were 10 and 20, respectively.

2.2 Treatment protocol for circadian rhythm sleep–wake disorders

The admitted patients underwent inpatient treatment for 6–8 weeks. They were not allowed to use electronic devices such as games, smartphones, and computers in the hospital. The protocol consisted of the following interventions: lights-out time for sleep at 21:00; phototherapy to induce waking, starting at either 6:00 or 7:00; 20–30 min of light exercise per day (e.g., walking) [12]. Occupational therapists assisted with exercise, clinical psychologists provided counseling, nurses educated the patients regarding the importance of good sleep, and hospital teachers gave lessons on school subjects such as English, Japanese, math, social studies, and science. A self-reported sleep diary [13] was used to collect information about

sleep (total sleep time, interrupted sleep, naps, and level of deep sleep), headache symptoms, light exercise, study, diet, and sleep logs. Sleep information was collected using a wrist actigraph (Actiwatch Spectrum Plus; Philips/Respironics, Murrysville, PA, USA) during the first week after admission. Our protocol was developed specifically for CRSWD in truant children [12]. Other programs have reported 3-week treatment protocols using phototherapy [14]. During the 6- to 8-week protocol, the discharge plan was discussed with the patient, the patient's family, and a social worker, as was a schooling plan, i.e., whether they would return to school or if alternate plans were needed once they were discharged. If the patient's sleep disorder did not improve, a pharmacological intervention was introduced, including melatonin (a hormone that regulates sleep–wake cycles) to induce sleep [15-17]. Risperidone (an atypical antipsychotic agent) was used to improve light sleep (i.e., decreased interrupted sleep) for patients who displayed irritability and aggression, such as those with ASD [18].

2.3 Examination

Upon both initial admission to the hospital and discharge, blood samples were collected from all patients at 8:00 for the hemogram assessment and to measure the concentrations of IGF-1, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, blood urea nitrogen, creatinine, total cholesterol, triglyceride, thyroid-stimulating hormone, free triiodothyronine and free thyroxine. PSG

(described below) was performed upon admission. The times of sleep onset and offset, total sleep duration, number and duration of every time point at which patients woke up from sleep, and the number and duration of napping periods were assessed using the sleep logs spanning the week before and after treatment. Daily means and standard deviations were calculated over these two 1-week periods [12].

2.4 Body temperature

CBT was measured on the first day of admission and after the treatment. On the first day of admission, patients visited our hospital at 9:00, received guidance for hospitalization, and took a bath at approximately 15:00. The 24-hour CBT measurement was initiated at 16:00. When they had free time, they read books and talked to other patients while sitting on a chair, and the medical staff awakened patients for daytime monitoring until the lights-out time for sleep at 21:00. The same schedule was followed on the first day after the treatment. Breakfast, lunch, and dinner were served at 7:30, 12:00, and 18:00, respectively.

The zero-heat-flux sensor (3M Bair Hugger™ Temperature Monitoring System) was placed on the patient's forehead, and the patient's movement was limited to the bedside because the sensor on the head was connected to the monitoring system with a 4-m cable. The sensor was switched off only when the participant visited the restroom. The nurse checked whether the sensor was on or off every 2 hours. CBT data were measured using a continuous monitoring

system every 10 min for 24 hours, and the data were collected using a data logger (High Precision 8 Channel Data Logger; N543 Nikiso-Therm Co., Ltd, Tokyo, Japan).

2.5 Polysomnography

In a designated private room of our pediatric ward, standard overnight PSG was performed for each patient to diagnose obstructive sleep apnea syndrome (OSAS) and central sleep apnea syndrome (CSAS) after the CBT measurement and within 3 days after admission. The PSG consisted of two electroencephalograms, two electrooculograms, one submental electromyogram, two anterior tibialis muscle electromyograms, and respiratory measures (Pro-Tech Body Position Sensors; Philips/Respironics) [12].

2.6 Phototherapy

Following completion of CBT measurements and PSG, phototherapy was initiated. The light was directed onto patients from a distance of 1 m (Circadian Control NQ71; Panasonic, Osaka, Japan). This faint light exposure was initiated 1 hour before the predetermined wake-up time, and the light gradually became brighter until reaching approximately 6,000 lux. Illuminance was maintained at 6,000 lux for 2 hours, and subsequently, the light gradually dimmed over 1 hour before finally turning off [12,19].

2.7 Statistical analysis

Microsoft Excel 2016 (Microsoft, Redmond, WA, USA) was used to perform all statistical analyses. Paired Student's *t*-tests were used to compare normally distributed data (i.e., the average ages of the participants). The non-parametric Mann–Whitney U test was used to compare data between the two groups with skewed distributions (i.e., the duration of truancy until admission for boys compared with that for girls and the maximum CBT). Friedman's test, along with Steel–Dwass' test, was used to compare data between the groups with skewed distributions (i.e., the time of sleep onset and offset and the total sleep duration for 1 week before admission, on the first day of admission, the first day after treatment, and for 1 week after treatment). The outliers in the number and average duration of awakenings from sleep and the number and average duration of daytime naps were excluded using the local outlier factor method [20]. Thereafter, Friedman's test, along with Steel–Dwass' post hoc test, was used to perform statistical analyses. The CBT measurements included outliers because the probe of the zero-heat-flux sensor placed on the forehead occasionally became unfixed. This was caused by the patient pulling the line when turning over in bed while sleeping and standing up. To exclude the outliers in each dataset of the CBT, a Hampel filter [21] was used, and data obtained from the alteration above the change of 1°C/10 min and <35°C were excluded as artifacts. After excluding outliers in CBT, paired Student's *t*-tests were used to compare normally distributed data [i.e., means of CBT, minimum and maximum CBT for boys and girls, means of CBT for

24 hours, awakening (7:00–21:00), sleeping (21:00–7:00), means of minimum and maximum CBT, difference in means between the minimum and maximum CBT] and the IGF-1 concentration on the first day of admission with that on the first day after treatment. Student's *t*-tests were used to analyze data between the minimum CBT of the melatonin-administered and non-melatonin groups and between the risperidone-administered and non-risperidone groups on the first day of admission and after treatment. p Values <0.05 were considered statistically significant.

Cosinor analysis [22] of chronometric rhythms in CBT for a period of 24 hours was performed using R software [23]. The times of maximum and minimum CBT were determined using the results of this analysis. Based on the difference between these times, the fluctuation period of CBT was determined for each patient. The cosinor analysis of the CBT was repeated using the determined fluctuation period of each patient. The differences in CBT were adjusted for by dividing according to the temperature range of each patient. Student's t-test was performed to compare normally distributed data including differences in CBT and duration between sleep onset and offset times, sleep onset and minimum CBT, and sleep offset and maximum CBT on the first day of admission and the first day after treatment. The Wilcoxon signed rank test was performed to analyze nonparametric data, including the difference in duration between sleep onset and minimum CBT at each time point.

3 Results

The CRSWD of the selected patients, particularly DSPD, indicated that their sleep patterns were delayed, causing them to sleep and wake later. This is frequently due to excessive online gaming, watching YouTube, using smartphones and computers, studying late at night for school, and being involved in club activities late after school [24]. The numbers of patients who complained of headache, abdominal pain, dizziness, and general fatigue on admission were 22, 6, 12, and 15 respectively. At the time of discharge, these numbers decreased to 7, 2, 1, and 5, respectively. According to PSG, the mean apnea-hypopnea index (AHI) of all patients was 0.76±0.92 events/hour, and the highest AHI was 3.70 events/hour, which was well within the none/minimal range for possible OSAS or CSAS. None of the patients had undergone surgery (e.g., bilateral tonsillectomy, adenoidectomy) or received treatment with continuous positive airway pressure. The mean sleep onset latency was 22.96±16.28 min, which was not bad because the reported value for typically developing children at the age of 7.6 years is 25.1±19.4 min [24]. No patient in this study had liver or kidney dysfunction or hyperthyroidism based on blood sample analysis.

The number of data points excluded as outliers of the number and average duration of awakenings from sleep, and the number and average duration of daytime naps in every 122 data points using the local outlier factor method were 3, 5, 0, and 3, respectively. In total, 135 data points as outliers in 8,120 points of all CBT data were excluded using the Hampel filter;

similarly, 10 data points were excluded by changing 1°C/10 min, and six were excluded by decreasing the temperature to <35°C.

Table 2 shows the mean time of sleep onset and offset, total sleep duration, number and average duration of awakenings from sleep, and number and average duration of daytime naps for 1 week before admission, on the first day of admission, the first day after treatment, and for 1 week after treatment. Daily means and SDs were calculated for 1 week before admission and 1 week after treatment. There were significant differences between the mean time of sleep onset for 1 week before admission (23:53±2:26) and on the first day of admission, on the first day after treatment, and for 1 week after treatment (21:14±0:48, 21:13±0:17, and 21:17±0:19, respectively; each p <0.001). Additionally, there were significant differences in the mean sleep offset time between 1 week before admission (9:58±2:15) and at every time point (6:53±0:49, 6:42±0:40, and 6:46±0:32, respectively; each p<0.001). There was no significant difference in the time of sleep onset and offset between the first day of admission, on the first day after treatment, or for 1 week after treatment (Figure 1). In addition, there were no significant differences between the means of the total sleep duration at every time point. Regarding the number of awakenings from sleep, there were no differences between any of the time points; however, the means of the average duration of awakening from sleep from 1 week before admission to the first day of admission and after treatment significantly decreased from 8.61±17.79 to 2.22±8.01 min (p=0.045) and to 0.74±2.67 min (p=0.027), respectively. There

were no significant differences in the number or average duration of daytime naps at any time point.

There were no significant differences in the mean CBT for 24 hours, minimum CBT, or maximum CBT between boys (n=10) and girls (n=18) on the first day of admission and after treatment (all $p>0.05$). The following results were calculated from the combined data of boys and girls.

Figures 2 and 3 show the 24-hour CBT means, CBT during awakening (7:00–21:00) and CBT during sleep (21:00–7:00) as well as the change in mean CBTs for 24 hours, on the first day of admission, and on the first day after treatment. Interestingly, the mean CBT was lower on the first day after treatment than on the first day on admission, especially during sleep. The mean CBT for 24 hours from the first day of admission to the first day after treatment significantly decreased from 36.96°C±0.18°C to 36.79°C±0.18°C ($p=0.011$) (Figure 3a). However, there was no significant difference in the mean CBT at awakening (7:00–21:00) between the first day of admission and the first day after treatment ($p=0.054$) (Figure 3b). In contrast, the mean CBT while sleeping (21:00–7:00) from the first day of admission to the first day after treatment significantly decreased from 36.71°C±0.21°C to 36.48°C±0.17°C ($p<0.001$) (Figure 3c).

The minimum and maximum CBTs were equally investigated on the first day of admission and on the first day after treatment (Table 3). The mean minimum CBT from the first day of

admission to the first day after treatment significantly decreased from 36.20°C±0.27°C to 35.93°C±0.22°C (p<0.001); however, there was no significant difference in the time of minimum CBT between the time points (p=0.361). In contrast, the means of the maximum CBT on the first day of admission and on the first day after treatment were 37.58°C±0.18°C and 37.52°C±0.25°C, respectively, and no significant difference was observed (p=0.240); however, the means of the time of the maximum CBT from the first day of admission to the first day after treatment significantly shifted from 16:27±2.20 to 17:35±1.95 (p=0.018). The difference between the means of the maximum and minimum CBT increased from 1.37°C±0.32°C on the first day of admission to 1.59°C±0.28°C on the first day after treatment (p=0.022).

Subsequently, the diagnosis and medication were focused on the minimum CBT. Changes in the mean minimum CBT value from the first day of admission to the first day after treatment in patients with ASD, ADHD, and ASD with ADHD as well as patients without a developmental disorder were surveyed. Only the change in patients with ADHD, i.e., 36.40°C±0.25°C to 35.82°C±0.14°C, was statistically significant (p<0.001) (Table 3). Regarding the means of the maximum CBT for diagnosis, there were no significant differences between the time points.

Additionally, the means of the minimum and maximum CBT were assessed in patients who received melatonin and risperidone on the first day of admission and on the first day after

treatment. Significant differences in minimum and maximum CBTs were not detected at any of the time points between the melatonin-administered and non-melatonin groups and risperidone-administered and non-risperidone groups.

The serum IGF-1 concentrations from the first day of admission to the first day after treatment significantly increased from 349.30±53.19 to 379.70±57.10 ng/mL (p<0.001) (Table 3).

Table 4 shows the cosinor analysis of the chronometric rhythms in CBT. The compensated difference in CBT between sleep onset and offset time from the first day of admission to the first day after treatment significantly decreased from 0.17° ± 0.31° to 0.01° ± 0.35° (p < 0.001). The compensated difference in CBT and time of sleep onset and minimum CBT at each point significantly decreased from 0.54° ± 0.21° to 0.46° ± 0.30° (p < 0.001), and from 0.25 ± 0.10 to 0.19 ± 0.08 minutes (p = 0.022), respectively. The compensated difference in CBT between sleep offset and maximum CBT at each point significantly decreased from 0.63° ± 0.18° to 0.54° ± 0.15° (p = 0.042). However, there were no statistically significant differences in the time between sleep onset and offset time at each point (from 0.39 ± 0.08 to 0.35 ± 0.07 minutes; p = 0.069), and sleep onset and offset time (from 0.39 ± 0.10 to 0.39 ± 0.08 min; p = 0.748).

4 Discussion

We investigated the change in CBT pre- and post-treatment in school-age children with CRSWD as well as the relationship among CBT, developmental disorders, and medications. The time of sleep onset and offset significantly improved between 1 week before admission and 1 week after treatment. Consequently, the patients had sufficient time to attend school after treatment. Overall, the CRSWD of the patients improved with the treatment. Upon admission, the serum IGF-1 value, which was reported as a biomarker for improved CRSWD in school-age children, also significantly increased on the first day of admission, relative to that on the first day after treatment [12]. Interestingly, the time of sleep onset and offset on the first day of admission occurred significantly earlier than that at 1 week before admission. This result seemingly indicated an improvement in the CRSWD for only 1 day. We believe that the study conditions, whereby patients woke up to visit our hospital earlier than usual, did not use electric devices, and were awakened by medical staff for daytime monitoring until the lights-out time for sleep at 21:00, played an important role in this improvement. On the first day of admission, although the patients were awake, they complained of sleepiness. After the end of the treatment protocol, they did not complain of sleepiness during the daytime, slept after the lights-out time of 21:00, and awakened naturally. It is important to note that there was no significant difference in the time of day of sleep onset and offset between the first day of admission and the first day after treatment, according to our data. The CBT measurements were performed under the same sleep conditions.

Our results showed that the mean CBT and minimum CBT during sleep on the first day of admission were higher than those on the first day after treatment. According to the cosinor analysis, the compensated difference in time between sleep onset and minimum CBT significantly decreased from the first day of admission to the first day after treatment, which was because the patients slept later before admission, compared with that after treatment.

A previous research indicated that the minimum CBT of subjects who were sleep-deprived and more or less continuously active was higher than that of subjects who sleep at night and pursue normal activities during daytime [1]. Numerous studies have reported that the heart rate, metabolic rate, cortisol and norepinephrine concentrations, and body temperature were elevated in patients with chronic insomnia [26-28]. However, this is the first report of continuous 24-hour measurement of CBT in school-age children with CRSWD during sleep, in which the pre-treatment CBT was clearly higher than that post-treatment. Therefore, the higher CBT in patients with CRSWD during sleep might be caused by high sympathetic nervous system activity [29,30] and neuroinflammation [31,32]; however, further research is necessary.

Among patients with developmental disorders, only those with ADHD showed a significant difference in the mean minimum CBT between the first day of admission and the first day after treatment. Several studies have assessed the correlation between peripheral inflammatory cytokine levels and childhood ADHD, suggesting low-grade inflammation

[33,34]. Similarly, ASD has been reported to be associated with inflammation. However, the relationship between the change in the minimum CBT and ASD was unclear in our study [35,36].

Melatonin is primarily produced by the pineal gland and is released into the bloodstream exclusively at night following the circadian rhythm, and CBT gradually decreases [37]. Melatonin functions as a natural nocturnal vascular modulator. Administration of melatonin has been reported to induce a decrease in CBT [38]. Our results did not reveal a significant difference in CBT between the melatonin-administered and non-melatonin groups. Melatonin may be released innately in patients who do not take melatonin. On the contrary, risperidone induced hypothermia in an experiment using rats [39-42]. Our results did not indicate any differences in the means of the minimum CBT between the risperidone-administered and non-risperidone groups. Therefore, additional research on this topic is necessary.

There are limitations to this study that should be acknowledged. First, the melatonin concentration in patients' serum or saliva was not measured. Second, the administered dose of risperidone was patient-dependent. Third, this study has a single-center design and included a relatively small sample.

5 Conclusion

To the best of our knowledge, this study was the first to report that the pre-treatment CBT in patients with CRSWD, especially during sleep, was higher than the post-treatment CBT. Improvements in the symptoms of school-age children with CRSWD were associated with a decrease in CBT during sleep, indicating that CBT is a parameter of improved CRSWD in school-age children. This result may lead to a better understanding of the cause of CRSWD.

Acknowledgements: We would like to thank the staff of the hospital ward at the Children's Rehabilitation, Sleep and Development Medical Center, Hyogo Prefectural Rehabilitation Central Hospital, especially Dr Kiyoshi Kikuchi, who gave us good advice for taking care of the patients.

Declarations of interest: None

Funding: This study was supported by a research grant from Hyogo Prefectural Rehabilitation Central Hospital [grant number 838-2]. The sponsor had no involvement in the study.

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Tables

Table 1. Patient characteristics

	Boys (n=10)	Girls (n=18)	Total (n=27)	*p*-Value, boys vs. girls
Age, years (mean±SD)	14.00±0.63	13.50±1.01	13.68±0.93	0.185[b]
Circadian rhythm sleep–wake disorder (n)				
Delayed sleep–wake phase disorder	8	13	21	
Irregular sleep–wake rhythm	0	1	1	
Non-24-hour sleep–wake rhythm	0	1	1	
Circadian rhythm sleep disorder, not otherwise specified	2	3	5[a]	
Developmental disorders (n)				
ASD	0	2	2	
ADHD	4	3	7	
ASD with ADHD	1	4	5	
Duration of truancy until admission				
1–6 mo (n)	1	9	10	N/A[c]
Duration, mo (mean±SD)	12±0	4.11±1.52	3.9 0±1.58	
7–12 mo (n)	7	3	10	0.357[c]
Duration, mo (mean±SD)	8.43±1.05	8.67±2.36	8.50±1.57	
>13 mo (n)	2	6	8	N/A[c]
Duration, mo (mean±SD)	16.5±13.5	37.83±20.89	33.75±19.88	
Total (n)	10	18	28	0.548[c]
Duration, mo (mean±SD)	10.40±7.05	16.11±19.64	14.07±16.53	
Medication during CBT measurement (n)				
Melatonin				
First day of admission	4	11	15	
First day after treatment	6	16	22	
Risperidone				
First day of admission	3	7	10	
First day after treatment	7	13	20	

SD, standard deviation; n, number of patients; ASD, autism spectrum disorder; ADHD, attention deficit–hyperactivity disorder; mo, month(s); N/A, not available due to small sample; CBT, core body temperature.

[a]Non-24-hour sleep–wake rhythm disorder, irregular sleep–wake phase disorder or long sleep were mixed in a patient.

[b]Student's *t*-test.

[c]Mann–Whitney's U test.

Table 2. Differences in time of sleep, sleep onset and offset, total sleep duration, and interrupted sleep and naps at various time points

	Admission		After treatment		Test statistics, significant pairwise comparisons
	(1) 1 week before	(2) First day	(3) First day	(4) 1 week	
Sleep onset (hours:min)	23:53±2:26	21:14±0:48	21:13±0:17	21:17±0:19	1 vs. 2, 3, and 4 (each p<0.001)
Sleep offset (hours:min)	9:58±2:15	6:53±0:49	6:42±0:40	6:46±0:32	1 vs. 2, 3, and 4 (each p<0.001)
TST (hours)	9.75±2.22	9.62±1.22	9.47±0.73	9.22±0.71	
Inter sleep (n)	0.14±0.31	0.11±0.31	0.11±0.31	0.15±0.27	
Inter sleep duration (min/day)	8.61±17.79	2.22±8.01	0.74±2.67	1.53±2.99	1 vs. 2 and 3 (p=0.045 and 0.027)
Nap (n)	0.03±0.05	0.07±0.26	0.00±0.00	0.00±0.00	
Nap duration (min/day)	2.92±8.99	2.14±7.78	0.00±0.00	0.00±0.00	

TST, total sleep time; Inter, interrupted; Inter sleep (n), number of awakenings from sleep (episodes/day); Inter sleep duration, average duration of awakenings from sleep; Nap (n), number of daytime naps (episodes/day); Nap duration, average duration of a daytime nap.

Values are presented as mean±standard deviation. Friedman's test, along with Steel–Dwass' test, was used to compare the time of sleep onset, sleep offset, and total sleep duration at various time points. The outliers in the number and average duration of awakenings from sleep and the number and average duration of daytime naps were excluded using the local outlier factor method. After data cleaning, Friedman's test, along with Steel–Dwass' post hoc test, was used for statistical analysis.

Table 3. Tmin and Tmax of CBT, Tmin of ASD and ADHD, and IGF-1 on the first day of admission and first day after treatment

	First day of admission	First day after treatment	*p*-Value
Tmin and Tmax of CBT			
Tmin of CBT (°C)	36.20±0.27	35.93±0.22	<0.001
Time of Tmin for CBT (hours:min)	2:21±9.95	2:46±4.07	0.361
Tmax of CBT (°C)	37.58±0.18	37.35±0.25	0.240
Time of Tmax CBT (hours:min)	16:27±2.20	17:35±1.95	0.018
Tmax−Tmin of CBT (°C)	1.37±0.32	1.59±0.28	0.022
Tmin of CBT in developmental disorders			
ASD (n=2)	36.38±0.41	35.91±0.04	0.381
ADHD (n=7)	36.40±0.25	35.82±0.14	<0.001
ASD with ADHD (n=5)	36.00±0.12	36.04±0.20	0.415
None (n=14)	36.16±0.24	35.94±0.26	0.064
Serum IGF-1 level (ng/mL)	349.30±53.19	379.70±57.10	<0.001

CBT, core body temperature; Tmin, minimum temperature; Tmax, maximum temperature; Tmax−Tmin, difference between Tmax and Tmin; ASD, autism spectrum disorder; ADHD, attention deficit–hyperactivity disorder; IGF-1, insulin-like growth factor 1.

Values are presented as mean±standard deviation. To exclude the CBT outliers in each dataset, Hampel filtering was used, and the data that exceeded the change of 1°C/10 min and <35°C (temperature) were excluded as artifacts. After excluding the CBT outliers, paired Student's *t*-test was used for the analysis.

Table 4. Cosinor analysis of the CBT rhythms on the first day of admission and first day after treatment

	First day of admission	First day after treatment	*p*-Value
Difference between sleep onset and offset time			
CBT (°C)	0.17±0.31	00.1±0.35	<0.001[a]
Time (min)	0.39±0.08	0.35±0.07	0.069[a]
Difference between sleep onset and minimum CBT			
CBT (°C)	0.54±0.21	0.46±0.30	<0.001[b]
Time (min)	0.25±0.10	0.19±0.08	0.022[a]
Difference between sleep offset and maximum CBT			
CBT (°C)	0.63±0.18	0.54±0.15	0.042[a]
Time (min)	0.39±0.10	0.39±0.08	0.748[a]

CBT, core body temperature.

Values are presented as mean±standard deviation. CBT and time were adjusted by dividing by the change in temperature and cycle time in 1 day.

[a]Paired Student's *t*-tests.

[b]Wilcoxon signed rank test for nonparametric data.

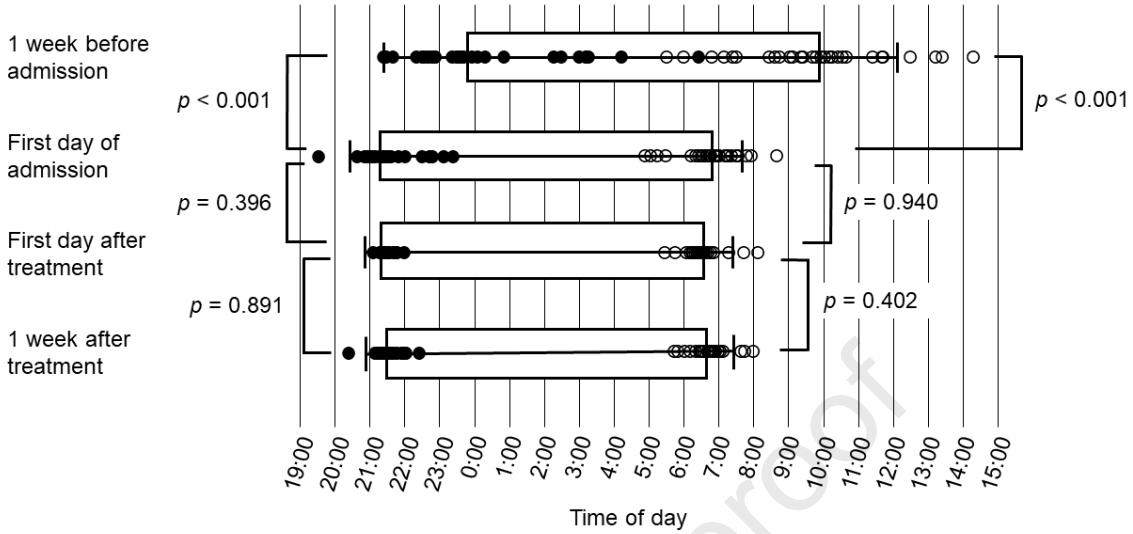


Figure 1. Changes in sleep onset and offset times at various time points

The unfilled square boxes indicate sleep time; error bars represent the standard deviation. The closed and open circles indicate onset and offset times, respectively. Friedman's test, along with Steel–Dwass' test, was used to compare the times of sleep onset and offset at various time points.

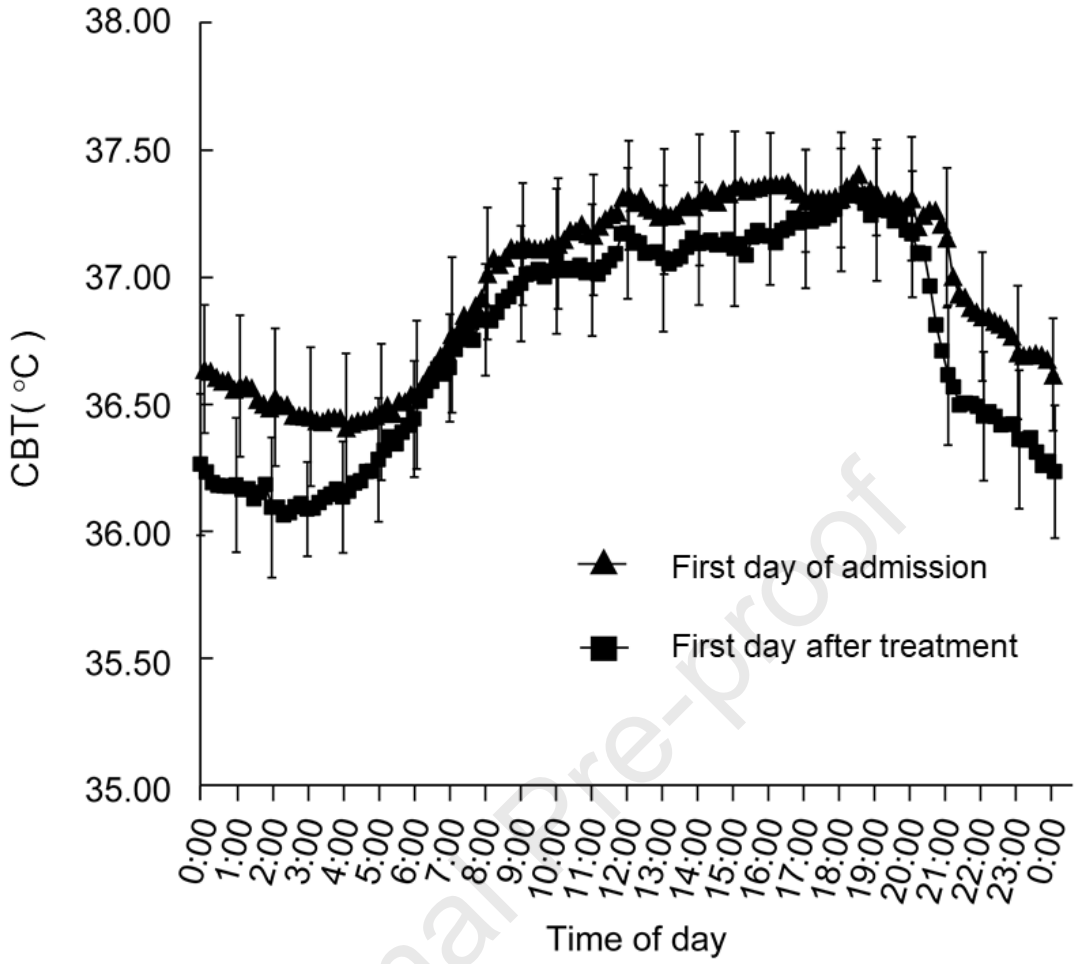


Figure 2. Time course of CBT means for 24 hours

CBT measurement performed on the first day of admission (▲) and on the first day after treatment (■).CBT, core body temperature. Vertical bars represent ±1 standard deviation from the mean.

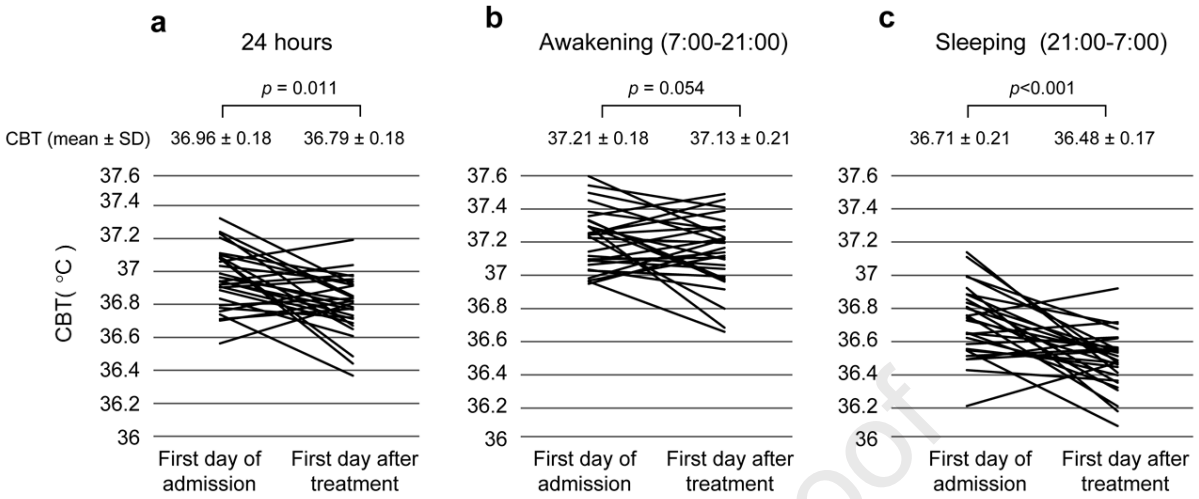
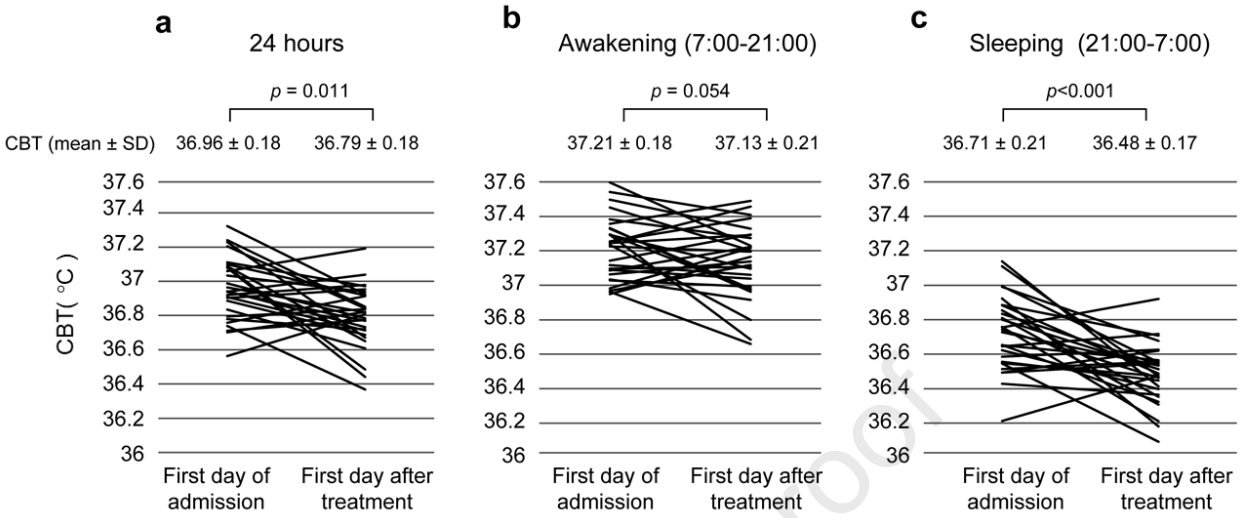
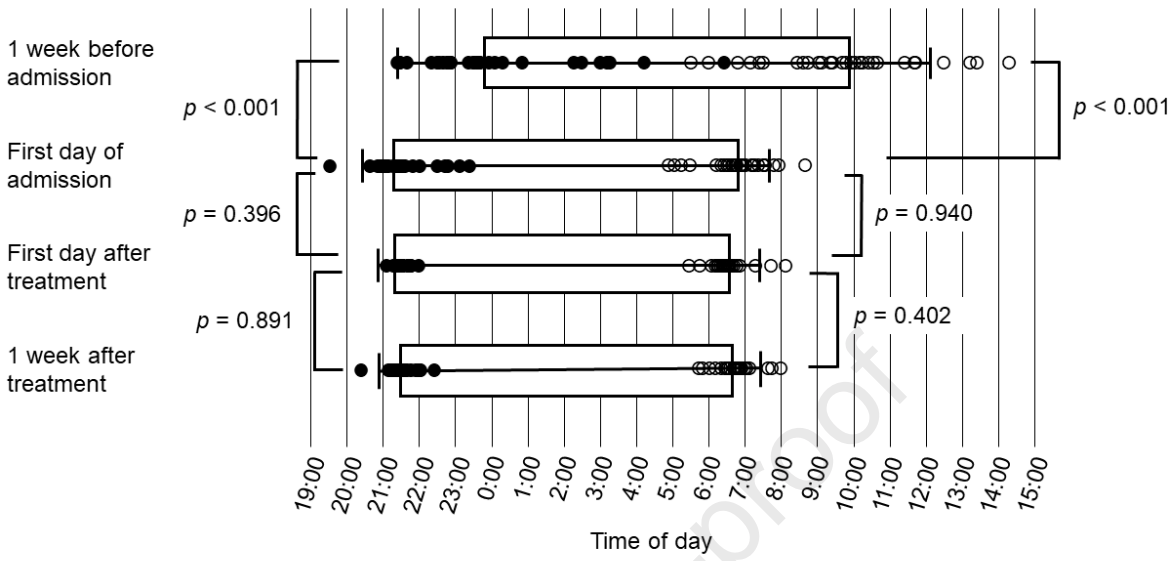
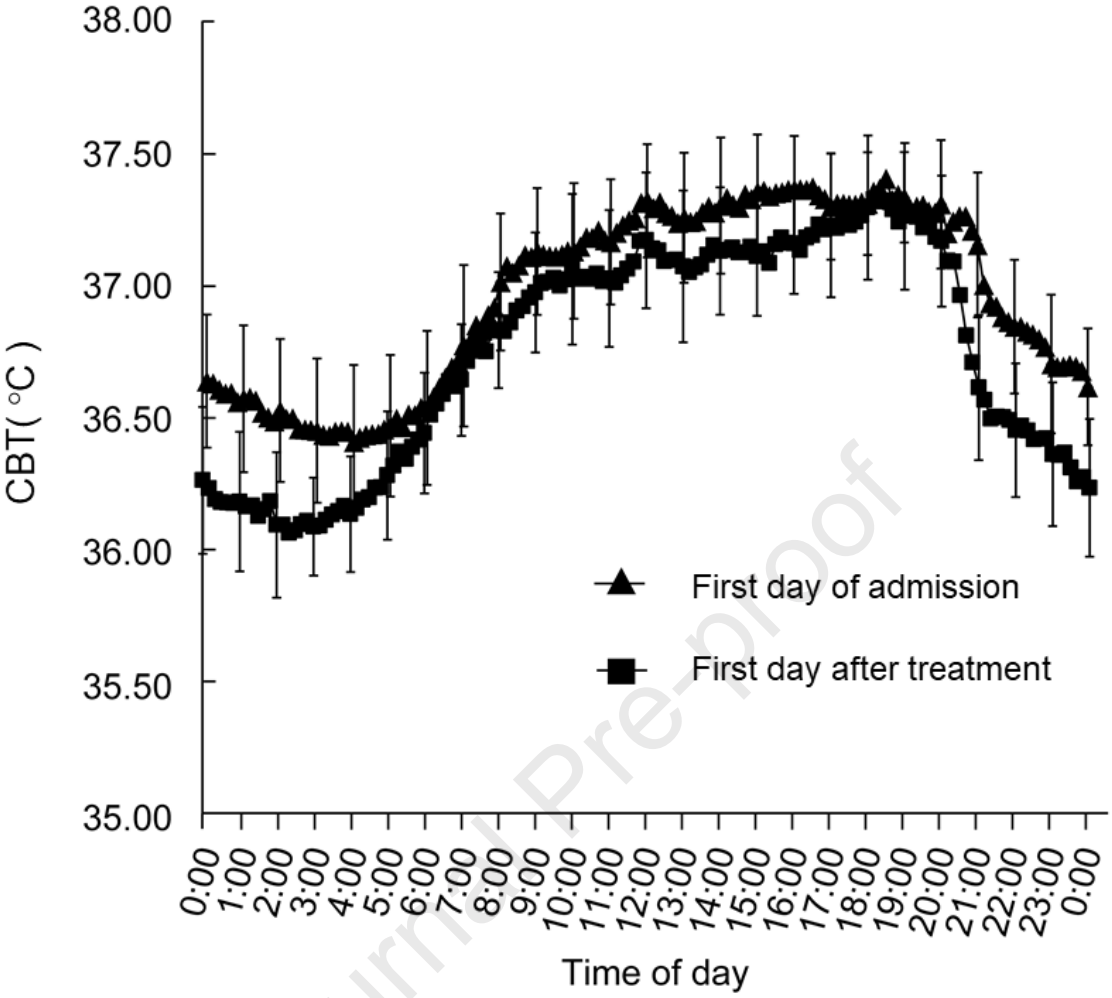


Figure 3. Change in mean CBT values from the first day of admission to the first day after treatment for 24 hours (a), awakening (b), and sleeping (c)

After excluding the outliers in CBT, paired Student's *t*-tests were used for analysis. CBT, core body temperature; SD, standard deviation.







Highlights

- Improvements in sleep disorder post-treatment decrease core body temperature.
- High core body temperature during sleep indicates high brain activity.
- The time to reach the minimum core body temperature occurred earlier after treatment.
- Core body temperature is a biomarker for improved sleep disorder.

Credit Author Statement

S. Kimura designed the study and obtained funding. S. Kimura, M. Toyoura, and S. Kohira collected data. Y. Takaoka and M. Ohta analyzed and interpreted the data. S. Kimura wrote original draft of the manuscript. Y. Takaoka, M. Toyoyra, and M. Ohta contributed to writing the paper. All authors read and approved the final manuscript.