A Case-control Study of Creutzfeldt-Jakob Disease in Japan: Transplantation of Cadaveric Dura Mater was a Risk Factor

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A case-control study was conducted to reveal the relative risk of cadaveric dura mater graft transplantation for Creutzfeldt-Jakob disease. Fifty-two cases with Creutzfeldt-Jakob disease that were reported to the surveillance of the disease, and 102 age- and sex-matched hospital controls were selected. Information on family history, occupations, and medical history was collected. Eight cases and no control had a history of cadaveric dura mater graft transplantation. Surgical operations without the dura mater graft, blood transfusion, and acupuncture did not elevate the risk.  

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After the report from the United Kingdom telling the relationship between bovin spongiform encephalopathy and new variant Creutzfeldt-Jakob disease 1, a nationwide epidemiologic survey of the disease in Japan was conducted in 1996 to determine whether such patients existed in the country 2. No such case was reported to the survey, but another problem arose. Of 821 patients reported to the survey, 43 cases had a history of cadaveric dura mater transplantation 2,3. Although several case reports implied the relationship, no analytic epidemiologic study such as case-control studies and cohort studies has been conducted to calculate the relative risk of Creutzfeldt-Jakob disease with cadaveric dura transplantation because there was not a clustering of such patients except in Japan. Using the data from the nationwide survey, we calculated the relative risk with an assumption that the annual number of patients with cadaveric dura mater transplantation was 20,000 4. The estimated relative risk in comparison with annual incidence rate of the disease in general population in Japan was between 29.2 and 104.9. However, the relative risk estimated was based on neither a case-control nor a cohort study and included some suppositions.

In order to evaluate cadaveric dura mater transplantation and other factors as risk factors of Creutzfeldt-Jakob disease, we conducted a case-control study.

MATERIALS AND METHODS

Since February 1996, the Ministry of Health and Welfare of the Japanese government had been conducting a surveillance of Creutzfeldt-Jakob disease in Japan till March 1999. A physician that diagnosed the disease should report the patient's data about demography, occupation, family history, past medical history, and clinical findings to the surveillance system. The data were focused on potential risk factors of the disease, such as surgical operations. Newly diagnosed cases reported were potential cases of the study, and information about the cases was obtained from the surveillance data.

We asked physicians who had reported the potential cases to draw controls among their patients. Originally, one control for one case was asked to be selected, but in the halfway through the study, the number of controls was increased to 3 to make the reliability high. Age- (within 2 years) and sex-matched
controls were selected from patients with injuries or diseases not relating to prion who visited the hospitals at first in the year of the case's first visit. If there were more than 3 potential controls fulfilling the enrolling criteria, 1 or 3 control(s) whose first visiting day was the closest to the case's first visiting day were selected. Identical information obtained in the surveillance excluding clinical findings were reported about the controls by the physicians.

Of 89 cases reported to the surveillance by the end of September 1998, 6 cases were excluded because the date of diagnosis of Creutzfeldt-Jakob disease was before 1996. About 83 cases, physicians who reported the cases to the surveillance were asked to participate in the case-control study.

Odds ratios with 95% confidence intervals were calculated to evaluate the effects of potential risk factors to the occurrence of Creutzfeldt-Jakob disease with conditional logistic models using SPSS® (ver. 8.0J).

RESULTS

Of the 83 physicians asked to contribute to the case-control study by selecting controls and providing their information, 53 participated in the study, and data of 102 controls were obtained.

There were 22 male cases and 31 females, whereas 44 males and 58 females were in the control group. Of the 53 cases, 26 cases were with a control per case, 5 were with two controls, and 22 were with 3 controls per case. Average and standard deviation (in parentheses) of age at onset were 63.7 years (10.4 years) for cases, and 62.5 years (11.6 years) for controls, respectively.

Calculated odds ratios and their 95% confidence intervals for observed factors are shown in the Table. Three cases and no control had a family history of dementia. Of the 3 cases with the history, one case had a mother and a cousin with Creutzfeldt-Jakob disease and the case patient had contacted with the mother having the disease. There was a nurse in the case group, but she worked in a gastrointestinal section of a hospital; the probability, therefore, to contact with a patient with Creutzfeldt-Jakob might be very low, even if it existed. Other cases and controls had no occupational connection with a patient with the disease.

Occupational and non-occupational contacts with animals elevated the risk of the disease, but the odds ratios were not significant. All the non-occupational contacts were pets such as dogs and cats.

There were 8 cases with a history of cadaveric dura mater transplantation, whereas no controls had such an experience; therefore the odds ratio was infinity. An experience of brain surgery elevated the risk of Creutzfeldt-Jakob disease, but such a surgery without a cadaveric dura mater graft was not a risk factors of the disease. Point-estimated odds ratios for gastrectomy and other surgeries were high but had wide 95% confidence intervals including 1.0. Human organ preparation, blood transfusion, and acupuncture were not observed as risk factors.

| factors                                      | cases (n=52) | controls (n=102) | odds ratio (95% confidence interval) |
|----------------------------------------------|--------------|------------------|-------------------------------------|
| family history of dementia (including Creutzfeldt-Jakob disease) | 3            | 0                | infinity                            |
| contact with patients with Creutzfeldt-Jakob disease             | 1            | 0                | infinity                            |
| occupational contacts with animals                | 4            | 4                | 2.0 (0.4-10.0)                      |
| other contacts with animals than occupation        | 8            | 12               | 1.7 (0.5-5.7)                       |
| medical history surgery                           | 22           | 45               | 0.9 (0.4-1.8)                       |
| surgery with cadaveric dura mater                | 8            | 0                | infinity                            |
| surgery (brain)                                   | 8            | 7                | 2.4 (0.7-7.9)                       |
| brain surgery without cadaveric dura mater        | 0            | 6                | 0.0 (0-1.8)                         |
| surgery (spinal cord)                             | 0            | 0                |                                     |
| surgery (nervous system)                          | 1            | 0                | infinity                            |
| surgery (injuries)                                | 1            | 3                | 0.6 (0-7.0)                         |
| gastrectomy                                      | 2            | 2                | 1.9 (0-2-19.8)                      |
| hysterectomy                                      | 1            | 6                | 0.3 (0-2-6)                         |
| appendectomy                                      | 5            | 11               | 0.8 (0-2-8)                         |
| colectomy                                        | 0            | 7                | 0.0 (0-1-4)                         |
| surgery (hepato-cystic)                          | 2            | 5                | 0.7 (0-1-4.6)                       |
| surgery (others)                                  | 7            | 10               | 1.4 (0-4-2)                         |
| organ preparation                                 | 0            | 1                | 0.0 (0-infinity)                    |
| blood transfusion                                 | 4            | 11               | 0.7 (0-2-5)                         |
| acupuncture                                       | 4            | 25               | 0.3 (0-1-1)                         |
DISCUSSION

To date, several case reports have pointed out the relationship between the risk of Creutzfeldt-Jakob disease and cadaveric dura mater grafts. Because the clustering of such cases was not observed before the nationwide epidemiologic survey in Japan in 1996, however, this is the first report to calculate a relative risk of Creutzfeldt-Jakob disease in relation to dura mater transplantation.

Before the current study, we calculated the relative risk of Creutzfeldt-Jakob disease among those with a history of cadaveric dura transplantation. However, the past study had two limitations. One disadvantage was that the number of exposed population was the only assumed one. No data about the number of patients receiving the dura grafts in Japan existed. The other was the lack of a referent group; the incidence rate among those with the history of transplantation was compared with the incidence rate in general population in Japan. Thus, the calculated relative risk was not a result from a real observation, but an estimation, and the current study showed the odds ratio at the first time.

In this case-control study, we were not able to obtain the exact odds ratio for the cadaveric dura transplantation because no control had such an exposure. Therefore, the odds ratio was observed to be infinity because the denominator was zero. This result might be by chance under the situation that an odds ratio with a real value exists; otherwise, no patients would never occur from population without the transplantation. In such a case as a 2 × 2 table with zero values at least one cell, there is a technique to add 0.5 to each cell. Using this method, we obtain an odds ratio of 32.5 (95% confidence interval: 2.6–infinity). This wide 95% confidence interval indicates the low reliability of the study because of the small sample size. On the other hand, the high and statistically significant odds ratio even after the modification of the table shows the high risk of the disease among those with the history of transplantation. We were not compare the results directly to the previous one, but the odds ratio of 32.5 was similar to the lowest relative risk estimated in the previous study.

Several case-control studies about Creutzfeldt-Jakob disease have been conducted to date to clarify risk factors of the disease. Although none of the studies showed the relationship between the disease and cadaveric dura mater graft transplantation, some interesting findings have been revealed. The only one case-control study in Japan before the current one, conducted by Kondo and his colleague, has shown the elevated relative risk of the disease among those having recent history of surgical operations and mechanical injuries. Davanipour et al. pointed out head-face-neck injury or operation, head trauma, and other trauma as risk factors of Creutzfeldt-Jakob disease. A history of surgeries on the brain is the risk factors without statistical significance. Collins shows a dose-response relationship between the occurrence of Creutzfeldt-Jakob disease and the number of surgical operation. Some types of the operation, such as heart and hemorrhoids, were significant risk factors, but surgical operation on the brain was included in the miscellaneous type that also elevated the risk with significance. On the other hand, Harries-Jones et al. have shown a protective effect of surgical operation against the disease. A pooled analysis of case-control studies also shows the protective effects of surgeries on the central nervous system, eye, and abdomen.

No such studies observed whether each subject had a history of surgical operation with a cadaveric dura mater graft; it is reasonable to the current study that surgical operation is a risk factor of Creutzfeldt-Jakob disease if some surgical operations included the dura transplantation. On the other hand, the current study showed there was no relationship between surgical operation not using a cadaveric dura mater graft and the disease. If the transplantation was not so prevalent in the Western countries as in Japan, the odds ratios between the surgical operation on the brain or the central nervous system and the disease might not be high even if the graft was very risky. In other words, many of the results from Western countries as well as only one result of the case-control study in Japan exists between our two results; no relationship with surgical operation without a dura graft, and quite a high risk with the graft. All of the previous studies included both types of the operation, and the proportion of those with the transplantation might be smaller in Western countries than in Japan.

It is important from the public health viewpoint to determine whether blood transfusion is a risk factor of Creutzfeldt-Jakob disease. Same as previous studies, the current study shows no relationship between them. In addition, acupuncture was also not the risk factor of Creutzfeldt-Jakob disease.

In conclusion, our data on the case-control study revealed the very close relationship between cadaveric dura mater transplantation and Creutzfeldt-Jakob disease.

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