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【 ORIGINAL ARTICLE 】

Characteristics of Neurological Symptoms in Adult Japanese Patients with Fabry Disease

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Abstract:

Objective Fabry disease (FD) is a hereditary lysosomal storage disease that has been highlighted as a possible etiology of stroke at a young age and presents with other various neurological symptoms. Since FD is rare, limited information is currently available on the prevalence of neurological symptoms in Japanese patients with FD. Therefore, we examined the characteristics of neurological symptoms and brain magnetic resonance imaging (MRI) findings in adult Japanese patients with FD.

Methods This was a retrospective, single-center study. We reviewed neurological symptoms and brain MRI findings in the medical records of 12 adult Japanese patients with FD diagnosed by a gene analysis of the α-galactosidase gene.

Results Ten out of 12 patients with FD presented with the following neurological symptoms: acroparesthesia (n=6), headache (n=5) [migraine (n=4)], hypohidrosis (n=5), and cerebral infarction (n=3). Two and three of the patients with migraine were complicated by ischemic stroke and coronary spastic angina, respectively. Five and 10 patients presented with periventricular hyperintensity and deep white matter hyperintensity, respectively, on brain MRI. Two out of eight patients had cerebral microbleeds. Seven out of 11 patients had a dilated basilar artery diameter on magnetic resonance angiography. There were no patients with the pulvinar hyperintensity sign.

Conclusion Patients with FD present with various neurological symptoms. Headache, particularly migraine, might be a major neurological symptom in patients with FD. Since migraine, ischemic stroke, and coronary spastic angina might occur together in FD, caution is needed when administering triptan to FD patients with migraine.

Key words: Fabry disease, neurological symptoms, stroke, headache, coronary spastic angina, brain MRI

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Introduction

Fabry disease (FD) is a rare X-linked multisystem lysosomal storage disorder caused by mutations in the α-galactosidase (GAL) A gene, which is located at Xq22 (1). It results in the progressive accumulation of neutral glycosphingolipids, mainly globotriaosylceramide, in various organs.

Disease symptoms are observed in both hemizygous men and heterozygous women (2, 3). The clinical symptoms of FD include renal dysfunction, cardiac disease, such as left ventricular hypertrophy, cutaneous angiokeratomas, corneal dystrophy, and neurological disorders (4). FD affects both the central nervous system (CNS) and peripheral nervous system (PNS). The clinical CNS symptoms of FD include ischemic stroke, psychiatric disorders, and headache, while PNS symptoms comprise peripheral neuropathy, acroparesthesia, and hypohidrosis (5, 6). The CNS, renal, and cardiac involvement are major complications of FD. Stroke is the

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most frequent and severe neurological event in patients with FD, and its prevalence in these patients has been intensively investigated (5-7). However, limited information is currently available on the prevalence of other neurological symptoms, particularly headache (6, 8, 9).

Magnetic resonance imaging (MRI)-detectable white matter hyperintensities, hyperintensities on T1-weighted images of the thalamic posterior area (the pulvinar sign), cerebral microbleeds, and dilation of the basilar artery (BA) are characteristic neuroradiological signs of FD (10). A previous study examined the prevalence of white matter hyperintensities, cerebral microbleeds, and the dilation of the BA in a cohort of Japanese patients with FD (9-11); however, the prevalence of the pulvinar sign remains unclear.

In the present study, we investigated the neurological symptoms, including stroke and headache, and brain MRI findings in 12 adult Japanese patients with FD.

Materials and Methods

This was a retrospective, single-center study. The center is located in Hokkaido Prefecture in northern Japan. Between January 2008 and December 2019, 12 consecutive patients were registered in the present study. All patients lived in Hokkaido Prefecture. The protocol was approved by the Ethics Committee of Asahikawa Medical University. Written informed consent was obtained from each patient prior to enrollment.

We reviewed the medical records of 12 Japanese patients with FD who were diagnosed based on the measurements of the α-GAL activity and a gene analysis of the α-GAL A gene. We measured the α-GAL A activity of patients using a dried blood spot test with a slight modification to the previously described method (12). α-GAL A activity <12 Agal U in men and <20 Agal U in women was considered abnormally low. In the DNA analysis, total genomic DNA was extracted from the leukocytes of patients. All seven exons and the flanking intronic sequences of the α-GAL A gene were amplified by polymerase chain reaction, and amplification products were analyzed by direct sequencing (12). Patients received genetic counseling from an experienced geneticist.

We analyzed neurological and other symptoms, as well as brain MRI findings in FD patients. Neurological and other symptoms comprised current and previous symptoms, including those in childhood. Migraine was diagnosed based on the established criteria of the international criteria of the International Headache Society (13). A statistical analysis was not performed for each measurement item due to the small number of cases.

Radiological investigation

We evaluated cerebral white matter hyperintensity, T1-signal hyperintensity of the pulvinar thalami, cerebral microbleeds, and the diameter of the BA using MRI and magnetic resonance angiography (MRA). MRI was performed using 1.5- or 3-T imaging systems, including a Signa and Discovery (GE Healthcare, Milwaukee, USA) and Achieva MR (Philips Healthcare Systems, Amsterdam, the Netherlands).

Periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs) were defined as hyperintense signal abnormalities surrounding the ventricles and in the DWM, respectively. They were observed on T2-weighted or fluid-attenuated inversion recovery images. We graded PVHs and DWMHs on a scale of 0 to 3 according to the Fazekas scale (14). Cerebral microbleeds were defined as punctuate hypointense lesions <10 mm in size on gradient-recalled echo.

The inner diameter of the BA was measured within time-of-flight sequences using the SYNAPSE VINCENT software program (FUJIFILM, Tokyo, Japan). BA diameters were defined as the average of three measured points: 1) caudal (shortly after the confluence of the vertebral arteries), 2) intermediate (in the middle of the BA), and 3) rostral (just before the bifurcation), as described previously (15). We examined the incidence of patients with a BA diameter >2.7 mm based on previous findings, showing that this was characteristic of FD (15).

Results

Patient characteristics

Two men and 10 women were registered in the present study. Their mean age was 53.8 years old. Patient 8 was the mother of Patient 1, Patients 9 and 10 were sisters, and Patients 5, 6, 7, 11, and 12 were of the same pedigree (Patients 6 and 7 were sisters, and Patients 5 and 11 were their niece and cousin, respectively; Patient 12 was a distant relative). Table 1 shows a summary of the clinical characteristics, α-GAL A activity, and mutations in the α-GAL A gene in these 12 patients with FD.

Ten of the 12 patients with FD presented with the following neurological symptoms: acroparesthesia (n=6), headache (n=5), hypohidrosis (n=5), cerebral infarction (n=3), psychiatric symptoms (n=2), epilepsy (n=2), aseptic meningitis (n=1), facial nerve palsy (n=1), and tremors (n=1). Of the three patients with cerebral infarction, two had lacunar infarction, and the other had cardiogenic embolism. All of the patients with headache developed headache in adulthood. Four out of the five patients with headache were diagnosed with migraine, one of whom also had an aura. These patients were mainly treated with acetaminophen and non-steroidal anti-inflammatory agents (e.g., loxoprofen sodium) and were not administered triptan. Two out of the four patients with migraine were complicated by ischemic stroke. Of the six patients with acroparesthesia, three only had this symptom during childhood. All of the patients with hypohidrosis had had this symptom since childhood.

All patients showed cardiac involvement, which included left ventricular hypertrophy on electrocardiography or echo-

Table 1. Clinical Characteristics of 12 Patients with Fabry Disease.

A. Clinical characteristics, α-GAL A activity, and gene mutaions in patients with Fabry disease

Patient No.	Sex	Age	Cerebral infarction	Headache	Acro-pares-thesia	Hy-pohi-drosis	Psychiatric symptoms	Epi-lepsy	Other symptpms	Cardiac involve-ment	Renal involve-ment	Corneal verticil-lata	Angio-kera-toma	Vascular risk factor	α-GAL A activity (Agal U)	Gene mutation	ERT duration
1	male	38	-	-	+	+	neurosis	-	-	+(CSA)	+	-	+	smoking	2.8	exon5, W236X	-
2	male	63	-	-	+	+	-	-	-	+(CSA)	+	-	-	-	9.0	exon4, M187V	-
3	female	39	lacunar (29y)	+ (migraine)	-	-	-	-	facial nerve palsy	+(CSA)	+	+	-	-	8.3	exon7, Del3b	3 years (36y)
4	female	47	lacunar (42y)	+	+	-	hallucination, delusion	-	aseptic meningitis	+	-	-	-	HT, DLp	11.9	Intron 4, IVS4-1G>A	-
5	female	52	-	+ (migraine)	-	+	-	-	-	+(CSA)	+	-	-	HT	16.1	exon4, G195V	8 years (44y)
6	female	67	cardiogenic (66y)	+ (migraine)	-	-	-	+	tremor	+	-	-	-	HT	10.0	exon4, G195V	9 years (58y)
7	female	66	-	-	-	-	-	-	-	+(CSA)	-	-	-	DLp	12.7	exon4, G195V	8 years (58y)
8	female	67	-	-	+	-	-	-	-	+(CSA)	-	-	-	DLp	8.2	exon5, W236X	-
9	female	47	-	+ (migraine)	+	+	-	-	-	+(CSA)	+	+	-	DLp, smoking	10.0	exon5, c.723 dupT	-
10	female	45	-	-	+	+	-	-	-	+(CSA)	+	+	-	-	13.0	exon5, c.723 dupT	-
11	female	70	-	-	-	-	-	-	-	+	-	-	-	DLp	8.8	exon4, G195V	-
12	female	44	-	-	-	-	-	+	-	+(CSA)	+	-	-	DLp	7.0	exon4, G195V	-

B. Summary of clinical characteristics of 12 patients with Fabry disease

Age, y, mean±SD	53.8±11.5
Woman, n (%)	10 (83.3)
Cerebral infarction, n (%)	3 (25.0)
Headache, n (%)	5 (41.7)
Migraine, n (%)	4 (33.3)
Acroparesthesia, n (%)	6 (50.0)
Hypohidrosis, n (%)	5 (41.7)
Psychiatric symptoms, n (%)	2 (16.7)
Epilepsy, n (%)	2 (16.7)
Cardiac involvement, n (%)	12 (100.0)
CSA, n (%)	9 (75.0)
Renal involvement, n (%)	7 (58.3)
Corneal verticillata, n (%)	3 (25.0)
Angiokeratoma, n (%)	1 (8.3)
HT, n (%)	3 (25.0)
DLp, n (%)	6 (50.0)
Current smoking, n (%)	2 (16.7)
ERT, n (%)	4 (25.0)

Numbers in ( ) are age at onset in the field of cerebral infarction and the initiation of enzyme replacement therapy in the field of ERT duration.
Cut-off value of α-GAL A activity;<12 Agal U in males,<20 Agal U in females.
α-GAL A: α-galactosidase A, CSA: coronary spastic angina, HT: hypertension, DLp: dyslipidemia, ERT: enzyme replacement therapy

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Table 2. MRI and MRA Findings of 12 Patients with Fabry Disease.

A. Measurement data of MRI and MRA findings

Patient No.	Fazekas score		Pulvinar sign	Micro-bleeds	Diametr of BA (mm)			
	PVH	DWMH			rostal	intermediate	caudal	average
1	0	1	0	0	3.73	3.47	3.92	3.71
2	3	3	0	NA	4.14	NA	NA	NA
3	0	0	0	0	2.35	2.16	2.53	2.35
4	1	1	0	0	3.35	2.54	3.09	2.99
5	0	2	0	0	2.73	2.35	2.8	2.63
6	3	3	0	NA	3.10	3.11	3.69	3.40
7	0	2	0	NA	3.43	2.66	3.06	3.05
8	2	3	0	NA	3.59	2.44	3.61	3.21
9	0	2	0	1	3.18	2.62	3.48	3.09
10	0	2	0	0	2.57	2.41	2.75	2.58
11	2	3	0	3	4.73	3.49	3.67	3.96
12	0	0	0	0	2.33	2.32	2.61	2.42

B. Summary of MRI and MRA findnigs

Fazekas score (n=12)	
PVH	
0	7
1	1
2	2
3	2
DWMH	
0	2
1	2
2	4
3	4

Pulvinar sign (n=12)	0

Cerebral microbleeds (n=8)		
Number of microbleeds		site
0	6	-
1	1	frontal lobe
3	1	frontal lobe, bilateral thalamus

BA average diameter (mm, n=11)	
Mean±SD	2.83±0.28
Median (IQR)	3.14 (2.76-3.55)
≤2.7 mm	4
>2.7 mm	7

Data are presented as number, except for the diameter of BA.

MRI: magnetic resonance imaging, MRA: magnetic resonance angiography, BA: basilar artey, PVH: periventrcular hyperintensities, DWMH: deep white matter hyperintensities, NA: not applicable, SD: standard deviation, IQR: interquartile range

cardiography, coronary spastic angina, and endomyocardial biopsy findings suggesting FD. Coronary spastic angina was detected in three out of the four patients with migraine. Seven patients had renal involvement, which included proteinuria, renal dysfunction receiving hemodialysis, and renal biopsy findings suggesting FD.

The α-GAL A activity was reduced in all patients. Four out of the 12 patients had been treated with enzyme replacement therapy when they participated in the present study.

Radiological findings

Table 2 shows a summary of the MRI findings. Figure shows the MRI and MRA findings of Patient 6, which demonstrated cerebral white matter lesions and the dilation of the BA. Eight patients were evaluated for cerebral microbleeds. It was not possible to measure the diameter of the BA in Patient 2 because the caudal part was not scanned.

Ten out of the 12 (83.3%) patients showed MRI findings of white matter lesions: 5 (41.7%) had PVH [grade 1 (n=1), grade 2 (n=2), and grade 3 (n=2)], while 10 (83.3%) had DWMH [grade 1 (n=2), grade 2 (n=4), and grade 3 (n=4)]. None of the patients had pulvinar hyperintensity lesions. Two out of the eight evaluated patients had cerebral microbleeds.

The mean diameter of the BA was 2.83 mm. Seven out of the 11 evaluated patients had a dilated BA diameter (>2.7 mm). None of the patients had the fetal-type variation in the circle of Willis. Two patients (Patients 8 and 12) had thicker posterior communicating arteries than the P1 portion of the posterior cerebral artery on the left side, and the remaining patients had the adult-type variation.

Discussion

The incidence of FD worldwide reportedly ranges between 1 in 40,000 and 1 in 117,000 (4). On Japanese newborn screening for FD, the frequency of FD patients with pathogenic variants was 1 in 11,854 (16). Therefore, FD is a rare X-linked multisystem lysosomal storage disorder, and neurological disorders in FD have not yet been elucidated in detail.

FD affects both the CNS and PNS. CNS involvement is a major complication of FD in addition to renal and cardiac involvement. The clinical CNS symptoms of FD include ischemic stroke, psychiatric disorder, and headache (17, 18). Stroke is one of the main complications of classical FD. A

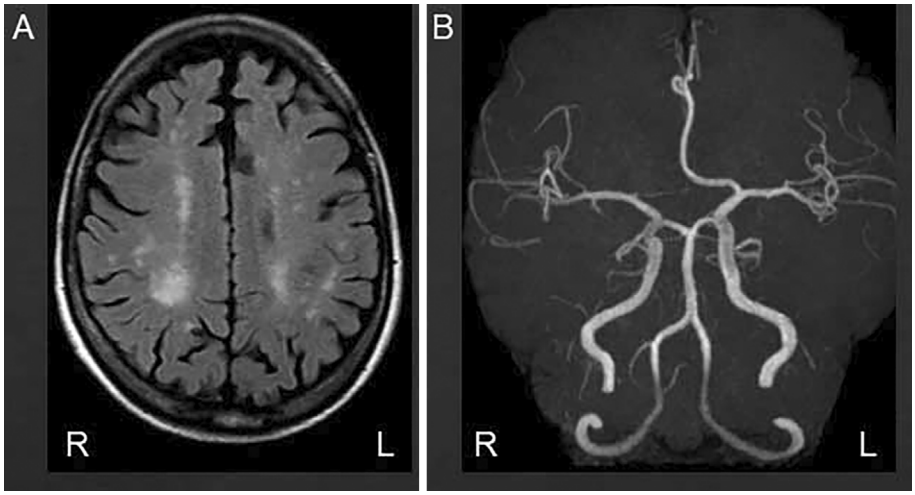

Figure. **Brain magnetic resonance imaging and magnetic resonance angiography of Patient 6. (A) Hyperintense signal abnormalities in the cerebral white matter on fluid-attenuated inversion recovery images (axial view). (B) The cerebral arteries, including the basilar artery, were dilated (average diameter of 3.40 mm).**

previous study on patients 18-55 years old with cryptogenic stroke reported a high prevalence of FD (5% of men and 3% of women) (19). We also found that 2 out of 259 patients with a history of stroke (0.8%) had a pathogenic mutation in the α-GAL gene (20). The prevalence of stroke in patients with FD in foreign countries was 5.6-26% (5-7). In a study on Japanese patients with FD, the cumulative incidences of cerebral infarction in women and men with FD at 60 years old were 30% and 44%, respectively (21). In the present study, 3 of the 12 patients (25%) with FD were complicated by cerebral infarction, which was consistent with previous findings. One of those three patients with cerebral lacunar infarction (Patient 3) was complicated by coronary spastic angina. We recently reported that the prevalence of coronary spastic angina complicated by FD was high (22, 23). Although it is difficult to prove a causal relationship, given the possibility that ischemic stroke is also associated with vasospasm, vascular vasospasm may be a common and important pathophysiological mechanism underlying damage in various organs.

Headache is a neurological symptom that develops in patients with FD (18, 24) but has not yet been characterized in detail. The prevalence of migraine was 26.6% in a previous study on patients with FD in Europe and North and South America (25). In contrast, the prevalence of FD in a cohort of patients with migraine was 1.37% (26). In the present study, 5 of the 12 (41.7%) patients presented with headache, and 4 of these patients were diagnosed with migraine. The overall prevalence of migraine in the Japanese population was previously reported to be 6.0-8.4% (27, 28), and, more specifically, approximately 20% and 18% in women in their 30s and 40s, respectively (27). Although the number of patients with FD in the present study was small and the population was female-dominant, headache, particularly migraine, might be a major neurological symptom in patients with FD. Numerous studies have linked migraine to an increased risk of ischemic stroke (29). In the present study, two of the four women with migraine were complicated by ischemic stroke. In contrast, many patients in the present study (9 of 12) were complicated with coronary spastic angina, and 3 out of the 4 patients with migraine were complicated by coronary spastic angina. As previously reported, the prevalence of spastic angina may be elevated in patients with FD. Therefore, it may be appropriate to avoid administering triptan to FD patients with migraine. Although the impact of enzyme replacement therapy on renal and cardiovascular complications in FD has already been reported, the effects of enzyme replacement therapy on cerebrovascular complications or other neurological disorders currently remain unclear (30). In the present study, three out of the five patients with headache had been treated with enzyme replacement therapy for more than three years. Therefore, enzyme replacement therapy may not be effective against headache in FD patients.

Psychiatric symptoms, particularly depression, are also neurological symptoms in FD (31-33). FD has been reported to produce a confused state and psychotic syndromes in rare cases (31, 34-36). One study indicated that the co-occurrence of FD and schizophrenia-like psychiatric symptoms was coincidental (36). However, another study suggested that thalamic lesions were involved in the pathogenesis of psychotic symptoms in FD (35). In the present study, two patients with FD presented with psychiatric symptoms, including hallucinations, delusions, and neurosis. In Patient 4, psychiatric symptoms and a fever emerged simultaneously, suggesting that aseptic meningoencephalitis caused by FD induced psychiatric symptoms (37). The patient exhibited psychiatric symptoms before a thalamic infarction occurred, and Patient 1 had no thalamic lesions on MRI. Thus, psychiatric symptoms might emerge in FD in the absence of thalamic lesions.

Two out of the 12 patients were diagnosed with epilepsy. One of these patients was diagnosed with symptomatic epilepsy due to cerebral infarction. Information on patients with FD and epilepsy is very limited (38); therefore, further studies are needed to elucidate the relationship between FD and epilepsy.

In the present study, 6 and 5 out of the 12 patients presented with acroparesthesia of the limbs and hypohidrosis, respectively. In previous studies, the prevalence of acroparesthesia of the limbs and hypohidrosis in patients with FD was 50.0-77.0% and 16.7-56.0%, respectively (3, 21, 25, 39, 40), findings that were consistent with the present results. Acroparesthesia disappeared in 50% of patients after they reached adulthood, whereas hypohidrosis persisted from childhood to adulthood in all patients. Therefore, acroparesthesia may disappear in a certain proportion of patients by adulthood.

MRI-detectable white matter hyperintensities are characteristic neuroradiological signs of FD. Microvascular degeneration because of GL-3-related endothelial damage may lead to injury and appears as abnormal hyperintensities in the white matter (8). White matter hyperintensities occur in the subcortical, deep, and periventricular white matter and generally in a symmetrical manner. In the present study, white matter lesions were DWMH-dominant. The proportion of patients that presented with DWMHs was higher than that in a previous study on Japanese patients with FD (10). This difference may be due to the older average age of the patients in the present study than in the previous study. Previous studies reported an increased risk of white matter hyperintensities in patients with migraine (29). In the present study, patients with and without migraine presented with white matter hyperintensities. At present, whether or not migraine affects the appearance of white matter hyperintensities in patients with FD remains unclear.

The pulvinar sign, represented by bilateral hyperintensities on T1-weighted images of the thalamic posterior area, is a characteristic finding of FD. The pulvinar sign may be caused by subtle dystrophic calcifications and end-organ damage associated with regional hyperperfusion; however, the underlying pathophysiology remains unclear (8). In addition, the pulvinar sign has been detected under other conditions (e.g., CNS infection, a sequel of chemotherapy and radiotherapy, and phakomatoses); therefore, its pathognomonic role has been reconsidered (8). Few studies have examined the incidence of the pulvinar sign. Burlina et al. detected the pulvinar sign in 5 out of 36 (13.9%) patients with FD (5 out of 16 men, 0 out of 20 women) (41). In contrast, Cocozza et al. showed a lower prevalence [4 out of 133 (3.0%); 4 out of 53 men, 0 out of 80 women] of the pulvinar sign in patients with FD (42). Apart from a previous study on two female FD patients with weak pulvinar signs (43), limited information is currently available concerning this sign in women. No patients with FD presented with the pulvinar sign on MRI in the present study, possibly due to the small number of cases and the female predominance; however, the incidence of the pulvinar sign may be significantly low in Japanese patients with FD.

Cerebral microbleeds are cerebral small-vessel disease markers of FD (8). Previous studies reported cerebral microbleeds in 6-30% of adult FD patients (9, 11, 44-46), which was consistent with the present results (25%).

A significantly increased BA diameter has been reported in patients with FD (8), the cause of which is postulated to be insufficient autoregulation leading to aberrant vascular remodeling. The diameter of the BA appears to be a promising radiological parameter for separating patients with FD from controls (47). The diameter of the BA was previously confirmed to be significantly larger in men with FD than in healthy controls (48), and vertebrobasilar dolichoectasia may serve as an early marker of neurovascular involvement in patients with FD (45). In the present study, the diameter of the BA in more than 50% of patients with FD was dilated, which is consistent with previous findings.

Several limitations associated with the present study warrant mention. This was a retrospective, single-center study, and analyses only included a small number of patients. Furthermore, there was a female predominance among patients with FD, which might have contributed to the presence of migraine and absence of the pulvinar sign on MRI. In addition, there is currently no standardized method for measuring the diameter of the BA. Thus, the present results cannot be directly compared with those of previous studies using other methods. In the future, large-scale studies on Japanese patients with FD are needed to elucidate the prevalence of neurological manifestations and evaluate the efficacy of treatment, including enzyme replacement therapy, for neurological symptoms.

In conclusion, we assessed the neurological symptoms and brain MRI findings in adult Japanese patients with FD. Patients with FD present with various neurological symptoms. Headache, particularly migraine, might be a major neurological symptom in these patients. Since migraine, ischemic stroke, and coronary spastic angina can occur together in FD, caution is needed when administering triptan to FD patients with migraine.

The authors state that they have no Conflict of Interest (COI).

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