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Epidemiologic features of 65 Creutzfeldt–Jakob disease patients with a history of cadaveric dura mater transplantation in Japan

Y. NAKAMURA[1]*, H. YANAGAWA[2], T. KITAMOTO[3] AND T. SATO[4]

[1] *Department of Public Health, Jichi Medical School, 3311-1 Yakushiji, Minamikawachi, Tochigi 329-0498, Japan*
[2] *Saitama Prefectural University*
[3] *Department of Neuropathology, Tohoku University School of Medicine*
[4] *Khonodai Hospital, National Center of Neurology and Psychiatry*

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SUMMARY

A total of 65 cases of Creutzfeldt–Jakob disease with a history of cadaveric dura transplantation in Japan were analysed to clarify the epidemiologic features of such patients and to explore whether other such patients will appear in the future. The age at transplantation averaged 44·4 years with a standard deviation of 14·4 years. The age at onset had an average of 53·0 years with a standard deviation of 14·1 years. The shortest latent period was 14 months, and the longest was 218 months with an average of 103·1 months and a standard deviation of 49·9 months. From the relationship between the calendar year at transplantation and the latent period, other such patients will appear in the near future. The current data suggested that several patients with Creutzfeldt–Jakob disease will occur from those receiving cadaveric dura mater grafts in the near future.

INTRODUCTION

Just after the report of the relationship between bovine spongiform encephalopathy and new variant Creutzfeldt–Jakob disease from the United Kingdom, a nationwide epidemiologic survey of Creutzfeldt–Jakob disease was conducted in Japan in 1996 [1]. Fortunately, no new variant case was reported to the survey, but another problem was revealed. Forty-three patients with Creutzfeldt–Jakob disease had a medical history of cadaveric dura mater transplantation before the onset of the disease [2]. Although some case reports presented the relationship between the dura mater transplantation and risk of Creutzfeldt–Jakob disease [3–8], this was the first report about the clustering of such patients. Using these data as well as an assumption that the annual number of patients with dura mater transplantation was 20000, the relative risk of Creutzfeldt–Jakob disease among those with the history of dura transplantation was estimated to be between 30 and 100 in comparison with those without [9].

After the nationwide survey, the Ministry of Health and Welfare of the Japanese Government started a surveillance system of the disease on February 1997 [9]. In this surveillance, a physician that diagnosed Creutzfeldt–Jakob disease was required to report demographic and clinical data to the Ministry. This surveillance had conducted till 31 March 1999, and after 1 April 1999, Creutzfeldt–Jakob disease was designated to be a reportable disease according to a new law about prevention and treatment of infectious diseases issued on that day.

In this study, newly reported Creutzfeldt–Jakob disease patients with cadaveric dura mater trans-

* Author for correspondence.

plantation to the surveillance conducted between February 1997 and March 1999 were analysed in addition to the 43 such cases reported to the nationwide survey in 1996 [2]. This study has two purposes. One is to clarify the epidemiologic features of CJD patients with dura transplantation, in particular the distribution of period of time between the transplantation and the disease onset. The other is to explore whether other such patients will appear in the future. Many of the patients received the dura before 1987, when the 1 normal sodium hydroxide (NaOH) treatment for dura mater graft started. Considering that Creutzfeldt–Jakob disease is an infectious disease, it is lucky if the latent period has passed for many patients who received the risky dura before 1987 because it is more than 10 years from the infection.

MATERIALS AND METHODS

Data of 43 patients with Creutzfeldt–Jakob disease having a history of cadaveric dura mater transplantation that were reported to the nationwide survey in 1996 [2] were used. In addition, 21 such patients reported to the surveillance conducted by the Ministry of Health and Welfare during 26 months from February 1997 through March 1999 were observed. There was another case who was reported to the survey in 1996 as Creutzfeldt–Jakob disease without dura transplantation, but after the survey was reported as a transplantation case; this was added to the analyses. Thus, a total of 65 cases were analysed.

Data observed were: sex, date of birth, calendar year and age at the transplantation, physical condition causing the transplantation, brand name of the dura (Lyodura® or Tutoplast®), calendar year and age at the onset of Creutzfeldt–Jakob disease, period of time from the transplantation through the onset, and diagnostic criteria (definite, probable, or possible) [10]. All the patients, including the possible cases without periodic synchronous discharge on electroencephalography, were clinically unequivocal Creutzfeldt–Jakob disease cases confirmed by neurologists using secondary survey data sheet for the survey cases, and by a special committee for the surveillance including neurologists.

RESULTS

A total of 65 Creutzfeldt–Jakob disease patients with cadaveric dura transplantation (26 males and 39 females) were reported in Japan so far. As shown in Figure 1, the year when they received the dura distributed from 1979 through 1991, but many cases were clustered between 1983 and 1987. The age distribution at transplantation is shown in Figure 2. The youngest patient was 1 year old and the oldest was 70 years at transplantation, with an average of 44·4 years and a standard deviation of 14·4 years of age. The physical conditions which required the transplantation were: tumour (30 cases), brain haemorrhage (9), aneurysms without haemorrhage (5), haematoma (3), anomaly (5), injury (1), others (11), and unknown (1). All of the 61 cases whose grafts' brand name was known received Lyodura; the other 4 cases had no information about the brand name, and there was no case with Tutoplast apparently.

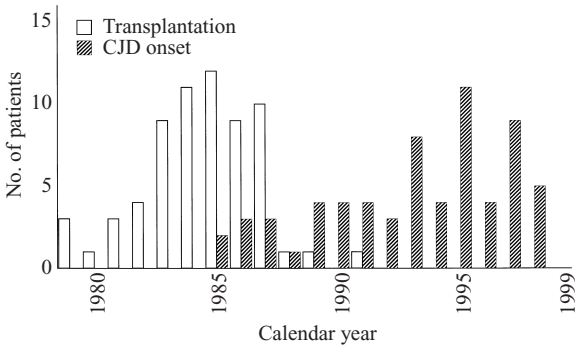

Fig. 1. Yearly distribution of dura mater transplantation and Creutzfeldt–Jakob disease (CJD) onset.

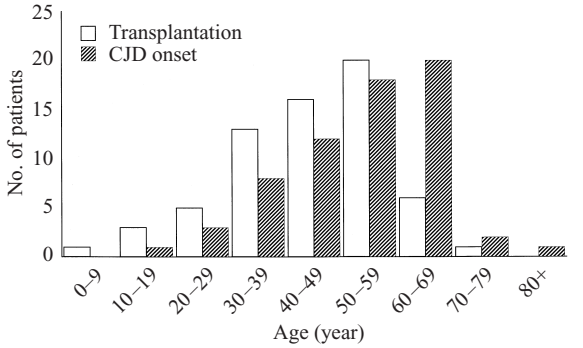

Fig. 2. Age at dura mater transplantation and Creutzfeldt–Jakob disease (CJD) onset.

As shown in Figure 1, new patients occurred in every year from 1985 through 1998, and many patients were observed in 1993, 1995, and 1997. Age at onset distributed from 15 through 80 years with an average of 53·0 years and a standard deviation of 14·1 years (Fig. 2). The duration between the transplantation and disease onset was shown in Figure 3. The shortest was 14 months, and the longest was 218 months with an average of 103·1 months and a standard deviation of 49·9 months. Relatively many patients had duration

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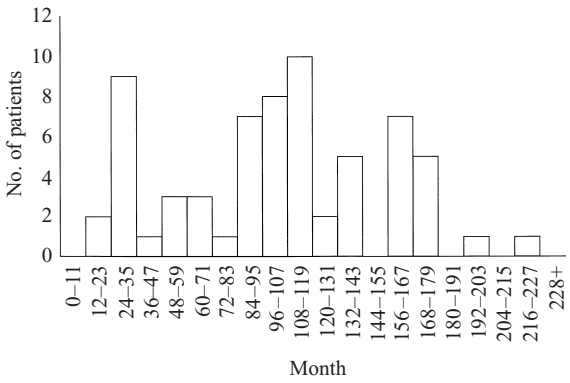

Fig. 3. Duration of time between dura mater transplantation and Creutzfeldt–Jakob disease (CJD) onset.

of 2 years, 7–9 years, and 13–14 years. There were 21 definite cases, 34 probable cases, and 10 possible cases.

Figure 4 shows the duration between the transplantation and onset by the calendar year of transplantation. The closed part of the table is future aspects. If the distribution of the duration of those who received the graft in 1979–81 are same as the distribution of those who received after then, other such patients will appear in the near future.

DISCUSSION

We investigated the epidemiologic features of the 65 Creutzfeldt–Jakob disease patients with a history of dura mater transplantation in Japan. The average of age at onset was 53·0 years and this was younger than that of all patients with Creutzfeldt–Jakob disease in Japan [1]. This is due to the fact that basic physical conditions that introduced the dura transplantation may occur in a young age generation. As shown in Figure 2, therefore, the age at the transplantation distributed from young to old age groups.

The calendar year at transplantation clustered in 5 years between 1983 and 1987, as shown in Figure 1. The reason why the number of patients that received the dura after 1987 decreased might be that Lyodura introduced the 1 normal NaOH treatment in 1987 [11]. However, because neither the company that produced Lyodura nor the government recalled the old dura grafts in the market such as retailers and hospitals, some patients received old graft after 1987 and might be affected by Creutzfeldt–Jakob disease.

The duration between the transplantation and Creutzfeldt–Jakob disease onset has prolonged. The average duration was 89 months for 43 patients reported to the 1996 survey [2], and the current study including the 43 cases showed an average of 103 months. This is because many of such cases received the dura with old treatment on and before 1987, and the observed period was prolonged; the nationwide survey in 1996 was till 1996, and the current study was till 1999.

In this study, the number of patients who received the dura before 1982 was small, but this does not indicate that dura transplantation before 1982 was less risky. The nationwide survey in 1996 targeted patients with Creutzfeldt–Jakob disease in and after 1985 [1]. As shown in Figure 3, one peak exists on the duration from the transplantation through the onset at year two. A patient receiving a dura graft before 1982 who manifested Creutzfeldt–Jakob disease 2 years after the transplantation would not have been reported to the nationwide survey. Besides, because the first report that indicated the relationship between the dura graft and the disease was published in 1987 [3], physicians and neurologists might not focus on the transplantation when they saw patients with Creutzfeldt–Jakob disease before then, even if such patients existed. Therefore, the duration observed may include an underestimate even in the short period of time.

The probability that other patients with Creutzfeldt–Jakob disease having received the dura graft will appear in the near future is high because of two reasons. One is that the longest latent period from the transplantation through the onset of Creutzfeldt–Jakob disease is still unknown. Two cases receiving the graft in 1979 were affected by the disease after 18 years and 16 years, as shown in Figure 4. It is possible that cases with longer latent periods will exist. The other reason is that the current observation was finished in 1999. As shown in Figure 3, another peak of the latent period exists in 13 or 14 years. On the other hand, those who received the dura after 1985 have not been observed yet for this peak of the latent period. These two reasons suggest to us that several patients with Creutzfeldt–Jakob disease who had a history of dura transplantation will occur in the near future.

The number of female patients were larger than that of males. This result is similar to that of all the Creutzfeldt–Jakob disease patients in Japan [1]. Because we do not have any information about the age-specific numbers of patients receiving dura grafts, which should be denominators to calculate the risk, however, we cannot discuss the sex difference of the risk more.

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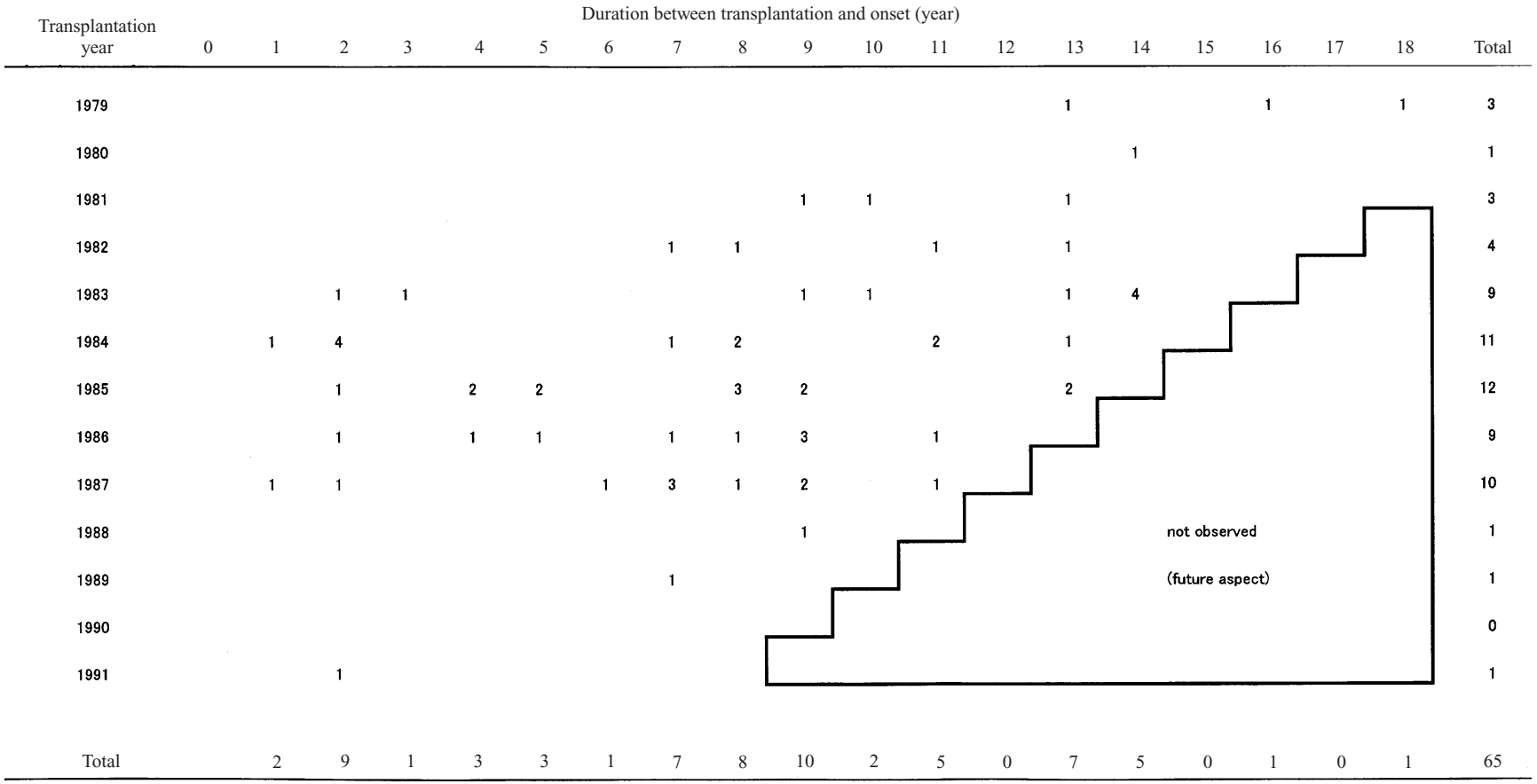

Fig. 4. Duration of time between dura mater transplantation and Creutzfeldt–Jakob disease onset, by the year at the transplantation.

In conclusion, we indicated in this study that several patients with Creutzfeldt–Jakob disease will occur in the near future in those receiving cadaveric dura mater grafts. In addition, epidemiologic features, such as age distribution and latent period, were presented.

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