JMAJ
Japan Medical Association Journal
Vol.49, No.1 January 2006

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Anxiety and Depression in Primary Care

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A reason anxiety and depression are often undetected by primary care physicians is that many doctors simply pay little attention to the possibility of anxiety disorder or depressive disorder when diagnosing an illness. However, in addition to this obvious reason, other possibilities include a patient tendency to complain only of the somatic symptoms specific to increasingly specialized consulting departments and the fact that the number of anxiety disorder and depressive disorder patients with difficult to diagnose symptoms, even by psychiatrists or doctors of psychosomatic medicine, has greatly increased. Also, mental distress is often masked by somatization. In a large-scale survey undertaken in 14 countries,[1] it was surprisingly reported that 69% of depressive patients complained only of somatic symptoms. Hence, the recognition of the characteristic symptoms of anxiety and depression underlying somatic symptoms is very important for early detection and effective treatment. The Maruyama et al. study published in this issue is of great significance because it concretely demonstrated the somatic symptoms (tiredness, sleep disturbance, musculoskeletal pain, dizziness, and gastrointestinal symptoms) of which anxious and depressive patients often complain to primary care physicians.

In the case of anxiety-induced somatic symptoms, the autonomic nerve-mediated symptoms are triggered by anxiety, and all do not appear at the same time but appear variably according to the severity of anxiety. In mild anxiety, almost all patients feel only slight, ambiguous somatic anxiety. When anxiety is moderate, the patients usually complain of palpitation, dry mouth, and sweating of the palms. In a state of severe anxiety, such as an anxiety disorder, the symptoms are categorized into 1) neurological symptoms, 2) cardiovascular symptoms, 3) gastrointestinal symptoms, and 4) respiratory symptoms. In adults, musculoskeletal pain, sweating of the palms, abdominal pain and diarrhea, headache, dry mouth, dizziness, chest pain and palpitation, urinary frequency and urinary retention, and tremor, in order of the highest to the lowest incidence may be present.[2] In children and adolescents (8–18 y), headache, epigastralgia, abdominal pain, and muscle pain occur more often than the other symptoms.[3]

Recently, we examined the somatic symptoms characteristic of the depression of 335 patients treated in our department.[4] The results indicated that, for both males and females, sleep disturbance was the most common problem, followed by loss of appetite. Of the significant differences between males and females, diarrhea and excessive sweating were specific to the former and bulimia and dysesthesia to the latter.

Overall, we were able to explain the somatic symptoms characteristic of anxiety and depression. Somatic symptoms not accounted for by any physical disease have been shown to afflict at least one-third of all patients, which suggests that many patients may be suffering from mental distress, such as from anxiety or depression. Careful attention by primary care physicians to the possibility of anxiety and depression in the treatment of patients is of critical importance for improving the quality of life of the patient and, in extreme cases, for preventing more serious outcomes, such as suicide. The treatment of anxiety and depression has been proven to considerably ameliorate both mental and somatic symptoms.

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Chronic Fatigue

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Fatigue generally indicates general tiredness and means that a person is tired even when he or she does nothing special. Even a healthy person feels fatigue after excessive physical labor. This fatigue can be relieved once he or she takes some rest. If a person easily becomes tired even when he or she is not working hard enough to cause fatigue or the feeling of fatigue cannot be relieved even after sufficient rest, it should be considered pathological.

On the other hand, if a person is left in a tense situation for a long time, he or she feels mental fatigue. Irrespective of physical labor, the person reports a feeling of fatigue caused by mental and psychological factors.

Some patients describe the status of lacking willingness to work as "fatigue". This should be called apathy. In many cases, these are often psychological disorders rather than physical illnesses.

"Fatigue" cannot be measured objectively. It is absolutely a subjective symptom, which patients describe.

Since "fatigue" is a symptom that can be seen in most such disorders and is not a property that can specify a particular disorder, differential diagnosis is difficult. For patients who report "fatigue," it is important to begin by eliminating major disorders that cause "fatigue."

The following is a list of major disorders that cause "fatigue." Consequently, when examining patients who report general tiredness, it is important to examine the patients in detail for other symptoms or physical findings, and to look for findings with even any minor disorder specificity.

When all clinical test results are normal and, in addition, there is insufficient physical finding to diagnose "fatigue" conventionally, psychiatric disorders, especially such as depression or nervous disorders, could be considered. However, nowadays, chronic fatigue syndrome (CFS) has come to occupy an important place.

Originally, chronic fatigue is a symptom with high frequency in daily clinical practice. Frequency in an ordinary primary care setting, according to reports from doctors, is said to be 20–25%, significantly more frequent with women.

Idiopathic chronic fatigue is defined as general tiredness that a person feels even when he or she is not working hard enough to cause fatigue, which lasts for more than 6 months without known cause and cannot be relieved after a night's sleep. Rating the degree of this feeling of fatigue is a problem. The CFS study group at the Ministry of Health, Labour and Welfare has set degrees of fatigue by performance status. According to this definition, the fatigue level for idiopathic chronic fatigue must be more than grade 3, which means that "a person cannot have a social life a couple of days a month due to such 'fatigue' and thus needs to rest at home" instead.

In Japan, diagnostic criteria of CFS in use are those prepared by the CFS study group at the Ministry of Health, Labour and Welfare. However, since these criteria lack objective evidence and depend on subjective symptoms, preparations to review the criteria are currently under way.

Of course, subjective symptoms that patients feel are important. However, degrees of each clinical symptom give important information in diagnosis.

In addition, since nosogenesis is actively studied and appreciable results can be obtained, it is expected to become a significant clue for differential diagnosis drawn from specificity and positive ratio of the test results.

To detect a microscopic organic disorder, its relation to a virus infection, immune dysfunction, endocrine-metabolic disorder, cerebral circulatory dysfunction and so forth would be a key to interpretation of CFS.

A list of major disorders that cause "fatigue"

1. anemia
2. low blood pressure
3. pulmonary tuberculosis
4. liver diseases
5. diabetes mellitus
6. kidney diseases
7. endocrine disorders
8. nutritional disorders
9. dehydration
10. congestive heart failure
11. neuromuscular diseases
12. exhaustional disorders, such as malignancy
13. psychiatric disorders
14. chronic fatigue syndrome
15. others

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Mental Health Problems in Primary Care: In the context of general health service in Japan

JMAJ 49(1): 3–14, 2006

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Abstract

Objectives To assess the prevalence of patients with anxiety and depression in general practice (GP) setting in Osaka, Japan and establish the usefulness of self-reported questionnaires as a screening tool. To evaluate the risk factors for psychological distress and to confirm the relationship between psychological distress and impaired daily functioning.

Methods Cross-sectional study

Main Outcome Measures Used GHQ (General Health Questionnaire)-6 items total scores for identifying anxiety and depression, and SOFA (Symptom of Fatigue and Anergia)-6 items total scores for somatic disorder, sociodemographic variables and disability measurement.

Results The prevalence of patients with common anxiety and depression was 33.9% for this sample of 449 patients. Risk factors significant for a GHQ-6 case were being female, separated/divorced/widowed and postmenopausal. The patients' self-reported general health status was highly suggestive of their psychological disorders. Impaired social functioning and productivity were significantly related to patients' psychological distress.

Conclusion High prevalence of psychological problems in the GPs setting in Japan was consistent with the previous reports. A poor self-rated health status and impaired social functioning were good indicators of psychological distress. The impact of psychological disorders on patients' quality of life requires early detection and intervention.

Key words Cross-sectional, GHQ, Primary care, GPs in Japan, Psychosomatic disorders, Predicting factors

Introduction

Mental health problems, particularly milder forms of depression and anxiety, not only have a high incidence but also a high prevalence across many cultures and countries.[1–3] Because the problems are often presented in less severe forms[2,4] and coexist with physical disorders, it is likely that in the primary care setting, mental health problems are under-detected[5,6] and remain unresolved over considerable time. The high prevalence of the impairment of quality of life due to mental health problems imposes a heavy burden on patients' families and their communities. This constitutes a major public health problem.

GPs in Japan have long been the first point of contact for many patients suffering from psychological problems but the data available in Japan relating to this problem is limited.[7,8] The purpose of this study is to determine the prevalence of patients with psychological disorders going to GPs in Japan by using a simple screening test that has been used in Australia.[9] Sociodemographic variables identified as risk factors for psychological distress were evaluated and compared with

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Table 1 GHQ-6 items and SOFA-6 items

GHQ-6 items	SOFA-6 items
5. Feeling nervous or tense	6. Muscle pain after activity
12. Feeling unhappy and depressed	16. Needing to sleep longer
20. Feeling constantly under strain	17. Prolonged tiredness after activity
27. Everything getting on top of you	25. Poor sleep
33. Losing confidence	30. Poor concentration
34. Being unable to over come difficulties	31. Tired muscles after activity

previous studies to define the subgroups at risk. This study also looks at common and non-specific physical symptoms of patients that are suggestive of psychological problems.

Methods

Selection of GPs: In the first instance, all 12 doctors who were affiliated with a department of general medicine of Osaka University Hospital and practiced in the Osaka area were approached. The purpose and method of the study, and the requirement of the submission of the cases of about 100 patients per doctor were explained. Seven doctors agreed to participate in the study. Two doctors who dropped out of the study at the early stage, stated that it created too much extra work for receptionists as their reason for doing so. Thus this study is based on patients who attended 5 GP clinics in the Osaka area in the period from October to November 2001.

The reasons given by the 4 doctors who would not participate was that they were too busy or that it was too busy a time of the year to carry out the study. Another doctor, who declined to participate in the study, stated that none of her patients showed any identifiable psychological problems and if there had been any, the patient would have already been referred to a specialist.

Subjects: Patients were selected as either the consecutive or every other attendee according to the decision made by the individual GP. Those patients who appeared to have acute upper respiratory infections and those with cognitive function disorders were excluded. Patients were asked by the receptionist to fill in the questionnaires while waiting for the doctor. Those who had made more than one visit to the clinic in the period of the study were not asked to fill out the questionnaires twice. A two-page patient' self-assessment questionnaires, SPHERE-JP (Appendix) was used to evaluate the prevalence and the predicting factors of psychological distress of patients. In addition, a follow-up interview with participating GPs was undertaken using a semi-structured questionnaire.

The questionnaire (Appendix) is a Japanese version, translated and back-translated, of the 34-item Australian SPHERE-GP (Somatic and Psychological Health Report). The SPHERE-GP questionnaire[10] was developed based on the assumption that 'Mental disorders in general practice are best characterized by mix of psychological and somatic distress.' (Table 1) Embedded in these 34-item questionnaires are 6 psychological items GHQ-6 (General Health Questionnaire) and six somatic items SOFA-6 (Symptom of Fatigue and Anergia) that best predict DSM-III (Diagnostic and Statistical Manual of Mental Disorders, III) diagnoses of GPs' patients with depression and anxiety dimension by CIDI (Composite International Diagnostic Interview). The response system employed for the 34 questions was: 'never or some of the time', 'a good part of the time' or 'most of the time' (scored '0-1-2', respectively). A pilot study was carried out with a group of 30 patients with a satisfactory compliance of all items.

In reference to previous reports,[7,11,12] Sociodemographic indicators (Appendix) included years of formal education, employment, marital status, household number, and number of children. General health status was self-rated by patients as being excellent, very good, good, fair or bad. Women indicated their health status, as either pre- or postmenopausal. Questions included social and daily functioning during the previous month. Level of functioning with regard

Table 2 Characteristics of GPs and their patients

Doctor characteristics	All subjects	Dr (group) 1	Dr (group) 2	Dr (group) 3	Dr (group) 4	Dr (group)5
Age		53	52	58	52	51
Gender		F	F	M	M	M
Year of practice		9	15	18	10	17
Adult patients per day		24	20	25	60	45
Style of visit (appointment: A/walk in: W)		W	W	W	W	W
N	449	91	87	99	97	75
Patients Characteristics						
Female patients (%)	65.0%	71.4%	63.2%	56.6%	66.0%	69.3%
Age of patient (Mean ± SD)	56.5 ± 15.4	56.7 ± 13.9	50.9 ± 17.2	57.8 ± 14.6	59.7 ± 15.2	56.8 ± 15.0
GHQ-6 total score (Mean ± SD)	1.46 ± 2.02	1.45 ± 1.75	1.10 ± 2.01	1.88 ± 2.47	1.62 ± 1.91	1.11 ± 1.72
GHQ cases (%)	33.9%	36.3%	20.7%	40.4%	41.2%	28.0%
Restricted days (range)	1.2 ± 3.4 (0–30)	1.2 ± 2.8 (0–15)	0.8 ± 2.9 (0–15)	1.2 ± 3.03 (0–15)	1.4 ± 4.1 (0–21)	1.0 ± 3.8 (0–30)
Days in bed (range)	0.7 ± 2.3 (0–20)	0.6 ± 1.7 (0–10)	0.4 ± 1.6 (0–10)	0.8 ± 2.1 (0–10)	0.8 ± 2.5 (0–15)	0. 8 ± 3.1 (0–20)
Number of people in household (range)	2.1 ± 1.6 (0–8)	NA	NA	3.5 ± 1.7 (0–8)	2.7 ± 1.6 (0–8)	3.0 ± 1.4 (0–7)
Number of children (Mean ± SD) (age range in years)	1.7 ± 1.1 (0–9)	1.7 ± 0.9 (0–5)	1.9 ± 1.1 (0–5)	1.8 ± 1.0 (0–4)	1.8 ± 1.3 (0–9)	1.6 ± 1.0 (0–4)
Years of education	13.5 ± 1.6	13.8 ± 1.3	13.6 ± 0.8	13.3 ± 1.5	13.5 ± 1.5	13.1 ± 1.7

Average number of people in Japanese households: 2.79
(Statistical Data Base System, Ministry of Health and Labor, 1999)
NA: Number of people in household not asked in questionnaires for patients of Drs 1 & 2.

to hobbies, housework, job, and relationships with others were self-rated by the patients. Subjects were also asked whether the reason for the visit was primarily psychological, physical or both.

Data analysis: A GHQ case, that is a patient with a likely psychiatric diagnosis was defined as having a total GHQ-6 item score (the anxiety and depression dimension) of 2 or more. A SOFA-case was defined as a total SOFA-6 item score (somatic dimension) of 3 or more. Since there is a strong positive correlation ($r = 0.58$, $P < 0.001$) between these two sets of questions, only the GHQ-6 scores were used in the statistical analysis. In a WHO Nagasaki study[7] that used the GHQ-6 questionnaire, a cut off point of 2 or more was also used and this point gave the best sensitivity 76.6% and specificity 74.7%.

As mentioned later in the results section (Table 6), a cut off of 2 or more for GHQ-6 total score discriminated a GHQ case from a Non-GHQ case with a significant difference in 'restricted days': missed days of work, school or regular responsibilities, or a level of impaired functioning over last one month. Mean restricted days for a GHQ case was 2.6 days while for a Non-GHQ case it was 0.47days. This finding also supported the appropriateness of a cut off point of 2 or more for a GHQ case.

All statistical analyses were conducted with the Statistical Package for Social Sciences (SPSS 10.0).

The Ethics Committees of the Geriatrics Department of Osaka University Medical School and the University of New South Wales approved this study.

Table 3 Comparison of GHQ-6 scores for social characteristics and health factors

		GHQ-6 score (SD)	n	*P* value[a]
Gender	Male	1.02 (1.60)	157	0.001
	Female	1.69 (2.18)	292	
Age	16–24	1.08 (1.66)	13	NS 0.82
	25–44	1.49 (1.99)	84	
	45–64	1.40 (2.00)	187	
	65–80	1.54 (2.09)	165	
Marital status	Not married	1.09 (1.64)	46	0.008[b]
	Married	1.36 (1.93)	316	
	Wid /Sep/Div	2.08 (2.47)	80	
Years of formal education	13 or more	1.45 (2.02)	297	NS 0.89
	12 or less	1.43 (2.03)	138	
Employment	Unemployed	1.39 (2.20)	97	NS 0.623
	Employed	1.39 (1.88)	184	
	Housewife	1.63 (2.21)	90	
Children	None	1.43 (2.09)	75	NS 0.889
	1 or more	1.46 (2.01)	374	
Live alone	Yes	1.39 (1.95)	38	NS 0.576
	No	1.60 (2.13)	233	
Self-rated health status	Excellent	0.22 (3.22)	9	<0.001[c]
	Very good	0.32 (0.89)	22	
	Good	0.58 (1.11)	125	
	Fair	1.74 (2.02)	261	
	Poor	3.44 (2.98)	27	
Menopausal	Premenopausal	1.31 (1.75)	87	0.037
	Postmenopausal	1.89 (2.33)	198	

[a]: One Way Anova
[b]: Post Hoc Test: not significant between Not married and Married
[c]: Post Hoc Test: not significant among Excellent, Very good and Good

Results

Internal consistency of somatic and psychological dimensions: Cronbach's alpha (a measure of internal consistency) for the GHQ-6 items was 0.80 for the study population, female 0.82 (n = 292) and male 0.73 (n = 157) respectively. For SOFA-6 items Cronbach's alpha was 0.74 for all respondents, female 0.74 (n = 292) and male 0.71 (n = 292) respectively. Both GHQ-6 items and SOFA-6 items showed high internal consistencies among their items and together constructed 2 major dimensions of the questionnaires. Cohen's kappa, a measurement of agreement between two scales, GHQ-6 and SOFA-6, was a low 0.316. This supports the use of GHQ-6 items as a scale for evaluation of psychological cases and SOFA-6 items as a scale for evaluation of somatic cases.

GPs' characteristics compared with GPs in Japan: Five doctors in this study have fairly typical general primary care practices. The five GPs (Table 2), 2 female and 3 male, ranging in age from 51 to 58, are solo, full-time, private practice doctors, affiliated with Osaka University Medical School. They share a similar career pathway; being trained in general medicine prior to starting their practices. They spent 8 to 18 years in clinical, research or teaching careers prior to commencing their practice as GPs. Years of private practice ranged from 9 to 18 years. They see primarily adult patients with general medical problems, though children below the age of 15 make up 20% to 40% of their patients. In order to compare these GPs to the average doctor in the Osaka area and in Japan as a whole, Dec. 30th 2000 database provided by the Ministry of Health, Labor and Welfare was used. Doctor

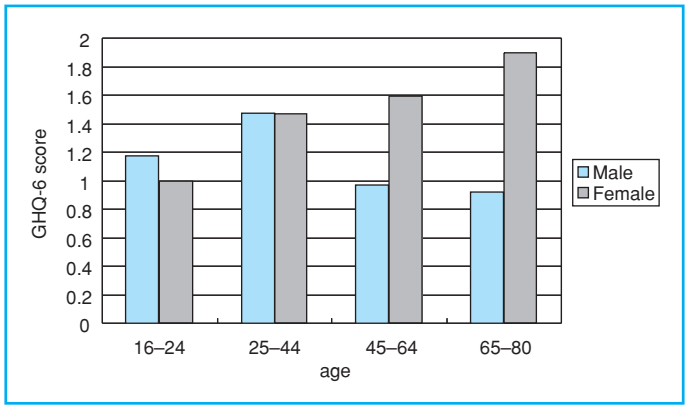

Fig. 1 Age and GHQ-6 total scores in males and females

distributions in Osaka prefecture are similar to those countrywide, except in that the ratio of doctors per 100,000 of the general population is higher in Osaka (223.3) than in Japan generally (191.6).

In the Osaka area and countrywide, the ratio of doctors working in hospitals to those in clinics is approximately 60% to 35%. Similarly in both Japan as a whole and the Osaka area, the ratio of male to female doctors is 85% to 15%, although for doctors under the age of 29 this drops to 2:1. While 80% of clinic doctors are full-time sole practitioners, the remaining 20% who practice with someone else usually do so with a family member. Among clinic doctors in Japan and in Osaka, nearly half of the doctors practice general medicine and function as the first point of contact for most patients in Japan.

Distribution of subjects (Table 2): The total number of subjects, n = 449, aged 16 to 80, included 157 male (35.0%) and 292 female (65.0%). The mean age of the study population was 56.5 ± 15.4 years and there were no significant age or age group differences found between males and females. The return rate of questionnaires was 95.7% (range, 97.0–92.8% from practice to practice).

Proportion of GHQ and SOFA cases: The over all rate of mental disorder (GHQ-6 item total score two or more) was 33.9% with mean total GHQ-6 score 3.78 ± 1.88 and the over-all rate of positive somatic items (SOFA-6 item total score 3 or more) was 41.6% with total GHQ-6 mean score 3.20 ± 2.60. The rate of those patients who were cases on both GHQ and SOFA scales was 23.4% with mean GHQ-6 total score 4.11 ± 2.03.

Significant sociodemographic factors (Table 3): The significant differences in GHQ-6 total score were found in each of the following variables: gender, age difference when male and female were considered separately, marital status, patient self-rated status of general health and menopausal status for women.

Gender difference: The GHQ-6 total score for all female subjects was 1.69 which was significantly higher than 1.02 for male ($P = 0.001$).

Age difference: No significant correlation was found between age and GHQ-6 scores ($r = 0.067$, $P = 0.08$, $n = 449$) in subjects when taken as a whole. When male and female scores were analyzed separately, there was a significant positive correlation between age and GHQ-6 scores for females ($r = 0.141$, $P = 0.015$, $n = 297$) but not for males ($r = -0.109$, $P = 0.176$, $n = 157$).

Male and female in different age groups (Fig. 1): Both genders had similar lowest scores at age 16 to 24 years, with GHQ-6 scores 1.17 for male and 1.00 for female respectively. Age 25 to 44 scores increased to 1.48 for males and 1.47 for females respectively. However men and women developed significantly different scores in higher age groups. The mean score for men decreased to 0.97 for age group 45–64 year and remained low 0.92 for age group 65 to 80. By contrast, women's GHQ-6 scores increased steadily with a corresponding increase in age: the youngest female group 16 to 24 years was 1.00, the score of women 45 to 64 was 1.59 and that of 65 to 80 year-old

Table 4 Comparison for GHQ-6 scores between male and female in different marital status

Marital status	Gender	N	Mean GHQ-6 score	*P* values*
Not married	Male	19	1.05	NS (0.970)
	Female	27	1.11	
	Total	46	1.09	
Married or de facto	Male	128	0.98	0.007
	Female	188	1.63	
	Total	316	1.36	
Separated/Divorced/Widowed	Male	7	1.43	NS (0.472)
	Female	73	2.14	
	Total	80	2.08	

*: One way Anova

Table 5 Physical symptoms as a risk factor for GHQ-cases, logistic regression analysis

	Physical symptoms	Affirmative respondents[a] %	GHQ cases[b] %	Odds Ratio[c] (95% CI)
Tiredness	17. Prolonged tiredness after activity	36.1	55.4	5.0 (2.6–9.4)
	29. Feeling tired after rest or relaxation	28.1	62.8	4.0 (2.6–6.9)
Sleep disturbance	25. Poor sleep	28.7	60.5	3.8 (2.2–6.6)
	16. Needing to sleep longer	49.5	45.2	3.3 (1.8–5.8)
Musculo-skeletal pain	21. Joint pain	21.5	48.8	3.0 (1.7–5.0)
	4. Pains in arms or legs	20.7	49.6	2.8 (1.7–4.7)
	15. Back pain	56.6	42.5	2.5 (1.4–4.5)
	1. Headaches	17.9	60.9	2.7 (1.7–4.4)
Dizziness	28. Dizziness	16.9	66.1	2.8 (1.7–4.4)
	9. Fainting spells	17.2	55.0	2.8 (1.6–4.8)
Gastrointestinal	24. Diarrhea or constipation	27.4	46.6	2.6 (1.6–4.4)
	13. Gas or bloating	17.9	46.8	2.6 (1.6–4.3)

[a]: The rate of respondents who in the affirmative to either 'a good part of the time' or 'most of the time' for each item
[b]: Rate of GHQ-6 cases among affirmative respondents
[c]: Odds ratio (95% confidence interval, $P=0.01$) for being a GHQ case (GHQ-6 items), adjusted for gender

women was 1.90.

Marital status (Table 3): Widowed/separated/divorced as one category had significantly higher GHQ-6 items score (2.08, $P=0.008$) than the group of not married (1.09) or married (1.36). No significant difference was found between the groups of not married and married.

Male and female in different marital status (Table 4): There was no significant gender difference for GHQ-6 item score within the category of not married (male 1.05 and female 1.11 respectively) or the group of separated/divorced/widowed (male 1.43, female 2.14). Within the category of married, married women had significantly higher GHQ-6 scores than married men (female 1.63 and male 0.98 respectively, $P=0.007$).

Comparing the scores of married men and women by age groups, a significant difference between the genders in married subjects was found in the age group 45 to 64 years and 65 to 80 years. Married females in the age group 45–64 years had a significantly higher GHQ-6 score of 1.70 than that of males 0.82 ($P=0.01$). Married females, in the age group of 65 to 80 also had a significantly higher GHQ-6 score 1.64 than that of male 0.89 ($P=0.02$).

There was no significant difference in the mean GHQ-6 total scores in relation to the following socio-demographic characteristics as predicting factors for a GHQ case; years of formal education, employment status, having children or

Table 6 GHQ cases,* Non-GHQ cases and debilities

	All samples n = 449	GHQ cases mean ± SD	Non-GHQ cases mean ± SD	*P* values
	100%	33.9% (AU** 37%)	66.1%	
GHQ-6 score	1.46 ± 2.02	3.78 ± 1.88	0.27 ± 0.44	<0.001
Restricted days	1.15 ± 3.38	2.60 ± 4.61	0.47 ± 2.29	0.003
Days in bed	0.67 ± 2.25	1.10 ± 2.74	0.43 ± 1.87	0.001

*: GHQ case (GHQ-6 items total score ≧2)
**: AU Australian data

not, and living alone or not.

Patient self-rated general health status: GHQ-6 items total scores were highly correlated with subjects' self-rated general health status (Table 3). The mean scores for the five degrees of the health status were, recorded as excellent (0.22), very good (0.32), good (0.58), fair (1.74) and poor (3.44) respectively.

Postmenopausal status (Table 3): Females who were postmenopausal had significantly higher scores than females who were premenopausal (1.89 for postmenopausal and 1.31 for premenopausal respectively, $P = 0.037$).

Reason for the visit: Among those who gave a reason for their visit (n = 267), 208 people indicated a physical reason (77.9%). Two subjects gave the reason for their visit as psychological (0.7%) and 16 (6.0%) stated that both physical and psychological factors prompted their visit. There was a significant difference in GHQ-6 mean scores between physical (score = 1.38) and both physical and psychological reasons given for the visit 3.63 ($P<0.001$). The only three patients who answered that they 'did not know' their reason for visit had the highest mean GHQ-6 scores 3.67.

Physical symptoms as risk factors for a GHQ case (Table 5): Twelve physical symptoms were grouped as tiredness (tiredness prolonged after activity, feeling tired after relaxation), sleep disorder (poor sleep, needing to sleep longer), muskulo-skelatal pain (joint pain, pains in arms or legs, headaches) and gastrointestinal problems (diarrhea or constipation).

55.8% of subjects reported having back pain. This was the highest reported symptom. 42.5% of these patients with back pain scored more than 2 on their GHQ-6 items and were identified as GHQ cases. These subjects were 2.5 times more likely to be GHQ cases than Non-GHQ cases (who had no back pain).

Tiredness and sleep disorder were the highest risks of being GHQ cases, with Odds Ratios 5.0 (prolonged tiredness after activity) and 3.8 (poor sleep) respectively. Dizziness and Gastrointestinal symptoms also had Odds Ratios 2.6 to 2.8 respectively.

GHQ cases, non-GHQ cases and debilities (Table 6): The percentage of GHQ cases (GHQ-6 total score ≧2) for the whole sample was 33.9%. The mean GHQ-6 total score for GHQ cases (3.78 ± 1.88) was significantly higher than that of Non-GHQ-6 case (0.27 ± 0.44, <0.001).

Two indicators for debility, restricted days and days in bed during last one month were compared between GHQ cases and Non-GHQ cases. Both the mean restricted days and days in bed were significantly longer in GHQ cases than in non-GHQ cases.

Degrees of impairment for social functions and GHQ-6 scores: The GHQ-6 scores of the four social functions, hobby, housework, job and social relations were rated according to 3 degrees of severity (not at all, sometimes, definitely). Significant relationships were found between GHQ-6 scores and the degree of debilities in all 4 indicators (range r = 0.31–0.52, $P<0.001$, 2-sided, n = 386–449).

Logistic regression, predictors for GHQ-6 cases: Variables analyzed by logistic regression for their predictive value in determining GHQ cases (GHQ-6 total score ≧2) were: gender (male, female), age groups (16–24, 25–44, 45–64, 65 ±), marital status (not married, married, widowed/separated/divorced), years of education (12 or less, 13 or more), employment status (unemployed, employed), children (none, any), live alone (yes, no), self-rated health status (excel-

lent/very good, good, fair/poor) and degree of impairment for social functions (hobby, house work, job, social activities affected or not).

Of these variables, the risk factors that predicted GHQ cases were: a self-rated general health status as fair/poor (OR = 7.7, $P = 0.001$), female gender (OR = 3.1, $P = 0.006$), decreased motivation for work (OR = 1.9, $P = 0.002$), and the two highest age groups 45–64 years, (OR = 2.5, $P = 0.08$) and 65 ± years (OR = 2.3, $P = 0.05$).

GP Interviews: Three out of five doctors were surprised at the prevalence of patients found to have psychological problems. Their rough guesses of the prevalence of patients with psychological problems were 5–10% (2 GP's), 10–20% (1 GP), and 30% (2 GP's). Other points of note from these interviews are:

(1) Different doctors identified different groups as being most at risk for psychological problems.
(2) The number of cases the doctors had referred to mental health specialists in the past 12 months ranged from 2 to 10. Diagnoses for these cases were mostly depression. All the patients had been referred to psychiatrists, none to any other kind of mental health professional.
(3) Depression and somatic complaints were the most common forms of the psychological disorders GPs saw in their patients.
(4) Prescription of Benzodiazepines for treatment of depression and anxiety was the major treatment choice in these primary care settings, although 3 out of the 5 doctors prescribed SSRI's and other new drugs for depression.
(5) The major barriers the doctors noted to giving more treatment for their patients' psychological problems were 1) lack of time, 2) lack of appropriate network or resources to refer their patients to, 3) lack of appropriate space in which to talk privately with their patients.
(6) To obtain more information, most doctors preferred easily accessible and useful information available either on the internet or in a newsletter. Mental health related topics rarely formed part of their continuing medical education.

Discussion

According to the results of this study, the prevalence of GPs' patients in Japan with psychological distress was 33.9%. This finding is supported by results of similar studies undertaken in Australia 37%[13] and by the WHO 32.5%.[6] Age and gender both play a significant role. It is not surprising given the population characteristics in Japan that the average age of the subjects was 56 years. The percentage of female patients was 65% (range 56–71% from practice to practice), which is higher than national average where women visiting out patient clinics is 55%.[14] Accessibility issues for men in the study area may, to some extent, have resulted in them visiting company doctors at their workplace in favor of their GPs.

According to Bebbington PE[15] women were two to five times more at risk of depressive disorders than men. Fujiwara et al.,[16] from their community survey in Japan, reported that women had a rate of depression 3.4 times that of men. This study also identified gender as a risk factor for depression and anxiety; women were 1.7 times more likely to have mental disorders than men. However, women are generally more willing to express their emotions while traditionally this has been seen as weakness in men and could have contributed to the larger number of women found seeking medical attention.

Men and women experience stressful periods at different ages. The major stressful period for men was during the working age 25 to 44 whereas in women psychological scores were higher after the age of child bearing: 45 and older. This could be attributed to men's major responsibilities at work and for families as a breadwinner, while women remained being solely or mainly responsible for housekeeping even after their husband's retirement. Data from this study also indicates that postmenopausal status was highly correlated with the negative psychological well-being of women. These findings should lend insights to discussions about the need to develop resources to assist groups identified as having psychological difficulties, and how these resources might best be deployed: men in the work-force and women after the age of 45 may be target groups.

Table 7 compares variables of this study with WHO-Nagasaki[7] and SPHERE-GP.[17] All three studies used GHQ-6 as a screening instrument.

Two variables, marital status and subjects' self-rated general health status, were closely related to the psychological scores in all three studies. Age difference was also found in three studies with the exception that in this study the age difference was found only in females.

Table 7 Comparing SPHERE-JP with Nagasaki report and SPHERE-GP (AU) for social characteristics and health status as risk factor for a GHQ case

	WHO-Nagasaki	SPHERE-JP	SPHERE-GP (AU)
Gender	−	+	+
Age	+	+*	+
Education	+	−	+
Marital status	+	+	+
Employed or not	−	−	+
Children or not	−	−	+
Live alone or not	NA	−	NA
Self-rated general health status	+	+	+
Post-menopausal	NA	+	NA

+: Significant difference in GHQ-6 scores in each factors; −: Not significant;
Vacant cell: not included in the questionnaire; *: Significant for female only; NA: not available

Gender as a risk factor for a GHQ case was found in this study and the Australian result but not in Nagasaki report. Given it was done 20 years prior to this study in Nagasaki, social, political, economical conditions had changed.

Unlike the Nagasaki and Australian reports that showed lower levels of education correlated with higher levels of psychological problems, this study did not support such a finding. The factor that their sample size is greater may have contributed to the difference.

Neither this nor the Nagasaki study found any correlation between employment and having children or not, and the psychological scores. These findings were different from those of the Australian study, which demonstrated that unemployment, and having children were risk factors for psychological problems.

It is of importance that a general question enquiring about patients' own opinion about their health status (from excellent to poor), without specifying the question as mental or physical had a high correlation with their psychological scores. In other words, patients' comments about their general well-being could well reflect their psychological status. Logistic Regression indicated that self-rated general health status is the best predicting factor in identifying patients with psychological difficulties among all the variables evaluated in this study. This mirrors the Australian[17] and Nagasaki findings[7] and supports the assumption that patients visiting GPs do not discriminate their physical problems from their mental problems.

When patients were asked a more specific question regarding whether their reason for visiting their doctor was psychological or physical, only 2 out of 267 reported that they visited doctors with a psychological reason. A report[14] showed that Japanese people seek medical assistance for psychosomatic symptoms rather than psychological symptoms and this fact may be a reason for the difference.

The highly correlated relationship between psychological and somatic symptom items suggested the strong link between psychological and physical symptoms in patients visiting GPs in Japan. The somatic symptoms reported by the patients yielded high Odds Ratios to the GHQ-6 cases. Back pain has the highest rate 55.8% among subjects in this study with an OR 2.5. This percentage is consistent with the National Survey of Health 1999 (Kokumin Eisei no Douko) that back ache is the most common complaint amongst the general population in Japan. The two items questioning about fatigue had the highest ORs (range 4.0–5.0) and this reconfirmed previous findings in Australia[18] and Japan[19] that prolonged fatigue syndromes are common in primary care settings and are strongly associated with current psychological distress. The physical symptoms; back pain, headache, fatigue, sleep disorder and digestive system disorders are all risk factors for psychological distress and these symptoms should be of concern for the medical professions when considering somatic disorders.

A community survey carried out in Japan by Tomoda,[20] compared the degree of debilities of subjects with major depression and sub-threshold depression. Thirteen percent of the interviewed subjects had sub-threshold depression and 40% of the subjects with sub-threshold depression reported some sort of functional debility. Our study also showed that debilities expressed in terms of 'restricted days in the last one month' and 'days in bed in the last one month' were highly correlated to patients with mild forms of anxiety and depression.

From interviewing 5 GPs for their responses and comments, 3 out of 5 doctors were surprised at the high prevalence of patients found by the study to have psychological problems. The two GPs who were not surprised with the outcome were not necessarily the less busy ones. 'Interest and Concern'[21] are major factors related to doctors' awareness of the problems. Although it may not be possible to modify doctors' 'concern', it should be possible to improve doctors' interview skill.

The number of cases that GPs referred to mental health specialists in the previous 12 months was less than 10 in any one of the GP practices in this study. None of the GPs referred their patients to psychologists or counselors. There seems to be a big gap between the needs of the GPs for psychiatrists and other professionals to assist in the treatment of their patients and what is available. When asked what groups were most at risk for psychological disorders, different doctors noted different groups, perhaps inadvertently selecting which patients they would be most likely look at more closely for psychological problems.

Conclusion

This study used the responses of 449 patients of 5 GPs in the Osaka area of Japan, to a simple patient self-rated questionnaire. Collection of information about the prevalence of mental health problems in patients attending primary care clinics in Japan is essential to raise awareness about these issues amongst doctors and within the health care system in general. This study found that 33.9% of patients attending primary care settings in Osaka had psychological disorders. The prevalence is high though consistent with other international reports.[6,13] A simple, quick screening questionnaire for psychological distress is useful and can assist doctors in better identifying the problems.

Groups found to be most at risk were females, females aged 45 or more, post-menopausal women, work-age men and anyone separated, divorced or widowed. This indicates an initial focus for the planning of mental health service delivery in primary care settings. An increased GHQ-6 total score was highly correlated with reduced productivity and impaired daily and social functioning. When all variables were tested by logistic regression, the best predictors for GHQ cases were patients who self-rated poor or fair general health status, female gender and decreased daily functioning.

This study identified a deficiency in the service provided to people with psychological problems in Japan. Learning from the comments of participating GPs and their experience with patients can help fill the gaps in the system of delivery of mental health services. In these days of rapidly increasing health care costs, it is in everyone's interest to identify people with psychological problems early and accurately.

Acknowledgements

I would like to thank Prof. Arie Rotem, Center for Public Health, University of New South Wales, Sydney and Prof. Ian Hickie, Professor of Psychiatry, the University of Sydney for their kindness and generosity in instructing me on this project

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Appendix

SPHERE-JP page 1/2

☐ Female ☐ Male, Age_____ Today's date_____

We would like to know about your general health.

For each question, please tick the appropriate response space.

Over the past few weeks have you been troubled by:							
	Some of the time or never	A good part of the time	Most of the time		Some of the time or never	A good part of the time	Most of the time
1. Headaches?				18. Sore throats?			
2. Feeling irritable or crancky?				19. Numb or tingling sensations?			
3. Poor memory				20. Feeling constantly under strain?			
4. Pain in your arms or legs?				21. Joint pain?			
5. Feeing nervous or tense?				22. Weak muscles?			
6. Muscle pain after activity?				23. Feeing frustrated?			
7. Waking up tired?				24. Diarrhoea or constipation?			
8. Rapidly changing moods?				25. Poor sleep?			
9. Fainting spells?				26. Getting annoyed easily?			
10. Nausea?				27. Everthing getting of top of you?			
11. Arms or legs feeling heavy?				28. Dizziness?			
12. Feeling unhappy & depressed?				29. Feeling tired after rest or relaxation?			
13. Gas or bloating?				30. Poor concentration?			
14. Fevers?				31. Tired muscles after activity?			
15. Back pain?				32. Feeling lost for words?			
16. Needing to sleep longer?				33. Losing confidence?			
17. Prolonged tiredness after activity?				34. Being unable to overcome difficulties?			

SPHERE-JP page 2/2

Over the past one month

1) Have you had to cut down or stop any activity you used to do such as hobbies, because of some illness or injury?
   a. Not at all b. Yes, sometimes or a little c. Yes, moderately or definitely

2) Have you not been able to do something that your family (or household) expected from you as part of your daily routine?
   a. Not at all b. Yes, sometimes or a little c. Yes, moderately or definitely

3) Have your personal problems decreased your motivation for work?
   a. Not at all b. Yes, sometimes or a little c. Yes, moderately or definitely

4) Has there been a deterioration in your social relations with friends, workmates, or other people?
   a. Not at all b. Yes, sometimes or a little c. Yes, moderately or definitely

5) How many days in total were you unable to carry out your usual activities fully?

6) How many days in total did you stay in bed all, or most of the day because of your injury or illness?

7) In general, would you say your health is
   1. Excellent 2. Very good 3. Good 4. Fair 5. Poor

8) The question for female patients only
   Are your menstrual periods 1. Regular 2. Irregular 3. Post-menopausal

9) The reason of your visit today is
   1. Physical 2. Mental 3. Both physical and mental 4. Do not know 5. MISC

D1) What is your current state of employment?
   1. Unemployed 2. Part time 3. Full time
   4. Home duties 5. Student (part time) 6. Student (full time)
   7. Disability payments (e.g. sickness) 8. retired 9. MISC

D2) Number of children: _____

D3) What is the highest level of education you have even completed?
   1. No formal education 2. Primary school 3. Junior high school
   4. Senior high school 5. Two-year college
   6. technical qualification/certificate/diploma 7. University

D4) Are you currently
   1. Never married or never de facto
   2. Married or current de facto
   3. Separated/divorced/Previously de facto/Widowed

D5) Including yourself, the number of people in your household is _____

Original Article

State of Usage and Problems Regarding Childcare Centers for Sick Children in Gifu City, Japan

JMAJ 49(1): 15–18, 2006

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Abstract

In Japan, a system of childcare centers for sick children was instituted in 1995 and the number of users has been increasing. In Gifu city, care for sick children was started by the Fukutomi Children's Clinic in April 1996, and the number of facilities that provide such care increased to four by 2000. Many children who use such childcare centers for sick children are less than one year old. Due to seasonal variation, there were more users in winter. The number of childcare centers for sick children is expected to increase due to societal requirement. Based on our experience, the required capacity is considered to be one child per approximately 1,000 preschool children, and one child per 200 children who attend childcare centers.

Key words Childcare, Sick children, Day care center

Introduction

In Gifu city, the first childcare center for sick children was opened in 1995, and since then the number of such facilities has increased to four. They serve as a significant support for working mothers. Care for sick children itself has become accepted by society and is now recognized as a form of childcare. We studied the necessary number and capacity of childcare centers for sick children in Gifu city.

Subjects and Methods

The subjects studied were sick children who used the childcare center of the Fukutomi Children's Clinic. We studied the childcare records of the clinic from 1996 to 2004. Data on the age of the children, the number of children per year, per month of the year, and per disease were included.

Results

Number of users (Table 1)

The numbers of users for the eight years were as follows: 169 (children) for 1996, 566 for 1997, 763 for 1998, 1,053 for 1999, 1,268 for 2000, 1,583 for 2001, 1,206 for 2002, 1,345 for 2003, 1,748 for 2004. After 1999, these numbers were more than 1,000 and gradually increased yearly. The number was the largest in 2004, reaching 1,748.

Number of users by month (Table 1)

The number of users by month tended to be high in winter, that is, from December through March, and low in summer, yearly.

Number of users by disease (Table 2)

According to disease, the numbers of users were high (68 to 80%), for common cold symptoms such as fever and cough, and low (0.7 to 5.2%)

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Table 1 Number of usage of sick children by month of the year, and by year

Month \ Year	1996	1997	1998	1999	2000	2001	2002	2003	2004	Total
1	0	19	38	79	172	73	92	165	103	741
2	0	27	79	101	138	128	122	92	220	907
3	0	24	45	141	116	144	119	124	182	895
4	1	70	41	106	100	157	86	150	176	887
5	8	77	44	63	77	147	98	102	121	737
6	23	39	75	85	86	162	99	102	128	799
7	21	62	74	87	108	155	122	103	135	867
8	25	29	45	55	73	115	83	121	148	694
9	22	37	62	72	98	72	82	51	93	589
10	12	37	76	68	74	80	78	77	109	611
11	14	71	75	70	87	186	100	100	145	848
12	43	74	109	126	139	164	125	158	188	1,126
Total	169	566	763	1,053	1,268	1,583	1,206	1,345	1,748	9,701

Table 2 Number of usage of sick children by disease

Disease \ Year	1996	1997	1998	1999	2000	2001	2002	2003	2004	Total
Common cold	137	397	573	839	986	1,077	845	981	1,257	7,092
Chicken pox	4	40	69	66	38	114	16	56	96	499
Measles	0	26	0	32	16	0	0	0	0	74
Mumps	11	28	67	13	26	9	46	2	100	302
Gastroenteritis	0	14	5	28	86	86	96	119	74	508
Impetigo	6	0	6	9	7	7	5	26	25	91
Bronchial asthma	0	0	0	7	19	12	30	12	9	89
Influenza	0	0	16	0	10	47	21	37	149	280
Hand foot mouth disease	0	30	11	0	20	20	89	0	16	186
Acute otitis media	0	8	0	2	11	40	5	21	1	88
Others	11	23	16	57	49	171	53	91	21	492
Total	169	566	763	1,053	1,268	1,583	1,206	1,345	1,748	9,701

for infectious diseases, such as measles and chicken pox.

Number of users by age (Table 3)

According to age, one year olds were the most frequent users yearly. The number of users decreased as age increased. A comparison of use between users at age three years or younger, and users four or older, showed a significantly large number of users for children of the former ($P<0.05$).

Use of four childcare centers for sick children in Gifu city (Table 4)

In Gifu city, a childcare center for sick children opened 1996, and the number of such centers increased to two in 1997, and to four in 2000. The number of users was the highest in 2004, at 4,398.

After 2001, the number of users was more than 3,000 and it gradually increased year-by-year.

Discussion

Childcare centers for sick children serve as a nursery for children who cannot attended a regular nursery due to sickness. This system of childcare centers for sick children in Japan differs from those in other countries. Several studies of day care centers for sick children have been conducted.[1–6] The history of childcare centers for

Table 3 Number of usage of sick children by age

Age \ Year	1996	1997	1998	1999	2000	2001	2002	2003	2004	Total	
0	23	38	18	97	45	100	58	95	49	523	
1	47	246	272	318	363	436	228	279	314	2,503	
2	29	131	181	241	283	249	263	231	260	1,868	
3	14	67	94	176	236	257	155	152	279	1,430	*
4	24	43	98	82	121	271	151	145	197	1,132	
5	20	24	48	61	55	126	175	185	157	851	
6	8	9	48	28	60	34	48	123	132	490	
7–9	4	7	2	50	83	71	106	83	276	682	
10	0	1	2	0	22	39	22	52	84	222	
Total	169	566	763	1,053	1,268	1,583	1,206	1,345	1,748	9,701	

*: $P<0.05$

Table 4 Number of usage of the four childcare centers for sick children in Gifu city

Center \ Year	1996	1997	1998	1999	2000	2001	2002	2003	2004	Total
A	169	566	763	1,053	1,268	1,583	1,206	1,345	1,748	9,701
B		108	445	516	479	698	730	744	815	4,535
C					429	931	680	687	849	3,576
D					272	758	822	941	986	3,779
Total	169	674	1,208	1,569	2,448	3,970	3,438	3,717	4,398	21,591

sick children in Japan started in large cities, such as Osaka and Tokyo, approximately 30 years ago. Working mothers started childcare centers where they could leave their sick children. The Health and Welfare Ministry recognized the need for such childcare centers, and started a day service model project for sick children in 1994. In 1995, the ministry institutionalized childcare for sick children, which gained recognition throughout Japan. In Gifu city, Fukutomi Children's Clinic started a childcare center for sick children in 1996. Subsequently, in 2000, the number of such facilities increased to four. At present, there are approximately 400 childcare centers for sick children nationwide, and the number continues to increase. A survey of the numbers of users of the four childcare centers for sick children in Gifu city for each year revealed that the number of users of each center increased steadily, and that, after the number of centers increased to four, the increase in the number of users slowed down. This indicates that four is the appropriate number of childcare centers for sick children in Gifu city, considering that the Ministry of Health, Labour and Welfare set a target of one facility per 100,000 population, and that the population of the city is approximately 410,000.

The Ministry of Health, Labour and Welfare announced that small childcare centers for sick children, and childcare workers being dispatched are part of the ministry's childcare activities. It was considered necessary to estimate the required capacity for the area, based on the number of children, and the number of children who attend childcare centers, in addition to the number of childcare centers for sick children. We considered the required capacity based on our experience. For example, in Gifu city, which has a population of 410,000, there are approximately 26,700 preschool children at age six years or younger, of which approximately 4,900 children attend childcare centers. The present capacity of each of the four childcare centers for sick children in the city is six, with a total capacity of 24. Considering these facts, the required capacity is one child per approximately 1,000 preschool children, and one child per 200 children who attend childcare centers. Taking into consideration the rate of use of

such centers, the annual number of actual users is 3,700; the daily number of users is 12 to 13, considering that the annual number of days of use is 300. As such, the rate of use is approximately 50% of the total capacity. Although the average rate of use annually is 50%, this excess level is considered necessary, because of the large difference in the number of users between winter and summer, and the use being temporary. The capacity and rates of use mentioned here are only those for Gifu city, but they can be used as an approximate standard when the number of childcare centers for sick children increase in other cities in the future.

After childcare centers for sick children were opened, the number of parents taking leave from work to take care of a child who suddenly became sick, and that of parents leaving a sick child with grandparents, significantly decreased, and unfavorable situations for children, such as being left with a friend of the parent, were often avoided. The increasing number of uses of childcare centers for sick children indicates that the requirement of childcare for sick children has been recognized.[7] Reports state that: Some parents who wanted to take care of their sick children themselves initially had concerns and difficulties in leaving their children in childcare centers; however, once they became accustomed to leaving their children in childcare centers for sick children, their concern and sense of discomfort decreased, and their trust toward the center's staff, such as nurses, increased. Other reports reveal that there was a reduction in the number of complaints from mothers in workplaces, the mothers were less often complained about or removed from responsible positions because they had stopped taking leave from work due to their children's illness. These reports show that childcare centers for sick children, which can be used without due concern to parents and is now considered necessary owing to the increase in the number of working mothers, is an accepted aspect in the field of childcare.

As many users of childcare centers for sick children are at age three years or younger, and children with different diseases are taken care of simultaneously, there are concerns about disease transmission among users and the psychological effect on users.[8] However, there have been no reports on new infection or the transmission of diseases in childcare centers for sick children, or such a psychological effect, and care in such centers for sick children seems to have been smoothly conducted thus far.

A childcare center for sick children is a great help to working mothers, and is a necessary aspect of childcare. The number of childcare centers is increasing nationwide. However, the working conditions of mothers have diversified, such as working early mornings and late evenings, and also on holidays, in addition to the increasing employment rate of mothers, perhaps due to the sluggish economy. It is desirable for childcare centers for sick children to improve their services so that they are easily accessible to working mothers. There are various changes in the working conditions of mothers, social structure, and concepts regarding child-rearing, which are not always easy to consider in the operation of childcare centers for sick children, but they should always be addressed by both the administration and implementing facilities to further improve the system to meet the requirements of working mothers.

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Review Article

Brain Science on Chronic Fatigue

JMAJ 49(1): 19–26, 2006

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Abstract

The sense of fatigue is one of the important bio-alarm systems like pain or fever. However, the neural and molecular mechanisms of fatigue remain unclear. Chronic fatigue syndrome (CFS), involving a long-lasting sensation of fatigue, seems to be a good model for studying these mechanisms underlying chronic fatigue sensation. Recently, to explore the neural and molecular mechanisms of fatigue/chronic fatigue and to investigate the pathogenesis of CFS, we organized a study group of Japanese investigators from various fields, such as virology, immunology, endocrinology, physiology, biochemistry, psychiatry, and neuroscience. From our recent results, CFS can be understood as a special condition based on abnormality of the psycho-neuro-endocrino-immunological system, with the distinguishing feature of CFS seeming to be the secondary brain dysfunction caused by several cytokines and/or autoantibodies.

Key words Chronic fatigue, Social stress events, Genetic background, Cytokines, Neurotransmitters

Introduction

In 1999, a Japanese study group supported by the Ministry of Health and Welfare of Japan (Leader: Dr. Teruo Kitani) investigated the incidence of fatigue of 3,015 Japanese residents based on their response to a questionnaire. From this study, it became clear that around 60% of Japanese people have felt fatigue and that the 37% had chronic fatigue (lasting longer than 6 months). Surprisingly, 5.1% of the people felt a deterioration of their ability to perform personal daily tasks, and 1.8% of the people had a loss of daily work-related activity because of chronic fatigue with unknown reason(s). Only 8 of 3,015 (0.26%) fulfilled the CFS criteria proposed by the CDC.[1] Therefore, chronic fatigue is becoming not only an important medical problem but also a serious social problem because of its big economical impact. Economical deficit by chronic fatigue and chronic fatigue syndrome was calculated and estimated to be over 10 billion US dollars.

In view of this situation, our proposal for studying the neural and molecular mechanisms of fatigue sensation was adopted in 1999 by the Japanese Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japanese Government, as one of the projects of the Special Coordination Funds for Promoting Science and Technology, and then more recently since 2004, it was also adopted as the 21st Century COE Program "Formation of Scientific and International Base to Overcome Fatigue" to our Osaka City University from MEXT. The pathogenesis of CFS was also investigated by the investigators from various fields, such as virology, immunology, endocrinology, physiology, biochemistry, psychiatry and neuroscience, and its mechanism is now becoming a little clearer. In this paper, we report our recent results and propose a hypothesis for neural and molecular mechanisms resulting in chronic fatigue, which account for the relationship among each of the abnormalities found in CFS.

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Table 1 Comparison of genotype distribution and allele frequencies between the CFS patients and the control subjects (Ref. 3)

	CFS	Controls	χ^2 test	Fisher's exact test
Genotype	n=78	n=50	$\chi^2=7.887$ $P=0.031$	$P=0.026$
S/S	42 (54%)	39 (78%)		
L/S	32 (41%)	10 (20%)		
L/L	3 (4%)	1 (2%)		
XL/L	1 (1%)	0		
Allele	n=156	n=100	$\chi^2=7.233$ $P=0.016$	$P=0.012$
S	116 (74%)	88		
L	39 (25%)	12		
XL/L	1 (1%)	0		

Pathogenesis of CFS

Social stress events

It is well known that social-stress events frequently become the trigger for acute mental fatigue, and occasionally cause chronic fatigue. There are some reports indicating that stressful events are associated with the onset of CFS, but there are others giving data showing the opposite. Thus, the roles of stress in CFS were unclear. Therefore, we studied the social-stress events of 71 Japanese patients with CFS and 223 age-matched healthy controls by using a questionnaire. Social stress was investigated by counting the events described in the Social Readjustment Rating Scale reported by Holmes and Rahe.[2] In the CFS group, the social-stress events were studied at the time of onset of CFS and during medical treatment. Most of the CFS patients in this study denied any association between social stress and their complaints. However, the average score in the CFS group was 8.3 at the time of onset and 6.0 at the time of medical treatment, which values were significantly higher than that for the healthy control group (4.4, $P<0.01$, Mann-Whitney U test). Therefore, it became clear that most of the Japanese CFS patients were under much social stress with or without being aware of it. However, we should emphasize that this result does not mean CFS to be a psychological illness. As described later, stressful social events are related to abnormality of the psycho-neuro-endocrino-immunological system; and the secondary brain dysfunction caused by the abnormal production of several cytokines and/or autoantibodies might be a key feature of CFS.

Genetic background

When evaluating a stress-related disease, we should pay attention not only to the absolute magnitude or frequency of stressful events but also to the susceptibility to and resistance against stress, which factors are thought to be related to personal character or disposition. Indeed, when we studied the personality in the patients with CFS, most of them had a predisposition toward perfectionism and/or over-adaptation, which tendencies were not related to the existence or not of mental illness. We suspect that such predisposition might be related to genetic polymorphism of transporters and/or receptors of various neurotransmitters.

Recently we examined the polymorphism of the promoter region of the serotonin transporter (5-HTT) gene, which region affects the transcriptional efficiency of 5-HTT, in 78 CFS patients by performing PCR amplification of their blood genomic DNA.[3] A significant increase in the frequency of longer (L and XL) allelic variants was found in the CFS patients compared to the controls both by genotype-wise and the allele-wise analyses ($P<0.05$, Table 1). Efficiency in the transportation of 5-HTT is known to be higher with the L allele than with the S allele. There was no significant difference in 2 other 5-HT-related polymorphisms, i.e., the 5-HT_{2A} receptor promoter polymorphism and the 5-HTT intron 2 VNTR polymorphism, between the CFS

patient group and control group. Therefore, we speculate that the polymorphism within the *5-htt* 5′ upstream region is closely linked to CFS and may be a risk factor for this disorder.

When we used fluvoxamine maleate, one of the selective serotonin reuptake inhibitors, i.e., 5-HTT inhibitors, for the treatment of 39 Japanese patients with CFS, 11 patients withdrew from the treatment within 2 weeks because of the side effects such as nausea, increased fatigue, and a loss of thinking ability. However, the remaining 28 patients were given the inhibitor for more than 2 months. As a result, 2 of them were cured from CFS after the treatment, and 8 of them recovered enough to return to work. Therefore, serotonergic hypofunction was considered as one of the aspects concerning the pathogenesis of CFS. However, there is another possibility of the existence of polymorphisms of genes for transporters and/or receptors of other neurotransmitters, and such studies are currently on-going in our laboratory.

Immunological abnormalities

It is well known that the prevalence of past history of allergy is high in patients with CFS. Furthermore, CFS patients were reported to have many immunological abnormalities of various types, such as low natural killer cell function, abnormality of T cell population, elevated levels of several kinds of cytokines, the presence of antinuclear antibody, an increased level of immune complexes, and abnormality of the RNase-L pathway.[4–9] Among these abnormalities, we are now focusing on the elevation of several kinds of cytokines, the presence of autoantibodies, and the abnormality of the RNase-L pathway.

It is also well known that flu-like symptoms are a common side effect of interferon (IFN) therapy; and elevated activity of 2′,5′-oligoadenylate synthetase, an enzyme involved in, is frequently found in peripheral blood mononuclear cells from CFS patients.[7–8] Therefore, much attention has been paid to the relationship between IFN and the pathogenesis of CFS. The abnormality of the RNase-L pathway is located in the downstream of the IFN pathway.

Recently Katafuchi et al.,[10] who was one of the members in our fatigue project, found a close association between the changes in the IFN-alpha mRNA content in the brain and immunologically induced fatigue. An intraperitoneal injection of a synthetic double-stranded RNA, poly I:C 3 mg/kg, was given to rats to produce immunologically induced fatigue. The daily amounts of spontaneous running wheel activity decreased to ca. 40–60% of the preinjection level until day 9, with normal circadian rhythm. Quantitative analysis of mRNA levels conducted by using the real-time capillary reverse transcriptase-polymerase chain reaction (RT-PCR) method revealed that IFN-alpha mRNA contents in the cortex, hippocampus, hypothalamic medial preoptic, paraventricular, and ventromedial nuclei were higher in the poly I:C group than in the saline and heat-exposed groups on day 7. These results suggest that brain IFN-alpha may play a role in the animal model for the immunologically induced fatigue mimicked with viral infection. They also found that the expression of 5-HTT mRNA in the brain was increased in this model and that treatment with a selective serotonin reuptake inhibitor (SSRI) was effective for blocking the decrement of the daily amount of spontaneous running wheel activity. Therefore, the relationship among viral infection, changes in cytokine production, and brain dysfunction is gradually becoming clearer.

Moreover, there is a possibility that the abnormalities of transforming growth factor beta (TGF-beta) are also deeply concerned with fatigue sensation. Inoue et al.[11] found that intracranial administration of cerebrospinal fluid (CSF) from exercise-exhausted rats to naïve mice produced a decrease in spontaneous motor activity, whereas CSF from sedentary rats had no such effect. This finding suggests the presence of a substance suppressing the urge for motion as a response to fatigue. Using a bioassay system, they found the level of TGF-beta in the CSF from exercise-fatigued rats to be increased; but there was no increase in the CSF from the sedentary rats. Furthermore, the injection of recombinant TGF-beta into the brains of sedentary mice elicited a similar decrease in spontaneous motor activity in a dose-dependent manner. These results suggest that TGF-beta might be involved in the fatigue upon exercise and thus suppresses spontaneous motor activity.

An elevated serum level of bioactive TGF-beta was also frequently found in patients with CFS,[5] and we also confirmed such an increase

in the majority of Japanese CFS patients. TGF-beta was reported to inhibit the production of dehydroepiandrosterone sulfate (DHEA-S),[12] which is known to regulate positively the activity of carnitine acetyltransferase,[13] which catalyzes the transfer of free carnitine to acylcarnitine, especially the acetylcarnitine. We found that most Japanese CFS patients had a deficiency in DHEA-S[14] and that in acetylcarnitine,[15] and so the increase in TGF-beta would appear to be related to these abnormalities.

Additionally, the presence of auto-antibodies including antinuclear antibody is also thought to be an important key immunological abnormality involved in the pathogenesis of CFS. It is known that antinuclear antibody is frequently found in fatigued patients throughout the world who have various indefinite complaints. However, the role of these auto-antibodies in these patients is unclear.

Recently, using a sensitive radioligand assay Tanaka et al.[16] examined the sera of CFS patients (n = 60), patients with autoimmune disease (n = 33), and healthy controls (n = 30) for auto-antibodies against various neurotransmitter receptors, i.e., recombinant human muscarinic cholinergic receptor 1 (CHRM1), mu-opioid receptor (OPRM1), 5-hydroxytryptamine receptor 1A (HTR1A), and dopamine receptor D2 (DRD2). The mean anti-CHRM1 antibody index was significantly higher in patients with CFS ($P<0.0001$) and autoimmune disease ($P<0.05$) than in healthy controls, and over a half of the patients with CFS (53.3%, 32/60) had anti-CHRM1 antibody. Antinuclear antibodies were also found in 56.7% (34/60) of the CFS patients, but their titers did not correlate with the activities of the above 4 auto-antibodies. The CFS patients with positive auto-antibodies against CHRM1 had a significantly higher mean score (1.81) of 'feeling of muscle weakness' than those negative for them (1.18) ($P<0.01$). Higher scores on 'painful lymph node,' 'forgetfulness,' and 'difficulty in thinking' were also found in CFS patients with anti-CHRM1 antibodies than in those without them, but statistical significance was not reached. Anti-OPRM1 antibodies, anti-HTR1A antibodies, and anti-DRD2 antibodies were also found in 15.2, 1.7, and 5.0% of patients with CFS, respectively; but no significant relationship was found between the symptoms and existence of these antibodies. Since anti-CHRM1 antibody is also frequently found in patients with schizophrenic disorders, mood disorders, and other psychiatric disorders, it is not specific for CFS; but the autoimmune abnormalities in neurotransmitter receptors might cause the secondary brain dysfunction including CFS.

Infection

At the onset of CFS, patients frequently complained the flu-like symptoms such as headache, sore throat, fever, painful lymph node, myalgia, and althralgia. Mass outbreaks of CFS have also sometimes been reported throughout the world. Therefore, many investigators have tried to find pathogens or pathogenic organisms as candidates for causing CFS; and many viruses and microorganisms have been reported to be involved in the pathogenesis of CFS. Examples include various herpes viruses (Epstein-Barr (EB) virus, human herpes virus-6, herpes simplex virus, varicella zoster virus, and cytomegalovirus), influenza virus, retroviruses, coxsackie B virus, Borna disease virus, hepatitis C virus, parvovirus, mycoplasma infection, and chronic rickettsial infections. Indeed, we have found some patients to acquire CFS after developing an acute infection such as mononucleosis caused by EB virus infection. However, the vast majority of pathogens or pathogenic organisms found in patients with CFS did not represent an initial acute infection, but rather a reactivation of various kinds of herpes viruses and/or chronic mycoplasma infections.[17–19] These infections might be related to deterioration of immune function, but the infections themselves seem not to be so serious for health. The important point is that most complaints given by these patients stem from cytokines produced by the immune response to these pathogens or pathogenic organisms, which cytokines cause secondary brain dysfunction.

Hypothalamo-pituitary-adrenal (HPA) dysfunction and metabolic abnormalities

In 1991, Demitrack et al.[20] reported the impaired activation of the HPA axis in patients with CFS; and thereafter several investigators addressed HPA dysfunction in patients with CFS, including lower basal plasma cortisol levels, reduced salivary cortisol levels, lower ACTH response in insulin tolerance test and psychosocial stress test, reduced ACTH responses to CRH, and prolonged

suppression of salivary free cortisol in the low-dose dexamethasone suppression test.[21–23] We also found that the majority of Japanese patients with CFS had a deficiency in serum DHEA-S.[14] Serum DHEA-S is one of the most abundantly produced hormones secreted from the adrenal glands, and its physiological role is thought to be a precursor of sex steroids. However, DHEA-S itself was recently shown to have physiological properties, acting as a neurosteroid associated with such psychophysiological phenomena as memory, stress, anxiety, sleep, and depression. Therefore, the deficiency in DHEA-S might be related to the neuropsychiatric symptoms in patients with CFS. As described above, there is also a possibility that the DHEA-S deficiency is associated with the increased serum level of TGF-beta.

Recently, we also found that most Japanese patients with CFS showed a low level of serum acetylcarnitine, which well correlated with the rating score of fatigue,[15] and that a considerable amount of the acetyl moiety of serum acetylcarnitine is taken up into the brain.[24] As mentioned earlier DHEA-S is known to regulate the activity of carnitine acetyltransferase.[13] Therefore, the decrease in DHEA-S might play an important role in endogenous acetylcarnitine deficiency in serum. Indeed, when we administered DHEA-S to patients with CFS, an apparent increase in serum acetylcarnitine was found. It was also found that the acetyl moiety taken up into the brain through acetylcarnitine is mainly utilized for the biosynthesis of glutamate.[25] Thus, this metabolic abnormality (i.e., low uptake of acetylcarnitine into the brain) might cause some of the secondary brain dysfunction in CFS.

Brain dysfunction

Recent single-photon emission computed tomography (SPECT) studies[26–28] using 99mTc-hexamethyl-propylene-amine oxime revealed that most CFS patients showed cerebral hypoperfusion in a variety of brain regions such as the frontal, temporal, parietal, and occipital cortices; anterior cingulate; basal ganglia; and brain stem, and suggested that the central nerve system (CNS) dysfunction might be related to the neuropsychiatric symptoms of CFS patients. To confirm these findings, we studied the regional cerebral blood flow (rCBF) in 8 CFS patients and 8 age- and sex-matched controls by use of ^{15}O-labeled water ($H_2{}^{15}O$) and positron emission tomography (PET), and found that the rCBF was lower in the CFS patient group than in the control group in the brain regions including the frontal, temporal, and occipital cortices, anterior cingulate; basal ganglia; and brain stem.[25] These brain regions correspond to various neuropsychiatric complaints: autonomic imbalance, sleep disturbance, many kinds of pain, and the loss of concentration, thinking, motivation, and short-term memory. Therefore, our results from the first quantitative rCBF study done on CFS patients with PET are in good agreement with the data from the previous SPECT studies, and indicate that various neuropsychiatric complaints found in CFS patients might be related to dysfunction in these regions of the CNS.

Furthermore, when we studied the cerebral uptake of [2-^{11}C]acetyl-L-carnitine in the same 8 CFS patients and 8 age- and sex-matched normal controls by using PET, a significant decrease was found in several brain regions of the patients' group, namely, in the prefrontal (Brodmann's area 9/46d) and temporal (BA21 and 41) cortices, anterior cingulate (BA24 and 33), and cerebellum.[25] These findings suggest that the levels of neurotransmitters biosynthesized through acetylcarnitine might be reduced in some brain regions of chronic-fatigue patients and that this abnormality might be one of the keys to unveil the mechanisms of chronic-fatigue sensation.

More recently, using MRI, we found that patients with CFS have reduced gray matter (GM) volume in the bilateral prefrontal cortices.[29] Furthermore, right-hemisphere GM volume correlated with subjects' fatigue ratings.[29] This is consistent with above-mentioned result that described a decrease of uptake of acetylcarnitine, maybe indicating a decrease in the biosynthesis of glutamate, in the prefrontal cortex. The prefrontal cortex might therefore be part of the neural underpinnings of fatigue.

We also studied 5-HT transporter (5-HTT) density in 10 patients with CFS and 10 age-matched normal controls by using PET with the radiotracer [^{11}C](+)McN5652. Analysis using a statistical parametric mapping software (SPM99) revealed that the density of 5-HTT in the rostral subdivision of the anterior cingulate was significantly reduced in CFS patients.[30] In addition, the density of 5-HTT of dorsal anterior cingulate

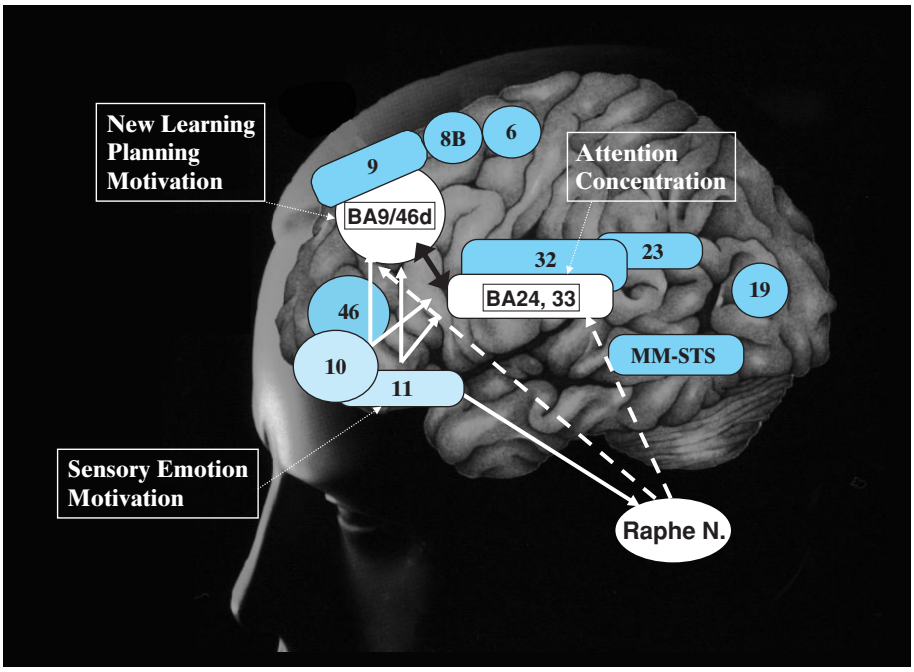

Fig. 1 Neural circuits for fatigue: from acute to chronic phase

was negatively correlated with the pain score.[30] Therefore, an alteration in the serotoninergic neurons in the anterior cingulate plays a key role in the pathophysiology of CFS.

These PET results on 5-HTT density seem to be apparently inconsistent with our results regarding the 5-HTT gene promoter polymorphism, where CFS patients could have a greater frequency of the L allele, which affords greater transporter efficiency. However, it might be the case that the reduction in 5-HTT density in CFS patients with L and XL allelic variants is less than that in CFS patients with S allelic variants. Since 5-HT synthesis in the brain is thought to deteriorate in patients with CFS, 5-HT deficiency in the synapses might be more serious in patients with L and XL allelic variants. If so, it is consistent with the finding that SSRI treatment is effective for some patients with CFS. To clarify the full particulars of brain dysfunction in patients with CFS, we are now studying the 5-hydroxy-L-tryptophan (5-HTP) uptake, L-DOPA uptake, and muscarinic acetylcholine receptor density by using PET. We could further report the results from these studies concerning brain dysfunction found in patients with CFS in the near future. But so far we propose the working hypothesis on the dysfunction in chronic fatigue, as shown in Fig. 1.

Hypothesis: neuronal and molecular mechanisms leading to chronic fatigue

It is becoming clear that various abnormalities found in CFS patients might not exist independently, but might be related to each other. That is, CFS can be understood to be a special condition based on the abnormality of the psycho-neuro-endocrino-immunological system caused by the psycho-social stress and some genetic components (Fig. 2). Under these conditions, a reactivation of various kinds of herpes virus infections and/or chronic mycoplasma infection might occur as a result of immune dysfunction, causing the abnormal production of several cytokines. A distinctive feature of CFS is thought to be the secondary brain dysfunction caused by the abnormal production of such cytokines.

As described above, the increase in TGF-beta might inhibit the production of DHEA-S, which inhibition might be related to the malmetabolism of acetyl-L-carnitine through the modulation of carnitine acetyltransferase activity. Indeed, when we administered DHEA-S to the patients

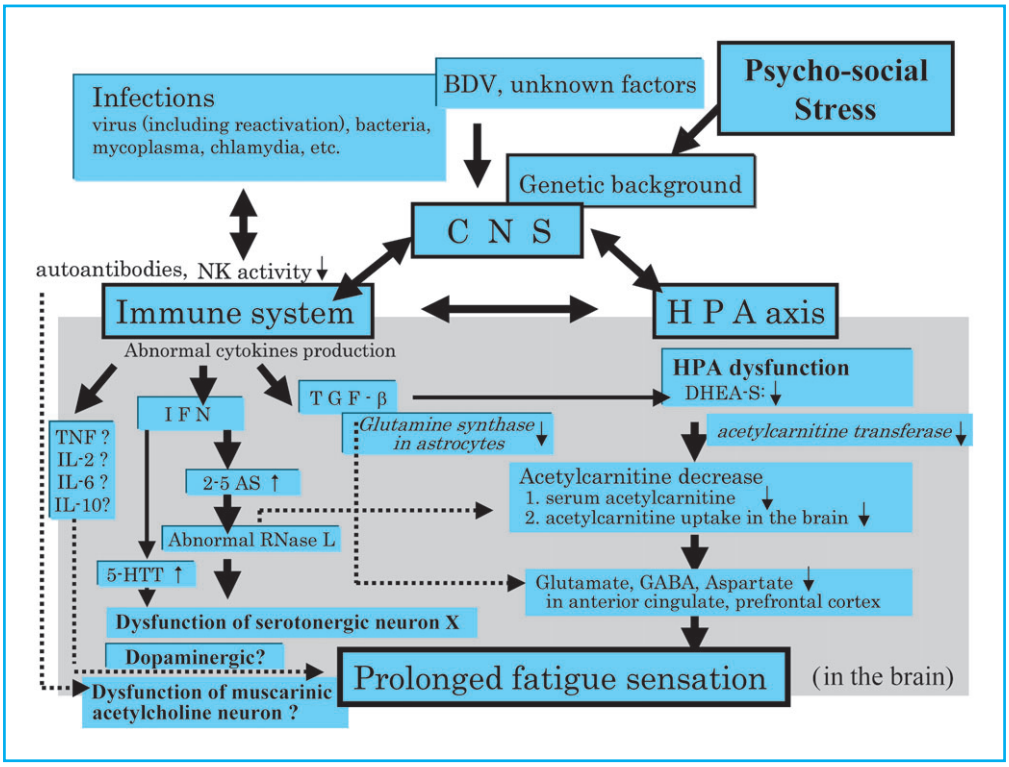

Fig. 2 Hypothesis: neuro-molecular mechanism leading to chronic fatigue

Most complaints given by CFS patients might stem from cytokines produced by the immune response to pathogens or pathogenic organisms, which cytokines cause secondary brain dysfunction.

BDV, Borna disease virus; CNS, central nervous system; NK, natural killer; HPA axis, Hypothalamic-pituitary-adrenal axis; IFN, interferon; TGF-β, transforming growth factor-β; 5-HTT, 5-hydroxytryptamine transporter; TNF, tumor necrosis factor; DHEA-S, dehydroepiandrosterone sulfate; 2-5 AS, 2′,5′-oligoadenylate synthetase

with CFS in a double-blind study, an apparent increase in serum acetylcarnitine was found in the patients treated with DHEA-S. Therefore, one of the pathways leading to CFS may be described as follows: "increase of TGF-beta" → "decrease of DHEA-S" → "acetylcarnitine malmetabolism" → "deterioration of biosynthesis of glutamate in anterior cingulate" → "autonomic imbalance and prolonged fatigue."

The abnormal production of IFN is another important pathway whose activation results in CFS. That is, "reactivation of various kinds of herpes virus infections or chronic mycoplasma infection" → "abnormal production of IFN in the brain" → "elevation of 5-HTT mRNA contents in the brain" → "5-HT deficiency in synapse" → "depression, chronic pain disorder, and prolonged fatigue." Abnormal production of IFN is thought to trigger yet another pathway leading to CFS, that is, "abnormal production of IFN" → "elevation of 2′,5′-oligoadenylate synthetase activity" → "abnormality of RNase-L pathway" → "CNS dysfunction" → "various neuropsychiatric complaints."

In this paper, we focused on TGF-beta and IFN, but tumor necrosis factor (TNF) might also be involved in fatigue sensation, since it is known that TNF is associated with the symptoms found in cachexia of patients with advanced cancer.[31] Also, an increased TNF-alpha level was reported in CFS patients.[6] There is a possibility that other kinds of cytokines such as IL-2, IL-4, IL-6, and IL-10 might also be involved in the secondary brain dysfunction in CFS. Furthermore, recent PET studies of ours have revealed that the brain dysfunction found in CFS involves not only abnormal serotonergic and glutamatergic system, but also abnormal dopaminergic system. There is a possibility that muscarinic cholinergic system might also be defective in patients with CFS.

Therefore, even if a distinctive feature of CFS is summarized as the secondary brain dysfunction caused by abnormal production of cytokines, its pathogenesis is obviously heterogeneous. In addition, the auto-antibodies against neurotransmitter receptors might also be involved in the pathogenesis of CFS in some cases.

Acknowledgements

Most of the studies presented here were performed through the support of the Special Coordination Funds for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government (MEXT), from April 1999 to March 2005, and by the 21st century COE program under MEXT from August 2004 up to present. We are indebted to all of the members of both study group. The authors especially thank Prof. Nobuya Hashimoto, Executive Board Member of Japan Medical Association for giving us this opportunity to review our data.

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Review Article

Post-Infectious Fatigue

JMAJ 49(1): 27–33, 2006

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Abstract

Chronic fatigue syndrome (CFS) and Gulf War Syndrome are diseases of unknown etiology which are accompanied by severe fatigue as a main complaint. Yet there may be some kind of "post-infectious fatigue syndrome" following any infection by a virus.

Post-infectious fatigue, which is caused by many different viruses, includes chronic active Epstein-Barr virus (EBV) infection and it is thought that the onset of this disease is associated with latent EBV infection in a very unusual manner. As there may be an unusual latent infection with human herpesvirus 6 (HHV-6) which may be an etiology of CFS in the CFS patients, the study on latent infection is considered to be important for elucidating CFS and Gulf War Syndrome.

Key words Infection, Fatigue, Chronic fatigue syndrome, Gulf War Syndrome, Epstein-Barr virus, Human herpesvirus 6

Introduction

Fatigue is caused by many different factors, of which infection is one of the very important causes. Fatigue, which not only deteriorates work efficiency but also constitutes causes of various diseases and death from overwork, poses a serious health problem for people. In spite of such importance, however, the mechanisms of fatigue, by which fatigue is caused and felt, have been hardly known.

It is easy to identify the presence of fatigue which is caused by bacterial or viral infection, because the time and cause of fatigue are known clearly. Post-infectious fatigue, therefore, attracts attention as an important subject in the study of the mechanism of fatigue. Also, in view of the fact that many cases with chronic fatigue syndrome (CFS), in which severe fatigue of unknown etiology continues for long time, occur following infectious disease, the relationship between infection and CFS is considered to have an important meaning.

This paper examines knowledge currently available on the mechanism of fatigue and discusses the relationship of infection with severe post-infectious fatigue, particularly with the onset of CFS.

Mechanism of Fatigue

In general, "fatigue" is defined as decreased physical functions attributable to prolonged physical and/or mental stresses, while "tiredness" indicates the condition in which the brain recognizes decreased physical functions. Tiredness is an important biological signal, as are pain and drowsiness, to maintain biofunctions.

Becoming fatigued or feeling tiredness might require the presence of substances which increase or accumulate through fatigue and/or a fatigue transmitting substance which transmits fatigue to the brain. Lactic acid has been long considered as a major fatigue-causing substance. However it was reported recently that lactic acid is not a fatigue-causing but a fatigue-preventing substance.[17] Presently, therefore, there is no proven

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Table 1 Pathogens reported as causing post-infectious fatigue

Organisms causing persistent or latent infection	Virus	Epstein-Barr virus, human herpesvirus 6, human herpesvirus 7, herpes simplex virus, human immunodeficiency virus, hepatitis C virus, parvovirus B19, Influenza virus
	Bacteria, etc.	Coxiella burnetii, Helicobacter pylori
Organisms causing no persistent or latent infection	Virus	polio virus, Coxsackie B virus, West Nile virus, smallpox vaccine, hemorrhagic fever with renal syndrome viruses
	Bacteria, etc.	Borrelia burgdorferi, Streptococcus pneumoniae, Trichinella spiralis, Trichinella pseudospiralis, Staphylococcus, Legionnaires

Organisms which have been reported as the causes of post-infectious fatigue are listed.

fatigue-causing substance or fatigue transmitting substance.

However, the most probable candidates for such fatigue-inducing or fatigue transmitting substances are cytokines, including interferon. This is strongly shown by the fact that the patients undergoing treatment of hepatitis virus using interferon or other cytokines feel severe tiredness.[9,16,19] It is also reported that TGF-β is associated with the occurrence of fatigue.[1,23] However, because the mutual interaction and association of multiple cytokines are involved in the production and activation of cytokines, it has not been identified which cytokine plays a central role in causing or transmitting fatigue.

Chronic Fatigue

Fatigue is usually cured with rest, whereas sometimes unrecoverable fatigue may be accumulated. The latter is defined as chronic fatigue and is divided roughly into two categories. One is the accumulation of physiological fatigue because of continuous labor without rest, and the other is the continuation of morbid fatigue accompanying disease. Accumulated physical fatigue may result in a tragic outcome known as "death from overwork" at worst, so it should not be neglected, although it is only the extension of the physical phenomena.

Major morbid fatigue includes post-infectious fatigue and chronic fatigue syndrome (CFS). Although the etiology of CFS is unknown, the involvement of infection with some pathogenic organism is suspected. Post-infectious fatigue and CFS, therefore, are not irrelevant.

Diagnostic criteria to define CFS can be simplified as follows: (1) A condition with serious tiredness which forces the absence from school or work for several days per month and continues for over 6 months or recurs many times; (2) No other disease is identified.

The patients with 8 or more of the following symptoms, which are often observed in CFS, are definitively diagnosed as CFS: 1) slight fever or chill, 2) throat pain, 3) swollen lymph nodes, 4) feeling of exhaustion of unknown etiology, 5) muscle pain, 6) general weariness, 7) headache, 8) joint pain, 9) psychoneurotic symptoms (memory impairment, confusion, impaired concentration, depression), 10) sleep disorders (insomnia, hypersomnia) and 11) sudden onset of symptoms (within several hours to several days).

Of these symptoms, 1), 2), 3), 5), 8) and 11) are often observed in virus infections, such as the common cold. The reasons why such symptoms are included in the diagnostic criteria are that the patients suspected of having CFS very frequently display symptoms similar to those of infectious diseases, and that CFS is considered to be caused by continuous fatigue following infection with some infecting factor. As a result, the study of post-infectious fatigue is important also for identifying the unestablished etiology of CFS.

Examples of Post-Infectious Fatigue

Many cases have been reported as post-infectious fatigue cases and, as shown in Table 1, the pathogenic organisms or infecting factors associated with the fatigue are wide ranging. This paper explains some cases which have important meaning for the subsequent studies and the understanding of post-infectious fatigue.

Table 2 Various latent infection forms of Epstein-Barr virus (EBV)

Type of latent infected cell	Form of latent infection	Manifested latent infected gene	Associated morbidity
B cell	latency 0	EBER 1, EBER 2, BARTs	Latent infection in healthy people
	latency I	EBER 1, EBER 2, BARTs, EBNA 1	Burkitt's lymphoma, etc.
	latency II	EBER 1, EBER 2, BARTs, EBNA 1, LMP-1, LMP-2A, LMP-2B	Nasopharyngeal carcinoma, etc.
	latency III	EBER 1, EBER 2, BARTs, EBNA 1, EBNA 2, EBNA 3A, EBNA 3B, EBNA 3C, EBNA-LP, LMP-1, LMP-2A, LMP-2B	In vitro immortalization or reactivation (?)
NK cell/T cell	latency II	EBER 1, LMP-1, LMP-2A	CAEBV

There are many different patterns of latent EBV infection, and the type of latency-associated gene, which appears, and the associated disease differ in each form. Latent infection with EBV infection usually occurs in B cells, while in chronic active EBV infection latent infection is established in NK cells and T cells.

Acquired immunodeficiency syndrome (AIDS)

Post-infectious fatigue is caused by various pathogenic organisms, and mass outbreak of post-infectious fatigue suggests an epidemic of some pathogenic infection. This is often an epidemic of a known pathogenic organism, such as influenza, but an unknown or unreported pathogen in the area can be discovered and identified sometimes as a cause of post-infectious fatigue. For example, until human immunodeficiency virus (HIV) was established as a cause, acquired immunodeficiency syndrome (AIDS) had attracted attention as a disease accompanied by fatigue of unknown etiology.[15]

Post-Rickettsia infectious fatigue

Coxiella burnetii, is an organism which causes Q-fever, belongs to the family Rickettsiaceae, and infects humans via cattle and pet animals. Many patients with Q-fever complain of symptoms such as fever, headache, muscle pain, respiratory symptom and strong systemic weariness. Infection with *Coxiella burnetti* often ends as acute infectious disease, whilst in about 5% of the patients, *Coxiella burnetti* remains in the body long after acute infection, and progresses to chronic Q fever.

Chronic Q fever accompanied by *Coxiella burnetii* infection for over 6 months is often more severe than acute Q fever. Chronic Q fever occurs in acute Q fever patients from one year to 20 years after the first infection and is often accompanied by infectious endocarditis.[2,6] Chronic Q fever patients complain of symptoms such as weariness, insomnia and joint pain. As these symptoms can continue for several to over ten years, they may be diagnosed as chronic fatigue syndrome (CFS).

Chronic active EBV infection

When it was found that some patients with severe persistent fatigue had high antibody titers to Epstein-Barr virus (EBV), EBV was considered as one of the causes of CFS. However, since EBV infection showing CFS-like symptoms was then recognized as chronic active EBV infection (CAEBV),[4,7] other EBV infectious diseases than CAEBV are considered as unrelated to CFS.[21, 22] CAEBV is a disease in which the symptoms of infectious mononucleosis (IM) appearing at the first EBV infection, such as fever, pharyngitis, swollen lymph nodes and hepatosplenomegaly continue for over 3 months, and CAEBV patients complain severe fatigue. IM is a disease often observed in acute EBV infection and subsides with disappearance of symptoms in 1–3 months. One of the reasons why IM-like symptoms continue for a long time in CAEBV is the different pattern of EBV latent infection. EBV latently infects B cells in general and this latent infection progresses asymptomatically in many cases, but it may cause various diseases depending on the pattern of latent infection (Table 2). In case of CAEBV, EBV latently infects NK cells and T cells, and induces active virus gene expression.[10] It is considered that this produces abnormal

immunoreactions and causes fever and intense weariness.

Of the three cases mentioned above, chronic Q fever and CAEBV particularly show CFS-like symptoms, and can be said to be the cause of CFS. However, according to the present diagnostic criteria, diseases of known etiology are not CFS so they are not categorized as such. This means that the identification of pathogenic organism like chronic Q fever and chronic active EBV infection is most important for identifying the etiology of the CFS that occurs following infection. Also, the example of CAEBV suggests that the infection with the same EBV may present completely different symptoms, depending on the pattern of EBV presence, particularly the pattern of latent EBV infection, and lead to persistent fatigue.

Chronic Fatigue Syndrome

As previously mentioned, the fact that infection with various organisms causes post-infectious fatigue has been known for decades. However, it appears that the morbidities such as "post-infectious fatigue" and "post-viral infectious fatigue" came to the attention of the public following an outbreak known as the "Lake Tahoe mystery", in which CFS-like symptoms affected a large number of people in the geographical area around Lake Tahoe in Nevada, USA. At this time, the concept of a "fatigue epidemic" was proposed.[3] This condition posed a serious social problem, and many infection specialists launched investigation of its etiology. The concept of chronic fatigue syndrome (CFS) was proposed also for this Lake Tahoe incidence.

The morbidity named "Gulf War Syndrome" made public know the importance of post-infectious fatigue. Gulf War Syndrome is a disorder observed in many veterans discharged from military service in the Gulf war which started in 1991. Their main symptoms are muscle pain, night sweats, skin rashes, headache and diarrhea, and central nervous symptoms such as impairment in memory or concentration.[5,8] Many researchers consider that Gulf War Syndrome is caused by infection through some factors including biological weapon.[18] Gulf War Syndrome is considered as a kind of CFS which supports the argument that the identification of the infectious factor is most important in examining the etiology of CFS.

In fact, the observation of abnormal production of 2-5A synthetase and RNase L, indicators of interferon production in CFS patients, suggests that tiredness, a symptom seen in CFS is associated with the abnormal interferon production.[20] This is one of the reasons why CFS is considered as a kind of post-infectious fatigue.

The diagnostic criteria for defining CFS include those which are known as the symptoms of infectious disease such as slight fever or chill, sore throat, swollen lymph nodes and sudden onset of disease. In other words, it cannot be denied that these criteria were established on the assumption that the most probable cause of CFS was post-infectious fatigue.

Herpesvirus and Chronic Fatigue Syndrome

CFS is a disease which lasts far longer than post-infectious fatigue. It is considered, accordingly, that the infection causing CFS is a persistent or latent infection with some virus. It is known that once infecting herpesvirus establishes latent infection and then produces some symptoms by frequent reactivation. Since these properties of herpesvirus can explain why the symptoms of CFS patients repeat remission and exacerbation, the theory that herpesvirus is a cause of CFS is supported by many people. Among various herpesviruses, particularly HHV-6 and EBV, are often indicated to be associated with CFS. HHV-6 was isolated in 1986 from patients with acquired immunodeficiency syndrome (AIDS) and malignant lymphoma. This was at the time when many patients who were presenting CFS-like symptoms wereTound in the area near Lake Taho (USA), (op. cit), leading to the recognition of CFS as a disease. Since this new-discovered virus was detected in the patients with "fatigue epidemic", HHV-6 was considered as the most probable candidate for the causative virus for CFS.[3] As EBV was detected frequently in the patients presenting CFS symptoms, the association of EBV with CFS was also strongly suspected. However, CFS-like diseases associated with EBV were categorized, (op. cit), as "chronic active EBV infection", and was defined as a different disease from CFS of unknown etiology.

Initial infection with HHV-6 in the early childhood, causing exanthem subitum, is followed by life-long latent infection in peripheral blood. As

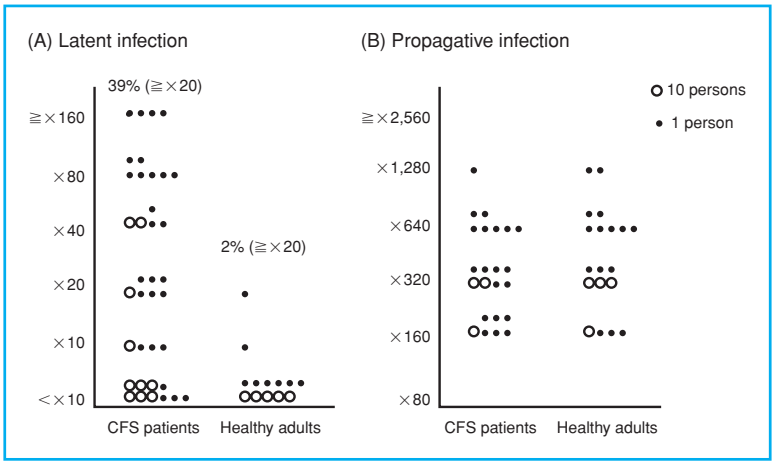

Fig. 1 Antibody titers to HHV-6 latent infection protein and structural protein

Antibody (A) to gene protein, which specifically appears in the latent HHV-6 infection, and the antibody titers (B) to virus structural protein, which mainly appears in the propagative infection, were examined in CFS patients and healthy adults. The antibody to structural protein often used in regular examination shows no significant difference between CFS patients and healthy adults, but that to latent infection protein shows substantial difference.

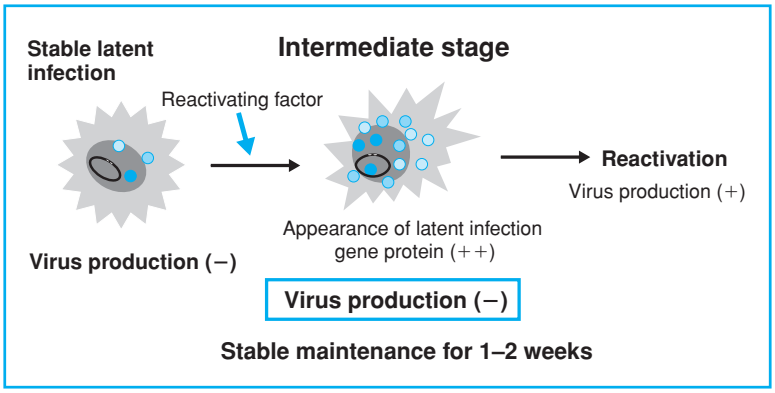

Fig. 2 Intermediate stage of HHV-6

HHV-6 shows the expression of mRNA from the gene (latent infection gene) which appears specifically in a stable latent infection stage. However, the mRNA does not produce protein, because its translation to protein is inhibited. However, the enhancement of transcription of latent infection genes and the removal of inhibition of the translation in the intermediate stage leads to active manifestation of the latency-associated virus protein, but no virus production (reactivation). It is thought that this stage lasts for several days to several weeks, followed by virus production in those progressing to reactivation. It is estimated that the intermediate state is important for the virus to prepare efficient reactivation and to the reproduction and maintenance of virus genes.

In view of the fact that CFS patients show abnormal immunoreaction to the latent infection protein which appears in this stage, it is considered that the presence of a large number of cells in this intermediate stage for a long period of time is associated with the onset of CFS.

the rate of infection of this virus is almost 100% in almost all countries, the antibody positive rate in adults is almost 100%. Whether or not a virus is associated with a particular disease is examined generally by identifying whether a patient has been infected with the virus, based on the presence of serum antibody, and whether the patient's past history is correlated with the occurrence of the disease. However, this examination cannot be applied to HHV-6, as HHV-6 incidence rate is 100% (Fig. 1B).

However, if HHV-6 infection follows a special pattern similar to CAEBV infection, it may possibly present CFS-like symptoms. To examine

such a special-pattern latent infection it seems important to identify an HHV-6 gene specific to the latent EBV infection and its encoded protein, which appears specifically in the latent EBV infection and plays an important role in the diagnosis and research of latent infection, such as a gene corresponding to Epstein-Barr Nuclear Antigen (EBNA).

Latent HHV-6 Infection and Chronic Fatigue Syndrome

HHV-6 establishes latent infection in macrophage and in the brain, and manifests latency-associated gene, mRNA specific to latent infection.[11–14]

In order to know the mechanism by which CFS is contracted, we researched to identify a special latent HHV-6 infection state, and latent HHV-6 infection protein corresponding to EBNA. The study revealed that HHV-6 had a third stage between latency and reactivation, in which the manifestation of the latent infectious gene is promoted (Fig. 2). This intermediate stage is observed in the first phase where HHV-6 commences reactivation, but is completely different from the reactivation in the respect that no virus is produced.

In order to examine the relationship between latent infection protein, whose manifestation is promoted in the intermediate stage, and disease, CFS patients' serum antibody titers to the cells in which latent infection protein is well manifested were examined. This examination revealed that about 40% of the CFS patients showed antibody reaction to latent HHV-6 infection, whereas healthy subjects showed virtually no reaction (Fig. 1A). It is possible that what is reacting with the infection is a virus protein which appears specifically in the latent HHV-6 infection, and has EBNA-like functions and diagnostic significance that is important in the diagnosis of latent infection and reactivation of EBV. We considered that such immunoreaction, which is clearly different between CFS patients and healthy subjects, is undoubtedly associated with CFS morbidities. On the other hand, what is examined usually by using serum antibody titers against HHV-6 is the antibody that appears when HHV-6 proliferates, particularly the antibody to structural protein required in virus formation. As shown in Figure 1B, the antibody titers to the protein involved in the HHV-6 productive infection show no significant difference between CFS patients and healthy subjects. This explains why no difference in HHV-6 infection between CFS patients and healthy subjects is observed in the regular examination.

It is considered that the higher antibody titers to the protein that appears and increases in the intermediary stage in latent HHV-6 infection in CFS patients suggest the presence of cells in this intermediate stage in the body of CFS patients. The cells constituting latent HHV-6 infection and the intermediate stage are macrophage and glia cells. This is consistent with the fact that CFS presents immunological and psychiatric symptoms.

Conclusions

It is considered that the issue of post-infectious fatigue is critical for investigating the etiology of CFS and Gulf War Syndrome, both of which present severe fatigue. However, knowledge about persistent and latent infection with pathogenic organism is indispensable for the investigation, and further progress of the investigation is required.

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Sibling Cases of Multiple Endocrine Neoplasia Type 1 (MEN1) Appearing in a Family with Epilepsy

JMAJ 49(1): 34–40, 2006

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Abstract

We experienced sibling cases of multiple endocrine neoplasia type 1 (MEN1). The younger sibling was an 18-year-old male who had been under medication for juvenile myoclonus epilepsy since the age of 12. He first attended our hospital at the age of 17 for the treatment of urolithiasis. He was found to have primary hyperparathyroidism and non-functioning pituitary adenoma. The elder sibling was a 20-year-old female who had been under medication for Gilles de la Tourette syndrome since the age of 11. She visited our hospital with the chief complaint of amenorrhea. She was found to have prolactinoma and tumor of the pancreas. A diagnosis of MEN type 1 was made, because mutation of the MEN1 gene was detected in the gene analysis of peripheral blood from both siblings and parathyroid tissues excised from the younger brother. Recent studies have suggested some role of menin, MEN1 gene product proteins in the central nervous system. This family may provide valuable information concerning the physiological roles of menin.

Key words Multiple endocrine neoplasia type 1, Epilepsy, Menin

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant genetic disease that produces multiple tumors typically in several endocrine glands, such as parathyroid tumor, endocrinoma of the pancreas, and pituitary tumor, within an individual as well as within a family.[1] The MEN1 gene is considered to be a tumor suppressor gene, and its product is called menin. While the function and tumorigenic mechanism of menin have been investigated by several groups, the physiological roles of menin have not been clarified.[2–5] The expression of menin occurs in various stages of murine embryogenesis not only in endocrine glands but also in many other tissues. The expression is reported to be particularly active in the central nervous system.[6] We experienced sibling cases of MEN1 in a family with epilepsy. Observations in these cases may provide valuable information for a better understanding of the actions of menin.

Description of Patients

[Patient 1] 18 years old, male.
[Chief complaints] Abdominal pain and hematuria.
[Past history] Juvenile myoclonus epilepsy at the age of 12.
[Family history] Chronic motor tic syndrome in grandmother and epilepsy in mother.
[History of present illness] The patient visited our hospital for abdominal pain and hematuria in 2003. Urolithiasis was detected. As detailed examination indicated the possibility of primary hyperparathyroidism, the patient was referred to

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Table 1 Laboratory data 1 (Case 1)

CBC		**Biochemistry**		**Endocrinology**	
WBC	5,830 /μl	TP	8.4 g/dl	ACTH	46 pg/ml
RBC	504×10^4 /μl	Alb	5.2 g/dl	Cortisol	19 μg/dl
Hb	15.5 g/dl	AST	14 IU/l	GH	5.0 ng/ml
Ht	46.3 %	ALT	12 IU/l	IGF-1	200 ng/ml
PLT	19.1×10^4 /μl	LDH	143 IU/l	TSH	3.57 μU/ml
		ALP	260 IU/l	FT4	1.1 ng/dl
Urinary		BUN	9.9 mg/dl	ATG	<100
PRO	—	Crea	0.65 mg/dl	AMC	<100
GLU	—	Na	142 mEq/l	LH	4.3 mIU/ml
BL	+3	K	4.3 mEq/l	FSH	5.8 mIU/ml
RBC	>100 /HPF	Cl	103 mEq/l	PRL	12.4 ng/ml
WBC	1–4 /HPF	Ca	12.0 mg/dl	intact PTH	89.9 pg/ml
		IP	2.4 mg/dl	IRI	3.2 μU/ml
		FPG	79 mg/dl	Glucagon	133 pg/ml
		HbA1c	4.5 %	Gastrin	47 pg/ml
		CRP	<0.2 mg/dl	Secretin	52 pg/ml

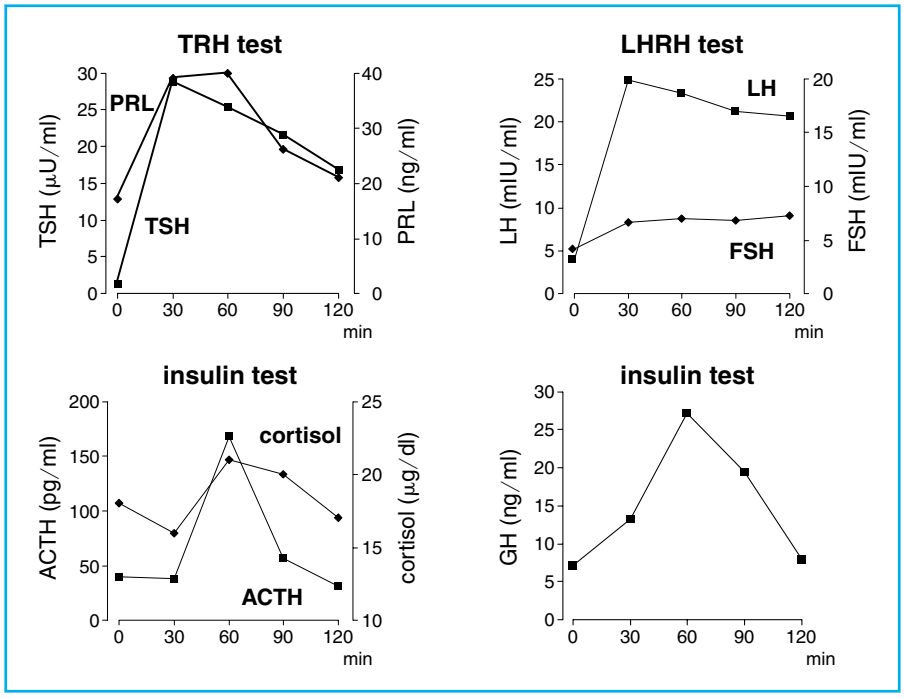

Fig. 1 Laboratory data 2 (Case 1)

our division for more detailed examination and treatment.

[Physical findings] Height 163.8 cm, body weight 51 kg, blood pressure 100/62 mmHg, heart rate 66/min. No evidence of goiter. No abnormal findings in the chest or the abdomen.

[Laboratory tests on admission] (Table 1 and Fig. 1) Hypercalcemia and a high level of intact PTH were noted. LHRH loading test revealed low response of FSH.

[Diagnostic imaging] Neck ultrasound examination revealed an elliptic smooth-edged hypoechoic mass measuring $18\times19\times8$ mm on the dorsal aspect of the right lobe of the thyroid

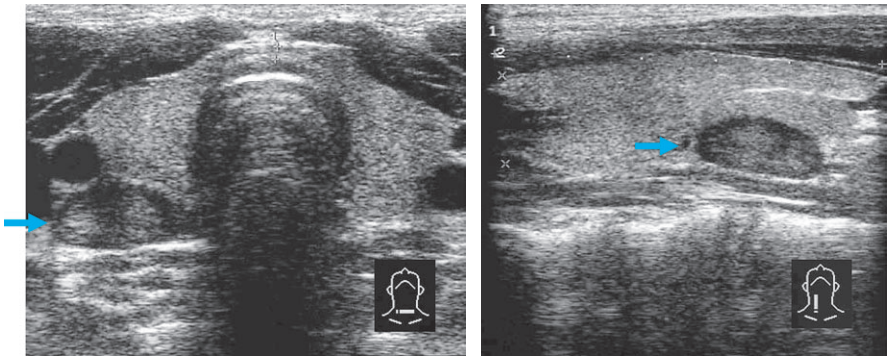

Fig. 2 Thyroid US (Case 1)

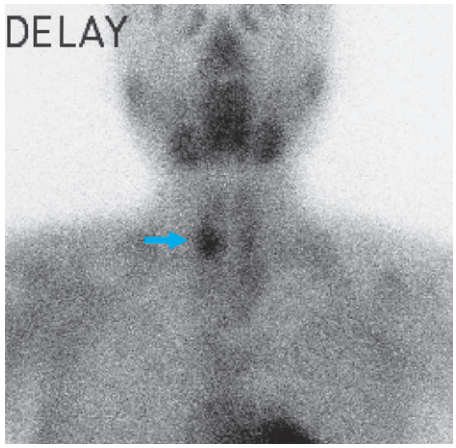

Fig. 3 Tc-MIBI scintigraphy (Case 1)

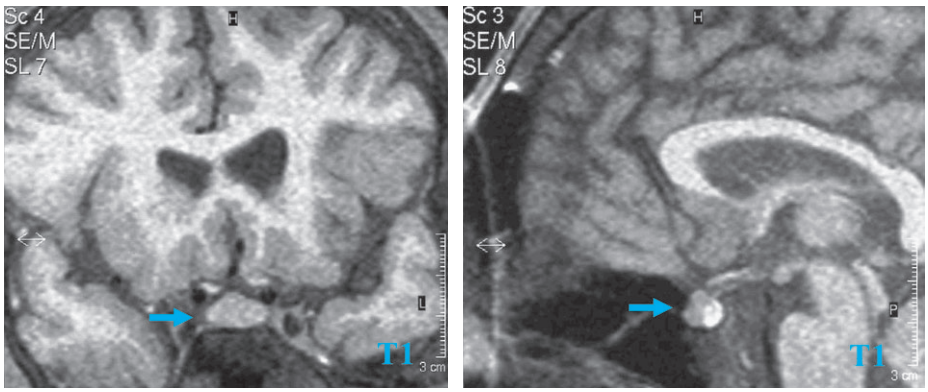

Fig. 4 Pituitary Gd enhance MRI (Case 1)

(Fig. 2). Tc-MIBI scintigraphy showed abnormal accumulation corresponding to this area (Fig. 3). Pituitary MRI proved pituitary adenoma showing upward expansion (Fig. 4).

[Excised parathyroid gland] The parathyroid gland on the right side with tumor was extracted because primary hyperparathyroidism was initially suspected. The other 3 glands had no

Table 2 Laboratory data 1 (Case2)

CBC		**Biochemistry**		**Endocrinology**	
WBC	7,510×10⁴ /μl	TP	7.9 g/dl	ACTH	31 pg/ml
RBC	426 /μl	Alb	5.0 g/dl	Cortisol	10 μg/dl
Hb	12.4 g/dl	AST	15 IU/l	GH	1.6 ng/ml
Ht	37.6 %	ALT	21 IU/l	IGF-1	300 ng/ml
PLT	31.5×10⁴ /μl	LDH	179 IU/l	TSH	1.95 μU/ml
		ALP	277 IU/l	FT4	0.8 ng/dl
Urinary		BUN	9.0 mg/dl	LH	<0.1 mIU/ml
PRO	—	Crea	0.69 mg/dl	FSH	<0.1 mIU/ml
GLU	—	Na	143 mEq/l	E2	29 pg/ml
BL	—	K	3.7 mEq/l	PRL	161.6 ng/ml
		Cl	110 mEq/l	intact PTH	36.3 pg/ml
		Ca	9.4 mg/dl	IRI	13.2 μU/ml
		IP	3.6 mg/dl	CPR	2.5 ng/ml
		FPG	91 mg/dl	Glucagon	153 pg/ml
		HbA1c	5.2 %	Gastrin	67 pg/ml
		CRP	<0.2 mg/dl	Secretin	81 pg/ml

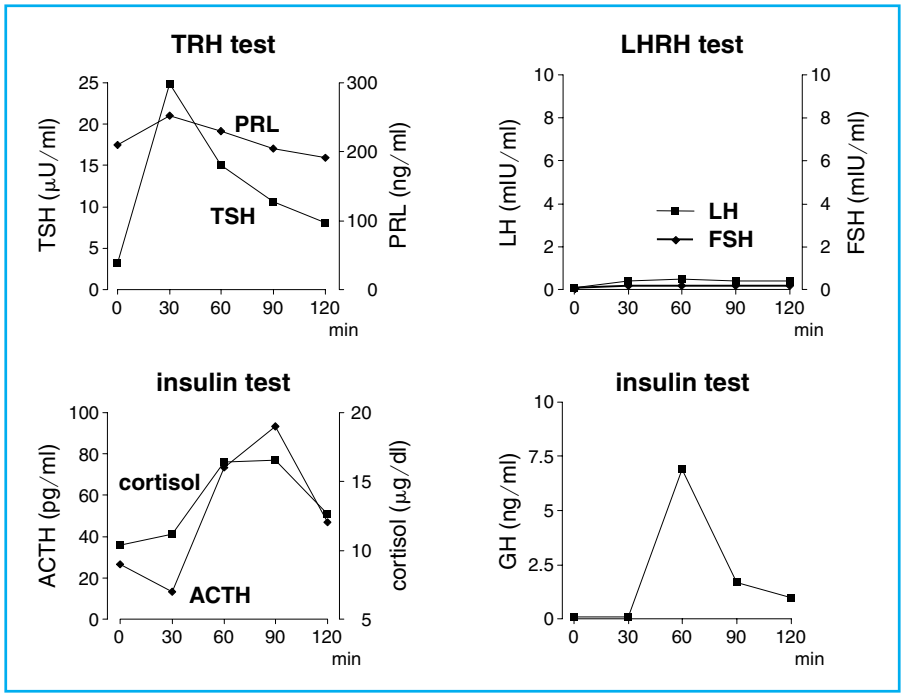

Fig. 5 Laboratory data 2 (Case 2)

macroscopic abnormality. The excised gland was 14×10×8 mm in size, which was contained in a capsule, and had clear margins. Duct formation was prominent and the degree of atypism was mild. Neither capsular nor vascular invasion was noted. The condition was consistent with parathyroid hyperplasia.

[Clinical diagnosis] The patient was diagnosed as having primary hyperparathyroidism and non-functioning pituitary adenoma accompanied with secondary hypogonadotropinemia.

[Patient 2] 20 years old, female.
[Chief complaint] Amenorrhea.

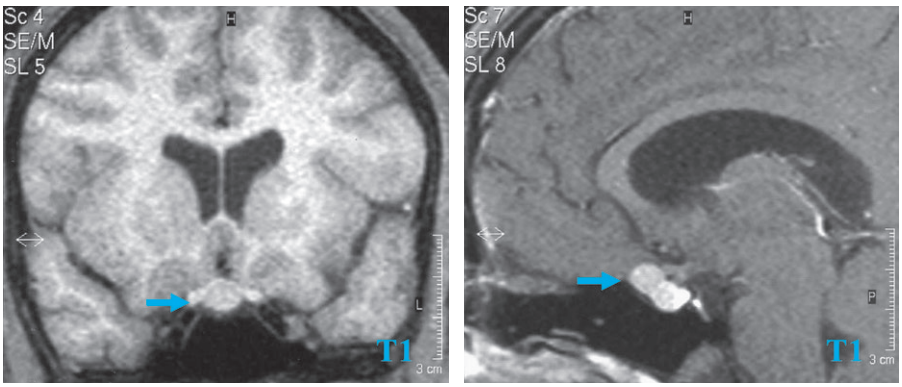

Fig. 6 Pituitary Gd enhance MRI (Case 2)

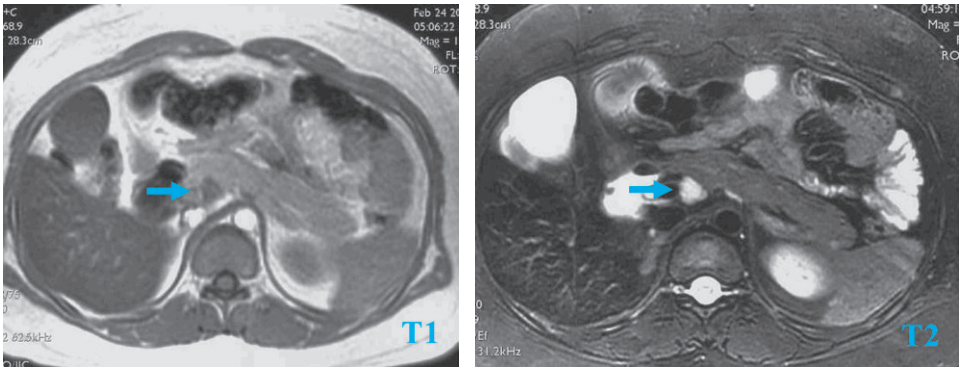

Fig. 7 Abdomen Gd enhance MRI (Case 2)

[Past history] Gilles de la Tourette syndrome at the age of 12.
[History of present illness] The patient visited a gynecology clinic for primary amenorrhea at the age of 18. As hyperprolactinemia was noted, she was referred to our division for detailed examination and treatment. Because the presence of endocrine abnormality in her younger brother indicated a possibility of MEN1, detailed examination focusing on MEN1 was conducted.
[Physical findings] Height 151.2 cm, body weight 71 kg, blood pressure 114/72 mmHg, heart rate 72/min. No evidence of goiter. No abnormal findings in the chest or the abdomen. Galactorrhea was present.
[Laboratory tests on admission] (Table 2 and Fig. 5) No hypercalcemia was noted and intact PTH was normal. Low levels of LH, FSH, and E2 as well as hyperprolactinemia were noted. TRH loading test revealed a high basal level and low response of PRL. LHRH loading test showed a lack of response of LH and FSH.
[Diagnostic imaging] Pituitary MRI revealed an hourglass-shaped pituitary adenoma expanding to the anterosuperior aspect of the anterior lobe of the hypophysis (Fig. 6). Abdominal MRI revealed an 18-mm tumor on the dorsal aspect of the head of the pancreas (Fig. 7).
[Clinical diagnosis] The patient was diagnosed as having prolactinoma and accompanied with secondary hypogonadism. With respect to the pancreatic tumor, biopsy was not performed and the patient was kept under observation, because endoscopic retrograde cholangiopancreatography (ERCP) showed no definite abnormality, although a slight elevation of glucagon level was noted.
[Gene tests] Because MEN1 was suspected based on the accumulation of endocrine disorders among siblings, gene analysis was performed on the peripheral blood from both siblings and the parathyroid tissues from Patient 1. A missense mutation from leucine to proline at codon 223 in

exon 4 was detected, and the diagnosis of MEN1 was confirmed.

Discussion

The MEN1 gene was identified as the causal gene for multiple endocrine neoplasia type 1 (MEN1) in 1997.[7–8] The MEN1 gene is located in the long arm of chromosome 11 (11q13) and comprises 10 exons. Exons from 2 to 10 encode menin consisting of 610 amino acid residues.[7] The mRNA for menin is expressed in a wide range of tissues, including the central nervous system, testes, and placenta, which are reported to show particularly abundant expression.[6] Although several recent studies have examined the function and tumorigenic mechanism of menin, the details of the physiological roles of menin have not been clarified. Because homozygous menin-knockout mice die on the 12th day of gestation, menin is considered to play some important roles related to the maintenance of life and embryonic development.[9]

Juvenile myoclonus epilepsy and Gilles de la Tourette syndrome observed in our patients are disorders causing involuntary movement. These are genetic diseases frequently presenting with a family history, but the mode of inheritance has not been clarified.[10–13] The facts that drug-induced involuntary movement is associated with hypersensitivity of the dopamine receptors on postsynaptic membranes[14] and that central dopamine blockers are effective in treating Gilles de la Tourette syndrome suggest that involuntary movement might be the result of a central hyperdopaminergic condition in the basal ganglia and the limbic system of the cerebrum.[15]

The coexistence of epilepsy and MEN1 in a patient has not been reported prior to the case described here. In our cases, the possibility that MEN1 developed incidentally in siblings in a family with epilepsy cannot be excluded. On the other hand, the marked expression of menin in the central nervous system suggests a possible relationship between epilepsy and menin. It has been reported that menin binds to JunD, a transcription factor for AP-1, and suppresses the transcriptional activity mediated by JunD.[3] While DOPA and dopamine are produced from tyrosine in chromaffin cells, JunD is involved in the gene expression of tyrosine hydroxylase, which is the rate-limiting enzyme of this process.[16] In view of these facts, it is considered possible that the inactivation of menin may counter the action of JunD to suppress the expression of tyrosine hydroxylase, resulting in a hyperdopaminergic condition.

Menin binds to Smad3, a transcription factor, and the inactivation of menin results in suppression of the TGF-β signal pathway through the inhibition of the binding of Smad3/4 to DNA.[4] On the other hand, TGF-β is also expressed in chromaffin cells.[17] It has been reported that TGF-β inhibits the proliferation and differentiation of chromaffin cells in vitro,[18] and that the in vivo suppression of TGF-β expression results in the promotion of the proliferation of chromaffin cells.[19] In addition, menin has been reported to interact with NF-kappaB, inhibiting its transcriptional activity.[5] NF-kappaB has been reported to have an anti-apoptotic effect on PC12 cells, a cell line of chromaffin cells.[20]

The line of consideration as discussed above leads to the possibility that the inactivation of menin may affect transcription factors such as JunD, Smad3, and NF-kappaB, and this may be involved in dopamine production from chromaffin cells or the proliferation, differentiation, and apoptosis of chromaffin cells.

No concrete information has been reported concerning the direct effect of menin on chromaffin cells or its involvement in dopamine production, and the details are still unknown. However, available information concerning the expression of menin in the central nervous system and its interaction with several transcription factors involved in dopamine production warrants further investigation.

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Advanced Medical Technology and Health Insurance in Japan

JMAJ 49(1): 41–43, 2006

Hideya Sakurai*1

Key words Advanced medical technology, Health insurance system, Medical fee, Central Social Insurance Medical Council

Introduction

Medical technology is constantly evolving with more and more advanced technologies being developed all the time. In Japan, "medical care" is considered "the social application of medical science", and how these advanced medical technologies are covered by the Japanese Health Insurance System is indeed a crucial issue for the social application of medical science. This article outlines the process by which newly developed advanced medical technologies become available through the Japanese Health Insurance System.

Japanese Health Insurance System

The health insurance system in Japan dates back more than 80 years. It was first established in the form of welfare for employees of factories, etc. In 1961, legislation was passed to ensure that all Japanese citizens be covered by some kind of regulated public health insurance program. This was the start of universal coverage by a health insurance system in Japan.

Citizens become "insured" by paying a "premium", which is predetermined according to their income or age, to the "health insurance societies (insurers)" so that they can receive health care services at any medical institution of their choice when they are sick. Equal provision of necessary care as required is guaranteed to all Japanese citizens.

Medical institutions claim the cost of medical care provided to patients (insured persons) as a "medical fee" from "insurers". The types of "medical fee" that can be claimed are detailed according to each specific medical practice, all of which are listed in the "Medical Fee Schedule" created by a public body called the "Central Social Insurance Medical Council". When a medical institution provides medical services not listed in this Schedule, such medical services must be paid by the persons who receive the services as they are not covered by insurance.

A Special Interim System for Advanced Medical Technology

Newly developed medical technologies are not covered by insurance until they become listed in the "Medical Fee Schedule". Therefore, a special system of medical care exists until they become permanently covered by insurance and available for provision generally. In this special system, patients are requested for payment which is not covered by insurance. The procedures to approve an advanced medical technology for cover by insurance are described below.

How the Newly Developed Advanced Medical Technologies Become Covered by Insurance

The special interim system stipulates that "if

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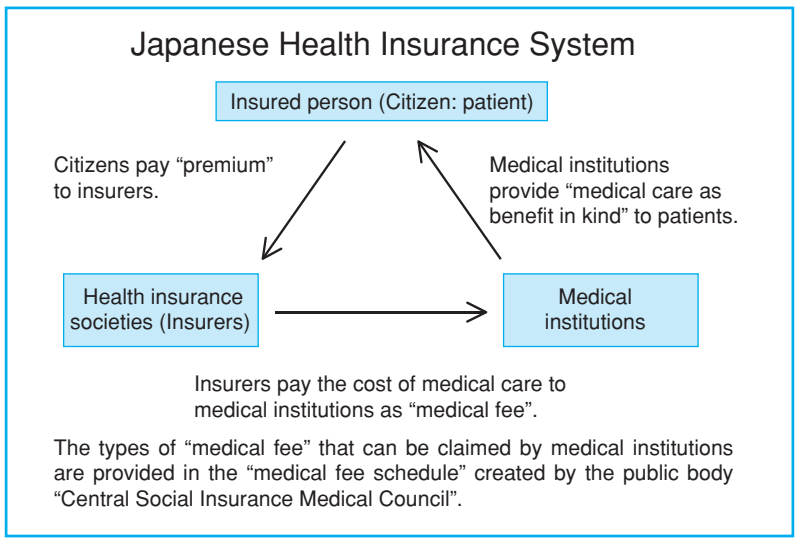

the highly advanced medical technology to be approved has been provided privately at a 'designated authorized insurance medical institution', a minimum level of safety and efficacy of the technology is considered to have been established. But since the technology has still not been widely implemented, it shall be subject to an interim system of provision before being commonly provided and covered by insurance". "Authorized institutions" are "Medical institutions with a high level medical infrastructure both qualitatively and quantitatively" that have been approved by the Ministry of Health, Labor, and Welfare in accordance with a separately prescribed set of regulations.

Designated authorized institutions themselves apply for approval to include new medical technology in the special system mentioned above. Each application is individually assessed to determine whether or not it should be approved. When a designated institution applies for approval related to an advanced medical technology, the Minister of Health, Labor, and Welfare reviews the technical particulars during a meeting of the "Council for Highly Advanced Medical Technology". This council is comprised of experts in medical technology and experts in healthcare services. When this council decides it appropriate to recommend the approval of an application, it reports to the Central Social Insurance Medical Council.

Based on this recommendation, the Central Social Insurance Medical Council then makes a decision as to whether or not to enter the technology, provisionally, in the special system. Once provisional approval has been given, the technology can be provided under the special interim system, one month following the Council's decision. However, availability of treatment using the New Advanced Technology is limited to the institution making the respective application. Such institutions must display, in their hospital, information about what kind of advanced medical technologies are available at their hospital and the cost burden to a patient who wants to have such treatment using such technologies.

Handling of Provisionally Approved Advanced Medical Technologies

The Minister of Health, Labor, and Welfare requires the designated institutions to submit an annual report on the New Advanced Technology. Based on this report, the Council for Highly Advanced Medical Technology assesses its efficacy and safety, and periodically reports to the Medical Council.

Based on these reports, the Medical Council has the authority to make one of three decisions:

1) It may decide to continue to include the New Advanced Technology as a provisional listing in the interim system, with treatment limited to the respective designated institution.
2) If the Council finds the technology concerned

to be safe and effective, it issues approval for it to be available as a "general medical service," in which case the Medical Fee Schedule listing will become possible and the technology can be offered at other institutions. At this stage the cost of the technology can be covered by insurance.

3) If, based on the Council for Highly Advanced Medical Technology's assessment of the effectiveness of the technology, it is deemed inappropriate to continue to list it in the interim system, the technology will be reviewed by the Medical Council and will be revoked from the interim system. In this case, the Medical Council will notify the corresponding designated authorized insurance medical institution with the reasons for revocation.

The following are some of the examples of the advanced technologies which have been once approved and then introduced into insurance or have been revoked.

1. Examples of "highly advanced medical technology" which have been approved and then included in "health insurance" cover

1) Artificial pancreas,
2) Diagnosis of hematopoietic tumors,
3) Leukocyte removal by centrifugal method for ulcerative colitis

2. Examples of "highly advanced medical technology" which have been approved and then the approval revoked

1) Electric coagulation for cerebrovascular lesions with micro copper wires,
2) Bone electrotherapy by d.c. current,
3) Intracranial pressure measurement by completely implanted cephalohemometer

Some Problems with the Current System

I have discussed the process by which advanced technologies are covered by insurance under the Japanese Health Insurance System. Finally, I would like to comment on some problems with the current system. Even though the special interim system was established so that new medical technologies could be covered promptly by the Japanese Health Insurance System, and so that every citizen could receive the most advanced medical care possible, it still takes significant time to secure the necessary approval, even for a provisional listing in the interim system. To ensure the safety and efficacy of medical technology, careful steps need to be taken. However, efforts are being made to address the length of time necessary for advanced medical technologies to become covered by insurance, without compromising the integrity of the process. These measures include:

(1) Simplifying administrative procedures required in the approval application process.
(2) Easing the approval conditions by which an institution becomes a designated authorized insurance medical institution.
(3) Increase the number of members in the Council for Highly Advanced Medical Technology, so that reviews can be carried out more promptly.

Together with other improvements implemented in 2004, these measures will serve to simplify the procedures for approval.

A second problem relates to financial issues. Some people believe that financial resources related to the provision of newly developed technologies should be capped. There are two groups of people who support this opinion. One group is connected to the Ministry of Finance. Under the Japanese Health Insurance System, funds come partly from taxes. If use of advanced medical technologies is covered by health insurance, costs will increase, resulting in an inflated burden on the Nation's finances. The other group is made up of people from the corporate sector. This sector is trying to reduce the scope of Japan's public health insurance in order to expand areas of self-paid medical care, to promote private insurance, and to stimulate a general business orientation in the health care sector.

The Japan Medical Association is strongly opposed to such movements. As I have already mentioned, making advanced medical technologies available under the Japanese Health Insurance System so that all citizens can receive medical services is advantageous to the people. Moreover, Japan's national medical expenses amount to only 7% of the country's GDP which, compared to other advanced countries, makes the Japanese Health Insurance System one of the most cost effective systems in the world. To protect the health and lives of the people, the Japan Medical Association maintains that the Japanese Health Insurance System should continue to develop and expand. We strongly believe that this is in the best interests of the people of this country.

Suicide Is Preventable

JMAJ 49(1): 44–46, 2006

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Key words Suicide, Depression, Prevention, Screening, Community

Introduction

The number of persons who die by suicide in Japan has remained above the 30,000 mark ever since it recorded a dramatic increase of almost 10,000 in 1998. This rapid increase mainly consisted of the increase in suicide committed by males in their 50s, in particular those who lost their jobs or were unemployed. In addition, the incidence of suicide among the elderly has remained high. These 2 age groups are considered mainly responsible for the increased incidence of suicide in Japan.

Japan is ranked high in the rate of suicide in the older age bracket in international comparisons. It is higher in rural areas than in urban areas. It has been demonstrated that the act of suicide committed by aged persons very frequently results in the termination of life. While suicide is completed in 1 out of 100 to 200 cases of attempted suicide among younger persons, the rate is 1 out of 4 among aged persons. The most frequent motivation to commit suicide in the older age bracket is the suffering from disease reported in more than 60% of cases, followed by family problems. Mental disorders such as depression are found commonly in the background. Aged persons tend to consult general physicians shortly before attempting suicide. Studies in Western countries have shown that more than 70% of aged persons who committed suicide visited general physicians within a month of the act of suicide.

Risk Factors of Suicide in Senile Depression

Depression in the general population, including the elderly, is associated with a high risk of suicide when it is severe or it accompanies delusion. Other factors considered to increase the risk of suicide in senile depression are:

1) Presence of suicidal ideas;
2) Coexistence of alcohol dependence or panic disorder;
3) Complication with hypochondriac predisposition or somatoform disorders;
4) Presence of the sense of hopelessness; and
5) Lowering of cognitive functions.

Suicide Prevention through Prevention of Depression: Experience in Japan

As demonstrated by various studies, more than 90% of persons who commit suicide have preceding psychiatric disorders, and depression is the most important factor leading to suicide among aged persons. Early diagnosis and treatment of depression is considered an effective measure for preventing suicide.

It is important that not only specialists, but also general physicians be involved in the prevention of suicide. Research in Gotland, Sweden, showed that the introduction of a training program for general physicians was effective in reducing the number of suicides. However, this study also showed that the effectiveness of train-

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ing declined with time. The prevention of suicide requires efforts that go beyond the conventional models of medical practice.

The experience in Japan, such as that in Matsunoyama Town, Niigata Prefecture, has proved the effectiveness of secondary prevention activities and the prevention activities aiming at better welfare. Not only secondary prevention targeted at the depressive state and depression, but also primary prevention aiming at better welfare, including enrichment of at-home welfare services, play vital roles in preventing suicide of the elderly.

In Nagawa Town, Aomori Prefecture, my colleagues and I have been performing activities in 3 fields: 1) depression screening, 2) education and promotional activities for general inhabitants, and 3) group support activities for the elderly.[1–3]

Depression screening

This is a secondary prevention program using the questionnaire for the screening of depression and suicide in the elderly, prepared by a study team of the Ministry of Health, Labour and Welfare. The questionnaire consists of 5 questions listed below. Depression is suspected strongly if 2 or more of these conditions are met for a period of 2 weeks or more and the person experiences mental distress or difficulty in daily living. The persons suspected of having depression are interviewed by visiting physicians and encouraged to seek treatment if required.

List of questions:

1) Is your life pretty full?
2) Do you still enjoy the things you used to?
3) Do you think it too much trouble to do the things you used to?
4) Do you feel that you are useful and needed?
5) Do you get tired for no reason?

Education and promotional activities for general inhabitants

Led by the Mayor, local administrative agencies are proactively promoting these activities, ensuring that the citizens understand the importance of activities. Lectures and other events are held to disseminate better knowledge of depression and suicide to members of the Social Welfare Council, as well as social workers and health promoters mediating the relationship between the citizens and the local government. Education and promotional activities also include workshops concerning depression held at community health classes and at regular meetings of elderly citizens' circles, the publication of articles featuring depression in the town bulletin throughout the year, and the distribution of leaflets concerning depression.

Group support activities for the elderly

Many elderly persons in the community strongly believe in the notion that they would rather die than live without the ability to work. When they have become unable to perform farming and housekeeping tasks due to aging or disease, they tend to feel as if they have lost their place in the family. Many elderly persons lack sufficient interactions with other family members even in a family consisting of 3 generations. To prevent elderly persons from withdrawal and becoming bedridden, to enhance the mental health of inhabitants, and to help them live a fulfilling life in this situation, community centers specifically addressing these issues, called Yoriaikko, are established and maintained through joint efforts of the Social Welfare Council, social workers, and health promoters.

In addition, other efforts are being made in liaison with the Town Office and related departments, such as the attention concerning mental health problems given to inhabitants seeking financial consultation, the support to inhabitants who have attempted suicide and their families, and assistance to inhabitants whose family members committed suicide.

Conclusion

This article outlined activities for preventing depression and suicide among the elderly in Japan. As the chronic nature of depression has become widely recognized, the roles of general clinical physicians have become all the more important, as well as the liaison with families and communities. On the other hand, psychiatric issues such as depression and suicide involve extremely private information. There must be thorough discussion on the regional level concerning the handling of information, obtaining of consent, and protection of privacy. Care must also be taken to avoid undue burden on individuals.

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