

うつ病、ひきこもり、学業成績低下など近年の高校生の様々な問題に睡眠不足が大きく影響していると推察される。その対策として最も簡単で実行できるのが昼休みの短時間の午睡であり、この有用性を明確にし、より詳細に具体的な方法を確立することによって、学校現場で実実に指導することが可能となる。

今回の研究結果より、昼休みに午睡をした者は午後の眠気が軽減し、授業に集中でき、学習効果や体調の維持につながることを示唆され、実施者本人も午睡の効果を強く実感していた。また、週3回以上午睡をした者はそれに加え、昼間の活動性が向上し、夜間の就寝時刻が一定となり、夜間の熟睡感は増し、目覚めも改善し、朝の起床時刻も一定となった。その結果、午前中の眠気も軽減し、1日の規則正しい生活リズムを確立することが可能になると推察される。

本邦では午睡の効用についての介入研究は未だ行われていない。十分な睡眠を必要とする高校生の多くが睡眠不足にあり、日中に我慢できない眠気を感じている中で、短時間の午睡の効果を明らかにすることは大変意義深いと思われる。特に本研究で示唆された週3回以上の午睡が特に有用であるという結果は学校あるいは臨床現場で指導していく上で重要であると思われる。

<結論>

昼休みに15分間午睡をすることによってそれ以後の眠気が減少し、午後の授業だけでなく、帰宅後の学習にも集中できた。また、週3回以上実施した者は昼夜のメリハリのある規則正しい生活リズムが確立し、夜の睡眠も深くなる。

<健康危険情報>

高校生の睡眠不足は午後の眠気を増大し、意欲低下、集中力低下などを認め、学力低下を引き起こし、また、QOLの低下を生じる。そのため昼食後の午睡を施行することに

よって眠気が軽減し、学力の向上やQOLの改善につながる。

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<知的財産権出願・登録状況>

なし

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研究成果の刊行に関する一覧表

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IV. 研究成果の別刷

Clinical Analyses of Sighted Patients with Non-24-Hour Sleep-Wake Syndrome: A Study of 57 Consecutively Diagnosed Cases

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Study Objectives: The objective of this study was to clarify the clinical features of sighted patients with non-24-hour sleep-wake syndrome.

Design: Clinical analyses of consecutive patients suffering from non-24-hour sleep-wake syndrome.

Setting: The sleep disorders clinic at Kohnodai Hospital, National Center of Neurology and Psychiatry, Japan.

Patients: Fifty-seven patients who were diagnosed consecutively as having non-24-hour sleep-wake syndrome between 1991 and 2001 were included in the study.

Measurements and Results: The clinical features and sleep characteristics of the patients were analyzed. A semistructured psychiatric interview that included the criteria for Axis I or II disorders of Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised was conducted, and relationships between psychiatric problems and non-24-hour sleep-wake syndrome were analyzed. The patient cohort included 41 (72%) men and 16 (28%) women. The onset of non-24-hour sleep-wake syndrome had occurred during the teenage years in 63% of the cohort, and the mean

(\pm SD) period of the sleep-wake cycle was 24.9 ± 0.4 hours (range 24.4-26.5 hours). The mean sleep length of the patients was 9.3 ± 1.3 hours, and 44% of them had a sleep length of between 9 and 10 hours. Psychiatric disorders had preceded the onset of non-24-hour sleep-wake syndrome in 16 patients (28%); of the remaining 41 patients, 14 (34%) developed major depression after the onset of non-24-hour sleep-wake syndrome.

Conclusions: These results represent the first detailed clinical review of a relatively large number of sighted patients with non-24-hour sleep-wake syndrome.

Keywords: Non-24-hour sleep-wake syndrome, circadian rhythm, evening type, sleep disorder, delayed sleep-phase syndrome, psychiatric disorder, mood disorder, depression

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INTRODUCTION

THE ENVIRONMENTAL LIGHT-DARK CYCLE IS THE STRONGEST SYNCHRONIZER OF THE CIRCADIAN RHYTHM IN HUMANS AND OTHER ANIMALS.¹ Individuals who live isolated from a normal 24-hour light-dark cycle exhibit a sleep-wake cycle that is longer than 24 hours.^{1,2} This long cycle leads to progressively later spontaneous bedtimes and wake times.

Non-24-hour sleep-wake syndrome (non-24-hour sleep-wake syndrome) is a rare condition that is characterized by a chronic steady pattern of about 1-hour delays in spontaneous sleep-onset and wake times in individuals living under normal environmental conditions.³ The *International Classification of Sleep Disorders (ICSD)*³ provides the following criteria for diagnosing non-24-hour sleep-wake syndrome in a clinical setting: (1) primary complaint of either difficulty initiating sleep or difficulty in

awakening, (2) progressive delays of sleep onset and offset with the inability to maintain stable entrainment to a 24-hour sleep-wake pattern, and (3) presence of the sleep pattern for at least 6 weeks.

Some previous clinical reports⁴⁻³⁶ have described individual or a few patients with non-24-hour sleep-wake syndrome. One study documented 322 patients having circadian rhythm sleep disorders, including 39 patients with non-24-hour sleep-wake syndrome, and reported some clinical characteristics of circadian rhythm sleep disorders as a whole.³⁷ However, so far there has been no published study analyzing a large number of patients suffering from non-24-hour sleep-wake syndrome. According to the ICSD,³ the clinical characteristics of non-24-hour sleep-wake syndrome, such as age at onset, sex ratio, or familial pattern, have not been clarified. In addition, the etiologic factors that affect the development of non-24-hour sleep-wake syndrome remain to be elucidated. Although there is little question that blindness is a strong predisposing factor for non-24-hour sleep-wake syndrome,³ the pathogenetic mechanisms underlying the development of the disorder in sighted humans have not been established.^{3,38,39} Psychiatric disorders are thought to be associated with non-24-hour sleep-wake syndrome in sighted patients,^{12,20,23,26,35} but no detailed clinical investigation has been carried out to confirm this causality. In the study presented here, we recruited patients with circadian rhythm sleep disorders to obtain a large cohort of sighted people with non-24-hour sleep-wake syndrome and studied their clinical features.

Disclosure Statement

This was not an industry supported study. Drs. Uchiyama, Hayakawa, Kamei, Shibui, Tagaya, Asada, Okawa, and Takahashi have indicated no financial conflicts of interest.

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SUBJECTS AND METHODS

Recruitment of Patients

Subjects were recruited for the present study by advertising in the media for people who had sleep problems due to a delay or an advance of the major sleep phase, an irregular sleep phase, or an incapacity to synchronize to a 24-hour day, as well as by giving information on circadian rhythm sleep disorders to general physicians and psychiatrists in the neighboring cities. We then sent a 6-week sleep-log form to be completed by the responders, together with a questionnaire comprising questions on sleep habits and psychosocial status. Thereafter, those who returned the sleep log and questionnaire were referred to our sleep disorders clinic at Kohnodai Hospital, National Center of Neurology and Psychiatry. Among the participants who visited the sleep disorders clinic of the institute for treatment between 1991 and 2001, 392 were diagnosed according to the ICSD criteria as having circadian rhythm sleep disorders by sleep disorder specialists (TH, YK, MU, and MO). After an observation period (4–6 weeks) when no therapeutic interventions were conducted, treatments of circadian rhythm sleep disorders were initiated. The study protocol was approved by the Institutional Review Board of the National Center of Neurology and Psychiatry, and each subject gave his or her informed consent after the procedures and the possible risks of the experiment had been explained in detail.

Diagnostic Procedures

Diagnoses were made by applying the ICSD criteria for non-24-hour sleep-wake syndrome. On the first visit, we asked the patients to keep a detailed sleep log for at least 4 to 6 weeks, together with actigraphic assessment for a consecutive 2-week period (Mini-Motionlogger, Ambulatory Monitoring Inc., Ardsley, NY). Of the 392 patients who were diagnosed as having circadian rhythm sleep disorders, 41 men and 16 women (26.2 ± 8.5 years, mean \pm SD) were diagnosed as having non-24-hour sleep-wake syndrome. The onset of non-24-hour sleep-wake syndrome was defined as the time when free running of the sleep-wake cycle began. An ophthalmologic specialist (KS) found no ophthalmologic abnormalities, except for myopia. Three psychiatrists (TH, YK, and MU) conducted a semistructured psychiatric interview,³⁸ which included the criteria for Axis I or II disorders of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised*⁴⁰ and an assessment of social functioning (descriptive form). Histories of shift work, psychiatric problems, physical problems, and preceding sleep disorders, as well as family history of circadian rhythm sleep disorders and psychiatric and neurologic disorders, were also investigated and reviewed by the psychiatrists. The clinical backgrounds of the patients are shown in Table 1.

All of the patients underwent examinations performed by the general physicians at the hospital, together with blood counts, urine examinations, serum biochemistry, electrocardiography, routine electroencephalography, and brain computed tomography or magnetic resonance imaging.

Evaluation of Sleep Log

Inspecting the sleep logs during the 4 to 6 weeks of the observation period from the first visit, 2 raters independently determined sleep onset and offset times in 30-minute bins. All the pa-

Table 1— Characteristics of 57 Consecutive Patients Diagnosed With Non-24 Hour Sleep-Wake Syndrome*

Characteristic	No. (%)
Sex	
Men	41 (72)
Women	16 (28)
Age at onset, y	
mean \pm SD	20.2 \pm 7.0
< 10	0 (0)
10-19	36 (63)
20-29	13 (23)
30-39	6 (11)
40-49	2 (3)
Marital status	
Married	6 (11)
Unmarried	51 (89)
Presence of family or roommate	
Yes	45 (79)
No	12 (21)
Social status at first visit	
Student	20 (35)
Employed	12 (21)
Part-time worker	3 (5)
Unemployed	22 (39)
Premorbid status	
Psychiatric problems	16 (28)
Physical problems	1 (2)
Delayed sleep-phase syndrome	15 (26)
Family history of mental, sleep, or neurologic disorder	
Yes	5 (9)
No	52 (91)

*Data are presented as number (%) unless otherwise indicated.

tients visited us when they were able to sleep during the nighttime and stay awake during the daytime. A delay of sleep onset longer than 4 hours per day was defined as a delayed phase jump. The patient was considered as a delayed-phase jumper when delayed-phase jumps were recognized at least 4 times per month during the observation period. Regression lines were fitted through the sleep-onset times for the 4 weeks from the first visit. The periods of the sleep-wake cycles were computed by adding the slope of the regression line of sleep-onset times to 24 hours.³⁸ A rhythm was considered not to be entrained to a 24-hour day when the 95% confidence intervals of the period did not cross 24 hours.

Evaluation of Actigraphic Data

Excluding missing data, we obtained at least 10 consecutive days of actigraphic data during the 2-week actigraphic assessment that started from the first visit (the first 2 weeks of the observation period). Based on automatically generated data (Action3 software, Ambulatory Monitoring, Inc.), sleep onset and offset times and sleep length were calculated in 5-minute bins. To calculate the period of the sleep-wake cycle based on the 10 days of actigraphic assessment, regression lines were fitted through the sleep-onset times in a manner similar to that described above (Figure 1).

Statistical Analyses

Statistical analyses were performed with Statview 5 for a Ma-

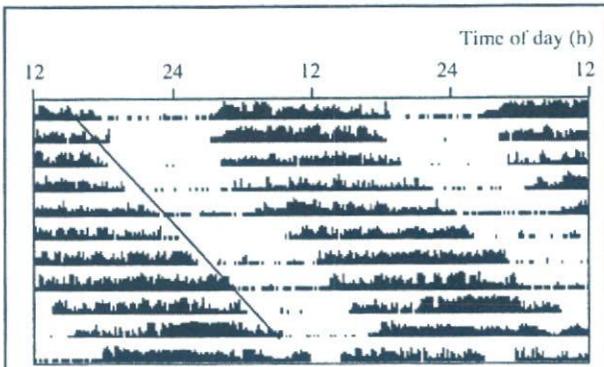


Figure 1—Wrist-activity measurements obtained from a representative patient (30-year-old man). To determine the period of the sleep-wake cycle, regression lines were fitted through the sleep-onset time obtained during 10 consecutive days. Linear-regression functions in this subject were computed with respect to sleep onset ($Y = 20.99 - 1.73 * X$; $R = 0.99$; 95% confidence interval, 1.54-1.92).

cintosh computer. The χ^2 test was used to compare categorical data from 2-dimensional tables, and the Mann-Whitney U test was used to compare group differences. The Spearman rank order correlation test was used to investigate correlation between 2 items. All numeric data are presented as the mean \pm SD. We accepted a P value less than 5% as statistically significant.

RESULTS

Clinical Characteristics

The patient cohort was male-dominated, comprising 41 (72%) men and 16 (28%) women (the ratio of men to women was 2.6:1). There was no significant difference between the mean age of the male and female patients (26.3 ± 9.2 years and 25.8 ± 6.9 years, respectively). The mean age at onset of non-24-hour sleep-wake syndrome was 20.2 ± 7.0 years, with sex having no effect (age at onset of non-24-hour sleep-wake syndrome: 20.8 ± 7.6 years and 18.8 ± 5.1 years for men and women, respectively). As seen in Table 1, all of the patients were over the age of 10 years at the onset of the non-24-hour sleep-wake syndrome. Indeed, most of the patients (63%) were in their teens at the time of onset. The mean interval between the onset of non-24-hour sleep-wake syndrome and the first visit to the sleep disorders clinic was 5.9 ± 6.2 years. With regard to premorbid status, 16 (28%) of the patients had psychiatric problems, 1 (2%) had physical problems, and 15 (26%) had suffered from persistent sleep phase delay diagnosed as delayed sleep phase syndrome prior to the onset of non-24-hour sleep-wake syndrome. Fifty-six patients (98%) had a history of severely disrupted social functioning, such as temporary absence from school, leaving school, temporary retirement from office work, or retirement. Six patients (11%) had been married, and 45 (79%) had lived with their family or a roommate. Regarding social status, at the first visit to the sleep disorders clinic, 35% were students, 21% were employed, 5% worked part time, and 39% were unemployed. None of the patients had a history of head injuries or meningitis, developmental abnormality in childhood, or significant sleep problems before the age of 10 years. A family history of sleep, psychiatric, or neurologic disorders was noted in 5 patients (Table 1); these included major depression ($n = 1$, 1.8%), delayed sleep-phase syndrome ($n = 2$, 3.5%), and schizo-

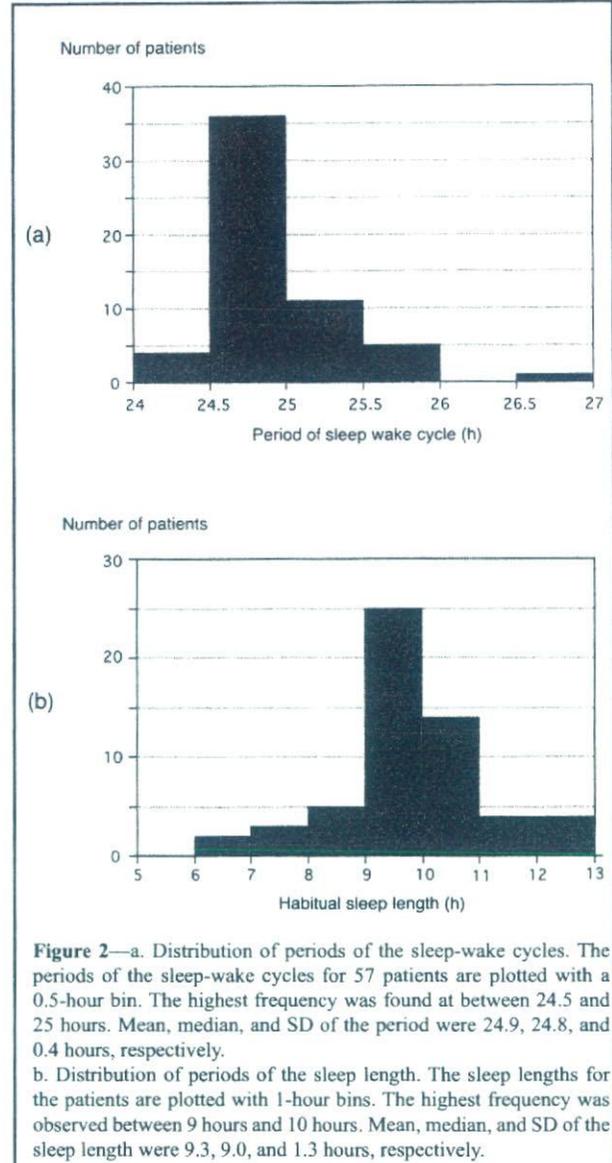


Figure 2—a. Distribution of periods of the sleep-wake cycles. The periods of the sleep-wake cycles for 57 patients are plotted with a 0.5-hour bin. The highest frequency was found at between 24.5 and 25 hours. Mean, median, and SD of the period were 24.9, 24.8, and 0.4 hours, respectively. b. Distribution of periods of the sleep length. The sleep lengths for the patients are plotted with 1-hour bins. The highest frequency was observed between 9 hours and 10 hours. Mean, median, and SD of the sleep length were 9.3, 9.0, and 1.3 hours, respectively.

phrenia ($n = 2$, 3.5%). The physical examinations performed at referral, including blood counts, urine examinations, serum biochemistry, electrocardiography, routine electroencephalogram, and brain computed tomography or magnetic resonance imaging, did not reveal any marked somatic disorders or neurologic conditions in any of the subjects.

Sleep Characteristics

The period of the sleep-wake cycle obtained from 10-day actigraphic assessment was longer than 24 hours in all of the patients, a finding that was confirmed by the fact that in any of the patients the 95% confidence intervals for the period did not cross 24 hours. In the 10-day actigraphic assessment, a single delayed-phase jump was found in 8 of the delayed-phase jumpers, but there were none in any of the non-delayed-phase jumpers. The mean period of the sleep-wake cycle for the patients was 24.9 ± 0.4 hours (range 24.4-26.5 hours; Figure 2a). The mean sleep

length of the patients was 9.3 ± 1.3 hours, the most prevalent range being 9 to 10 hours (experienced by 44% of the patients; Figure 2b). There was no correlation between the period of the sleep-wake cycle and sleep length. Neither the period of the sleep-wake cycle nor sleep length was affected by sex (U-test). Differences in social status (employed, unemployed, and student) did not have significant effects on the period of the sleep-wake cycle nor on the sleep length (Kruskal Wallis nonparametric analysis of variance). Thirty-one patients (54%) were considered as delayed-phase jumpers. The delayed-phase jumps were found when the patients' sleep-onset time was delayed into the daytime. The period of sleep-wake cycle for 10-day actigraphic assessment did not differ between the delayed-phase jumpers (24.9 ± 0.5 hours) and the non-delayed-phase jumpers (24.9 ± 0.4 hours) (U-test). The period of the sleep-wake cycle for the 4-week sleep-log assessment was significantly prolonged in the delayed-phase jumpers (26.1 ± 0.8 hours) as compared with the non-delayed-phase jumpers (24.9 ± 0.5 hours) ($P < .0001$, U-test).

Psychiatric Problems

A semistructured psychiatric interview revealed that psychiatric disorders preceded the onset of non-24-hour sleep-wake syndrome in 16 patients (28%). These included adjustment disorders ($n = 6$, 10.5%), major depression ($n = 3$, 5.3%), schizophrenia ($n = 2$, 3.5%), obsessive-compulsive disorder ($n = 2$, 3.5%), social phobia ($n = 1$, 1.8%), generalized anxiety disorder ($n = 1$, 1.8%), and mental retardation ($n = 1$, 1.8%). In 15 of these 16 patients (93.7%), social withdrawal had accompanied the development of their psychiatric disorders. One typical case of a patient with a psychiatric disorder and associated social withdrawal is documented in a case report below (Case 1).

Of the 41 patients in this study who did not have a history of psychiatric disorders prior to the onset of non-24-hour sleep-wake syndrome, 14 (34%) developed major depression. No other psychiatric disorders developed after the onset of non-24-hour sleep-wake syndrome. The mean age of onset of the non-24-hour sleep-wake syndrome in the patients who developed major depression (23.6 ± 2.4 years) was significantly higher than that of the group who did not develop depression (19.2 ± 1.0 years; U test, $P < .05$).

In 5 of the patients who developed major depression after the onset of non-24-hour sleep-wake syndrome, their depressive complaints were aggravated when their sleep episodes occurred out of phase (ie, when they slept during the daytime) and slightly ameliorated when their sleep episode occurred in phase (ie, when they slept during the nighttime), as described for Case 2 below.

Case 1

This patient was a 26-year-old woman who had left school at the age of 16 years because of adjustment disorder. After leaving school, her sleep pattern was such that she fell asleep at 2:00 AM and awoke at 11:00 AM. At the age of 17 years, she enrolled at a night school but did not attend regularly because of difficulty coping with school life. At the age of 19 years, she became unable to fall asleep until the morning and unable to wake up until the late afternoon and stayed at home almost all day. After a couple of months, there began a gradual and daily delay in her sleep-onset time. At the age of 21 years, this patient consulted a clinic and was treated with benzodiazepine hypnotics, but these were inef-

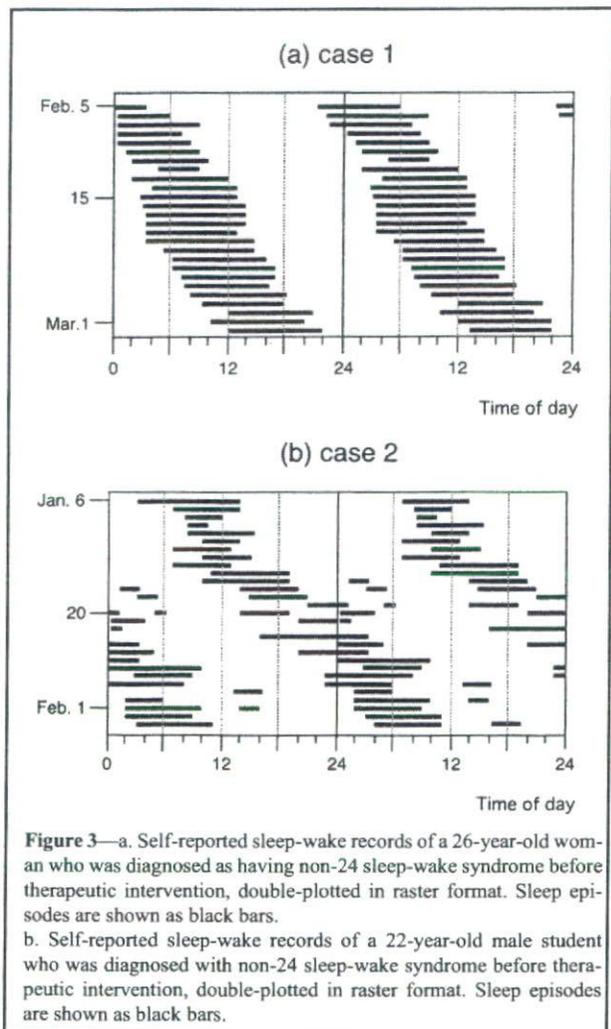


Figure 3—a. Self-reported sleep-wake records of a 26-year-old woman who was diagnosed as having non-24 sleep-wake syndrome before therapeutic intervention, double-plotted in raster format. Sleep episodes are shown as black bars. b. Self-reported sleep-wake records of a 22-year-old male student who was diagnosed with non-24 sleep-wake syndrome before therapeutic intervention, double-plotted in raster format. Sleep episodes are shown as black bars.

fective.

On referral to our clinic, no abnormal findings were detected in routine electroencephalogram and magnetic resonance imaging investigations, blood count, biochemistry, or thyroid function test. A semistructured psychiatric interview revealed that she had adjustment disorder (according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*). Her sleep-wake record before the therapeutic intervention is documented in Figure 3a. Her sleep-wake rhythm exhibited a free-running sleep-wake cycle with a 24.8-hour period. She was diagnosed as having non-24-hour sleep-wake syndrome on the basis of the ICSD. There was no family history of circadian rhythm sleep disorders or psychiatric disorders, and her medical history was also unremarkable.

Case 2

This patient was a 22-year-old male student who, at the age of 15 years, began to have difficulty falling asleep until 3:00 AM and difficulty rising in the morning, resulting in frequent absences from morning classes at school. When he entered college at the age of 18 years, he noticed that his sleep onset was gradually delayed each day. After several months, he started complaining