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Vitamin B_{12} Treatment for Sleep–Wake Rhythm Disorders

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Summary: Vitamin B_{12} (VB_{12}) was administered to two patients suffering for many years from different sleep–wake rhythm disorders. One patient was a 15-year-old blind girl suffering from a free-running sleep–wake rhythm (hypernychthemeral syndrome) with a period of about 25 h. In spite of repeated trials to entrain her sleep–wake cycle to the environmental 24-h rhythm, her free-running rhythm persisted for about 13 years. When she was 14 years old, administration of VB_{12} per os was started at the daily dose of 1.5 mg t.i.d. Shortly thereafter, her sleep–wake rhythm was entrained to the environmental 24-h rhythm, and her 24-h sleep–wake rhythm was maintained while she was on the medication. Within 2 months of the withholding of VB_{12}, her free-running sleep–wake rhythm reappeared. The VB_{12} level in the serum was within the normal range both before and after the treatment. The other patient was a 55-year-old man suffering from delayed sleep phase syndrome since 18 years of age. After administration of VB_{12} at the daily doses of 1.5 mg, his sleep–wake rhythm disorder was improved. The good therapeutic effect lasted for more than 6 months while he was on the medication. **Key Words:** Hypernychthemeral syndrome—Delayed sleep phase syndrome—Vitamin B_{12}—Melatonin—Blind.

The mechanisms underlying sleep–wake rhythm disorders are not yet well understood, and treatment of sleep–wake rhythm disorders is often very difficult. Usually, hypnotic drugs are not effective for sleep–wake rhythm disorders. Chronotherapy has been used for the treatment of delayed sleep phase syndrome (DSPS) (1,2), although in many patients its effect is not long-lasting.

Among the sleep–wake rhythm disorders, non–24-h sleep–wake rhythm (hypernychthemeral syndrome) (3–7) and DSPS (8) are most annoying conditions, often creating difficulties in the social life of the patients and often resisting trials for treatment. For example, hypernychthemeral syndrome in a patient presented in our previous report (9) resisted intensive trials to entrain her sleep–wake rhythm by reinforcing zeitgebers.

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Successful treatment with vitamin B_{12} (VB_{12}) of non–24-h sleep–wake rhythm in a patient with hypothyroidism was first reported by Kamgar-Parsi et al. (6). It was a serendipitous treatment of the sleep–wake rhythm disorder, as VB_{12} was administered for the treatment of his hypothyroidism. Recently, Sugita et al. (10) reported another patient with hypernychthemeral syndrome who was successfully treated by VB_{12}.

We administered VB_{12} to two patients suffering from sleep–wake rhythm disorders for many years: one patient with non–24-h sleep–wake rhythm and the other with DSPS. VB_{12} had good therapeutic effects on their sleep–wake rhythm disorders.

CASE REPORTS

Case 1

A 15-year-old blind girl with severe mental retardation was reported clinically in our previous paper (9). The patient had congenital blindness due to microphthalmus and cataracta in both eyes. At 15 months of age, shortly after she started walking, she began to have epileptic generalized convulsions. At about the same time, her mother noticed that the child went to sleep about an hour later each day. She had no epileptic seizure between the age of 2.5 and 10 years. However, she still showed an unusual sleep–wake rhythm, i.e., she fell asleep and awoke about an hour later each day, showing an approximate 25-hour rhythm of sleep–waking. The child could not attend school during the periods when she slept in the daytime. After she was admitted to Akita University Hospital at 10 years of age, trials to entrain her sleep–wake rhythm to the usual 24-h rhythm by means of phototherapy, restricted meal time, forced awakening, and hypnotics were totally ineffective.

In August 1987, at 14 years of age, she was readmitted to Akita University Hospital for treatment of her unusual sleep–wake rhythm. Her sleep diary showed a persistent non–24-h sleep–wake rhythm (Fig. 1). One week after her admission, administration per os of VB_{12} at the daily dose of 1.5 mg t. i. d. was started. Five days after the beginning of the VB_{12} administration, she began to sleep at about 7:00 p.m. every day and to wake up between 3:00 and 6:00 a.m. Although she usually took a nap in the daytime, she showed a fairly regular 24-h sleep–wake rhythm. After the administration of VB_{12}, no significant changes were observed in her visual perception and intelligence.

During the summer holidays in August and September 1988, we stopped the VB_{12} administration because of an extremely high level of serum VB_{12}. About a week after the discontinuation, her sleep–wake rhythm tended to show a non–24-h rhythm during the 2 months (Fig. 1).

Laboratory findings at the time of her readmission at the age of 14 were as follows: red blood cell count (RBC) was $514 \times 10^4/\mu l$, hemoglobin (Hb) was 15.3 g/dl, and white blood cell count (WBC) was $9.3 \times 10^3/\mu l$. Concentrations of blood urea nitrogen (BUN), creatinine, total protein, albumin/globulin ratio, sodium, potassium, chloride, and protein-bound iodine were within the normal ranges.

The waking electroencephalogram (EEG) revealed 8–9-Hz waves dominant in the bilateral occipital areas, whereas the EEG recorded during sleep showed sporadic spikes in the left midtemporal and central areas. Daily total sleep time was 9.4 ± 0.85 h (mean $\pm$ SD).

Results of examinations of serum VB_{12} and melatonin rhythm were as follows: serum VB_{12} showed a normal level of 660 pg/ml before the treatment and 1,000 pg/ml and 2,770 pg/ml at 1 month and 1 year, respectively, after starting the VB_{12} administration (its

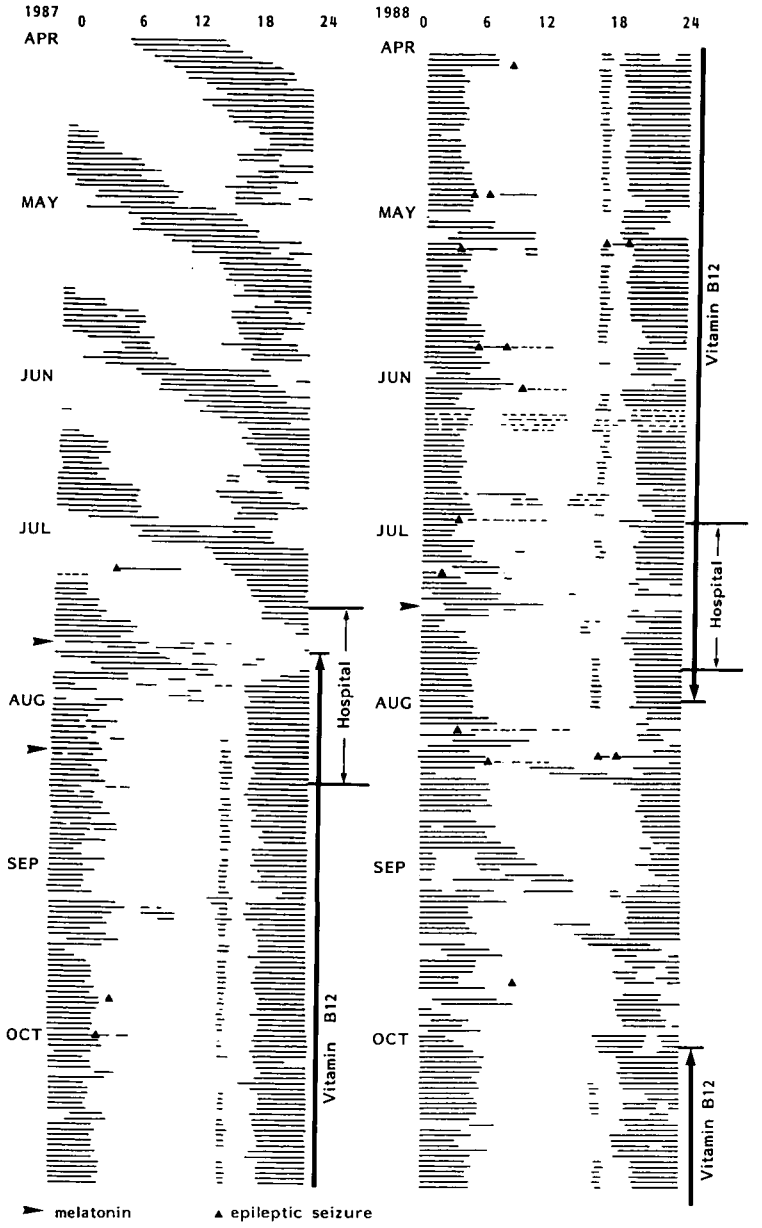

FIG. 1. The sleep–wake record in case 1 for 14 months in 1987 and 1988. Black horizontal bars represent sleep. Small triangles indicate epileptic seizures. Until late July 1987, free-running rhythms with a period of 24.7–24.9 h persisted. Since the administration of VB_{12} in early August 1987, sleep started after dinner, between 6:00 and 7:00 p.m., and ended between 3:00 and 6:00 a.m. However, her sleep was sometimes disturbed by unexpected episodes of epileptic seizures, cyanosis. After discharge, on July 25, 1988, VB_{12} treatment was discontinued. Her sleep–wake rhythm sometimes tended to show a free-running rhythm. After restarting of VB_{12} administration, the patient regained a 24-h sleep–wake rhythm. The days of blood samplings for measuring melatonin secretion rhythm are indicated by horizontal arrows in the left column.

normal blood level is 250–1,000 pg/ml). Blood samplings 7–11 times/day to examine the diurnal rhythm of melatonin secretion were performed on three occasions: on July 24 and 25, 1987, during the period of non–24-h sleep–wake rhythm; on August 12 and 13, 1987, during the period of entrained 24-h sleep–wake rhythm (2 weeks after the start of VB_{12} administration); and on July 12 and 13, 1988, 1 year after the start of VB_{12} administration when the 24-h sleep–wake rhythm was maintained (Figs. 1 and 2). Serum melatonin was assayed by the sensitive radioimmunoassay method with the use of antiserum and ^{3}H-melatonin (11). In all of these examinations, serum melatonin showed a high level during the sleeping period and a low level during the waking period. The peak level of melatonin was between 70 and 90 pg/ml for all three examinations, which was within the normal range.

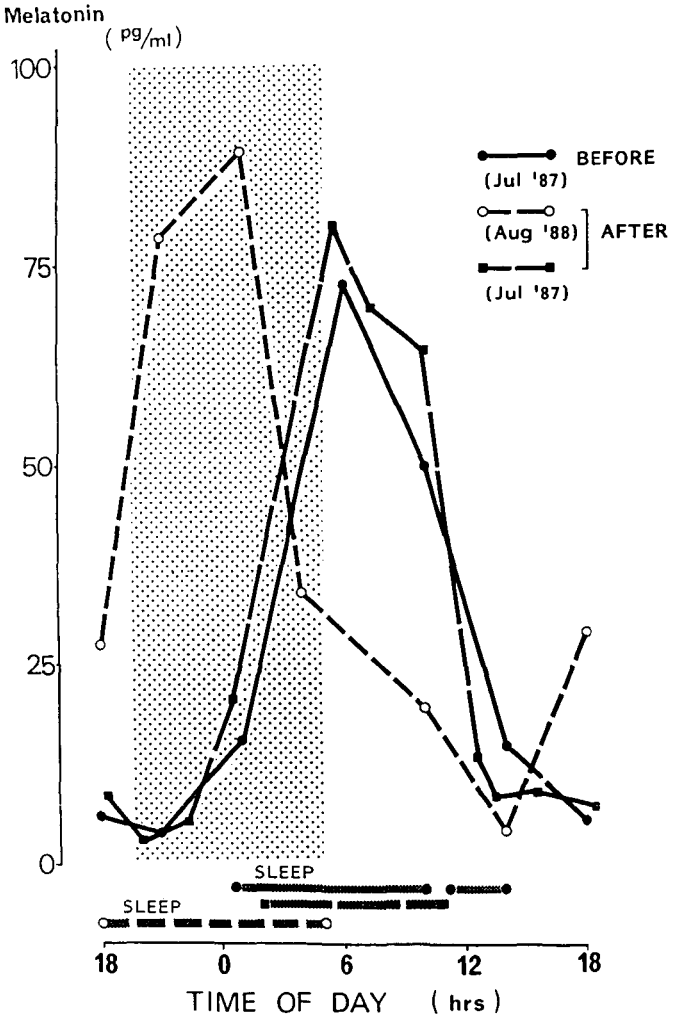

FIG. 2. Secretion pattern of melatonin before and after VB_{12} treatment. Horizontal lines in the bottom show the sleeping period on the day of blood sampling indicated in Fig. 1. Serum melatonin shows a high level during the sleeping period.

Case 2

A 55-year-old man, a local governmental official, suffered from difficulty in falling asleep since 18 years of age. He took several over-the-counter drugs for a year, but his sleep disorders did not improve. His sleep disorder was diagnosed as DSPS. He had neither neurological nor psychiatric disorders at that time. All previous attempts at treatment were unsuccessful.

At the age of 35, he had hypertension, and at the age of 46, it was found that he had diabetes mellitus and chronic nephritis. In August 1987, at the age of 53, he was admitted to Akita University Hospital for the treatment of chronic nephritis. He stayed at the hospital for 1 month. During his stay in the hospital, he had difficulty both in falling asleep and in maintaining sleep, in spite of regular time schedules for food intake and exposure to light.

Because of his sleep disorder, he was referred to our department. Hypnotic drugs, such as nitrazepam, triazolam, and barbiturate derivatives, were not effective, and his sleep disorders continued after discharge from the hospital. In October 1987, he had dysarthria and gait disturbance, which were due to multiinfarction in the brain. In December 1987, administration of VB_{12} per os at the daily dose of 1.5 mg was started. His sleep–wake rhythm disorder was improved shortly after the beginning of this drug administration: sleep onset usually occurred between 8:00 and 10:00 p.m., and awakening occurred between 6:00 and 8:00 a.m. (Fig. 3). He has been free from the sleep disorder for more than 6 months.

Physical examination of the patient in August 1987, disclosed that he had hypertension (180–110 mm Hg), slight dysarthria, and numbness and paresthesia in both his palms and feet.

Laboratory findings are shown in Table 1. Blood examination showed renal insufficiency. All-night sleep examinations indicated insomnia of initiating and maintaining sleep.

A sleep diary was kept from November 1987 to January 1988. Daily total sleep time averaged 4.9 ± 0.71 h before the VB_{12} treatment (Fig. 3).

His sleep–wake rhythm showed delayed phase insomnia before the treatment, whereas a normal 24-h sleep–wake rhythm was found after the treatment (Fig. 3).

DISCUSSION

The first report of using VB_{12} for the sleep–wake rhythm disorder concerned a patient who had suffered from insomnia and headache for many years and who was diagnosed as having the hypernychthemeral syndrome on the basis of his sleep diary (6). In addition, he had mild hypothyroidism. Given the reported high incidence of VB_{12} deficiency in patients with thyroid disease, he decided to medicate himself with VB_{12} capsules, which unexpectedly improved his sleep–wake rhythm disorder. The second successful case of VB_{12} treatment was reported by Sugita et al. (10). Their patient was a student who had suffered from the hypernychthemeral syndrome for many years, and VB_{12} was administered with the combination of sun-bathing. In the present study, VB_{12} did show very favorable effects on the sleep–wake rhythm disorder of DSPS as well as on the hypernychthemeral syndrome. Patients originally described as having DSPS were not reported to have had severely disturbed sleep, but only abnormality of the timing of sleep (6). Our case 2 may be diagnosed as having DSPS with a complication of a disorder of sleep continuity. In the first reported patients (6), DSPS also appeared

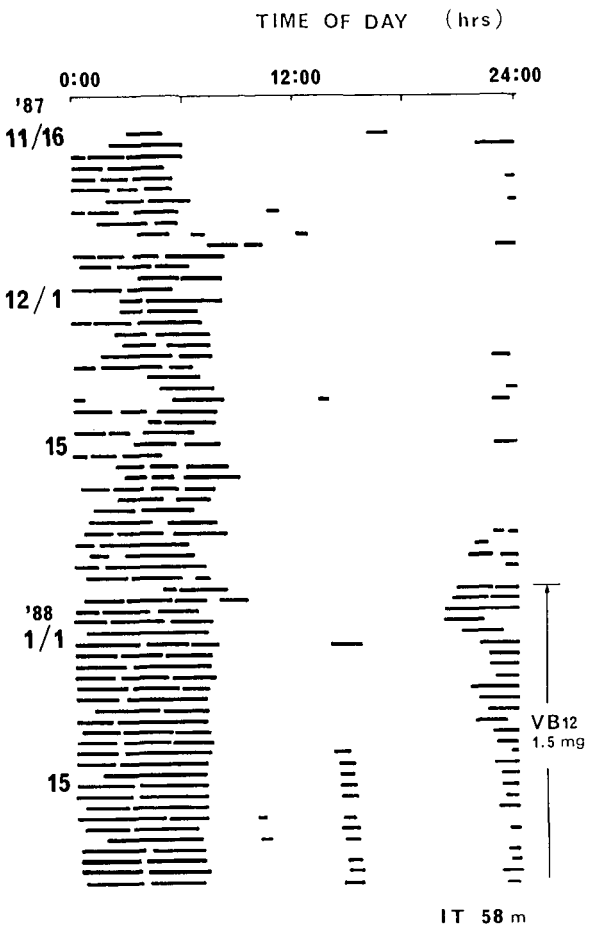

FIG. 3. Sleep–wake records in case 2. Before VB_{12} treatment, onset of sleep was irregular and late and total sleep time was shorter than after VB_{12} treatment. Sleep–wake rhythm was almost entrained to a 24-h rhythm accompanied by short naps in the daytime.

transiently as a prodrome of his eventual non–24-h syndrome. Both the hypernychthemeral syndrome and DSPS may be considered as having the common underlying mechanism of a failure to entrain the endogeneous rhythm to the environmental 24-h rhythm. Based on the present findings, it is conceivable that VB_{12} treatment is effective

TABLE 1. *Laboratory data of case 2*

Blood examination		All-night sleep recording	
WBC	4.7×10^3	Total sleep time	258 min
RBC	514×10^4	Sleep latency	115 min
Hb	11.1 g/dl	Total time of sleep stages 3 and 4	20 min
Hct	33.8%		
BUN	86 mg/dl	REM sleep time	32 min
Creatinine	6.3 mg/dl	Total time in bed	421 min
TSH, ^{131}I uptake, T2, T3: normal		Sleep efficiency	61.3%

WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin, Hct, hematocrit; BUN, blood urea nitrogen; REM, rapid-eye-movement.

not only for the hypernychthemeral syndrome, but also for DSPS. However, it should be noted that this study was not double-blind, and the detailed conclusion should be drawn later.

The mechanism through which VB_{12} produces beneficial effects on sleep–wake rhythm disorders is unclear at present. Possible mechanisms are as follows: (a) VB_{12} may change the period of the sleep–wake rhythm, (b) VB_{12} may improve the difficulty of entraining the endogeneous sleep–wake rhythm to the environmental 24-h rhythm, or (c) VB_{12} may simply cause an increased capacity for sleep. For case 1, mechanism a might be plausible, as her sleep–wake rhythm with the period of about 25 h changed to 24 h. On the other hand, this is not relevant for case 2, as he showed DSPS, which is considered to be a disorder in phase, and not period, of the circadian rhythm of sleep–waking. For case 2, mechanism c might be plausible, as his total sleep time increased after the VB_{12} treatment; for case 1, mechanism c seems irrelevant, as her total sleep time did not show much change with the administration of VB_{12}. As both the hypernychthemeral syndrome and DSPS can be considered as commonly failing to entrain the endogeneous rhythm to the environmental 24-h rhythm, mechanism b seems more plausible.

It would be interesting to know if the patients whose sleep disorder was improved after VB_{12} administration had a VB_{12} deficiency. In the previously reported patients (6,10), the baseline blood level of VB_{12} was not measured. Case 1 in this report did show normal VB_{12} levels before the VB_{12} treatment.

Deficiency of VB_{12} is known to accompany hematologic and neurologic abnormalities. Case 1 in this report did not show any of the symptoms of VB_{12} deficiency. Case 2 had a slight paresthesia in the feet, but this was not improved after VB_{12} administration. This indicates that although the blood level of VB_{12} was not measured in this patient, his slight paresthesia in the feet was not due to VB_{12} deficiency. In both of our patients, therefore, it was difficult to find any sign or symptom indicating VB_{12} deficiency. However, in both of our patients and in previously reported patients (6,10), the improvement of the sleep–wake rhythm disorders after treatment with VB_{12} was striking. In addition, the sleep–wake rhythm disorder in one of our patients relapsed several days or a few weeks after discontinuation of the medication.

The method of measuring serum VB_{12} level suffers from a lack of specificity, particularly if it is used as a screening test for patients with unexplained hematologic, neuropsychiatric, or other abnormalities (12–17). Based on the study of a large number of patients with "neuropsychiatric abnormalities," it was concluded that many kinds of neuropsychiatric symptoms were due to VB_{12} deficiency (17). In that study, VB_{12} deficiency was determined by laboratory tests, including assays of serum methylmalonic acid and homocystein, both of which are metabolized by the enzymes requiring VB_{12}, and it was suggested that the measurements of these metabolites are very helpful in finding VB_{12} deficiency (17). It is interesting and noteworthy that many of their patients with VB_{12} deficiency were free of well-known signs and symptoms of VB_{12} deficiency. There is therefore still the possibility that our patients have some abnormality in the metabolism of methylmalonic acid and homocystein that we have not yet examined.

The serum level of melatonin is known to show an endogeneous circadian rhythm with increased secretion during the night hours. Melatonin production appears to be a highly useful marker of the human endogeneous circadian pacemaker (18) and does not

appear to be affected by diet, sleep, or acute changes in the activity–rest cycle (19–24). In humans, as in lower animals, the light–dark cycle appears to be important in determining the melatonin production rhythm.

In our study, the melatonin secretion pattern in case 1 was synchronized with her sleep–wake rhythm, i.e., the melatonin and sleep–wake rhythms seemed to be phase-locked on three occasions (Fig. 3). Recent investigation by Lewy and Newsome (25) disclosed that 6 of 10 blind subjects had unusual melatonin secretion patterns. Furthermore, Sack et al. (26) have studied totally blind subjects longitudinally and have found that nearly half of them showed a free-running rhythm of melatonin secretion, despite the fact that their activity–rest cycle appeared to be entrained. In our case 1, however, it is not clear if she had a free-running melatonin rhythm. Thus, a further conclusion about the relationship between melatonin secretion and sleep–wake rhythm should be postponed at this time.

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