Incidence rate of Creutzfeldt-Jakob disease in Japan

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Background The objective of this study is to clarify the incidence rate of Creutzfeldt-Jakob disease (CJD) during the last decade in Japan.

Methods A nationwide mail survey was conducted in all hospitals with a minimum bed capacity of 100 and having at least one of three departments: neurology, psychiatry, and neuropathology. The survey required the patient’s sex, date of birth, date of diagnosis, diagnostic criteria, medical history and CJD incidence in the family.

Results From 493 hospitals throughout the country, 821 patients with CJD were reported from January 1985 through March 1996. The annual incidence rate was 0.49 per million population for males and 0.68 for females. The age-specific incidence rate was highest among those 70–79 years of age, followed by the 60–69, and 50–59 age groups. The incidence and mortality increased during the observed period; however, the incidence rate among younger generations did not rise.

Conclusion A nationwide incidence survey of CJD in Japan revealed the incidence and distribution of the disease over the recent decade. It was found that the incidence and mortality rates had increased during the observed period.

Keywords Creutzfeldt-Jakob disease, incidence rate, mortality rate, epidemiology, nationwide surveys

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Creutzfeldt-Jakob disease (CJD) is a rare neurological affliction and its incidence rate is believed to be approximately one per one million population per year.1 The probability of transmission through cadaveric dura grafts2–4 and variant cases suspected to be associated with bovine spongiform encephalopathy have attracted attention to the disease.5

In Japan, the annual incidence rate of the disease was 0.45 per million population, but that observation was made approximately 20 years ago.6 Since then no epidemiological incidence surveys have been conducted so that it is not known whether the incidence has increased, especially in the young, some of whom may be variant cases. To clarify the trends in incidence of CJD, the Ministry of Health and Welfare organized a special research committee in 1996. The committee, with one of the authors (TS) acting as its chairman, conducted a nationwide incidence survey of the disease.

Methods
The Epidemiologic Research Committee of Creutzfeldt-Jakob Disease (CJD), sponsored by the Ministry of Health and Welfare of the Japanese Government, conducted a nationwide mail survey in June 1996. Subjects were all hospitals with a minimum bed capacity of 100 and having at least one of three departments: neurology, psychiatry, and neuropathology. If one hospital had two or three of these departments, each department received a separate survey form.

In the primary survey, the hospitals were asked whether or not there had been any patients with CJD since 1985. If the answer was positive, the hospital was asked to provide specific information for each patient on: sex, date of birth, date of diagnosis, diagnostic criteria (definite, probable, or possible), and medical history, and incidence of CJD in the family. If a major hospital which a patient might have visited failed to respond, the chairman of the Committee got in touch with it by telephone and asked for its co-operation. In this manner we tried to get information on all the patients in Japan with CJD.

We used the diagnostic criteria proposed by Masters et al.7 Based on the primary survey, a secondary mail survey was conducted to gather clinical and pathological information on each patient reported in the primary survey. The results of the secondary survey will be reported in another paper.

The incidence rates were calculated by using the population listed in the 1990 census as denominator. Age-specific rates by sex were calculated for three conditions; all reported patients with CJD, sporadic cases excluding familial cases, and sporadic

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cases without cadaveric dura graft transplantation. To observe the difference in incidence among districts, standardized morbidity ratios of the incidence (SMR) were calculated for all 47 prefectures in Japan, based on the nationwide age- and sex-specific incidence rates. The SMR with 95% confidence interval (CI) (calculated under the assumption that there was a Poisson distribution) that did not include 1.0 were considered to be statistically significant. In addition, the distribution of prefectures where familial cases emerged was observed because some familial incidence clustered in specific prefectures. In this study, information on familial cases was derived from the questionnaires filled out by the physicians or neurologists that were in charge of individual patients. We have no information as to whether or not gene analyses were conducted on them.

Besides the incidence rate, we calculated mortality rates for the disease using data from vital statistics.

Results
Of the 3965 departments to which the questionnaires were sent, 2899 (73.1%) responded. The response rate was highest in Niigata prefecture (88%) and lowest in Wakayama prefecture (58%), while the rates were between 60% and 80% in most prefectures. Of those 2899 departments, 493 reported one or more patients with CJD. The average bed capacity of these hospitals was larger than that of the hospitals with no CJD patients (475.1 versus 229.7).

In all, 821 patients with CJD (337 males and 484 females) were located. This group was divided into: definite (299); probable (431); and possible (87) cases. The distribution of age and calendar year at onset was shown in Table 1. The Committee requested the date of onset for patients who were diagnosed in or after 1985; 58 patients had been affected before 1985. The annual incidence rate was 0.49 for males and 0.68 for females per million population over 11 years and 5 months (the observation period). Taking into account only definite and probable cases, the annual incidence rate was 0.43 for males and 0.60 for females. The age-specific incidence rate by sex is shown in Figure 1. Of the 821 patients, 83 had a family history of CJD and 43 had a history of cadaveric dura graft transplantation (one case had both). The rate was higher among females than males in all age groups except the 80 plus group. The incidence rate was highest for both sexes in the age group 70–79 years, followed by the 60–69 and 50–59 years groups. The highest figures in the 70–79 year-old group were 2.4 per million years, followed by 50–59 and 70–79 years. In spite of the increase in patients of all ages, the number of patients under 40 years (the age level where variant cases were prevalent in the UK) did not increase. One patient was 15 years old at onset; however, according to the detailed clinical observations, he suffered from typical CJD, not a variant type. Further, there was no family history of the disease or dura transplantation to confuse an investigator about the route of transmission.

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![Figure 1](image.png)
population per year for females, and 2.1 for males. Similar trends were observed when only definite and probable cases were taken into account.

The SMR for 47 prefectures are shown in Figure 2 and the results of statistical tests in Figure 3. Some prefectures had high SMR but there was no clustering of prefectures with high or low incidence. The same is true with the distribution of sporadic cases and sporadic cases without cadaveric dura graft transplantation. To date, two studies have reported clustering of CJD in Japan (in Yamanashi\textsuperscript{12} and Fukuoka\textsuperscript{13} prefectures). The SMR in Yamanashi was 1.78 (95\% CI: 0.86–3.28), and in Fukuoka 1.32 (95\% CI: 0.93–1.81) in the current study. Both were slightly high but not statistically significant.

Of the 83 cases with a family history of CJD, information was collected on the prefectures where 54 patients were born (eight in metropolitan Tokyo, seven in Yamanashi prefecture, and six in Fukuoka prefecture).

Figure 4 shows the recent chronological trend in the incidence rate and mortality rate of CJD. Both have increased recently, with the former doing so more rapidly. Thus, the gap between the two became evident in the 1990s. The incidence rate for all age groups approached 1.0 per million per year.

Discussion

We have reported the incidence rate of CJD and its distribution in Japan. The number of patients with the disease, its incidence, and mortality all increased during the last decade.

One of the most serious problems associated with nationwide mail surveys is the response rate. In this study, it was as high as 73\% because a special effort was made by personal telephone appeal to several leading neurologists who had failed to respond by September 1996. Thus almost all of the major hospitals where patients with CJD might have presented were covered in the study. This effort ensured that the number of patients with CJD that were not reported to the study was very small, or even zero, and therefore there was no need to consider the variation in response rate among prefectures when we examined the SMR. In addition, the bed capacity of the hospitals that did not respond to the survey was likely to be smaller than that of participating hospitals; or it may be that many of these hospitals that did not respond to the survey had no patients with CJD.

Many neurologists, not only in Japan but also in western countries, believe that the annual incidence rate of this disease is one per million population throughout the world, except for some special population groups. The results of the current study support this. However, the incidence rate for all age groups was lower than this figure but it was only one-half that for those aged 60–79 years, when the disease is likely to develop.

Creutzfeldt-Jakob disease was found in several patients under 40 in Japan but the number remained unchanged. Detailed clinical and pathological results on these patients obtained from the secondary survey will be introduced in another report. In addition, a detailed report of 43 cases with a history of cadaveric dura graft transplantation is currently being prepared.
When epidemiologists note increasing incidence of a specific disease, they should make certain whether the increase is genuine. In studying CJD as well as other neurological diseases, a false increase might occur through improved case finding. Along with an increase in the number of physicians in Japan, the number of neurologists has also increased. Currently a number of neurologists maintain their own clinics, whereas they practised only in large hospitals a few decades ago. This may give rise to a false increase. On the other hand, the clinical findings of CJD are so specific that many patients with such features might have been readily referred to neurologists in the past. If so, the increase in the incidence of CJD is plausible. Surveillance for CJD is required to confirm whether or not the increase is real; and for this reason the Ministry of Health and Welfare of Japan has been conducting such a surveillance since February 1997.

Several reports have shown that patients with CJD cluster in some areas in Japan, e.g. Yamanashi,\textsuperscript{12} and Fukuoka.\textsuperscript{13} The current study shows the SMR of these two prefectures were higher than 1.0 but without statistical significance. Akita, Tochigi, and Tokyo showed significantly high SMR. The incidence and mortality from cerebrovascular disease have been high in Akita and Tochigi.\textsuperscript{14} If physicians in these areas focus on the neurological findings of patients because of the high incidence of cerebrovascular disease, the probability of case-finding may be high enough to raise the incidence rate. Unfortunately, the only available information on our patients was the residence (prefecture) of the patients: there were no further details so a
more detailed analysis was not possible. However, we were able to show that patients with CJD existed throughout the country, with no specific clustering in particular prefectures (Figure 2).

Several familial cases of CJD, clustering in Yamanashi prefecture, have been reported.9–12 We observed that seven out of 54 patients with familial CJD were born in Yamanashi, a fact that coincides with data given in previous reports. In Fukuoka prefecture, where six patients with familial CJD had been born, clustering of the disease has also been reported; but the authors of this paper stated that neither a family history of CJD nor a relative relationship among the cases existed.13 On the other hand, three familial cases were reported by a hospital in Fukuoka prefecture,15 but the authors did not give detailed addresses except that they lived on the island of Kyushu, which includes Fukuoka.

As shown in Figure 4, a gap between mortality and incidence exists in recent years. Because CJD is a fatal disease, the mortality rate from CJD in Japan will increase following the increase in incidence, with an average delay between onset and death.

In conclusion, a nationwide incidence survey of CJD in Japan revealed the incidence and distribution of the disease over the recent decade. The incidence rate and mortality rate have increased during the period of observation.

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References


