Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8213-21
Intern Med 61: 1727-1730, 2022
http://internmed.jp

【 CASE REPORT 】

The 30-year Natural History of Non-classic Fabry Disease with an R112H Mutation

Reiko Muto[1], Koji Inagaki[2], Noritoshi Kato[1], Shoichi Maruyama[1] and Toshiyuki Akahori[2]

Abstract:
Fabry disease is a rare X-linked lysosomal storage disorder caused by mutations in the alpha-galactosidase A (GLA) gene that results in deficiency of the enzyme GLA and leads to the accumulation of globotriaosylceramide (GL-3) in cells. The accumulation of GL-3 may lead to life-threatening complications. Significant advances in genetic sequencing technology have led to a better understanding of genotype-phenotype interactions in Fabry disease. Fabry disease with an R112H mutation is known as the non-classic type. However, the long-term clinical course of the disease remains unknown. We herein report a patient with a 30-year natural history of non-classic Fabry disease with an R112H mutation.

Key words: Fabry disease, R112H, mutation, GLA, non-classic

(Intern Med 61: 1727-1730, 2022)
(DOI: 10.2169/internalmedicine.8213-21)

Introduction

Fabry disease is a rare X-linked lysosomal storage disorder caused by mutations in the alpha-galactosidase A (GLA) gene that results in a complete or partial deficiency of the enzyme GLA and subsequently leads to the accumulation of mainly globotriaosylceramide (GL-3) in several cell types and body fluids. The accumulation of GL-3 may lead to life-threatening renal, cardiac, and cerebrovascular complications during the third to fifth decades of life (1).

Fabry disease is mainly categorized into classic and non-classic types. The classic type has clear criteria for diagnosis, including a multisystem involvement, such as anhidrosis, acroparesthesia, and angiokeratoma in childhood. It involves little or no GLA activity, resulting in severe renal, cardiac, and cerebrovascular manifestations in adulthood. Therefore, this type has the most severe prognosis, with a median cumulative survival of 50 years and very few individuals still alive beyond 60 years old, even with the advent of renal dialysis or transplantation (2). However, non-classic Fabry disease may be difficult to diagnose accurately, as patients harboring any variant in the GLA gene with residual enzyme activity and variable X chromosome inactivation patterns often present with non-specific symptoms (3).

Over the past few decades, progress in genetic sequencing technology has led to a paradigm change in the understanding of the GLA variants and their clinical significance in Fabry disease. In general, Fabry disease with an R112H mutation is categorized as a non-classic type and is thought to only involve the renal system (4). However, the long-term clinical course of the disease remains unknown.

We herein report a patient with a 30-year natural history of non-classic Fabry disease with an R112H mutation.

Case Report

A 21-year-old Japanese man was referred to our department due to proteinuria, which had been present for 1 year. He had not had any neurologic, renal, ocular, or dermatologic manifestations during his childhood. He had no pertinent family history of disease.

A physical examination indicated that he was 175 cm tall, weighed 62.5 kg, and had a blood pressure of 122/70 mmHg and a heart rate of 78 beats/min in sinus rhythm. His clinical laboratory findings were as follows: white blood cells, 4,600/μL; platelets, 21.7×10^4/μL; blood urea nitrogen 17.6 mg/dL; creatinine, 0.9 mg/dL; sodium, 139 mmol/L;

[1]Department of Nephrology, Nagoya University Graduate School of Medicine, Japan and [2]Department of Nephrology, Chutoen General Medical Center, Japan
Received: June 24, 2021; Accepted: October 12, 2021; Advance Publication by J-STAGE: November 20, 2021
Correspondence to Dr. Reiko Muto, muto21@med.nagoya-u.ac.jp

potassium, 3.7 mmol/L; total serum protein, 8.3 g/dL; serum albumin, 5.4 g/dL; IgG, 1,240 mg/dL; IgA, 263 mg/dL; IgM, 108 mg/dL; urinary red blood cells/high-power-field (HPF), negative; and urinary protein, 0.9 g/day (Table 1).

A renal biopsy was performed. Immunofluorescence images showed no evidence of immune complex deposition (data not shown). Light microscopy showed that the glomeruli had lacy lipid inclusions in the podocytes (Fig. 1a). The tubules had abundant lipid deposits (Fig. 1b). Electron microscopy revealed that podocytes with characteristic lipid inclusions had a zebra pattern (Fig. 1c). Based on a renal biopsy and his mild symptoms, such as proteinuria, we diagnosed him with non-classic Fabry disease. These findings led his mother to be diagnosed with Fabry disease.

Table 1. Laboratory Data at the Kidney Biopsy.

Parameter	Value	Reference range
White blood cells (/μL)	4,600	3,300-8,400
Platelets (×10⁴/μL)	21.7	13.0-34.0
Blood urea nitrogen (mg/dL)	17.6	8.0-20.0
Creatinine (mg/dL)	0.9	0.2-0.8
Total serum protein (g/dL)	8.3	6.7-8.3
Serum albumin (g/dL)	5.4	3.9-4.9
Sodium (mmol/L)	139	135-145
Potassium (mmol/L)	3.7	3.5-5.0
Chloride (mmol/L)	102	98-102
Uric acid (mg/dL)	5.6	<7.0
IgG (mg/dL)	1,240	870-1,700
IgA (mg/dL)	263	110-410
IgM (mg/dL)	108	33-190
Urinary β2 microglobulin (μg/mL)	1.2	<0.23
Urinary red blood cells (/HPF)	0	<1-4
Urinary protein (g/day)	0.9	<0.3

HPF: high-power-field

The patient was then administered imidapril. Even after enzyme replacement therapy (ERT) approval in Japan, he did not agree to a genetic test, an enzyme activity test, or ERT. However, at 47 years old, he agreed to undergo all of these approaches. Genetic testing then revealed an R112H missense mutation (c.335 G>A). The leukocyte GLA activity was low (<1, control: 17-65 nmol/h/mg protein), and plasma lyso-Gb3 was high (5.3, reference interval: 0.38-0.70 nmol/L, liquid chromatography-tandem mass spectrometry, LC-MS/MS). He was then administered agalsidase alfa at 0.2 mg/kg every 2 weeks.

At 51 years old, Holter electrocardiography and cardiac magnetic resonance imaging (MRI) showed no abnormalities. Echocardiography findings at 21, 44, 48, and 51 years old also showed no cardiac manifestations (Table 2), as did brain MRI. For 30 years, his renal function gradually decreased without progressing to end-stage renal disease (ESRD); however, he had no manifestations in other organs (Fig. 2).

Discussion

Although the renal function gradually deteriorated without progressing to ESRD, our non-classic Fabry disease patient with an R112H mutation has not developed multi-organ damage in the past 30 years. As he has been a non-recipient of ERT for 26 years, we speculate that his clinical course demonstrates the natural history of the R112H mutation in non-classic Fabry disease.

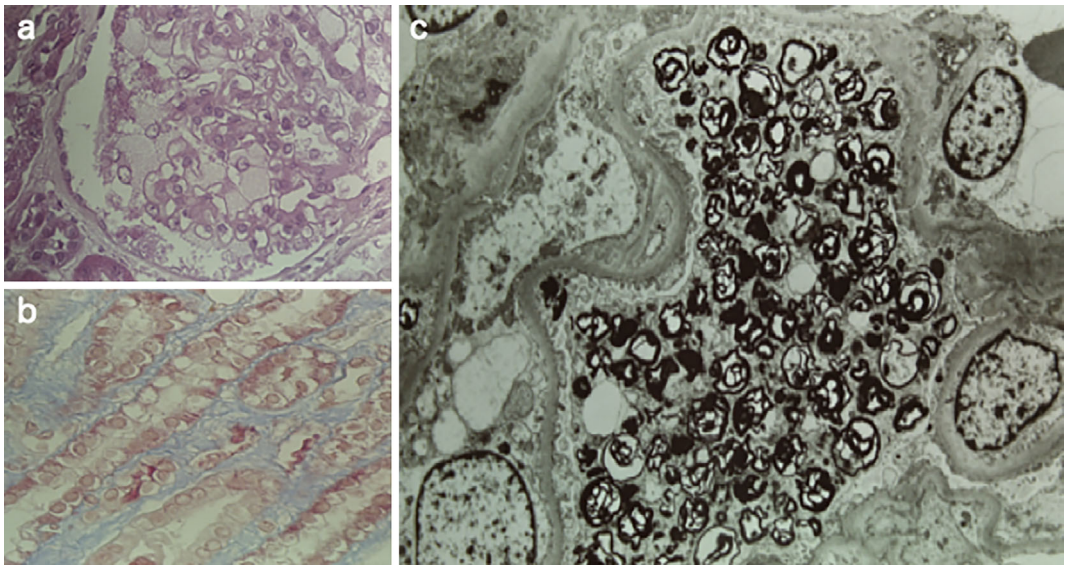

Figure 1. Kidney biopsy results. Kidney sections under light microscopy show a lacy lipid inclusion in podocytes (a: Periodic acid-Schiff staining, original magnification ×400). The tubules have abundant lipid deposits (b: Masson's trichrome staining, original magnification ×400). Podocytes with characteristic lipid inclusions have a zebra pattern (c: Electron microscopy, original magnification ×1,500).

Table 2. Echocardiography Findings at 21, 44, 48, and 51 Years Old.

	Value				
Parameter	21-year-old	44-year-old	48-year-old	51-year-old	Reference range
IVST (mm)	8.3	10.1	9.6	9.4	7-11
PWT (mm)	7.9	9.0	8.3	7.9	7-11
EF (%)	60.1	54.0	66.0	58.0	>55

IVST: interventricular septum thickness, PWT: posterior left ventricular wall thickness, EF: ejection fraction

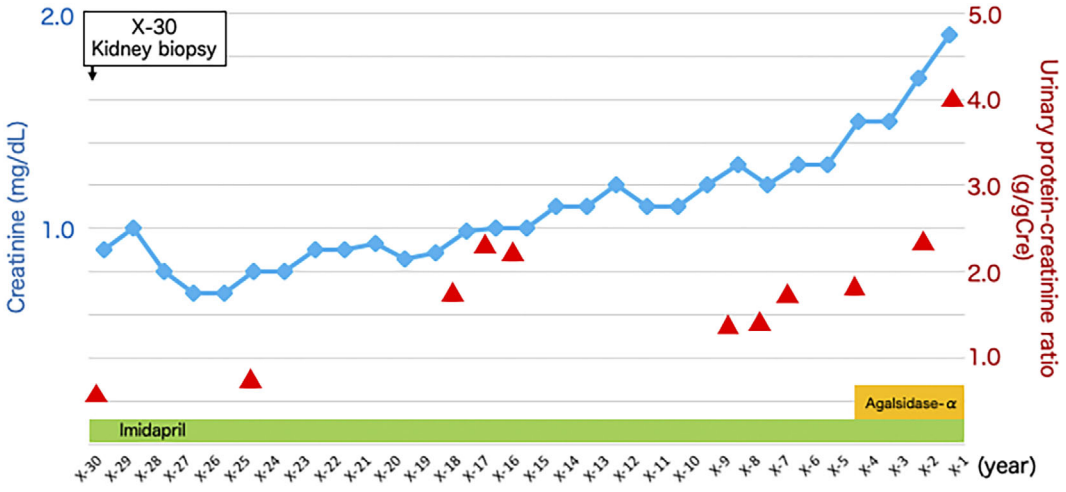

Figure 2. Clinical course. The x-axis shows the time in years since the diagnosis of Fabry disease. The left y-axis shows the level of creatinine (mg/dL). The right y-axis shows the level of urinary protein-creatinine ratio (g/gCre).

In newborn screening studies, the birth prevalence of GLA mutations was increased from previous estimates of 1: 40,000-170,000 up to 1:1,250 owing to the advancement of recent genetic sequencing technology (3). Furthermore, the relationship between genomic variants and their clinical significance has been revealed. Fabry patients with an R112H mutation have attracted interest, as these patients can exhibit residual GLA activity, resulting in a non-classic type of disease (5). However, the long-term clinical course of non-classic Fabry disease with an R112H mutation remains unknown.

Nishida et al. reported a 13-year-old boy diagnosed with non-classic Fabry disease with an R112H mutation based on renal pathology. His creatinine level was 1.12 mg/dL, and his urinary protein level was 0.18 g/gCre. The follow-up duration was nine months (6). Yamashita et al. reported a 61-year-old man diagnosed with Fabry disease with an R112H mutation who had undergone hemodialysis at 39 years old and also had cardiac manifestations, such as left ventricular hypertrophy (7). The details of his clinical course are unclear.

Our patient did not develop ESRD beyond 50 years old, which was consistent with the majority of non-classic Fabry disease patients with an R112H mutation who show relatively mild manifestations, such as proteinuria (6). However, some studies have reported severe manifestations, such as ESRD in one patient at 39 years old (7). Therefore, the R 112H mutation may have a wide phenotypic spectrum, ranging from mild to severe manifestations. Even when the mutation is the same, the enzyme activity of individuals is thought to be affected by many diverse factors, including enzymes related to the biosynthetic and degradative systems of glycolipids in each organ. A previous report also showed that GLA was effective at a low pH (8). This might be one reason why patients with the same mutation demonstrate such a wide phenotypic spectrum, with the varied pH in cells resulting in discrepancy in GLA activity. However, admittedly there is no direct evidence to support this notion. Further investigations are thus warranted to determine the mechanism underlying the wide phenotypic spectrum in Fabry patients with the R112H mutation.

A previous report revealed that classic types show leucocyte GLA activity deficiency coupled with high levels of plasma lyso-Gb3 (5). In our case, the leukocyte GLA activity was low. Furthermore, the plasma lyso-Gb3 was higher than in healthy controls but lower than that in classic types (our case: 5.3 nmol/L, healthy control: 0.37±0.11 nmol/L, classic type: 140±47 nmol/L) (9). Therefore, we speculate that our patient had residual GLA activity that could degenerate lyso-Gb3 in cells, resulting in a clinical non-classic type.

Treatment of Fabry disease has largely involved intrave-

nous ERT with agalsidase alfa or agalsidase beta. However, treatment options for some patients with Fabry disease have recently expanded with the approval of migalastat, an oral molecular chaperone. Chemical chaperones can bind to defective enzymes and help correct folding, maturation, and trafficking of the enzyme to the appropriate functional site. Chaperone therapy with migalastat is now available for amenable mutations, which have been estimated to be 35-50% of Fabry disease mutations (10). A randomized controlled trial designed to investigate migalastat in patients previously treated with ERT showed that the left ventricular mass index decreased further in the migalastat group than in the ERT group after 18 months; however, there were no significant differences in the renal function (11). Furthermore, discrepancies between the effectiveness of migalastat according to *in vitro* amenability assays for some mutations and the outcomes observed in Fabry disease patients with those mutations treated with migalastat have been points of concern (12). Further refinements are required to ensure the appropriate identification of amenable mutations. However, the R112H mutation in our patient is indicated for migalastat therapy; therefore, we considered switching from ERT to migalastat as treatment.

In conclusion, to our knowledge, this is the first report to describe the long-term clinical course of non-classic Fabry disease with an R112H mutation. We herein report a patient with a 30-year natural history of non-classic Fabry disease with an R112H mutation.

Written informed consent for the publication of this report was obtained from the patient.

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

Acknowledgement

We are grateful to Yuriko Sawa, Norihiko Suzuki, and Naoko Asano for their excellent technical assistance.

References

1. Hopkin RJ, Banikazemi M, Clarke L, et al. Caracterization of Fabry disease in 352 pediatric patients in the Fabry registry. Pediatr Res **5**: 550-555, 2008.

2. Branton MH, Schiffmann R, Sabnis SG, et al. Natural history of Fabry renal disease: influence of alpha-galactosidase A activity and genetic mutations on clinical course. Medicine **81**: 122-138, 2002.

3. Svarstad E, Marti HP. The changing landscape of Fabry disease. Clin J Am Soc Nephrol **15**: 569-576, 2020.

4. Eng CM, Desnick RJ. Molecular basis of Fabry disease: mutations and polymorphisms in the human α-galactosidase A gene. Hum Mutat **3**: 103-111, 1994.

5. Sakuraba H, Tsukimura T, Togawa T, et al. Fabry disease in a Japanese population-molecular and biochemical characteristics. Mol Genet Metab Rep **26**: 73-79, 2018.

6. Nishida M, Kosaka K, Hasegawa K, et al. A case of Fabry nephropathy with histological features of oligonephropathy. Eur J Pediatr **173**: 1111-1114, 2014.

7. Yamashita S, Saotome M, Satoh H, et al. Plasma globotriaosylsphingosine level as a primary screening target for Fabry disease in patients with left ventricular hypertrophy. Circ J **83**: 1901-1907, 2019.

8. Modrego A, Amaranto M, Godino A, Mendoza R, Barra JL, Corchero JL. Human α-galactosidase A mutants: priceless tools to develop novel therapies for Fabry disease. Ing J Mol Sci **22**: 6518, 2021.

9. Sueoka H, Ichihara J, Tsukimura T, Togawa T, Sakuraba H. Nano-LC-MS/MS for quantification of lyso-Gb3 and its analogues reveals a useful biomarker for Fabry disease. PloS One **10**: e-127048, 2015.

10. Felis A, Whitlow M, Kraus A, Warnock DG, Wallace E. Current and investigational therapeutics for Fabry disease. Kidney Int Rep **5**: 407-413, 2019.

11. Hughes DA, Nicholls K, Shankar SP, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from randomized phase III ATTRACT study. J Med Genet **54**: 288-296, 2017.

12. Lenders M, Stappers F, Niemietz C, et al. Mutation-specific Fabry disease patient-derived cell model to evaluate the amenability to chaperone therapy. J Med Genet **56**: 548-556, 2019.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).