Internal Medicine
The Japanese Society of Internal Medicine

【 CASE REPORT 】

Clinical Diversity in Patients with Anderson-fabry Disease with the R301Q Mutation

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Abstract:
Anderson-Fabry disease (AFD) is a rare X-linked disorder caused by deficient activity of the lysosomal enzyme α-galactosidase A (α-GAL A). We herein report 10 cases of AFD in 5 families (3 men and 7 women) that were found to have a specific common mutation in R301Q [G-to-A transition in exon 6 (codon 301) resulting in the replacement of a glutamine with an arginine residue]. We evaluated their clinical characteristics, residual enzymatic activity, and plasma concentrations of globotriaosylsphingosine (Lyso-Gb3). Although all 10 cases had cardiac and renal manifestations in common, their clinical manifestations were markedly divergent despite the same genetic abnormality.

Key words: Anderson-Fabry disease, α-galactosidase mutant (R301Q), hypertrophic cardiomyopathy, renal failure

Introduction

Anderson-Fabry disease (AFD) is a multisystem, X-linked, lysosomal storage disorder caused by a mutation in the α-galactosidase A (α-GAL A) gene (1). This leads to the major disease manifestations, including acroparesthesias (burning sensations in the extremities), angiokeratoma (wart-like, red to black papules), hypohidrosis (decreased sweating), corneal opacities, and progressive vascular disease of the kidney, heart, and central nervous system (2). These diverse clinical manifestations are important characteristics of AFD (2). Phenotypic variability has frequently been reported in the same AFD family, suggesting that other factors besides the genotype might be involved in the clinical expression of the disease (3, 4).

In order to verify the intrafamilial phenotype variability in our patients, we analyzed 10 cases in 5 families with the same R301Q mutation. The ethics committee of Tohoku University Hospital approved the study protocol (2015-1-860).

Case Reports

We herein report the clinical, biochemical, and molecular characteristics of 10 AFD patients (3 men and 7 women). The pedigrees of the five families are shown in the Figure, and the relevant enzymatic, molecular, and clinical data are shown in Table 1. Table 2 shows the clinical characteristics and echocardiography data of the AFD patients, and Table 3 shows the renal biopsy and urinalysis data. All patients were diagnosed with AFD based on a reduced α-GAL A activity and/or the findings of an α-GAL A gene mutation analysis (Table 1). The α-GAL A activity was severely reduced in all three men but was within the normal range in all seven women. Similarly, the globotriaosylsphingosine (Lyso-Gb3) levels were higher in all men but were in a relatively low range (2-4.5 ng/mL) in all women (Table 1). Four patients had cardiac hypertrophy, and one of them had undergone implantable cardioverter defibrillator (ICD) implantation.

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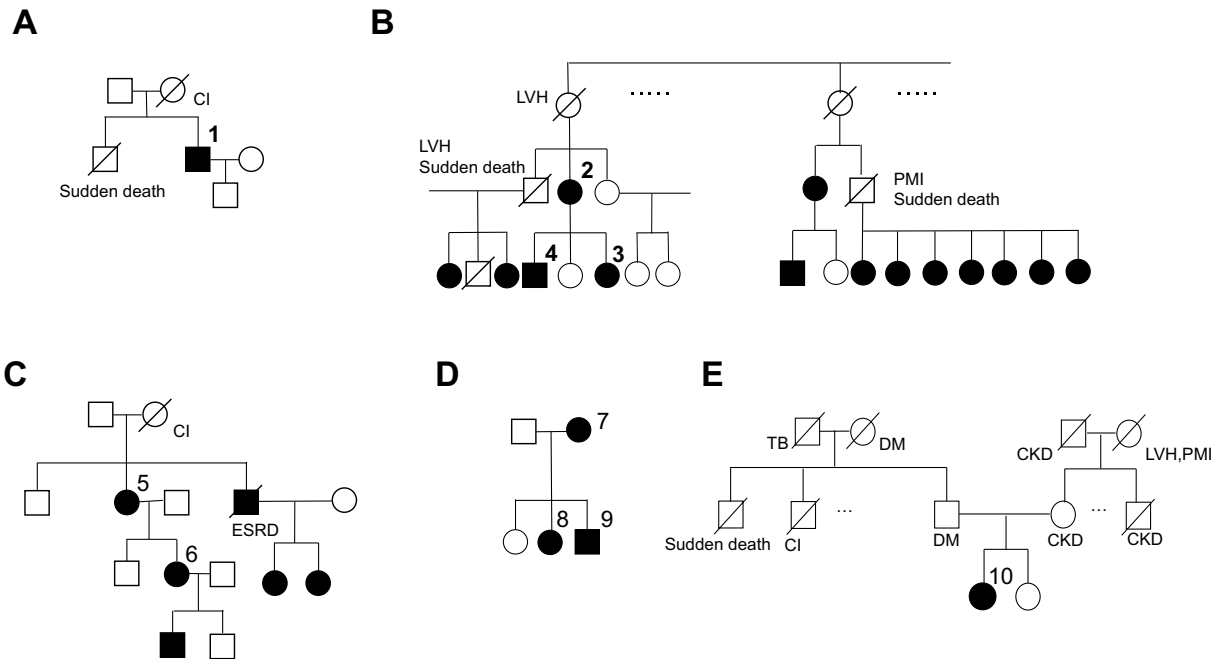
Figure. The pedigrees of the five families. ○ Woman without the α-GAL A gene mutation or not tested. ● Woman with the α-GAL A gene mutation. □ Man without the α-GAL A gene mutation or not tested. ■ Man with the α-GAL A gene mutation. / Dead. CI: cerebral infarction, CKD: chronic kidney disease, DM: diabetes mellitus, ESRS: end-stage renal disease, LVH: left ventricular hypertrophy, PMI: pacemaker implantation, TB: tuberculosis

Five patients had renal impairment, including one with end-stage renal disease (ESRD) (Table 3, 4).

Family A

Case 1 was transferred to our hospital by ambulance due to ventricular tachycardia (VT). Left ventricular hypertrophy (LVH) was confirmed by echocardiography, and infero-posterior LV wall thinning was also noted, indicating advanced cardiac involvement. An ICD was implanted, and enzyme replacement therapy (ERT) was initiated. Since then, his clinical course has been stable without ventricular arrhythmic events. His elder brother died suddenly at 52 years of age, and his mother died of cerebral infarction at 70 years of age.

Family B

Case 2 visited our hospital voluntarily because many of her relatives had LVH and sudden death. Cases 3 and 4 were suspected of having AFD because of their familial history and were diagnosed with AFD by a genetic diagnosis. Case 3 had complaints of acroparesthesias and gastrointestinal discomfort, although cardiac or renal involvement had not manifested.

Family C

Case 5 was referred to our hospital because of arrhythmic events. Her younger brother had been diagnosed with AFD, and hemodialysis was initiated because of severe renal failure at a relatively young age. Case 6, her daughter, and her grandson were also diagnosed with AFD genetically. Case 5,

who refused to receive ERT, has been followed up by with echocardiography alone on a regular basis and has gradually progressed from LVH to LV enlargement with a reduced ejection fraction. Case 6 has been free from symptoms or organ dysfunction throughout 12 years of observation since the first visit.

Family D

Case 9 was admitted for hypertension and proteinuria at the age of 18. His laboratory tests revealed a normal kidney function with low α-GAL A activity and the presence of Mulberry cells on a urinalysis. Although ERT was initiated after the diagnosis of AFD by a renal biopsy, the renal function rapidly deteriorated, and hemodialysis was introduced after four years. Cases 7 and 8, who had been asymptomatic, were screened for and diagnosed with AFD since they were blood relatives of Case 9.

Family E

Case 10 was found to have proteinuria without renal dysfunction at 41 years of age. Renal biopsy specimens showed enlarged podocytes and foamy change (vacuolization). Podocytes were positive for GL-3 by immunohistochemistry. These findings were compatible with Fabry nephropathy. Given that her urine protein level has been stable and renal impairment has been unprogressive for 10 years, ERT may exert significant benefit for AFD.

In addition to ERT, AFD patients were also administered the following medications: renin-angiotensin system (RAS) blockers (angiotensin-converting enzyme inhibitor and an-

Table 1. Characteristics of AFD Patients.

No	Family	Age (years)	M/F	Age at diagnosis (years)	Age at ERT initiation (years)	Type of ERT	Chief complaint of first consultation	Host specialties	α-GalA activity *	Serum Lyso-Gb3 **	Angio-keratoma	Hypo-hidrosis	Acropara-esthesias	Corneal opacities
1	A	59	M	56	56	beta	LVH	Cardiologist	0.7	18.9	-	-	-	-
2	B	69	F	69	69	beta	By chance	Cardiologist	31.3	2.8	-	-	-	-
3	B	34	F	34	34	beta	Family	Cardiologist	29.4	2.1	-	-	+	-
4	B	36	M	36	36	beta	Family	Cardiologist	2.1	39.4	-	-	-	-
5	C	73	F	61	not yet	-	Family	Cardiologist	76	4.5	-	-	-	-
6	C	41	F	32	36	alfa	Family	Cardiologist	54.5	3.3	-	-	-	-
7	D	51	F	51	53	alfa	Family	Nephrologist	13	<2	-	-	-	-
8	D	26	F	26	27	alfa	Family	Nephrologist	16	4.3	-	-	-	-
9	D	23	M	18	18	alfa	Proteinuria	Nephrologist	0.5	3.9	-	-	-	-
10	E	53	F	43	43	beta	Proteinuria	Nephrologist	60.4	N/A	-	-	-	-

All of the diagnoses of AFD were made by a genetic analysis.

α-GAL A: α-galactosidase A, ERT: enzyme replacement therapy, F: female, Lyso-Gb3: globotriaosylceramide, M: male

*nM/mgPro (normal range<50 nM/mgPro); **ng/mL (normal range<2 ng/mL)

The Lyso-Gb3 level was measured only after ERT in Case 7.

giotensin II receptor blocker) in Cases 1, 2, 4, 5, and 7-9; beta-blockers in Cases 1 and 4; calcium channel blockers in Cases 2, 4, and 5; diuretics in Case 2; and hydroxymethylglutaryl (HMG)-CoA reductase inhibitor in Case 5.

Discussion

We herein report the diverse clinical phenotypes in 10 AFD cases in 5 families with the same R301Q mutation. AFD is characterized by two major phenotypes: classical and variant, with considerable differences in the clinical course (5). Because of the residual α-GAL A levels, patients with variant phenotype do not always have all of the major clinical manifestations of classic AFD but often present later in the life with elements of AFD, such as cardiomyopathy and renal disease (6, 7). The R301Q mutation, which is one of the mutations of variant phenotype AFD, was reported from Japan by Sakuraba et al. (8). In that case series, there was only one patient with classical symptoms of AFD, and their age at the diagnosis was in adolescence or later. In the present study, five patients had renal failure, and four had LVH with variable severity, a finding consistent with those of a previous report from Pan et al. (9). It has also been reported that patients with the L415P mutation showed diverse findings with regard to the degree of organ impairment (10). Considering these differences among AFD patients, physicians should routinely examine various organs in patients suspected of having AFD.

In general, male AFD patients with complete deficiency of α-GAL A activity (classical type) show severe symptoms, whereas female patients with residual α-GAL A activity show symptoms restricted to the heart or kidney, even at a relatively old age (11). Since variant type patients retain some α-GAL A activity, the balance between the residual enzymatic activity and other factors, such as the production rate of the substrate, cell division rate, and tolerance against accumulated substrate in each organ or tissue, may determine the clinical phenotype (12). Random X chromosomal inactivation (Lyonization) may be one explanation for this phenomenon (13, 14). In addition to the changes in the genotypes, epigenetic changes should be considered in order to explain the phenotypic diversities among patients with the same mutations (15). As epigenetic abnormalities contribute to the development of certain cancers and autoimmune diseases, AFD may also be affected by epigenetic changes (15). In addition, acquired factors, such as hypertension, diabetes mellitus, and obesity, may contribute to the clinical manifestations of AFD, although this point remains to be fully elucidated (16). In the present study, due to the small number of patients, we were unable to address this point.

In summary, we showed in the present study that AFD patients with the same mutation exhibited variable manifestations. Future studies in a larger number of patients are needed to elucidate the factors relevant to the phenotypic variabilities in AFD patients.

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

Table 2. Clinical and Echocardiographic Data of AFD Patients.

No.	NYHA	BNP pg/mL	Tropnin T ng/mL	EF %	LVDd mm	LVDs mm	IVS mm	LVPW mm	E/A	Dct msec	E/e
1	2	48	0.033	64	42	27	18	8	0.89	150	12.69
2	2	62	0.016	79	38	20	14	14	0.73	171	15.8
3	1	10.6	0.003	64	44	29	7	7	1.63	150	6.6
4	1	14	0.008	55	49	35	13	14	0.9	167	11
5	2	19.6	0.014	61	39	21	15	12	0.77	188	N/A
6	1	5.8	0.003	62	45	27	10	9	1.57	187	7.7
7	1	N/A	N/A	75	38	20	10	10	0.81	229	6.65
8	1	11.8	0.007	66	44	28	10	11	1.01	118	10.2
9	1	N/A	N/A	55	50	34	10	14	1.8	90	6.28
10	1	N/A	N/A	74	46	32	8	8	N/A	N/A	N/A

Echocardiographic parameters are presented. The normal ranges of BNP and Troponin T are 0.00-18.4 pg/mL and 0.000-0.014 pg/mL, respectively. The normal ranges of EF, LVDd, LVDs, IVS, LVPW, E/A, and Dct are 58-71%, 41-52 mm, 25-34 mm, 7-10 mm, 7-10 mm, 1.0-2.0, and 160-240 msec, respectively. E/e is<15.

BNP: brain natriuretic peptide, Dct: deceleration time, EF: ejection fraction, IVS: interventricular septum, LVDd: left ventricular internal dimension, LVDs: left ventricular end-systolic diameter, LVPW: left ventricular post wall, NYHA: New York Heart Association

Table 3. Renal Biopsy and Urinalysis Findings of AFD Patients.

No	eGFR (mL/min/1.73m^2)	Proteinuria (g/gCre)	Albuminuria (mg/gCre)	Renal biopsy	Podocyte score (0-3)	Urine Gb3	Mulberry cell
1	83	0.1	13	No	-	N/A	+
2	98	1	385	No	-	N/A	-
3	126	0.04	7.2	No	-	N/A	-
4	113	0.07	5	No	-	N/A	-
5	54	0	5.8	No	-	N/A	+
6	77	0.1	39	No	-	N/A	-
7	96	0.1*	119	Yes	2	-	+
8	95	5.5	N/A	No	-	+	+
9	180	1.0*	N/A	Yes	3	+	+
10	92	0.3	N/A	Yes	3	N/A	-

The results of renal function tests at the first visit are presented. *Presented as g/day.

eGFR: estimated glomerular filtration ratio, Gb3: globotriaosylsphingosine, N/A: not available

Table 4. Summary of AFD Patients.

No	BMI	HT	DM	Classical symptom	LVH	Renal failure	Cerebral infarction	Event
1	21.9	-	-	-	+	-	-	ICD
2	25.1	+	-	-	+	+	-	Syncope
3	20.2	-	-	+	-	-	-	-
4	27.3	+	-	-	+	-	-	-
5	32	+	-	-	+	+	-	dHCM
6	17	-	-	-	-	-	-	-
7	24.4	-	+	-	-	-	-	-
8	43.3	-	+	-	-	+	-	-
9	29.9	+	-	-	-	+	-	ESRD
10	31.6	+	-	-	-	+	N/A	-

Symptoms of AFD and complications unrelated to AFD are presented.

Renal failure was defined as eGFR <60 mL/min/1.73 m^2 or level of albuminuria >30mg/g·Cre.

BMI: body mass index, dHCM: dilated hypertrophic cardiomyopathy, DM: diabetes mellitus, ESRD: end-stage renal disease, HT: hypertension, ICD: implantable cardioverter defibrillator, LVH: left ventricular hypertrophy, N/A: not available

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