5 まとめ

難治性肝疾患の全国疫学調査による2004年1年間の患者数は，PBCが12,800人程度，AIHは9,500人程度，FHは430人程度と推定された．

謝　辞

調査に関するご指導を賜りました1998年～2004年までの難治性の肝疾患に関する調査研究班・主任研究者の戸田剛太郎先生，同事務局長の銭谷幹男先生に深く感謝致します．調査にご協力下さいました多くの先生に深謝致します．資料の取りまとめをご担当下さいました名古屋大学大学院医学研究科健康社会医学専攻社会生命科学大講座予防医学・医学推計・判断学事務の服部秀美様に感謝致します．本研究は，厚生労働省厚生労働科学研究費補助金（難治性疾患克服研究事業）からの補助を受けて，難治性の肝・胆道疾患に関する調査研究班と特定疾患の疫学に関する研究班との共同で行われた．

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Reprinted from HEART, June 2007, Vol 93, p 711-715

HEART FAILURE AND CARDIOMYOPATHY

Prognosis and prognostic factors in patients with hypertrophic cardiomyopathy in Japan: results from a nationwide study

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Heart 2007;**93**:711–715. doi: 10.1136/hrt.2006.095232

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Accepted 26 September 2006
Published Online First 3 November 2006

Objective: To investigate prognosis and prognostic factors in patients with hypertrophic cardiomyopathy (HCM) in Japan.
Design: A nationwide epidemiological study.
Setting: Hospitals selected randomly from among all hospitals in Japan.
Patients: Clinical and epidemiological information for 2155 patients with HCM were collected in 1999.
Main outcome measures: Patients were classified on the basis of baseline prognostic factors. Survival rates up to 5 years were calculated by Cox's proportional hazard model for 1605 patients.
Results: During the follow-up period, 241 deaths were recorded. The crude 5-year survival rate for the entire cohort was 86% (95% CI 84 to 88), and annual mortality ranged from 2.2% to 3.0%. A higher cardiothoracic ratio on chest x ray (HR 1.61; 95% CI 1.26 to 2.05, with 1 SD (6.2%) increase), a lower left ventricular ejection fraction (HR 1.42; 95% CI 1.20 to 1.69, with 1 SD (13%) decrease) and the presence of left bundle branch block (HR 3.14; 95% CI 1.28 to 7.71) were independently associated with a poorer prognosis, whereas the presence of apical hypertrophy at baseline (HR 0.58; 95%CI 0.36 to 0.92) predicted a better chance of survival.
Conclusions: The nationwide survey of patients with hypertrophic cardiomyopathy yielded important information on its prognosis and prognostic factors. These observations afford, for the first time, a measure of risk stratification in patients with HCM in Japan.

Hypertrophic cardiomyopathy (HCM) is a relatively common cardiac disease that has been the subject of intense investigation over the past few decades, especially in Western populations.[1–5] By contrast, few large-scale and prospective studies have been conducted to examine the prognosis and prognostic factors of HCM in the far-east Asian populations. Asian patients may differ considerably from Western patients in the pattern of hypertrophy distribution and clinical manifestations.[1 6] Because of marked heterogeneity in clinical expression, it is necessary to identify the prognostic factors and their association with death, within the broad disease spectrum of HCM, to obtain a realistic clinical perspective in the far-east Asians.

In 1999, the Japanese research committees on epidemiology of intractable diseases undertook a nationwide epidemiological survey of idiopathic cardiomyopathy in Japan to describe the detailed clinicoepidemiological features for appropriate health service planning. A detailed description of the clinicoepidemiological features of patient characteristics have been presented elsewhere.[7] The estimated total number of patients with HCM was 21 900 (95% confidence interval (CI) 20 600 to 23 200), with a crude prevalence rate of 17.3/100 000.[8] The purpose of this study was to evaluate the 5-year survival rate according to the presence and/or level of baseline prognostic factors from this nationwide study on patients with HCM in Japan, and to clarify factors that can predict the prognosis of this disease independently and effectively.

METHODS

The nationwide survey on cardiomyopathies, including HCM, was designed to show the prevalence and clinical features of HCM in Japan. Detailed methods have been described elsewhere.[7 8] The Japanese Research Committee on idiopathic cardiomyopathies prepared classification criteria, which were on the basis of the report of the World Health Organization/International Society and Federation of Cardiology task force on the definition and classification of cardiomyopathies.[9 10] HCM was characterised by disproportionate hypertrophy of the left ventricle and occasionally also of the right ventricle, which typically involves the septum more than the free wall, but occasionally is concentric. Specific heart muscle disease, defined as heart muscle disease of known aetiology or associated with disorders of other systems, was excluded from the survey. The hospitals included in each survey were randomly selected by stratified sampling of all departments of internal medicine, cardiovascular medicine and paediatrics throughout Japan, identified in a directory of names, department addresses and number of hospital beds obtained from the Ministry of Health and Welfare in Japan.

Data acquisition

The survey investigated patients with HCM as either inpatients or outpatients in the randomly selected departments in 1998. Firstly, the questionnaire for the survey on the number of patients with HCM was mailed directly to 2414 departments in January 1999. Of those 2414 departments, 1409 (58.4%) departments responded, reporting data on 7262 patients. The second survey was performed to collect detailed clinical data. From a total of 577 departments that reported one or more patients with HCM in the first survey, 235 departments agreed to participate in the second survey and detailed clinical data were collected from a total of 2155 patients. Patients who died before 1998 or those visiting a hospital for the first time after

Abbreviations: AF, atrial fibrillation; BMI, body mass index; HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LV, left ventricular; NYHA, New York Heart Association

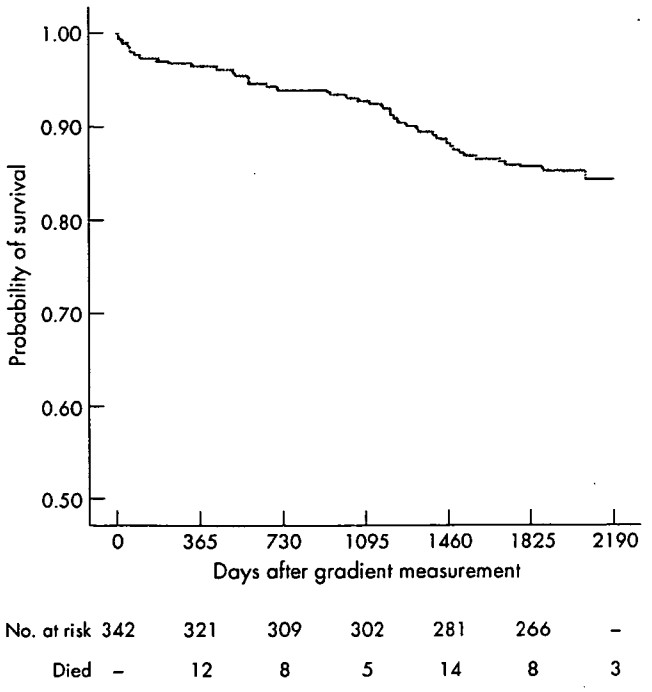

Figure 1 Kaplan–Meier survival curve of 342 patients with hypertrophic cardiomyopathy after first diagnosis in 1998.

1999 were excluded from this study as inappropriate cases, as were patients whose data were reported from more than one department (duplicate cases). The questionnaire requested detailed clinicoepidemiological information for each patient, including age, sex, symptoms and New York Heart Association (NYHA) functional class. Data from a physical examination and baseline laboratory measurements, including standard 12-lead ECG, chest *x* ray and echocardiography (for measuring left ventricular ejection fraction (LVEF), thickness of interventricular septum (IVS), and left ventricular (LV) shape), were available. LV hypertrophy by ECG was determined by left high voltage (Minnesota code: 3–1 or 3–3). M mode echocardiographic assessment for LVEF and two dimensional echocardiographic assessment for maximum IVS thickness and LV shape were conducted for nearly all patients. Apical hypertrophy was defined as LV wall thickness confined to the most distal region at the apex below the papillary muscle level. Data on blood tests and cardiac catheterisation were only obtained for a small portion of the subjects and, therefore, we did not include them in our analysis.

Medication

Patients were generally given medical treatment as reported previously from this study.[7] Medical treatment was directed toward control of symptoms, arrhythmias, coexisting hypertension and prevention of embolisation.

Follow-up

Of 235 departments reporting 2155 patients, 182 departments (reporting 1693 patients) agreed to participate in the 5-year follow-up survey. Patients' vital status was reported by doctors, with vital status for 607 withdrawn cases obtained from the residence-based register of the local government for each patient. However, follow-up was not possible for 88 patients, so these patients were excluded. Therefore, the 5-year follow-up was completed for 1605 (74.5%) patients. With regard to follow-up bias, we found no significant difference for sex, age, body mass index (BMI) and NYHA functional class distribution between those who participated and those who did not participate in the follow-up. The ethical committees of the Kanazawa Medical University and the Kyoto University Graduate School of Medicine approved the study protocol.

Statistical analysis

Survival estimates were calculated using the Kaplan–Meier method, and the 5-year survival probability was calculated for the overall cohort. Patients were classified on the basis of baseline prognostic factors. The significant differences in survival rates among classifications were tested by the log rank test for trends. Hazard ratios (HRs) according to baseline characteristics were calculated by Cox's proportional hazard model, with 95% CI up to the longest follow-up time of 2190 days. The model includes variables with a p value <0.05 by the log rank test for the 5-year survival and some other important variables. HRs for continuous variables were reported for 1 SD change. The log minus log plotted against survival time for each covariate did not show any deviation from the proportionality assumption. The data were analysed with SPSS V.12.0J. All reported significance levels are $p<0.05$ (two tailed tests).

RESULTS

Of the 1605 patients identified at baseline, 241 (15%) died during the follow-up period. The probability of actuarial survival was calculated from the time of the baseline survey for 342 patients who were initially diagnosed in 1998 (fig 1). The crude 5-year survival rate for those diagnosed in 1998 was 86% (95% CI 82 to 90). The crude 5-year survival rate for the whole cohort was 86% (95% CI 84 to 88).

Table 1 shows the baseline characteristics of the patients. Of the 1605 patients in the study, 30.3% were women and 57.1% were aged >60 years. Most patients (94.5%) had experienced none or only mild symptoms (NYHA function classes I or II) at baseline.

Clinical, echocardiographic and standard 12-lead ECG variables were examined for an association with survival during the follow-up period (table 1). Crude 5-year survival rates significantly decreased with decreasing BMI, higher grade of NYHA classification, presence of atrial fibrillation (AF) or flutter, presence of left bundle branch block (LBBB), increasing CTR, decreasing LVEF and decreasing number of hospital beds. The presence of apical hypertrophy was associated with a better survival rate. There was no significant difference in the crude survival rate between men and women. Thickness of IVS, family history of HCM, the presence or absence of hypertension, and smoking and drinking habits were not associated with the 5-year survival rates.

Table 2 presents the results of proportional hazard analysis. The model includes nine variables, which were statistically significant in table 1 (age, BMI, diabetes mellitus, NYHA classification, rhythm, LBBB, apical hypertrophy, CTR and LVEF), and two other important variables (sex and IVS thickness). The multivariate-adjusted HR for all-cause mortality was not significantly different between men and women. The presence of LBBB was an independent predictor of death (HR = 3.14), and the presence of apical hypertrophy, seen in 41.1% of study patients, resulted in a better prognosis (HR = 0.58). The multivariate-adjusted HR for death significantly and independently increased with a 1 (6.2%) SD increase of CTR, and with a 1 (13%) SD decrease of LVEF. The Wald statistic showed that these two factors had the strongest relationship with prognosis of all the factors in the model. BMI and IVS thickness were not independently related to prognosis. A backward elimination stepwise analysis to check if there is confounding among the non-significant factors, did not find a significant difference with the results in the original model.

Table 1 Five-year survival rates for predictive variables in patients with hypertrophic cardiomyopathy in Japan

	n (%)	Deaths	5-year survival rate	p Value for log rank test
Sex				
Men	1118 (69.7)	142	0.87	
Women	487 (30.3)	85	0.84	0.151
Age (years)				
<30	157 (9.9)	14	0.90	
30–59	531 (33.1)	42	0.92	
≥60	917 (57.1)	158	0.82	<0.001
BMI (kg/m^2)				
<20	182 (14.0)	40	0.77	
20–24.9	733 (56.3)	92	0.87	
≥25	387 (29.7)	39	0.90	<0.001
Family history of HCM				
Yes	207 (16.9)	27	0.87	
No	1015 (83.1)	132	0.87	0.991
Hypertension				
Yes	456 (31.2)	68	0.85	
No	1005 (68.8)	129	0.87	0.336
Diabetes mellitus				
Yes	131 (8.9)	30	0.76	
No	1332 (91.1)	178	0.86	0.002
Alcohol drinking				
Yes	475 (36.3)	71	0.85	
No	832 (63.7)	113	0.86	0.525
Smoking				
Yes	535 (39.3)	68	0.87	
No	825 (60.7)	115	0.86	0.524
NYHA classification				
I	908 (65.3)	89	0.90	
II	406 (29.2)	62	0.84	
III	62 (4.5)	28	0.53	
IV	14 (1.0)	7	0.43	<0.001
Rhythm				
Sinus rhythm	1347 (91.4)	161	0.88	
Atrial fibrillation	113 (7.7)	28	0.74	
Atrial flutter	13 (0.9)	4	0.68	<0.001
Left ventricular hypertrophy (detected by ECG)				
Yes	1021 (68.9)	132	0.86	
No	461 (31.1)	61	0.87	0.814
LBBB				
Yes	45 (3.3)	15	0.66	
No	1303 (96.7)	165	0.87	<0.001
Apical hypertrophy				
Yes	532 (41.1)	56	0.89	
No	763 (58.9)	110	0.85	0.031
CTR (%)				
<50	353 (26.7)	25	0.93	
50–54	484 (36.7)	54	0.89	
55–59	283 (21.4)	36	0.87	
≥60	200 (15.2)	59	0.70	<0.001
LVEF (%)				
<50	67 (5.9)	27	0.59	
50–59	88 (7.8)	19	0.77	
60–69	243 (21.5)	29	0.88	
70–79	439 (38.9)	49	0.89	
≥80	292 (25.9)	31	0.89	<0.001
Thickness of IVS (mm)				
<11	145 (9.8)	17	0.88	
11–15	540 (36.5)	62	0.88	
16–20	476 (32.1)	68	0.85	
21–25	208 (14.0)	37	0.83	
≥26	112 (7.6)	18	0.83	0.255
Hospital beds				
<299	140 (8.9)	27	0.79	
300–399	93 (5.9)	19	0.80	
400–499	121 (7.7)	14	0.88	
≥500	360 (22.8)	60	0.83	
University hospital	867 (54.8)	93	0.89	0.002
Time from diagnosis (years)				
<1	463 (30.6)	62	0.86	
1–1.9	116 (7.7)	16	0.85	
2–2.9	144 (9.5)	15	0.89	
3–3.9	97 (6.4)	14	0.85	
4–4.9	97 (6.4)	14	0.85	
5–9.9	312 (20.6)	35	0.89	
≥10	283 (18.7)	51	0.81	0.231

BMI, body mass index; CTR, cardiothoracic ratio; HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 2 Multivariate-adjusted HRs of predictive variables for all-cause mortality in patients with hypertrophic cardiomyopathy

	Adjusted HR* (95% CI)	Wald statistic	p Value
Sex			
Men	1		
Women	0.77 (0.46 to 1.30)	1	0.324
Age			
1-year increase	1.02 (1.01 to 1.04)	8.2	0.004
Diabetes mellitus			
Yes	1.03 (0.47 to 2.28)	<0.1	0.941
No	1		
NYHA classification			
I	1		
II	1.19 (0.74 to 1.94)	0.5	0.472
III	3.41 (1.75 to 6.67)	12.9	<0.001
IV	2.85 (0.87 to 9.39)	3.0	0.084
Rhythm			
Sinus rhythm	1		
Atrial fibrillation	1.36 (0.75 to 2.46)	1.0	0.306
Atrial flutter	0.62 (0.16 to 2.30)	0.5	0.471
LBBB			
Yes	3.14 (1.28 to 7.71)	6.2	0.013
No	1		
Apical hypertrophy			
Yes	0.58 (0.36 to 0.92)	5.4	0.021
No	1		
CTR† (increase of 6.2%)	1.61 (1.26 to 2.05)	14.4	<0.001
BMI† (increase of 3.4 kg/m^2)	0.80 (0.63 to 1.01)	3.7	0.056
Thickness of IVS† (increase of 5.8 mm)	1.15 (0.94 to 1.40)	1.9	0.163
LVEF (decrease of 13%)	1.42 (1.20 to 1.69)	16.4	<0.001

BMI, body mass index; CTR, cardiothoracic ratio; IVS, interventricular septum; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
*All variables are included in the same model.
†Hazard ratio for 1 SD increase or decrease; value of 1 SD given in parentheses.

DISCUSSION

In this paper, we report the crude probability of death and the HRs for all-cause mortality by baseline prognostic factors, from a nationwide study of HCM in Japan. To our knowledge, this is the first nationwide follow-up survey in Japan conducted on patients with HCM.

One methodological issue in this survey involves the diagnostic criteria used. In 1995, the World Health Organization/International Society and Federation of Cardiology task force reported a new definition and classification of cardiomyopathy in which the cardiomyopathies were defined simply as diseases of the myocardium associated with cardiac dysfunction.[11] However, we used the definition and classification provided by the earlier task force of 1980,[9 10] in which idiopathic cardiomyopathy was distinguished from other specific heart muscle diseases. Our reasons for doing this were, firstly, that nearly all cardiologists and specialists in general medicine in Japan have been applying this definition to their diagnosis of cardiomyopathies for a long time; and secondly, that numerous previous reports have also used the same definition, allowing us to compare our data with those reports.

General clinical outcome

Several previous clinical studies on the natural history and prognosis of HCM have been based on populations of selected patients from referral centres,[12–14] and therefore, on the basis of different levels of care and management, various prognoses would be expected. The clinical outcome and perception of prognostic factors in HCM is profoundly affected by a bias in patient selection.[15] However, our study is free from this referral bias since patients were recruited from all over the nation and from different diagnostic centres.

The average (SD) age at entry into study was 58.0 (17.5) years. Both the overall crude probability of 5-year survival in our study (86%) and the annual mortality (2.2–3.0%) were comparable with the results from Western studies,[14 16] which were based on selected referral centres. According to previous report,[8] the male/female ratio for HCM is 2:3 in Japan. In our study, the probability of survival did not differ between women and men, a finding which is consistent with previous data on sex comparisons of survival in patients with HCM.[16] However, in Chinese patients, HCM was found to have a worse clinical outcome in female patients.[13] The reason for this inconsistency between our data and Chinese patients is not clear, but the small number of participants in the Chinese study and the point that less female than male patients were in the stage I of the NYHA function class in their study may explain the difference with our result.

Prognostic factors

Our results suggest for the first time that a simple chest *x* ray could be a reliable prognostic predictor in HCM. Although a CTR of 55–59% (21.4% of study patients) posed a slight increase in the risk of mortality, a CTR of >60% (15.2% of study patients) was strongly associated with a poorer prognosis. LVEF at baseline was also found to be a significant predictor of all-cause mortality in our study, with an LVEF of <60% (13.7% of study patients) associated with poorer prognosis. Progression of HCM to LV dilatation and systolic dysfunction sometimes occurs, although the mechanism of this is not fully understood.[17] However, data are limited on the prognosis of different LVEF levels in patients with HCM. Our findings confirmed the result of a previous study involving 10 patients with HCM, which concluded that an LVEF of <50% was associated with poor prognosis.[18]

Apical hypertrophy has been associated with a more benign prognosis and rarely with cardiovascular mortality and morbidity in Western populations of patients with HCM.[19 20] Our data support this finding, as patients with apical hypertrophy had a better prognosis in the multivariate model. Previous studies in the Japanese population have also indicated a benign prognosis in patients with this condition.[21 22]

A direct relationship between LV wall thickness and the risk of sudden death or heart failure-related death has been reported in patients with HCM.[23–25] Our data did not support this finding, as LV wall thickness did not show a significant relationship with prognosis. Our results support previous findings that suggest LV wall thickness should not be considered as an isolated risk factor for mortality due to cardiovascular diseases in patients with HCM.[26 27] Olivotto *et al*[27] proposed that the presence of LV hypertrophy might be a potential risk factor for sudden death only in those patients diagnosed with HCM at a very young age.

In a community-based HCM study, AF was reported to be a substantial risk factor for heart failure-related mortality and severe functional disability.[28] The prevalence of AF was lower (7.7% of study patients) in our study than the 22% seen in this previous report.[28] In our study, the crude survival rate for all-cause mortality in patients with AF at baseline was significantly lower than for those patients with sinus rhythm. However, the significant relationship with AF disappeared in the multivariate model. We observed that the presence of LBBB at baseline was associated with a poorer prognosis on multivariate analysis. The infrequent occurrence of LBBB in our study (3.3%) was comparable with previous data, which showed a prevalence of 6% among 204 patients with obstructive HCM and free from obstructive coronary artery disease.[29]

Study limitations

Although the follow-up time in our study was limited to 5 years, shorter than follow-up times in previous studies,[13 20 27] our study group was an average of 10 times larger than that of those studies, thus covering a comparable number of patient-years for the subgroups of baseline prognostic factors. A limitation of this study, which is shared by other studies,[13 26] is that a single measurement of prognostic factors, although reproducible and practical for clinical purposes, does not accurately reflect the total burden of predictors in individual patients. Another limitation of this study is that we failed to differentiate HCM-related deaths including sudden deaths and deaths caused by end-stage cardiac failure from other causes of mortality, and we reported all-cause mortality as our main outcome.

CONCLUSIONS

HCM has relatively good prognosis in Japanese patients. A poorer prognosis in HCM is predicted by high cardiothoracic ratio, low LVEF and the presence of LBBB, with a better prognosis in patients with apical hypertrophy. The presence of hypertension, AF and the level of IVS thickness were not independent predictors of prognosis during the 5-year follow-up period.

This study was supported by a grant-in-aid for the Epidemiology of Intractable Diseases Research Committee and a grant-in-aid for Idiopathic Cardiomyopathy Research Committee from the Ministry of Health and Welfare of Japan.

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Competing interests: None declared.

We disclose that there are no other financial, personal or professional relationships with other people or organisations that could be perceived as conflicts of interest, or as potentially influencing or biasing this work.

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特発性大腿骨頭壊死症の疫学

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特定疾患である特発性大腿骨頭壊死症は発生がまれであるため，本邦における疫学は主として全国規模の調査により明らかにされてきた。本稿では，厚生労働省（あるいは旧厚生省）の研究班で実施されてきた調査を中心に，本疾患の臨床疫学特性および規定要因を概括する。

Epidemiology of Idiopathic Osteonecrosis of the Femoral Head in Japan.

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The Ministry of Health, Labour and Welfare (MHLW) designates idiopathic osteonecrosis of the femoral head (ION) as so-called "intractable diseases" and has been promoting research. To summarize descriptive or analytic epidemiology of the ION in Japan, we present findings obtained through nationwide studies with the support of MHLW.

はじめに

疫学は，その手法により記述疫学と分析疫学に大別される。記述疫学とは，「疾病の流行状況を把握し，その特徴と関連を示す他の現象を見出すことによって，その流行に関与する要因を"推定"する」ものである。一方，分析疫学とは「疾病の流行に関与すると推定される要因を"検証"する」手法である。

特定疾患である特発性大腿骨頭壊死症（idiopathic osteonecrosis of the femoral head：ION）は発生がまれであるため，本邦における疫学は主として全国規模の調査により明らかにされてきた。本稿では，厚生労働省（あるいは旧厚生省）の研究班で実施されてきた調査を中心に，本疾患の臨床疫学特性および規定要因を概括する。

記述疫学

記述疫学は主として，疾病の全体像を把握する

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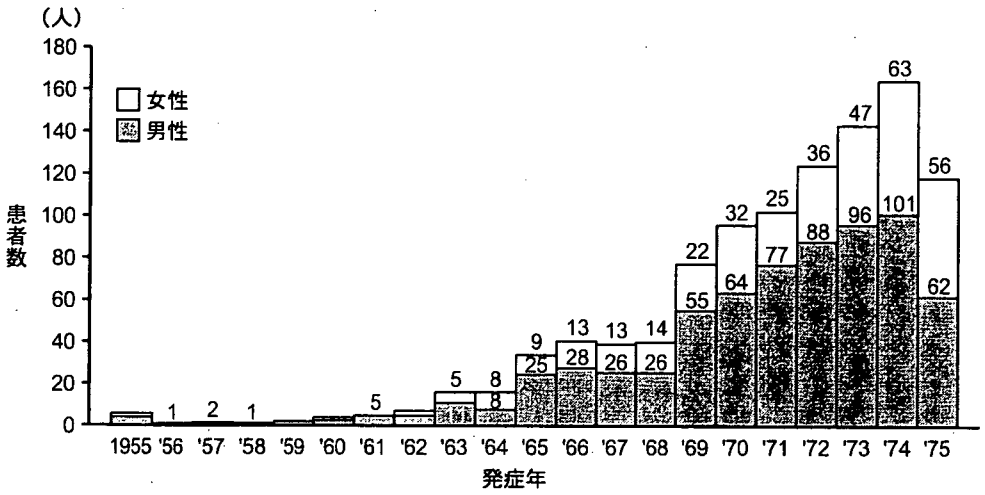

図1　ION の患者発生数の推移

1955 ～ 1976 年の新患症例 1,155 人について，発症年別に集計している。発生数は 1965 年より増加し，1969 年以降に急増を認める。なお，1975 年の患者数が減少してみえるのは，発症年で図示しているため当該年の新患の一部が 1974 年に移動したことによる。

ION：特発性大腿骨頭壊死症　　（文献 1 より）

ための基本情報を得ることが目的である。しかし，当該疾病の病因論展開の糸口を提供するという観点からも，重要な位置づけを有する。

1．全国調査

本邦における全国調査は，厚生省「ION 調査研究班」が 1976 ～ 1977 年にかけて独自に実施したものが最初であろう[1)2)]。全国 857 病院のうち「ION 症例あり」と回答した 199 病院を対象とし，報告された新患症例 1,155 人について発症年別に集計した結果，1969 年頃から患者数が急増していることが示唆された（**図1**）。その後も「ION 調査研究班」独自の全国調査が 2 回実施され[2)～4)]，基本的な臨床疫学特性が明らかにされてきた。さらに，1995 年に厚生省「難病の疫学調査班」と共同で実施した全国疫学調査では，1994 年の年間受療患者数が初めて推計された[2)5)]。

直近の全国疫学調査は，厚生労働省「ION に関する研究班」と「特定疾患の疫学に関する研究班」が共同で 2005 年に行っている[6)]。1995 年の全国疫学調査と同じく，既に確立されたプロトコール[7)]に従って実施した。全国の整形外科から，層化無作為抽出法にて選定した 999 科を対象に一次調査を実施した結果，回答が得られた 577 科（58%）から 5,612 人の患者数が報告された。これにより，2004 年 1 年間の受療患者数は 11,400 人（95%信頼区間：10,100 ～ 12,800），新患数は約 2,200 人と推定された。二次調査では 178 科より受療患者 1,502 人の情報を収集し，**表1**に示すような特性の概要を得ている。

2．定点モニタリングシステム

上述のような全国調査は，確度が高い疫学情報を得ることができる一方，多大な労力を要するため度々の実施は現実的に困難である。このような点を踏まえ，厚生労働省「ION に関する研究班」で

ION：idiopathic osteonecrosis of the femoral head（特発性大腿骨頭壊死症）

表1　2005年実施のION全国疫学調査：二次調査結果の概要

全国の整形外科から層化無作為抽出法にて選定した999科のうち，178科から報告されたION患者1,502人の臨床疫学特性を集計した。

- 現在の年齢のピーク：男女ともに50代
- 確定診断時年齢のピーク：男性は40代，女性は30代
- 誘因の分布
  - ステロイド全身投与歴あり 51%・・・対象疾患はSLEが最多（31%）
  - アルコール愛飲歴あり　31%
  - 両方あり　3%
  - 両方なし　15%
- 確定診断時の病型分類：Type C-2が最多（52%）
- 確定診断時の病期分類：Stage 2が最多（28%）
- 手術：60%に施行・・・内訳は人工骨頭・人工関節置換術65%，骨切り術25%

ION：特発性大腿骨頭壊死症，SLE：全身性エリテマトーデス　（文献6より）

は「定点モニタリングシステム」を運営し，継続的な情報収集を行っている。本システムは，当該研究班の班員が所属する医療施設を定点として，新患および手術症例を所定の様式により逐一（あるいは随時）報告し，登録するものである[8]。1997年6月に開始し，1997年1月以降の症例について報告を得ている。2006年12月31日現在，データベースに新患症例1,722人，手術症例1,242人を蓄積しており，基本的臨床疫学特性を随時集計している。

本システムにより収集した情報は，全国疫学調査結果と比較して，ION確定診断時年齢が低く，骨切り術施行の頻度が多い傾向があるものの，性比や誘因等，その他の基本的特性に関しては統計学的に有意な相違点を認めないことが示されている。さらに，本システムにより全国疫学調査における報告新患症例の約40%の情報をカバーすることも試算されており，より効率的に記述疫学特性を把握できる有効な手法と考えられる[9]。

分析疫学

記述疫学により得られた「ION患者の31%にアルコール愛飲歴あり」という知見は，IONとアルコールの関連を強く示唆するが，本質的に「ION患者の31%に朝夕毎日歯磨きをする習慣あり」という情報と変わりない。記述疫学を通じて設定された仮説は，分析疫学による検証を経ることによって，はじめて関連の程度や因果性が明らかになる。

分析疫学の研究デザインとしては，介入研究，コホート研究，症例・対照研究が該当する。このうち，IONのように発生がまれな疾病に関しては，実行可能性および費用の面から，症例・対照研究デザインを選択するのが最も合理的である。

1．飲酒との関連

本邦における症例・対照研究結果は，これまでに2編報告されている[10][11]。Matsuoらの研究は西日本の4医療施設をベースに実施し，Hirotaらの研究は厚生省「ION調査研究班」と「難病の疫学調査研究班」が共同で全国20施設をベースに実施したものである。いずれも非ステロイド性（ステロイド全身投与歴を有さない）ION患者を症例とし，対照は症例ごとに医療機関，初診日，性，年齢をマッチさせて選択している。飲酒歴については，Matsuoらは電話インタビューにより，Hirotaらは自記式質問表票により情報を得ている。

両研究ともに，IONに対する飲酒のオッズ比

表2　非ステロイド性ION に対する飲酒の影響：2つの症例・対照研究結果の比較

両研究ともに，各要因のレベルが上昇するに従ってオッズ比も増大している。また，現在の飲酒量，積算飲酒量のいずれもがIONのリスクを増大させていることから，飲酒はION発生に即時効果と累積効果の両者を有していると考えられる。

要因	OR (95%CI またはp値)	
	Matsuo ら	Hirota ら
現在の飲酒習慣		
飲酒歴なし	1.0	1.0
禁酒者	4.0 (0.6～26.0)	1.0 (0.2～6.2)
時々飲酒	5.1 (1.4～17.5)	3.2 (1.1～9.2)
毎日飲酒	7.8 (2.6～23.6)	13.1 (4.1～42.5)
現在の飲酒量［エタノール (mL) / 週］		
非飲酒者	1.0	1.0
＜400	3.3 ($p < 0.01$)	2.9 (1.0～7.9)
400＋	11.0 ($p < 0.001$)	10.7 (3.6～31.6)
積算飲酒量［drink-years］		
飲酒歴なし	1.0	1.0
＜4,000	3.2 ($p < 0.05$)	2.2 (0.7～6.9)
4,000＋	8.3 ($p < 0.001$)	9.7 (2.6～36.1)
10,000＋	31.3 ($p < 0.001$)	12.9 (3.8～43.4)

ION：特発性大腿骨頭壊死症，OR：オッズ比，95%CI：95%信頼区間

（文献10，11より）

(OR)が上昇し，量反応関係も認められた(表2)。なお，ORとは相対危険の推定値であり，「要因を有さない者と比較して，要因を有する者が当該疾病に何倍なりやすいか」を示す指標である。Hirotaらの結果を例にとると，“飲酒歴なし”と比較して，“毎日飲酒”では13.1倍IONになりやすい(IONのリスクが上昇する)と解釈できる。また，現在の飲酒量，積算飲酒量のいずれもがIONのリスクを増大させていることから，飲酒はION発生に即時効果と累積効果の両者を有していると考えられた。

2．ステロイドとの関連

特に全身性エリテマトーデス(SLE)患者を対象とした多くの研究結果が報告されているが，長期にわたるステロイド投与状況，特に総投与量や平均投与量の把握が極めて困難であるため，必ずしも一致した結果は得られていなかった。

これらの点を踏まえ，廣田らは，「ION調査研究班」において，SLE患者あるいは腎移植患者を対象とした2つの多施設共同症例・対照研究を実施している[12][13]。過去のステロイド投与歴については，日誌形式の調査票に投与方法，剤名，投与量を担当医が記入，あるいはwall-chartの写しの提出を依頼することにより，詳細に収集している。

SLE確定診断後，あるいは腎移植後1年間のステロイド総投与量，最高投与量，1日平均投与量，およびパルス療法について検討した結果，両研究ともに1日平均投与量で最も鮮明な関連を認めた(表3)。つまり，SLE再燃時あるいは腎移植後の拒絶反応に対して，比較的多量のステロイドを長期間にわたって継続することは，ONのリスクを

OR：オッズ比，SLE：全身性エリテマトーデス

表3　ステロイド性 ION に対するステロイド投与法の影響：2つの症例・対照研究結果の比較

ステロイドのレベルは各研究における対照の三分位により分類している。両研究ともに1日平均投与量で最も鮮明な関連を認めた。

評価項目	SLE 患者			腎移植患者		
	レベル	OR (95%CI)	p 値	レベル	OR (95%CI)	p 値
総投与量 (g)	< 10.5	1		< 3.55	1	
	10.5 +	2.5 (0.7 ～ 9.0)	0.175	3.55 +	1.8 (0.3 ～ 12.2)	0.526
	28.4 +	4.6 (0.6 ～ 37.9)	0.154	5.50 +	4.3 (0.5 ～ 35.6)	0.175
	Trend : p = 0.114			Trend : p = 0.072		
最高投与量 (mg)	< 50	1		< 60	1	
	50 +	1.3 (0.5 ～ 3.1)	0.557	60 +	0.7 (0.2 ～ 2.2)	0.506
	80 +	2.8 (0.99 ～ 7.9)	0.053	70 +	1.1 (0.3 ～ 3.7)	0.851
	Trend : p = 0.061			Trend : p = 0.802		
パルス療法 (回数または mg)	0	1		0	1	
	1	3.2 (1.2 ～ 8.9)	0.024	< 1,250	0.7 (0.3 ～ 2.0)	0.524
	2 ～ 5	1.2 (0.2 ～ 7.0)	0.801	1,250 +	1.8 (0.7 ～ 4.3)	0.193
	Trend : p = 0.157			Trend : p = 0.202		
1 日平均投与量 (mg)	< 12.3	1		< 14.92	1	
	12.3 +	0.9 (0.3 ～ 2.5)	0.790	14.92 +	2.4 (0.9 ～ 6.6)	0.093
	16.6 +	3.4 (1.1 ～ 10.7)	0.034	20.40 +	5.0 (1.6 ～ 15.7)	0.006
	Trend : p = 0.032			Trend : p = 0.005		

ION：特発性大腿骨頭壊死症，OR：オッズ比，SLE：全身性エリテマトーデス，Trend：傾向性の検定，95%CI：95%信頼区間　（文献 13 より）

増大させると解釈できる。むしろ，ステロイドを短期間に多量投与することにより活動性を早期に抑制し，その後速やかに維持量まで減量することの重要性が示唆された。

3．実施中の研究について

現時点で，ステロイドは ION に対する真のリスク要因と考えられており，「ステロイド性 ION」という疾病概念も既に確立しているものの，「ステロイド非投与に対する投与のリスクの推定」が課題として残されている。また，飲酒の影響については一定の見解に達したものの，アルコールの代謝に関与する aldehyde dehydrogenase 2 (**ALDH2**) 活性と，ION リスクの違いについては十分な検討がなされていない。さらに，狭義の ION の規定要因も依然として未知である。

現在，厚生労働省「ION に関する研究班」ではこれらの問題に取り組み，ステロイド性・アルコール性などの誘因にかかわらず，すべての ION 患者を症例とした症例・対照研究を実施している。本研究の最終的な結果が得られれば，本邦における ION の規定要因に関する疫学的知見について，一応の決着がつくことになると思われる。

おわりに

いわゆる難病の疫学を明らかにすることは，患者数が少ないことに加え，疾病概念の複雑さからも極めて困難な作業である。本邦では厚生労働省

ALDH2：aldehyde dehydrogenase 2

(あるいは旧厚生省)により全国規模の共同研究が推進されてきたため，系統だった調査が行われてきたが，このような調査は諸外国でも例を見ないものである。

ION の記述疫学に関する今後の方向性については，定点モニタリング等のシステムを有効活用することにより，上質の情報をいかに効率よく収集するかが重要な課題となるだろう。また，分析疫学に関しては，ION 発症に至るステロイド投与量や飲酒量の閾値など，さらなる詳細な検討に焦点が移ってゆくと思われる。

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Statistical Data

Creutzfeldt-Jakob Disease Mortality in Japan, 1979-2004: Analysis of National Death Certificate Data

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BACKGROUND: Trend of the mortality rate of Creutzfeldt-Jakob disease (CJD) in Japan is still unclear. This study aimed to estimate annual crude mortality rates due to CJD and examine the CJD mortality trend in Japan during the period of 1979-2004.
METHODS: National death certificate data on CJD were used (CJD coded as 046.1 for ICD-9 and A81.0 for ICD-10). Trends in age-standardized mortality rates for CJD were examined by using time series analyses including the joinpoint regression analysis.
RESULTS: A total of 1,966 deaths (862 males and 1,104 females) were identified with CJD coded as the underlying-cause-of-death. The annual number of deaths and crude mortality rates peaked in 2004 at 163 (66 for males and 97 for females) deaths and 1.28 (1.06 for males and 1.48 for females) deaths per million population per year, respectively. The age-specific mortality rates rapidly increased with age between 50 and 74 years, especially among females, and sharply declined at 80+ years. Throughout the observed period, there were no significant change points, and the annual percentage changes (95% confidence intervals) were +3.09 (2.18 - 4.02) % for males and +3.90 (2.98-4.83) % and females. The total number of CJD deaths under 50 years of age was 131, and there was found no increase in the annual number of deaths for the past few years in this age group.
CONCLUSION: CJD mortality in trend data based on death certificates has significantly increased in Japan during the period of 1979-2004.
J Epidemiol 2007; 17:133-139.

Key words: Creutzfeldt-Jakob Syndrome, Regression Analysis, Mortality, Death Certificate, Japan.

Creutzfeldt-Jakob disease (CJD), the most common human prion disease or transmissible spongiform encephalopathy, is a rapidly progressive neurodegenerative disorder with a fatal outcome. It is divided into four types: sporadic, familial, iatrogenic, and variant CJD.[1] The disease has received academic as well as public attention in Japan because of iatrogenic CJD (iCJD) transmitted through cadaveric dura grafts [2-5] and variant CJD (vCJD) suspected to be associated with bovine spongiform encephalopathy (BSE).[6,7] Contaminated cadaveric dura grafts with the CJD agents were used for neurosurgery in Japan during the period of 1978-1991.[8] Miyashita reported a case with CJD, in 1991, who had received the contaminated cadaveric dural material 33 months before the onset of the disease.[9] In 2006, Yamada reported the first Japanese case of definite vCJD, who were affected at the age of 48 in 2001.[7]

A nationwide hospital-based survey on CJD, conducted in 1996, previously pointed out the increase of incidence and mortality rates of the disease during the period of 1985-1995 [10] but after then the trend of frequency of the disease in Japan has not been observed. It is important to estimate the mortality rates of CJD, and thus we examined the CJD mortality trends in Japan for the extended period of 1978-2004.

Received September 13, 2006, and accepted March 18, 2007.
This study was supported by a research grant for an epidemiological study on intractable diseases by the Ministry of Health, Labour and Welfare of the Japanese Government.
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METHODS

Data

Cause-of-death classifications are based on the International Classification of Diseases, Ninth (ICD-9) [11] and Tenth Revisions (ICD-10).[12] These documents designate CJD deaths by codes 46.1 and 331.5, and A81.0 and F02.1, respectively. In Japan, 46.1 and A81.0 are valid codes for the underlying cause-of-death for CJD during the periods of ICD-9 (from 1979 through 1994) and ICD-10 (from 1995 and thereafter). Although the grafting of the contaminated cadaveric dural material had begun in 1978, we had to skip 1978 due to unavailability of coding for CJD in the ICD-8 (from 1968 through 1978). [13]

In Japan, death certificates are systematically stored on magnetic tape data files by the Ministry of Health, Labour and Welfare. These certificates are filled in by medical doctors at hospitals or clinics, and are changed into computerized files at the Ministry. We used the mortality data (1979-2004) on CJD based on death certificates derived from the computer tapes with the permission of the Ministry. The data files used contained the codes for the underlying cause-of-death for CJD as well as basic information coded for sex, age, date and place at death, date of birth, household occupation, and place of residence where the deceased had lived. It did not contain an individual's name or residential address.

Population data were obtained from the 1975, 1980, 1985, 1990, 1995, and 2000 censuses. For each year between the censuses, population estimates were interpolated by using a linear model. The 2005 census data were not available at the time of this analysis so that the population estimates for 2001-2004 were used, being provided by the Statistics Bureau, Ministry of Internal Affairs and Communications.[14]

Statistical Analyses

The total number of deaths due to CJD from 1979 through 2004 was counted, and age-specific mortality rates were calculated according to 5-year age interval groups. The annual number of deaths from CJD was counted for each year during the observed period. In addition, the annual number of CJD deaths under 50 years of age was counted over this period. Because vCJD, which emerged in the United Kingdom in 1994, has the distinct clinical course features; the median age at death was 28 years, and most of the cases died at an age under 50 years.[6,15]

CJD mortality rates in 1979-2004 were classified and obtained in two ways: (1) The annual crude mortality rates were calculated as the number of CJD deaths per million persons per year, on the basis of the Japanese populations for the respective years aforementioned; and (2) the annual age-standardized mortality rates were calculated by the direct method[16] using the 1985 Japanese standard population.

Trends in age-standardized mortality rates for CJD were firstly examined graphically using a moving average technique, and then quadratic and cubic regression analyses were conducted to test the non-linear trend. The trends were also analyzed by using a joinpoint regression model.[17] The joinpoint regression technique is useful for delineating changes in trend data, especially when the number of change points is unknown. This method identifies the number of significant change points by performing a sequence of permutation tests of the null against alternative hypotheses to select the final model. The joinpoint regression analysis provides the estimated annual percentage change and the corresponding 95% confidence interval (CI). In addition, autocorrelation coefficients were calculated to examine the independency of residuals from the regression line.[18]

Statistical analyses were performed using SAS® version 9.1.3 and SEER*® Stat software, developed by the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute of the USA, was employed for the joinpoint regression analysis.[19]

RESULTS

Table 1 shows the sociodemographic characteristics of the deceased from CJD. Of a total of 1,966 deaths (862 males and 1,104 females), 56.2% were females, and 75.2% were persons aged 60 years and older. The household occupation for half of the deaths was being unemployed. Most deaths (95.2%) occurred at hospitals. Figure 1 shows the number of deaths and mortality rates due to CJD by 5-year age groups. The age-specific mortality rates increased rapidly with age, particularly between 50 and 74 years of age, and declined sharply in persons older than 80 years of age. The rates were slightly higher in females than males for those aged 50-79 years. There were no CJD deaths under 20 years of age.

There was a variation in the number of annual CJD deaths, from the minimum of 22 in 1979 to the maximum of 163 in 2004 (Figure 2). Figure 3 shows CJD deaths under 50 years of age. Of those, the highest annual records (10 deaths per year) occurred in 1994, 1995, and 2001. For the recent 3 consecutive years, however, the annual number of deaths slightly decreased in this age group (4 to 5 deaths per year).

Figure 4 presents annual crude mortality rates due to CJD from 1979 through 2004. The rates ranged from 0.21 /million/year in 1979 to 1.12 in 2003 for males, and from 0.17 in 1979 to 1.48 in 2004 for females.

Figures 5 and 6 display the annual age-standardized mortality rates due to CJD for males and females, respectively. According to the joinpoint regression analyses, there were no significant change points in the trends from 1979 through 2004. For each trend, the corresponding figure presents a single linear regression line fitted with age-standardized mortality rates. The estimated annual percentage changes (95% CIs) were +3.09 (2.18-4.02) % for males and +3.90 (2.98-4.83) % for females.

The trends in the annual age-standardized mortality rates for CJD were examined graphically using a moving average technique, and confirmed that the increasing trends were approxi-

mately linear. In addition, quadratic and cubic regression analyses were conducted to test the non-linear trend, but it was not statistically significant. These findings supported the results obtained from joinpoint regression analyses that showed no change points during the observational period. Autocorrelation coefficients for residuals of the regression line were small and non-significant regardless of the time intervals between data points, indicating that the deviations of annual age-standardized mortality rates from the regression line were random noise.

Table 1. Creutzfeldt-Jakob disease deaths by sex, age, household occupation, and location of death, Japan, 1979-2004.

Characteristics		n	%
Sex	Male	862	43.8
	Female	1,104	56.2
Age (year)	-19	0	0.0
	20-29	7	0.4
	30-39	25	1.3
	40-49	99	5.0
	50-59	356	18.1
	60-69	714	36.3
	70-79	626	31.8
	80+	139	7.1
Household occupation	Agriculture	162	8.2
	Self employed	199	10.1
	Employee I*	235	12.0
	Employee II†	220	11.2
	Other‡/Unemployed	1,150	58.5
Location of death	Hospital§	1,876	95.4
	Clinic§	24	1.2
	Home	54	2.7
	Nursing Home/Other	12	0.6

*: Employee I indicates a full-time worker as manager, clerk, teacher, sales person, engineer or health professional.
†: Employee II is a full-time worker other than Employee I.
‡: Other means a part-time or contingent worker.
§: Hospitals and clinics have 20 or more and 19 or less inpatient beds, respectively.

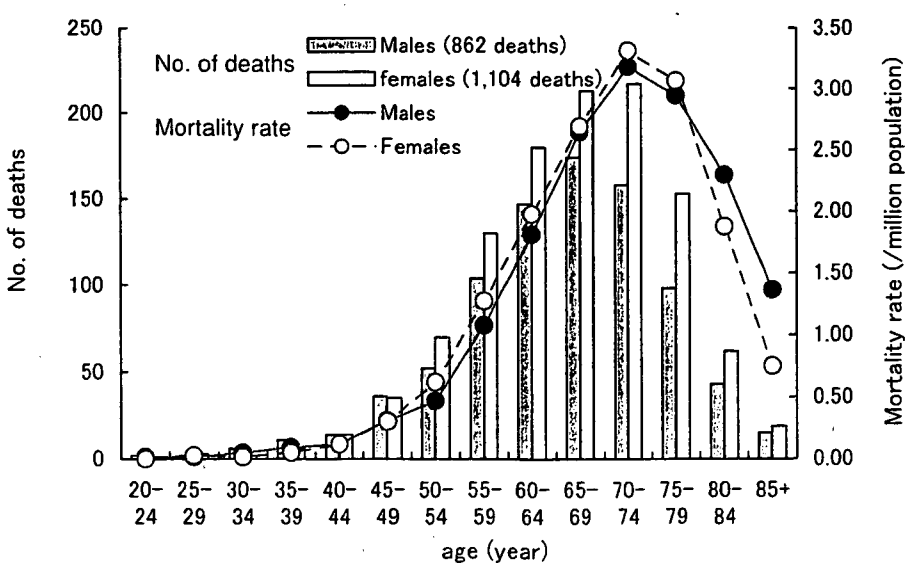

Figure 1. Number of deaths and mortality rates due to Creutzfeldt-Jakob disease by age, Japan, 1979-2004.

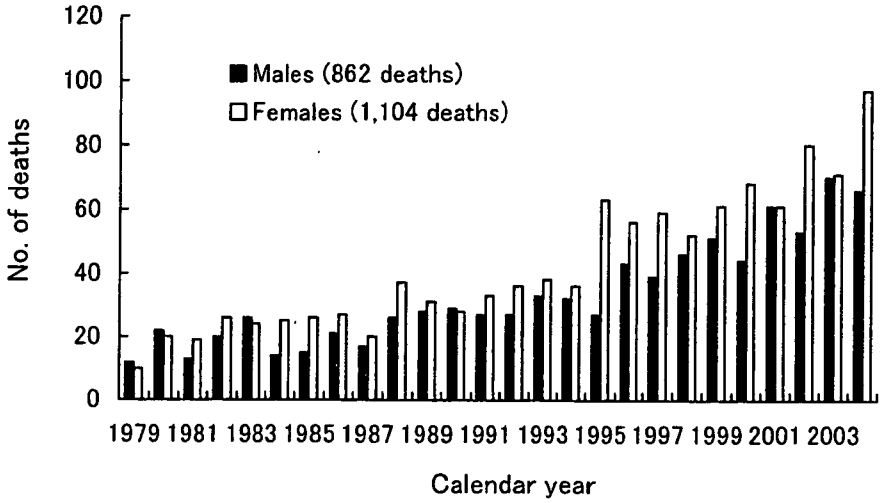

Figure 2. Annual number of deaths due to Creutzfeldt-Jakob disease, Japan, 1979-2004.

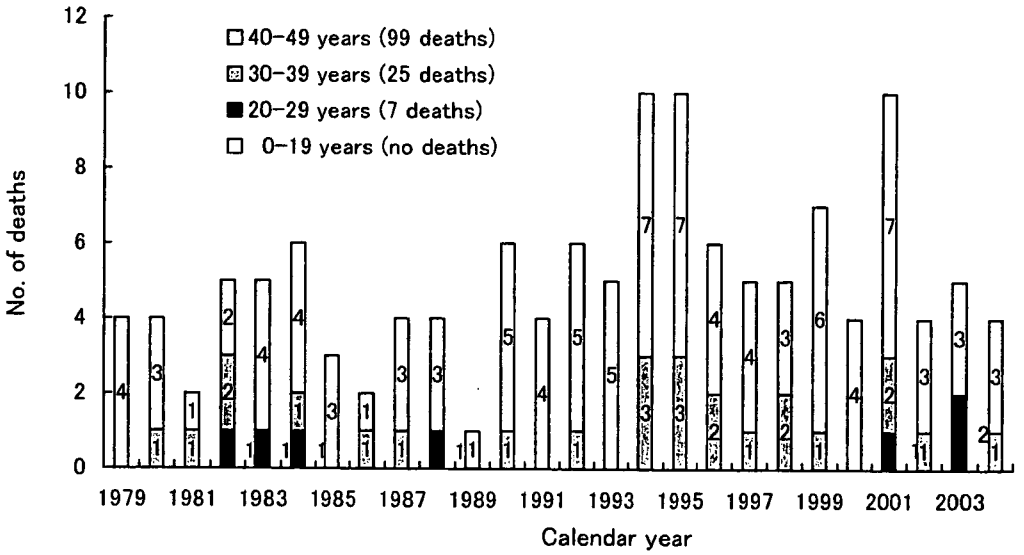

Figure 3. Annual number of deaths due to Creutzfeldt-Jakob disease under 50 years of age, Japan, 1979-2004.

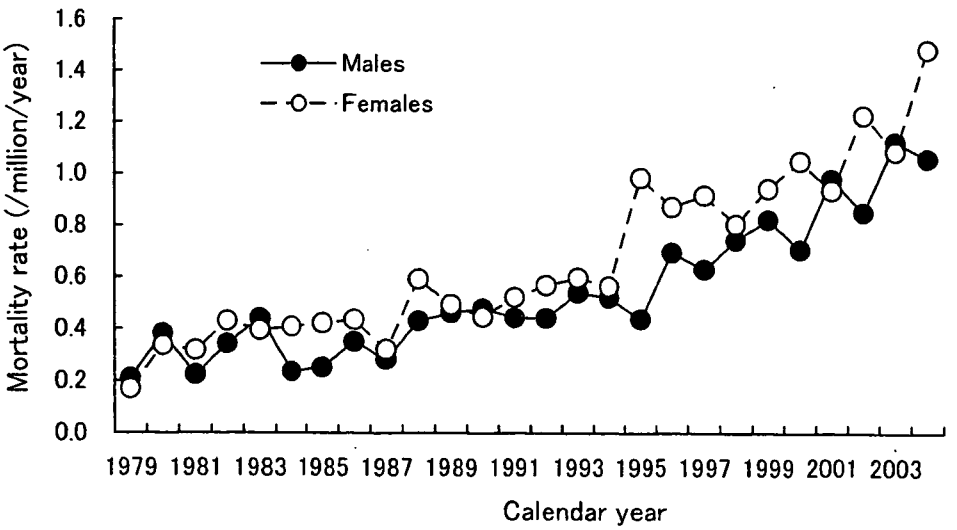

Figure 4. Annual crude mortality rates due to Creutzfeldt-Jakob disease, Japan, 1979-2004.

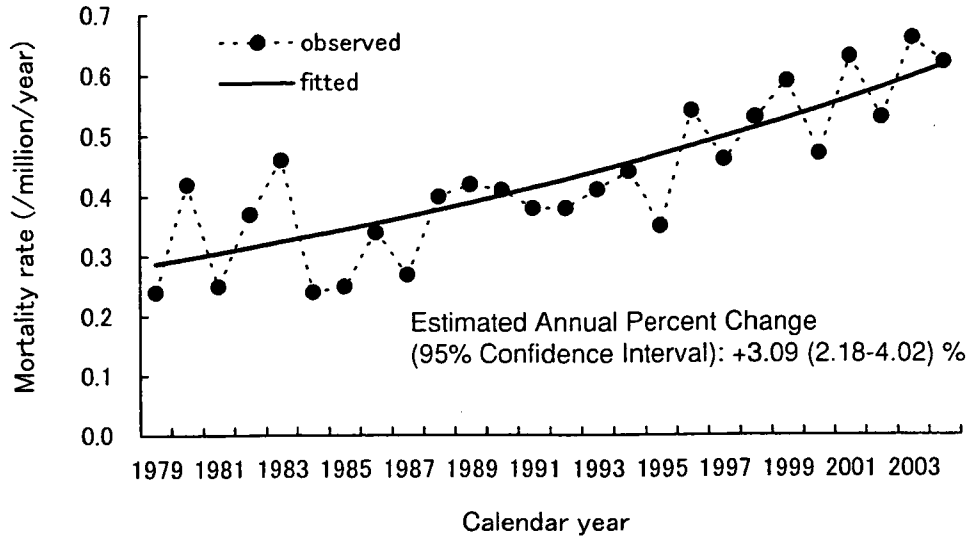

Figure 5. Trends in annual age-standardized mortality rates due to Creutzfeldt-Jakob disease among males, Japan, 1979-2004.

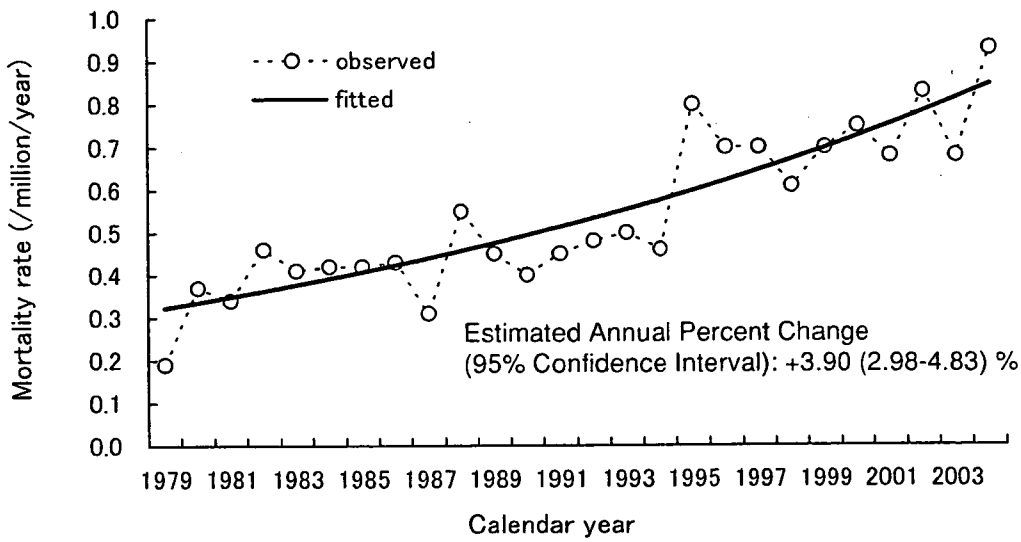

Figure 6. Trends in annual age-standardized mortality rates due to Creutzfeldt-Jakob disease among females, Japan, 1979-2004.

DISCUSSION

The present study identified the total number of 1,966 deaths (862 males and 1,104 females) due to CJD based on death certificate data in Japan during the period of 1979-2004. The number of deaths and crude mortality rates per year peaked in 2004 at 163 (66 for males and 97 for females) deaths and 1.28 (1.06 for males and 1.48 for females) deaths per million population, respectively. We discuss, first of all, whether or not CJD mortality has increased in Japan over the past 26 years. As demonstrated in this study, we found a significant linear increase in trends for age-standardized mortality rates from the disease, with +3-4% of annual percentage change, between 1979 and 2004. In interpreting the results, we should consider some factors that might contribute to a false increase in mortality, such as the change of ICD codes and the enhancement of case findings (e.g., physicians' recognition of the disease, diagnostic tests, and quality of health care). No revolutionary new diagnostic test for CJD became available throughout the observational period. On the other hand, there were a few critical points of time to consider: in 1991, patients with CJD transmitted by cadaveric dura transplants were identified in Japan;[9] in 1995, the ICD code for CJD was changed from 9th to 10th version in Japan; and in 1996, a new case of vCJD causally linked to BSE was reported from the United Kingdom.[6] Without an abrupt rise of age-standardized mortality rates from CJD after these years for both sexes, however, it is unlikely that these events artificially affected the increase in CJD mortality.

Rather, it may be the true fact that in Japan our results reflect to a large extent a genuine increase in CJD. The number of iCJD cases may still increase even after the total ban on the practice of causal grafts.[5-8] Regarding sporadic CJD (sCJD), a recent report from the European Union's collective study on CJD suggests that the mortality rates from sCJD increased with time between 1993 and 2002.[20] It is quite probable that this temporal increase of sCJD may also exist in Japan. The increase may have been accompanied to some extent by the improvement of physicians' diagnostic skills for CJD since 1997 when a manual for clinical practice on CJD was introduced in our country.[20,21]

Consistent with the previous findings,[22-28] the present study showed that the CJD mortality rates rapidly increased with age between 50 and 74 years, especially among females, and sharply declined at 80+ years of age, although the causal mechanism remains unexplained. These findings were comparable with those for patients with CJD reported to the Surveillance.[29,30]

We focus hereafter our discussion on CJD deaths in young patients, younger than 50 years of age. The vCJD associated with BSE has a course and pathology distinct from sCJD: younger age at onset, prominence of psychiatric and sensory symptoms, and a long disease course.[6,15] Most of such cases died at an age under 50 years.[15] In Japan, there has been only one case with definite vCJD, confirmed by the Japanese Creutzfeldt-Jakob Disease Surveillance Committee, who died at the age of 51 in December 2004, and had a history of visiting the UK, 1990, when the BSE outbreak was increasing there, but the causal association is unclear.[7] As Bradley and Liberski pointed out,[31] human populations are still exposed to epidemics of BSE, although the epidemics in different countries are at different stages: the UK, the rest of the EU, and North America and other countries including Japan have all reported BSE in native-born cattle. Until January 2007, a total of 198 patients with vCJD were identified around the world: 162 in the UK, 21 in France, 4 in Ireland, 3 in the USA, 2 in Netherlands, and 1 each in Canada, Italy, Portugal, Spain, Saudi Arabia, and Japan.[15] Thus it is important for us to trace back the frequency of CJD deaths for this age group in the past, in terms of roughly estimating the background risk. We could not ascertain the clinical types of CJD deaths observed in our study because of the lack of such information. We assume, however, excluding a single case of vCJD, 57%, 29% and 14% for sporadic, iatrogenic and familial types of CJD among the deaths, respectively, from the findings reported to the Surveillance.[30]

We finally refer to the validity of the data used in our study, which were based on the underlying cause-of-death obtained from death certificates. Potential inaccuracies in death certificate data used for our study could not be ignored because autopsy findings and clinical information to confirm the diagnosis of CJD were not available (e.g., definite, probable, and possible; sporadic, familial, iatrogenic, and variant). However, the seriousness is not so great, considering the following points: (1) Over 90% of CJD patients die within a few years of the onset of symptoms; [15,23,24,29,30,32] (2) Diagnosis is ascertained at the end of the clinical course; and (3) 95.2% of CJD deaths observed in this study occurred at hospitals.

Despite these limitations, the national death certificate data can work as an efficient tool for monitoring CJD mortality because it covers all the deaths from CJD that have occurred throughout the country. In addition, an annual review of national CJD death certificate data has the possibility of providing incidence information as a surrogate for ongoing CJD surveillance in Japan, regarding a quite short period of time from the onset through death of this disease. This will be effective, especially for the detection of small clusters of deaths at an age under 50 years, of which the occurrence still remains low. So, the combined data of death certificate and surveillance information should be taken into account for monitoring morbidity and mortality of CJD in the future.

In conclusion, our present study suggests that CJD mortality based on death certificate data significantly increased in Japan during the period of 1979-2004.

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日本における難病による死亡の時系列推移（1972～2004年）

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目的　国は，1972年に，原因不明で治療方法が未確立であり，経過が慢性で後遺症を残すおそれが少なくなく，身体的のみならず精神的，経済的にも負担の大きい疾病を難病と指定し対策を進めてきた。本研究の目的は日本における難病による死亡の時系列推移（1972-2004年）について検討することである。

方法　難病に指定されている特定疾患治療研究対象疾患45疾患のうち，年間死亡数が100を超す再生不良性貧血，パーキンソン病，全身性エリテマトーデス，潰瘍性大腸炎，特発性血小板減少性紫斑病，結節性動脈周囲炎，アミロイドーシスを対象疾患とし，人口動態調査死亡票をもとに，粗死亡率と年齢調整死亡率（直接法）を算出し，ジョインポイント回帰モデルを用い時系列推移について分析した。

結果　最新（2004年）の各疾患の粗死亡率（人口100万対）は，男女それぞれ，パーキンソン病で25.55，25.93，再生不良性貧血で5.41，6.92，全身性エリテマトーデスで0.87，3.50，アミロイドーシスで2.93，2.36，結節性動脈周囲炎で1.40，1.54，特発性血小板減少性紫斑病で1.34，1.61，潰瘍性大腸炎で1.02，0.74，であった。年齢調整死亡率の年変化率を全期間でみると，潰瘍性大腸炎（男－5.2%，女－7.5%），再生不良性貧血（男－3.6%，女－3.7%），特発性血小板減少性紫斑病（男－2.1%，女－3.0%）と全身性エリテマトーデス（男－0.9%，女－2.6%）で減少，アミロイドーシス（男＋3.3%，女＋3.5%），結節性動脈周囲炎（男＋3.2%，女＋4.0%），パーキンソン病（男＋0.7%）で増加していた。最新の時系列相に注目すると，アミロイドーシス（男）では有意に増加していたが，結節性動脈周囲炎（女）とパーキンソン病（女）では有意に減少していた。一方，潰瘍性大腸炎（男）は減少傾向が止まった状態が続いている。

結論　対象とした難病の多くは，この約30年間で，年齢調整死亡率が有意に減少した。難病に効果的な一次予防の手立てがないことから，死亡率の改善は，診断治療の進歩による可能性が大きいと考えられる。しかしながら，根治療法の開発や病因の解明など未解決の部分も多く，患者支援とともに，さらなる研究が必要である。

Key words：難病（特定疾患），死亡率，ジョインポイント回帰分析，再生不良性貧血，パーキンソン病，全身性エリテマトーデス，潰瘍性大腸炎，特発性血小板性紫斑病，結節性動脈周囲炎，アミロイドーシス

I　緒　　言

1972年より，国は，原因不明で治療方法が未確立であり，かつ，後遺症を残すおそれが少なくなく，経過が慢性にわたり，単に経済的な問題のみならず介護などに著しく人手を要するため家族の負担が重く，また精神的にも負担の大きい疾病を，いわゆる難病として指定（特定疾患）し，その対策を進めてきた[1]。

難病は，その名の通り難治性であり，致命率の高いものも多い。したがって，これらの難病による死亡者の頻度・分布を知ることは，病因の追求のみならず，難病の対策全般を考える上にも重要である[2]。特定疾患の疫学に関する研究班では，人口動態統計の死亡票をもとに，これまでに，疾患ごとの死亡統計の検討を定期的に行なってき

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