Saito et al. Renal Replacement Therapy (2016) 2:69
DOI 10.1186/s41100-016-0081-8

Renal Replacement Therapy

CASE REPORT Open Access

# A case of rapid progression of Fabry nephropathy with remarkable glomerulomegaly: a case report and mini literature review of weak response to enzyme replacement therapy (ERT)

Ayako Saito[1], Tomoyoshi Kimura[2], Yoichi Takeuchi[1], Ken Matsuda[1], Hirotaka Fukami[1], Hiroyuki Sato[1], Yoshitsugu Iwakura[1], Hiroshi Sato[3] and Tasuku Nagasawa[1*]

## Abstract

**Background:** Fabry disease is a rare X-linked hereditary disorder (Xq22) caused by a deficiency in alpha-galactosidase (α-GAL) activity. This enzyme deficit results in the systemic accumulation of glycophospholipids, leading to multi-organ failure including the heart, kidneys, and brain. Enzyme replacement therapy (ERT) improves the prognosis of patients with Fabry disease. We describe a case showing progressive renal failure despite ERT.

**Case presentation:** An 18-year-old obese male patient (body mass index (BMI) 29.9 kg/m$^2$) was admitted for detailed examination of mild degree hypertension (150/65 mmHg) and proteinuria occurring for 2 years prior to admittance. Laboratory tests revealed mostly normal kidney function (serum creatinine 0.5 mg/dL, estimated glomerular filtration rate 181 mL/min/m$^2$) with low α-GAL activity, a significant level of proteinuria (0.5–1.0 g/day), and the presence of mulberry cells in the urinary sediment. Renal biopsy demonstrated marked glomerulomegaly with diffuse vacuolization of the glomerular epithelial cells and focal segmental glomerulosclerosis. Electron microscopy revealed typical zebra bodies in the glomerular epithelial cells and effacement of foot processes of the epithelium. We could not find any cause of glomerulomegaly except for obesity. α-GAL gene analysis revealed a missense mutation in R301Q. Although ERT with agalsidase α was initiated, his renal function declined, and hemodialysis was initiated at 22 years of age.

**Conclusions:** We present a case of rapid progression of Fabry nephropathy despite ERT. As with other renal diseases, obesity may aggravate the progression of Fabry nephropathy.

**Keywords:** Fabry disease, Focal segmental glomerulosclerosis, Obesity-related glomerulopathy, Alpha-galactosidase, End-stage renal failure, Mulberry cells

* Correspondence: tasukunagasawa0903@gmail.com
[1]Department of Nephrology, Japanese Red Cross Ishinomaki Hospital, 71 Nishimichisita Hebita, Ishinomaki, Miyagi 986-8522, Japan
Full list of author information is available at the end of the article

## Background

Fabry disease (FD) is a rare X-linked hereditary disorder (Xq22) caused by a deficiency in alpha-galactosidase (α-GAL) activity. Because of this mode of inheritance, men usually become symptomatic while women are sometimes asymptomatic carriers. α-GAL deficits result in the systemic accumulation of glycophospholipids (globotriaosylceramide; Gb3), leading to multi-organ failure including the heart, kidneys, and brain. The phenotype of FD is variable. The classical phenotype includes severe neuropathic or limb pain (acroparesthesias), which may be precipitated by stress; extreme heat or cold and physical exertion; heat intolerance (usually associated with exercise intolerance and avoidance of outdoors in summer months); decreased tear, saliva, or sweat production (hypohidrosis); and cutaneous vascular lesions (angiokeratomas). Renal manifestations occur in at least 50% of male patients and approximately 20% of female patients [1, 2].

Newborn screening in Japan has demonstrated the incidence of FD to be 0.14% [3]. In Japan, the prevalence rate of FD in patients with left ventricular hypertrophy is reported to be 3.0% and the prevalence in patients receiving dialysis is 0.02–1.2% [4–10]. Enzyme replacement therapy (ERT) improves the prognosis of patients with FD [11]; however, not all FD patients necessarily respond to ERT. Factors for the low response to ERT include a low-estimated glomerular filtration rate (eGFR) [12, 13], proteinuria [14], and antibodies to agalsidase α [15].

Here, we describe a case of progressive renal failure despite ERT. Renal biopsy showed glomerulomegaly and focal segmental glomerulosclerosis (FSGS). Obesity may have played an important role in the progression of Fabry nephropathy (FN) in this patient. In addition, data from three other patients with FD at our hospital further support the conjecture that obesity worsens FN as with other renal diseases.

## Case presentation

An 18-year-old Japanese patient presented with proteinuria 2 years prior to renal biopsy. He was admitted for examination due to persistent proteinuria. On admission, his blood pressure was 150/65 mmHg, heart rate was 80 beats per minute, height was 180 cm, and weight was 97 kg with a body mass index of 29.9 kg/m$^2$. Physical examination revealed no abnormalities except for obesity and hypertension.

The serum creatinine level was 0.5 mg/dL, with an eGFR of 181 mL/min/1.73 m$^2$, 24-h creatinine clearance rate of 124 mL/min, and proteinuria of 0.5–1.0 g/day. The results of a complete blood count, as well as those of serum glucose, lipid, electrolyte, and liver function tests were all within the normal range. The hemoglobin A1c content was 5.7%. Serum complement factor and immunoglobulin levels were within the normal range. Mulberry cells were detected in the urinary sediment; therefore, investigations for FD were conducted. Leukocyte alpha-galactosidase (α-GAL) activity was 0.8 nmol/mg protein/h, which was markedly low (normal range, 49.8–116.4 nmol/mg protein/h).

The patient's family tree is shown in Fig. 1. There was no history of consanguineous marriage. The patient's father had a history of hypertension and aortic dissection and had no characteristic symptoms of FD. His mother had diabetes mellitus and dyslipidemia and was later diagnosed with FD. The patient had two maternal uncles, both in good health. His paternal grandfather died of acute myocardial infarction (AMI) at the age of 75 years. His maternal grandfather had a history of AMI, underwent pacemaker implantation, and died of pneumonia at the age of 63 years. His maternal grandfather had six siblings; the grandfather's younger brother underwent hemodialysis and died of undetermined causes at 49 years of age. His maternal grandmother died of unknown causes at the age of 77 years and displayed no indication of FD. One elder sister was diagnosed with FD. Another elder sister had not been investigated at this time. A summary of all related cases of FD is presented in Table 1.

The patient did not present with any characteristic symptoms of FD, such as pain in the extremities, angiokeratomas, decreased sweating, or gastrointestinal disturbance. Chest radiography showed no signs of cardiomegaly or congestion, and the results of a 12-lead electrocardiogram were normal.

Renal biopsy was performed. Thirty-five glomeruli were evaluated under light microscopy, all of which demonstrated foamy changes in the podocytes (Fig. 2) and six glomeruli had segmental sclerosis (Fig. 3). We classified this FSGS as a perihilar variant according to the Columbia classification [16]. The podocyte score was 3 according to previous literature [17]. The glomeruli showed hypertrophy. Of the 35 glomeruli evaluated, 19 glomeruli had intact Bowman's capsules. The major length of those glomeruli was 270 ± 44 μm. An immunofluorescence study revealed an intense deposition of C1q and C3c in the area of the segmental sclerosis, with faint granular deposits of immunoglobulins G, A, and M at the same location. Electron microscopy revealed no immune complex deposition (Fig. 4). We concluded that there were no specific findings.

The patient had not taken medications in the past (except temporarily for a cold) and had no history of any infections, diabetes mellitus, or sickle cell anemia. There was no evidence of prior nephron loss such as congenital absence, low birth weight, or surgical removal of a kidney. He did not experience fever accompanied with costovertebral angle tenderness. In addition, he had not undergone cystourethrography. Thus, the possibility of repeated pyelonephritis was low.

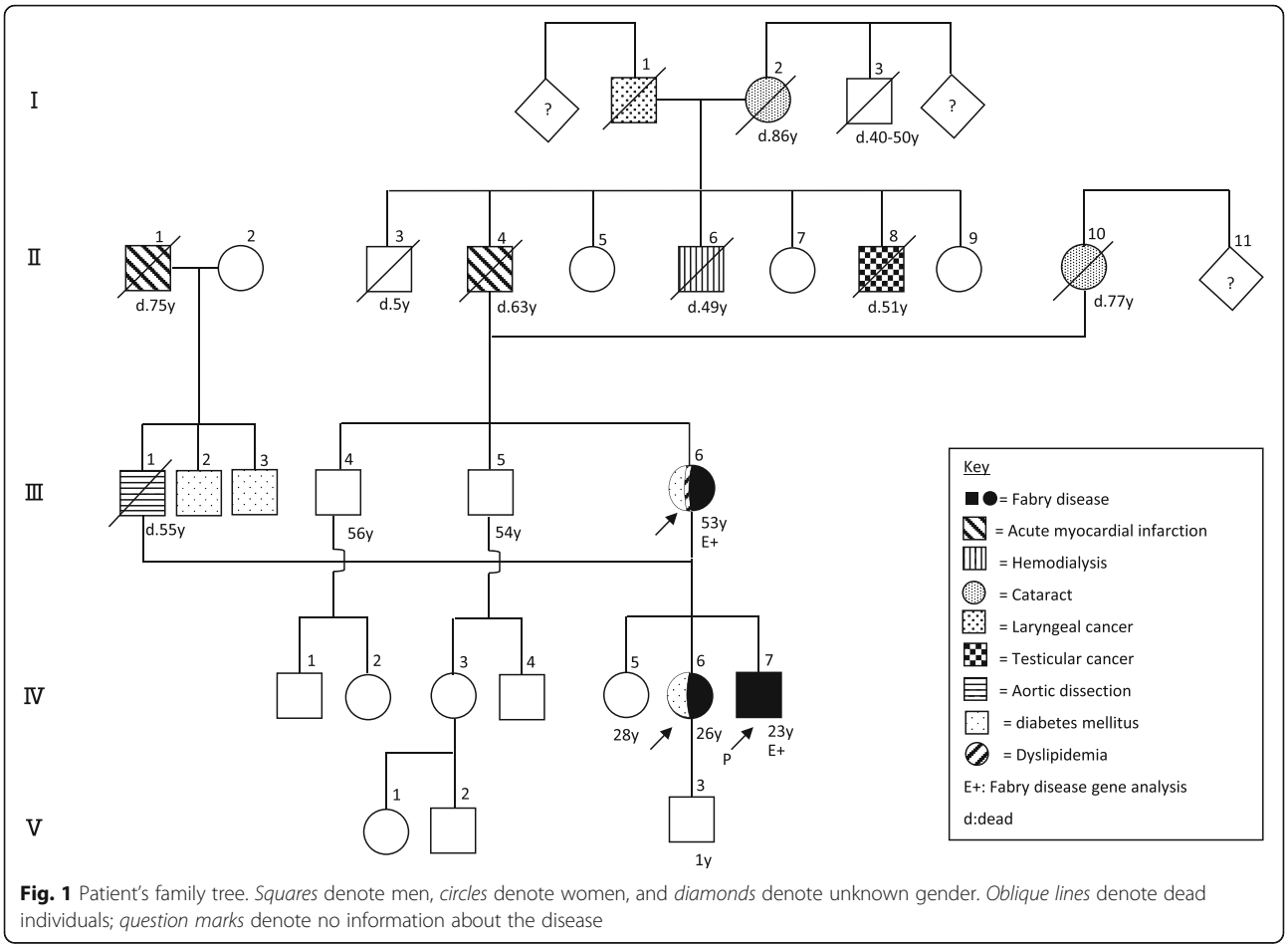


**Fig. 1** Patient's family tree. *Squares* denote men, *circles* denote women, and *diamonds* denote unknown gender. *Oblique lines* denote dead individuals; *question marks* denote no information about the disease

Electron microscopy revealed zebra bodies, which are myelin-like inclusions in the cytoplasm of podocytes. Effacement of the foot process was also observed (Fig. 4). As these findings supported the diagnosis of FD, a final diagnosis of the coexistence of obesity-related glomerulopathy (ORG) and FD was established.

We prescribed lifestyle changes, such as the discontinuation of smoking, increased exercise, and weight reduction. ERT was initiated in order to slow progression of FD. Intravenous administration of agalsidase α at a dose of 17.5 mg bi-weekly (0.2 mg/kg) was initiated. At the time of ERT initiation, the patient's serum creatinine level was 0.62 mg/dL, urinary protein content was 1.8 g/day, serum Gb3 level was 3.9 nmol/mL, and urinary sediment Gb3 level was 1650 nmol/day. Other laboratory findings were all within the normal range.

The patient continued ERT and his height and weight increased. His height increased to 184 cm, and weight increased to 113 kg (body mass index (BMI) = 33.4 kg/m$^2$) at the age of 20 years. We increased the dose of agalsidase α to 21 mg (0.2 mg/kg) once the patient reached his maximum height; after that, the dose was adjusted according to his weight.

At 20 years of age, the patient's serum creatinine level was elevated at 1.2 mg/dL (eGFR, 69 mL/min/1.73 m$^2$), proteinuria was 3.7 g/day, and total protein content was 6.7 g/dL. His systolic blood pressure was maintained at 130–140 mmHg with 16 mg of oral azelnidipine; renin-angiotensin-aldosterone axis blockers and nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs were not administered.

At the age of 21 years, his serum creatinine level had increased to 2.95 mg/dL (eGFR, 25 mL/min/1.73 m$^2$), proteinuria was 3.4 g/day, and total protein content was 6.2 g/day. Systolic blood pressure was controlled at 130–140 mmHg by using 16 mg of oral azelnidipine. Renal function continued to decline, although no nephrotoxic drugs were used. Ultrasound of the kidneys revealed bilateral atrophy with a thin cortex. The patient's serum creatinine level ultimately reached 12.75 mg/dL, at which point hemodialysis via an arterial–venous fistula was initiated. ERT was continued along with maintenance hemodialysis. Currently, 2 years since the initiation of hemodialysis, the patient has not had any complications.

Following the initiation of hemodialysis, the patient and his mother agreed to undergo genomic screening.

**Table 1** Summary of four patients with Fabry disease

| | Sex | Age at diagnosis | Age at ERT start | BMI at diagnosis | α-GAL activity (mmol/h/mg protein) | Cre at diagnosis (mg/dl) | Up at diagnosis (g/day) | HT | DM | Serum lyso-Gb3 (nmol/L) before ERT | Serum lyso-Gb3 (nmol/L) after ERT | Urine Gb3 before ERT | Urine Gb3 after ERT | Gene mutation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Normal value | | | | | 20–80 | | | | | <2 | <2 | | | |
| Mother | F | 53 | 53 | 24.4 | 13 | 0.51 | 0.1 | − | + | <2 | N/A | − | N/A | R301Q (cga→caa) |
| Patient | M | 18 | 18 | 29.9 | 0.5 | 0.5 | 1.0 | + | − | 3.9 | 3.0 | + | + | R301Q (cga→caa) |
| Sister | F | 26 | No | 43.3 | 16 | 0.62 | 5.5[a] | − | + | 4.3 | N/A | + | N/A | R301Q (cga→caa) |
| Unrelated | M | 34 | 34 | 34.4 | 0 | 1.49 | 0.5 | − | − | 131 | N/A | + | N/A | W340X (tgg→tag) |

*HT* hypertension, *DM* diabetes mellitus, *BMI* body max index, *ERT* enzyme replacement therapy, *Cre* creatinine, *Up* urinary protein, N/A not available
[a]Value was presented as g/gCre

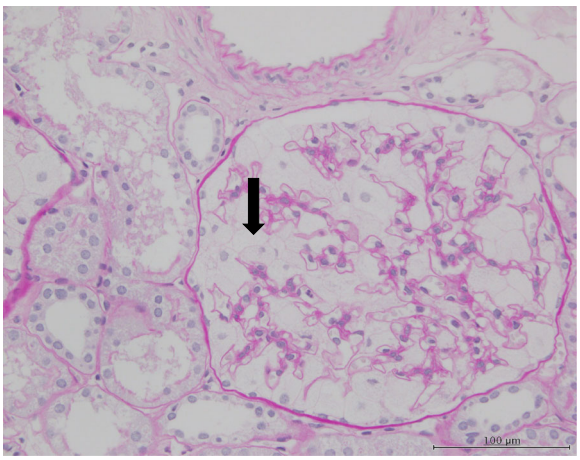


**Fig. 2** Periodic acid–Schiff staining findings on light microscopy. Foamy changes in podocytes are visible (*closed arrow*)

Gene analysis revealed a missense mutation of the *GAL* gene p.Arg301Gln. This missense mutation was described according to standard mutation nomenclature in molecular diagnostics [18] and has been previously reported in FD cases [19]. In this case, the patient's mother also had the same genetic mutation; however, she remained asymptomatic and only had mild diabetes mellitus. Her α-GAL activity was 13 nmol/mg protein/h, which is lower than the normal level (20–80 nmol/mg protein/h). She did not show any of the characteristic symptoms of FD, such as pain in the extremities, angiokeratomas, decreased sweating, or gastrointestinal disturbance. Her serum creatinine level was 0.51 mg/dl. She showed normal proteinuria (0.1 g/gCre), but the urinary albumin level was 119 mg/day. Her left ventricular mass index was 114.2 g/m$^2$. She had chronic kidney disease and mild cardiac hypertrophy. She also underwent renal biopsy. Seventeen glomeruli were evaluated under light microscopy, all of which demonstrated foamy changes in the podocytes, and no glomeruli had segmental sclerosis (Fig. 5). The podocyte score was 2. The major length of the glomeruli was 231 ± 25 μm. Electron microscopy revealed zebra bodies. Her serum and urine Gb3 level was under the detection level, but to avoid further complication of FD, ERT with agalsidase α (0.2 mg/kg bi-weekly) was initiated. Her condition was stable, without any complications following ERT.

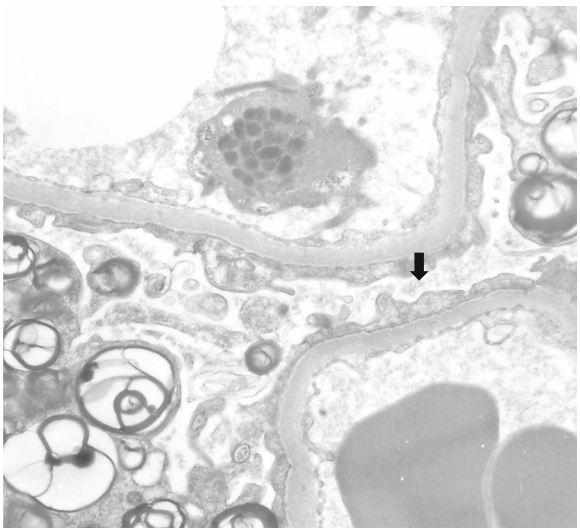

**Fig. 4** Electron microscopy findings. *Open arrow*: zebra bodies (myelin-like inclusion) are visible in the podocytes. *Closed arrow*: effacement of foot processes was also observed

His elder sister also had the same mutation. She was obese (160 cm, 111 kg, BMI 43.3 kg/m$^2$) and had diabetes mellitus. She also did not show any of the characteristic symptoms of FD, such as pain in the extremities, angiokeratomas, decreased sweating, or gastrointestinal disturbance. We recommended ERT because her α-GAL

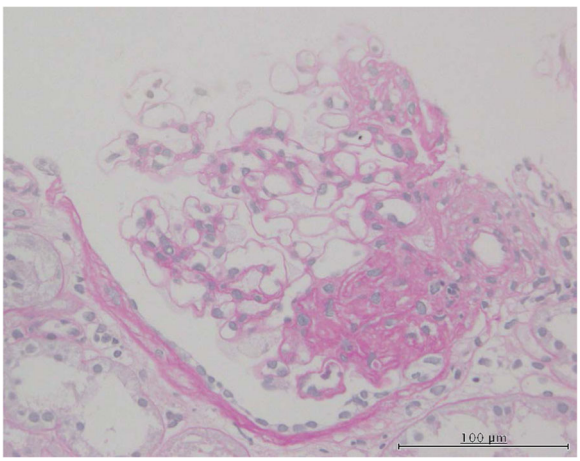


**Fig. 3** Periodic acid–Schiff staining findings on light microscopy. Segmental sclerosis of glomerulus is seen at the 4 to 6 o'clock position

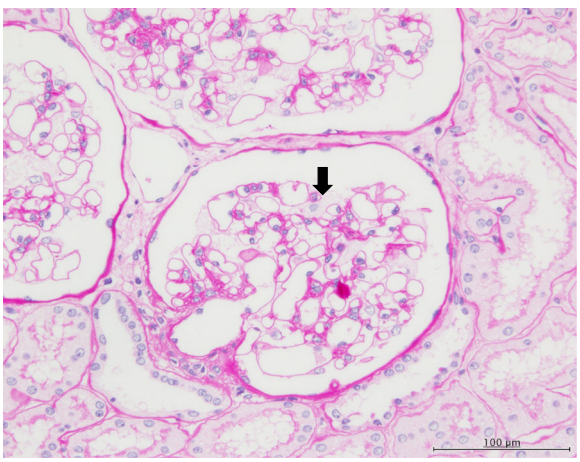


**Fig. 5** Periodic acid–Schiff staining findings on light microscopy. Foamy changes in podocytes are visible (*closed arrow*)

activity was low, proteinuria was present (5.5 g/gCre), and serum/urine Gb3 level was elevated (Table 1). However, as she decided not to initiate ERT, we only prescribed lifestyle changes such as the discontinuation of smoking, increased exercise, and weight reduction.

## Discussion with mini-review of low responsiveness to ERT

This case showed aggressive progression of FN despite ERT that was initiated when the patient still had normal renal function. We review the literature and discuss which factors could have contributed to the low responsiveness to ERT in this case.

### *Proteinuria and histological findings*

A past report showed that more than 60% of a patient's kidney function was due to the response to ERT [20]. In addition, the presence of proteinuria and advanced histological finding is a predictor of progression. Proteinuria is one of the known risk factors for renal failure. Schiffmann et al. reported that untreated male patients with FN and a baseline eGFR >60 mL/min/1.73 $m^2$ were found to progress at a mean rate of −2.93 mL/min/1.73 $m^2$/year, and the severity of proteinuria was found to be associated with a more rapid loss of eGFR [14]. In addition, this previous report showed that patients with FN and proteinuria >1.0 g/g creatinine had a steeper eGFR slope (−6.9 mL/min/1.73 $m^2$/year). Similarly, Warnnock et al. reported that proteinuria is associated with the loss of renal function in FD [20]. Our patient was at a high risk of renal failure owing to progressive proteinuria.

ERT is one of the established therapies for FN. Both types of ERT treatment (agalsidase α and agalsidase β) can have a favorable effect on the kidneys [20–22]. Germain et al. reported that some FN patients treated with agalsidase β demonstrated a steep eGFR slope. All of those patients were in the high renal involvement group (patients with urinary protein creatinine ratio >0.5 g/g creatinine or ≥50% sclerotic glomeruli at baseline), as was the patient in this study [13]. This suggests that some FD patients have a weak response to ERT.

Fogo et al. showed that the podocyte vacuoles score correlated with globotriosylceramides (GL-3) accumulation [17]. In this case, the patient's podocyte vacuoles score was 3. Renal function should have decreased due to advanced FN, but the presence of obesity most likely caused hyperfiltration. These factors offset each other, and he appeared to have normal renal function at the time of presentation.

### *Presence of antibody to agalsidase α*

Deegan suggested that the presence of a high-titer antibody to galactosidase might be a factor in the poor response to ERT [15]. The incidence of antibodies observed during agalsidase α is considered to be 0–56% [14]. However, the patient in this case did not have a high antibody titer. A twofold or greater change in agalsidase-alpha-specific quantitative antibody titers in paired sera was considered as significant.

### *Selection of antihypertensive drugs*

The calcium channel blocker, azelnidipine, was used to control the patient's blood pressure. The systolic blood pressure was maintained at 130–140 mmHg. It may have been preferable to lower the systolic pressure further to less than 130 mmHg, according to the current recommendation for the management of FN [12]. We could have added other antihypertensive medications such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers that have renoprotective effects in FN. However, the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is only 40–79% [12, 13].

### *Dose of ERT*

The drug doses used in the ERT regimen may have been too low. Tøndel et al. showed that the clearance of Gb3 from podocytes is dose dependent; however, this had little impact on the decline in kidney function [22]. Schiffmann et al. showed that weekly infusions of agalsidase α at a dosage of 0.2 mg/kg might be beneficial [23]. In our study, the patient demonstrated a continued decline in renal function despite bi-weekly infusion of conventionally dosed agalsidase α therapy (0.2 mg/kg every other week) for 4 years. Weekly administration generally leads to a slower decline in eGFR. If the Japanese insurance system had allowed us to choose this option, we would have increased the frequency of ERT.

Our patient showed a marked decline in eGFR 2 years after ERT initiation while the patient was still in his growth phase. He gained in height and weight during the first 2 years of ERT therapy. Ries et al. reported that a pediatric population (6–18 years old; mean age, 11.8 years) showed rapid clearance of agalsidase α [23], which might have contributed to a weak response to ERT in our patient.

**Gene mutation and lyonization** Future studies should evaluate the correlation between the genetic mutation type and disease prognosis. At present, at least 600 variants in the α-GAL gene have been described [24]. However, the relationship between the type of mutation and prognosis is not clear. R301Q mutations cause several phenotypes (http://fabry-database.org). For example, cases of nephropathy only, classic type, and an atypical variant have been reported [8, 25, 26]. In addition, Politei et al. revealed that patients with the same mutation as the current case (L415P) show different organ damage [27]. These findings suggest that gene mutation is not

the only factor involved in organ damage. Acquired factors may also be important.

Differences in gene mutations result in three different functions of the alpha-GAL enzyme, including incomplete protein (lack of enzyme activity), weak or no enzymatic activity within the lysosome, or impairment in the transfer of the protein from the endoplasmic reticulum (ER) to the lysosome. R301Q alpha-GAL mutations result in the retention of the abnormal protein in the ER, which are degraded without processing [28]. Notably, our case also had this gene mutation and poor renal prognosis.

Lyonization is also an important factor for females. The mother and sister had the same mutation of the GLA gene but showed a different phenotype, with a different level of Gb3, potentially explainable by lyonization [29]. At the moment, the degree of lyonization is unmeasurable.

### Present case

Despite the degree of proteinuria, our patient had an extraordinarily steep eGFR curve (approximately −25 mL/min/1.73 $m^2$ per year). Renal biopsy revealed FSGS with no other significant underlying factors except for obesity. FN itself causes FSGS [30]. To our best knowledge, Fabry disease itself did not cause the glomerulomegaly. The patient was obese and had nephrotic-range proteinuria in the absence of nephrotic syndrome. The renal biopsy specimen showed segmental sclerosis accompanied by glomerulomegaly. These clinical presentations are similar to those observed in previous reports on obesity-related glomerulopathy ORG [31–33]. From a clinical point of view, a high eGFR value at the time of renal biopsy could be explained by excessive filtration, which is similar to the features observed in ORG. Therefore, we believe that ORG played an important role in the rapid eGFR decline in our patient's FN.

Obesity is known as a risk factor for end-stage renal disease (ESRD) [34–38]. In addition, when patients have a risk factor for ESRD, including unilateral kidney after nephrectomy and IgA nephropathy, obesity is known to affect the progression of chronic kidney disease (CKD) [32, 39, 40]. A relationship between obesity and FN has not previously been investigated. FD patients are generally lean, possibly due to gastrointestinal symptoms. Only three published reports describe BMI and the frequency of obesity in FD [40–42]. Of four patients with FD at our hospital, the three obese patients showed progressive FN (Table 1). Although the sample size is too small to indicate obesity as the culprit, we believe that obesity exacerbates FN as with other renal diseases. FD is a rare disease, and it is currently not possible to anticipate which patients will have a weak response to ERT. Importantly, we can prescribe lifestyle changes to reduce weight, which may improve the prognosis for obese patients with FD. Future studies should focus on a potential correlation between obesity and FN.

In order to determine the factors, genotype, and severity of histology that promote renal dysfunction in FN, as well as the optimal dose of ERT for treatment of FN, all FD cases should be reported globally. Moreover, as FD is a rare disease, its early detection is also important. One useful test in FN screening involves the detection of mulberry cells in urinary sediment, which has a low cost and is less invasive than other tests such as renal biopsy or gene analysis [43]. All of our four cases presented with mulberry cells in their urine sediment. Mulberry cells are very small (usually <10 μm) and require training to detect. In addition, a method for the early detection of FD needs to be established to avoid subsequent organ failure.

## Conclusions

To the best of our knowledge, this is the first report suggesting that obesity accelerates the progression of FN. Renal histology showed remarkable glomerulomegaly. In addition, this case is a unique example of a different manifestation of FD with a poor response of FN to ERT.

#### Abbreviations

AMI: Acute myocardial infarction; BMI: Body mass index; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; ERT: Enzyme replacement therapy; ESRD: End-stage renal disease; FD: Fabry disease; FN: Fabry nephropathy; FSGS: Focal segmental glomerulosclerosis; Gb3: Globotriaosylceramide; LV: Left ventricular; ORG: Obesity-related glomerulopathy; α-GL: Alpha-galactosidase

#### Acknowledgements

We thank Hitoshi Sakuraba (Department of Clinical Genetics, Meiji Pharmaceutical University, Kiyose), Takahiro Tsukimura, and Tadayasu Togawa (Department of Functional Bioanalysis, Meiji Pharmaceutical University) for the genetic analysis. We also thank Kiyomi Kisu for preparing the beautiful electron microscopy photograph. We also thank Dr. Takashi Nakamichi (Tohoku University) for his professional advice regarding the manuscript and clinical suggestions. We thank Yuri Yasuda (Certified Genetic Counselor) for preparing the family tree.

#### Funding

Not applicable.

#### Availability of data and materials

The datasets generated during and/or analyzed during the current study are available in the Red Cross Ishinomaki Hospital's repository.
The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.
All data generated or analyzed during this study are included in this published article.
The datasets generated during and/or analyzed during the current study are not publicly available due to protect patient's personal information (because Fabry disease is rare and hereditary disease,) but are available from the corresponding author on reasonable request.
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

#### Authors' contributions

AS and TN planned this review and drafted the manuscript. TK and HS supervised and made suggestions for the drafting of the manuscript. AS,TK,YT, KM, HF, HS, YI, and TN took care of this patient and participated in the decision of treatment. AS, TK, YT, KM, HF, SH, YI, and TN diagnosed and

treated the patient. AS, TK, SH, and TN wrote the manuscript. TK, HS, and TN edited the manuscript. All authors read and approved the manuscript.

#### Competing interests
The authors declare that they have no competing interests.

#### Consent for publication
Written informed consent was obtained from all patients for the publication of this case report and any accompanying images.

#### Ethics approval and consent to participate
This case was approved by the Ethical Committee of Japanese Red Cross Ishinomaki Hospital (approval no: 15–21).

#### Author details
[1]Department of Nephrology, Japanese Red Cross Ishinomaki Hospital, 71 Nishimichisita Hebita, Ishinomaki, Miyagi 986-8522, Japan. [2]Department of Nephrology, Japan Community Health Care Organization Sendai Hospital, 3-16-1 Tsutsumimachi, Aoba-ku, Sendai 981-8501, Japan. [3]Clinical Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3, Aoba, Aramaki, Aoba-ku, Sendai City 980-8578, Japan.

Received: 7 April 2016 Accepted: 8 December 2016
Published online: 09 January 2017

#### References
1. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010;5:30.
2. Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry registry. Mol Genet Metab. 2008;93(2):112.
3. Inoue T, Hattori K, Ihara K, Ishii A, Nakamura K, Hirose S. Newborn screening for Fabry disease in Japan: prevalence and genotypes of Fabry disease in a pilot study. J Hum Genet. 2013;58:548–52.
4. Nakao S, Takenaka T, Maeda M, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. N Engl J Med. 1995;333:288–93.
5. Saito O, Kusano E, Akimoto T, et al. Prevalence of Fabry disease in dialysis patients: Japan Fabry disease screening study (J-FAST). Clin Exp Nephrol. 2015;20:284–93.
6. Utsumi K, Kase R, Takata T, Sakuraba H, Matsui NSH. Fabry disease in patients receiving maintenance dialysis. Clin Exp Nephrol. 2000;4:49–51.
7. Nakao S, Kodama C, Takenaka T, et al. Fabry disease: detection of undiagnosed hemodialysis patients and identification of a "renal variant" phenotype. Kidney Int. 2003;64:801–7.
8. Ichinose M, Nakayama M, Ohashi T, Utsunomiya Y, Kobayashi M, Eto Y. Significance of screening for Fabry disease among male dialysis patients. Clin Exp Nephrol. 2005;9:228–32.
9. Tanaka M, Ohashi T, Kobayashi M, et al. Identification of Fabry's disease by the screening of alpha-galactosidase A activity in male and female hemodialysis patients. Clin Nephrol. 2005;64:281–7.
10. Maruyama H, Takata T, Tsubata Y, et al. Screening of male dialysis patients for Fabry disease by plasma globotriaosylsphingosine. Clin J Am Soc Nephrol. 2013;8:629–36.
11. Pisani A, Visciano B, Roux GD, et al. Enzyme replacement therapy in patients with Fabry disease: state of the art and review of the literature. Mol Genet Metab. 2012;107:267–75.
12. Warnock DG, Daina E, Remuzzi G, West M. Enzyme replacement therapy and fabry nephropathy. Clin J Am Soc Nephrol. 2010;5:371–8.
13. Germain DP, Charrow J, Desnick RJ, et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. J Med Genet. 2015;52:1–6.
14. Schiffmann R, Warnock DG, Banikazemi M, et al. Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. Nephrol Dial Transplant. 2009;24:2102–11.
15. Deegan PB. Fabry disease, enzyme replacement therapy and the significance of antibody responses. J Inherit Metab Dis. 2012;35:227–43.
16. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis. 2004;43:368–82.
17. Fogo AB, Bostad L, Svarstad E, et al. Scoring system for renal pathology in Fabry disease: report of the International Study Group of Fabry Nephropathy (ISGFN). Nephrol Dial Transplant. 2010;25:2168–77.
18. Ogino S, Gulley ML, Den Dunnen JT, Wilson RB. Standard mutation nomenclature in molecular diagnostics practical and educational challenges. J Mol Diagnostics. 2007;9:1–6.
19. Sakuraba H, Oshima A, Fukuhara Y, et al. Identification of point mutations in the alpha-galactosidase A gene in classical and atypical hemizygotes with Fabry disease. Am J Hum Genet. 1990;47:784–9.
20. Biegstraaten M, Arngrímsson R, Barbey F, Boks L, Cecchi F, Deegan PB, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. Orphanet J Rare Dis. 2015;10:36.
21. Tøndel C, Bostad L, Larsen KK, et al. Agalsidase benefits renal histology in young patients with Fabry disease. J Am Soc Nephrol. 2013;24:137–48.
22. Schiffmann R, Askari H, Timmons M, Robinson C, et al. Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing. J Am Soc Nephrol. 2007;18:1576–83.
23. Ries M, Clarke JT, Whybra C, Mehta A, et al. Enzyme replacement in Fabry disease: pharmacokinetics and pharmacodynamics of agalsidase alpha in children and adolescents. J Clin Pharmacol. 2007;47:1222–30.
24. Iemolo F, Pizzo F, Albeggiani G, Zizzo C, Colomba P, Scalia S, Bartolotta C, Duro G1. De novo mutation in a male patient with Fabry disease: a case report. BMC Res Notes. 2014;7:11.
25. Sawada K, Mizoguchi K, Hishida A, et al. Point mutation in the alpha-galactosidase A gene of atypical Fabry disease with only nephropathy. Clin Nephrol. 1996;45:289–94.
26. Germain DP, Shabbeer J, Cotigny S, Desnick RJ. Fabry disease: twenty novel alpha-galactosidase A mutations and genotype-phenotype correlations in classical and variant phenotypes. Mol Med. 2002;8(6):306–12.
27. Politei J, Schenone AB, Cabrera G, Heguilen R, Szlago M. Fabry disease and enzyme replacement therapy in classic patients with same mutation: different formulations—different outcome? Clin Genet. 2015;89(1):88–92.
28. Ishii S, Chang H-H, Kawasaki K, Yasuda K, et al. Mutant alpha-galactosidase A enzymes identified in Fabry disease patients with residual enzyme activity: biochemical characterization and restoration of normal intracellular processing by 1-deoxygalactonojirimycin. Biochem J. 2007;406:285–95.
29. Pinto LL, Vieira TA, Giugliani R, Schwartz IV. Expression of the disease on female carriers of X-linked lysosomal disorders: a brief review. Orphanet J Rare Dis. 2010;28(5):14.
30. Svarstad E, Bostad L, Kaarbøe O, Houge G, Tøndel C, Lyngdal PT, et al. Focal and segmental glomerular sclerosis (FSGS) in a man and a woman with Fabry's disease. Clin Nephrol. 2005;63:394–401.
31. Praga M, Hernandez E, Herrero JC, et al. Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy. Kidney Int. 2000;58:2111–8.
32. Abitbol CL, Chandar J, Rodriguez MM, et al. Obesity and preterm birth: additive risks in the progression of kidney disease in children. Pediatr Nephrol. 2009;24:1363–70.
33. Gonzalez E, Gutierrez E, Morales E, et al. Factors influencing the progression of renal damage in patients with unilateral renal agenesis and remnant kidney. Kidney Int. 2005;68:263–70.
34. Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S. Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int. 2004;65:1870–6.
35. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: an emerging epidemic. Kidney Int. 2001;59:1498–509.
36. Ejerblad E, Fored CM, Lindblad P, Fryzek J, Mclaughlin JK, Nyre O. Obesity and risk for chronic renal failure. J Am Soc Nephrol. 2006;17(6):1695–702.
37. Bonnet F, Deprele C, Sassolas A, et al. Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. Am J Kidney Dis. 2001;37:720–7.
38. Tanaka M, Tsujii T, Komiya T, et al. Clinicopathological influence of obesity in IgA nephropathy: comparative study of 74 patients. Contrib Nephrol. 2007;157:90–3.
39. Hsu C, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease. Arch Intern Med. 2009;169:342.
40. Rolfs A, Böttcher T, Zschiesche M, Morris P, Winchester B, Bauer P, et al. Prevalence of Fabry disease in patients with cryptogenic stroke: a prospective study. Lancet. 2005;366:1794–6.

41. Thadhani R, Wolf M, West ML, Tonelli M, Ruthazer R, Pastores GM, et al. Patients with Fabry disease on dialysis in the United States. Kidney Int. 2002;61:249–55.
42. Hauser AC, Gessl A, Lorenz M, Voigtländer T, Födinger M, Sunder-Plassmann G. High prevalence of subclinical hypothyroidism in patients with Anderson-Fabry disease. J Inherit Metab Dis. 2005;28:715–22.
43. Nakamichi T, Miyazaki M, Nakayama K, et al. Fabry's disease discovered with chance urinary mulberry cells: a case report. CEN Case Rep. 2013;2:49–52.