

and seem to choose mental health over unhelpful levels of denial.⁷

Insistence on recovery was previously believed to be a negative indicator of functional improvement in disabled stroke patients, but our data⁴⁶ contradict this view, such that an appropriate level of insistence on recovery is actually associated with reduced depression and apathy, resulting in enhanced improvement of disability after a stroke. Thus, when caring for patients, we should inform them of their prognosis in such a way that they do not completely abandon all hope.

PHYSICAL DISABILITY AND PSD/APATHY

As described above, depression and apathy are typically thought to have a negative impact on stroke rehabilitation, with PSD/apathy being strongly correlated with cognitive disturbance. We have also examined correlations between PSD/apathy and aspects of physical disability, namely trunk balance and walking ability.^{22,53} Trunk balance was examined using a 10-min sitting balance task. Disturbed trunk balance was associated with fewer improvements in activities of daily living associated with the presence of depression/apathy.⁵³ In addition, proportional hazards analysis was used to determine the indepen-

dent effect of PSD/apathy on walking disability. Kaplan–Meier survival curves for reaching independence in walking showed highly significant differences in achievement rate and time to reach goals for each subgroup based on the presence of depression/apathy (Fig. 6).²²

We also examined the effect of improved walking ability on depression/apathy, finding that patients who could not walk on admission but could walk at discharge showed lower levels of depression and apathy, whereas those who could not walk during hospitalization showed no such tendency to improve (Fig. 7). Post-stroke physical disturbance appears to be closely correlated with levels of depression and apathy.

‘Classical’ disabled stroke patients show a droopy posture, with downward-looking eyes and reduced walking efficacy. This reduced mobility can render patients housebound, which, in turn, promotes depressive and apathetic mood disorders, resulting in a further obstacle to achieving functional improvement (a vicious cycle). Rehabilitation may be useful in correcting abnormal gait, thereby enabling patients to break out of this vicious cycle. Interventions that foster gait normalization should be promoted and made available as far as possible.

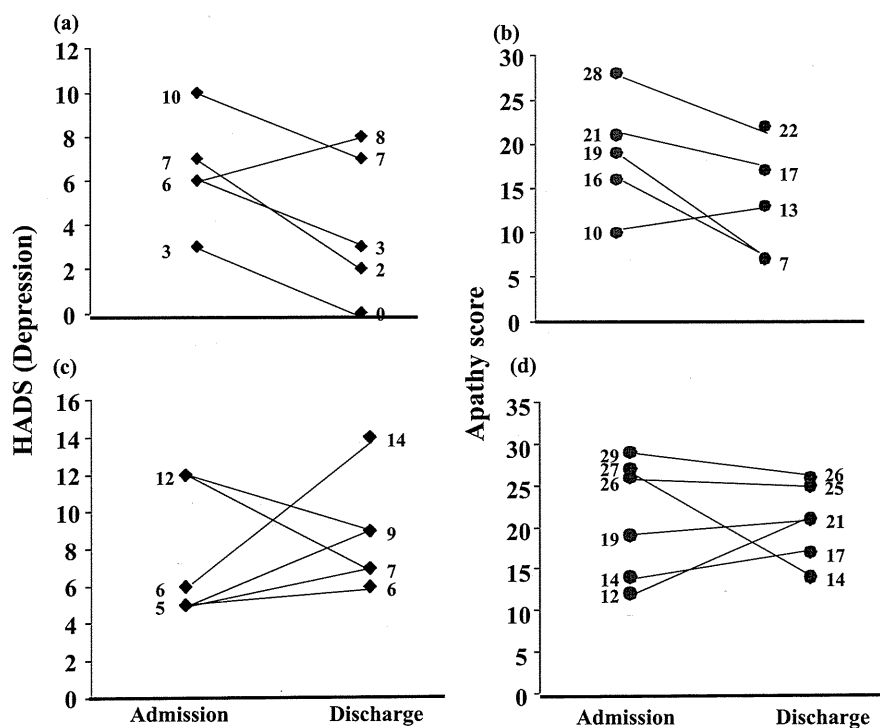


Figure 7 Correlations between (a,b) improvements and (c,d) no improvement in gait disturbance according to changes in symptom scores for (a,c) depression (Hospital Depression and Anxiety Scale; HADS) and (b,d) apathy (Apathy Scale; AS) from admission to discharge.

CONCLUSIONS

Specific brain lesions are thought to lead to increased vulnerability to the negative effects of stress. After stroke, many patients suffer from some disabilities, which results in a mourning process. This emotional response is thought to be a normative one to post-stroke problems. However, depression and/or apathy can develop in cases of extreme vulnerability to stress or failure to cope. Depression and apathy can interfere with functional improvement during rehabilitation. However, appropriate levels of insistence on recovery can serve to reduce or prevent depression and apathy. Moreover, improvements in activities of daily living (e.g. walking) have a positive effect on mood disorders. Reductions in PSD/apathy can enhance improvements in post-stroke disabilities. Helping patients to recover from PSD/apathy requires a multidisciplinary approach, focused on the neuroanatomical/neurobiological, emotional, and physical (rehabilitation) aspects of recovery.

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Long-Term Prognosis of Patients with Major Depression and Silent Cerebral Infarction

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Key Words

Elderly · Major depression · Silent cerebral infarction · Magnetic resonance imaging · Prognosis · Dementia

Abstract

Objective: Many studies have examined the effects of cerebrovascular changes on treatment response in geriatric depression. However, few such studies have examined the relationship between cerebrovascular changes and long-term prognosis. We examined the effects of cerebrovascular changes on the course of geriatric depressive symptoms, dementia rates, and mortality over a follow-up period of approximately 10 years. **Method:** Participants were 84 patients with major depression (age of onset over 50 years); patients suffering from strokes, neurological disorders, and other psychiatric disorders were excluded. Magnetic resonance imaging findings were used to classify all patients into silent cerebral infarction (SCI)-positive ($n = 37$) or SCI-negative groups ($n = 47$). Prognoses were ascertained using a review of clinical charts and mailed questionnaires. **Results:** Only 5% of patients with SCI were able to maintain remission whereas 36% of patients without SCI were able to do so. Total duration of depressive episodes was significantly longer in the SCI-positive group than in the SCI-negative group. SCI was also associated with a higher risk of dementia. **Conclu-**

sion: The results of this long-term follow-up study demonstrate that the presence of SCI is associated with a relatively poor prognosis in geriatric depression.

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Introduction

A growing body of evidence supports an association between cerebrovascular disease (CVD) and geriatric depression [1–4]. The term ‘vascular depression’ has been used to describe a depression subtype occurring later in life and characterized by cerebral changes that may be related to depression onset.

We have previously examined the relationship between geriatric depression and the presence of silent cerebral infarction (SCI), as detected by magnetic resonance imaging (MRI). SCI is detectable by MRI and other imaging modalities but has not been associated with the occurrence of strokes, focal neurological symptoms, or dementia. Depressive patients with SCI closely resemble those with vascular depression. Our earlier findings suggest that depressed patients with SCI show poor treatment responses to antidepressant pharmacotherapy compared to depressed patients without SCI [5–7]. Other researchers have also demonstrated a relatively poor prog-

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nosis and increased mortality of geriatric depressive patients with CVD [8]. Cognitive impairment in elderly depressed patients with CVD has also been reported, both during the depressed phase of the illness [9] and after recovery [10]. However, to our knowledge the relationships between the presence of CVD and two key variables, long-term prognosis and onset of dementia, have not been investigated in elderly depressed patients.

We aimed to test the following hypothesis: patients with depression and SCI will have higher rates of recurrence, dementia onset, and mortality than depressive patients without SCI.

Method

This study was designed in accordance with institutional guidelines and was approved by an institutional ethics review committee. All participants gave their written informed consent to take part in this study.

Participants

We initially assessed 172 patients with unipolar depression (meeting DSM-III-R or DSM-IV criteria for a major depressive episode), all of whom were over 50 years old. All patients were first admitted to either the Hiroshima University School of Medicine or Hiroshima Prefectural Hospital during the period of 1990 to 1999.

The patients included in this study were examined using MRI within 3 months of admission, and all met either the DSM-III-R criteria for major depression [11] or the DSM-IV criteria for major depressive disorder [12]. Patients showing evidence of stroke or focal neurological signs were excluded from the study. In addition, patients with alcoholism, cerebral degenerative disease, dementia, brain injury, systemic disease, and those taking medications that could induce depression were also excluded.

Eighty-nine patients were followed during the course of the study (representing 52% of the original sample assessed). Eighty-three patients had stopped receiving treatment within 5 years of admission and did not elect to participate in the study. Of the remaining 89 patients, we randomly selected 84 patients in a blind manner, matching for age and sex across the two groups. There were no significant differences between the patients who provided complete data on the variables age, sex, age of depression onset and those who did not, nor was there a significant difference in the proportions of patients with SCI and without SCI.

Magnetic Resonance Imaging Procedure

MRI was performed using a 1.5-tesla apparatus (General Electric Co., Milwaukee, Wisc., USA) at the Hiroshima University School of Medicine and a 1.5-tesla apparatus (Picker Co.) at the Hiroshima Prefectural Hospital. T₂-weighted images (repetition time TR, 4,000 ms; echo time TE, 100 ms) were obtained in the transverse plane parallel to the orbitomeatal line, and T₁-weighted images (TR, 400 ms; TE, 14 ms) were obtained as coronal slices at 5-mm thickness, with a 2.5-mm gap between sections. Infarcts were defined as high-intensity lesions that were larger than

5 mm in diameter on T₂-weighted images that coincided with low-intensity T₁-weighted lesions.

In the present study, as in our previous reports, an SCI was defined as the presence of 4 or more infarcts in the same hemisphere, and these patients were assigned to the SCI-positive group [5–7, 10, 13]. Patients with fewer than 4 infarcts were assigned to the SCI-negative group. Periventricular hyperintensity was not assessed. Details regarding the location and the particular hemisphere containing the SCI were not assessed given that almost all of the patients displayed multiple lesions. MRI scans were combined in a randomized order and were evaluated by a research psychiatrist (T.F.) prior to data collection.

Outcome Measures

Three main outcomes were assessed: course of depressive symptoms, dementia onset, and mortality. Reviews of patients' clinical charts were used to assess outcomes. In addition, all patients and their family members underwent detailed questioning by mail. The required minimum follow-up period for this study was 5 years. Patients who stopped receiving treatment within 5 years (i.e. whose clinical courses after stopping treatment were unknown) were excluded from data analysis.

We examined the number of relapses/recurrences, duration of depression, and the number of admissions for treating unipolar depression. The presence of manic episodes, either spontaneous or induced by antidepressant treatment, was also examined. Finally, the incidence of neurological disorders other than stroke (such as parkinsonism), the incidence of delirium, onset of dementia, and mortality were examined. The DSM-IV definition of dementia was used [12].

Analytic Strategy

Parametric data are reported as means \pm SD. Student's *t* test was used to compare mean differences between the groups. The χ^2 test was used to compare nonparametric numerical data points. A *p* value <0.05 was considered statistically significant.

Results

There were no significant differences between the patients with SCI and those without on the variables of age, sex, age of depression onset, years of education, kind of MRI acquisition (1.5 or 0.5 T), duration of study follow-up period, and kind of follow-up used (clinical chart, mailed questionnaire or both) (table 1).

Prognosis of Affective Disorders

Prognosis data for our study sample are shown in table 2. Only 5% of patients with SCI experienced sustained remission although 36% of patients without SCI were able to do so. The number of depressive episodes during the follow-up period was not significantly different across the groups. However, total duration of depressive episodes, percentage of depressed periods during follow-up, and number of hospital admissions due to depression

Table 1. Characteristics of depressed patients

	SCI-negative (n = 47)	SCI-positive (n = 37)	p value
Male/female	18/29	13/24	0.77
Age at the start of follow-up, years			
Mean \pm SD	60.2 \pm 6.5	63.0 \pm 6.7	0.05
Range	53–74	52–74	
Age at the end of follow-up, years			
Mean \pm SD	70.3 \pm 6.9	71.8 \pm 7.4	0.35
Range	59–87	60–87	
Years of follow-up			
Mean \pm SD	10.1 \pm 3.6	8.7 \pm 3.3	0.06
Range	5–15	5–15	
Kind of follow-up			0.95
Clinical chart	29	24	
Questionnaire by mail	4	3	
Both	14	10	
Age at onset of depression, years			
Mean \pm SD	56.3 \pm 7.2	56.8 \pm 9.0	0.78
Range	50–70	50–71	
Type of MRI acquisition			0.49
1.5 T	41	34	
0.5 T	6	3	
Years of education			
Mean \pm SD	11.8 \pm 2.5	11.8 \pm 2.4	0.91
Range	6–16	6–16	

were all greater in patients with SCI than in those without SCI. The two groups did not differ on the presence of manic episodes.

Other Disorders and Mortality

There were no significant group differences in the numbers of patients who developed delirium, stroke, and parkinsonism during follow-up (table 3). Mortality rates did not differ across the groups. However, the dementia onset rate during follow-up was significantly higher in patients with SCI than in those without SCI.

Discussion

While there are several reports on the effects of cerebrovascular change on treatment response in geriatric depression, to our knowledge no previous report has addressed the relationship between cerebrovascular changes and long-term prognosis of geriatric depression.

In the present study, only 5% of patients with SCI remained in remission during the follow-up period whereas 36% of the patients without SCI remained in remission.

Table 2. Prognosis of affective disorders

	SCI- negative	SCI- positive	p value
Continued remission, n	17 (36%)	2 (5%)	<0.001
Depressive episodes, n	1.4 \pm 3.8	2.3 \pm 2.4	0.24
Total duration of depression, years	1.3 \pm 2.1	2.5 \pm 2.2	0.02
Years of depression, %	16.0 \pm 27.1	34.8 \pm 30.3	0.007
Admissions due to depression, n	0.4 \pm 0.7	1.0 \pm 1.3	0.008
Presence of manic episode(s), n	3 (6%)	6 (16%)	0.15

Table 3. Other disorders and mortality

	SCI- negative	SCI- positive	p value
Mortality, n	6 (13%)	7 (19%)	0.44
Dementia, n	2 (4%)	7 (19%)	0.04
Delirium, n	0 (0%)	2 (5%)	0.11
Stroke, n	3 (6%)	6 (16%)	0.15
Parkinsonism, n	3 (6%)	5 (14%)	0.27
Somatic comorbidities, n	0.5 \pm 0.7	0.8 \pm 1.0	0.17

Total duration of depression was significantly longer in the SCI-positive group than in the SCI-negative group. In addition, SCI was associated with a higher risk of developing dementia.

The present results are consistent with the findings of previous studies that examined treatment responses in geriatric depression. Post [14] found that only 26% of a sample of 92 elderly depressed inpatients made a sustained recovery during a 3-year follow-up period: 25% of patients continued to experience chronic mild depression, and 12% were continuously ill throughout the follow-up period. Murphy [15] reported that 35% of a sample of 124 elderly depressed patients (>65 years of age) had a good outcome; 19% relapsed, 29% were continuously ill, 3% developed dementia, and 14% died. Murphy [15] concluded that geriatric depression is associated with poor treatment response compared to depression in younger patients. However, neither Post nor Murphy addressed the presence of organic brain disease.

Simpson et al. [16] conducted a 24-week naturalistic study on the treatment of geriatric depression and the effects of cerebrovascular changes on the course of depressive symptoms. They reported that subcortical hyperin-

tensities were more numerous in treatment-resistant patients and that neuropsychological impairment was restricted to such patients. In earlier studies [5, 7], we had also noted a relationship between the presence of cerebrovascular changes and poor treatment response to antidepressant therapy as well as a relatively poor prognosis in these patients during a 3-year follow-up period [6]. In contrast to our observations, Krishnan et al. [17], who investigated the 6-month recovery from an index episode of major depression in subjects with and without MRI-confirmed vascular brain changes, found no significant differences between the courses of patients with and without vascular depression. However, most of these earlier studies involved follow-up periods of less than 5 years and did not address dementia rates.

The mechanism that underlies the poor long-term prognosis of patients with affective disorders and SCI remains unclear, but one possible explanation is that the relatively poor cognitive functioning of these patients is itself associated with poor long-term prognosis. Baldwin et al. [18] showed that resistance to treatment of late-onset depression may be associated with impaired executive functioning, and they speculated that subtle cerebrovascular mechanisms might underlie this cognitive impairment. Cognitive impairment in elderly depressed patients with CVD has been reported during the depressive phase of the illness [9] as well as after recovery [10]. This study demonstrated that onset rates of dementia were significantly higher in patients with SCI than in those patients without.

Concerning the relationship between dementia and depression, Hebert et al. [19] investigated cohort incidence rates of vascular dementia by following 8,623 subjects over a 5-year period. They identified a number of risk factors for this form of dementia, including age, depression, diabetes, hypertension, heart problems, taking aspirin, and others. These researchers speculated that previous episodes of depression could represent a premonitory syndrome for vascular dementia or a marker of the severity of cerebral damage. Kokmen [20] reported that previous episodes of depression and hypertension increase the incidence rates of Alzheimer's disease. However, they had not initially investigated the existence of a vascular pathology using a neuroimaging modality such as computed tomography or magnetic resonance imaging.

Although little is known about the pathophysiological mechanism underlying this association, a growing number of reports demonstrate that depression may affect the coagulation system, thereby increasing the risk of stroke [21]. One possibility is that previous or current episodes

of depression may affect preexisting SCI and thereby increase the risk of dementia.

Incidence rates of dementia in the general population aged from 60 to 70 years old have been reported as 1–6 persons per 1,000 person-years [22–24]. The incidence rate of dementia in the present SCI-negative group was about 4 persons per 1,000 person-years. Previous episodes of depression alone appear to exert little effect on dementia onset although the coexistence of depression and SCI appears to constitute a potentially deadly combination.

A major limitation of our study is the lack of a comparison group of nondepressed controls. Future studies should include such a group to strengthen any potential findings. We were not able to assess dementia onset risk associated with the presence of SCI or depression alone, nor were we able to examine the two synergistically.

A second limitation is the lack of treatment data for this cohort during the follow-up period. Chronic exposure to medications may have neuroprotective or neurotrophic effects in some regions, including the basal ganglia, hippocampus, and subgenual anterior cingulate [25], and the anticholinergic effects of antidepressants may worsen cognitive functioning [26]. We therefore cannot exclude potential medication effects on the present findings.

A third limitation was our use of different magnet field strengths to detect infarcts. The field strength of 0.5 T results in more false-negative findings compared to the field strength of 1.5 T. However, we believe that this difference exerted a minimal effect on our results, given that the proportion of participants tested with the 0.5-tesla magnet did not differ across the SCI-positive and SCI-negative groups.

We conclude that among elderly patients with major depression, the presence of SCI is associated with a relatively poor prognosis. In addition, the presence of SCI is a risk factor for the onset of dementia among patients with geriatric depression.

Additional studies are needed to replicate these findings and to elucidate the mechanisms. In particular, studies will need to investigate the location of cerebrovascular change, type of dementia, the influence of ongoing treatment of depression and of comorbidities.

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Cerebrospinal fluid metabolite and nigrostriatal dopaminergic function in Parkinson's disease

Ishibashi K, Kanemaru K, Saito Y, Murayama S, Oda K, Ishiwata K, Mizusawa H, Ishii K. Cerebrospinal fluid metabolite and nigrostriatal dopaminergic function in Parkinson's disease.

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Objectives – To evaluate the association between cerebrospinal fluid (CSF) homovanillic acid (HVA) concentrations and nigrostriatal dopaminergic function assessed by positron emission tomography (PET) imaging with carbon-11-labeled 2β-carbomethoxy-3β-(4-fluorophenyl)-tropane (¹¹C-CFT), which can measure the dopamine transporter (DAT) density, in Parkinson's disease (PD). **Methods** – ¹¹C-CFT PET scans and CSF examinations were performed on 21 patients with PD, and six patients with non-parkinsonian syndromes (NPS) as a control group. **Results** – In the PD group, CSF HVA concentrations were significantly correlated with the striatal uptake of ¹¹C-CFT ($r = 0.76$, $P < 0.01$). However, in the NPS group, two indices were within the normal range. **Conclusions** – In PD, CSF HVA concentrations correlate with nigrostriatal dopaminergic function. Therefore, CSF HVA concentrations may be an additional surrogate marker for estimating the remaining nigrostriatal dopaminergic function in case that DAT imaging is unavailable.

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Key words: cerebrospinal fluid; dopamine transporter; homovanillic acid; Parkinson's disease; positron emission tomography; ¹¹C-CFT

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Introduction

In humans, homovanillic acid (HVA) is the major end-product of dopamine metabolism. The HVA in the cerebrospinal fluid (CSF) is largely derived from the nigrostriatal dopaminergic pathway; therefore, HVA concentration in the CSF has been used as an index of dopamine synthesis and presumed to reflect nigrostriatal dopaminergic function. However, even with the availability of a rigorous collection protocol, especially with respect to puncture time and pre-procedural resting, considerable inter-individual and intra-individual variability has been reported with regard to the concentration of CSF HVA in subjects with normal nigrostriatal function (1–3). Therefore, the extent to which CSF HVA concentrations reflect the nigrostriatal dopaminergic function is still unknown, and no study has specifically elucidated the association between the concentration of

CSF HVA and the function of nigrostriatal dopamine.

Many studies have shown that the concentration of CSF HVA substantially reduces in patients with Parkinson's disease (PD), which is a neurodegenerative disorder caused by nigrostriatal dopaminergic dysfunction (4–12). However, the extent of reduction also varied a great deal among patients with PD. Because of the variability, the relationship of clinical disability with CSF HVA concentrations and the accuracy of CSF HVA concentrations in differentiating PD from other parkinsonian syndromes have yet to be determined. Several authors have reported an inverse relationship between CSF HVA concentrations and the clinical severity (5–7, 10, 11), while others have denied such a relationship (9, 12, 13). Other neurodegenerative disorders caused by the dysfunction of nigrostriatal dopaminergic system, such as multiple system atrophy (MSA), progressive

supranuclear palsy (PSP) and corticobasal degeneration, also show the reductions of CSF HVA concentrations as compared to normal subjects (8, 14, 15). Therefore, the usefulness of measuring CSF HVA concentrations in daily clinical practice has not yet been established.

In order to address the physiological and pathophysiological backgrounds of these issues, we evaluated the correlation between CSF HVA concentrations and nigrostriatal dopaminergic function. Furthermore, we have discussed the mechanism by which the concentration of CSF HVA reduces in patients with PD.

As means of evaluating nigrostriatal dopaminergic function, we performed carbon-11-labeled 2 β -carbomethoxy-3 β -(4-fluorophenyl)-tropane (^{11}C -CFT) positron emission tomography (PET) scans which can reveal the dopamine transporter (DAT) density in the striatum. DAT imaging has been recognized as a standard marker for the diagnosis of PD, because it is a very sensitive, reproducible, and reliable marker of nigrostriatal dopaminergic function (16–21).

Materials and methods

Subjects

The present study was a retrospective study. The subjects comprised 35 patients [19 men and 16 women; age 60–83 years (mean age = 71.7 years, SD = 6.0)]. They visited the neurological outpatient clinic at Tokyo Metropolitan Geriatric Hospital from April 2001–November 2004. Of the 35 patients, 29 had parkinsonian symptoms and on the basis of each clinical criteria (22–24), 21 were diagnosed with PD, three with MSA, and five with PSP. The remaining six patients had no parkinsonian symptoms: three were clinically diagnosed with Alzheimer's disease (AD), two with spinocerebellar degeneration (SCD), and one with amyotrophic lateral sclerosis (ALS). Table 1 shows the

demographic data. The patients with MSA and PSP were classified in the patients with non-PD (NPD) group, while the patients with AD, SCD and ALS were classified in the patients with non-parkinsonian syndromes (NPS) group. The CSF examinations and the ^{11}C -CFT PET scans were performed within 5 months of each other. None of the patients had any concomitant hereditary disorder that could cause parkinsonian symptoms. All the patients were drug naive.

The normal range of HVA was determined by examining the CSF of 13 normal control subjects [five men and eight women; age, 65–88 years (mean = 77.2 years, SD = 8.2)]. Similarly, the normal range for nigrostriatal dopaminergic function was determined by performing ^{11}C -CFT PET scans of eight normal control subjects [five men and three women; age, 55–74 years (mean age = 62.3 years, SD = 6.9)]. All the control subjects were healthy and did not have any underlying diseases or abnormalities, as determined on the basis of their medical history and their physical and neurological examinations. None of them were on any medications at the time of the study. All the subjects also underwent routine MRI examinations.

All the CSF examinations and ^{11}C -CFT PET scans were performed for research. This study protocol was approved by the Ethics Committee of the Tokyo Metropolitan Institute of Gerontology and written informed consents were obtained from all the participants.

CSF analysis

Lumbar puncture was performed in the lateral decubitus position to obtain CSF samples from each subject. The first few milliliter of CFS was discarded. The next 3 ml of CFS was used for routine determinations of cell counts, protein and sugar and an additional 2 ml was stored at -70°C until the assays were performed. The concentration of CSF HVA was measured by injecting 80 μl CSF

Table 1 Demographics of patients and control subjects

	Subjects		Age (years)	Duration (years)	Striatal uptake of ^{11}C -CFT (Uptake ratio index)	CSF HVA (ng/ml)
	<i>n</i>	M:F				
Parkinson's disease	21	11:10	72.9 \pm 5.0	1.8 \pm 1.3	0.94 \pm 0.20	12.8 \pm 9.35
Hoehn-Yahr 1	1	1:0	62	1	1.38	36.8
Hoehn-Yahr 2	8	4:4	71.6 \pm 4.6	1.4 \pm 0.9	1.03 \pm 0.14	15.6 \pm 9.4
Hoehn-Yahr 3	12	6:6	74.7 \pm 3.9	2.1 \pm 1.5	0.85 \pm 0.17	8.9 \pm 5.4
Non-Parkinson's disease	8	4:4	70.5 \pm 7.7	1.6 \pm 0.8	1.00 \pm 0.19	16.4 \pm 7.7
Non-parkinsonian syndromes	6	4:2	68.8 \pm 6.3	4.5 \pm 2.4	2.48 \pm 0.28	31.9 \pm 13.0
Control for PET study	8	5:3	62.3 \pm 6.9		2.68 \pm 0.44	
Control for CSF study	13	5:8	77.2 \pm 8.2			36.0 \pm 13.8

Data are expressed as mean \pm SD; *n* = number, CSF, cerebrospinal fluid; HVA, homovanillic acid.

samples into a high-performance liquid chromatography system equipped with 16 electrochemical sensors (CEAS Model 5500; ESA, Bedford, MA, USA), as described previously (14).

PET imaging

¹¹C-CFT PET data acquisition – PET studies were performed at the Positron Medical Center, Tokyo Metropolitan Institute of Gerontology using a SET 2400W scanner (Shimadzu, Kyoto, Japan) in the three-dimensional scanning mode (25). The ¹¹C-CFT was prepared as described previously (26). Each subject received an intravenous bolus injection of 388 ± 75 (mean \pm SD) MBq of ¹¹C-CFT. Each subject was then placed in the supine position with their eyes closed in the PET camera gantry. The head was immobilized with a customized head holder in order to align the orbitomeatal line parallel to the scanning plane. To measure the uptake of ¹¹C-CFT, a static scan was performed for 75–90 min after the injection. The specific activity at the time of injection ranged from 7.1–119.6 GBq/ μ mol. The transmission data were acquired using a rotating ⁶⁸Ga/⁶⁸Ge rod source for attenuation correction. Images of 50 slices were obtained with a resolution of $2 \times 2 \times 3.125$ mm voxels and a 128×128 matrix.

Analysis of ¹¹C-CFT PET images – Image manipulations were carried out by using the Dr View software (version R2.0; AJS, Tokyo, Japan). The individual PET images were resliced in the transaxial direction, parallel to the anterior–posterior intercommissural (AC–PC) line. Circular regions of interest (ROIs) were placed with reference to the brain atlas and individual MRI images. Five ROIs (diameter, 8 mm) were placed on the

striatum on both the left and right sides in each of the three contiguous slices (the AC–PC plane, and regions 3.1 and 6.2 mm above the AC–PC line). Of the five ROIs, one ROI was placed on the caudate and four on the putamen. A total of 50 ROIs (diameter, 10 mm) were selected throughout the cerebellar cortex in five contiguous slices. To evaluate the striatal uptake of ¹¹C-CFT, we calculated the uptake ratio index by the following formula (17, 18), as previously validated (27, 28).

$$\text{Uptake ratio index} = \frac{\text{activity in the striatum} - \text{activity in the cerebellum}}{\text{activity in the cerebellum}}$$

Statistical analysis

Differences in the averages were tested using a Student's *t*-test. Correlations between the two groups were assessed by linear regression analysis with Pearson's correlation test. $P < 0.01$ was considered to indicate statistical significance.

Results

The inter-individual variability in the concentrations of CSF HVA in each group was relatively large (Fig. 1A). CSF HVA concentrations in both the PD ($P < 0.01$) and NPD groups ($P < 0.01$) were significantly lower than that in the control group (mean \pm 2SD, 36.0 ± 27.6), while no significant difference was observed between the NPS and control groups.

The striatal uptake of ¹¹C-CFT in the PD and NPD groups was below the normal range (mean \pm 2SD, 2.68 ± 0.87 ; Fig. 1B). In the PD group, CSF HVA concentrations were significantly

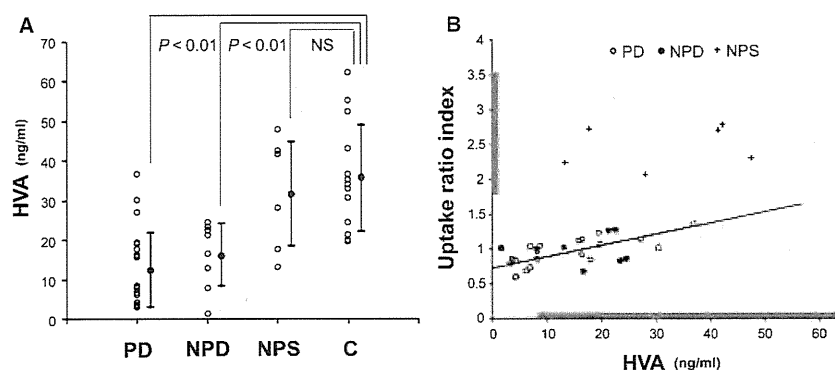


Figure 1. (A) The comparison of CSF HVA concentrations among the disease and control groups. Vertical bars represent mean \pm SD. (B) Relationship between CSF HVA concentrations and the striatal uptake of ¹¹C-CFT. A solid line represents the regression line for the PD group. Linear correlation was significant ($r = 0.76$; $P < 0.01$). The grey bars beside the *x*- and *y*-axes represent the normal range (mean \pm 2SD) for HVA (36.0 ± 27.6) and the striatal uptake of ¹¹C-CFT (2.68 ± 0.87). PD, Parkinson's disease; NPD, non-Parkinson's disease with parkinsonism; NPS, non-parkinsonian syndromes; C, controls; NS, not significant; CSF, cerebrospinal fluid; HVA, homovanillic acid.

correlated with the striatal uptake of ^{11}C -CFT ($r = 0.76$, $P < 0.01$). In the NPD group, although the correlation between the two indices was not statistically significant, the distribution pattern between the two indexes showed the same tendency as that in the PD group. However, in the NPS group, both CSF HVA concentrations and the striatal uptake of ^{11}C -CFT were within the normal ranges.

Discussion

We evaluated the correlation between CSF HVA concentrations and nigrostriatal dopaminergic function by performing ^{11}C -CFT PET scans. ^{11}C -CFT PET scans showed that all patients with PD and NPD had the dysfunction of nigrostriatal dopaminergic system and all patients with NPS had normal function. The CSF HVA concentrations of all patients with PD and NPD were significantly lower than those of normal subjects, in accordance with previous studies (5–12, 14, 15), whereas, there was no significant difference in CSF HVA concentrations between normal subjects and patients with NPS. These results suggest that CSF HVA concentrations could reflect nigrostriatal dopaminergic function. However, in accordance with previous reports (1–9, 13, 14), all groups showed large inter-individual variability in CSF HVA concentrations and relatively wide overlaps among groups were found. Therefore, in clinical practice, measuring CSF HVA concentrations may be of limited value in the diagnosis of PD.

This is the first study that investigated the correlation between CSF HVA concentrations and nigrostriatal dopaminergic dysfunction. Regardless of relatively high inter-individual variability, CSF HVA concentrations in the PD group showed a considerably high correlation with the striatal uptake of ^{11}C -CFT. The NPD group with nigrostriatal dopaminergic dysfunction showed the same tendency as the PD group, although without significant correlation probably because of the small number of patients. On the other hand, the NPD group with normal nigrostriatal dopaminergic function showed normal ranges in both the HVA level and the striatal uptake of ^{11}C -CFT. Therefore, CSF HVA concentrations may be an additional surrogate maker for estimating the nigrostriatal dopaminergic function in patients with PD, in case that DAT imaging, which has been recognized as a standard maker for the diagnosis of PD, is unavailable.

It is important to note that the DAT images of patients with PD are unique; in the pre-symptomatic phase the reduction in the availability of

striatal DAT was detected, presumably as a result of both the degeneration of nigral dopaminergic cells and the compensatory downregulation of DATs on the presynaptic site to maintain normal synaptic dopamine concentrations (17–21). Furthermore, the striatal DAT availability declined at an annual rate of 5–10% (19, 21, 29–31).

Considering our results and the unique characteristics of the DAT images, a possible explanation about the association between CSF HVA concentrations and the striatal uptake of ^{11}C -CFT is as follows (Fig. 2). The first stage of the disease is a compensatory and asymptomatic phase. Along with the progression of nigrostriatal degeneration, the striatal DAT availability begins to decrease, as described earlier (17–21). However, due to several compensatory mechanisms, including the downregulation of DATs and the upregulation of dopamine synthesis, the striatal dopamine concentrations are kept within the normal range (32). As a result, CSF HVA concentrations are also kept in the normal range because CSF HVA is the major end-product of striatal dopamine metabolism. This phase would show relatively large intra-individual and inter-individual variability in CSF HVA concentrations, as observed in subjects with normal nigrostriatal dopaminergic function, because of the reserve capacity for adjusting its levels. The second stage of the progression of the disease is an advanced and symptomatic phase. The compensatory mechanisms to maintain normal synaptic

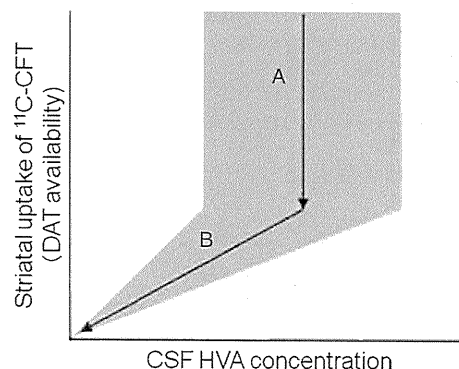


Figure 2. Schematic representation of the mechanism of CSF HVA reduction in patients with PD. (A) The nigrostriatal degeneration begins with a decrease in DAT availability, but due to several compensatory mechanisms, striatal dopamine concentrations (CSF HVA concentrations) are maintained within the normal range. There is a large variability with regard to CSF HVA concentrations. (B) The compensatory mechanisms break down and striatal dopamine concentrations (CSF HVA concentrations) begin to decrease along with the decrease in DAT availability. The variability in CSF HVA concentrations gradually becomes smaller. The grey zone represents the range of variability in CSF HVA concentrations to the striatal uptake of ^{11}C -CFT. DAT, dopamine transporter; CSF, cerebrospinal fluid, HVA, homovanillic acid.

dopamine concentrations break down and the striatal dopamine and CSF HVA concentrations begin to decrease with the reduction of DAT availability. In this phase, the intra-individual and inter-individual variability in CSF HVA concentrations would gradually decrease because of a lesser capacity for adjusting its levels. Consequently, CSF HVA concentrations remain within a narrow range that corresponds to the remaining nigrostriatal dopaminergic function. In symptomatic patients with PD, CSF HVA concentrations correlate with nigrostriatal dopaminergic function. To verify this explanation, a study with larger number of patients is needed.

In conclusion, we found a significant correlation between CSF HVA concentrations and the striatal uptake of ^{11}C -CFT in patients with PD. Although we should remember that CSF HVA concentrations show large variability, CSF HVA concentrations may be an additional surrogate maker for estimating the remaining nigrostriatal dopaminergic function in patients with PD in case that DAT imaging is unavailable.

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特集1

体内時計と身近な病気

生物リズムと双極性障害

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SUMMARY

双極性障害では、睡眠障害や症状の日内変動、日内リズムの変化などの概日リズム障害の問題と、症状の季節変動などの概年リズムの問題が想定され、光に対するメラトニン反応の変化や繊維芽細胞における遺伝子発現リズム振幅の低下などの報告もある。断眠やリズム変化に対する再発脆弱性、逆に生活リズムを整える社会リズム療法の予防効果などからも、生物リズムとの関連が示唆される。しかしながら、体内時計機構そのものの破綻ではないことは明らかであり、時計遺伝子等に注目するよりも、生物時計を調節する脳内機構に着目した研究が必要と思われる。

KEY WORDS

双極性障害
概日リズム
光周性
リチウム
Clock

はじめに

双極性障害では、睡眠の障害、日内リズムの乱れ、病相の周期性など、さまざまな観点から生物リズムの障害が推定され、時計遺伝子の変異検索がなされたり、時計遺伝子の遺伝子改変マウスがモデルマウスとして検討されるなど、生物リズムとの関係が指摘されている¹⁾。

本稿では、双極性障害においてどのようなリズム異常が想定されるのかについて検討する。

I. 臨床研究

1. 睡眠

うつ状態では睡眠障害が見られる。単極性うつ病では、典型的には不眠が見られ、特にメランコリー型うつ病では早朝覚醒が典型的である。一方、非定型うつ病では過眠が特徴的である。双極性障害におけるうつ状態では、非定型の特徴を持つことが多いとされており、単極性うつ病に比べると、過眠が見られる場合が多い。そのため、うつ病において過眠が見られることは、双極性障害の予測因子となる²⁾。

また、躁状態でも、睡眠欲求の減少という睡眠障害が見られる。

うつ病に対して断眠療法が有効であるとの報告があ

特集1 体内時計と身近な病氣

るが、双極性うつ病（双極性障害の大うつ病エピソード）の場合は、断眠が躁転を誘発するリスクが指摘されている。躁状態が悪化すると睡眠時間が減少し、これが躁状態を更に悪化させる、という悪循環が生じていると考えられる。

2. 日内リズム

メランコリー型のうつ病では、抑うつ気分が朝に悪いという症状の日内変動が見られる。これは双極性障害でも見られる場合はあるが、特徴的とはいえない。

また、時計型の行動量測定計を用いて24時間の行動量を計測した研究によれば、躁状態では、日内リズムの振幅低下、日中の行動量比率の減少、頂点位相の前進などが見られた。寛解期の患者でも、位相前進などいくつかのパラメーターに健常者と比較して差異がみられた⁹⁾。また、質問紙による調査では、双極性障害では夜型の人が多いという⁴⁾。

3. 年単位のリズム

一般にうつ状態は秋～冬に、躁状態は春～初夏に多いといわれている⁹⁾。

反復性のうつ病の中には、毎年冬にうつ状態になる、季節型という亜型が存在し、季節性気分障害、冬季うつ病などと呼ばれる。このタイプのうつ病は、高緯度地方に多く見られ、光療法が奏効する。また、過眠、過食あるいは炭水化物飢餓（甘いものが欲しくなる）という、非定型症状を示すことが多い。

季節性気分障害の患者の中には、冬にうつ状態、春に軽躁状態を示す、双極II型障害の場合もある。

II. 生物学的マーカー

1. REM 潜時の短縮

一般にうつ病ではREM睡眠潜時が短縮しているといわれており、双極性障害でも同様の所見が報告されている⁶⁾。

2. 光に対するメラトニン反応の変化

双極性障害患者では、光によるメラトニン分泌抑制の亢進が報告され、注目された⁷⁾。しかし、その後の研究では、光照射の有無にかかわらず、メラトニンが

低下していると報告されている⁸⁾。

3. サーカディアンリズム関連遺伝子と双極性障害と関連

CLOCK, BMAL1, DBP, TIMELESS, CSNK1E など、時計遺伝子および関連遺伝子の多型と双極性障害の関連が報告されている^{9, 10)}。一方、ゲノムワイド関連研究では、ANK3, CACNA1C など、イオン輸送関連遺伝子との関連が報告されているが¹¹⁾、時計遺伝子との関連は報告されていない。時計遺伝子との関連を見いだした研究を含め、過去の双極性障害における遺伝子関連研究は、症例数が少なく、ゲノムワイド関連研究でオッズ比の高い関連遺伝子が同定されなかった現状を鑑みると、これらの報告の多くは擬陽性所見の可能性が大きいと考えざるを得ない。

4. 線維芽細胞におけるリズム

12名の双極性障害患者由来線維芽細胞を12名の対照群由来細胞と比較した研究では、概日リズムの周期には差がなかったが、REV-ERBa や DBP など、いくつかの遺伝子の概日リズム振幅の低下が見られた¹²⁾。この所見は、独立サンプル（各5名ずつ）でも再現された。GSK3β のリン酸化については個人差が大きかったが、罹患者が低値を示すような家系もあった。

III. 危険因子

1. 断眠等のリズム変化に対する再発脆弱性

断眠は、躁状態を誘発する。躁状態とうつ状態の再発の誘因を比較すると、生活リズムの乱れが誘因となって再発するのは、躁状態のみであった¹³⁾。

2. 光による躁病の悪化

10000 Lux の高照度光を毎日長時間浴びた後に急速交代型気分障害を発症した症例が報告されている¹⁴⁾。

VI. 直接リズムを標的とした治療法

急速交代型双極性障害に対する臥床暗期延長療法（extended bed rest and darkness）の有効性が報告されている¹⁵⁾。また、躁状態に対する暗室療法（dark

表1 双極性障害と生物リズムの関連のまとめ

<p>症 状</p> <ul style="list-style-type: none"> ・睡眠障害 ・夜型 (evening type) が多い ・気分の日内変動 ・行動や体温などの日内リズムの変化 (頂点位相の前進, 振幅低下) ・症状の季節変動 <p>生物学的マーカー</p> <ul style="list-style-type: none"> ・REM 潜時の短縮 ・光に対するメラトニン反応の変化 ・サーカディアンリズム関連遺伝子と双極性障害と関連 ・繊維芽細胞におけるリズム振幅の低下 <p>悪 化</p> <ul style="list-style-type: none"> ・断眠やリズム変化に対する再発脆弱性 ・光による躁病の悪化 <p>治療法</p> <ul style="list-style-type: none"> ・双極性障害に対する社会リズム療法の予防効果 ・躁病の暗室療法の効果 ・急速交代型に対する長期臥床療法の有効性 ・治療薬の生物リズムへの効果
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therapy) の有効性が報告されている¹⁶⁾。

これらは、逸話的な報告にとどまっているが、双極性障害に対する対人関係社会リズム療法 (IPSRT) の有効性は、大規模な臨床試験で実証され、注目されている¹⁷⁾。対人関係療法は、もともとうつ病に対して用いられ、うつ病が悪化する契機として統計学的にも証明されているような誘因とそれに対するアプローチの集大成というべきものである。これを双極性障害に拡張しようとした時、双極性障害の再発の最大の誘因となる、徹夜などの生活リズムの乱れを無視できなくなり、拡張されたのが、対人関係社会リズム療法である。この治療法は、社会的同調因子理論 (social zeitgeber theory) に基づいている。すなわち、ライフイベントによって生活リズムの破綻を来たし、その結果、内因性のサーカディアンリズムの乱れが引き起こされ、躁

うつに至る、という考えである。この治療法では、起床時間、人と初めて会った時間、仕事などを始めた時間、夕食の時間、就寝の時間を毎日記録し、人との接触の度合いや気分の評価と共に記録し、社会リズムをコントロールしていく。

このように、光曝露が双極性障害を悪化させ、暗期を延長させ、リズムを一定にすることが有効であることが示唆されている。

▶ V. 既存の治療薬のリズムへの効果

GSK-3 β (glycogen synthase kinase 3 β) は、多くの基質が知られているリン酸化酵素で、当初は、双極性障害の予防に有効な気分安定薬であるリチウムの催奇形作用の作用機序として、GSK-3 β 阻害作用が注

目された¹⁸⁾。その後、GSK-3 β がニューロトロフィンのシグナル伝達に関与することや、バルプロ酸にもGSK-3 β 阻害作用が見つかったことなどから、むしろ双極性障害に対する作用機序として注目されるに至った。

一方、リチウムが概日リズム周期を延長させる作用は古くから知られていたが、そのメカニズムは不明であった。しかしながら、ショウジョウバエで、時計細胞のみにGSK-3 β を過剰発現させた変異体(PdfGAL4:UASsgg)ではサーカディアン周期が短縮し、この周期をリチウムが延長させた¹⁹⁾。これらのことから、リチウムの概日リズム周期に与える作用は、GSK-3 β を介していると考えられた。さらに、この際のGSK-3 β の基質は、オーファン核内受容体REV-ERB α であると考えられた²⁰⁾。REV-ERB α は、Bmal1の発現量に関与することによって、概日リズムの周期と位相に影響する。GSK-3 β はREV-ERB α をリン酸化することで安定化させるため、リチウムによるGSK-3 β 阻害は、REV-ERB α を急速に消失させる。リン酸化部位を失わせ、安定化させた変異型REV-ERB α を発現させると、Bmal1誘導が障害されることから、この系はリズムの形成に重要であると考えられた。

VI. 動物モデル

1. Clock 変異マウス

ニトロソウレアによる mutagenesis によって作出された変異マウスの中からのスクリーニングによって得られた、dominant negative 型の Clock 点変異マウスは、フリーラン周期の延長²¹⁾、睡眠減少²²⁾など、種々の概日リズム異常を示す。

McClung らのグループは、このマウスが躁病の動物モデルになると提案している²³⁾。このマウスは、持続的に多動を示し、うつ様行動の低下(強制水泳で無動時間が短縮、学習性無力試験で回避の失敗が少ない)、不安の低下(高架式十字迷路でオープンアームによく入る、オープンフィールド試験で中心にいることが多い)などの所見が見られた。また、コカインやショ糖の報酬としての価値が高まり、脳内自己刺激実験でも、弱い報酬で自己刺激してしまうという。このように、このマウスの行動は、躁状態における気分高

揚や多幸感と類似していると考えられた。また、これらの行動変化がリチウムで改善したことから、予測妥当性を満たすと考えられた。このマウスでは、中脳腹側被蓋野(VTA)のドーパミンニューロンの発火が増加していた²⁴⁾。そこで、このマウスのVTAに、Clock発現ベクターを注入したところ、多動は改善したという。

双極性障害でさまざまなリズム異常が見られることや、Clock 遺伝子多型と双極性障害の関連を示す遺伝子関連研究などから、このマウスは双極性障害モデルマウスとして提案されている。しかし、前述の通り、Clock 遺伝子多型と双極性障害の関連は疑わしく、双極性障害では位相前進や振幅の低下が示唆されているものの、フリーラン周期の変化を示唆する所見は乏しいなど、構成的妥当性の点で疑問が残る。

彼女らのグループは、最近、中脳腹側被蓋(VTA)特異的にClockをノックダウンしたモデルマウスを作成した²⁵⁾。このマウスは、多動になり、不安様行動が低下すると同時に、うつ様行動が増加(強制水泳試験における無動時間の増加、学習性無力試験における回避失敗の増加)したことから、「混合状態を呈した」と解釈されている。また、VTA特異的なノックダウンにもかかわらず、概日リズムのフリーラン周期の短縮、振幅低下が見られたことから、VTAのClockは行動の概日リズムに関与していると考えられる、と考察している。

これらのモデルは持続的に多動を示している。多動を示す遺伝子改変マウスは多数存在し、多動だけを根拠に躁病モデルということは難しい。すなわち、周期的な行動変化が見られないことが最大の難点である。また、双極性障害のモデルであれば、やはり躁状態とうつ状態が周期性を持って現れることに期待したいところであり、これらが同時に見られ、混合状態である、とするのは、少々無理があると思われる。

2. 変異 Polg1 マウス

我々は、生物リズム仮説とは関係なく、双極性障害モデル動物の研究を行ってきた。

双極性障害患者における磁気共鳴スペクトロスコピーによる研究で、ミトコンドリア病と類似した脳エネルギー代謝異常が見られたこと、重度のうつ病を呈した慢性進行性外眼筋麻痺(CPEO)の症例で、筋だ

けでなく脳にも mtDNA 欠失が見られたと報告されていること、双極性障害患者に死後脳で mtDNA 欠失が増加している者がいること、CPEO と双極性障害が連鎖する家系があることなどから、CPEO と双極性障害の関連に着目した。遺伝性 CPEO の原因遺伝子の 1 つが、ミトコンドリア DNA 合成酵素、ポリメラーゼをコードする、*POLG1* である。D181A 変異により校正活性を失わせた *Polg1* の変異体に神経細胞特異的なプロモーター (CAMKII α) をつけたトランスジェニック TG マウスを作製したところ、このマウスでは、mtDNA 欠失が加齢に伴って脳内に蓄積し、大欠失を持つ 2 kb 程度の短い mtDNA が蓄積していた。

このマウスは、感覚・運動、記憶・学習、情動性の顕著な異常は認めなかった。また、恒常暗条件における概日リズムは保たれており、周期にも変化はなかった。より双極性障害に近い行動学的表現型を探索するため、輪回し行動量の長期測定を行った。輪回し行動の日内リズムを検討したところ、明期になっても輪回しをしばらく続け、暗期になる前からまた動き始めるという特徴が見られた。また、このマウスに、双極性障害患者で躁転や急速交代化などの悪化を招く三環系抗うつ薬を投与したところ、日内リズム異常が悪化し、一部のマウスは、日中にもかかわらず動き続け、翌日から行動量が急に増加するなど、躁転によく似た行動変化を示した。一方、メスの遺伝子改変マウスでは、性周期に一致した 4~5 日周期の輪回し行動量の顕著な変動が見られた²⁶⁾。この周期的な行動変化は、リチウムにより改善した。また、頭部に電気けいれん刺激を与えたところ、日内リズムの異常は通電直後から顕著に改善した²⁷⁾。なお、ECT は、恒常暗条件における概日リズム位相には影響せず、この作用はリズムに対する作用を介しているとは考えられなかった。

本 TG マウスは、気分障害を伴う CPEO の原因遺伝子に変異を導入した点で構成的妥当性を、周期的な行動量変化がみられる点で表面的妥当性を、そしてリチウムの効果の点で予測妥当性を満たす、双極性障害モデルマウスと考えられた。さらに、このマウスにおけるより長期の行動観察では、輪回し量低下の期間が 2 週間程度続く、うつ状態様のエピソードも見られた。

この研究では、ミトコンドリア機能障害仮説という、生物リズムとは関係のない仮説に基づいて作成したモ

デル動物が、ある種のリズム異常を示した。恒常暗条件におけるリズムは保たれていることから、この異常は、生物時計機構そのもの異常とは考えられず、リズムの制御機構の問題であると考えられる。また、ミトコンドリア機能障害を基盤として、何らかの神経系が障害されたことが、こうした表現型につながると考えられ、どのような神経系の問題なのかが今後の課題である。

VII. 理論

1. ビート仮説

双極性障害では、内因性的リズムがフリーランしており、24 時間の外因性リズムとの間でうねり (ビート) が出現しており、これが躁状態、うつ状態の波である、という仮説である²⁸⁾。リチウムが概日リズム周期を延長させる作用を持つことは、この説を支持している。この仮説が全ての双極性障害にあてはまるとは考えにくい。急速交代型の患者の中にこのようなケースが存在する可能性が指摘されている⁹⁾。

2. 位相前進仮説

これは、外因性的リズムに対して内因性的リズムが前進しているために、両者が脱同期しているとの仮説である。前述の通り、これを支持する所見も報告されている。季節性感情障害における光療法の効果はこの説を支持するともいえるが、光療法は施行時間にかかわらず有効であるとのデータもあり、この所見はこの仮説とは矛盾している。

3. 位相不安定仮説・振幅低下仮説

双極性障害では、内因性リズムの振幅が低下し、位相が不安定になるなど、リズムがはっきりしなくなっている、という説である。

4. 光感受性異常説

双極性障害では、概日リズム自体は正常に機能しているが、これを外界の同調因子 (zeitgeber) である光により制御する、網膜から視床下部に至る網膜視床下部路の機能が障害されているとの仮説である²⁹⁾。光に対するメラトニン反応の亢進や、光による悪化、暗室

療法の効果などはこれを支持している。

5. 光周性異常説

近年、一年間の日照時間の変化に伴う生物の反応、すなわち光周性の研究が進んでいる。

ウズラでは、日照時間が長くなると、下垂体の隆起薬で甲状腺刺激ホルモン (TSH) が合成され、これが上衣細胞に作用し、甲状腺ホルモンを活性化する酵素である DIO2 (2 型脱ヨウ素酵素) を増加させる³⁰⁾。その結果、T4 (低活性型の甲状腺ホルモン) が T3 に変換される。これによって、性腺刺激ホルモン放出ホルモンが分泌され、繁殖活動が盛んとなる³¹⁾。

光周性の起点となるのは、夜に分泌されるホルモン、メラトニンであり、日照時間が長くなると、メラトニン分泌が減少することが光周性に関係していると考えられる。マウスで、メラトニンの変化が光周性に与える影響も、TSH を介しているが³²⁾、ほとんどの実験用マウスは元々メラトニンを欠損している。これは、メラトニンがないと性腺の発達が早くなるために、こうしたマウスが選択されてきたと考えられる³³⁾。

8 種の鶏とその先祖である野生の鶏において、次世代シーケンサーを用いてゲノム差異を調べたところ、家禽化に伴って TSH 受容体の変異が生じていることが見出された³⁴⁾。これは、光周性が失われることによって、年中繁殖できるようになったことが経営上有利であったため、こうした鶏が選択されてきたと考えられた。

甲状腺機能低下症に伴ううつ病、難治性うつ病に対する甲状腺ホルモン剤の増強療法の有効性、リチウムによる TSH 上昇とそれに伴う急速交代化など、これまでさまざまな形で、気分障害と甲状腺機能の関係が指摘されてきた。甲状腺刺激ホルモンとして知られていた TSH が、年周期のリズム制御にも関与していることが明らかとなったことにより、これらの所見についても、再検討が必要と考えられる。ヒトにおける年単位のリズムと TSH の関連、および気分障害の病態への関与については、今後のさらなる研究が必要である。

おわりに

このように、生物リズムと双極性障害の関係については、確実なデータが少ない一方で、多くの仮説が入り乱れているのが現状である。

概日リズムの問題なのか、概年リズムの問題なのか、時計遺伝子にかかわる細胞内のシグナル伝達の問題なのか、脳内におけるリズム制御にかかわる神経系の問題なのか、こうした基本的な問いにさえ、未だ答えられない状況にはない。

しかしながら、繊維芽細胞の研究が示すように、双極性障害が、概日リズムを司る時計機構の遺伝的異常によりリズムが失われている疾患でないことは明らかである。これまでは、時計遺伝子の遺伝子解析や時計遺伝子の遺伝子改変モデル動物の研究などが多かったが、今後は、細胞内の時計機構の遺伝子ネットワークよりも、概日リズムの調節を行う神経系へと研究をシフトさせた方がよいのではないだろうか。

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