

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.

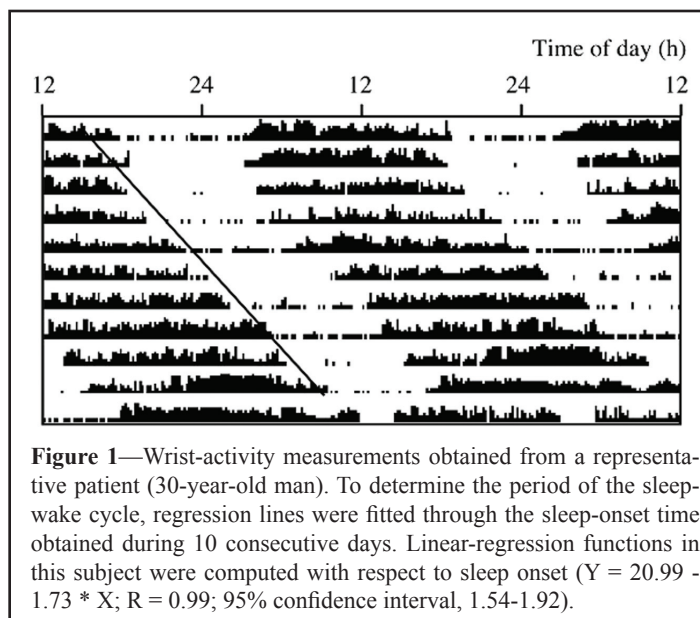
tients visited us when they were able to sleep during the nighttime and stay awake during the daytime. A delay of sleep onset longer than 4 hours per day was defined as a delayed phase jump. The patient was considered as a delayed-phase jumper when delayed-phase jumps were recognized at least 4 times 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-

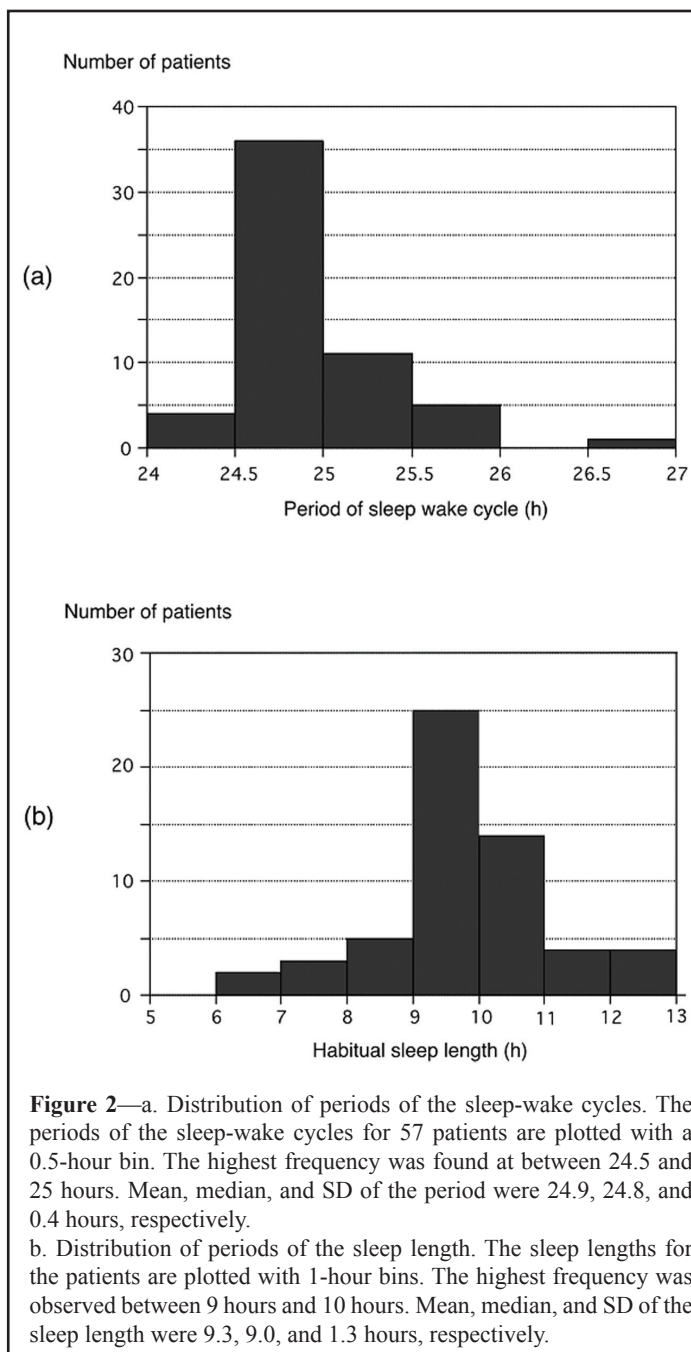


intosh computer. The χ^2 test was used to compare categorical data from 2-dimensional tables, and the Mann-Whitney U test was used to compare group differences. The Spearman rank order correlation test was used to investigate correlation between 2 items. All numeric data are presented as the mean \pm 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-



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 ineffecti-

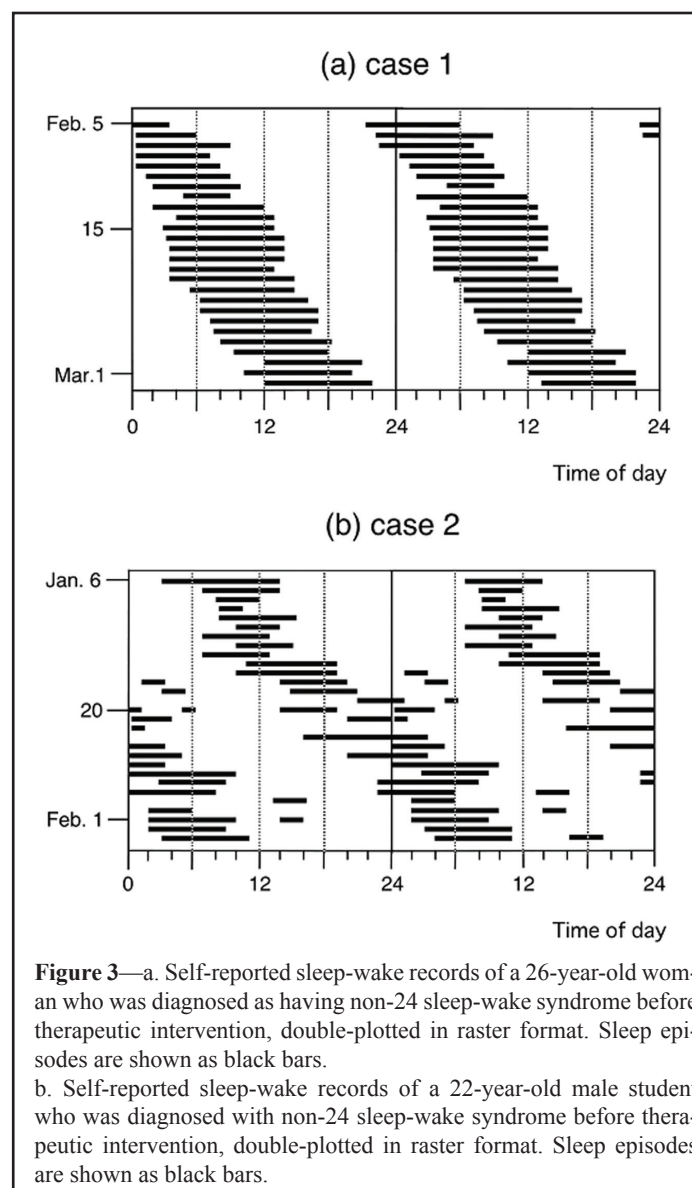


Figure 3—a. Self-reported sleep-wake records of a 26-year-old woman who was diagnosed as having non-24 sleep-wake syndrome before therapeutic intervention, double-plotted in raster format. Sleep episodes are shown as black bars.

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

of dysphoric mood and loss of interest. His depressive symptoms tended to be worse while his sleep phase was in the daytime. At the age of 19 years, he failed to attend college because of his sleep problems and depression and finally left college at the age of 21 years.

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 he had major depression (according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*). His sleep-wake rhythm before any therapeutic intervention is documented in Figure 3b; it exhibited a free-running sleep-wake cycle with a 24.7-hour period. He 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 his medical history was also unremarkable.

DISCUSSION

This is the first study of a large cohort of sighted patients suffering from non-24-hour sleep-wake syndrome. The prevalence of non-24-hour sleep-wake syndrome in the general population has not been established, but it is presumed to be rare.³ Although the exact prevalence of non-24-hour sleep-wake syndrome in the blind has not been clarified, it does seem to occur relatively frequently in totally blind individuals.⁴⁻¹⁰ Furthermore, Lockley et al⁴¹ have reported that 57% of subjects without any light percep-

tion exhibited a free-running melatonin rhythm. Sack et al⁴² have also reported that 50% of totally blind subjects had free-running plasma melatonin rhythms. These reports indicate that development of non-24-hour sleep-wake syndrome may be attributable to a free-running circadian pacemaker.

Non-24-hour sleep-wake syndrome has also been reported to occur in sighted individuals,¹¹⁻³⁶ but the basic characteristics of such patients, such as sex, age, or age at onset, remain unknown.³ In the study described here, of the 57 consecutively diagnosed patients with non-24-hour sleep-wake syndrome, 72% were men, making it a male-dominant cohort. This is comparable with previous studies: of the 39 sighted patients reported in previous studies¹¹⁻³⁶ (Table 2), 33 (85%) were male.

The detailed clinical histories taken in the present study revealed that the commencement of a free-running sleep-wake cycle occurred mostly when patients were in their teens (63%) or 20s (23%). In none of the patients did onset of non-24-hour sleep-wake syndrome occur before the age of 10 years. In previous studies of sighted people with non-24-hour sleep-wake syndrome, the age of onset was also reported to be predominantly the teens (38%) and 20s (43%), as shown in Table 2. Indeed, of the 39 cases described in all of the previous studies, only 1 patient (2.6%), who also suffered from mental retardation, experienced onset of non-24-hour sleep-wake syndrome before the age of 10 years³³ (Table 2). Thus, the results of our study, together with those of the previous studies of sighted patients with non-24-hour sleep-wake syndrome, indicate that the onset of non-24-hour sleep-wake syndrome in sighted patients occurs predominantly in

Table 2—Published Reports of Sighted Patients With Non-24-Hour Sleep-Wake Syndrome

Author	Year	No.	Sex	Age, y First visit Onset	Social status at first visit	Period of sleep- wake cycle, h	Premorbid Psychiatric Problems	Premorbid Sleep Disorder
Elliott ¹¹	1970	1	M	NA NA	NA	26		
Kokkoris ¹²	1978	1	M	34 26	Unemployed	24.8	Schizoid personality	
Weber ¹³	1980	1	M	28 24	College student	25.6		
Kamgar-Parsi ¹⁴	1983	1	M	32 22	Unemployed	25.1		DSPS
Wollman ¹⁵	1986	1	M	26 22	Student	27.4		
Sugita ¹⁶	1987	1	M	25 23	Student	25		
Eastman ¹⁷	1988	1	M	26 High school	NA	25		
Hoban ¹⁸	1989	1	F	40 NA	Artist	25.1		
Moriya ¹⁹	1990	1	M	16 15	Student	24.2-25		
Sasaki ²⁰	1990	1	F	22 21	NA	NA	Bipolar affective disorder	
Ohta ²¹	1991	1	M	17 15	Student	24.6		
Oren ²²	1992	2	M	22, 28 NA	NA	NA		DSPS
Tagaya ²³	1993	1	M	20 18	Unemployed	25.3	Schizophrenia	
Emens ²⁴	1994	1	M	31 22	NA	25.2		
Tomoda ²⁵	1994	1	M	18 17	Student	25		
McArthur ²⁶	1996	1	M	41 41	Computer programmer	25.1	Depression, social phobia	DSPS
Uchiyama ²⁷	1996	1	M	30 18	Designer	27.2		
Yamadera ²⁸	1996	13	10 M	23.2* 19.8*	7 students, 3 unemployed, 2 employed, 1 part time worker	NA		
Nakamura ²⁹	1997	1	M	26 NA	Student	NA		DSPS
Shibui ³⁰	1998	1	M	43 41	Local government officer	25.8		
Hashimoto ³¹	1998	1	M	26 26	Student	NA		
Hayakawa ³²	1998	1	M	20 16	Student	25		
Akaboshi ³³	2000	1	M	5 4	Kindergarten	24.9	Mental retardation	
Watanabe ³⁴	2000	1	M	17 17	NA	NA		
Morinobu ³⁵	2002	1	M	22 20	NA	NA	OCD	
Boivin ³⁶	2003	1	F	39 32	NA	NA		

*Mean, NA: refers to not available, OCD: obsessive-compulsive disorders, DSPS: delayed sleep-phase syndrome.

the teens and 20s.

In the study presented here, 56 of the 57 patients (98%) had a history of disturbed social functioning due to inability to regularly attend school or work. Only 1 patient (2%), who worked as a designer, had no consequential problems in his work schedule; this was probably due to his flexible work schedule—he went to work when he rose and worked for about 8 hours each day.

We found that 26% of our patients had suffered from persistent sleep-phase delay, which was diagnosed as delayed sleep-phase syndrome, prior to the onset of non-24-hour sleep-wake syndrome. A review of the previous relevant studies (Table 2) showed that persistent sleep-phase delay preceded the symptoms of non-24-hour sleep-wake syndrome in 5 out of 39 sighted patients (13%).^{14,22,26,29} Oren et al²² reported that 2 patients with delayed sleep-phase syndrome had developed non-24-hour sleep-wake syndrome after chronotherapy in which their sleep phase was scheduled to be delayed by 3 to 4 hours in an attempt to obtain the desired sleep phase, suggesting that, in patients with delayed sleep-phase syndrome, an enforced sleep-phase delay is a trigger for non-24-hour sleep-wake syndrome and that these 2 circadian rhythm sleep disorders share a common pathology.

The mean habitual sleep length in the patients in our study was 9.3 ± 1.3 hours. The habitual sleep length reported in the 6 previously published relevant articles ranged between 7.6 and 10 hours (mean 8.8 hours) in sighted people with non-24-hour sleep-wake syndrome.^{12-15,26,34} Previous controlled studies have reported that sleep length is longer in patients with non-24-hour sleep-wake syndrome (9.2 hours) than in age-matched controls (7.3 hours).⁴³ The present study and most previous studies strongly suggest that habitual sleep length appears to be longer in patients with non-24-hour sleep-wake syndrome.

In the current study, the patient's sleep-wake cycle was objectively evaluated by using wrist-worn actigraphy for 2 weeks when the patient's sleep started during the nighttime and when delayed-phase jumps or irregular sleep patterns due to out-of-phase sleep episodes were least likely to occur.²⁷ We found that the mean period of the sleep-wake cycle for this 10-day actigraphic observation was 24.9 ± 0.4 hours. This sleep-wake period is comparable to that observed in classic human free-running experiments (around 25 hours), in which the subjects are allowed to select when they rise and retire, thus timings of light on and light-off.⁴⁴ The sleep-wake period is slightly longer than that of the circadian temperature or melatonin rhythm in totally blind patients (24.3-24.5 hours)⁴¹⁻⁴⁴ or normal subjects living under a forced desynchrony protocol (24.2 hours),⁴⁷ in which the sleep-wake cycle is forced to be outside the range of entrainment of the human circadian pacemaker and zeitgebers are either eliminated, minimized, or evenly distributed across the circadian cycle. Emens et al²⁴ reported that a sighted man with non-24-hour sleep-wake syndrome and a sleep-wake cycle of 25.17 hours under a normal 24-hour day-night condition displayed a shorter core body temperature rhythm of 24.50 hours under the forced desynchrony protocol for 3 weeks. It seems that his sleep-wake period was prolonged under a self-selected light-dark cycle relative to his endogenous circadian period and that an illumination on the delay portion of the human phase-response curve was likely to be responsible for this phenomenon.

In the present study, 54% of the patients were classified as delayed-phase jumpers, who displayed more than 3 delayed-phase jumps per month. An analysis of self-written sleep logs for 4 weeks showed that the period of the sleep-wake cycle was longer

in delayed-phase jumpers (26.1 hours) than in non-delayed-phase jumpers (24.9h), suggesting that delayed-phase jumps that occur primarily when the patient's sleep started during the daytime prolonged the period of the sleep-wake cycle in the delayed-phase jumpers. We previously observed sleep-wake cycle and core body temperature rhythm in a patient with non-24-hour sleep-wake syndrome and found that an extremely long period of core body temperature rhythm (31.2 hours) with delayed-phase jumps of sleep onset appeared when his sleep onset was delayed into the daytime, whereas core body temperature rhythm and sleep-wake cycle displayed a period of 24.6 hours when his sleep onset occurred during the nighttime.²⁷ Similar variation of the period of the sleep-wake cycle has been observed in other early case reports of sighted patients with non-24-hour sleep-wake syndrome¹²⁻¹⁵ but has not been recognized in totally blind patients with the syndrome.

Our previous case control studies have demonstrated that sleep in patients with non-24-hour sleep-wake syndrome is delayed relative to core body temperature rhythm⁴³ and melatonin rhythm under dim light condition³⁸ in comparison with age-matched controls. This altered phase relation between sleep and endogenous circadian phase, which has also been reported in other single case reports,^{12,18} is likely to provide an opportunity that the patient's delay portion of the phase-response curve to light is more strongly illuminated. Thus, we postulate that the longer circadian period in sighted patients with non-24-hour sleep-wake syndrome in the present study, as compared with that in blind patients with non-24-hour sleep-wake syndrome, may be a consequence of light-provoked prolongation of the circadian period; we also propose that the extreme manifestation of such provoked prolongation might be a delayed-phase jump. This also provides an explanation for the observation by Emens et al²⁴ and a possible similarity between individuals in temporal isolation under a self-selected light-dark schedule and sighted individuals with non-24-hour sleep-wake syndrome.

Of the total cohort in the present study, 28% had developed psychiatric problems before the onset of non-24-hour sleep-wake syndrome. This suggests that withdrawal due to psychiatric problems is one of the etiologic factors of non-24-hour sleep-wake syndrome. There have been several reports of sighted patients with non-24-hour sleep-wake syndrome preceded by schizophrenia, bipolar disorder, depression, obsessive-compulsive disorder, or schizoid personality.^{12,20,23,26,35} Kokkoris et al¹² have reported on a patient in whom onset of non-24-hour sleep-wake syndrome was preceded by development of a schizoid personality and postulated that this patient's non-24-hour sleep-wake syndrome sleep-wake cycles were the result of either a primary defect in the mechanism underlying entrainment or weakened social zeitgebers due to a personality disorder. Tagaya et al²³ have described a patient in whom the onset of non-24-hour sleep-wake syndrome was preceded by schizophrenia and noted that the sleep-wake cycle, which was related to the severity of the psychiatric symptoms, might be prolonged by social isolation.

Among the present patients who had no psychiatric problems before the onset of non-24-hour sleep-wake syndrome, 14 (34%) developed major depression thereafter. In 5 of these, the symptoms of depression were exacerbated 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 night). This suggests that a reduc-

tion in exposure to sunlight is a possible cause of depression, as described with respect to seasonal affective disorder.⁴⁸ The mean age at onset of the non-24-hour sleep-wake syndrome in those patients who developed major depression was 23.6 ± 2.4 years. It is possible that these patients had tried to adapt themselves to their social life and failed, leading to psychological stresses that could have precipitated their depression.

Some reports have indicated that depression is the most common psychopathology associated with delayed sleep-phase syndrome,^{49,50} but no reports have described the relationship between non-24-hour sleep-wake syndrome and depression. There have, however, been various studies on the relationship between biologic rhythm and depression. Some of the evidence suggests that late arising itself may predispose to depression. Wehr et al⁵¹ introduced the circadian-rhythm phase-advance hypothesis in which it has been inferred that, in depression, the circadian rhythm is phase advanced relative to the sleep phase. Another study suggests that an acute sleep-phase delay in some normal subjects causes depressive mood changes.⁵² Our previous studies^{38,39} revealed that sleep phase was delayed relative to melatonin rhythm in patients with non-24-hour sleep-wake syndrome, as compared with controls. The delay of sleep phase relative to the circadian pacemaker may be an etiologic factor of the depression that is associated with non-24-hour sleep-wake syndrome. Another possible trigger for this depression is the social disruption caused by the circadian rhythm sleep disorder.

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