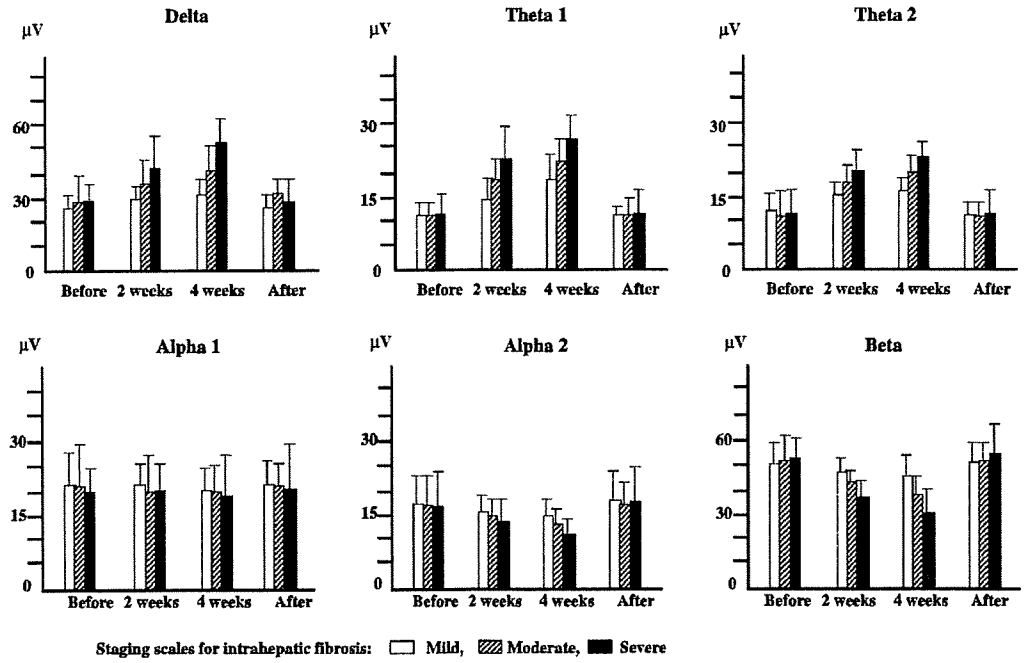

Figure 1. Alterations in absolute power values (means±standard deviations) by stage (of intrahepatic fibrosis) for each frequency band at the following 4 time points: before IFN-α treatment, at 2 and 4 weeks of treatment, and at 2-3 days after conclusion of treatment. Increasing power values for slow waves (delta, theta 1 and 2) and decreasing power values for alpha 2 and beta waves during IFN-α treatment, in comparison with those before and after IFN-α treatment, were evident for all stages. Moreover, alterations in power values became more pronounced as stage increased in all frequency bands except for alpha 1 and total power values.

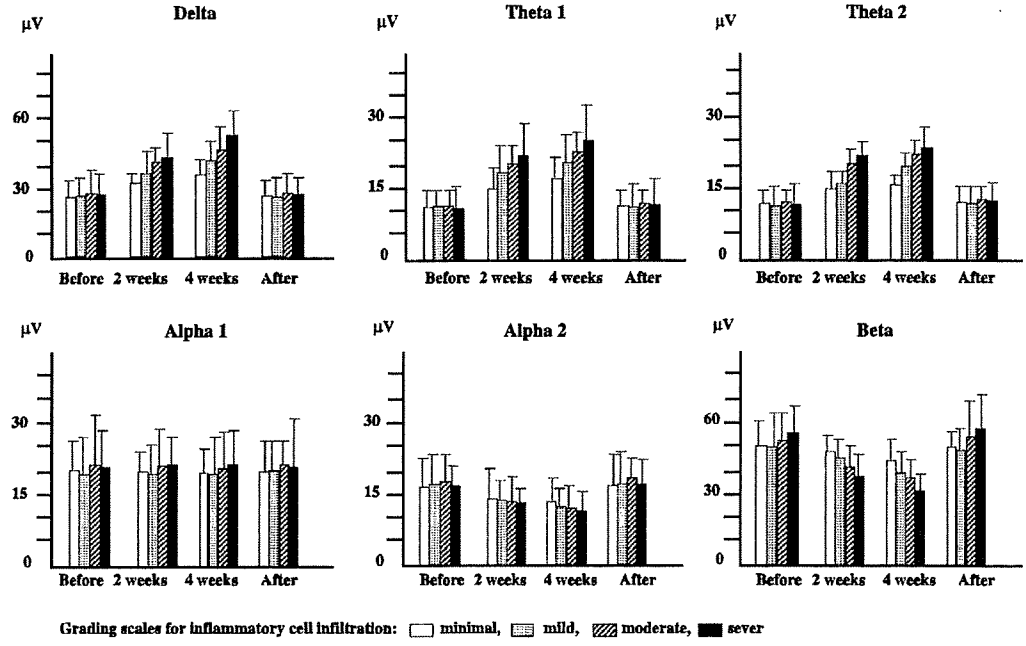

Figure 2. Alterations in absolute power values (means±standard deviations) by grade (of inflammatory cell infiltration) for each frequency band at the following 4 time points: before IFN-α treatment, at 2 and 4 weeks of treatment, and at 2-3 days after conclusion of treatment. Increasing power values for slow waves (delta, theta 1 and 2) and decreasing power values for alpha 2 and beta waves during IFN-α treatment, in comparison with those before and after IFN-α treatment, were evident for all grades. Moreover, the alterations in power values became more pronounced with increase in grade in all frequency bands except for alpha 1 and total power values.

Table 2. Repeated Measures Analysis of Variances between Alterations in Power Values during IFN-α Treatment and Stage (Intrahepatic Fibrosis) or Grade (Inflammatory Cell Infitraion)

Factors	
Alteration of power values during IFN-α treatment (Alteration of power values)	$p< 0.0001$ (F=30.338)
Alteration of power values × Difference of staging scale (Difference in stage)	$p< 0.0001$ (F=14.531)
Alteration of power values × Difference of grading scale (Difference in grade)	$p< 0.0001$ (F=12.071)
Alteration of power values × Frequency bands	$p< 0.0001$ (F=48.781)
Alteration of power values × Electrode location	NS
Alteration of power values × Difference in stage × Frequency bands × Electrode location	NS
Alteration of power values × Difference in grade × Frequency bands × Electrode location	NS

NS = not significant; × = interaction.

Table 3. Statistical Comparisons by Post-hoc ANOVA of Alterations in Power Values during IFN-α Treatment for Each Frequency Band between Stages and Grades

Comparison of stages and grades based on biopsies		Power values (μV)						
		delta	theta 1	theta 2	alpha 1	alpha 2	beta	total
Stage (intrahepatic fibrosis)	mild vs. moderate	**	**	*	NS	NS	**	NS
	moderate vs. severe	**	**	**	NS	*	**	NS
	mild vs. severe	**	**	**	NS	*	**	NS
Grade (inflammatory cell infiltration)	minimal vs. mild	**	**	**	NS	NS	*	NS
	minimal vs. moderate	**	**	**	NS	*	**	NS
	minimal vs. severe	**	**	**	NS	*	**	NS
	mild vs. moderate	**	**	**	NS	NS	*	NS
	mild vs. severe	**	**	**	NS	*	**	NS
	moderate vs. severe	**	**	**	NS	*	**	NS

NS = not significant; * = $0.01 \leq p < 0.05$; ** = $p < 0.01$.

versible after completion of the treatment (4). Moreover, neuropsychiatric complications have been described as difficult to evaluate following IFN-α treatment in patients with chronic viral hepatitis (8). In view of the considerable numbers of patients undergoing IFN-α treatment, detailed information on the factors affecting EEG alterations due to IFN-α treatment seems vital for prediction of the appearance of such adverse effects on brain function following IFN-α treatment. Patient age was recently identified as one of the factors involved in such alterations of EEGs during IFN-α treatment (6). However, no other factors affecting alterations of the EEG during IFN-α treatment have been reported. The findings of the present study indicated that severity of hepatitis based on liver biopsies is one such factor. However, there are some statistical limitations to the present study. Since we evaluated alterations of q-EEG during four different periods (pre-treatment, at 2 and 4 weeks of treatment, and post-treatment), the scales of severity based on liver biopsy findings were handled as continuous variables in rANOVA of present study.

The etiology of this type of encephalopathy remains unclear regarding whether it involves direct or indirect toxic effects on the central nervous system. Several possible indirect mechanisms can be considered. IFN plays a role in the production of secondary cytokines such as interleukin-1 and tumor necrosis factor (9). Neuroendocrine hormone alterations may also be induced by IFN. IFN displays structural and functional similarities to neuroendocrine hormones such as ACTH (10, 11), and increased cortisol levels have been observed during IFN treatment. Such metabolic vulnerability might result in the diffuse slowing of brain waves observed on the EEG. LC is the most severe stage in Desmet's classification. Some degree of asymptomatic hypofunction of the brain might thus be evident even in patients with CH, as in patients with LC. Our finding of a significant correlation between alteration of qEEG during IFN administration and the severity of liver biopsy findings suggests that the EEG alterations observed in the present study might be detected the brain hypofunction of mild encephalopathy due to IFN in addition to the some degree of brain hypofunction in the patients with severe CH.

The diffuse slowing of EEG observed in the present study was reversible after the completion of treatment (Figs. 1, 2). This alteration of EEG was thus considered to be an asymptomatic and mild type of encephalopathy. However, the alterations of the EEG occurring during IFN-α treatment were marked in older aged patients and also in those with a high stage and grade based on liver biopsy findings. These findings suggest that the administration of IFN-α should be discontinued in patients with neuropsychiatric complications such as depression in the presence of EEG slowing. Serial EEG monitoring thus appears to be of value in detecting alterations of brain function during IFN-α treatment in chronic viral hepatitis patients, and alterations on serial EEGs should be carefully monitored in older patients and in those with severe stage and grade on liver biopsies.

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Fatigue in Japanese Patients with Parkinson's Disease: A Study Using Parkinson Fatigue Scale

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Abstract: The objective of this multicenter cross-sectional study was to determine the prevalence of fatigue and factors contributing to it in a large sample of Japanese patients with Parkinson's disease (PD). We used the 16-item Parkinson Fatigue Scale (PFS-16), which was designed to assess fatigue exclusively associated with PD. We carried out this study using PFS-16, the Unified Parkinson's Disease Rating Scale, Zung's Self-Rating Depression Scale, Parkinson's Disease Sleep Scale (PDSS), and the PD quality of life (QOL) scale (PDQ-39) by interview using questionnaires and physical examination by neurologists in 361 nondemented PD patients. Fatigue (an average PFS score of 3.3 or greater) was revealed in 151 patients (41.8%). Multiple logistic regression analysis indicated that the significant independent variables related to the presence of fatigue were the scores of PDSS and PDQ-39. Depression score was not a significant contributing factor. Our study revealed that the prevalence of fatigue in Japanese PD patients is as high as that in Western countries, and that fatigue is a relatively independent symptom, although sleep disturbance may be associated with fatigue. Since fatigue is significantly related to QOL reduction, therapeutic interventions including treatment of sleep disturbance are important. © 2009 Movement Disorder Society

Key words: Parkinson's disease; fatigue; sleep disorder; quality of life

The subjective experience of fatigue is common in patients with systemic, psychiatric, and neurologic diseases including Parkinson's disease (PD).[1] Fatigue has been reported in more than 40% of PD patients and its prevalence is consistently higher than that in age-matched healthy controls.[2–7] Despite its high prevalence, fatigue is still inadequately recognized and under-diagnosed in terms of its negative impact on patient's quality of life (QOL).[8,9] Indeed, Shulman et al. reported that 42% of PD patients showed evidence of fatigue but only 14% of their treating neurologists recognized the condition.[8] They also showed that physicians were least sensitive to the presence of fatigue among nonmotor symptoms such as depression.

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The pathogenesis of fatigue remains largely unclear. It has been considered to be related to other features such as depression and nocturnal sleep disturbance.[1,3,5,7,10] However, the results of the studies of contributing factors varied. One of the reasons for this discrepancy may be, except for the Norwegian studies, the relatively small number of patients studied. Recent studies have shown that comorbidities such as depression may contribute to the experience of fatigue, but they cannot readily explain the high prevalence of fatigue.[3,7] For instance, as much as 40% of PD patients who did not have depression or sleep disturbance also reported fatigue.[3,7,9]

Although there are many instruments assessing fatigue such as the Fatigue Severity Scale (FSS), they have not been validated in PD and are not PD-specific.[11,12] Recently, Brown et al. have developed the 16-item self-report instrument, Parkinson Fatigue Scale (PFS-16).[13] This scale was designed specifically for assessing the physical aspects of Parkinsonian fatigue, and items would have a minimal overlap with other motor and nonmotor symptoms of PD. The objective of this multicenter study was to determine the prevalence and characteristics of fatigue in a large sample of Japanese patients with PD using PFS-16 for the first time. We also examined the predisposing comorbidities such as depression and sleep disturbance using validated scales.

PATIENTS AND METHODS

Patient Definitions

A total of 411 consecutive patients with idiopathic PD, men and women patients beyond the age of 30, and who agreed to participate in this study were initially considered eligible. The definition of idiopathic PD and exclusion criteria are described below. Patients were evaluated and diagnosed by neurologists specializing in movement disorders. This study was carried out in 11 medical university hospitals (Kanto Parkinson Study Group) in the Kanto area of Japan during the period from January to December 2007. The Kanto area includes the city of Tokyo, which is called the metropolitan area. This study group consists of nearly the same members as those who previously participated in the studies of the characteristics of sleep disturbances and the correlation of depressive symptoms with nocturnal disturbances in Japanese PD patients.[14–16] Among the 411 patients, 361 were included in this study, whereas the remaining 50 patients were excluded. Among the excluded patients, 21 had comorbid disorders such as heart failure, pulmonary diseases, chronic kidney diseases, cancer, arthritis, anemia, and other neurological or psychiatric diseases. Twenty-nine patients were excluded because they had dementia. Cognitive function and dementia were evaluated by Mini-Mental State Examination (MMSE), and a score of less than 24 points was regarded as indicative of dementia.[17,18] The mean age of the patients was 66.5 ± 9.2 years (± SD) and the mean disease duration was 6.6 ± 5.1 years.

The diagnosis of idiopathic PD was made according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.[19] PD patients were defined as having bradykinesia and at least one of the following three symptoms: resting tremor, muscular rigidity, and/or postural instability. On the basis of clinical features and neurological findings, we excluded other forms of parkinsonism that included (1) drug-induced parkinsonism, (2) vascular parkinsonism, and (3) atypical parkinsonism such as progressive supranuclear palsy, parkinsonian type of multiple system atrophy, or corticobasal degeneration.

Assessments

All the 361 patients underwent the same assessments, including those of their detailed PD history, drug history, Hoehn and Yahr (H&Y) stage,[20] and Unified Parkinson's Disease Rating Scale (UPDRS) motor score.[21] The Zung Self-Rating Depression Scale (SDS) was used for evaluating depression.[22] SDS is widely used as a self-administered psychological test, and a high score indicates a more severe depression. Several studies have used SDS to evaluate depression in PD.[23] As in our previous studies, Parkinson's Disease Sleep Scale (PDSS) was used for evaluating sleep disturbances.[24,25] PDSS consists of 15 individual items of sleep disorders associated with PD (see Appendix), and the maximum total score for PDSS is 150 (i.e., the patient is free of symptoms associated sleep disorders). PDSS enables assessment of nocturnal sleep conditions characteristic of PD. The Japanese version of PDQ-39 (Parkinson's Disease Questionnaire-39) was used for assessing dysfunction of daily living and QOL.[26] The questionnaire provides scores on eight dimensions: mobility, activities of daily living, emotions, stigma, social support, cognitions, communication, and bodily discomfort.[27,28] For the estimation of fatigue, PFS-16 was used.[13] PFS consists of 16 items (see Appendix), and for each question, response options were "strongly disagree," "disagree," "do not agree or disagree," "agree," and "strongly agree," which are scored 1 to

5, respectively. The overall PFS score was calculated as the mean response across all items (range, 1.0–5.0). According to the original paper,[13] an average score of 3.3 or greater optimally identified patients who perceived fatigue to be a problem with a sensitivity of 84.7% and a specificity of 82.1%. Therefore, in the present study, a cutoff point of 3.3 was used to indicate the existence of fatigue.

Although PFS was designed to assess fatigue in PD patients, we collected data from control subjects. We recruited 100 age-matched, nondemented control subjects from patients' spouses or relatives.

Statistical Analysis

SPSS software *version 15.0* (SPSS, Chicago, IL) was used for analysis. The level of statistical significance in this study was defined as 0.05.

Assessment of Differences in All Variables Between Patients With and Without Fatigue

Fisher's exact probability test was employed for estimating the difference in sex between patients with and without fatigue and for comparing the frequency of levodopa (L-dopa) administration. Mann–Whitney's *U* test was performed to estimate the differences in M-values between the two groups in terms of age at assessment, duration of the disease, H&Y stage, and UPDRS motor, SDS, PDQ-39, PDSS, and MMSE scores. Correlations between the PFS scores and clinical characteristics were assessed by Spearman's rank order correlation coefficient.

Multiple Logistic Regression Analysis of Predisposing Factors for Fatigue in PD

Multiple logistic regression analysis was employed to assess the predisposing factors for fatigue in PD. A dichotomous dependent variable of fatigue was assigned a value of 0 when the mean 16-item PFS score was less than 3.3, and 1 when the score was 3.3 or greater. The independent variables were (1) age at assessment (years; real number), (2) duration of the disease (years; real number), (3) score of part III (motor examination) of the UPDRS (real number), (4) score of SDS (real number), (5) score of PDSS (real number), (6) score of PDQ-39 (real number), and (7) administration of L-dopa (no = 0, yes = 1). Moreover, multiple logistic regression analysis including that of the scores of individual items of PDSS as independent variables was carried out. In addition, multiple logistic regression analysis including that of the scores of eight dimensions of PDQ-39 as independent variables was also performed.

RESULTS

The demographic and clinical features of the groups of patients that were separated by score of 3.3 on the PFS are summarized in Table 1. The 361 PD patients included 166 men and 195 women [mean age at this assessment, 66.5 years (range, 34–90), with a mean disease duration of 6.5 years (range, 0.5–32)]. Fatigue, defined by a mean PFS score of 3.3 or greater, was revealed in 151 patients studied (41.8%). Among the 100 control subjects (mean age 66.1 years, range 42–85), the mean PFS score was 1.84 (SD 0.74). Only 5 subjects (5%) revealed a PFS score of 3.3 or greater. Since the mean score + 2SD in controls was 3.32, the cutoff score of 3.3 determined by Brown et al.[13] seems reasonable.

Differences in All Variables Between Patients With and Without Fatigue

The differences in all variables between the patients with and without fatigue are summarized in Table 1. The mean duration of the disease, H&Y stage, and the scores of UPDRS motor examination, SDS, and PDQ-39 were higher in the patients with fatigue than in those without fatigue. The score of PDSS was significantly lower (worse) in the patients with fatigue. The frequency of L-dopa administration and the mean dosage of L-dopa were higher in the patients with fatigue. Significant correlations were found between PFS scores

TABLE 1. *Demographic and clinical characteristics of patients*

	Without fatigue (PFS < 3.3) (n = 210)	With fatigue (PFS ≥ 3.3) (n = 151)	*P* value
Age, yr (SD)	65.9 (8.9)	67.7 (9.4)	0.049
Sex, male (%)	43%	50%	0.241
Duration, yr (SD)	5.4 (4.3)	8.2 (5.8)	<0.001
H&Y, on (SD)	2.1 (0.7)	2.7 (0.7)	<0.001
H&Y, off (SD)	2.3 (0.9)	3.1 (0.9)	<0.001
UPDRS, motor (SD)	19.3 (9.1)	25.3 (9.4)	<0.001
SDS (SD)	41.0 (8.5)	47.9 (8.8)	<0.001
PDQ-39 (SD)	32.8 (24.0)	68.8 (26.7)	<0.001
PDSS (SD)	123.6 (19.7)	99.2 (26.6)	<0.001
MMSE (SD)	28.2 (1.9)	27.9 (2.0)	0.143
Levodopa (%)	64%	89%	<0.001

H&Y, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; SDS, Self-rating Depression Scale; PDQ-39, Parkinson's Disease Questionnaire; PDSS, Parkinson's Disease Sleep Scale; MMSE, Mini-Mental State Examination; Levodopa, Administration of levodopa.

TABLE 2. *Correlations between the PFS scores and clinical characteristics of the patients*

	Spearman's rank-order correlation coefficient	*P* value
Age, yr	0.124	0.014
Duration, yr	0.305	<0.001
H&Y, on	0.409	<0.001
H&Y, off	0.422	<0.001
UPDRS, motor	0.339	<0.001
SDS	0.450	<0.001
PDQ-39	0.667	<0.001
PDSS	−0.489	<0.001
MMSE	−0.118	0.021

Correlations was assessed by Spearman's rank-order correlation coefficient.

PFS, Parkinson Fatigue Scale; H&Y, Hoehn and Yahr stage; UPDRS, Unified Parkinson's Disease Rating Scale; SDS, Self-rating Depression Scale; PDQ-39, Parkinson's Disease Questionnaire; PDSS, Parkinson's Disease Sleep Scale; MMSE, Mini Mental State Examination.

and clinical characteristics (i.e., age at assessment, duration of the disease, H&Y stage, UPDRS motor, SDS, PDQ-39, PDSS, and MMSE scores), as shown in Table 2.

Independent Variables Related to Presence of Fatigue in PD

The results of multiple logistic regression analysis in relation to fatigue (Table 3) indicated that the significant independent variables related to the presence of fatigue in PD were sleep disturbance, as measured by PDSS [odds ratio = 0.979 (95% CI: 0.967–0.991), $P = 0.001$], and reduced quality of life (PDQ-39) [odds ratio = 1.037 (95% CI: 1.024–1.051), $P < 0.001$]. Other factors, including duration of the disease, depression (SDS), motor function evaluated by UPDRS part III, and administration of L-dopa, were not significant. The H&Y stage was also not a significant independent variable related to the presence of fatigue as determined by multiple logistic regression analysis, when the H&Y stage was entered to this model instead of the score of UPDRS part III.

When multiple logistic regression analysis was employed to assess individual items in PDSS together with the above seven variables, sleep refreshment (Item 14) [odds ratio = 0.859 (95% CI: 0.778–0.950), $P = 0.003$] and urinary incontinence due to nocturnal "off" symptoms (Item 9) [odds ratio = 1.194 (95% CI: 1.033–1.381), $P = 0.017$] were the significant contributing factors. Multiple logistic regression analysis assessing each of the eight dimensions of PDQ-39 as independent variables showed that scores for mobility [odds ratio = 1.074 (95% CI: 1.035–1.114), $P < 0.001$] and cognition [odds ratio = 1.134 (95% CI: 1.009–1.275), $P = 0.034$] predicted the PFS scores.

DISCUSSION

The present study showed that excessive fatigue, as assessed by the PD-specific instrument PFS-16, was experienced in 41% of Japanese patients with PD. In contrast, the prevalence of problematic fatigue in age-matched control subjects was quite low when determined using this scale.

In 1993, two studies of fatigue in PD were published. Friedman and Friedman used a questionnaire to examine fatigue in 51 PD patients visiting a PD clinic.[1] They showed a high mean score of FSS comparable to that in multiple sclerosis. van Hilten et al. studied the prevalence of fatigue in 90 nondepressed PD patients, and excessive daytime fatigue was reported by 43% of the patients.[2] Karlsen et al. found that 44% of 233 Norwegian PD patients in community-based population reported fatigue.[3] Shulman et al. reported that 40% of 99 nondemented PD patients suffered from fatigue.[8] Recently, fatigue has been investigated in a cohort of previously untreated patients with early PD enrolled in the Earlier vs. Later Levodopa (ELLDOPA) clinical trial.[29] In the study, 128 of 349 patients (37%) were classified as fatigued at baseline, and the prevalence increased to 50% by week 42.[29] Our findings confirm the high prevalence of fatigue in PD patients in previous studies in Western countries.

A previous study showed that the duration of the disease, disease severity (UPDRS motor score and H&Y stage), depression, and L-dopa dose are associated with fatigue by bivariate analyses.[3] These results are consistent with our results. In addition, we found that the degree of sleep disturbance and reduced QOL

TABLE 3. *Results of multiple logistic regression analysis in relation to fatigue*

	Odds ratio	95% CI	*P* value
Age	1.016	0.985–1.495	0.295
Duration	0.991	0.934–1.051	0.757
UPDRS motor	1.010	0.977–1.044	0.550
SDS	1.029	0.992–1.067	0.121
PDSS	0.979	0.967–0.991	0.001
PDQ-39	1.037	1.024–1.051	<0.001
Levodopa	1.895	0.892–4.022	0.096

UPDRS, Unified Parkinson's Disease Rating Scale; SDS, Self-rating Depression Scale; PDQ-39, Parkinson's Disease Questionnaire; PDSS, Parkinson's Disease Sleep Scale; Levodopa, administration of levodopa.

are associated factors. However, because PD is a slowly progressive disorder, the interpretation as to which variables are actually contributing to fatigue is difficult. For instance, patients with longer disease duration may have severer disability, more depressive symptoms, and taking higher doses of antiparkinsonian medications. We therefore evaluated the correlated factors for fatigue by multiple logistic regression analysis including the above-mentioned factors as independent variables. The results obtained revealed that only sleep disturbance and reduced QOL were significant independent variables, whereas the duration and severity of the disease and depressive symptoms was not significant.

Sleep disturbance and excessive daytime sleepiness (EDS) are frequent problems associated with PD. In our previous Japanese study using PDSS, PD patients had more severe sleep disorders than control subjects, and EDS correlated significantly with disease severity.[14,15] We did not investigate fatigue at that time. Although association between fatigue and sleep disturbance has been suggested, there have been no reports showing that sleep disturbance is a statistically significant determinant of PD fatigue after adjusting confounding factors. Only Alves et al. showed that EDS, but not nocturnal sleep disturbance, is associated with fatigue, as determined using a multiple logistic regression model. Therefore, our study is the first to show a significant correlation of fatigue with sleep disturbance, as evaluated by a PD-specific sleep scale, using multiple logistic regression analysis.

When multiple logistic regression analysis was performed including all individual items of PDSS, fatigue was significantly related to sleep refreshment (Item 14) and nocturnal incontinence due to off symptoms (Item 9). EDS (Item 15) was not significant. It is reasonable that disturbance of sleep refreshment (feeling tired and sleepy after waking up) significantly correlated with fatigue because of the overlapping of symptoms. Our data may suggest that patients having fatigue feel tiredness even in the morning. This is consistent with the results of the study by van Hilten et al., in that most patients complaining of excessive fatigue did not report a preferential time for fatigue (morning, afternoon, or evening), although EDS showed a clear diurnal pattern with a peak in the early afternoon.[2]

The present study failed to show a significant correlation of depression with fatigue by multiple logistic regression analysis. Although several studies showed associations between depression and fatigue in PD patients,[1,3,8] there are also many patients with fatigue but not depression.[3,7] Indeed, Karlsen et al. showed that 44.2% of 233 PD patients reported fatigue, but about the same percentage (43.5%) of patients who did not have depression and dementia also reported fatigue.[3] Therefore, to date, fatigue is considered a rather independent symptom, but may overlap with depressive symptoms.[7]

In this study, we also demonstrated that fatigue significantly contributed to poor QOL. This result is in line with the previous Norwegian study by Herlofson and Larsen.[9] They assessed fatigue using FSS in 66 nondemented, nondepressed PD, and evaluated QOL using PDQ-39 and the Short-Form 36. Patients with fatigue reported more distress in the dimensions of emotional well-being, mobility, and PDQ summary index. Our results also showed that PDQ total score and score for mobility were significantly associated with fatigue. It is interesting that self-rated subjective mobility restriction significantly correlated with fatigue, whereas motor dysfunction objectively evaluated by UPDRS part III or H&Y stage did not when multiple logistic regression analysis was employed. These findings suggest that the presence of fatigue markedly affects the QOL of PD patients. It is therefore particularly important to provide optimal treatment and care to PD patients with fatigue. Recently, a randomized, double-blind, placebo-controlled trial showed the effectiveness of methylphenidate for fatigue in PD.[30] In addition, the ELLDOPA study showed that levodopa might prevent the progression of fatigue in early and untreated PD over the 42 weeks of follow-up.[29] Further well-designed studies are necessary to develop more effective treatments for fatigue in PD.

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APPENDIX

Parkinson Fatigue Scale (From Brown et al.)

1. I have to rest during the day.
2. My life is restricted by fatigue.
3. I get tired more quickly than other people I know.
4. Fatigue is one of my three worst symptoms.
5. I feel completely exhausted.
6. Fatigue makes me reluctant to socialize.
7. Because of fatigue it takes me longer to get things done.
8. I have a feeling of "heaviness."
9. If I was not so tired I could do more things.
10. Everything I do is an effort.
11. I lack energy for much of the time.
12. I feel totally drained.
13. Fatigue makes it difficult for me to cope with everyday activities.
14. I feel tired even when I have not done anything.
15. Because of fatigue I do less in my day than I would like.
16. I get so tired I want to lie down wherever I am.

Parkinson's Disease Sleep Scale (From Chaudhuri et al.)

1. The overall quality of your night's sleep is.
2. Do you have difficulty falling asleep each night?
3. Do you have difficulty staying asleep?
4. Do you have restlessness of legs or arms at night?
5. Do you fidget in bed?
6. Do you suffer from distressing dreams at night?
7. Do you suffer from distressing hallucination at night (seeing or hearing things that you are told do not exist)?
8. Do you get up at night to pass urine?
9. Do you have incontinence of urine because you are unable to move due to "off" symptoms?
10. Do you experience numbness or tingling of your arms or legs that wake you from sleep at night?
11. Do you have painful muscle cramps in your arms or legs whilst sleeping at night?
12. Do you wake early in the morning with painful posturing of arms or legs?
13. On waking do you experience tremor?
14. Do you feel tired and sleepy after waking in the morning?
15. Have you unexpectedly fallen asleep during the day?

For question 1: Awful = 0, Excellent = 10. For question 15: Frequently = 0, Never = 10. For the remainder of the questions: Always = 0, Never = 10.

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The Relationship Between Slowing EEGs and the Progression of Parkinson's Disease

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Abstract: The previous association study confirmed that diffuse slowing of EEGs was present in Parkinson's disease (PD), demonstrated with the use of the quantitative EEG technique. This study was the first to assess the relationship between progression of PD and quantitative EEG. A total of 106 patients with PD with a mean Hoehn-Yahr stage of 2.73 were serially enrolled. Lack of ischemic lesions was confirmed in all patients by magnetic resonance imaging. Absolute power values were measured for four frequency bands from delta to beta. The electrodes were divided among six locations: frontal pole, frontal, central, parietal, temporal, and occipital locations. Spectral ratio was calculated as the sum of power values for the alpha and beta waves divided by the sum values for the slow waves. The relationship between the progression of PD and spectral ratio was assessed by the Jonckheere-Terpstra trend test. At all electrode locations, spectral ratio significantly decreased with progression of Hoehn-Yahr stage (frontal pole, $P = 0.007$; frontal, $P = 0.005$; central, $P = 0.031$; parietal, $P = 0.017$; temporal, $P = 0.005$; occipital, $P = 0.010$). This shows that the slowing of EEGs became more obvious with PD progression.

Key Words: Parkinson's disease, Quantitative EEG, Electrode distribution, Hoehn-Yahr stage.

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Diffuse and localized slowing of EEGs in patients with Parkinson's disease (PD), as evaluated by visual inspection, has been described (Neufeld et al., 1988; Yeager et al., 1966). Comparisons of quantitative EEG (qEEG) analysis between PD patients and age-adjusted normal control subjects have been reported in only five studies (Neufeld et al., 1994; Pezard et al., 2001; Primavera et al., 1992; Soikkeli et al., 1991; Tanaka et al., 2000). We recently reported the results of assessment of the difference in qEEG findings between PD patients and normal control subjects, using multiple logistic regression analysis, and confirmed that diffuse slowing of EEG was present in PD (Serizawa et al., 2008). In this article, it was described that the significant predictive variables in PD were the spectral ratios at all electrode locations except for the frontal pole. Conversely, the relation between the frontal lobe dysfunction and PD was widely known, and it was reported that the executive dysfunction was more obvious with PD progression (Kamei et al., 2007). However, no study has assessed the relationship between progression of PD and EEG changes in a quantitative fashion. The aim of this investigation was to assess the relationship between progression of PD and qEEG changes.

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PATIENTS AND METHODS

Patient Definitions

The subjects comprised 106 consecutive patients who were diagnosed as having sporadic PD at the Neurology Clinic, Nihon University Itabashi Hospital during the period from December 2004 to July 2006. The clinical diagnosis of sporadic PD was made according to the UK PD Brain Bank criteria (Gibb and Lees, 1988). On the basis of clinical features and neuroradiological findings, we excluded other forms of parkinsonism including (1) dementia with Lewy bodies (Geser et al., 2005; McKeith et al., 1996), (2) drug-induced parkinsonism, (3) vascular parkinsonism, and (4) atypical parkinsonism with absent or minimal responses to antiparkinsonian drugs. All patients were scanned for T1- and T2-weighted images, fluid-attenuated inversion recovery images, and diffusion images using a cranial magnetic resonance imaging (1.5-T Siemens Magnetom Symphony, Munich, Germany). We defined patients without any intracerebral ischemic changes including even only one asymptomatic lacuna or slight periventricular hyperintensity in accordance with the reported classification of PVH (Fazekas et al., 1987) on T2 and fluid-attenuated inversion recovery images. At more than 12 months after onset, the subjects had thus showed good responses to anti-Parkinsonian drugs and did not have a history of visual hallucinations or fluctuation of cognitive ability suggestive of a clinical diagnosis of dementia with Lewy bodies. At the outset of this study, patients were assessed on the mini-mental state examination based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria for dementia in accordance with a previously reported study (Burn et al., 2006). These 106 patients with PD were, therefore, enrolled in this study. Informed written consent for participation in this study was obtained from each subject according to a protocol approved by the Institutional Research Review Board of Nihon University.

Assessments

The EEG recordings and qEEG analysis in this study were performed as described previously (Kamei et al., 1999, 2002, 2005). Briefly, the EEG was obtained with each subject in the resting awake condition with the eyes closed. The EEG was recorded on a magnetic optical disk from 16 electrode locations according to the 10-20 International system using a digital EEG instrument (Neurofax EEG-1100, Nihon Kohden, Tokyo, Japan). The EEG was referenced to the ipsilateral earlobes. A minimum 60 seconds of qEEG data were selected visually for each subject and digitized at 200 Hz. A high-frequency filter was set at 60.0 Hz with the time constant of

0.3 seconds. Thirty or more epochs with a 2.56-seconds duration were, thus, collected from the subsequent resting period with eyes closed for qEEG analysis. The procedure used for analysis involved application of fast Fourier transformation of the collected EEG signals with a frequency analyzer (QP-220A, Nihon Kohden, Tokyo, Japan). The frequency ranges were divided into four bands, which are as follows: delta (1.17–3.91 Hz), theta (4.30–7.81 Hz), alpha (8.20–12.89 Hz), and beta (13.28–30.08 Hz). The absolute powers of each frequency band were calculated at each electrode location in each subject. The absolute power value was obtained by integrating the appropriate part of the spectrum.

TABLE 1. Clinical Features of PD Patients

	Men (n = 57)	Women (n = 49)
Age at assessment (years)	34, 67.9, 71, 87	46, 67.7, 68, 84
Duration from onset (months)	1, 70.6, 60, 228	5, 68.4, 60, 287
Hoehn-Yahr stage (%)		
Stage I	7	2
Stage II	38.6	36.7
Stage III	36.8	49.0
Stage IV	14.0	6.1
Stage V	3.5	6.1
Mini-mental state examination	12, 25.0, 26, 30	6, 26.3, 29, 30

Continuous variables were expressed as the minimum, mean, median, and maximum, whereas categorical variables are expressed as percentages.
n, number of patients; PD, Parkinson's disease.

TABLE 2. Relationships Between Clinical Features and Hoehn-Yahr Stage

	n	Age (Years)	Duration (Months)	MMSE
Group 1				
Yahr I and II	45	34, 62.71, 64, 84	5, 51.36, 48, 228	20, 27.39, 27, 30
Group 2				
Yahr III	45	50, 70.49, 72, 84	1, 71.2, 57, 196	14, 25.69, 27, 30
Group 3				
Yahr IV and V	16	57, 74.50, 75.5, 87	52, 116.44, 84, 287	6, 19.79, 19.5, 30
P		<0.001*	<0.001*	0.001*

Clinical variables (age at assessment, duration from onset, and score on MMSE) were expressed as the minimum, mean, median, and maximum. Differences of clinical variables among three groups were examined by the Kruskal Wallis test.
*Statistically significant ($P < 0.05$).
MMSE, Mini-mental state examination; n, number of patients; Yahr, Hoehn-Yahr stage.

Statistical Analysis

SPSS software version 15.0 (SPSS Inc., Chicago, IL) was used for statistical analyses. The Shapiro-Wilk normality test was used to evaluate whether continuous variables exhibited a normal distribution. Parametric analysis was applied to normal data, whereas nonparametric analysis was applied to nonnormal data. The patients with PD were divided into three groups based on Hoehn-Yahr staging of PD (Hoehn and Yahr, 1967): group 1 (stage I and II), group 2 (stage III), and group 3 (stages IV and V).

This study was based on the analysis of combined data for absolute power values in the right- and left-sided electrode locations. The electrodes were divided among six locations as follows: frontal pole (Fp: Fp_1 and Fp_2), frontal (F: F_3, F_4, F_7, and F_8), central (C: C_3 and C_4), parietal (P: P_3 and P_4), temporal (T: T_3, T_4, T_5, and T_6), and occipital (O: O_1 and O_2) locations. For evaluation of slowing of the qEEG in this study, we calculated the spectral ratio, using the same method of analysis as in a previously reported assessment of EEG slowing in Alzheimer's disease (Lindau et al., 2003). The spectral ratio is the ratio of the sum of absolute powers in the alpha and fast frequency bands divided by the sum of absolute powers in the delta and theta frequency bands.

Differences between the right and left cerebral absolute power values in the subjects were evaluated by the Wilcoxon signed-rank test. There were no significant differences in absolute power values between the right- and left-sided locations in the patients with PD ($P = 0.861$). Localization of the alpha band was assessed by the Friedman test. We performed *post hoc* tests for the significance of differences among each of the electrode locations, using the Wilcoxon signed-rank test for the following combinations of electrode locations: Fp versus F, Fp versus C, Fp versus P, Fp versus T, Fp versus O, F versus C, F versus P, F versus T, F versus O, C versus P, C versus T, C versus O, P versus T, P versus O, and T versus O ($P < 0.0033$ each). The relationship between the spectral ratio in each electrode location and the progression of PD was assessed using the Jonckheere-Terpstra trend test and Kruskal Wallis test, respectively. We performed *post hoc* tests for the significance of differences, using the Mann-Whitney *U* test for the following combinations of PD groups: group 1 versus group 2, group 1 versus group 3, and group 2 versus group 3 ($P < 0.017$ each). Clinical variables (age at assessment, duration from onset, and score on mini-mental state examination) were expressed as minimum, mean, median, and maximum. The relationships between these clinical variables and progression of PD were examined by the

TABLE 3. Ratios of Absolute Power Values in Each Frequency Band and Electrode Location to Total Power Value in 106 Patients With PD

	Electrode Location											
	FP		F		C		P		O		T	
Frequency Band	M ± SE	%*	M ± SE	%*	M ± SE	%*	M ± SE	%*	M ± SE	%*	M ± SE	%*
Delta	0.096 ± 0.005	32.9	0.063 ± 0.002	25.5	0.069 ± 0.003	22.7	0.131 ± 0.005	22.6	0.062 ± 0.003	23.5	0.040 ± 0.001	22.8
Theta	0.074 ± 0.003	25.3	0.065 ± 0.001	26.2	0.077 ± 0.002	25.2	0.140 ± 0.004	24.2	0.061 ± 0.002	23.1	0.044 ± 0.001	25.0
Alpha	0.058 ± 0.002	19.7	0.060 ± 0.001	23.9	0.078 ± 0.002	25.7	0.159 ± 0.004	27.5	0.079 ± 0.004	29.8	0.043 ± 0.001	24.7
Beta	0.065 ± 0.002	22.1	0.061 ± 0.001	24.5	0.080 ± 0.002	26.4	0.149 ± 0.003	25.7	0.062 ± 0.002	23.6	0.048 ± 0.001	27.4
Sum of ratios at each electrode location	0.292 ± 0.012	100	0.250 ± 0.005	100	0.303 ± 0.007	100	0.578 ± 0.016	100	0.265 ± 0.011	100	0.175 ± 0.005	100

*Percentage of absolute power value in each frequency band against sum of power values at each electrode location.
M, mean value; SE, standard error; FP, frontal pole; F, frontal; C, central; P, parietal; T, temporal; O, occipital location; PD, Parkinson's disease.

Kruskal Wallis test. The level of statistical significance for this study was $P = 0.05$.

RESULTS

The clinical features of the patients with PD enrolled in this study are summarized in Table 1. The numbers of patients at each Hoehn-Yahr stage were as follows: stage I (n = 5, 4.7%), stage II (n = 40, 37.7%), stage III (n = 45, 42.5%), stage IV (n = 11, 10.4%), and stage V (n = 5, 4.7%). Patients were treated with the following agents: levodopa (n = 84, 79.2%), dopamine agonists (n = 68, 64.2%), amantadine (n = 20, 18.9%), monoamine oxidase inhibitors (n = 25, 23.6%), L-threo-3,4-dihydroxyphenylserine (n = 12, 11.3%), and no medication (n = 7, 6.6%). Age at assessment, duration from onset, and mini-mental state examination score each differed significantly among the three groups (Table 2).

The ratios of absolute power values in each frequency band and at each electrode location to the total absolute power values in the 106 patients are shown in Table 3. Localization of the alpha band differed significantly among electrode locations ($P < 0.001$). *Post hoc* testing revealed significant differences between the following electrode locations: Fp versus C ($P < 0.001$), Fp versus P ($P < 0.001$), Fp versus O ($P = 0.001$), Fp versus T ($P < 0.001$), F versus C ($P < 0.001$), F versus P ($P < 0.001$), F versus T ($P < 0.001$), C versus T ($P < 0.001$), P versus T ($P < 0.001$), and T versus O ($P < 0.001$).

The spectral ratios in each electrode location exhibited a significant decrease with progression of PD (Table 4). The P values for electrode locations were as follows: $P = 0.007$ (Fp), $P = 0.005$ (F), $P = 0.031$ (C), $P = 0.017$ (P), $P = 0.005$ (T), and $P = 0.010$ (O).

At all electrode locations except C, a significant difference was found among the three groups: groups 1, 2, and 3. The P value for electrode locations were as follows: $P = 0.017$ (Fp), $P = 0.013$ (F), $P = 0.059$ (C), $P = 0.041$ (P), $P = 0.008$ (T), and $P = 0.010$ (O). *Post hoc* testing revealed significant differences between groups 1 and 3 at the following electrode locations: Fp, F, T, and O (with P values of 0.006, 0.004, 0.003, and 0.002, respectively).

DISCUSSION

There were only two large-scale studies in patients with PD about EEG abnormalities based on its visual estimates (Neufeld et al., 1988; Yeager et al., 1966). Yeager et al. reported that 36.3% of 223 patients with PD exhibited abnormal findings on EEG, which consisted of diffuse slowing, localized slowing, or both. Neufeld et al. also found that mild slowing on EEG was present in 34% of 128 patients with PD. Recently, several investigations of qEEG in PD have featured comparisons with aged control subjects (Primavera et al., 1992; Soikkeli et al., 1991; Tanaka et al., 2000), and revealed slowing of EEGs in PD. Because slowing of EEGs has also been reported in patients with vascular parkinsonism (Zijlmans et al., 1998), we suspected that the presence of intracerebral ischemic lesions in our subjects might influence qEEG findings. Patients with intracerebral ischemic lesions as assessed by magnetic resonance imaging were, therefore, excluded from this study.

To the best of our knowledge, this study was the first to confirm slowing of EEGs in each electrode location. This slowing of EEG exhibits a significant correlation with progression of Hoehn-Yahr Stage in PD. Neufeld et al. reported that relative alpha amplitude in several individual electrodes was unrelated to motor disability as measured by the qEEG technique (Neufeld et al., 1994). However, the number of subjects in their study was limited to 20, making it difficult to definitively assess the relationship between slowing of the EEG and motor disability in PD.

The relationship between slowing of the EEG and cognitive impairment in PD was reported by Caviness et al (2007). They divided 66 patients with PD into three groups: PD-cognitively

TABLE 4. The Relationship Between Spectral Ratios in Each Electrode Location and Hoehn-Yahr Stage

	n	Spectral Ratio						
		FP	F	C	P	O	T	
Group 1								
Yahr I and II	45	0.0984, 0.837, 0.612, 4.803	0.1555, 1.0911, 0.8273, 5.840	0.1594, 1.3490, 0.9870, 7.7061	0.1425, 1.5084, 0.9702, 6.0932	0.1651, 1.8050, 0.9396, 10.9358	0.1247, 1.2608, 0.9551, 4.5229	
Group 2								
Yahr III	45	0.0794, 0.739, 0.428, 4.7074	0.1078, 0.8465, 0.5441, 3.3749	0.1287, 1.0154, 0.6664, 3.3667	0.0938, 1.1816, 0.8663, 4.0023	0.1067, 1.4790, 0.8326, 8.2388	0.1114, 1.0028, 0.8534, 3.9648	
Group 3								
Yahr IV and V	16	0.0573, 0.380, 0.305, 1.0837	0.0765, 0.4651, 0.3605, 1.3164	0.0976, 0.6109, 0.4103, 2.176	0.1116, 0.6875, 0.4033, 2.8016	0.1074, 0.5741, 0.3992, 1.8523	0.0863, 0.5713, 0.2940, 2.1113	
P		0.007*	0.005*	0.031*	0.017*	0.010*	0.005*	

The spectral ratios in each electrode location were expressed as the minimum, mean, median, and maximum. Trends of the spectral ratio in each electrode location among three groups were assessed by the Jonckheere-Terpstra test.
Spectral ratio: sum of absolute power values for alpha and beta waves divided by sum of absolute power values for delta and theta waves.
*Statistically significant ($P < 0.05$).
FP, frontal pole; F, frontal; C, central; P, parietal; T, temporal; O, occipital location; MMSE, mini-mental state examination; n, number of patients; Yahr, Hoehn-Yahr stage.

normal (n = 42), PD-mild cognitive impairment (n = 16) (Petersen et al., 1999), and PD-dementia patients (n = 8) (McKeith et al., 1996), and they assessed differences in dominant posterior background rhythm frequency. A significant correlation was demonstrated between cognitive status and dominant posterior background rhythm frequency.

In our study, mini-mental state examination score significantly decreased with progression of PD. Progression of Hoehn-Yahr Stage and Unified Parkinson's Disease Rating Scale score (Fahn et al., 1987) in PD was reported to be related to the progression of cognitive impairment (Riedel et al., 2008). Caviness et al also reported that the correlation coefficient was 0.47 ($P < 0.001$) between Unified Parkinson's Disease Rating Scale motor score and the three groups: PD-cognitively normal, PD-mild cognitive impairment, and PD-dementia patients (Caviness et al., 2007).

According to the concept of PD progression of Braak et al. (2004), components of the autonomic, limbic, and somatomotor systems become damaged as the disease advances. In Braak et al.'s PD stages 3 to 4 of the pathologic process, the substantia nigra and other regions of nuclear gray matter in the midbrain and forebrain become the focus of initially slight and then severe pathologic changes. At this point, most individuals probably cross the threshold to the symptomatic phase of illness. In Braak et al.'s PD stages 5 to 6, the pathologic process comes to involve the neocortex in diffuse fashion, and the disease is manifested in all of its clinical dimensions. The progression of diffuse slowing of EEGs in PD patients observed in this study seems to be consistent with Braak et al.'s concept of progression in PD.

In conclusion, this study was, to our knowledge, the first to assess the relationship between the progression of PD Hoehn-Yahr stages and the degree of slowing of EEG measured by qEEG. We demonstrated that slowing of the EEG in each electrode showed a significant correlation with progression of PD. This finding seems consistent with Braak et al.'s concept of the progression of PD.

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インフルエンザワクチン接種後にみられたてんかん3例の病態の検討

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要　旨

インフルエンザワクチン後に極めて稀ながら，てんかんを認めることがある．その病態と治療を検討するために，インフルエンザワクチン接種後にみられたてんかん3症例で，治療と髄液免疫マーカーを検討した．

3症例ともインフルエンザワクチン接種後3日目よりてんかんを認め，Granzyme Bが髄液中で高値であったことから，細胞障害性T細胞の関与が考えられた．症例2では，細胞障害性T細胞に加えて，IL-6, INF-γなども上昇しており，Th1細胞の関与も考えられた．3例中症例1・2では，50～60病日にステロイドパルス療法を行い，発作及び知的予後は良好である．症例1・3では調節性T細胞が分泌するIL-10が髄液中で低値であった．

インフルエンザワクチン接種後にてんかんを認めた場合，自己免疫機構の関与を早期に検討する必要がある．

キーワード：インフルエンザワクチン，てんかん，ステロイドパルス療法，Granzyme B，細胞障害性Ts細胞

はじめに

独立法人医薬品医療機器総合情報機構によると，平成18年度の，インフルエンザワクチンの出荷本数は約1,877万本（推定）で，接種による副作用が疑われる症例が107人報告されている[1]．このうち主な副作用としては，急性散在性脳脊髄炎（acute disseminated encephalomyelitis, ADEM）(20件)，発熱(11件)，発疹等（8件），注射部位の紅斑・腫脹等（8件），肝機能障害等（7件），ショック・アナフィラキシー様症状（7件），痙攣（6件），ギラン・バレー症候群（4件）などが挙げられている．一方，米国の2歳未満の調査では13シーズンで166例の副作用症例報告があり，そのうち28例が痙攣を呈し，19例は有熱性痙攣，8例は無熱性発作であったという[2]．無熱性発作8例中6例はワクチン接種から2日以内，1例は14日，1例は30日に起こっていた．また，インフルエンザワクチン接種2日後より全身倦怠感，ふらつきが出現し，MRI（T2WI）で，左海馬体部，海馬傍回を含む領域に高信号を認め，非ヘルペス性辺縁系脳炎を呈したと考えられてた症例も報告されている[3]．

インフルエンザワクチン後にみられるてんかんなどの発作性疾患・急性脳症は極めて稀であるが，その早期治療法の確立は，ワクチンの改良とともに，インフルエンザ予防対策としての大きな柱であるワクチン接種率向上に良い影響を与えると考えている．

今回我々は，インフルエンザワクチン接種後にてんかんを認め，画像に炎症性所見を有し，ステロイドパルス療法が有効であった2症例を経験し，インフルエンザワクチン後のてんかん治療について，3症例の髄液免疫学的マーカーとの関連で検討したので報告する．

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症　例　1

16歳男性
主訴：けいれん発作
家族歴：特記すべき事なし
周産期歴：特記すべき事なし
既往歴：小児喘息
生活歴：普通高校在籍

現病歴：2003～2004年シーズンのインフルエンザワクチン接種1回目の翌日に37度台の微熱が出現し，接種3日目には右手が勝手に伸びる，ピクピクするといった単純部分発作（SPS：simple partial seizure）が出現した．8日目には，SPSから始まり，二次性全般化する発作が出現し，近医にてフェニトインが開始された．その後も同じ症状のSPSが繰り返し出現し，接種後40日目には，右下肢のみが痙攣する焦点運動発作が自然に頓挫するまでに30分以上持続した．この時よ

表1　入院時検査所見（血液検査，心理学的検査）

ND = not detected

血液検査	症例1	症例2	症例3
WBC（/ml）	7,660	5,130	4,370
Hb（g/dl）	16.9	12.6	11.1
Plt（/ml）	17.9万	38.4万	12.4万
AST（IU/l）	23	26	35
ALT（IU/l）	25	26	13
BUN（mg/dl）	7.6	11.8	11.8
Crea（mg/dl）	0.92	0.32	0.3
Na（mEq/l）	142	143	
K（mEq/l）	4.1	4.2	
Cl（mEq/l）	102	104	
IgG（mg/dl）	1,150	953	1,243
IgA（mg/d）	326	142	42
IgE（IU/ml）	230	43	
CD3（%）	57.1	75	
CD4（%）	26.3	43.4	
CD8（%）	39.6	31.2	
抗 ds-DNA	＜5	＜5	
Granzyme B（pg/ml）	ND	ND	
心理学的検査	WAIS-R FIQ 124 VIQ 124 PIQ 117	田中ビネー IQ 117	田中ビネー IQ 48

り，フェニトインからバルプロ酸に変更された．その後も，SPSを抑制できないため，50日目に当科紹介入院となった．

入院時現症：発作間欠時に意識障害はなく，直腸膀胱障害などの明らかな神経学的所見を認めなかった．

入院時検査所見：血算，生化学所見では，IgEの軽度上昇以外は明らかな異常を認めなかった（表1）．髄液検査では，細胞数，蛋白に異常はなかったが，Granzyme B，TNF-αが上昇していた（表2）．

発作症状：右手の違和感を感じ，右手に力が入りにくくなる．その後，右手，右口角のピクツキが始まり眼球，顔面が左回旋する．この間意識はありSPSと考えられた．

発作時脳波：右手がピクピクし，しばらくした後に，C3P3より，やや不規則ではあるが，律動的な徐波が出現，その後，左半球広汎性に拡がった．

頭部MRI：入院時の頭部MRI（FLAIR画像）で，両側頭頂葉及び前頭葉の皮質下白質と，左前頭葉皮質に高信号病変を認めた（図1-ABC）．同部位は，T2強調画像でも高信号を呈し，T1強調画像では，やや低信号域を呈した．拡散強調画像では，異常所見は認めなかった．

臨床経過：MRI所見からはADEMが鑑別として挙がるが，Lauren Bらが報告しているADEMの定義[4]と照らし合わせると，臨床的に発作間欠時には意識障害，脊髄症状，錐体外路症状がなく，7病日以降は無熱性の定型的な発作症状のみを呈していること，髄液中MBPが正常であることから，ADEMというより炎症に基づくてんかんと考えた．また，髄液中Granzyme Bなどの細胞障害性T細胞活性化を示す異常検査値が見られたことから，自己免疫が関連した病態と判断し，ワクチン接種後60日目よりカルバマゼピンを追加し，ステロイドパルス療法（メチルプレドニゾロン1 g/日×3日間）を行った．その後，てんかん発作は消失したが，髄液抗GluRε2抗体（IgM）が出現したためステロイドパルス療法を1か月おきに1年間行った．18歳時，髄液抗GluRε2抗体（IgG）が持続陽性を示していたため，遠方の大学に進学したことを契機に，ステロイドパルス療法をタクロリムスの内服に変更した．20歳において，MRI（FLAIR画像）皮質下白質病変に変化はないものの，前頭葉の皮質病変は消退し，てんかん発作は再燃せず，精神神経症状などの後遺症は見られていない（図1-DEF）．

症　例　2

4歳女児

主訴：けいれん発作

家族歴：母親に中心・側頭部に棘波を持つ良性小児

表2　臨床時期と発作・髄液検査所見

	症例1			症例2		症例3
時期（ワクチン後月数）	急性期（1M）	回復期（15M）	回復期（21M）	急性期（1M）	回復期（10M）	進行期（4M）
発作	+	—	−	+	−	発作群発
細胞数（3.4±7.0/mm³）	1.0	0.7	0.7	25.0	0.3	1.0
蛋白（24.1±13.7mg/dl）	20	20	16	15	5.0	24
CD4⁺T細胞（34.7±15.0%）		57.2	63.9	72.8	62.7	
CD8⁺T細胞（23.4±7.0%）		53.1	31.1	21.9	38.1	
Granzyme B（1.2±1.2pg/ml）	9.8	6.5		5.6		4.3
IL-6（4.1±2.5pg/ml）	4.9	4.0		13.9		6.5
TNF-α（4.0±2.4pg/ml）	38.5	32.8		56.0		35.3
INF-γ（9.5±2.9pg/ml）	4.2	3.8		12.4		6.3
IL-10（3.8±4.6pg/ml）	1.5	1.2		2.7		1.4
IL-12（1.0±1.1pg/ml）	2.0	1.9		2.4		2.1
IL-17（6.0±4.9pg/ml）	10.1	6.6		12.9		10.5
IL-8（33.6±20.2pg/ml）	16.3	17.0		165.0		78.3
MIP1-β（21.7±8.4pg/ml）	10.2	9.5		10.8		31.3
IP-10（629.8±429.9pg/ml）	412.8	327.0		17,542.3		3,202.2
MCP-1（249.0±99.4pg/ml）	164.2	194.7		141.7		271.2
抗GluRε2抗体（IgG）	—	+	−	—	−	+
抗GluRε2抗体（IgM）	—	−	−	—	−	+
MBP（pg/ml）	＜40					
オリゴクローナルIgGバンド	—					

てんかんの既往がある．

周産期歴：特記すべき事なし

既往歴：特記すべき事なし

生活歴：幼稚園在籍

現病歴：2006～2007年シーズンのインフルエンザワクチン2回目接種翌日より，不機嫌となり，3日目に，ボーとしたあと，眼球左偏倚し，両上肢屈曲硬直し，間代痙攣へと移行する二次性全般化発作が出現した．近医で，熱性けいれんと診断されたが，接種後5日目より同じ症状の発作が無熱時に出現する様になった．発作間欠時脳波に異常がないため経過観察されていたが，接種後20日目に無熱性発作が群発し，カルバマゼピンを開始された．しかし，発熱及び全身に発疹が出現し，スティーブンスジョンソン症候群を疑われ，バルプロ酸徐放剤に変更となった．しかし，その後も発作，不機嫌が持続し，接種後45日目，当科紹介入院となった．

入院時現症：発作間欠時に意識障害はなく，軽度の不機嫌は見られたが，明らかな神経学的所見を認めなかった．

入院時検査所見（表1，2）：血液検査所見には，明らかな異常を認めなかった．髄液検査では，細胞数，Granzyme B，TNF-α，IL-12，IL-17，IL-8，IP-10，MCP-1，IL-6，INF-γ等が上昇していた．

発作時間欠時脳波：覚醒時，P3優位に高振幅徐波を認めた．

頭部MRI：拡散強調画像で左後頭葉・頭頂葉主体に，高信号病変を認めた（図2-A）．FLAIR画像では，明らかな異常は認めなかった（図2-B）．

臨床経過：臨床経過，髄液所見で各種サイトカインが上昇していること，拡散強調画像で高信号を示す所見があることから，自己免疫が関連したてんかん病態と判断し，接種後48日目ステロイドパルス療法（メチルプレドニゾロン30mg/kg/日×3日間）を行った．その後，発作消失，機嫌も良くなり，笑顔が見られるようになり，接種後約3か月目に退院となった．その後拡散強調画像にて高信号病変が残存するため，2か月に一回のパルス療法を施行し，発作は再発なく，高信号病変も改善傾向にある（図2-C，D）．6歳となった現在明らかな後遺症は見られていない．

症　例　3

この3歳女児例は，インフルエンザワクチン1回目接種後3日目に，複雑部分発作（CPS：complex partial seizure）で発症し，抗てんかん薬投与にもかかわらず，3か月後頃より次第に群発を繰り返すようになり，発症5か月の時点で一時間ごとに発作を起こすようになり，ガンマグロブリン大量療法を行った症例で，てんかん重積状態を脱することができた症例として報告されている[5]．この症例はその後，当センターに紹介とな

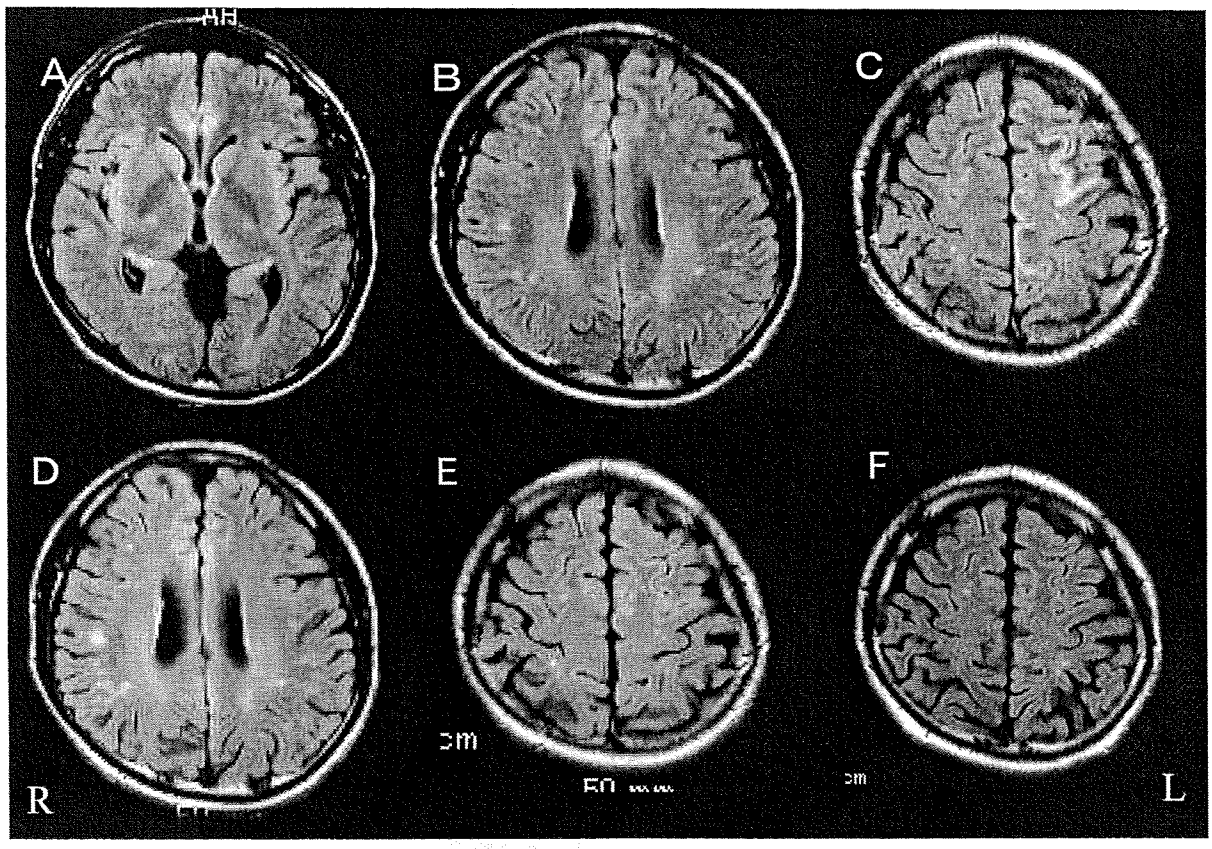

図1　症例1の頭部MRI所見
入院時（接種後50日）の頭部MRI-FLAIR画像では，両側頭頂葉及び前頭葉皮質下白質，左前頭葉皮質に高信号病変を認めたが，基底核には病変を認めない（図1-ABC）．接種後110日のMRIにおいても皮質下白質FLAIR画像病変が消退していない（図1-D）が，左前頭葉皮質高信号病変は軽減しつつある（図1-E）．2年3か月後には左前頭葉皮質高信号病変は消失したが，皮質下白質病変は変化していない（図1-F）．

り，9歳となった現在も月単位にてんかん発作が群発する日があり，中等度の精神発達遅滞が見られている．

考　察

近年，てんかんにおける脳の炎症病態は注目を浴びる領域となっていて，炎症によるてんかん原性獲得についての研究が増えている[9]．3症例はワクチン接種後3日目に発作で発病し，徐々に発作が増加したが意識障害などは伴わず，てんかんとしての臨床特徴を共通して示した．症例1・2では初期に発熱があり，画像所見からは炎症性の機転が推測されることからADEMとの鑑別が必要となる．しかし，ADEMは多巣性の臨床症状（歩行障害・意識障害・排尿障害・感覚障害など）で，混迷や興奮などの行動変化・意識障害に規定される脳症症状が不可欠と考えられていて，MRI病変は白質主体で，稀に灰白質も巻き込まれるが通常は基底核，視床が多いとされている[4]．症例1・2ともに発作以外の脳症を示唆する臨床症状及び多巣性の症状がなく，灰白質MRI病変は基底核ではなく皮質にあり，臨床・画像的にADEMとは異なる特徴を示したと考えている．

てんかん発病とインフルエンザワクチンとの厳密な意味での因果関係は証明する方法はなく，インフルエンザワクチン投与例中の無熱けいれんの頻度は極めて低いことなどから，いわゆる“紛れ込み”は否定できないが，3例とも医薬品機構に申請し，政府の副作用認定を受けている．3例とも接種後3日に発病，その後徐々に部分発作の頻度増加という共通特徴があり，インフルエンザワクチン接種後に“みられた”てんかんとして，免疫学的に病態を検討した．

3例の髄液の免疫学的検査値を比較すると（表2），症例1では急性期から回復期にかけて，$CD8^+$T細胞が高値で，$CD8^+$T細胞が分泌するGranzyme Bも高値，TNF-αも上昇していた．その後パルス療法を行ったところ，$CD8^+$T細胞・Granzyme Bは改善し，抗GluRε2抗体も消退した．症例2では，急性期にGranzyme B・TNF-αの上昇に加えて，細胞数の上昇，IL-6が高値であり，炎症の存在が示唆され，$CD4^+$T細胞が上昇し，

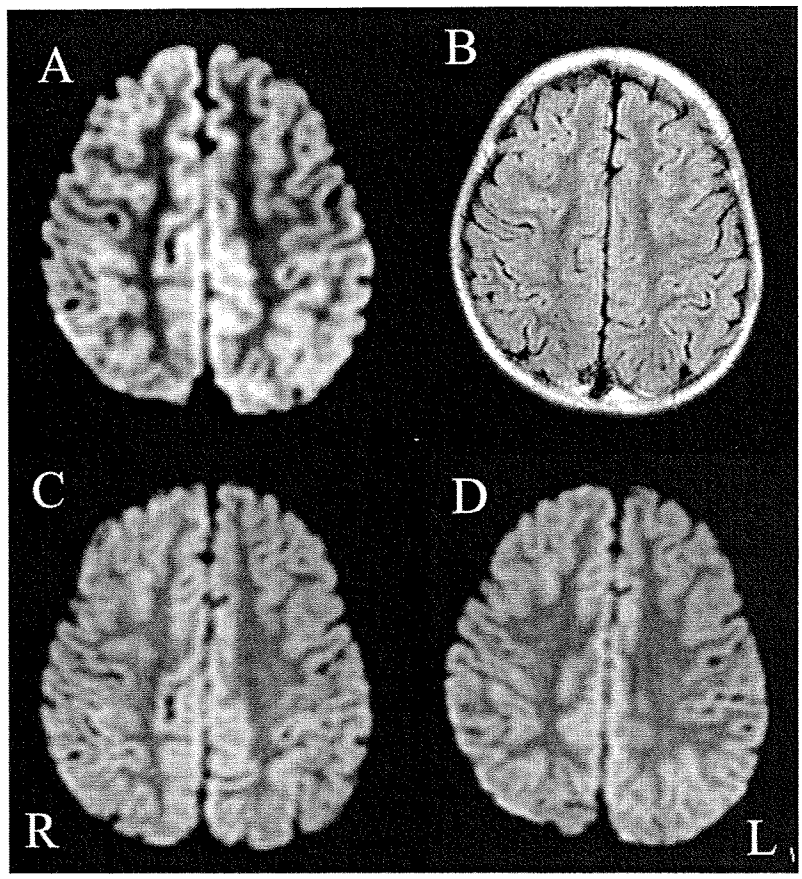

図2　症例2の頭部MRI所見
接種後36日の拡散強調画像（A），FLAIR画像（B）では，拡散強調画像で左後頭葉・頭頂葉主体に，高信号病変を認めたが，FLAIR画像では明らかな異常は認めなかった(図2-B)．Cは接種後66日，Dは接種後160日の拡散強調画像で，左後頭葉・頭頂葉内側面の高信号は徐々に改善している．

IFN-γがやや上昇，IL-12も高値であり，Th1細胞の関与も考えられる．その後パルス療法を行い，細胞数・$CD4^+$T細胞は改善傾向を示した．症例3のてんかん重積状態となった進行期では，Granzyme Bが上昇し，TNF-αも上昇，抗GluRε2抗体も認められた．以上より，3例ともGranzyme Bが上昇し，細胞障害性T細胞の病態への関与が推定され，症例2では，さらにTh1細胞の関与も考えられた．症例1・2では，血清のGranzyme Bは感度以下で，髄液のみで上昇していたことはラスムッセン症候群と同様に，インフルエンザワクチンにより感作された細胞障害性T細胞がCNSに侵入し，CNSおいて抗原を認識し，Granzyme Bを分泌していることを示すと思われる[7)8)]．

症例1,2では，発症約1か月でステロイドパルス療法を行い，予後は良好であり，症例1では，GranzymeBが9.8→6.5と低下したことを確認できた．よってステロイドパルス療法により，活性化された細胞障害性T細胞を抑制できたことが，症例1,2の予後を改善した可能性があると考えている．症例3では進行した，5か月の時点で，ガンマグロブリン大量療法を行われたが，発作予後，知的予後は改善できなかった．これは，インフルエンザワクチン後のてんかんの病態に，ガンマグロブリン大量療法が無効なのか，早期であれば有効なのか，今後の検討が必要なことを示している．症例1・2と3の経過の違いは治療の違いのみで説明できない可能性もあり，パルス治療が本当に有効なのかを含めて，今後多数例での検討が必要である．

症例1では急性期に見られたMRI-FLAIR病変の内，皮質下白質病変は不変であったが，左前頭部の皮質病変は経過とともに消失し（図1），てんかん発作も抑制されている．皮質下白質FLAIR病変が発病前からあったものかどうか確認できないが，てんかんの責任病巣は左前頭部のFLAIR皮質病変が主体であったかもしれない．症例2では症例1とは異なりFLAIR病変ではなく拡散強調画像病変が見られ，発作の抑制とともに消退してきている．今回の2症例で見られたFLAIR病変と拡散強調画像病変の出現の違いの明らかな理由は免疫学的バイオマーカーから示せないが，

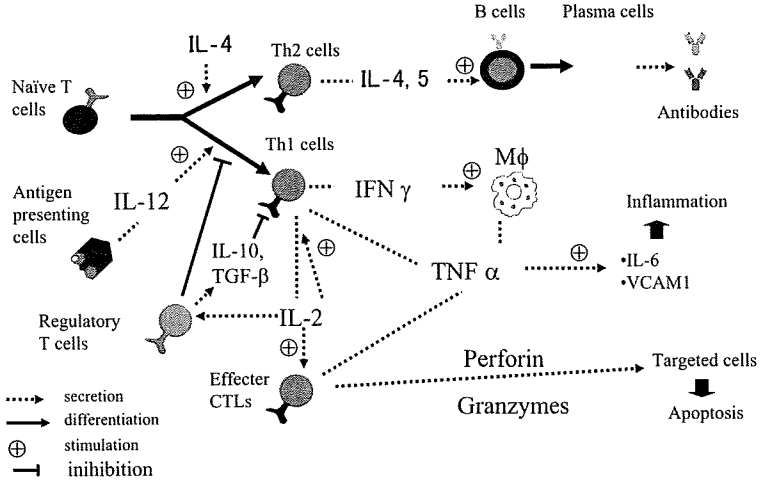

図3　T細胞・サイトカインと自己免疫病態

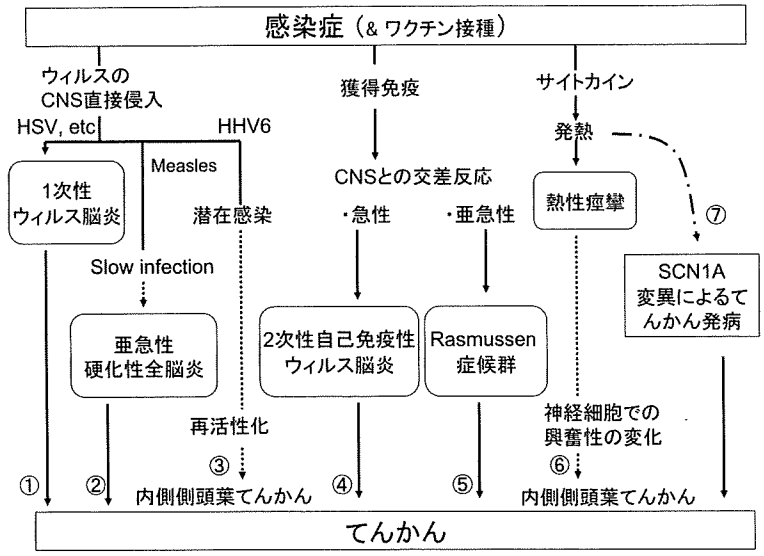

図4　感染症・ワクチンからてんかん発病へ
Y Takahashi, Future Neurology, 2006；1：291-302.

急性辺縁系脳炎においてもFLAIR・拡散強調画像の画像病変出現頻度は異なり[9]，炎症性神経疾患での画像病変出現機序の今後の解明が待たれる．

3症例ではワクチン接種から3日で発作が起こり，髄液中のTNF-αが高値を示した．通常感染から3日でてんかん原性が形成されるとは考えにくく，初期の発作は急性発作（acute seizure）と考えるべきである．感染による急性発作の動物実験ではTNF-αは濃度依存性にけいれん閾値を制御することが分かっている[6)10)11)]．ある範囲の濃度のTNF-αは炎症による急性発作を起こし易くすると考えられ，今回の3症例では急性期発作の発症にTNF-αが関与した可能性がある．またTNF-αは高濃度でAMPAによる神経細胞の興奮毒性死を高めたり[12]，シナプスのAMPA受容体を増加させ$GABA_A$受容体を減少させたり[13]，TNF-α transgenic miceが発作を起こすようになることが報告されている[14]．このような特性からTNF-αは急性期発作出現以降においても，徐々に神経興奮性を変化させ，てんかん原性獲得に寄与した可能性があると推定される．

症例1・3では調節性T細胞が分泌するIL-10が髄液中で低値であり，調節性T細胞の機能が低下していることを示唆している（図3）[8]．すなわち，調節性T細胞による自己反応性T細胞の抑制が低下しているために，自己免疫的反応が，インフルエンザワクチン後に起こった可能性がある（図4）．インフルエンザワクチンによる自己免疫的副作用が疑われる症例では，その後のワクチン接種のリスク等を評価するために調節性T細胞のマスター遺伝子であるFoxP3などの測定が必要かもしれない[15]．