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

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ABSTRACT

Objectives: Details of abnormal prion protein (PrP^{Sc}) propagation in the human central nervous system (CNS) are unclear. To assess the spread of PrP^{Sc} 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: nationwide surveillance data of human prion diseases in Japan over the past 12 years were applied for the study.

Participants: Clinical data were obtained from 84 dCJD patients.

Outcome measures: The clinical courses in cases of dCJD were analysed 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 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^{Sc} commonly shows direct propagation into the CNS from contaminated dura mater grafts.

ARTICLE SUMMARY

Article focus

- Evaluation of the relationship between initial manifestation and the site of dura mater graft in patients with dura mater graft-associated Creutzfeldt-Jakob disease (dCJD).
- We analysed the clinical data taking into account not only the 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 did 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 directly from the grafted dura mater to the adjacent brain 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.[1 2] Details of abnormal prion protein (PrP^{Sc}) propagation in the human central nervous system (CNS) are not fully understood.[3] Previous studies of dCJD cases disclosing the relationship between initial manifestation and the site of grafting proposed that PrP^{Sc} may propagate directly from the contaminated dura mater graft to the adjacent brain regions and spread from the initially infected regions to

other brain regions.[4–6] In previous studies of the dCJD case series, however, results were obtained without considering the dCJD pathological subtypes.[5 6]

There are two subtypes of dCJD: non-plaque type and plaque type. The non-plaque type is characterised by typical clinical features of CJD and synaptic-type PrP^{Sc} deposits without PrP^{Sc} plaques in the brain. In contrast, the plaque type is characterised by atypical clinical features and plaque-type PrP^{Sc} deposits in the brain.[7–9] These subtypes arise from two distinct prion strains.[7–9] Each prion strain has different characteristics of incubation period and neuropathological features when inoculated into defined inbred mice[8 10]; it was proposed that each prion strain must show a distinct propagation process in the human brain.[10] Therefore, the disease pathological subtypes (prion strains) should be taken into consideration when clinical features are analysed in dCJD cases. This study made use of the prospective prion disease surveillance in Japan to analyse 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.[11] 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 four categories: (1) sporadic CJD, (2) acquired prion diseases (iatrogenic CJD or variant CJD), (3) genetic prion diseases and (4) unclassified prion disease. Sporadic CJD was diagnosed according to the classical criteria established by Masters *et al*.[12] The WHO criteria (WHO, 1998)[13] 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 categorised (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 the occurrence of dura mater grafting. Cases of dCJD were categorised into two pathological subtypes: the non-plaque type, which shows synaptic-type PrP^{Sc} deposits without PrP^{Sc} plaques; and the plaque type, which shows plaque-type PrP^{Sc} deposits.[7] In cases without pathological confirmation, we classified cases showing periodic sharp-wave complexes in the EEG within 12 months of disease onset as non-plaque type and cases showing no periodic sharp-wave complexes in the EEG within 12 months of disease onset as plaque type.[7] As the plaque-type dCJD patients without pathological confirmation never satisfied the criteria for probable case,[7] possible cases were included in this analysis in addition to definite and probable cases. We analysed 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.

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 analysed 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 codons 129 and 219 was also collected from patients who underwent genetic analysis. Moreover, we analysed 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 χ^2 test or Fisher's exact probability test. Statistical significance was defined as $p<0.05$. Statistical analyses were performed using SPSS V.19 (IBM, Armonk, New York, USA).

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 cases 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 (B Braun, Melsungen, Germany) was transplanted in all proven cases. The grafting site was confirmed in 77 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%).

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

	Total (n=84)*	Supratentorial group (n=36)	Infratentorial group (n=39)	p Value†
Type classification‡				
Non-plaque type (%)	53 (63)	20 (56)	28 (72)	ns
Plaque type (%)	18 (21)	9 (25)	8 (21)	ns
Male/female	35/49	19/17	10/29	0.015
Age at dural grafting§ (years)	45 (1–65)	45 (1–60)	51 (7–65)	ns
Incubation period§ (years)	15 (6–30)	15 (8–30)	14 (6–25)	ns
Age at onset§ (years)	61 (15–80)	61 (15–79)	66 (24–80)	ns
Initial manifestations¶ (%)	(n=63)	(n=30)	(n=26)	
Unsteady gait	30 (48)	16 (53)	11 (42)	ns
Dementia	16 (25)	8 (27)	6 (23)	ns
Vertigo	9 (14)	1 (3)	8 (31)	0.007
Behavioural abnormality	7 (11)	5 (17)	2 (8)	ns
Ataxia	7 (11)	4 (13)	1 (4)	ns
Diplopia	4 (6)	0 (0)	4 (15)	0.041
Sensory disturbance	4 (6)	2 (7)	2 (8)	ns
Visual disturbance	3 (5)	0 (0)	1 (4)	ns
Extrapyramidal signs	2 (3)	1 (3)	1 (4)	ns
Others**	5 (8)	5 (17)	0 (0)	—
Manifestations during clinical course (%)				
Cerebellar signs	62/82 (76)	23/36 (64)	32/37 (87)	0.024
Psychiatric feature	51/79 (65)	20/32 (63)	27/38 (71)	ns
Dementia	82/84 (98)	35/36 (97)	38/39 (97)	ns
Visual disturbance	36/81 (44)	16/35 (46)	18/37 (49)	ns
Myoclonus	71/82 (87)	31/36 (86)	34/37 (92)	ns
Extrapyramidal signs	53/82 (65)	25/36 (69)	26/37 (70)	ns
Pyramidal signs	58/81 (72)	28/35 (80)	25/37 (68)	ns
PrP gene polymorphisms	(n=58)	(n=25)	(n=27)	
Codon 129	MM 56, MV 2	MM 25	MM 25, MV 2	ns
Codon 219	EE 52, EK 3	EE 21, EK 3	EE 26	ns

*Total includes two cases with spinal cord regions and seven cases with uncertain grafting regions.
†p Value was assessed between the supratentorial group and the infratentorial group.
‡Thirteen cases of type classification were unclear.
§Median.
¶Twenty-two 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; MM, methionine homozygote; MV, methionine/valine heterozygote; ns, not significant; PrP, prion protein.

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 of 18 plaque type (78%) cases proven by autopsy.

The clinical features of dCJD for all patients, the supratentorial group and the infratentorial group are summarised in table 1. The proportion of women 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 two 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 behavioural abnormality suggesting dysfunction of the cerebrum demonstrated no significant difference between the groups. In the infratentorial group, eight cases (31%) developed dementia or behavioural abnormalities. The incubation periods of cases developing dementia or behavioural abnormalities in the supratentorial group and the infratentorial group, reported as the 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 did the supratentorial group. There was no significant difference in the proportion of the PrP genotype or the type classification of dCJD between the two groups. In addition, two cases with spinal cord region grafting developed dementia, diplopia or unsteady gait.

Table 2 Clinical manifestations of non-plaque-type cases

	Total (n=53)*	Supratentorial group (n=20)	Infratentorial group (n=28)	p Value†
Pathologically confirmed cases (%)	18 (34)	9 (45)	7 (25)	ns
Initial manifestations‡ (%)	(n=39)	(n=16)	(n=19)	
Unsteady gait	12 (31)	4 (25)	7 (37)	ns
Dementia	11 (28)	6 (38)	5 (26)	ns
Vertigo	6 (15)	0 (0)	6 (32)	0.017
Behavioural abnormality	6 (15)	4 (25)	2 (11)	ns
Ataxia	6 (15)	3 (19)	1 (5)	ns
Diplopia	5 (13)	0 (0)	4 (21)	0.074
Sensory disturbance	2 (5)	1 (6)	1 (5)	ns
Extrapyramidal signs	1 (3)	1 (6)	0 (0)	ns
Visual disturbance	1 (3)	0 (0)	1 (5)	ns
Others§	3 (8)	3 (19)	0 (0)	—
Manifestations during clinical course (%)				
Cerebellar signs	35/51 (69)	10/20 (50)	22/26 (85)	0.014
Psychiatric feature	32/50 (64)	11/17 (65)	19/28 (68)	ns
Dementia	51/53 (96)	19/20 (95)	27/28 (96)	ns
Visual disturbance	21/51 (41)	8/19 (42)	12/27 (44)	ns
Myoclonus	50/52 (96)	20/20 (100)	25/26 (96)	ns
Extrapyramidal signs	30/51 (59)	12/20 (60)	17/26 (65)	ns
Pyramidal signs	40/51 (78)	18/20 (90)	19/26 (73)	ns

*Total includes two cases with spinal cord regions and three cases with uncertain grafting regions.
†p Value was assessed between the supratentorial group and the infratentorial group; ns, not significant.
‡Thirteen 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.

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 behavioural abnormalities demonstrated no significant difference between the two groups. In the infratentorial group, seven cases (37%) demonstrated dementia or behavioural abnormalities as initial manifestations. Similar to the analysis of the sample population as a whole, the median incubation period of cases developing dementia or behavioural abnormalities showed no significant difference between the supratentorial and infratentorial groups (data not shown). Cerebellar signs were realised significantly more often 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 did the 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 directly from the grafted dura mater to the adjacent brain. In experimental studies, PrP^{Sc} has the ability to spread from cell to cell.[3] Mice experiments with PrP^{Sc} inoculated directly into the brain showed that PrP^{Sc} accumulated at the site of initial inoculation and spread around that area.[14–16] 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^{Sc} in the transplanted cortical areas.[17] Concerning the plaque-type prion strain, there was no significant difference between the infratentorial grafting and supratentorial grafting groups. The plaque-type PrP^{Sc} 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.[7] In this study, three of four plaque-type patients developed unsteady gait after supratentorial grafting (table 3). These results suggest that the plaque-type PrP^{Sc} strain, which must have a distinct nature from the non-plaque-type PrP^{Sc} strain, might damage specific brain regions causing gait disturbance during the early stage of the disease process in spite of the difference in

Table 3 Clinical manifestations of plaque-type cases

	Total (n=18)*	Supratentorial group (n=9)	Infratentorial group (n=8)	p Value†
Pathologically confirmed cases (%)	14 (78)	7 (78)	6 (75)	ns
Initial manifestations‡ (%)	(n=14)	(n=8)	(n=5)	
Unsteady gait	9 (64)	6 (75)	2 (40)	ns
Dementia	2 (14)	1 (13)	1 (20)	ns
Vertigo	3 (21)	1 (13)	2 (40)	ns
Diplopia	1 (7)	0 (0)	0 (0)	ns
Sensory disturbance	1 (7)	0 (0)	1 (20)	ns
Others§	2 (14)	2 (25)	0 (0)	—
Manifestations during clinical course (%)				
Cerebellar signs	16/18 (89)	8/9 (89)	7/8 (88)	ns
Psychiatric feature	10/16 (63)	4/8 (50)	5/7 (71)	ns
Dementia	18/18 (100)	9/9 (100)	8/8 (100)	ns
Visual disturbance	11/18 (61)	5/9 (56)	5/8 (63)	ns
Myoclonus	14/18 (78)	8/9 (89)	6/8 (75)	ns
Extrapyramidal signs	14/18 (78)	8/9 (89)	6/8 (75)	ns
Pyramidal signs	8/17 (47)	5/8 (63)	3/8 (38)	ns

*Total includes one case with an uncertain grafting region.
†p Value was assessed between the supratentorial group and the infratentorial group; ns, not significant.
‡Four cases of the total, two cases of the supratentorial group and one case of the infratentorial group developed more than one initial manifestation.
§Others include individual cases of incontinence and hearing disturbance.

grafting sites, possibly through transportation of PrP^{Sc} 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.[8] Furthermore, another animal study showed that sporadic CJD MV2 prions could also induce plaque-type dCJD pathology (TK unpublished data). CJD VV2 and CJD MV2, which might cause plaque-type prions, are well known as ataxic forms of CJD.[18] Meanwhile, the small number of plaque-type cases might influence these results, resulting in no significant difference between the supratentorial and the infratentorial groups.

Our study suggests that generally brain tissue near the grafting site was damaged earlier and more severely through direct propagation of PrP^{Sc} from the grafts. However, some cases have also suggested that there were different patterns of PrP^{Sc} propagation. For instance, 31% of all infratentorial grafting cases and 37% of the non-plaque type with infratentorial grafting cases developed dementia or behavioural abnormalities, indicating initial dysfunction of the cerebrum. Moreover, two 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^{Sc} in addition to the direct invasion of brain tissue, via the cerebrospinal fluid, bloodstream or lymphatic drainage from the CNS. Recently, it has been suggested that lymphatic systems could play an important role in the PrP^{Sc} infection of the brain.[19] In most cases of prion infection regarding variant CJD, the point of PrP^{Sc} entry can be outside the nervous system.[19] After the infection of the organs outside the nervous system, PrP^{Sc} moves into the blood and lymphoid fluids and replicates in the lymphoid organs. PrP^{Sc} is then transported to the brain through the peripheral nervous system.[19 20] In addition to variant CJD cases, PrP^{Sc} was detected in the muscles, intramuscular nerve fibres and dorsal root ganglia in sporadic CJD, in which causes of the disease are uncertain.[21–23] PrP^{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^{Sc} deposition in tissues other than the CNS in dCJD are available, PrP^{Sc} was detected in the peripheral nerves in cases of dCJD in an immunohistochemical study and western blot analysis.[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 fibres connecting to the cerebellum also cause ataxia.[25] Moreover, several case reports presented patients showing rotational vertigo in the clinical course of stroke in the cerebral hemisphere.[26]

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 MRI, 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.

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