Spatial Clusters of Creutzfeldt-Jakob Disease Mortality in Japan between 1995 and 2004

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Key Words

Creutzfeldt-Jakob disease • Mortality • Death certificate • Flexible scan statistic • Spatial disease cluster

Abstract

Background: There is suggested to be a geographical difference in Creutzfeldt-Jakob disease (CJD) mortality in Japan. We performed a study to detect localized clusters and hot-spot areas of deaths from CJD in Japan during the 10-year period from 1995 to 2004. **Methods:** The diagnosis of CJD was taken from the death certificate (coded as A81.0 in the ICD-10). A total number of 1,168 CJD deaths (500 males and 668 females) were used for analysis using empirical Bayes estimates of standardized mortality ratios and the flexible spatial scan statistic to detect clusters. To detect the most likely cluster, p values were obtained using Monte Carlo hypothesis testing (with $p < 0.05$ as statistical significance). **Results:** The most likely cluster of CJD mortality was located in the northwest region from the base of Mt. Fuji, stretching over the two neighboring prefectures of Yamanashi and Shizuoka (relative risk = 2.28, $p = 0.021$). Some other clusters were detected but were not significant. **Conclusions:** The present study supports the evidence of geographical clustering of deaths from CJD at a specific location in Japan.

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Background

Creutzfeldt-Jakob disease (CJD), the most common human prion disease, is a progressive and fatal neurodegenerative disorder. It occurs in familial, acquired (e.g. variant and iatrogenic) and sporadic forms [1]. The disease remains a significant threat to society through a variety of transmission routes of the causal agent.

Variant CJD is suspected to be caused by human infection with the causative agent of bovine spongiform encephalopathy [2]. A total of 202 variant CJD cases have been reported worldwide as of November 2007 [3], including a Japanese man who had resided in the UK in 1990 and died in Japan in 2004 [4]. Considering the globalization of human migration and product distribution, there is the possible danger that variant CJD could spread across borders of confined countries, the UK, France, the Republic of Ireland, Italy, the USA, Canada, Saudi Arabia, Japan, the Netherlands, Portugal and Spain, where variant CJD deaths were officially identified. The two most important causes of iatrogenic CJD are contaminated cadaveric human growth hormone and dura mater grafts. More than half of all dura-related cases have occurred in Japan [5, 6]. The latest recorded number of dura-related CJD cases registered by the Creutzfeldt-Jakob Disease Surveillance Committee of Japan was 132,

which has almost doubled in the last 7 years [6, 7]. The occurrence of new cases, the increase in the mean and range of the latency period, and the suspected cases under investigation all suggest that this outbreak is ongoing [7, 8]. In sporadic CJD, it is speculated that exposure to a common unknown factor (e.g. diet, occupation, surgery, contact with animals and other cases) plays a role in the etiology. Sporadic CJD may arise, as another putative mechanism, due to spontaneous endogenous events rather than by infection from another individual or an environmental source [9].

In fact, the incidence and age-adjusted mortality rates have increased in Japan between 1979 and 2004 [10, 11]. The annual mortality rates for CJD in 2004 were 1.06 and 1.48 per million persons for males and females, respectively [11]. Geographical studies can provide an important clue for taking countermeasures against the spread of the disease. A recent epidemiological study suggested excess CJD standardized mortality ratios (SMRs) in some of the 47 prefectures in Japan [12]. Therefore, in the present study, we aimed to specifically detect localized clusters and hot-spot areas of deaths from CJD in Japan during the period 1995–2004.

Methods

Mortality, Geographical and Population Data

The mortality data for CJD from 1995 to 2004 were used in the present study, after obtaining permission for their use from the Statistics and Information Department of the Ministry of Health, Labor and Welfare. Underlying-cause-of-death classifications from death certificates were based on the 10th revision of the International Classification of Diseases (ICD-10) [13]. CJD deaths were defined as those with code A81.0 of the ICD-10. Human prion diseases other than CJD, such as Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia and kuru coded as A81.8, were excluded from this study. The data tape used for this study contained the codes for CJD and basic information on sex, age and residence (municipality). It did not include any personal identifiable information (e.g. individuals' names or residential addresses). Because of the aforementioned reasons, this study did not need to be institutionally reviewed, according to the ethical guidelines for epidemiological research stipulated by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare.

At the time of this study, there were a total of 3,371 municipalities (150 wards in Tokyo and other metropolitan cities, 651 cities, 1,994 towns and 576 villages) nested in 47 prefectures of Japan. Prefectural governments defined the secondary medical care zone (SMCZ) for medical care planning according to the Medical Service Law. Geographical analyses in the present study were conducted at the SMCZ level. There were 359 SMCZs, each of which consisted of neighboring municipalities. Geographical

coordinates (latitude and longitude) for each SMCZ were computed as the population-weighted means of coordinates of the municipal government offices in each of the SMCZs [14]. For each year from 1995 to 2004, population estimates for each SMCZ were calculated using a linear interpolation of the two census populations for 1995 and 2000.

Statistical Analyses

Geographical Distribution of CJD Mortality

SMRs, defined as the observed number divided by the expected number of fatal cases, have been used in previous studies to describe the geographical distribution of mortality rates for CJD. However, the estimation of SMRs takes no account of population size and is sensitive to variation in the observed number of deaths so that estimates of SMRs are highly dependent on the population size of the areas studied. This is especially true for such a rare disease as CJD. Therefore, we did not adopt the traditional SMRs, but employed empirical Bayes estimates of standardized mortality ratios (EBSMRs) to examine how CJD deaths are geographically distributed among SMCZs throughout Japan. EBSMRs weight the observed SMRs according to how far they are from the estimated *a priori* mean and how precise they are [15–17]. EBSMRs were calculated for each sex as well as the sexes combined.

Spatial Disease Clustering of CJD Mortality

The circular spatial scan statistic [18] has been widely applied to epidemiologic studies for disease cluster detection [19–21]. This method superimposes an infinite number of circles with different radii on a map at different locations and identifies the circle with the maximum likelihood as the cluster that is least likely to have occurred by chance. Since this scan statistic uses circular windows, it encounters difficulties in correctly detecting noncircular clusters such as those along the coast. Japan consists of the mainland, three islands (Hokkaido, Shikoku and Kyushu) and thousands of small scattered islands. In that case, it may happen that the circular spatial scan statistic fails to detect noncircular clusters or includes the sea, where there is clearly no elevated risk, in the largest part inside circular clusters.

To overcome this problem, we adopted another method as a spatial scan statistic, that is the flexible spatial scan statistic, which places an infinite number of arbitrarily shaped windows over a map to look for irregular or noncircular clusters. As with the circular spatial scan statistic, the cluster with the maximum likelihood is defined as the most likely cluster. *p* values are obtained using Monte Carlo hypothesis testing, comparing the test statistic from the observed data set with the test statistics from 999 random data sets generated under the null hypothesis of no clustering. Statistical significance was determined as a *p* value less than 0.05. Hot-spot areas, which are included in the most likely cluster, can be identified. The details of the flexible spatial scan statistic were previously published elsewhere [22]. Flexible spatial scanning for cluster detection was conducted for each sex as well as the sexes combined.

Analyses were performed using EB Estimator for Poisson-Gamma Model version 2.0 and FlexScan version 2.0, which were developed by Takahashi et al. [23, 24]. FlexScan detects all clusters for which *p* values are less than 1.0 by Monte Carlo hypothesis testing. They are available from the website of the National Institute of Public Health, Japan, on the internet.

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Fig. 1. EBSMRs of CJD for males, Japan, 1995–2004.

Fig. 2. EBSMRs of CJD for females, Japan, 1995–2004.

Fig. 3. EBSMRs of CJD for both males and females, Japan, 1995–2004.

Fig. 4. Clusters of deaths from CJD detected using flexible spatial scan for males, Japan, 1995–2004.

Table 1. Spatial clusters of CJD mortality detected using flexible spatial scan statistic for males and females, Japan, 1995–2004

Cluster	Approximate cluster location	Number of SMCZs	Expected cases	Observed cases	Relative risk	p value
Males (n = 500)						
Most likely cluster	A1: northwest of Mt. Fuji on the mainland	8	8.24	26	3.16	0.016
Second cluster	A2: around Lake Biwa on the mainland	10	11.66	29	2.49	0.164
Third cluster	A3: along Japan Sea in the northeast of the mainland	5	4.15	14	3.37	0.567
Females (n = 668)						
Most likely cluster	B1: northeast of the mainland	10	11.88	28	2.36	0.387
Second cluster	B2: Tokyo Metropolitan area on the mainland	11	58.11	85	1.46	0.897
Third cluster	B3: northwest of Mt. Fuji on the mainland	9	9.41	21	2.23	0.973
Both (n = 1,168)						
Most likely cluster	C1: northwest of Mt. Fuji on the mainland	10	20.63	47	2.28	0.021
Second cluster	C2: along Japan Sea in the northeast of the mainland	5	10.37	27	2.60	0.205
Third cluster	C3: around Lake Biwa on the mainland	11	46.25	76	1.64	0.367

Results

The total number of CJD deaths was 1,168 (500 males and 668 females) in the observed 10-year period from 1995 to 2004. The geographical variations in EBSMRs of CJD adjusted for age are shown for males (fig. 1), females (fig. 2), and both males and females (fig. 3).

Table 1 shows the most likely, second and third clusters of CJD mortality detected with the flexible spatial scan statistic: A1, A2 and A3 for males, B1, B2 and B3 for females, and C1, C2 and C3 for both males and females, respectively (fig. 4–6).

As shown in figure 4, for males, there were 1 statistically significant cluster (A1) and 2 clusters with no significance (A2 and A3). The most likely cluster with an elevated risk for CJD mortality was located in the northwest region from the base of Mt. Fuji, stretching over the two neighboring prefectures of Yamanashi and Shizuoka (relative risk = 3.16, $p = 0.016$; table 1 and fig. 4, A1). For females, figure 5 shows 3 detected clusters, which were not statistically significant (B1, B2 and B3). The most likely cluster of CJD mortality for females extended from the Japan Sea to the Pacific Ocean in the northeast of the mainland, where the observed number of deaths was 28 compared to 12 expected (relative risk = 2.36, $p = 0.387$; table 1 and fig. 5, B1). Figure 6 and table 1 indicate, for both males and females, that there were 1 statistically significant cluster (C1: relative risk = 2.28, $p = 0.021$) and 2 clusters with no significance (C2 and C3). As shown in figure 7, the most likely cluster contained 10 hot-spot areas located along the rivers in this region, the Fuji River, Ohi River and a part of the Tenryu River.

Discussion

About 5–15% of CJD cases show the familial or genetic form [1, 25], and the percentage of other forms varies according to the degree of exposure to the causal agent. Genetic CJD is related to an underlying mutation in the prion protein (PRNP) gene on human chromosome 20. The 200K PRNP mutation accounts for 70% or more of genetic CJD cases and is autosomal dominantly inherited. It is reported that 4 independent mutational events are responsible for the current worldwide distribution of genetic CJD associated with this mutation, in Libya, Tunisia, Italy, Chile, Spain, Slovakia, Poland, Germany, Sicily, Austria and Japan [25]. In Japan, a series of clinical cases of genetic CJD patients with the E200K PRNP mutation have been reported, which appeared in the Fuji River Basin across Yamanashi and Shizuoka Prefectures [26, 27]. A part of Yamanashi Prefecture in this region is the place where a small cluster of familial and sporadic CJD patients were identified about 30 years ago [28].

In the present study, we found that 7 of 10 hot-spot areas in the most likely cluster corresponded almost exactly to the Fuji River Basin where genetic CJD patients had previously been reported [26]. Of note, the most likely cluster extended from the Fuji River Basin toward the southwest in Shizuoka Prefecture. This is evidence that has never been reported before in such previous studies as clinical case studies, regional epidemiological surveys and geographical analyses at the prefectural level [10, 12, 26–28]. Although we cannot clarify how the disease has been transmitted there because of a lack of genetic and

Fig. 5. Clusters of deaths from CJD detected using flexible spatial scan for females, Japan, 1995–2004.

Fig. 6. Cluster of deaths from CJD detected using flexible spatial scan for both males and females, Japan, 1995–2004.

clinical information on patients who died from CJD, we suggest the existence of some endogenous or exogenous factors for CJD common to these areas: PRNP mutation, migration of PRNP mutant carriers, repeated point-source outbreaks of infection, gene-gene or gene-environment interactions, and iatrogenic transmission [7, 9, 25, 29–32]. Four of 8 hot-spot areas detected for males appeared in a part of the cluster for females as well, which, however, was not statistically significant. The reason for the sex difference in cluster formation is unclear.

The limitations of our present study should be taken into account. One is case ascertainment. The diagnosis of CJD was based on underlying cause of death recorded on death certificates, and such notations in death certificates may include inaccuracies. However, this is not so serious, considering the following points: (1) the number of neurologists is so large that the probability of the case finding artifact is small with CJD [10]; (2) neurologists, psychiatrists and brain surgeons generally follow a manual for clinical practice on CJD [33, 34], and (3) the annual number of CJD deaths observed in our study was close to the number of patients with CJD reported as a

Fig. 7. Most likely cluster of deaths from CJD detected using flexible spatial scan for both males and females, Japan, 1995–2004.

notifiable infectious disease, which was specified in 1999 by the Infectious Disease Law (table 2). The other is a lack of clinical and genetic data on CJD. Therefore, we could not separately analyze the data for each form of CJD. We assume, however, excluding a single case of variant CJD, incidences of 81.4, 7.6 and 10.9% for the sporadic, iatrogenic and familial forms of CJD, respectively. Familial CJD includes cases without PRNP mutation but with a family history [8].

In conclusion, the present study revealed evidence of geographical clustering of deaths from CJD at a certain location in Japan. Some other clusters existed across the country but did not show statistical significance. Due to the nature of descriptive studies, our study cannot elucidate the etiology or confirm the mode of transmission. Nevertheless, it contributes a new insight for future genetic and environmental epidemiological studies on CJD. In addition, it is important to carefully monitor the geographical pattern of CJD mortality from the perspectives of disease prevention and health care services.

Table 2. Annual number of deaths from CJD based on national death certificate data used for the present study and number of patients with CJD reported as notifiable infectious disease, Japan, 1999–2004

Calendar year	Deaths from CJD	Patients with CJD
1999	112	92
2000	112	108
2001	122	133
2002	133	147
2003	141	118
2004	163	175

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References

- Johnson RT: Prion diseases. *Lancet Neurol* 2005;4:635–642.
- Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, Poser S, Pocchiari M, Hofman A, Smith PG: A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996;347:921–925.
- The National Creutzfeldt-Jakob Disease Surveillance Unit. <http://www.cjd.ed.ac.uk/vcjdworld.htm> (accessed December 4, 2007).
- Yamada M, Variant CJD Working Group: Creutzfeldt-Jakob disease Surveillance Committee Japan: the first Japanese case of variant Creutzfeldt-Jakob disease showing periodic electroencephalogram. *Lancet* 2006;367:874.
- Brown P, Preece M, Brandel JP, Sato T, McShane L, Zerr I, Fletcher A, Will RG, Pocchiari M, Cashman NR, d'Aignaux JH, Cervenáková L, Fradkin J, Schonberger LB, Collins SJ: Iatrogenic Creutzfeldt-Jakob disease at the millennium. *Neurology* 2000;55:1075–1081.
- Nakamura Y, Aso E, Yanagawa H: Relative risk of Creutzfeldt-Jakob disease with cadaveric dura transplantation in Japan. *Neurology* 1999;53:218–220.
- CDC: Update: Creutzfeldt-Jakob disease associated with cadaveric dura mater grafts – Japan, 1979–2003. *MMWR* 2003;52:1179–1181.
- Creutzfeldt-Jakob Disease Surveillance Committee of Japan: Surveillance reports on Creutzfeldt-Jakob Disease for the fiscal year of 2006 (in Japanese). <http://www.wam.go.jp> (accessed December 4, 2007).
- Linsell L, Cousens SN, Smith PG, Knight RS, Zeidler M, Stewart G, de Silva R, Esmonde TF, Ward HJ, Will RG: A case-control study of sporadic Creutzfeldt-Jakob disease in the United Kingdom: analysis of clustering. *Neurology* 2004;63:2077–2083.
- Nakamura Y, Yanagawa H, Hoshi K, Yoshino H, Urata J, Sato T: Incidence rate of Creutzfeldt-Jakob disease in Japan. *Int J Epidemiol* 1999;28:130–134.
- Doi Y, Yokoyama T, Sakai M, Nakamura Y: Creutzfeldt-Jakob disease mortality in Japan, 1979–2004: analysis of national death certificate data. *J Epidemiol* 2007;17:133–139.
- Nakamura Y, Watanabe M, Nagoshi K, Yamada M, Mizusawa H: Geographic difference of mortality of Creutzfeldt-Jakob disease in Japan. *J Epidemiol* 2007;17:19–24.
- World Health Organization: International statistical classification of diseases and related health problems, 10th revision (ICD-10). Geneva, World Health Organization, 1992, vol 1.
- Japan Map Center: Directory of Location Information on Cities, Wards, Towns and Villages of Japan in the Year of 2000 (in Japanese). Tokyo, Japan Map Center, 2001.
- Clayton D, Kaldor J: Empirical Bayes estimates of age-standardized relative risks for use in disease mapping. *Biometrics* 1987;43:671–681.
- Mollie A, Richardson S: Empirical Bayes estimates of cancer mortality rates using spatial models. *Stat Med* 1991;10:95–112.
- Clayton D, Bernardinelli L: Bayesian methods for mapping disease risk; in Elliot P, Cuzick J, English D, Stern R (eds): *Geographical and Environmental Epidemiology: Methods for Small-Area Studies*. Oxford, Oxford University Press, 2000, pp 205–220.
- Kulldorff M, Nagarwalla N: Spatial disease clusters: detection and inference. *Stat Med* 1995;14:799–810.
- Fang Z, Kulldorff M, Gregorio DI: Brain cancer mortality in the United States, 1986 to 1995: a geographic analysis. *Neurooncology* DOI:10.1215/S1152851703000450.
- D'Aignaux JH, Cousens SN, Delasnerie-Lauprêtre N, Brandel JP, Salomon D, Laplanche JL, Hauw JJ, Alperovitch A: Analysis of the geographical distribution of sporadic Creutzfeldt-Jakob disease in France between 1992 and 1998. *Int J Epidemiol* 2002;31:490–495.
- Cousens N, Smith PG, Ward H, Everington D, Knight RSG, Stewart G, Smith-Bathgate EAB, Macleod M-A, Mackenzie J, Will RG: Geographical distribution of variant Creutzfeldt-Jakob disease in Great Britain, 1994–2000. *Lancet* 2001;35:1002–1007.

- 22 Tango Y, Takahashi K: A flexibly shaped spatial scan statistic for detecting clusters. *Int J Health Geographics* DOI:10.1186/1476-072X.
- 23 <http://www.niph.go.jp/soshiki/gijutsu/download/ebpoig/index.html>.
- 24 <http://www.niph.go.jp/soshiki/gijutsu/download/flexscan/index.html>.
- 25 Lee HS, Sambuughin N, Cervenakova L, Chapman J, Pocchiari M, Litvak S, Qi HY, Budka H, del Ser T, Furukawa H, Brown P, Gajdusek DC, Long JC, Korczyn AD, Goldfarb LG: Ancestral origins and worldwide distribution of the PRNP 200K mutation causing familial Creutzfeldt-Jakob disease. *Am J Hum Genet* 1999;64:1063–1070.
- 26 Miyakawa T, Inoue K, Iseki E, Kawanishi C, Sugiyama N, Onishi H, Yamada Y, Suzuki K, Iwabuchi K, Kosaka K: Japanese Creutzfeldt-Jakob disease patients exhibiting high incidence of the E200K PRNP mutation and located in the basin of a river. *Neurol Res* 1998; 20:684–688.
- 27 Kawauchi Y, Okada M, Kuroiwa Y, Ishihara O, Akai J: Familial Creutzfeldt-Jakob disease with the heterozygous point mutation at codon 200 of the prion protein gene (Glu → Lys) – report of CJD200 brothers of Yamanashi Prefecture origin (in Japanese). *No To Shinkei (Brain and Nerve)* 1997;49:460–464.
- 28 Akai J, Ishihara O, Higuchi S: Creutzfeldt-Jakob disease in Japan: an epidemiological study done in a select prefecture between 1976 and 1986. *Neuroepidemiology* 1989;8: 32–37.
- 29 Mead S, Mahal SP, Beck J, Campbell T, Farrall M, Fisher E, Collinge J: Sporadic – but not variant – Creutzfeldt-Jakob disease is associated with polymorphisms upstream of PRNP exon 1. *Am J Hum Genet* 2001;69: 1225–1235.
- 30 Coppede F, Mancuso M, Siciliano G, Migliore L, Murri L: Genes and the environment in neurodegeneration. *Biosci Rep* 2006;26:341–367.
- 31 Collins S, Law MG, Fletcher A, Boyd A, Kaldor J, Masters CL: Surgical treatment and risk of sporadic Creutzfeldt-Jakob disease: a case-control study. *Lancet* 1999;353:693–697.
- 32 Sutton JM, Dickinson J, Walker JT, Raven ND: Methods to minimize the risks of Creutzfeldt-Jakob disease transmission by surgical procedures: where to set the standard? *Clin Infect Dis* 2006;43:757–764.
- 33 AIDS and Disease Prevention Division, Health Service Bureau, Ministry of Health and Welfare of Japan: A Manual for Clinical Practice on Creutzfeldt-Jakob Disease (in Japanese). Tokyo, Shin Nihon Kikaku Shuppansha, 1997.
- 34 Disease Prevention Study Group: A Manual for Clinical Practice on Creutzfeldt-Jakob Disease, Revised (in Japanese). Tokyo, Taiyo Bijutsu Printing Co, 2002.