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RESEARCH PAPER

Gastrostomy in patients with prion disease

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ABSTRACT. Patients with prion diseases can live for long periods of time in a state of akinetic mutism given appropriate management of their symptoms. To study symptom support in these cases, we performed gastrostomies on 3 patients with V180I genetic Creutzfeldt-Jakob disease (CJD) who had become akinetic and mute, and compared them to 14 other similar patients being fed by tube. In the 3 gastrostomy cases, there were no direct complications due to the gastrostomy or tube feeding, nor were there episodes of discontinuation of tube feeding or initiation of continuous drip infusion due to severe complications. Antibiotics were administered for mild infections, a complication of CJD, with 0.2% and 8.8% of the total time after gastrostomy being used for intravenous or transluminal administration, respectively. We compared the present patient series with that of our previous report statistically, and found that patients undergoing gastrostomy required significantly fewer discontinuations of tube feeding than those who did not. No significant difference in antibiotic administration was found between groups, however. It is our conclusion that gastrostomy should be allowed for symptom support in akinetic patients with prion disease, but adequate informed consent must be provided to the patient's family.

KEYWORDS. akinetic mutism state, Creutzfeldt-Jakob disease, codon 180, gastrostomy, prion disease, symptomatic treatment, tube feeding

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INTRODUCTION

Prion diseases are extremely rare, fatal forms of neurodegenerative diseases, and can be classified as sporadic, acquired by infection, or familial (i.e., gene mutation).[1] Creutzfeldt-Jakob disease (CJD) is the most common human prion disease, with an annual mortality rate of approximately 1 to 2 per million.[1] Symptoms of typical CJD cases include rapidly progressive cognitive dysfunction, myoclonus, and periodic sharp-wave complexes (PSWCs) on an electroencephalogram (EEG); within several months of disease onset, patients reach a state of akinetic mutism.[1,2] In general, Japanese prion disease cases show considerably longer total disease duration than North American and European cases.[2,3] We previously demonstrated that this is related to the extended survival period after reaching the akinetic mutism state[3–5]; survival up to such a state Japanese CJD cases is similar to that for Caucasians. We speculated that the extended survival period in the akinetic mutism state was a result of the extent of symptom support therapies offered to patients with CJD in Japan.[4,5] These supportive therapies include tube feeding, drip infusion, administration of antibiotics to treat bacterial infection, and other treatments of CJD's various complications.[3–5] The drip infusion therapies, including peripheral intravenous infusion and central intravenous high-calorie infusion, are administered to patients with prion disease for symptom and nourishment management in Japan.[4,5] Of these therapies, we had hypothesized that tube feeding is the most influential factor modulating total disease duration in patients with prion disease,[3,4] and indeed, in one study we identified tube feeding statistically as an independent factor influencing the survival period.[5] More than half of Japanese prion disease cases are supported with tube feeding when the patient has progressed to akinetic mutism[3–5]; of these, nasal tube feeding is chosen in the majority of the cases because of the concern of prion infection during such an invasive procedure as gastrostomy.[4,5]

We sought to determine whether the better clinical practice is to continue nasogastric tube feeding, or to be more liberal in allowing surgical intervention (i.e., gastrostomy) to support the symptoms of CJD. We describe here 3 prion disease cases for which we performed gastrostomy, including the rate and type of complications. We also compared these results with those presented in our previous investigation, in which tube feeding was used exclusively.[4]

MATERIALS AND METHODS

The authors were attending physicians for the 3 patients with prion disease who underwent gastrostomy; these patients came from a 17 patient series admitted to the Oyamada Memorial Spa hospital after 2007. Each patient's kin provided informed consent for the procedure at the time. We retrospectively analyzed each patient's background, clinical findings and courses, and prognosis after the gastrostomy. Furthermore, we investigated the complications and their treatment, in particular the administration of antibiotics, discontinuation of tube feeding, and enforcement of drip infusion. We compared these data to those of our previous report of a similar group of patients with prion disease who had reached a state of akinetic mutism.[4,5] Between-group differences were analyzed statistically using a 2-sided Mann-Whitney's U test in Excel 2010 (Microsoft; Redmond, WA, USA) with the add-in software, Statcel 2 (OMS; Tokyo, Japan). Statistical significance was set at a p-value of < 0.05.

Prior to surgery, the advantages and disadvantages of both nasal tube feeding and gastric fistula tube feeding, including those related to the gastrostomy itself, were explained to the patient's families by the doctor using a hospital-provided document. After obtaining written consent from the family, percutaneous endoscopic gastrostomy (PEG) was performed by specialized physicians and medical staff.

The endoscope was hand-washed clean after its use in the gastrostomy, and then treated with the usual mechanical irrigation according to the current prion disease infection prevention guidelines.[6] Once used in the first case, the endoscope was then dedicated for patients with

prion disease; surgery for the other 2 cases described herein used this same endoscope. No issues or complications directly related to the gastrostomy occurred in any of the cases.

RESULTS

There were 17 patients admitted with prion diseases. Of these, 12 were considered to be sporadic CJD (9 definite MM1-type sporadic CJD cases, one definite MM2-cortical-type sporadic CJD case, one definite MM1+2-type sporadic CJD case, and one probable sporadic CJD case); 4 were considered genetic CJD cases (all were Val to Ile point mutations at codon 180 of the prion protein (PrP) gene, 2 were definite, and 2 were probable); one was identified as a definite P102L mutation (in codon 102 of PrP), and thus diagnosed as Gerstmann-Sträussler-Scheinker disease (GSS). Tube feeding was started in all 17 cases after oral nutrient intake became difficult even with medical staff assistance. Gastrostomy was performed in 3 cases (17.6%), all of which were V180I mutations. The 3 patients were all Japanese and all female (see Table 1 for more detailed information). The other 14 cases were provided only nasogastric intubation (nasal tube-feeding). None of the cases was treated with quinacrine or pentosan polysulfate (i.e., none were enrolled in prion disease clinical trials). No tracheostomies, tracheal intubation, or respirator use was performed in any case. There were no patients with other fatal non-neurological disorders at the onset of prion disease.

The overall observation period for the 3 cases was 2341 d in total after the gastrostomy. The 3 cases received financial aid for intractable disease treatment by the Ministry of Health, Labour and Welfare of Japan.

Case by case clinical findings and courses

Specific details regarding the clinical courses of the patients are presented in Table 2. Additionally, the most relevant results are presented below.

Case 1

The patient was a woman for whom the disease initially developed as disorientation at age 78. Approximately 16 months after onset, the patient had become akinetic and mute. The patient's family requested a gastrostomy at this point. For the next several months, she could take in nourishment orally via assistance from the medical staff, but due to the progression of dysphagia, a gastrostomy was performed 30 months after onset. After each of 2 episodes of mild respiratory tract infection (both diagnosed as bronchitis), the patient was administered antibiotics transluminally via a gastric fistula catheter for 14 d in total. She was maintained in generally stable condition with tube feeding, but at 33 months after onset, the patient died of respiratory failure (i.e., 3 months after the gastrostomy). Prior to that, there were no episodes of tube feeding discontinuation or drip infusion enforcement.

Case 2

The patient was a woman for whom CJD developed initially as a behavior disorder at the age of 76. The patient progressed to a state of akinetic mutism approximately 17 months after onset, but with assistance, she continued to take in nourishment orally for more than one year after that. Aspiration pneumonia occurred at 34 months after onset. The patient was initially provided parenteral nutrition in accordance with the family's wishes, but sepsis occurred twice due to infection of the venous indwelling catheter. The family approved of a gastrostomy at that point; after the surgery (38 months after onset), the patient demonstrated a general improvement in her status. However, she suffered numerous mild infections, totaling 14 episodes involving the respiratory tract and skin (bronchitis, folliculitis, and phlegmon). For these episodes, the patient was provided transluminal antibiotics (13 episodes, 127 d in total) or instillation of antibiotics (one episode, 5 d in total). Tube feeding was continued, and the patient is generally stable as of this writing.

TABLE 1. Clinical characteristics of the cases of V180I Creutzfeldt-Jakob disease receiving gastrostomy.

	Case 1	Case 2	Case 3
Clinical features			
Age at onset	78	76	69
Age at death	81	Alive	Alive
Sex	Female	Female	Female
Family history	−	−	−
Past history (age)	Cerebral infarction (73) Pituitary gland adenoma operation (65)	N. P.	Femoral neck fracture operation (50)
Comorbidity at clinical onset	Hypertension, Hyperlipidemia	N. P.	N. P.
Initial symptom	Disorientation	Abnormal behavior	Speech disturbance
Major symptoms and signs	Dementia, abnormal behavior	Dementia, disorientation	Dementia, disorientation
Cerebral cortical dysfunction	+	+	+
Visual symptoms	−	−	−
Parkinsonism	+	+	+
Cerebellar symptoms	−	−	−
Myoclonus	+	+	+
Startle reaction	+	+	+
Pathological laughing	+	+	+
MRI study			
T2 cortical swelling	+	+	+
DWI hyperintensity	+	+	+
EEG study			
PSWCs	−	−	−
Slowing	+	+	+
Akinetic mutism (Onset, months after admission)	16 months	17 months	13 months
Complications before gastrostomy*	N. P.	once aspiration pneumonia, twice sepsis	twice aspiration pneumonia
Disease duration until gastrostomy	30 months	38 months	14 months
Post-operative complications and treatment (Total episodes; total duration)	Bronchitis; Transluminal administration of antibiotic (2; 14 days) No episode of the intravenous administration	Bronchitis, folliculitis, and phlegmon; Transluminal (13; 127 days) and intravenous (1; 5 days) administrations of antibiotic	Bronchitis and phlegmon; Transluminal administrations of antibiotic (6; 65 days)
Episodes of tube feeding discontinuation	None Tube feeding was continued until death	None	None
Cause of death	Respiratory failure	Alive	Alive
Total disease duration	33 months	> 77 months	> 49 months
PrP gene analysis			
Codon 129 polymorphism	Met/Met	Met/Met	Met/Met
Codon 219 polymorphism	Glu/Glu	Glu/Glu	Glu/Glu

+, present; —, absent; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; EEG, electroencephalogram; PSWCs, periodic sharp-wave complexes; PrP, prion protein, Met, methionine; Glu, glutamic acid.

N. P., not present, PrP, prion protein. *Duration between onset of akinetic mutism and gastrostomy

TABLE 2. Clinical course and treatment of patients with prion disease following the advent of akinetic mutism.

Case No.	Diagnosis	Observation period after induction of tube-feeding (months)	Coexistent disease (Therapy)	Complication (No. of times)	Cause of death	Administration		
						Nutrition (Calories (kcal.) / day)	Intravenous (No. of times; total duration)	Transluminal (No. of times; total duration)
Present series								
1	V180I genetic CJD (Definite)	3	Hypertension, Hyperlipidemia (Hypotensor, Hyperlipidemia medicine)	BC (2)	RF	Gastrostomy (800 – 1,000)	None	Ab (2; 14 days)
2	V180I genetic CJD (Probable)	39	Hypertension (Hypotensor)	BC (6), Fo (6), Ph (1)	Alive	Gastrostomy (600 – 1,000)	No CI , Ab (1; 5 days)	Ab (13; 127 days)
3	V180I genetic CJD (Probable)	35	None	BC (5), Ph (1)	Alive	Gastrostomy (1,000)	None	Ab (6; 65 days)
Our previous report								
A	V180I gCJD (Definite)	21	Pemphigoid (Steroid)	BC (6), GE (1),	RF	Nasal-tube (800)	CI (4; 42 days)(including CVC (1; 6 days); No HA), Ab (5; 20 days)	Ab (4; 26 days)
B	sCJD (Definite)	1	Bronchial asthma (Bronchodilator)	AP (1), BC (1),	RF	Nasal-tube (800)	CI (1; 18 days)(including CVC (1; 16 days); HA (1; 11 days)), Ab (1; 16 days)	Ab (1; 4 days)
C	sCJD (Definite)	23.5	None	AP (2), BC (15), HZ (1), UTI (1)	RF	Nasal-tube (800 – 1,000)	CI (2; 45 days)(including CVC (2; 35 days); HA (2; 29 days)), Ab (3; 29 days)	Ab (24; 94 days), Av (1; 7 days)
D	P102L GSS (Definite)	17.5	None	AP (3), BC (2), Cellulitis (2), PM (1)	RF with AP	Nasal-tube (600 – 800)	CI (3; 49 days)(including CVC (3; 60 days); HA (3; 35 days)), Ab (4; 51 days), Af (1; 11 days)	Ab (3; 23 days)
E	sCJD (Definite)	7	None	BC (6), UTI (1),	RF	Nasal-tube (1,000 – 1,400)	None	Ab (7; 55 days)
F	sCJD (Definite)	22	None	BC (9), GE (1)	RF	Nasal-tube (1,000)	None	Ab (10; 74 days)
G	sCJD (Definite)	8	None	AP (1), ARF (1), GE (7), UTI (1)	ARF with AP	Nasal-tube (800 – 1000)	CI (5; 124 days)(including CVC (2; 4 days); HA (2; 58 days)), Ab (3; 33 days)	Ab (3; 21 days)
H	sCJD (Probable)	8	None	BC (2)	—	Nasal-tube (1,000)	None	Ab (2; 14 days)
I	sCJD (Definite)	12	None	AP (1), BC (1)	RF with AP	Nasal-tube (1,000 kcal)	CI (1; 1 day), Ab (1; 1 day)	Ab (1; 7 days)
J	sCJD (Definite)	3.5	None	AP(1), BC (1), UTI (1), GE (2)	RF with AP	Nasal-tube (1,200)	CI (1; 5 days)(including CVC (1; 3 days); HA (1; 2 days)), Ab (1; 5 days)	Ab (3; 18 days)
K	sCJD (Probable)	8	Hypertension (Hypotensor)	GE (2)	—	Nasal-tube (1,000)	CI (1; 10 days), Ab (1; 10 days)	Ab (1; 3 days)
L	sCJD (Probable)	2	None	BC (2)	—	Nasal-tube (1,000)	CI(1; 14 days), Ab (1; 14 days)	Ab (1; 5 days)

CVC, central venous catheter; Ab, antibiotic; Af, antifungal; Av, antiviral.

AP, aspiration pneumonia; ARF, acute renal failure; BC, bronchitis; Fo, folliculitis; GE, gastroenteritis; HZ, herpes zoster; Ph, phlegmon; PM, pulmonary mycosis; RF, respiratory failure; UTI, urinary tract infection.

CI, continuous infusions, HA, hyperalimentation.

No. of times, Number of times that the treatment was administered; Total duration, the total length of time for which all treatments of the same type were administered.

Complication, Complication for which treatment was needed.

*Modified from our previous study.[4]

There was no episode of tube feeding discontinuation or initiation of drip infusion.

Case 3

The patient was a woman for whom CJD first expressed as a speech disturbance at the age of 69. The patient's family approved of a gastrostomy from her admission. Approximately 13 months after onset, the patient had progressed to a state of akinetic mutism. The patient was able to take nutrition orally with assistance for another month, but twice developed aspiration pneumonia. After successful treatment of the pneumonia, gastrostomy was performed (i.e., about 14 months after onset). The patient had 6 episodes of mild infections involving the respiratory tract and skin (bronchitis and phlegmon), and each time was treated via transluminal administration of antibiotics (65 d in total). Tube feeding was continued and the patient is generally stable as of this writing; there was no episode of tube feeding discontinuation or initiation of drip infusion.

Statistical analysis and comparison with previous data

The results of our statistical comparisons are presented in Table 3. Briefly, for the previous patient series, we had analyzed 12 admitted cases of prion disease (none of whom were included in the current study) who had reached the state of akinetic mutism and were undergoing nasal tube feeding.[4] The total hospitalization in days after onset of akinetic mutism and initiation of tube feeding was 3968. The number of episodes that tube feeding was discontinued and continuous drip infusion initiated as a result of severe complications such as aspiration pneumonia was 19 (308 d in total, and 7.8% of the total days in akinetic mutism described above).[4] Compared to the percentage of total days for the 3 gastrostomy cases herein (zero percent), the nasal tube feeding group was significantly higher ($p < 0.04$). Milder complications (infections), such as bronchitis, were treated with antibiotics in both groups. In the nasogastric tube group there were 20 episodes of intravenous antibiotic administration (179 d in total, 4.8%) and 60 episodes of transluminal antibiotic administration (344 d in total, 8.7%).[4] In the present 3 cases, intravenous administration of antibiotics occurred once (5 d in total; 0.2%) and transluminal administration occurred 21 times (206 d in total; 8.8%). Neither intravenous nor transluminal antibiotic administration was significantly different between the nasogastric group and the gastrostomy group ($p = 0.11$ and $p = 0.77$, respectively).

Discussion

Although nasal tube feeding is a classic, time-proven technique, its prolonged use can

TABLE 3. Comparison of the nasal tube feeding group* and gastric fistula tube feeding group.

			Proportion of the total observation period
(1) Total enforcement time (days) of continuous infusions			
Nasal tube feeding group*	308		7.8 %
Gastric fistula tube feeding group	0		0.0 %
Statistical analysis		$p = 0.04$**	
(2) Total days of drip infusion administration of antibiotic drugs			
Nasal tube feeding group*	179		4.5 %
Gastric fistula tube feeding group	5		0.2 %
Statistical analysis		N.S. ($p = 0.11$)**	
(3) Total days of transluminal administration of antibiotic drugs			
Nasal tube feeding group*	344		8.7 %
Gastric fistula tube feeding group	206		8.8 %
Statistical analysis		N.S. ($p = 0.77$)**	

Total observation periods were 3,968 d in 12 cases with nasal tube feeding, and 2341 d in 3 cases with gastric fistula tube feeding.

*Modified from our previous study.[4]

**Mann-Whitney's U test, N.S.; Statistically not significant.

lead to complications such as lesions to the nasal wing, chronic sinusitis, gastro-esophageal reflux, and aspiration pneumonia.[7] Gastrostomy is in high demand for patients with swallowing disorders, and is generally used when there is a need for enteral nutrition for a longer time period.[7] Gomes et al.[7] evaluated the effectiveness and safety of gastrostomy versus nasal tube feeding for adults with swallowing disturbances; there, they concluded that gastrostomy was associated with a lower probability of intervention failure, suggesting the endoscopic procedure may be more effective and safer than nasal tube feeding. However, there was no statistically significant difference in mortality rates between comparison groups, or in adverse events such as aspiration pneumonia.[7]

To our knowledge, there are no other independent reports that have investigated the efficacy of tube feeding or gastrostomy in prion disease cases. In addition, there are no nationwide epidemiological survey data in prion disease patients to draw upon. In our previous study using 51 autopsy-confirmed cases of MM1-type sporadic CJD,[5] 35 cases (68.6%) received tube feeding after the patients had reached the state of akinetic mutism. There, the average total disease duration was 4.0 ± 1.6 months in patients who were not tube fed, and 16.1 ± 9.4 months in those who were; the difference between the 2 durations was statistically significant. Notably, there were 3 gastrostomies performed in that study as well. There, the average total disease duration was 15.5 ± 9.2 months for nasal tube feeding and 23.0 ± 9.5 months for gastric fistula tube feeding, a difference which was not statistically significant.

We speculated previously that intensive, life-sustaining treatments are not commonly administered to patients with progressive, fatal neurologic disorders such as CJD in Western countries due to financial and ethical concerns.[5] The Japanese healthcare system includes universal health insurance and free access to hospitals, which encourages patients to undergo intensive medical treatments that prolong their survival period. The Japanese social environment and traditional ethical values also encourage patients with end-stage neurological disorders to receive intensive, life-sustaining treatments. Furthermore, we found that Japanese physicians tend to hold negative attitudes toward withdrawal of treatments, even in cases of severe disability such as the akinetic mutism related to CJD.[5] To the best of our knowledge, no biological reasons for the extended survival time in Japanese populations have been found, and the same treatment modalities are available in Japan and the West. Thus, we must conclude that the described societal and cultural traits are responsible for the difference; the application of our results to Western medical practice will need to be balanced with the ethical question of whether prolonging survival at all costs and in any patient condition is the best course of action for that patient and the family.

Our hospital actively admits patients with prion diseases transferred from other hospitals. Here, tube feeding is introduced in all prion disease cases after a patient reaches a state of akinetic mutism, as long as informed consent is obtained from his/her family. In the present study, the patients' spouses or children provided informed consent. We speculated that the slow progression of the disease in these 3 cases was one of the reasons why the family consented to gastrostomy. The V180I mutation form of CJD is extremely rare in Caucasian patients with CJD,[8] but is the most frequent type of genetic CJD in Japan.[9] It carries unique clinical characteristics for a prion disease, including: development primarily in elderly people, a prolonged, slowly progressing clinical course, an initial presentation with cerebral cortical symptoms (such as hemiplegia, aphasia, or dementia), limited or no myoclonus but pathological startle reaction and/or laughing, little or no PSWCs on an EEG, extensive hyperintensity regions in the cerebral cortex in diffusion weighted imaging, and characteristic cortical swellings in T_2-weighted and fluid-attenuated inversion recovery (FLAIR) images.[10,11] According to the clinical course of the present cases, we also noted that patients with V180I CJD could continue their oral nutrition intake with assistance for a while after reaching the state of akinetic mutism. This relative prolongation of assisted oral intake may in fact be a clinical feature of the V180I type of CJD. Previously, we

suggested that the state of akinetic mutism in patients with prion disease should be defined as a state in which patients lacked voluntary movement or the ability to produce meaningful words.[3,5] In this state, involuntary movements such as myoclonus, startle reaction, and convulsions could be present, and patients may still be able to produce linguistically meaningless sounds such as groans. According to the present study, we feel the need to emphasize that the state of akinetic mutism in patients with prion disease still meets the above definition even if oral intake of nutrition is still possible with assistance.

Although endoscopic procedures including gastrostomy, and those procedures used for prevention of the spread of infectious prions, are both described in the Japanese prion disease infection prevention guidelines, gastrostomy is not an actively recommended procedure.[6] We believe that gastrostomy in patients with prion disease should be actively considered as a supportive therapy, but only when the patient's family is provided enough information to make fully informed consent. We continue our efforts to accumulate evidence and provide accurate reporting, in the hope that our validated results will be useful for establishing guidelines for tube feeding in patients with prion disease.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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