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SCIENTIFIC INVESTIGATIONS

Serum concentrations of insulin-like growth factor-1 as a biomarker of improved circadian rhythm sleep-wake disorder in school-aged children

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Study Objectives: We aimed to investigate whether improvements in the symptoms of circadian rhythm sleep-wake disorder after treatment were associated with an increase in serum insulin-like growth factor-1 (IGF-1) concentration.

Methods: Eighty-seven school-aged children (32 males, 55 females), aged 14.31 ± 1.50 years (mean ± standard deviation), who were admitted to our hospital with circadian rhythm sleep-wake disorder received treatment for 6–8 weeks consisting of the following protocol: (1) lights-out for sleep occurred at 21:00, (2) phototherapy for waking started at 06:00 or 07:00, and (3) light exercise was required every day (eg, a 20- to 30-minute walk). Blood samples were collected at 08:00 AM to measure the serum concentrations of IGF-1, pre- and posttreatment.

Results: The mean times of day of sleep onset and offset at the pre- and posttreatment timepoints were 23:32 ± 4.21 and 10:27 ± 2.98, and 21:26 ± 0.55 and 06:50 ± 0.70, respectively. The mean times of day of sleep onset and offset measured at the posttreatment timepoint were significantly earlier compared with the pretreatment baselines ($P < .01$). The mean serum levels of IGF-1 significantly increased from 315.59 ± 68.26 ng/mL at pretreatment to 335.09 ± 69.78 ng/mL at posttreatment ($P < .01$).

Conclusions: Improvements in the symptoms of patients with circadian rhythm sleep-wake disorders were associated with increased serum concentrations of IGF-1, suggesting that serum IGF-1 may be a biomarker of improvements in school-aged children with circadian rhythm sleep-wake disorder.

Keywords: insulin-like growth factor-1, circadian rhythm sleep-wake disorder, therapeutic effect, biomarker, school-aged children

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Growth hormone stimulates insulin-like growth factor-1 (IGF-1) production in the liver and other tissues; its secretion is characterized by pulsatile circadian rhythms, with concentrations peaking during nighttime hours and daily fluctuations in IGF-1 levels remaining relatively stable. However, several studies have reported increased serum IGF-1 levels in children with obstructive sleep apnea (OSA) posttreatment, including tonsillectomy and adenotonsillectomy, but its role in circadian rhythm sleep disorders is unknown.

Study Impact: After admission and treatment at our hospital, patients with circadian rhythm sleep-wake disorder, some of whom also had autism spectrum disorder, exhibited significantly increased serum IGF-1 concentration posttreatment, suggesting that serum IGF-1 levels could be a biomarker of improvements after circadian rhythm sleep-wake disorder treatment.

INTRODUCTION

Growth hormone (GH) stimulates insulin-like growth factor-1 (IGF-1) production in the liver and other tissues,[1] and its secretion is characterized by a pulsatile circadian rhythm, with concentrations peaking during nighttime hours.[2,3] Circulating concentrations of IGF-1 are strongly related to diurnal GH secretion, reflecting mean daily GH levels, and are correlated with physiologic changes in GH secretion.[4] However, daily variations in IGF-1 levels are relatively stable when compared with the daily variations in GH levels.[5] Quantifying IGF-1 concentration is complicated by the wide range of normal basal levels, and marked variability in concentrations is observed based on age and sex. IGF-1 is often useful as a biomarker for several types of pituitary disease, undernutrition, and growth problems,[6–8] and physicians often use IGF-1 levels as a biomarker during screening tests for GH deficiency in patients of short stature. It is also a useful biomarker for acromegaly and gigantism[9] and for hyperthyroidism,[10] which are associated with high IGF-1 concentrations.

Pediatric OSA may occasionally lead to life-threatening complications, but less serious complications, such as failure to thrive, are more commonly recognized.[11] To explain this latter observation, it has recently been reported that serum levels of IGF-1 in children with OSA are increased after surgery, including tonsillectomy and adenotonsillectomy,[12–14] and when they are treated using continuous positive airway pressure (CPAP).[15] This finding highlights the association between OSA and reduced levels of IGF-1.[16,17]

Disruptions during sleep, such as in OSA, can affect GH and IGF-1 levels because GH is preferentially released during slow-wave sleep,[18] which is also reduced in OSA.[19] Other sleep issues

can also affect GH/IGF-1. Total sleep deprivation in twelve healthy men, aged 29.1 ± 3.3 years is transiently associated with a decrease in the concentration of circulating free IGF-1, which is restored after 1 night of recovery, concomitant with an increase in total IGF-1 concentration.[20] In addition, a delay in sleep can result in a decrease in GH secretion.[21] In circadian rhythm sleep-wake disorders there is a desynchronization between one's internal sleep-wake rhythms and the light-darkness cycle. Individuals with circadian rhythm sleep-wake disorders are unable to naturally go to sleep or wake up at the time necessary for their work, school, or social obligations. In delayed sleep-wake phase disorder, people fall asleep several hours after they intended to, and in advanced sleep-wake phase disorder the sleep and waking times are shifted several hours earlier than the desired or customary time. Two other types of circadian rhythm sleep-wake disorders are an irregular sleep-wake rhythm, in which people do not have a clear circadian rhythm, and a non-24-hour sleep-wake rhythm, in which a person's natural circadian rhythm does not align with the 24-hour day.[22] Any of these disruptions in sleep can affect GH and IGF-1 levels.[21]

Sleep problems are common in autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD).[23] Sleep-onset insomnia or difficulty initiating sleep (increased sleep latency or time to fall asleep) and sleep-maintenance insomnia (decreased sleep duration, decreased sleep continuity, and increased and early awakenings) are the most common sleep problems reported in ASD. Several studies on ADHD have reported that the most frequent sleep problems are sleep-onset insomnia, increased nighttime awakenings, snoring, parasomnias and nightmares, short total sleep time, and subsequent daytime sleepiness.[23] However, many studies have reported that behavioral problems related to ASD and ADHD are associated with circadian dysregulation[24,25] and that they can be ameliorated by normalizing these rhythms.

There is currently no biomarker of circadian rhythm sleep-wake disorder from blood and urine samples to assess the therapeutic effects, despite the obvious need for one. Therefore, this study aimed to investigate the possibility of using IGF-1 concentrations as a biomarker not only for OSA but also for circadian rhythm sleep-wake disorders. We hypothesized that treatment of circadian rhythm sleep-wake disorders would be associated with an increase in IGF-1.

METHODS

Patients

A total of 2,401 patients between 6 months to 18 years of age visited the pediatric department of our hospital for treatment of a sleep disorder from April 2017 to March 2019. Of those patients, 143 were admitted for further examination (ie, polysomnography, multiple sleep latency tests) but received treatment for < 6 weeks because they did not stay for the full recommended 6- to 8-week treatment protocol. An additional 105 patients with circadian rhythm sleep-wake disorders were admitted, some of whom were truant from school because of sleep disorders that left them unable to wake up on time for school, who then participated in a 6- to 8-week treatment specially designed for circadian rhythm sleep-wake disorders. Eighteen of these patients were unable to continue hospitalization because of difficulties in being in a hospital setting. Therefore, a total of 87 patients completed the sleep protocol, 64 of whom were truant from school. The patients who received 6–8 weeks of treatment had a more severe delayed sleep-wake phase disorder than those who received < 6 weeks of treatment.

This was a retrospective study, analyzing the medical records of patients diagnosed with circadian rhythm sleep-wake disorder who were admitted and treated in our hospital from April 2017 to March 2019. The study was approved by the independent ethics committee of our hospital and conformed with the tenets 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 a comprehensive informed consent was also obtained from the participants' families. The 87 patients who completed the protocol participated in the study.

Protocol for the treatment of circadian rhythm sleep-wake disorders

The admitted patients underwent inpatient treatment for the entire 6–8 weeks. The protocol consisted of the following interventions: (1) lights-out time for sleep at 21:00; (2) phototherapy to induce waking, starting at either 06:00 or 07:00; and (3) 20–30 minutes per day of light exercise (eg, walking). Occupational therapists assisted with exercise, clinical psychologists provided counseling, nurses educated 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 sleep diary[26] completed by the participants was used to collect information about sleep (total sleep time, interrupted sleep, naps, and level of deep sleep), headache symptoms, light exercise, study, and diet.

Our protocol was developed specifically for circadian rhythm sleep-wake disorders in children who are truant. Other programs have reported 3-week treatment protocols using phototherapy.[27] In patients for whom a 3-week therapy was implemented, we had found that after the patients left the hospital, their sleep disorders gradually returned to the same state as before their admission. Accordingly, we designed a longer treatment intervention. During the 6- to 8-week protocol, we discussed with patients, along with their family and a social worker, the plan for when they would leave the hospital: for example, whether they would return to school or if alternate plans were needed once they were discharged. We thereby found that more than 3 weeks were required and that the treatment effects using our protocol were longer-lasting (data not shown).

If a patient's sleep disorder did not improve, then a pharmacological intervention was introduced, including melatonin (a hormone that regulates sleep-wake cycles) to induce sleep,[28] suvorexant (a dual orexin receptor antagonist) to induce sleep and decrease sleep interruptions,[29] and risperidone (an atypical antipsychotic agent), which increases slow-wave sleep and improves light sleep (ie, decreases interrupted sleep) and was also used in case of irritability and aggression, particularly in participants with ASD.[30]

Examination

All patients were surveyed and classified according to the *International Classification of Sleep Disorders*, 3rd edition[31]

into 1 of the circadian rhythm sleep-wake disorder categories upon admission to the hospital. Information regarding an existing ASD or ADHD diagnosis was also collected during admission. In addition, we noted information in the medical records that resembled some characteristics of ASD (eg, impaired social interactions, limited and repetitive interests and behavior, irritability, and aggression). For all patients, when admitted to the hospital and when discharged, blood samples were collected at 08:00 AM 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, triglycerides, thyroid-stimulating hormone, free-triiodothyronine, and free-thyroxine. Polysomnography (described in the paragraph below) was performed at admission. Height and weight were measured at the pre- and posttreatment timepoints to calculate the Rohrer index. This index, which is commonly used to evaluate the physical constitution of Japanese schoolchildren,[32] was calculated as body weight (g)/height (cm^3). The times of sleep onset and offset, total sleep duration, number and duration of the periods in which patients awoke from sleep, and number and duration of napping periods were assessed using sleep logs spanning a period from 1 week before and for 1 week after the treatment. Daily means and standard deviations were calculated over these two 1-week periods.

Polysomnography

In a dedicated private room of our pediatric ward, standard overnight polysomnography was performed for each patient, consisting of 2 electroencephalograms, 2 electrooculograms, 1 submental electromyogram, 2 anterior tibialis muscle electromyograms, and respiratory measures (Pro-Tech Body position sensors, Phillips/Respironics Murrysville, PA, USA). The AHI was defined as the average number of apnea and hypopnea episodes experienced per hour.

Phototherapy

For phototherapy,[33] the light was directed onto patients from a distance of 1 m (Circadian Control NQ71, Panasonic, Osaka, Japan); this faint light exposure started 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 then the light gradually became dimmer over the course of 1 hour before finally turning off.

Statistical analysis

Microsoft Excel version 2016 (Microsoft, Redmond, WA) was used to perform all the statistical analyses except for the Rohrer index calculation. Paired Student *t* tests were used to compare normally distributed data—ie, serum IGF-1 and albumin levels, mean difference in IGF-1 concentrations between post- and pretreatment timepoints in patients who were administered melatonin, total sleep duration, and Rohrer indices. A nonparametric Mann-Whitney *U* test was used to compare data with skewed distributions—ie, the time of sleep onset and offset, the number and average duration of awakenings from sleep, and the number and average duration of daytime naps. *P* values < .05 from 1-sided tests were considered statistically significant. The Pearson correlation coefficient was used to assess the associations between the variables, pre- and posttreatment, for the multilevel analysis based on sex. Both a positive 0.8 and a negative –0.8 indicated equally strong correlations, except in opposite directions. The Rohrer index was calculated using the Rohrer index calculator (http://www.math.kobe-u.ac.jp/HOME/kodama/tips-BMI.html).

Two types of multilevel analyses were performed. Three models (male, female, and male and female combined) were tested to assess whether age was associated with the difference between pre- and posttreatment IGF-1, albumin, time of sleep onset and offset, and total sleep time. In addition, a multivariate analysis of variance and *t* tests were used to compare 5 groups of patients based on the IGF-1 level change: patients with a large IGF-1 level increase (n = 3; rate of change [RC] posttreatment/pretreatment > 1.46); those with an IGF-1 level increase (n = 50; 1.04 < RC < 1.46); those with no IGF-1 level change (n = 11; 0.96 < RC < 1.04); those with an IGF-1 decrease (n = 22; 0.70 < RC < 0.96); and those with a large IGF-1 level decrease (n = 1; RC < 0.70). The multivariate analysis of variance and *t* tests assessed the differences in the following predictor and outcome variables: AHI; the difference between pre- and posttreatment heights, weights, Rohrer indices, and serum albumin levels; the time of sleep onset and offset; the total sleep time; the average durations of awakenings from sleep; and the average durations of naps. The multivariate analysis of variance and *t* tests were calculated using the mean of each variable.

RESULTS

The 87 participants primarily had delayed sleep-wake phase disorder (83.9%; n = 73), although a non-24-hour sleep-wake rhythm disorder (10.3%; n = 9) and an irregular sleep-wake phase disorder (5.7%; n = 5) were also present. Sixty-four of the 87 participants had confirmed truancy.

The means and standard deviations of the height, weight, Rohrer index, and AHI of each patient are shown in **Table 1.** The mean Rohrer index of male patients, female patients, and all patients was 120.31 ± 3.66 g/cm^3, 153.07 ± 2.71 g/cm^3, and 140.57 ± 3.02 g/cm^3, respectively, upon admission to our hospital. Seven patients had scores > 160 g/cm^3, indicating obesity, and 4 had scores < 100 g/cm^3, indicating being underweight. The mean Rohrer index of all patients at the posttreatment timepoint was 131.40 ± 3.87 g/cm^3. There was no difference in the average Rohrer index of all participants between the pre- and posttreatment timepoints (P = .381). The mean AHI of all participants was 0.55 events/h, and the highest AHI was 3.60 events/h, which is well within the none/minimal range of possible OSA. None of the participants had undergone surgery (eg, bilateral tonsillectomy, adenoidectomy) and none were treated with CPAP.

The number of patients diagnosed with ASD, ADHD, or ASD with ADHD was 14, 4, and 6, respectively; however, 74 of the 87 patients had comments in their medical records noting behaviors characteristic of ASD. The numbers of patients who complained of headaches, abdominal pain, and dizziness on admission were 60, 49, and 49, respectively. Seventy-two patients were administered melatonin, 58 received risperidone,

and 12 were given suvorexant before sleep at least once during their admission.

The times of sleep onset significantly improved from 23:32 ± 4.21 to 21:26 ± 0.55, as did the times of sleep offset, from 10:27 ± 2.98 to 06:50 ± 0.70 ($P < .01$) (**Table 2**). The mean total sleep duration measured at the pretreatment timepoint was significantly longer compared with the posttreatment timepoint (9.89 ± 1.96 hours and 9.37 ± 0.83 hours, respectively; $P = .016$) (**Table 2**).

The mean number of awakenings from sleep at the pre- and posttreatment timepoints was 0.11 and 0.22 episodes/night, respectively ($P = .716$), and the mean duration of the periods of awakening from sleep at the pre- and posttreatment timepoints was 7.00 and 6.38 minutes/night, respectively ($P = .946$). The number of awakenings increased by more than 0.5 episodes/day, and the duration of the awake periods was longer than 20 minutes/day in 3 patients after treatment, compared with the pretreatment baselines.

The mean number of daytime naps significantly decreased from 0.07–0.02 episodes/day ($P < .01$), and the mean duration of the nap periods also significantly decreased from 10.21–0.94 minutes/day ($P < .01$) after treatment, compared with the pretreatment baselines.

No patients had liver or kidney dysfunction or hyperthyroidism, based on the blood sample analysis. The serum IGF-1 concentrations increased significantly in male patients from 333.00 ± 53.32 ng/mL to 349.56 ± 64.42 ng/mL ($P < .01$) and in female patients from 305.45 ± 61.90 ng/mL to 326.67 ± 58.61 ng/mL ($P < .01$; **Table 2**). The mean concentration of serum IGF-1 from all patients (both male and female patients) significantly increased between the pre- and posttreatment timepoints (315.59 ± 68.26 ng/mL to 335.09 ± 69.78 ng/mL; $P < .01$). There was no difference in the serum albumin concentrations between the pre- and posttreatment timepoints (4.70 ± 0.52 ng/mL and 4.65 ± 0.60 ng/mL; $P = .239$; **Table 2**).

A multilevel analysis of variance assessing age and the difference between the pre- and posttreatment IGF-1 level, albumin level, time of sleep onset and offset, and total sleep time in the 3 groups based on sex showed that age was positively correlated with the time of sleep offset in the male group ($r = 0.32$). However, there were no correlations among the other groups and factors ($r < 0.20$). Another multilevel analysis between the 5 groups—which had significant differences among them ($P < .01$)—based on IGF-1 changes revealed that the average height of the group in which the IGF-1 increased was significantly higher than that of the group in which the IGF-1 decreased ($P < .05$). However, there were no differences between the 5 groups in terms of AHI, the difference between pre- and posttreatment weight, Rohrer indices, serum albumin, time of sleep onset and offset, total sleep time, average duration of awakenings from sleep, and average duration of naps ($P > .05$).

DISCUSSION

Nearly all of the patients in our study were truant from school because of circadian rhythm sleep-wake disorders that left them unable to awaken on time for school. Of these patients, 26 were diagnosed with ASD and/or ADHD at admission. The circadian rhythm sleep-wake disorders of our patients, particularly delayed sleep-wake phase disorder, meant that their sleep pattern was delayed, causing them to both go to sleep and wake up later. This disorder frequently results from excessive online gaming, watching YouTube, using smartphones and computers, studying late at night for school, and being involved in club activities late after school.[34]

The times of sleep onset significantly improved between the pre- and posttreatment timepoints from 23:32 ± 4.21 to 21:26 ± 0.55, as did the time of sleep offset, from 10:27 ± 2.98 to

Table 1—Characteristic data (mean ± SD) of patients with sleep disorders.

	n	Age (y)	Height (cm)	Weight (kg)	Rohrer Index (g/cm^3)	AHI (events/h)
Male	32	14.08 ± 1.11	162.43 ± 10.43	51.64 ± 12.65	120.31 ± 3.66	0.83 ± 0.85
Female	55	14.64 ± 1.70	155.80 ± 6.81	51.37 ± 10.38	153.07 ± 2.71	0.39 ± 0.39
Total	87	14.31 ± 1.50	158.24 ± 8.83	51.47 ± 11.13	140.57 ± 3.02	0.55 ± 0.63

SD = standard deviation.

Table 2—Differences in sleep parameters and serum protein concentrations before and after treatment.

	Pretreatment (mean ± SD)	Posttreatment (mean ± SD)	*P* Value
IGF-1 (ng/mL)			
Male	333.00 ± 53.32	349.56 ± 64.42	< .01[a]
Female	305.45 ± 61.90	326.67 ± 58.61	< .01[a]
Total	315.59 ± 68.26	335.09 ± 69.78	< .01[a]
Serum albumin concentration (g/dL)	4.70 ± 0.52	4.65 ± 0.60	.239[a]
Time of day of sleep onset	23:32 ± 4.21	21:26 ± 0.55	< .01[b]
Time of day of sleep offset	10:27 ± 2.98	06:50 ± 0.70	< .01[b]
Total sleep duration (h)	9.89 ± 1.96	9.37 ± 0.83	.016[a]

[a]Student *t* test. [b]Mann-Whitney *U* test. IGF-1 = insulin-like growth factor-1, SD = standard deviation.

06:50 ± 0.70. A consensus statement of the American Academy of Sleep Medicine recommends that children aged 6–12 years should sleep for 9–12 hours per day and that teenagers aged 13–18 years should sleep for 8–10 hours.[35] Whereas most patients were truant from school, if they did attend school, then they needed to go to bed at approximately 22:00 and wake up at approximately 07:00. The patients were provided enough time to go to school after receiving the treatment. We focused on the larger standard deviation of the time of sleep onset and offset from pretreatment to posttreatment. These results showed that the times of sleep onset and offset were highly variable before treatment; however, the circadian rhythms normalized after treatment. Consequently, almost all headaches, abdominal pain, and dizziness reported by the patients upon admission were reduced after treatment,[36] suggesting that our treatment paradigm was effective.

Serum IGF-1 concentrations can vary according to age, sex, malnutrition, pituitary disease, GH deficiency in patients of short stature, and acromegaly and giantism, which are associated with high IGF-1 concentrations. The IGF-1 levels of both male and female patients significantly increased after treatment. None of the patients had a pituitary disease because their IGF-1 serum levels were all normal. As to whether this increase resulted from a change in nutrition, there was no significant difference in the Rohrer index between the pre- and posttreatment timepoints, suggesting that there was no significant change in the patients' diet. Blood sample analyses of the serum protein and total cholesterol levels were normal at both the pre- and posttreatment timepoints; the level of serum albumin, which is an indicator of malnourishment, was normal in all patients and did not differ between the pre- and posttreatment timepoints. Therefore, the increase in IGF-1 concentration was not associated with nutrient intake.

IGF-1 concentrations can vary by age; however, in teenagers aged 13–15 years, there tends not to be a lot of variability. For example, Isojima et al[8] previously reported that the mean IGF-1 levels of male patients at ages 13, 14, and 15 years in Japan were 315 ng/mL, 315 ng/mL, and 310 ng/mL, respectively; for females, IGF-1 levels were 349 ng/mL, 344 ng/mL, and 341 ng/mL at ages 13, 14, and 15 years, respectively. The mean ages of the male and female patients in our study were 14.08 ± 1.11 and 14.64 ± 1.70 years, respectively. The mean IGF-1 concentration in male patients was 333 ± 53.31 ng/mL pretreatment and 349.56 ± 64.42 ng/mL posttreatment; for female patients, IGF-1 levels were 305.45 ± 61.90 pretreatment and 326.67 ± 58.61 ng/mL posttreatment. Because the duration of treatment was only 6–8 weeks, it was unlikely that the age progression was responsible for the changes in the IGF-1 levels in these patients.

A few studies have reported that melatonin levels are directly related to IGF-1 concentrations.[37] Seventy-two patients in this study were administered melatonin at least once during treatment. The mean difference in IGF-1 concentrations between the post- and pretreatment timepoints in the patients who were administered melatonin was 18.01 ± 53.64, whereas for patients who did not receive melatonin, the mean difference was 17.78 ± 51.45; there was no statistically significant difference between these 2 groups (P = .215). The mean IGF-1 concentrations at pretreatment were 314.96 ± 66.13 and 314.50 ± 78.15, respectively. Relationships between risperidone and IGF-1 concentrations and suvorexant and IGF-1 concentrations have not been reported. Therefore, the observed increase in IGF-1 concentrations posttreatment is unlikely to have been related to the medication the patients received during their treatment.

IGF-1 is an essential neurotrophic factor for brain development and plasticity. Neurons derived from patients with ASD display abnormal neurogenesis and reduced synaptogenesis, leading to functional defects in neuronal networks; interestingly, these neuronal network defects could be caused by decreased levels of IGF-1.[38] Moreover, it has been reported that the concentration of IGF-1 in the cerebrospinal fluid of patients with autism is low.[24] Because the current study was retrospective and had a heterogeneous cohort (eg, ADHD, ASD, and medications), prospective controlled studies are needed in the future to ascertain the relationship between these factors and IGF-1.

Peak serum GH concentrations typically last 1.5–3.5 hours, resulting in a stimulated production of IGF-1 coinciding with the onset of deep sleep[39]; this peak does not depend on the time of sleep onset but on maximal GH release that occurs within minutes of the onset of stage 3 or 4 sleep.[40,41] Increased IGF-1 levels could be indicative of improved quality of sleep by the maintenance of regular circadian rhythms of sleep, and our patients felt that they slept better compared to the pretreatment baseline measures.

CONCLUSIONS

This is the first study to report that increased concentrations of serum IGF-1 are associated with an improvement in symptoms of circadian rhythm sleep-wake disorders. It is possible that the increase in IGF-1 could be an incidental finding not related to sleep. However, according to our multilevel analysis, other factors (without IGF-1) were not associated with the improvement of circadian rhythm sleep-wake disorders, although the average height of the group in which IGF-1 increased was significantly higher than that of the group in which IGF-1 decreased. Future studies are needed to further explore additional factors. We conclude that IGF-1 is a biomarker of not only OSA, but also of circadian rhythm sleep-wake disorder.

ABBREVIATIONS

ADHD, attention deficit hyperactivity disorder
ASD, autism spectrum disorder
CPAP, continuous positive airway pressure
GH, growth hormone
IGF-1, insulin-like growth factor-1
OSA, obstructive sleep apnea
RC, rate of change

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