ORIGINAL CONTRIBUTION

Descriptive Epidemiology of Chronic Fatigue Syndrome Based on a Nationwide Survey in Japan

Masumi Minowa and Mei Jiamo*

In order to clarify the epidemiological features of chronic fatigue syndrome (CFS), a nationwide survey was conducted using the Japanese version of the CDC Criteria prepared by the CFS Research Group of Japan. All clinical departments of internal medicine, pediatrics, psychiatry and neurology at university hospitals and at ordinary hospitals with 200 or more beds were surveyed. Major results were as follows : (1) Period prevalence adjusted for response rate was 0.85 (0.63 for males and 1.02 for females) per 100,000 population during the year 1992 ; (2) Based on the first and final dates of hospital visits, the prevalences on January 1 of 1992 and 1993 were 0.40 and 0.60 per 100,000 population, respectively, suggesting an increasing trend ; (3) Reported new cases during 1992 were 301, and the response adjusted-incidence was estimated to be 0.46 per 100,000 person-years ; (4) The proportion of post-infectious CFS cases was 14.8% for both sexes, and tended to be slightly higher among females than males, but was not related to age. Three clusterings of two cases were reported. *J Epidemiol*, 1996; 6 : 75-80.

chronic fatigue syndrome, descriptive epidemiology, nationwide survey

Chronic fatigue syndrome (CFS) is a clinically defined condition[1,2] characterized by severe disabling fatigue and a combination of symptoms that prominently feature self-reported impairments in concentration and short-term memory, sleep disturbances, and musculoskeletal pain. CFS or related conditions, which have been described over a long period of time in western countries[3-7] have attracted a great deal of attention, particulary in the lay press. As this syndrome is apt to occur as a small or large epidemic in Western communities, many of the epidemiological reports of this syndrome have described such outbreaks[3-8], and a few reports have dealt with the prevalence and incidence in a particular population[9-14]. Outbreaks of CFS have not been reported in Japan, to date. Rather, the occurrance of sporadic cases is a major concern for medical personnel in Japan. Therefore, a nationwide epidemiological survey of CFS was conducted based on the Japanese version of the CDC Criteria for CFS[15] prepared by the CFS Research Group of Japan[16]. The Japanese version is essentially comparable to the CDC Criteria for CFS, in which a case of CFS must fulfill both major criteria, and the following minor criteria : 6 or more of the 11 symptom criteria and 2 or more of the 3 physical criteria ; or 8 or more of 11 symptom criteria. In the Japanese version, however, a case which fulfills both of major criteria, but not the minor criteria is defined as a suspected CFS case, and CFS which follows a comfirmed infection is defined as post-infectious CFS.

METHODS

Following the standard precedure for nationwide epidemiological surveys established by the Epidemiology of Intractable Diseases Research Committee, Ministry of Health and Welfare of Japan[17], clinical departments of internal medicine (including those of gastrointestinal, respiratory and circulatory diseases), pediatrics, psychiatry and neurology at university hospitals and at ordinary hospitals with 200 or more beds were surveyed. During March, 1993, letters requesting cooperation with the survey and a reporting format were sent to directors of the concerned departments together with a pamphlet including the concept of and the diagnostic criteria for CFS. The reporting format included the experience of diagnosing CFS cases during the period of January 1 to December 31, 1992, and, if available, sex, date of birth, residence, dates of first and final visits to the department, prognosis, certainty of diagnosis, and

Received September 8, 1995 ; accepted March 1, 1996.
Department of Epidemiology, National Institute of Public Health, Tokyo, Japan.
* Present affiliation is Jianxi Health and Anti-epidemic Station, Nanchang, China.
Address for correspondence: Masumi Minowa, Department of Epidemiology, National Institute of Public Health, 4-6-1 Shirokanedai Minato-ku Tokyo, 108 Japan.

temporal relationship with infection, as well as whether the reporter suspected any clustering of the disease around the index cases. Details of individual CFS cases were not requested in order to improve the response rate.

Although the deadline for responding was set at April 31, 1993, the response rate was quite low (33.8%) even on June 20, and a reminder to prompt an eventual reply was sent to the departments which had not returned the reporting format. Ultimately, responses received until December 31, 1993 were subjected to analysis.

In order to estimate the prevalence and incidence adjusted for the response rate to this survey, observed rates were divided by the response rate, assuming that hospital departments which had not returned the reporting formats had also diagnosed a similar number of CFS cases.

RESULTS

Response

The questionnaires were sent to 7,858 departments (7,247 of ordinary hospitals and 609 of university hospitals), from which the reporting formats were returned by 3,698 departments of ordinary hospitals (51.0%) and 430 departments of university hospitals (70.6%), or 4,128 departments (52.5%) in total. Among these, 18.9% of replies from ordinary hospitals and 16.6% of those from university hospitals were obtained after the reminder. Proportions of replies which reported CFS cases were 3.8% and 3.7%, respectively, before and after the reminder.

In total, 560 reported cases were mainly from internal medicine departments (448 cases or 80%, including 75 cases from respiratory departments, 83 cases from gastroenterology departments and 10 cases from circulatory departments), followed by neurological departments (52 cases or 9.3%), psychiatric departments (33 cases or 5.9%), and pediatric departments (24 cases or 4.3%).

Prevalence and incidence

In this survey, 154 departments reported 560 CFS cases diagnosed during 1992. Among these cases, 118 (21.1%) were reported to be suspected CFS cases. According to the standard procedure for a nationwide epidemiological survey established by the Epidemiology of Intractable Diseases Research Committee, mainly epidemiology based on the total number of cases will be described herein.

The period prevalence adjusted for response rate was 0.85 (0.63 for males and 1.02 for females) per 100,000 population (Table 1), and the number of CFS cases was estimated to be 1,066 during the year 1992. Based on the first and final dates of hospital visits, the prevalence rates on the January 1 of 1992 and 1993 were 0.40 and 0.60 per 100,000 population, respectively, suggesting an increasing trend. Reported new cases during the period of January 1 to December 31, 1992 were 301, and the response adjusted-incidence rate was estimated to be 0.46 per 100,000 person-years. Applying the relationship ($P=I\times L$) among prevalence (L), incidence (I) and mean morbidity period (P), the mean morbidity period was estimated to be 1.3 years (the onset of the disease was assumed to be the same of the date of the first hospital visit).

Ages of the reported cases ranged from 8 to 83 years old, and the diagnosis was most prevalent in the 20's and 30's age groups. The average age was 35.4 years old (S.D. 12.3) for males, 37.3 (S.D. 14.1) for females and 36.7 (S.D. 13.6) for both. The prevalence was higher among females than males (1 : 1.61) (Table 2).

Post-infectious CFS and clustering

The proportion of post-infectious CFS, which followed a confirmed infection, was 14.8% in both sexes, and tended to be slightly higher among females than males, but was not related to age (Table 3). Three clusterings of two cases were reported. Among these, two pairs occurred familially, in one of which a male case appeared seven years after the mother's onset of CFS.

Prognosis

Although cases who recovered from CFS accounted for less than 10%, nearly half of the cases were reported to have recov-

Table 1. Prevalence and incidence of CFS in Japan, 1992 (95% confidence interval)

	Point prevalence		Period prevalence	Incidence
	Jan. 1, 1992	Jan. 1, 1993	Jan. 1 to Dec. 31,1992	Jan. 1 to Dec. 31,1992
Reported cases				
Male	82	129	199	117
Female	166	244	334	168
Sex unknown	11	20	27	16
Total	259	393	560	301
Response-adjusted rate per 100,000 population				
Male	0.25 (0.20-0.30)	0.40 (0.33-0.47)	0.63 (0.53-0.70)	0.36 (0.30-0.43)
Female	0.51 (0.42-0.57)	0.75 (0.64-0.82)	1.02 (0.89-1.11)	0.51 (0.43-0.58)
Total	0.40 (0.35-0.44)	0.60 (0.54-0.66)	0.85 (0.78-0.92)	0.46 (0.41-0.51)

Table 2. Age- and sex-specific period prevalence of CFS in 1992 (95% confidence interval)

	Reported cases				Response-adjusted prevalence/100,000			
Age*	Unknown	Male	Female	Total	Male	Female	Total	Female/Male
0-9	0	2	0	2	0.06 (0-.14)	0.0	0.04 (0-.07)	-
10-19	4	16	21	41	0.34 (.17-.50)	0.48 (.27-.67)	0.44 (.31-.58)	1.31
20-29	3	48	100	151	1.01 (.72-1.30)	2.19 (1.77-2.63)	1.62 (1.35-1.87)	2.08
30-39	7	70	93	170	1.64 (1.26-2.04)	2.25 (1.77-2.69)	2.02 (1.72-2.32)	1.33
40-49	4	37	58	99	0.70 (.48-.93)	1.12 (.84-1.39)	0.95 (0.76-1.14)	1.57
50-59	8	18	34	60	0.44 (.23-.61)	0.78 (.51-1.03)	0.70 (.52-.88)	1.89
60-69	1	7	20	28	0.23 (.06-.38)	0.55 (.32-.81)	0.42 (.26-.57)	2.86
70-89	0	0	8	8	0.0	0.25 (.75-.41)	0.15 (.04-.25)	-
Unknown	0	1	0	1				
Total	27	199	334	560	0.63 (.53-.70)	1.02 (.89-1.11)	0.85 (.78-.92)	1.61

* Age as of December 31, 1992.

Table 3. Post-infectious CFS cases by sex (%)

Sex	Infectious	Non-infectious	Unknown	Total
Male	28(14.1)	162(81.4)	9(4.5)	199(100.0)
Female	52(15.6)	269(80.5)	13(3.9)	334(100.0)
Unknown	3(11.1)	22(81.5)	2(7.4)	27(100.0)
Total	83(14.8)	453(80.9)	24(4.3)	560(100.0)

Table 4. Sex-specific prognosis by follow-up period (%)

Follow-up (days)	Sex	Prognosis: Recovered	Ameliorated	Unchanged	Deteriorated	Unknown	No answer	Total
-180	Male	2 (3.8)	20 (37.7)	9 (17.0)	0 (0.0)	22 (41.5)	0 (0.0)	53 (100.0)
	Female	9 (12.7)	17 (23.9)	22 (31.0)	1 (0.4)	20 (28.2)	2 (2.8)	71 (100.0)
	Unknown	0	1	2	0	3	0	6
	Total	11 (8.5)	38 (29.2)	33 (25.4)	1 (0.8)	45 (34.6)	2 (1.5)	130 (100.0)
181-365	Male	5 (10.2)	21 (42.9)	19 (38.8)	0 (0.0)	3 (6.1)	1 (2.0)	49 (100.0)
	Female	11 (14.1)	37 (47.4)	27 (34.6)	0 (0.0)	3 (3.8)	0 (0.0)	78 (100.0)
	Unknown	0	2	5	0	0	0	7
	Total	10 (11.9)	60 (44.8)	51 (38.1)	0 (0.0)	6 (4.5)	1 (0.7)	134 (100.0)
366+	Male	5 (6.1)	30 (36.6)	39 (47.6)	1 (1.2)	6 (7.3)	1 (1.2)	82 (100.0)
	Female	4 (2.5)	88 (55.0)	55 (34.4)	7 (4.4)	6 (3.8)	0 (0.0)	160 (100.0)
	Unknown	0	3	10	0	0	0	13
	Total	9 (3.5)	121 (47.5)	104 (40.8)	8 (3.1)	12 (4.7)	1 (0.4)	255 (100.0)
Unknown	Male	1	6	7	0	1	0	15
	Female	7	10	5	0	3	0	25
	Unknown	0	0	1	0	0	0	1
	Total	8	16	13	0	4	0	41
Total	Male	13 (6.5)	77 (38.7)	74 (37.2)	1 (0.5)	32 (16.1)	2 (1.0)	199 (100.0)
	Female	31 (9.3)	152 (45.5)	109 (32.6)	8 (2.4)	32 (9.6)	2 (0.6)	334 (100.0)
	Unknown	0	6	18	0	3	0	27
	Total	44 (7.9)	235 (42.0)	201 (35.9)	9 (1.6)	67 (12.0)	4 (0.7)	560 (100.0)

Table 5. Sex-specific prognosis by follow-up period (%)

	Prognosis						
Age	Recovered	Ameliorated	Unchanged	Deteriorated	Unknown	No answer	Total
-19	5 (11.6)	22 (51.2)	11 (25.6)	0 (0.0)	5 (11.6)	0 (0.0)	43 (100.0)
20-29	17 (11.3)	52 (34.4)	61 (40.4)	3 (2.0)	18 (11.9)	0 (0.0)	151 (100.0)
30-39	10 (5.9)	68 (40.0)	60 (35.3)	4 (2.4)	24 (14.1)	4 (2.4)	170 (100.0)
40-49	9 (9.1)	46 (46.5)	37 (37.4)	1 (1.0)	6 (6.1)	0 (0.0)	99 (100.0)
50-59	2 (3.3)	29 (48.3)	19 (31.7)	0 (0.0)	10 (16.7)	0 (0.0)	60 (100.0)
60+	1 (2.8)	18 (50.0)	12 (33.3)	1 (2.8)	4 (11.1)	0 (0.0)	36 (100.0)
Unknown	0	0	1	0	0	0	1

Table 6. Prognosis and diagnosis (%)

	Prognosis						
Diagnosis	Recovered	Ameliorated	Unchanged	Deteriorated	Unknown	Noanswer	Total
Definite	1(0.8)	32(27.1)	53(44.9)	1 (0.8)	29 (24.6)	2 (1.7)	118(100.0)
Suspected	29(8.8)	158(48.2)	102(31.1)	4 (1.2)	33 (10.1)	2 (0.6)	328(100.0)
No answer	14(12.3)	45(39.5)	46(40.4)	4 (3.5)	5 (4.4)	- (-)	114(100.0)

Table 7. Prognosis and post-infectious CFS (%)

	Prognosis						
Infection	Recovered	Ameliorated	Unchanged	Deteriorated	Unknown	No answer	Total
+	7 (8.4)	48 (57.8)	20 (24.1)	2 (2.4)	5 (6.0)	1 (1.2)	83 (100.0)
−	30 (6.6)	174 (38.4)	179 (39.5)	7 (1.5)	61 (13.5)	2 (0.4)	453(100.0)
No answer	7 (29.2)	13 (54.2)	2 (8.3)	- (-)	1 (4.2)	1 (4.2)	24 (100.0)

ered or experienced amelioration of symptoms during the follow-up periods, and less than 2% of cases were reported to have deteriorated. Table 4 shows the sex-specific prognosis broken down by follow-up period. Among the cases followed for 180 days or less, the proportion of prognosis-unknown was greater than in the other two groups of follow-up periods. In contrast, a higher proportion was reported to have recovered or experienced symptom amelioration among the cases followed-up longer than 180 days as compared to those followed-up 180 days or less ($p<0.01$, χ^2 test). Although female cases were more likely to recover or experience amelioration of symptoms than male cases ($p<0.05$, χ^2 test), this tendency was not consistent for follow-up periods (Table 4).

The proportion of recovered cases increased with decreasing age ($p<0.05$, Cochran-Armitage test) (Table 5). The prognosis of definite cases was better than that of suspected cases ($p<0.01$, Mann-Whitney's U-test), and the amelioration rate tended to be higher in the suspected cases regardless of the follow-up period (Table 6). Post-infectious CFS showed a better prognosis than non-post-infectious CFS ($p<0.05$, U-test) (Table 7).

DISCUSSION

Descriptive epidemiology, especially descriptions of prevalence and incidence rates are the first step in epidemiological studies on diseases of unknown etiology. In the epidemiology of CFS, however, even this first step is quite difficult. Grufferman[6] listed the underlying problems thwarting the development of incidence and prevalence estimates for CFS : (1) absence of any systematic public health information system ; (2) vagueness of the diagnostic criteria ; (3) lack of specific International Classification of Diseases code ; (4) the fact that few patients with the syndrome are hospitalized ; (5) a wide spectrum of symptomatology and great variation in its severity, which probably leads to only a subset of patients receiving

medical attention ; (6) widespread skepticism within the medical community regarding the validity of the syndrome ; (7) fortunately very low, if any, mortality ; (8) availability of only sparse information regarding the natural history and duration of the illness ; (9) possible overlap of symptoms of CFS and depression ; and (10) possible overlap of the signs and symptoms of CFS with those of fibromyalgia and infectious mononucleosis. Among these, vagueness of the disease entity and resulting complicated diagnostic criteria might be central, and it would be of interest to ascertain whether the syndrome is actually discontinuous with related conditions such as depression, infectious mononucleosis, and so forth.

The prevalence of this syndrome based on hospital-based surveys has been reported to be 37.1 per 100,000 population in Australia[9], 127 in New Zealand[10], 130 in England[12] and 4.6-11.3[11] in the United States. Population-based prevalence surveys of CFS using the CDC Criteria have not been reported. The period prevalence (adjusted for the response rate) in this survey, 0.85 per 100,000 population, may be considerably lower than those reported from Western countries. The annual incidence was reported to be 3[14] or 51[13] per 100,000 in Scotland, which may also be higher than our result.

The disease entity of CFS is not well-known among Japanese medical community, and this may have lead to underreporting of CFS cases in this survey. In fact, an apparent increasing trend from the New Year's day of 1992 to that of 1993 may suggest an increased clinical interest in this disease. If interest in this disease is increasing among medical personnel in Japan, more cases with CFS may be reported. On the other hand, however, all reported cases including suspected cases were included in the analysis of our survey responses. This might cause overestimation of the prevalence and incidence of CFS in this survey. Thus, in calculating our estimates of the prevalence and incidence of CFS cases in Japan some underestimation or overestimation could not be avoided. However, these cannot account for the considerable difference in the prevalence and incidence of this disease between Japan and Western countries.

Reported sex ratios (female/male) of CFS have ranged from 1.2 to 3.8, and are mainly between 1.3 and 2.0[8,9,19-24], which is reasonably consistent with the 1.6 obtained in this survey. The average age of the prevalent cases was reported to range from 31.1 to 45.4 years old[8,9,19,20,22,25], which is also consistent with the average age of 36.7 years old observed in the present study. Thus, it is reasonable to suggest that these selected demographic features of CFS cases reported in Japan are generally consistent with those in Western countries.

The percentage of postinfectious cases among the sporadic cases was reported to be 91% in Minnesota[22], 75% in Australia[9], and 56% in Toronto[19]. In the present survey, however, the proportion of 14.8% was considerably lower than those reported from Western countries. A lower proportion of postinfectious cases may be a trend in CFS epidemiology in Japan along with an absence of apparent outbreaks.

In this report, it was assumed that hospital departments which did not return the reporting formats had also experienced a similar number of CFS cases. This assumption is partly ascertained because the proportions of replies reporting experiences with CFS cases were essentially the same before and after the reminder.

ACKNOWLEDGEMENT

This survey was conducted in fiscal year 1993 as a task of the CFS Study Group of Japan granted by the Ministry of Health and Welfare, Japan.

REFERENCES

1. Holms GP, Kaplan JE, Gantz NM, Komaroff AL, Schonberger LB, Straus SE, et al. CFS : A working case definition. Ann Intern Med. 1988 ; 108 : 387-389.
2. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A, et al. The CFS : A comprehensive approach to its definition and study. Ann Intern Med. 1994 ; 121 : 953-959.
3. White DN, Burtch RB. Iceland disease : A new infection simulating acute anterior poliomyelitis. Neurology 1954 ; 4 : 506-516.
4. Crowley NC, Nelson M, Stovin S. Epidemiological aspects of an outbreak of encephalomyelitis at the Royal Free Hospital, London, in the summer of 1955. J Hygiene 1957 ; 55 : 102-122.
5. Poskanzer DC, Henderson DA, Kunkle EC, Kalter SS, Clement WB, Bond JO. Epidemic neuromyasthenia : An outbreak in Punta Gorda, Florida. N Eng J Med 1957 ; 257 : 356-364.
6. Parish JG. Early outbreaks of 'epidemic neuromyasthenia'. Postgraduate Med J 1978 ; 42 : 711-717.
7. Jenkins R. Epidemiology: Lessons from the past. Br Med Bull 1991 ; 47 : 952-965.
8. Levine PH, Jacobson S, Pocinki AG, Cheney P, Peterson D, et al. Clinical, epidemiologic, and virologic studies in four clusters of the chronic fatigue syndrome. Arch Intern Med 1992 ; 152 : 1611-1616.
9. Lloyd AR, Hickie I, Boughton CR, Spencer O, Wakefield D. Prevalence of chronic fatigue syndrome in an Australian population. Med J Aust 1990 ; 153 : 522-528.
10. Klonoff DC. Chronic fatigue syndrome. Clin Infect Dis 1992 ; 15 : 812-823.
11. Gunn WJ, Connell DB, Randall B. Epidemiology of chronic fatigue syndrome : The Center for Disease Control study. Chronic Fatigue Syndrome, Wiley, Chichester (Ciba Foundation Symposium 173) 1993 ; 83-101.
12. Ho-Yen DO, McNamara I. General practioners' experience of the chronic fatigue syndrome. Br J Gen Pract 1991 ; 41 : 324-326.

13. Ho-Yen DO. The epidemiology of post viral fatigue syndrome. Scot Med J 1988 ; 33 : 368-369.
14. Behan PO, Behan WMH, Bell EJ. The postviral fatigue syndrome--an analysis of the findings in 50 cases, J Infect 1985 ; 10 : 211-222.
15. Holmes GP, et al. Chronic fatigue syndrome : A working case definition. Ann Int Med 1988 ; 108 : 387-389.
16. Kitani T, Kuratsune H, Yamaguchi K. Diagnostic Criteria for CFS proposed by the CFS Study Group in Japan. Jap J Clin Med 1992 ; 50 : 2600-2605 (in Japanese).
17. Ohno Y, et al. Mannual of the nationwide epidemiological survey for the estimation of number of cases with intractable diseases. Epidemiology of Intractable Diseases Research Committee, Ministry of Health and Welfare 1990 (in Japanese).
18. Grufferman S. Issues and problems in the conduct of epidemiologic research on chronic fatigue syndrome. Rev Infect Dis 1991 ; 13(Suppl) : S60-67.
19. Salit IE. Sporadic postinfectious neuromyasthenia. Can Med Assoc J 1985 ; 133 : 659-663.
20. Murdoch JC. Myalgic encephalomyilitis (ME) syndrome--an analysis of the clinical findings in 200 cases. NZ Family Phisician 1987 ; 14 : 51-54.
21. Manu P, Lane T, Matthews DA. The frequency of the chronic fatigue syndrome in patients with symptoms of persistent fatigue. Ann Inern Med 1988 ; 109 : 554-556.
22. Peterson PK, Schenk CH, Sherman R. Chronic fatigue syndrome in Minnesota. Minnesota Med 1991 ; 74 : 21-26.
23. Ho-Yen DO. General practitioner's experience of the chronic fatigue syndrome. Br J Gen Prac 1991 ; 41 : 324-326.
24. Hilgers A, Krueger GRF, Lembke U, Ramon A. Postinfectious chronic fatigue syndrome : Case history of thirty-five patients in Germany. In Vivo 1991 ; 5 : 201-206.
25. Bates DW, Schmitt W, Buchwald D, Ware N, Lee J, Thoyer E, Kornish RJ, Komaroff AL. Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. Arch Intern Med 1993 ; 153 : 2759-2765.