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BRIEF REPORT

The Clinical Practice for Hippocampal Neurogenesis by Chronobiological Therapy

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The hippocampal neurogenesis in rats has been studied. In addition, when enough activities are provided in daytime, it is suggested that the memory consolidation during sleep will be achieved by hippocampal neurogenesis. We introduce our clinical practice of the chronobiological therapy regarding six dementia cases. Our therapy is based on awakening-sleep rhythm. We performed the medication to promote the changes from sleep to awakening in morning and to stabilize non-REM sleep at night. We also treated the autonomic nervous disorders so that the internal organs became active with Japanese Kampo Medicines, which were integrated with Western medicines. We set our occupational therapy in the daytime. The clinical evaluation was performed by psychological examinations and voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) of MRI. As for Z-score showing the hippocampal atrophy in VSRAD we accomplished the improvement of 0.55 points from 0.03 about six dementia cases by the chronobiological therapy. These improvements were accompanied by the better changes of the cognitive functions. We speculate that the hippocampal neurogenesis may be derived by reconstructing awakening-sleep rhythm.

Keywords: Hippocampal neurogenesis; Chronobiological therapy; Awakening-sleep rhythm; Japanese Kampo Medicine; Voxel-based Specific Regional Analysis System for Alzheimer's Disease

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INTRODUCTION

The recent studies are successful in the hippocampal neurogenesis in vivo [1,2]. The neurogenesis by herbal medicine has been reported [3,4]. It is expected that there is the element which connects neurogenesis with clinical application in those medicine.

Circadian rhythm forms awakening-sleep rhythm, and the disorder of awakening-sleep rhythm produces each autonomic nervous disorder [5-8]. In the brain, during daytime there is fluctuating cognition (FC) that awakening (action) is mixed by rest (sleep) [9]. If patients have autonomic nervous disorder, in the circulatory organ, this condition will produce orthostatic hypotension during awakening by day [10]. In the digestive organs, loss of appetite will be seen in morning [11]. In the bladder, pollakiuria will be recognized during night [12]. If, against these dysfunctions, each organ awakes all together in the daytime and forms a sleep status in nighttime, the disorder of awakening-sleep rhythm will be improved.

METHODS

We reconstructed the awakening-sleep rhythm with internal medicines and Japanese Kampo Medicines (JKMs).

We performed Schellong's test to detect orthostatic hypotension. By the electroencephalogram (EEG), we evaluated presence of mixture of slow waves such as theta train and diagnosed the FC. As for the examination of psychology, Mini-Mental State Examination (MMSE) and the brief questionnaire form of the Neuropsychiatric Inventory (NPI-Q) were held [13,14]. Voxel-based specific regional analysis system for Alzheimer's disease (VSRAD), which is the software used widely in Japan, was conducted [15]. VSRAD uses MRI images and evaluates the atrophy degree of the hippocampal volume as compared with normal brain. This software uses 80 healthy persons' data. As a result of the statistics which compared a subject image and the healthy person average image, the Z score of VSRAD is a value to show the multiple of standard deviation which is far from the mean of the healthy person group. In the conventional study, it is shown that the Z-scores

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in VSRAD grow bigger with the brain atrophy in the progression of dementia [16]. The version of VSRAD plus with 1.0 tesla MRI was used before September in 2017. The version of VSRAD advance 2 with 1.5 tesla MRI was used after September in 2017.

When we considered the autonomic nervous disorder of circulatory organ, we used a diuretic or Toki-Shakuyaku-San. High blood pressure was treated by angiotensin II receptor blocker [17]. When pollakiuria was detected during night, we used Hachimi-Jio-Gan. When gastrointestinal peristalsis was considered, we treated lansoprazole in morning. Lansoprazole stabilizes the receptive relaxation of stomach in morning [18]. When we diagnosed low motivation, we used Ninjin-Yoei-To. When EEG pointed out FC, we chose JKMs containing Toki, Japanese Angelica Root. When it was necessary to make the end of activity towards night, we chose JKMs containing Chotoko, Uncaria Hook. Yokkan-San is a representative reconstructing the awakening-sleep rhythm. We performed a stabilization of the sleep accompanied with REM sleep behavior disorder by clonazepam and nitrazepam [19,20]. The light of the hospital room is turned on at 6:00 A.M. and the inpatients receive photic stimulation by white fluorescent lamp every morning. We set occupational therapy from half past 9 to half past 11 and from 13 to 15 o'clock.

RESULTS

The study included six patients who were followed in National Hospital Organization Kikuchi Hospital between July 2012 and December 2019. The six patients provided informed consent for the publication of their medical data. We obtained consent from the patients in Case 3 and 6 who was able to declare own intention and from the caregivers in Case 1, 2, 4, and 5 who did not have own intention. They were informed that data that were collected in medical records would be used for research study in accordance with privacy rule. The summary of cases is shown in Table 1.

Case 1

An 86-year-old man presented with a four-year history of memory disturbance. He was diagnosed as Alzheimer's disease at the age of 83 [21,22]. He was admitted to our hospital at the age of 85 years. We used 15 mg of lansoprazole, 2.5 mg of nitrazepam, and 6 g of Ninjin-Yoei-To. Two months after, MMSE score became 19/30 from 14/30 and Z-score of VSRAD became 4.14 from 4.17, which were examined by 1.5 tesla MRI and version of VSRAD advance 2.

Case 2

A 72-year-old man presented with a three-year history of memory disturbance. He was diagnosed as Alzheimer's disease at the age of 70. We gave 40 mg of valsartan, 5 g of Yokkan-San, 1.25 g of Toki-Shakuyaku-San, 0.25 mg of clonazepam, and 2.5 mg of nitrazepam. In about one year and two months, MMSE score became 23/30 from 19/30 and Z-score of VSRAD became 1.92 from 2.05, which were examined by 1.5 tesla MRI and version of VSRAD advance 2.

Case 3

A 65-year-old woman presented with a three-year history of memory disturbance. She was admitted to our hospital at the age of 63. She scored 17/30 on MMSE and showed 1.48 on Z-score, which was performed by 1.0 tesla MRI and version of VSRAD plus. She was diagnosed as Alzheimer's disease. We used 7.5 g of Bohu-Tsusho-San as the mood stabilizers containing Toki; and 2.5 mg of nitrazepam, 0.25 mg of clonazepam, and 2.5 g of Yokkan-San-Ka-Chinpi-Hange were added for the sleep rhythm. She scored 19/30 on MMSE and showed that the Z-score, which was examined by 1.5 tesla MRI and version of VSRAD advance 2, was 0.93 at the age of 65.

Case 4

A 93-year-old woman presented with a 7-year history of FC and memory disturbance. She was diagnosed as dementia with Lewy bodies at the age of 93 [23,24]. Her autonomic nervous disorder

Table 1. Summay of the six dementia cases with chronobiological therapy

Case	Age	Sex	Diagnosis	MMSE		NPI-Q		Z score		Recovered points
				1st	2nd	1st	2nd	1st	2nd	
1	86	Male	AD	14	19			4.17	4.14	0.03
2	72	Male	AD	19	23			2.05	1.92	0.13
3	65	Female	AD	17	19			1.48	0.93	0.55
4	93	Female	DLB	11	10	20	9	2.37	2.33	0.04
5	95	Female	DLB	14	11	21	2	5.7	5.58	0.12
6	73	Female	DLB	22	29			1.5	1.46	0.04

MMSE and NPI-Q were held. MMSE is the examination of cognitive function for dementia and its perfect score is 30. The patient is suspected to be dementia when the patient shows the score of 23 or less. NPI-Q is the scale of question form about BPSD. And it counts the severity and care burden degree of ten items about BPSD. We employed the disease severity in this study. Its perfect score is 30. BPSD is severe when NPI-Q score is near 30. VSRAD calculated Z scores, which show the atrophy degree of the hippocampal volume as compared with normal brain. We define the inspection at the time of the intervention with the chronobiological therapy as the first one and define the inspection after the intervention as the second one. Recovered points demonstrate the improvement points from the first Z score. AD, Alzheimer's disease; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination; NPI-Q, brief questionnaire form of the Neuropsychiatric Inventory; BPSD, behavioral and psychological symptoms of dementia; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease

was the QT interval prolongation on electrocardiogram. We prescribed 0.25 mg of clonazepam, 80 mg of valsartan, 20 mg of furosemide, 15 mg lansoprazole, and 7.5 g of Yokkan-San-Ka-Chinpi-Hange. In two months, the severity of NPI-Q became 9/36 from 20/36 and her Z-score of the medial temporal lobe in 1.5 tesla MRI and version of VSRAD advance 2 became 2.33 from 2.37.

Case 5

A 95-year-old woman presented with a 15-year history of memory disturbance. The instability of systolic blood pressure was shown in the range of 76 to 155 mm Hg at the age of 94. She was diagnosed as dementia with Lewy bodies. We prescribed 0.125 mg of clonazepam, 15 mg lansoprazole, and 2.5 g of Yokkan-San-Ka-Chinpi-Hange. We started 5 g of Keishi-Ka-Shakuyaku-To, which promoted motion of intestine. The severity of NPI-Q changed from 21/36 of the first day to 2/36 about 170 days after the hospitalization. And her Z-score in 1.5 tesla MRI and version of VSRAD advance 2 became 5.58 from 5.7.

Case 6

A 73-year-old woman presented with a five-year history of FC. She visited our hospital for amnesia at the age of 68. Her basic activity of 11 Hz alpha waves were mixed by theta train on EEG. Her Z-score, which was performed by 1.0 tesla MRI and version of VSRAD plus, was 1.50. Her score of MMSE was 22/30. She was diagnosed as dementia with Lewy bodies. We prescribed 15 mg of lansoprazole, 0.5 mg of clonazepam, and 2.5 mg of nitrazepam. We also gave her 4.5 mg of rivastigmine patch and 7.5 g of Yokkan-San. Her MMSE score was 29/30 on the 34th day after hospitalization. The Z-score was 1.46 at the age of 73.

Data analysis

Regarding the Z-scores at the time of and after the intervention with chronobiological therapy, the Pearson correlation coefficient was 0.994.

DISCUSSION

The neurodegenerative disease with dementia such as Alzheimer's disease has been regarded as a disease indicating progressive progress conventionally [25]. We introduced the chronobiological therapy against dementia cases. We reduced FC and autonomic nervous dysfunction of each organ by reconstructing awakening-sleep rhythm. Furthermore, we made the patients participate in the rehabilitation for cognitive functions.

Altman and Das [26] succeeded in hippocampal neurogenesis in rats in 1965. We thought that the hippocampal volume would be changed by the dominant factors based on the relation between the neurogenesis vs neurodegeneration.

We showed the chronobiological therapy to produce the improvement of hippocampal atrophy clinically in VSRAD study. It is suggested that this improvement is based on hippocampal neurogenesis.

Funding Statement

None

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article.

Author Contributions

Conceptualization: Masaki Shiozawa. Data curation: Masaki Shiozawa. Formal analysis: Masaki Shiozawa. Investigation: Masaki Shiozawa. Methodology: Masaki Shiozawa, Kenjiro Watanabe. Project administration: Masaki Shiozawa. Resources: Masaki Shiozawa. Software: Masaki Shiozawa. Supervision: Masaki Shiozawa. Validation: Masaki Shiozawa, Kenjiro Watanabe. Visualization: Masaki Shiozawa, Kenjiro Watanabe. Writing—original draft: Masaki Shiozawa, Kenjiro Watanabe. Writing—review & editing: Masaki Shiozawa, Kenjiro Watanabe.

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