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CIRCADIAN RHYTHM SLEEP DISORDERS: A BRIEF REVIEW WITH SPECIAL REFERENCE TO LONG-TERM FOLLOW-UP

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ABSTRACT

This article reviews the hygiene of new sleep disorders such as delayed sleep phase syndrome (DSPS) and non-24-hour sleep-wake syndrome which are classified as the circadian rhythm sleep disorders in the *International Classification of Sleep Disorders* (ICSD) published in 1990. It was clear in this study that these sleep schedule disturbances developed by preference in adolescence and youth, and the prevalence of DSPS in this generation was presumed to be 0.25—0.4%. Patients with certain disorders, such as entrainment to external time cues, were treated with non-pharmacological interventions and/or pharmacological agents. These therapies were effective in some cases when each was administered alone, but their effectiveness in other cases was not evident until two or more of therapies were used in combination. The prognosis of these two syndromes was significantly positive, particularly in the adolescent cases, suggesting the benefits of early discovery and treatment.

Key Words: Circadian rhythm sleep disorders, Delayed sleep phase syndrome, Non-24-hour sleep-wake syndrome, Vitamin B12, Long-term follow-up

INTRODUCTION

The biological rhythm called the circadian rhythm is not an immutable rhythm but one that is controlled by certain stimuli in the outside world, namely time cues (Table 1). This cue is said to have five forms in the case of humans: 1) Time on a clock, 2) Light and darkness, 3) Social interaction, 4) Meal time and 5) Sleep-wake schedule. Social interaction has been regarded as the most potent time cue in humans, while animals and plants are most susceptible to the influence of light.[1] In recent years, it has become increasingly clear that light exerts a strong influence on human circadian rhythms.[2,3]

In cases where humans have been deprived of time cues, the body shows a rhythm that has a cycle different from the entrained rhythm, and in many cases has a rhythm with a cycle longer

Table 1. Time Cues For Human Circadian Rhythm

1. To find time on a clock
2. Light and darkness by light
3. Social interaction
4. Timing for taking meals
5. Sleep-wake schedule

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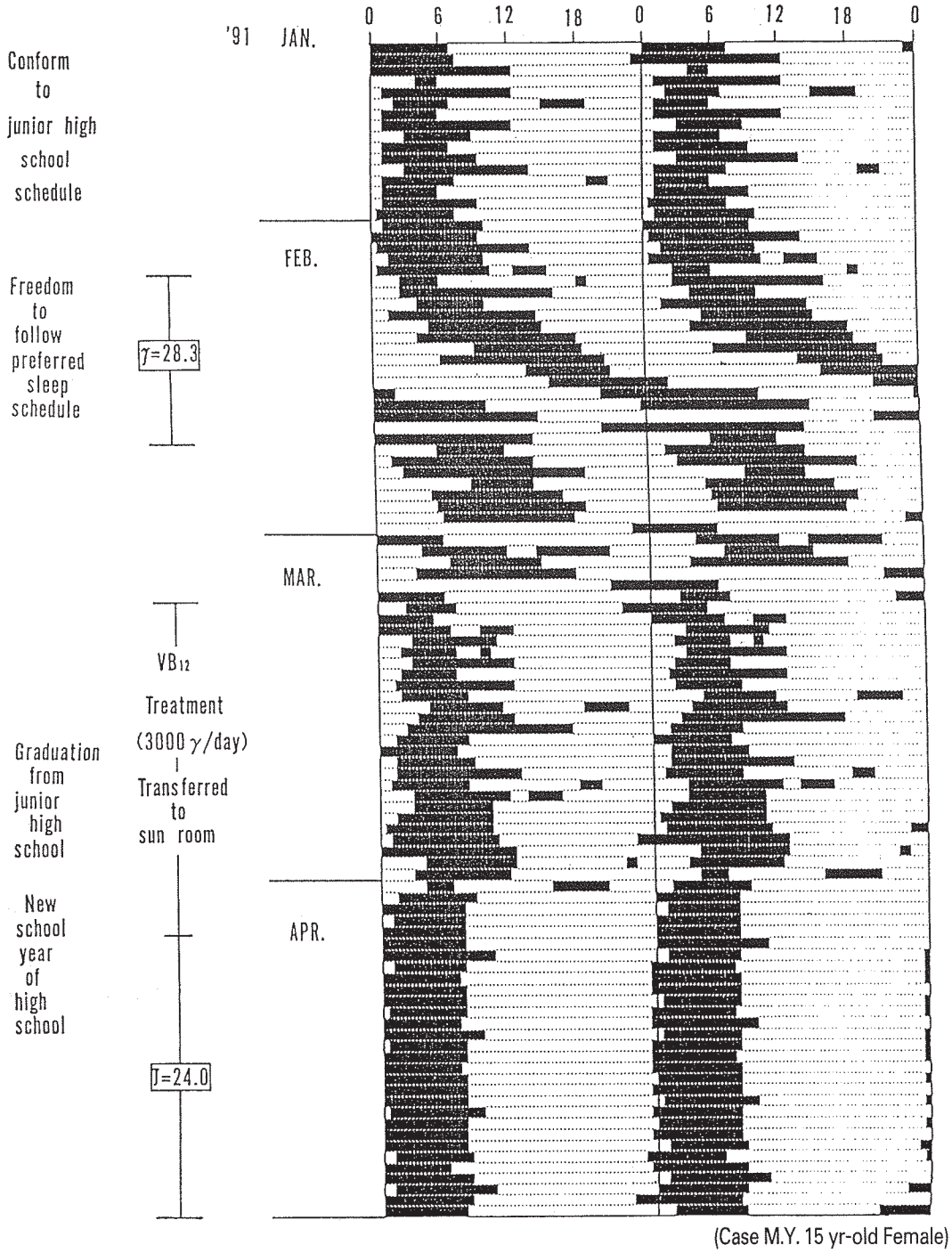

Fig. 1. Patient with non-24-hour sleep-wake syndrome: 15-year-old junior high school girl.

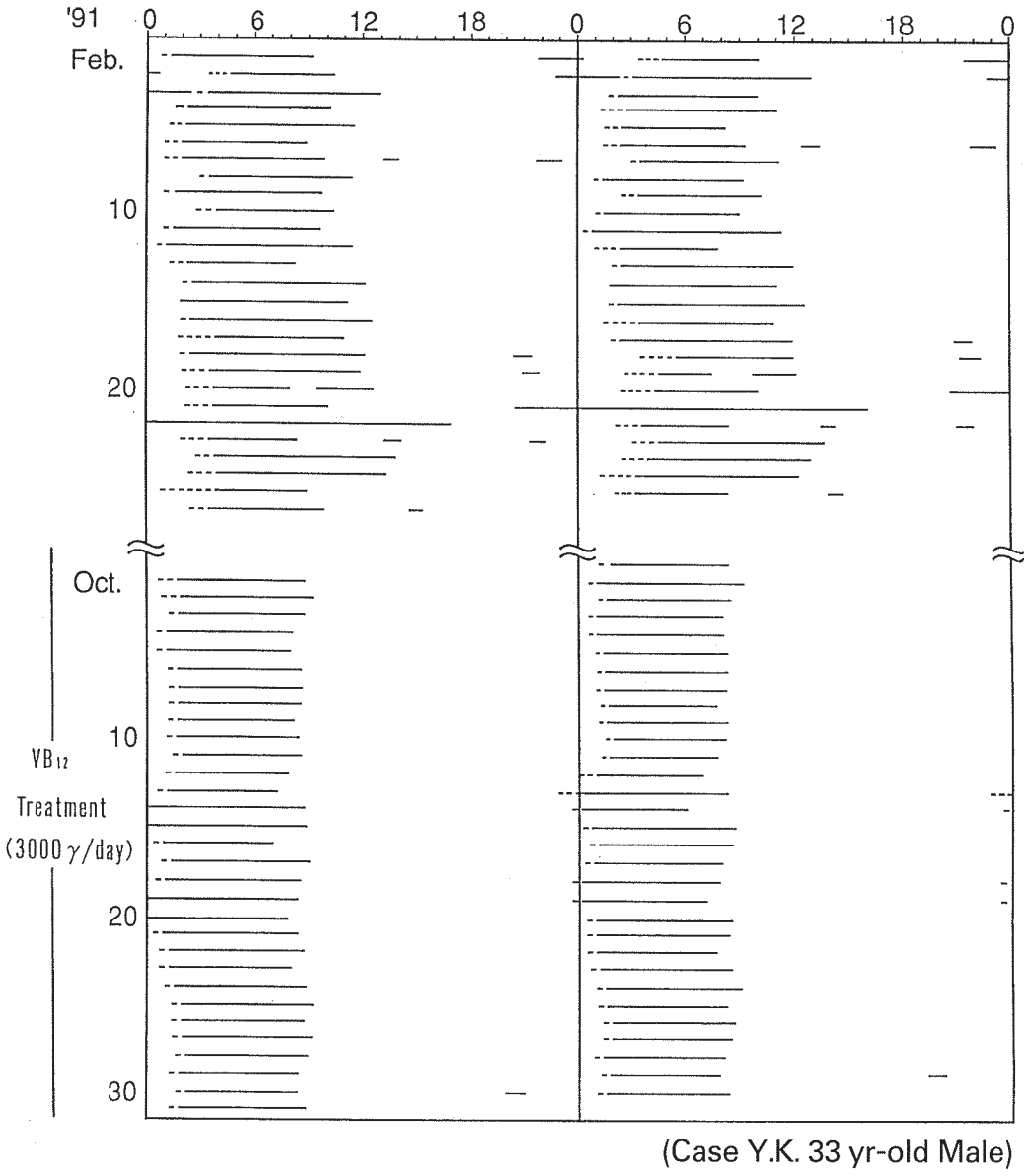

Fig. 2. Patient with delayed sleep phase syndrome: 33-year-old computer programmer.

than 24 hours. This rhythm is called the free running rhythm. In addition, time cue deprivation causes a lag in the cycle between the biological rhythms which is called internal desychronization. A free running rhythm and internal desynchronization do not occur when time cues exist in the environment.[4] Even in the presence of the time cue, however, these phenomena can exist and the body also undergoes changes where the condition changes rapidly.

I. PERSISTENT SLEEP RHYTHM DISORDERS — CASE REPORT —

1. In the past 10 years, reports have been published concerning people who show a sleep-wake rhythm cycle which resembles the free running rhythm.[5] Fig. 1 shows the case of a 15-year-old girl who was seen at our clinic, complaining of an increase in her frequency of being late to and absent from school because of a sleep-wake rhythm disorder. This pattern of sleep behavior was recorded in Fig. 1 from a sleep-wake log using the double-plot method. At first, the sleeping hours seem irregular because of her efforts to attend school, but when it was so arranged that she could sleep when she wanted to, her sleep pattern resembled the free running rhythm as shown below the middle row. This case is what is called non-24-hour sleep-wake syndrome or hypernychthemeral syndrom. She has managed to continue through senior high school using a novel therapy involving the oral administration of vitamin B12 with and without phototherapy.

2. Fig. 2 shows a male with DSPS. He was seen at our hospital because he couldn't go to sleep until late at night, had difficulty rising in the morning and failed to leave for work. As in this case, DSPS is characterized by a sleep time zone so delayed that the patient cannot adapt to normal life in society. As shown in the lower half of the sketch of Fig. 2, the sleep phase in this case advanced with long-term oral administration of vitamin B12, making it possible for the patient to live a normal life.

II. CLASSIFICATION

As the pathophysiology of sleep-wake disorders has been clarified in recent years, diagnostic classifications have been put in order. In the ICSD[6] published in 1990 (Table 2), sleep rhythm disorders such as non-24-hour sleep-wake syndrome and DSPS mentioned earlier are grouped together as circadian rhythm sleep disorders and treated as dyssomnias. Of the circadian rhythm sleep disorders (Table 3), 1 and 2 are transient and 3 to 6 include persistent disorders. The irregular sleep-wake pattern (where one cannot sleep in a fixed time zone) and the advanced

Table 2. The International Classification of Sleep Disorders

DYSSOMNIAS
- A. Intrinsic Sleep Disorders
- B. Extrinsic Sleep Disorders
- C. Circadian Rhythm Sleep Disorders

RARASOMNIAS
- A. Arousal Disorders
- B. Sleep-Wake Transition Disorders
- C. Parasomnias Usually Associated with REM Sleep
- D. Other Parasomnias

SLEEP DISORDERS ASSOCIATED WITH MEDICAL/PSYCHIATRIC DISORDERS
- A. Associated with Mental Disorders
- B. Associated with Neurological Disorders
- C. Associated with Other Medical Disorders

PROPOSED SLEEP DISORDERS

(ICSD, 1990[6])

Table 3. Circadian Rhythm Sleep Disorders

1. Time Zone Change (Jet Lag) Syndrome
2. Shift Work Sleep Disorder
3. Irregular Sleep-Wake Pattern
4. Delayed Sleep Phase Syndrome
5. Advanced Sleep Phase Syndrome
6. Non-24-Hour Sleep-Wake Disorder
7. Circadian Rhythm Sleep Disorder NOS

(ICSD, 1990[6])

sleep phase syndrome (where the sleeping time is fixed in a period from evening to midnight) are included in the persistent sleep rhythm disorder category.

III. DEMOGRAPHIC FEATURES

The etiology of these sleep rhythm disorders is unknown, and it will take considerable time to elucidate it. According to a multi-center study report on sleep-wake rhythms conducted in Japan from 1990 to 1991, 4.7% of the patients received medical treatment and 2.1% had primary rhythm disorder without psychiatric symptoms among 4,295 people who were recruited by news-papers and participated in the study. The age of disorder onset converged around 16 to 19 years and the mean age for the initial hospital visit was several years later, but these findings substantiate earlier reports that this type of disturbance develops by preference in adolescence and youth[7,8] (Table 4). Table 5 shows that the premorbid pattern of activity was the evening type in about 70% of these cases and the cause of development was determined in just over 50% of the cases. The data suggest that the evening type of life style is a precondition for development of this disorder in many cases.[9-11] There have been few studies reporting the prevalence of these sleep rhythm disorders. DSPS in the general population was 0.17% in Norway,[12] and the ratio prevalent in adolescents and youth (18–22 years-old) was 0.25% in that study. By comparison, the prevalence of possible DSPS patients in 7,217 high school students was 0.4% in our study.

Table 4. Recruitment of Patients with Sleep-Wake Rhythm Disorders

Request for Questionnaire	**4,295**	**Ratio to the Total Subjects**
		%
Questionnaire Returned	491	11.4
Referred to the Institutes	249	5.8
Interview	202	4.7
Sleep-Wake Rhythm Disorders	128	3.0
Primary	**92**	**2.1**
Secondary	36	0.9

(Multi-Center Study, Japan, Dec. 1990–Sep. 1991)

Table 5. Premorbid Activity Pattern of Sleep-Wake Rhythm Disorders

		Morning	Evening	Not Identified	Unknown	Total
Non-24-Hour		1	8	5	0	14
DSPS		3	38	13	0	54
IS-WP		3	11	4	1	19
Long Sleeper		0	5	0	0	5
		7	62	22	1	92
	%	(7.6)	(67.4)	(23.9)	(1.1)	(100)

(Multi-Center Study, Japan, Dec. 1990–Sep. 1991)

IV. TREATMENT

Definitive or standardized treatments for these sleep thythm disorders are not available now, but various contrivances are often tried. In this study, therapy was roughly divided into two criteria, namely non-pharmacotherapy and pharmacotherapy (Table 6). Chronotherapy, phototherapy and solidification of time cues were considered to be non-pharmacotherapy, while administration of vitamin B12 (methylcobalamin), benzodiazepines such as triazolam and clonazepam as well as methylphenidate and melatonin were considered to be pharmacotherapy. Chronotherapy is mainly used to treat DSPS[13] and advanced sleep phase syndrome. Therapy for DSPS consists of delaying the sleep phase by not more than 3 hours a day (Fig. 3), whereas treatment for advanced sleep phase syndrome involves advancing the sleep phase by about 3 hours in 2 days. In this author's experience,[5] sleep phase resetting by way of chronotherapy was performed in all cases of DSPS. However, use of this therapy alone rarely resulted in success, invariably the delay in sleeping time recurred before long. As a result, other therapies were employed in concert with chronotherapy. As to bright light treatment, it is clear that a light of 2500 lux or more influences the phase and amplitude of the human biological rhythm,[2,3] and this treatment is used to treat seasonal affective disorder (SAD). This therapy is sometimes effective for sleep rhythm disorders where an artificial white fluorescent light is used.[14] Bright light therapy is generally administered for about 2 hours between 6:00 and 9:00 a.m. every morning. In the first case mentioned earlier, this therapy coupled with oral administration of vitamin B12 was effective. As previously discussed, vitamin B12 is widely used in Japan as pharamacotherapy. Since a report[15] by the National Institute of Mental Health (NIMH) in the U.S. was

Table 6. Treatment of Sleep-Wake Rhythm Disorders

NON-PHARMACOTHERAPY
Chronotherapy
Phototherapy
Solidification of Time Cues
PHARMACOTHERAPY
Vitamin B12 (Methylcobalamin)
Benzodiazepines (Triazolam, Clonazepam etc.)
Methylphenidate
Melatonin

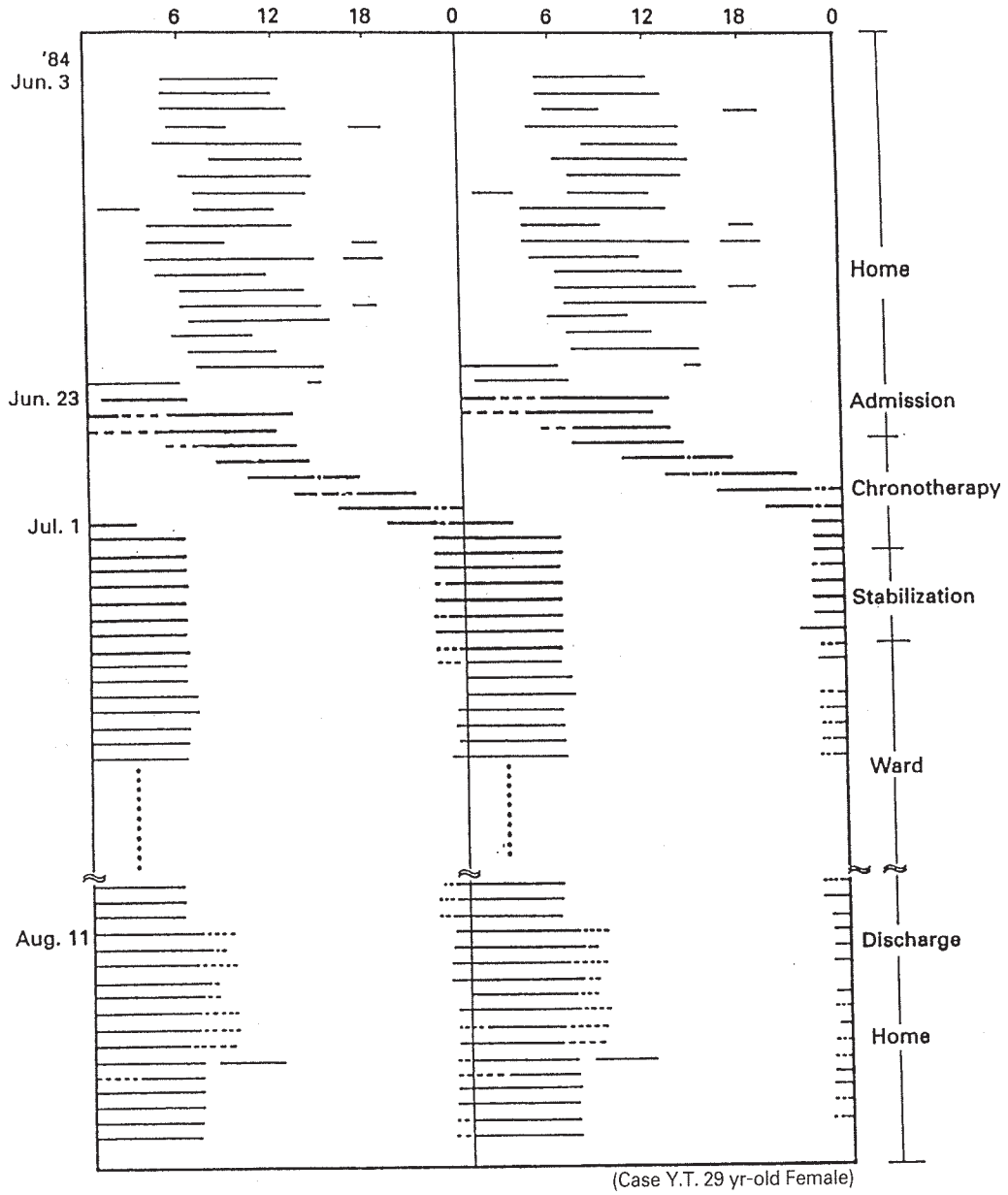

Fig. 3. Sleep-wake log before and after chronotherapy. The patient's sleep phase was strictly reset just after chronotherapy with the phase shift delayed, but a gradual delay reappeared when the patient returned home: 29-year-old female (Ohta et al., 1992[5])

published in 1983 on a case in which chance use of vitamin B12 was markedly effective in treating non-24-hour sleep-wake syndrome, therapy using vitamin B12, particularly methylcobalamin or other methyl types of B12, has been frequently used in Japan with excellent results.[16-18] Generally speaking, methylcobalamin is administered daily in oral doses of 1.5 to 3mg or in doses of 0.5 to 1mg using intravenous or subcutaneous injection. This therapy was effective in about 60% of the non-24-hour type disorders and in 30% of the DSPS types, accordings to the multi-center open trial. In our experience, none of these cases showed marked vitamin B12 deficiency or hypothyroidism.[19] On the other hand, triazolam and clonazepam which have the effect of advancing the phase of the biological rhythm in animals were reported to be effective in some patients.[20-23] Methylphenidate, a psychostimulant, and melatonin, a pineal gland hormone, were also reportedly effective.[24,25] The therapies mentioned above were effective in some cases when each was administered alone, but in other cases effectiveness could not be established until two or more of them were used in combination. So effective therapies of this nature have not been established yet and are still being tested by trial and error.

V. LONG-TERM FOLLOW-UP

What are the therapeutic results in these sleep rhythm disorders? So far as we know, there have been no reports on the long-term prognosis of these disorders. Using cases whose clinical course could be followed since 1981 (when our first DSPS case was reported[26]) we divided the cases into those in which the disease developed in adolescence (under 20 years of age) and those in which the age of onset was over 20 years, and investigated their prognosis. The adolescent cases with a mean follow-up period of 3.9 years and a mean age of 15.1 years at onset were investigated from two aspects, namely, the severity of the rhythm disorder and the degree of social adaptation.[27] Social adaptability improved significantly as shown in Fig. 4. A similar trend was seen with the adult-onset cases.[28] ICD-9-CM or DSM-III-R criterion cases with evident neuro-

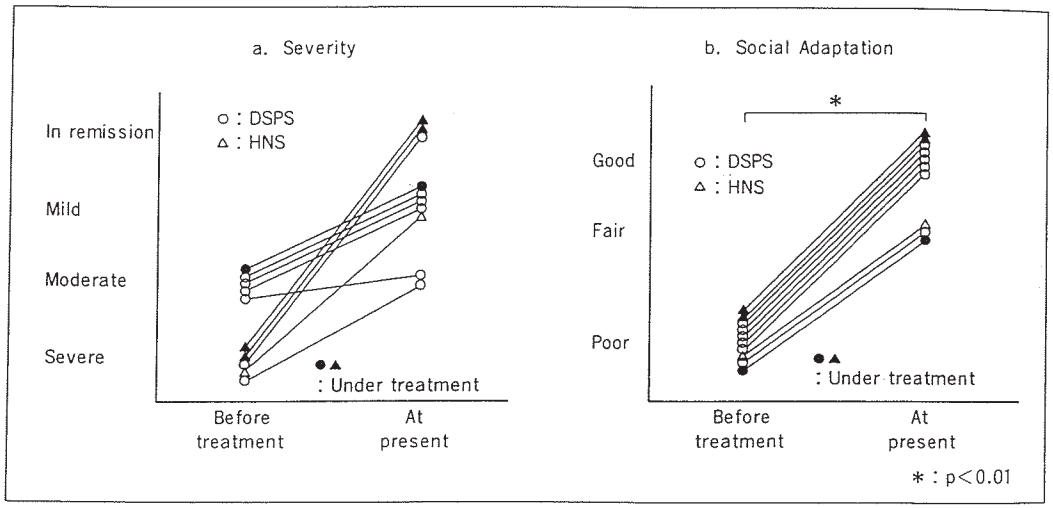

Fig. 4. Long-term follow-up of 10 adolescent patients. Changes in the severity level and social adaptation level. ○: Delayed sleep phase syndrome, △: non-24-hour sleep wake syndrome. Solid figures mean the patient was under treatment at follow-up (Ando et al., 1994[27])

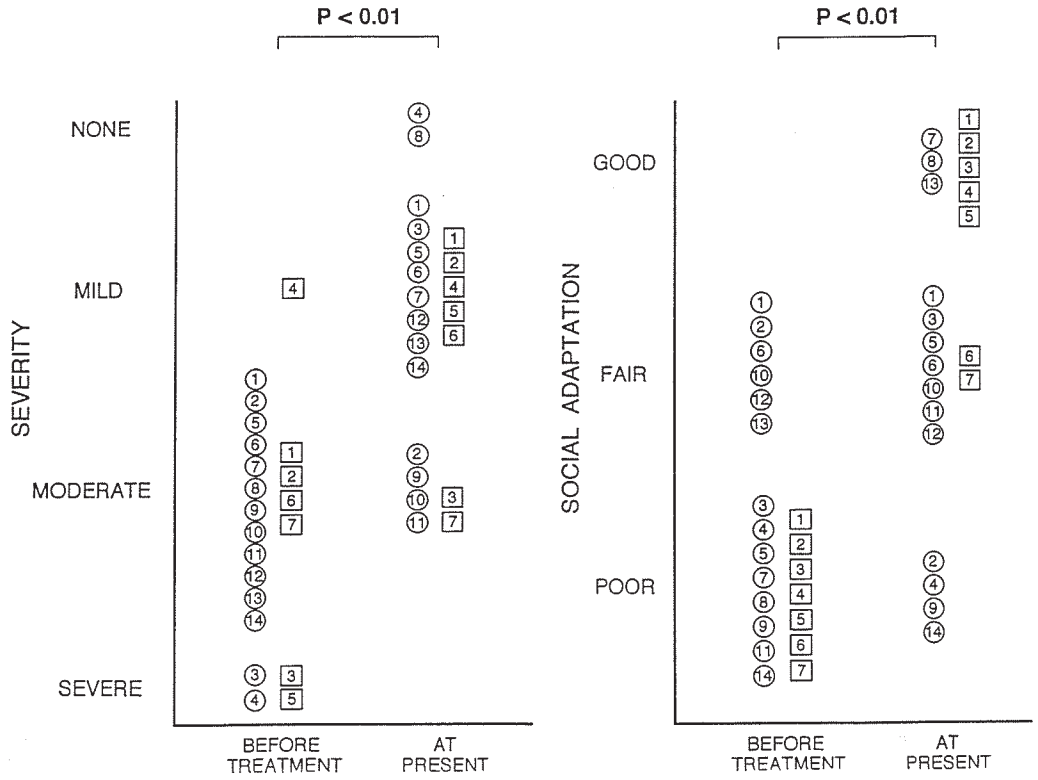

Fig. 5. Long-term follow-up of 21 DSPS patients. ○: Adult patients (N=14), □: adolescent patients (N=7) (Ohta et al., 1994[30])

psychiatric or personality disorders were excluded from these samples. Figure 5 shows the results of the follow-up study on our DSPS patients. Although DSPS is said to be more resistant to treatment than other sleep disorders,[29] the prognosis of this so-called primary sleep rhythm disorder is relatively good in our study and this is especially evident in the adolescent cases, suggesting the benefits of early discovery and treatment of this disease.[30]

VI. CONCLUSION

According to a survey which Nihon Hoso Kyokai (NHK, Japan Broadcasting Corporation) conducts every 5 years, the average sleeping time of the Japanese people on weekdays over the past 20 years has decreased by 18 minutes. As to the average sleep-onset time, it has increased by about 1 hour from about 10 p.m. to about 11 p.m. over the past 30 years. These findings show that the average living pattern of the Japanese is gradually shifting to the evening type. Whether or not there is any relationship between this phenomenon and the appearance of the sleep rhythm disorders mentioned above remains unknown, but there is a possibility that this change in lifestyle could effect the sleep-wake rhythm of young children. Elucidating this point will become an important subject of study from the standpoint of improving not only sleep hygiene but also mental health.

VII. ACKNOWLEDGEMENTS

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REFERENCES

1) Aschoff, J.: Circadian rhythms in man. Science, 148, 1422–1432 (1965).
2) Lewy, A.J., Wehr, T.A., Goodwin, F.K., Newsome, D.A. and Markey, S.P.: Light suppresses melatonin secretion in humans. Science, 210, 1267–1269 (1980).
3) Czeisler, C.A., Allen, J.S., Strogatz, S.H., Ronda, J.M., Sanchez, R., Rois, C.D., Freitag, W.O., Richardson, G.S. and Knonauer, R.E.: Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. Science, 223, 667–671 (1986).
4) Wever, R.: The circadion system of man: Results of experiments under temporal isolation. New York, Springer-Verlag, (1979).
5) Ohta, T., Iwata, T., Kayukawa, Y. and Okada, T.: Daily activity and persistent sleep-wake schedule disorders. Prog. Neuro-psychopharmacol. & Biol. Psychiat., 16, 529–537 (1992).
6) Diagnostic Classification Steering Committee, Thorpy M.J., Chairman. International classification of sleep disorders: Diagnostic and coding manual. Rochester, Minnesota: American Sleep Disorders Association, pp.128–133 (1990).
7) Ichikawa, H., Sato, T. and Takahashi, K.: Sleep-waking rhythm disorders observed in five school refusers. Jpn. J. Psychiatry Neurol., 44, 188 (1990).
8) Thorpy, M.J., Korman, E., Spielman, A.J. and Glovinsky, P.B.: Delayed sleep phase syndrome in adolescents. J. Adolesc. Health, Care., 9, 22–27 (1988).
9) Weitzman, E.D., Czeisler, C.A., Coleman, R.M., Zimmerman, J.C. and Dement, W.C.: Delayed sleep phase syndrome: A Chronobiological disorder with sleep-onset insomnia. Arch. Gen. Psychiatry, 38, 737–746 (1981).
10) Ohta, T., Ando, K., Hayakawa, T., Kogawa, S., Iwata, T., Terashima, M., Kayukawa, Y., Okada, T. and Kasahara, Y.: Treatment of adolescent patients with sleep-wake schedule disturbances who complain of non-attendance at school. Prog. Clin. Biol. Res., 341B, 65–72 (1990).
11) Alvarez, B., Dahlitz, M., Vignau, J. and Parkes, J.: The delayed sleep phase syndrome: Clinical and investigative findings in 14 subjects. J. Neurol. Neurosurg. Psychiat., 55, 665–670 (1992).
12) Schrader H., Bovim, G. and Sand, T.: The prevalence of delayed and advanced sleep phase syndromes. J. Sleep Res., 2, 51–55 (1993).
13) Czeisler, C.A., Richardson, G.S., Coleman, R.M., Zimmerman, J.C., Moore-Ede, M.C., Dement, W.C. and Weitzman, E.D.: Chronotherapy: Resetting the circadian clocks of patients with delayed sleep phase insomnia. Sleep, 4, 1–21 (1981).
14) Rosenthal, N.E., Joseph-Vanderpool, J.R., Levendosky, A.A., Johnston, S.H., Allen, R., Kelly, K.A., Souetre, E., Schultz, P.M. and Starz, K.E.: Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. Sleep, 13, 354–361 (1990).
15) Kamgar-Parsi, B., Wehr, T.A. and Gillin, J.C.: Successful treatment of human non-24-hour sleep-wake syndrome. Sleep, 6, 257–262 (1983).
16) Okawa, M., Mishima, K., Nanami, T., Shimizu, T., Iijima, S., Hishikawa, Y. and Takahashi, K.: Vitamin B12 treatment for sleep-wake rhythm disorders. Sleep, 13, 15–23 (1990).
17) Ohta, T., Ando, K., Iwata, T., Ozaki, N., Kayukawa, Y., Terashima, M., Okada, T. and Kasahara, Y.: Treatment of persistent sleep-wake schedule disorders in adolescents with methylcobalamin (Vitamin B12). Sleep, 14, 414–418 (1991).
18) Uchiyama, M., Mayer, G. and Meier-Ewert, K.: Effect of vitamin B12 on circadian body temperature. Jpn. J. Psychiatry Neurol., 48, 504–505 (1994).
19) Ohta, T., Kayukawa, Y., Okada, T., Iwata, T. and Terashima, M.: Resetting the sleep-wake cycle of schedule disorders and vitamin B12 treatment. In Biological Psychiatry volume 1, edited by Racagni, G., Brunello, N. and Fukuda, T., pp.791–793 (1991), Excerpta Medica, Amsterdam.
20) Turek, F.W. and Losee-Olson, S.: A benzodiazepine used in the treatment of insomnia phase-shifts the mammalian circadian clock. Nature, 32, 167–168 (1986).

21) Uruha, S., Mikami, A., Teshima, Y., Sugita, Y., Hondo, H., Inatani, K., Tachibana, N., Tsutsumi, T., Egawa, I. and Iijima, S.: Effect of triazolam for delayed sleep phase syndrome. Sleep Res., 16, 650 (1987).
22) Ozaki, N., Iwata, T., Ito, A., Ohta, T., Kasahara, Y., Kogawa, S. and Okada, T.: A treatment trial of delayed sleep phase syndrome with triazolam. Jpn. J. Psychiatry Neurol., 43, 51–55 (1989).
23) Wollman, M. and Lavie, P. and Peled, R.: A hypernychthemeral sleep-wake syndrome: A treatment attempt. Chronobiol. Int., 2, 277–280 (1988).
24) Dahlitz, M., Alvarez, B., Vignau, J., English, J. and Parkes, J.D.: Delayed sleep phase syndrome response to melatonin. Lancet, 337, 1121–1124 (1991).
25) Lewy, A.J., Ahmed, S., Jackson, J.M.L. and Sack, R.L.: Melatonin shifts circadian rhythms according to a phase-response curve. Chronobiol. Int., 9, 380–392 (1992).
26) Ohta, T., Iwata, T., Terashima, M., Okada, T. and Kasahara, Y.: Chronobiological study of delayed sleep phase syndrome. Sleep Res., 12, 270 (1983).
27) Ando, K., Hayakawa, T., Ohta, T., Kayukawa, Y., Ito, A., Iwata, T. and Okada, T.: Long-term follow-up study of 10 adolescent patients with sleep-wake schedule disorders. Jpn. J. Psychiatry Neurol., 48, 37–41 (1994).
28) Ito, A., Ando, K., Hayakawa, T., Iwata, T., Kayukawa, Y., Ohta, T. and Kasahara, Y.: Long-term course of adult patients with delayed sleep phase syndrome. Jpn. J. Psychiatry Neurol., 47, 563–567 (1993).
29) Regestein, Q.R. and Monk, T.H.: Delayed sleep phase syndrome: a review of its clinical aspects. Am. J. Psychiatry, 152, 602–608 (1995).
30) Ohta, T., Hayakawa, T., Ito, A., Ando, K., Ozaki, N., Kogawa, S., Imai, M., Yamaguchi, N., Koyama, E., Yamamoto, S., Abiru, T., Iwata, T., Kayukawa, Y. and Okada, T.: Long-term follow-up study on sleep-wake rhythm disorders: Comprehensive survey of patients in adolescent and adult. Jpn. J. Psychiatry Neurol., 48, 455–457 (1994).