**Graft-related disease progression in dura mater graft-associated Creutzfeldt–Jakob disease: a cross-sectional study**

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Graft-related disease progression in dura mater graft-associated Creutzfeldt–Jakob disease: a cross-sectional study

Kenji Sakai, MD, PhD,1 Tsuyoshi Hamaguchi, MD, PhD,1 Moeko Noguchi-Shinohara, MD, PhD,1 Ichiro Nozaki, MD, PhD,1 Ichiro Takumi, MD, PhD,2 Nobuo Sanjo, MD, PhD,3 Yosikazu Nakamura, MD, MPH,4 Tetsuyuki Kitamoto, MD, PhD,5 Nobuhito Saito, MD, PhD,6 Hidehiro Mizusawa, MD, PhD,3 Masahito Yamada, MD, PhD1

1 Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan
2 Department of Neurosurgery, Nippon Medical School Musashi Kosugi Hospital, Kawasaki, Japan
3 Department of Neurology and Neurological Science, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan
4 Department of Public Health, Jichi Medical University, Shimotsuke, Japan
5 Departments of Prion Protein Research, Division of CJD Science and Technology, Tohoku University Graduate School of Medicine, Sendai, Japan
6 Department of Neurosurgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

Correspondence to: Professor Masahito Yamada
Department of Neurology and Neurobiology of Ageing, Kanazawa University
Graduate School of Medical Science
13-1 Takara-machi, Kanazawa 920-8640, Japan
Fax: +81-76-234-4253
Phone: +81-76-265-2290
E-mail: m-yamada@med.kanazawa-u.ac.jp

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Abstract

Objectives: Details of abnormal prion protein (PrPSc) propagation in the human central nervous system (CNS) are unclear. To assess the spread of PrPSc through the human CNS, we evaluated dura mater graft-associated Creutzfeldt-Jakob disease (dCJD) cases focusing on sites of grafting and dCJD pathological subtypes.

Design: A cross-sectional study.

Setting: A nationwide surveillance data of human prion diseases in Japan over the past 12 years was applied for the study.

Participants: Clinical data was obtained from 84 dCJD patients.

Outcome measures: The clinical courses in cases of dCJD were analyzed according to the grafting sites (supratentorial and infratentorial groups) and the pathological subtypes (non-plaque and plaque types).

Results: Of the 84 cases of dCJD in this study, 36 (43%) were included in the supratentorial group and 39 (46%) were included in the infratentorial group. As initial manifestations, vertigo (P = 0.007) and diplopia (P = 0.041) were significantly more frequent in the infratentorial group than in the supratentorial group. During their clinical course, cerebellar signs appeared more frequently in the infratentorial group.
than in the supratentorial group ($P = 0.024$). In the non-plaque type cases ($n = 53$), the infratentorial group developed vertigo more frequently than the supratentorial group ($P = 0.017$); moreover, cerebellar signs appeared more frequently in the infratentorial group ($P = 0.014$). However, there was no significant difference between the groups in the plaque type ($n = 18$).

**Conclusions:** The high frequency of clinical manifestations related to brain stem and cerebellar dysfunction in the non-plaque type dCJD with infratentorial grafting suggests that PrP$^\text{Sc}$ commonly shows direct propagation into the CNS from contaminated dura mater grafts.

(268 words)
Article summary

Article focus


- We analyzed the clinical data taking into account not only grafting site but also the pathological subtypes of dCJD.

Key messages

- Infratentorial grafting cases in non-plaque type developed manifestations related to dysfunction of the brain stem and cerebellum more frequently than supratentorial grafting cases.

- Cerebellar signs also appeared more frequently in the infratentorial group during their clinical course.

- Plaque type cases showed no significant difference between the supratentorial and the infratentorial groups.

Strengths and limitations of this study

- This study suggests that the non-plaque type abnormal prion protein (PrP^Sc) strain...
would propagate from grafted dura mater to the adjacent brain directly and damage it earlier and more severely.

- It would be difficult to determine focal brain lesions by PrP Sc accumulation and subsequent neuronal damage from only information about clinical manifestations.
- Another limitation of this study includes the relatively small number of plaque-type patients, which demonstrated no noteworthy results.
Introduction

Dura mater graft-associated Creutzfeldt–Jakob disease (dCJD) is an acquired Creutzfeldt–Jakob disease (CJD) related to previous dura mater graft transplantation.\textsuperscript{1,2} Details of abnormal prion protein (PrP\textsuperscript{Sc}) propagation in the human central nervous system (CNS) are not fully understood.\textsuperscript{3} Previous studies of dCJD cases disclosing the relationship between initial manifestation and the site of grafting proposed that PrP\textsuperscript{Sc} may propagate directly from the contaminated dura mater graft to the adjacent brain regions and may spread from the initially infected regions to other brain regions.\textsuperscript{4–6} In the previous studies of dCJD case series, however, the results were obtained without considering dCJD pathological subtypes.\textsuperscript{5,6}

There are 2 subtypes of dCJD: non-plaque type and plaque type. The non-plaque type is characterized by typical clinical features of CJD and synaptic-type PrP\textsuperscript{Sc} deposits without PrP\textsuperscript{Sc} plaques in the brain. In contrast, the plaque type is characterized by atypical clinical features and plaque-type PrP\textsuperscript{Sc} deposits in the brain.\textsuperscript{7–9} These subtypes arise from 2 distinct prion strains.\textsuperscript{7–9} Each prion strain has different characteristics of incubation period and neuropathological features when inoculated into defined inbred mice;\textsuperscript{8,10} it was proposed that each prion strain must
show a distinct propagation process in the human brain. Therefore, the disease pathological subtypes (prion strains) should be taken into consideration when clinical features are analyzed in dCJD cases. This study made use of the prospective prion disease surveillance in Japan, to analyze clinical manifestations of dCJD cases taking into account not only their grafting sites but also their pathological subtypes.

Materials and Methods

Patients

In Japan, the prospective surveillance of human prion disease by the CJD Surveillance Committee in Japan started in April 1999. Details of the Japanese surveillance system and case definition were reported previously. Briefly, all patients suspected of having a prion disease were registered by the CJD Surveillance Committee, and their diagnoses were judged. Prion diseases were classified into 4 categories: (i) sporadic CJD; (ii) acquired prion diseases (iatrogenic CJD or variant CJD); (iii) genetic prion diseases; and (iv) unclassified prion disease. Sporadic CJD was diagnosed according to the classical criteria established by Masters. The World Health Organization (WHO) criteria (WHO, 1998) were applied from April 2009. Regarding the patients...
with previous medical procedures which might be related to CJD, details of the information were collected, and the diagnosis of iatrogenic CJD was decided carefully. Iatrogenic CJD was also diagnosed and categorized (definite, probable, and possible) using the criteria for sporadic CJD. In patients with iatrogenic CJD, the diagnosis of dCJD was decided by confirmation of dura mater grafting. The medical records, information from each neurosurgeon, or the autopsy findings were used to ensure dura mater grafting occurred. Then, cases of dCJD were categorized into 2 pathological subtypes: the non-plaque type, which shows synaptic-type PrP\textsuperscript{Sc} deposits without PrP\textsuperscript{Sc} plaques; and the plaque type, which shows plaque-type PrP\textsuperscript{Sc} deposits.\textsuperscript{7} In cases without pathological confirmation, we classified cases showing periodic sharp-wave complexes in the electroencephalogram (EEG) within 12 months of disease onset as non-plaque type, and classified cases showing no periodic sharp-wave complexes in the EEG within 12 months of disease onset as plaque type.\textsuperscript{7} As the plaque type dCJD patients without pathological confirmation never satisfied the criteria for probable case,\textsuperscript{7} possible cases were included in this analysis in addition to definite and probable cases. We analyzed all dCJD patients identified by the current surveillance system up to and including February 2012.
Written informed consent to participate in this study was obtained from the families of all the patients. The study protocol was approved by the medical ethics committee of Kanazawa University and Tokyo Medical and Dental University.

Clinical studies

We collected the following information regarding dura mater grafting: calendar year when the surgical operation was performed; the brand name of the dura mater graft; and the site of the dural grafting. In addition to the grafting sites (supratentorial or infratentorial), we also analyzed the following parameters: sex; age at dural grafting; incubation period; age at CJD onset; information about initial manifestation; and symptoms which appeared during their clinical course, including cerebellar signs, psychiatric features, dementia, visual disturbances, myoclonus, extrapyramidal signs, and pyramidal signs. Since several patients developed more than one initial manifestation, we counted each manifestation separately. Information about PrP gene polymorphisms at codon 129 and 219 was also collected from patients who underwent genetic analysis. Moreover, we analyzed the initial symptoms and clinical manifestations that emerged during their clinical course in each pathological subtype,
and compared the supratentorial grafting cases with the infratentorial grafting cases.

Statistical analysis

Any difference in age at dural grafting, incubation period, and age at CJD onset between the supratentorial group and the infratentorial group was assessed using the Mann-Whitney *U* test. Pathological subtype classification, sex, initial symptoms, clinical manifestations, and PrP gene polymorphisms were assessed using a chi-square test or Fisher’s exact probability test. Statistical significance was defined as *P* < 0.05.

Statistical analyses were performed using SPSS version 19 (IBM, Armonk, NY).

**Results**

The CJD Surveillance Committee in Japan identified 84 patients with dCJD between April 1999 and February 2012. Fifty-eight patients with dCJD had already been reported by previous investigations,\(^9,11\) therefore, the total number of dCJD was 142.\(^2\)

The surgeries with dura mater grafts were performed between 1975 and 1993. The brand name of grafted dura mater was identified in 74 cases (88%). Lyodura\(^\text{®} \) (B.Braun, Melsungen, Germany) was transplanted in all proven cases. The grafting
site was confirmed in 77 out of 84 cases (92%); 36 in supratentorial regions, 39 in
infratentorial regions, and 2 in spinal cord regions (Table 1). An autopsy was
performed in 32 cases (38%).

The 84 dCJD cases were classified into 53 cases (63%) of the non-plaque type and
18 cases (21%) of the plaque type. It was not possible to classify the pathological
subtype in 13 cases (16%) due to an inadequacy of clinical or pathological information
(Table 1). There were 18 of 53 non-plaque type cases (34%) proven by autopsy and 14
out of 18 cases plaque type (78%) cases proven by autopsy.

The clinical features of dCJD for all patients, the supratentorial group, and the
infratentorial group are summarized in Table 1. The proportion of females in the
infratentorial group was larger than that in the supratentorial group ($P = 0.015$). Age at
dural grafting, incubation period, or age at CJD onset showed no significant difference
between the 2 groups. Regarding initial manifestations, vertigo (31% and 3%; $P =
0.007$) and diplopia (15% and 0%; $P = 0.041$) were more frequently observed in the
infratentorial group than in the supratentorial group. Dementia and behavioral
abnormality suggesting dysfunction of the cerebrum demonstrated no significant
difference between the groups. In the infratentorial group, 8 cases (31%) developed
dementia or behavioral abnormalities. The incubation periods of cases developing dementia or behavioral abnormalities in the supratentorial group and the infratentorial group, reported as median (range), were 15 (11–30) years and 16 (10–25) years, respectively ($P = 0.847$). During the clinical course, the infratentorial group showed cerebellar signs (87% and 64%; $P = 0.024$) more frequently than the supratentorial group. There were no significant difference in the proportion of the PrP genotype or the type classification of dCJD between the 2 groups. In addition, 2 cases with spinal cord region grafting developed dementia, diplopia or unsteady gait.

Results from the analysis of the non-plaque type cases were similar to those of the sample population as a whole (Table 2). Vertigo was more frequently observed as an initial manifestation in the infratentorial group than in the supratentorial group (32% and 0%; $P = 0.017$). There was a trend in the increase of diplopia frequency in the infratentorial group (21% and 0%; $P = 0.074$). Dementia and behavioral abnormalities demonstrated no significant difference between the 2 groups. In the infratentorial group, 7 cases (37%) demonstrated dementia or behavioral abnormalities as initial manifestations. Similar to the analysis of the sample population as a whole, the median incubation period of cases developing dementia or behavioral abnormalities
showed no significant difference between the supratentorial and infratentorial groups (data not shown). Cerebellar signs were significantly more often realized in the infratentorial group during their clinical course than in the supratentorial group (87% and 50%; \( P = 0.041 \)). In contrast, there was no significant difference between the supratentorial group and the infratentorial group concerning initial manifestations or manifestations during their clinical course in the analysis of the plaque type cases (Table 3).

**Discussion**

In this study of dCJD cases, we have reported that infratentorial grafting cases in not only the sample population as a whole but also the non-plaque type cases developed manifestations related to dysfunction of the brain stem and cerebellum more frequently than supratentorial grafting cases. Moreover, cerebellar signs appeared more frequently in the infratentorial group during their clinical course. In contrast, plaque type cases showed no significant difference between the supratentorial and the infratentorial groups.

These results suggest that the non-plaque type PrP\(^{Sc}\) strain would propagate from
grafted dura mater to the adjacent brain directly. In experimental studies, PrP<sup>Sc</sup> has the ability to spread from cell to cell. Mice experiments with PrP<sup>Sc</sup> inoculated directly into the brain showed that PrP<sup>Sc</sup> accumulated at the site of initial inoculation and spread around that area. A mouse model of dCJD, in which a small collagen sheet absorbing prion-infected brain homogenates was transplanted onto the brain surface, also disclosed spongiform changes and accumulation of PrP<sup>Sc</sup> in the transplanted cortical areas. Concerning the plaque-type prion strain, there was no significant difference between infratentorial grafting and supratentorial grafting groups. The plaque type PrP<sup>Sc</sup> strain may have a propagation process that is distinct from the non-plaque type prion strain. A case series study of dCJD demonstrated that plaque-type patients were likely to develop gait disturbance. In this study, 3 out of 4 plaque type patients developed unsteady gait after supratentorial grafting (Table 3). These results suggest that the plaque-type PrP<sup>Sc</sup> strain, which must have a distinct nature from the non-plaque type PrP<sup>Sc</sup> strain, might damage specific brain regions causing gait disturbance during the early stage of the disease process in spite of the difference in grafting sites, possibly through transportation of the PrP<sup>Sc</sup> to the specific brain regions. An animal study proved that the plaque type dCJD could be caused by
cross-sequence transmission of sporadic CJD VV2 prions to individuals that are
methionine homozygotes at codon 129 of the PrP gene. Furthermore, another animal
study showed that sporadic CJD MV2 prions could also induce plaque type dCJD
pathology (Kitamoto T. Unpublished data). CJD VV2 and CJD MV2, which might
cause plaque-type prions, are well known as an ataxic form CJD. Meanwhile, the
small number of plaque type cases might influence these results, resulting in no
significant difference between the supratentorial and infratentorial groups.

Our study suggests that, generally, brain tissue near the grafting site was damaged
earlier and more severely through direct propagation of PrP\textsuperscript{Sc} from the grafts.

However, some cases also suggested that there were different patterns of PrP\textsuperscript{Sc}
propagation. For instance, 31% of all infratentorial grafting cases and 37% of the
non-plaque type with infratentorial grafting cases developed dementia or behavioral
abnormalities, indicating initial dysfunction of the cerebrum. Moreover, 2 cases of
spinal cord grafts did not develop symptoms related to spinal cord dysfunction.

Interestingly, the cerebellar signs throughout the clinical course in the supratentorial
group were demonstrated less frequently than those in the infratentorial group in all
cases and in the non-plaque type cases.
These results may suggest the presence of different propagation pathways of PrP\textsuperscript{Sc} in addition to the direct invasion of brain tissue, via cerebrospinal fluid, blood stream, or lymphatic drainage from the CNS. Recently, it has been suggested that lymphatic systems could play an important role in PrP\textsuperscript{Sc} infection of the brain.\textsuperscript{19} In most cases of prion infection regarding variant CJD, the point of PrP\textsuperscript{Sc} entry can be outside the nervous system.\textsuperscript{19} After the infection of the organs outside the nervous system, PrP\textsuperscript{Sc} moves into the blood and lymphoid fluids, and replicates in the lymphoid organs. Then, PrP\textsuperscript{Sc} is transported to the brain through the peripheral nervous system.\textsuperscript{19,20} In addition to variant CJD cases, PrP\textsuperscript{Sc} was detected in muscles, intramuscular nerve fibers, and dorsal root ganglia in sporadic CJD, in which causes of the disease are uncertain.\textsuperscript{21-23} PrP\textsuperscript{Sc} contamination of dural grafts may have a similar process of indirect infection of the CNS in addition to the direct invasion of the adjacent brain tissue. Although little data regarding PrP\textsuperscript{Sc} deposition in tissues other than the CNS in dCJD is available, PrP\textsuperscript{Sc} was detected in the peripheral nerves in cases of dCJD on immunohistochemical study and western blot analysis.\textsuperscript{24} In this study, no significant difference in the incubation period was revealed between the patients with suggested direct infection and the patients with suggested indirect infection. Further
examination regarding PrP$^{Sc}$ accumulation in other organs is necessary to confirm this indirect infection of PrP$^{Sc}$ into the CNS in dCJD cases.

In addition to a hypothesis of indirect propagation of PrP$^{Sc}$ into the CNS, various combinations of clinical manifestations and brain lesions may influence the symptoms of dCJD patients. Ataxia is a common manifestation stemming from cerebellar or brain stem dysfunction; however, lesions involving cerebral areas and fibers connecting to the cerebellum also cause ataxia. Moreover, several case reports presented patients showing rotational vertigo in the clinical course of stroke in the cerebral hemisphere. It would be difficult to determine focal brain lesions by PrP$^{Sc}$ accumulation and subsequent neuronal damage from only information about the clinical manifestations in each case. Therefore, analyses with imaging techniques, including magnetic resonance imaging, single-photon emission tomography, and positron emission tomography, are necessary to confirm the relationship between the grafting site and PrP$^{Sc}$ propagation in human CNS.

In conclusion, our results indicate that PrP$^{Sc}$ of non-plaque type dCJD tends to spread from the grafted sites to the adjacent brain, although different propagation pathways may be present in some cases.
(2,312 words)
Acknowledgements

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Competing interests

None.

Ethics approval
This study was conducted with the approval of the institutional ethics committee at Kanazawa University and Tokyo Medical and Dental University.

Contributors

Dr. Sakai: study concept and design, analysis and interpretation of data, statistical analysis, drafting/revising the manuscript. Dr. Hamaguchi: study concept and design, drafting/revising the manuscript. Dr. Noguhi-Shinohara: acquisition of data, revising the manuscript. Dr. Nozaki: acquisition of data, revising the manuscript. Dr. Takumi: acquisition of data, revising the manuscript. Dr. Sanjo: acquisition of data, revising the manuscript. Dr. Nakamura: acquisition of data, statistical analysis, revising the manuscript. Dr. Kitamoto: acquisition of data, revising the manuscript. Dr. Saito: acquisition of data, revising the manuscript. Dr. Mizusawa: acquisition of data, revising the manuscript, study supervision. Dr. Yamada: study concept and design, acquisition of data, drafting/revising the manuscript, study supervision.

Data sharing statement

no additional data available.
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molecular characterization of the two distinct subtypes. *Neuropathology*


worldwide occurrence and the significance of familial and sporadic clustering. *Ann
Neurol* 1979;5:177–188.


Table 1. Clinical features of the dura mater graft-associated Creutzfeldt–Jakob disease cases for all cases, the supratentorial group, and the infratentorial group.

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<th></th>
<th>Total (n = 84)*</th>
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<th>Infratentorial group (n = 39)</th>
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<td><strong>Type classification‡</strong></td>
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<td>Non-plaque type (%)</td>
<td>53 (63)</td>
<td>20 (56)</td>
<td>28 (72)</td>
<td>n.s.</td>
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<td>Plaque type (%)</td>
<td>18 (21)</td>
<td>9 (25)</td>
<td>8 (21)</td>
<td>n.s.</td>
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<td><strong>Male/Female</strong></td>
<td>35/49</td>
<td>19/17</td>
<td>10/29</td>
<td>P = 0.015</td>
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<td><strong>Age at dural grafting§ (years)</strong></td>
<td>45 (1–65)</td>
<td>45 (1–60)</td>
<td>51 (7–65)</td>
<td>n.s.</td>
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<td><strong>Incubation period§ (years)</strong></td>
<td>15 (6–30)</td>
<td>15 (8–30)</td>
<td>14 (6–25)</td>
<td>n.s.</td>
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<td><strong>Age at onset§ (years)</strong></td>
<td>61 (15–80)</td>
<td>61 (15–79)</td>
<td>66 (24–80)</td>
<td>n.s.</td>
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<td><strong>Initial manifestations§ (%)</strong></td>
<td>(n = 63)</td>
<td>(n = 30)</td>
<td>(n = 26)</td>
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<td>Unsteady gait</td>
<td>30 (48)</td>
<td>16 (53)</td>
<td>11 (42)</td>
<td>n.s.</td>
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<tr>
<td>Dementia</td>
<td>16 (25)</td>
<td>8 (27)</td>
<td>6 (23)</td>
<td>n.s.</td>
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<tr>
<td>Vertigo</td>
<td>9 (14)</td>
<td>1 (3)</td>
<td>8 (31)</td>
<td>P = 0.007</td>
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<td>Behavioral abnormality</td>
<td>7 (11)</td>
<td>5 (17)</td>
<td>2 (8)</td>
<td>n.s.</td>
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<tr>
<td>Ataxia</td>
<td>7 (11)</td>
<td>4 (13)</td>
<td>1 (4)</td>
<td>n.s.</td>
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<tr>
<td>Diplopia</td>
<td>4 (6)</td>
<td>0 (0)</td>
<td>4 (15)</td>
<td>P = 0.041</td>
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<tr>
<td>Sensory disturbance</td>
<td>4 (6)</td>
<td>2 (7)</td>
<td>2 (8)</td>
<td>n.s.</td>
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<tr>
<td>Visual disturbance</td>
<td>3 (5)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>n.s.</td>
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<td>Manifestations during clinical course (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cerebellar signs</td>
<td>62/82 (76)</td>
<td>23/36 (64)</td>
<td>32/37 (87)</td>
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<tr>
<td>Psychiatric feature</td>
<td>51/79 (65)</td>
<td>20/32 (63)</td>
<td>27/38 (71)</td>
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<tr>
<td>Dementia</td>
<td>82/84 (98)</td>
<td>35/36 (97)</td>
<td>38/39 (97)</td>
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<td>Visual disturbance</td>
<td>36/81 (44)</td>
<td>16/35 (46)</td>
<td>18/37 (49)</td>
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<td>Myoclonus</td>
<td>71/82 (87)</td>
<td>31/36 (86)</td>
<td>34/37 (92)</td>
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<td>Extrapyramidal signs</td>
<td>53/82 (65)</td>
<td>25/36 (69)</td>
<td>26/37 (70)</td>
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<tr>
<td>Pyramidal signs</td>
<td>58/81 (72)</td>
<td>28/35 (80)</td>
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PrP gene polymorphisms

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<tr>
<th>Codon 129</th>
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<tr>
<td>Codon 219</td>
<td>EE 52, EK 3</td>
<td>EE 21, EK 3</td>
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</table>

* Total includes 2 cases with spinal cord regions and 7 cases with uncertain grafting regions.

† P value was assessed between the supratentorial group and the infratentorial group;

n.s. not significant.

‡13 cases of type classification were unclear.

§ median

|| 22 cases of the total, 9 cases of the supratentorial group and 8 cases of the
infratentorial group developed more than one initial manifestation.

†Others include individual cases of hemiparesis, dysarthria, incontinence, hearing disturbance, and nystagmus.


EE: glutamine homozygote, EK: glutamine/lysine heterozygote.
Table 2. Clinical manifestations of non-plaque type cases.

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Total (n = 53)</th>
<th>Supratentorial (n = 20)</th>
<th>Infratentorial (n = 28)</th>
<th>P value^†</th>
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<tr>
<td>Pathologically confirmed cases (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 (34)</td>
<td>9 (45)</td>
<td>7 (25)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Initial manifestations‡ (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsteady gait</td>
<td>12 (31)</td>
<td>4 (25)</td>
<td>7 (37)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dementia</td>
<td>11 (28)</td>
<td>6 (38)</td>
<td>5 (26)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Vertigo</td>
<td>6 (15)</td>
<td>0 (0)</td>
<td>6 (32)</td>
<td>P = 0.017</td>
</tr>
<tr>
<td>Behavioral abnormality</td>
<td>6 (15)</td>
<td>4 (25)</td>
<td>2 (11)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ataxia</td>
<td>6 (15)</td>
<td>3 (19)</td>
<td>1 (5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diplopia</td>
<td>5 (13)</td>
<td>0 (0)</td>
<td>4 (21)</td>
<td>P = 0.074</td>
</tr>
<tr>
<td>Sensory disturbance</td>
<td>2 (5)</td>
<td>1 (6)</td>
<td>1 (5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Extrapyramidal signs</td>
<td>1 (3)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Others§ (%)</td>
<td>3 (8)</td>
<td>3 (19)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Manifestations during clinical course (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>35/51 (69)</td>
<td>10/20 (50)</td>
<td>22/26 (85)</td>
<td>P = 0.014</td>
</tr>
<tr>
<td>Psychiatric feature</td>
<td>32/50 (64)</td>
<td>11/17 (65)</td>
<td>19/28 (68)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dementia</td>
<td>51/53 (96)</td>
<td>19/20 (95)</td>
<td>27/28 (96)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Manifestation</td>
<td>Supratentorial</td>
<td>Infratentorial</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>21/51 (41)</td>
<td>8/19 (42)</td>
<td>12/27 (44)</td>
<td></td>
</tr>
<tr>
<td>Myoclonus</td>
<td>50/52 (96)</td>
<td>20/20 (100)</td>
<td>25/26 (96)</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal signs</td>
<td>30/51 (59)</td>
<td>12/20 (60)</td>
<td>17/26 (65)</td>
<td></td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>40/51 (78)</td>
<td>18/20 (90)</td>
<td>19/26 (73)</td>
<td></td>
</tr>
</tbody>
</table>

* Total includes 2 cases with spinal cord regions and 3 cases with uncertain grafting regions.

† *P* value was assessed between the supratentorial group and the infratentorial group;

n.s. not significant.

‡ 13 cases of the total, 5 cases of the supratentorial group and 8 cases of the infratentorial group developed more than one initial manifestation.

§ Others include individual cases of hemiparesis, dysarthria, and nystagmus.
Table 3. Clinical manifestations of plaque type cases.

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Total group (n = 18)</th>
<th>Supratentorial group (n = 9)</th>
<th>Infratentorial group (n = 8)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologically confirmed cases (%)</td>
<td>14 (78)</td>
<td>7 (78)</td>
<td>6 (75)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Initial manifestations‡ (%)</td>
<td>(n = 14)</td>
<td>(n = 8)</td>
<td>(n = 5)</td>
<td></td>
</tr>
<tr>
<td>Unsteady gait</td>
<td>9 (64)</td>
<td>6 (75)</td>
<td>2 (40)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dementia</td>
<td>2 (14)</td>
<td>1 (13)</td>
<td>1 (20)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Vertigo</td>
<td>3 (21)</td>
<td>1 (13)</td>
<td>2 (40)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diplopia</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sensory disturbance</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>1 (20)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Others§</td>
<td>2 (14)</td>
<td>2 (25)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Manifestations during clinical course (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>16/18 (89)</td>
<td>8/9 (89)</td>
<td>7/8 (88)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Psychiatric feature</td>
<td>10/16 (63)</td>
<td>4/8 (50)</td>
<td>5/7 (71)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dementia</td>
<td>18/18 (100)</td>
<td>9/9 (100)</td>
<td>8/8 (100)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>14/18 (78)</td>
<td>8/9 (89)</td>
<td>6/8 (75)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Extrapyramidal signs</td>
<td>14/18 (78)</td>
<td>8/9 (89)</td>
<td>6/8 (75)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>8/17 (47)</td>
<td>5/8 (63)</td>
<td>3/8 (38)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

* Total includes 1 case with an uncertain grafting region.
† P value was assessed between the supratentorial group and the infratentorial group;

n.s. not significant.

‡ 4 cases of the total, 2 cases of the supratentorial group and 1 cases of the

infratentorial group developed more than one initial manifestation.

§ Others include indivisual cases of incontinence and hearing disturbance.
STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Title and abstract** | 1  
(a) Indicate the study’s design with a commonly used term in the title or the abstract  
We used common words in the title and the abstract.  
(b) Provide in the abstract an informative and balanced summary of what was done and what was found  
The abstract summarized the study well. |
| **Introduction** | 2  
Explain the scientific background and rationale for the investigation being reported  
The introduction satisfied sufficiently these points. |
| **Objectives** | 3  
State specific objectives, including any prespecified hypotheses  
The research objected was stated in page 8, lines 4–6. |
| **Methods** | 4  
Present key elements of study design early in the paper  
The study design was described in the ‘Patients’ section in pages 8–10. |
| **Setting** | 5  
Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  
Details of the setting were mentioned in the ‘Patients’ section. |
| **Participants** | 6  
(a) Give the eligibility criteria, and the sources and methods of selection of participants  
The ‘Patients’ section gave the information regarding participants. |
| **Variables** | 7  
Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable  
These points were mentioned in the ‘Patients’ section. |
| **Data sources/ measurement** | 8*  
For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group  
The ‘Clinical studies’ section clearly described them. |
| **Bias** | 9  
Describe any efforts to address potential sources of bias  
We tried to avoid any bias. |
| **Study size** | 10  
Explain how the study size was arrived at  
This point was described in the ‘Patients’ section. |
| **Quantitative variables** | 11  
Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why  
We analyzed all patients who met the inclusion criteria for the study. |
| **Statistical methods** | 12  
(a) Describe all statistical methods, including those used to control for confounding  
(b) Describe any methods used to examine subgroups and interactions  
(c) Explain how missing data were addressed  
(d) If applicable, describe analytical methods taking account of sampling strategy  
(e) Describe any sensitivity analyses  
The statistical methods were mentioned in the ‘Statistical analysis’ section in page 11. |
| **Results** | 13*  
(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
(b) Give reasons for non-participation at each stage

(c) Consider use of a flow diagram

The numbers of patients analyzed were described in page 11 and tables.

Descriptive data 14*

(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders

(b) Indicate number of participants with missing data for each variable of interest

These points were mentioned in page 12, lines 9–11.

Outcome data 15*

Report numbers of outcome events or summary measures

These points were mentioned in pages from 11 to 14.

Main results 16

(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

(b) Report category boundaries when continuous variables were categorized

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

The results including the tables mentioned difference between two groups we analyzed. The results were provided by p values.

Other analyses 17

Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results 18

Summarise key results with reference to study objectives

The key results were mentioned at the beginning of the discussion section.

Limitations 19

Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

These points were described in the discussion section.

Interpretation 20

Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

These points were described throughout the discussion section.

Generalisability 21

Discuss the generalisability (external validity) of the study results

The generalisability of the study was discussed in pages 16 and 17.

Other information

Funding 22

Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Funding was stated in pages 20.

*Give information separately for exposed and unexposed groups.

Graft-related disease progression in dura mater
graft-associated Creutzfeldt-Jakob disease: a
cross-sectional study

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Ichiro Takumi, Nobuo Sanjo, Yosikazu Nakamura, Tetsuyuki Kitamoto,
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