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Case report

Early onset of nephrogenic diabetes insipidus due to fabry disease in a child with *GLA* N215S mutation: Case report and literature review☆

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ABSTRACT

Background: Fabry disease (FD) is a rare X-linked lysosomal storage disorder. Renal involvement in FD is characterized by proteinuria and progressive renal decline. Reports on FD with nephrogenic diabetes insipidus as the initial manifestation are rare. In this paper, we report a pediatric case with an N215S variant.

Results: A boy with an onset of polydipsia and polyuria at approximately 4 years of age was diagnosed with nephrogenic diabetes insipidus. Whole-exome sequencing showed a GLA N215S variation with no secondary cause of diabetes insipidus. No family history of polydipsia or polyuria was reported; however, the patient's maternal grandmother and her two younger brothers had hypertrophic cardiomyopathy. Both brothers required surgery due to severe cardiac involvement, and the youngest brother died of heart disease at the age of 50 years. The patient's polydipsia and polyuria worsened over the next 7 years. Serum sodium was normal, but the patient required high-dose potassium chloride to maintain normal serum potassium levels. His physical and intellectual development was normal, with no common complications of nephrogenic diabetes insipidus, such as anemia, malnutrition, vomiting, high fever, or convulsions. Dried blood spot testing showed α-galactosidase A (α-gal A) activity of 0.6 μmol/L/h and a Lyso-GL-3 level of 7.01 ng/ml. The patient developed mild proteinuria and mild myocardial hypertrophy. Renal biopsy showed myeloid bodies and zebra bodies. After more than 1 year of ERT, his urine specific gravity increased to 1.005–1.008, which was a new sign reflecting the efficacy of ERT, although urine output was maintained at 3–5 ml/kg/hour. We will continue to monitor the patient's renal tubular function and urine output.

Conclusions: Nephrogenic diabetes insipidus may be the initial manifestation in children with FD and/or N215S variation. In FD, the same mutation in a family may present a completely different phenotype.

☆ Terminal academic degree: All the authors are medical doctors.

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1. Introduction

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by abnormalities in the activity of α-galactosidase A (α-Gal A) due to *GLA* variation, which results in the significant accumulation of metabolic substrates in the body and, ultimately, multiple organ diseases [1]. Renal involvement in FD is usually characterized by proteinuria, progressive renal decline, and, ultimately, renal failure [2]. Reports of FD with nephrogenic diabetes insipidus as the initial manifestation are rare. In this paper, we report the case of a boy with an N215S variant who developed nephrogenic diabetes insipidus. Urine-specific gravity increased after 12 months of enzyme replacement therapy (ERT).

2. Case report

A boy aged 4 years and 11 months visited our hospital for "polydipsia and polyuria for nearly one year". One year prior to his visit, the patient had unexplained polydipsia and polyuria. He drank up to 6 L of water a day and had a daily urination frequency of more than 10 times and a daily urine output of 3–4 L. He woke up several times at night to urinate. He had no nausea, vomiting, diarrhea, or fever. Urine analysis showed a specific gravity of 1.000, protein -, ketone bodies -, glucose -, and pH 5.0. He had no known history of previous illnesses or food or drug allergies. Personal history: The patient was born full-term, with a birth weight of 3.15 kg; his physical growth and development were normal (appropriate for his age). The patient's family denied any history of hypertension, diabetes, tumor, or similar polydipsia and polyuria disorders. His physical examination were unremarkable with normal blood pressure (100/53 mmHg) and no visible dehydration. Laboratory findings was shown in Table 1. Genetic metabolic panel, hepatitis B, syphilis, hepatitis C, HIV, and ANA were normal. Chest X-ray, electrocardiogram, abdominal ultrasound B, and pituitary MRI were unremarkable. The 24-h urine output was 3030–3770ml.A vasopressin test (after fasting from water) indicated nephrogenic diabetes insipidus. The patient was discharged and instructed to take hydrochlorothiazide tablets 12.5 mg bid and to follow up at the local hospital for blood electrolyte analysis. Later next-generation sequencing suggested *GLA* variation (c.644A > G p. Asn215Ser). Further inquiry showed that the patient's maternal grandmother and her two younger brothers had hypertrophic cardiomyopathy. Both brothers underwent heart surgery, and the youngest brother died of heart disease at the age of 50 years. This finding confirmed the presence of FD. However, whether the patient had two rare diseases or FD with renal involvement manifesting as nephrogenic diabetes insipidus was unclear.

The patient presented no other common FD symptoms over the next 7 years, such as limb pain, hypohidrosis, or skin angiokeratoma. He still drank a large amount of water every day, his urine output gradually increased to 6–8 L per day, and his urine specific

Table 1
Laboratory findings of the patient.

Laboratory Findings	First Admission	One Year After Treatment	Reference Range
Leukocytes, $\times 10^9$/L	7.97	8.27	4–12
Hemoglobin, g/L	129	156	110–155
Thrombocytes, $\times 10^9$/L	298	244	100–400
CRP, mg/L	<1	<1	<1
PH	7.43	7.426	7.35–7.45
Bicarbonate, mEq/L	20.4	23.7	21–28
Glucose, mEq/L	5.2	5.6	3.6–6.11
Sodium, mEq/L	144	140	135–145
Potassium, mEq/L	3.5	3.6	3.5–5.5
Chlorine, mEq/L	112	107	98–106
Ionized calcium, mEq/L	2.46	2.39	2.2–2.65
Albumin, g/L	45.7	44	32–55
Alanine aminotransferase, U/L	12	18	5–50
Uric acid, μmol/L	320	511	65–420
Serum creatinine, μmol/L	48	60	15–77
eGFR,[a] mL/min/1.73 m^2	103.1	102.2	
Aldosterone, ng/L	recumbent: 151.41	–	30–180
	standing: 170.61	–	50–313
Ceruloplasmin, mg/L	202	–	200–600
Urinary Analyses			
PH	5.5	5.5	5.5–6.5
Urinary protein	–	–	Negative
urine specific gravity	1.000–1.001	1.005–1.008	1.003–1.030
ketone bodies	–	–	Negative
glucose	–	–	Negative
White blood cell	–	–	Negative
Red blood cell	–	–	Negative
24H urine protein, mg	139	121.8	<150
24H urine potassium, mmol/kg	3.12	4.16	0.33–1.73
24H urine natrium, mmol/kg	1.96	3.3	<5
24H urine calcium, mg/kg	0.47	0.34	0–4

[a] Calculated using the Schwartz equation.

gravity was 1.000–1.003. His physical and intellectual development was normal (currently 11 years and 10 months old, with a weight of 52 kg and a height of 159 cm). The patient had no anemia, malnutrition, anorexia, vomiting, fever, constipation, or convulsions. Serum sodium was normal, which differs from previous reports. To maintain normal serum potassium, the patient took oral potassium chloride tablets every day (15 g/d, which was higher than the adult dose; his serum potassium was approximately 3.5 mmol/L). To reduce urine output, the dose of hydrochlorothiazide tablets was gradually increased from 12.5 mg bid po to 37.5 mg bid po. The patient took indomethacin but discontinued the drug after 6 months due to adverse reactions.

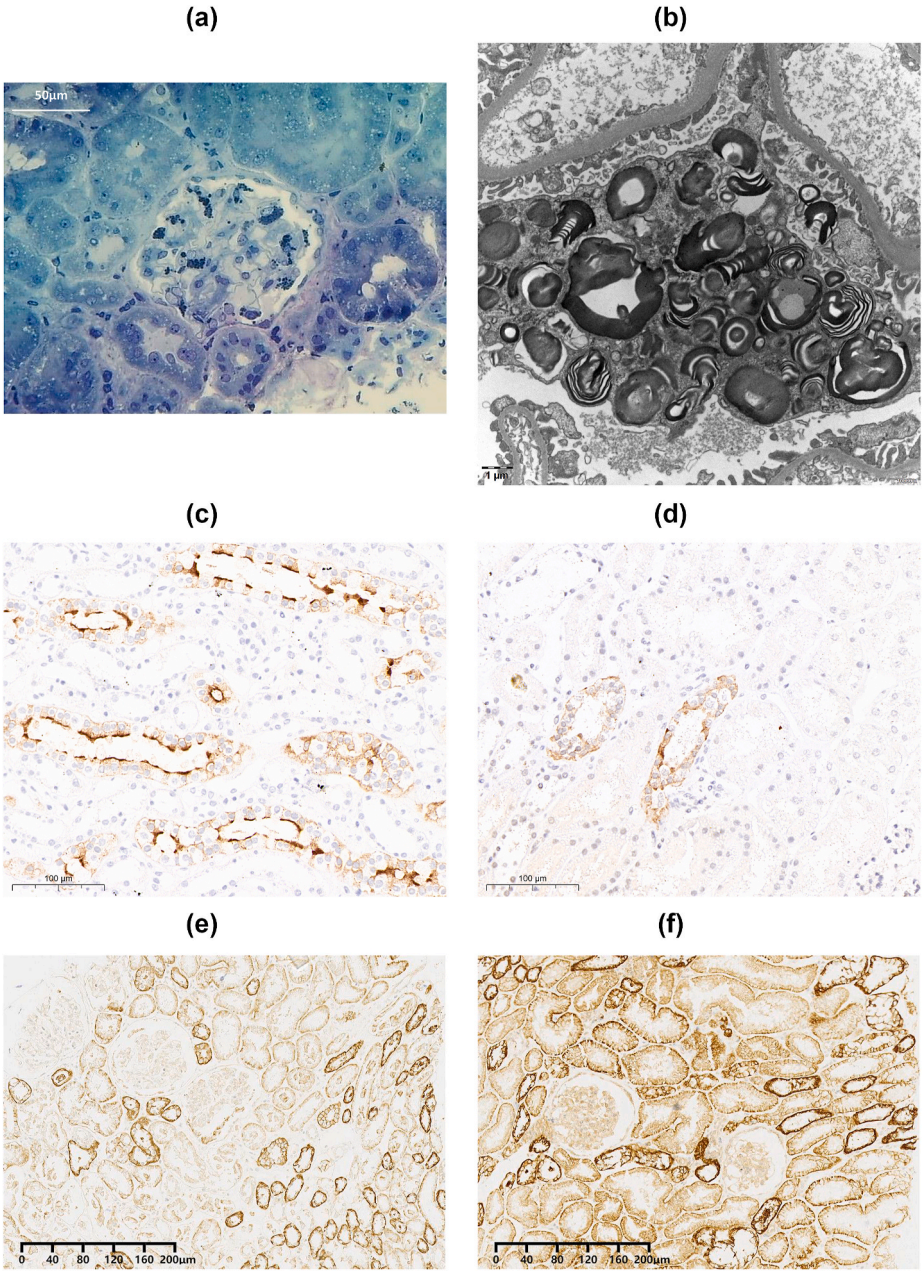

Fig. 1. Renal histopathology and urine specific gravity change after ERT. **A.** Toluidine blue staining of semi-thin sections of kidney tissue under light microscopy (× 400); **B.** Electron microscopy showed no significant thickening of the basement membrane; vacuolar degeneration of the podocytes with secondary lysosomes increased and a large number of myeloid bodies and zebra bodies were observed; and vacuolar degeneration of tubular cells, indicating Fabry nephropathy. **C.** The AQP2 expression in control by immunohistochemistry; **D.** The AQP2 expression in patient by immunohistochemistry; **E.** The Na/K-ATPase expression in control by immunohistochemistry; **F.** The Na/K-ATPase expression in patient by immunohistochemistry; **G.** The number of renal tubular epithelial cells was compared between control and patient. Ten fields of $2.3 \times 10^4 \mu m^2$ were taken from each section and the number of renal tubular epithelial cells was counted. **H.** The change of urine specific gravity and serum potassium concentration after ERT.

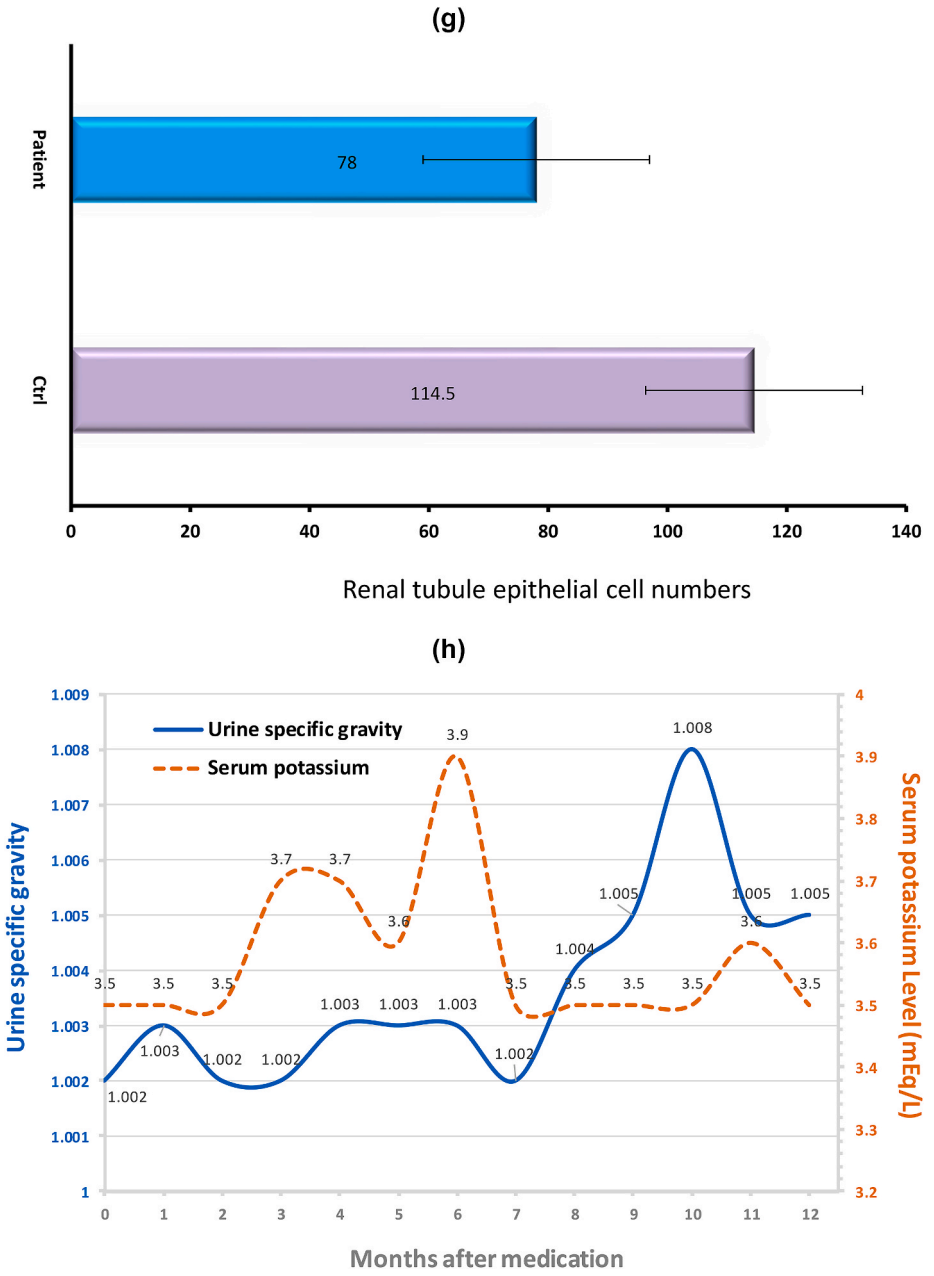

Fig. 1. (*continued*).

Last year, ERT for FD became available in the country. The patient was readmitted to our hospital. Dried blood spot testing showed α-gal A activity of 0.6 μmol/L/h (ref. 2.4–17.65 μmol/L/h) and a Lyso-GL-3 level of 7.01 ng/ml (ref. < 1.11 ng/ml). His mother was confirmed as a carrier (α-gal A activity 1.59 μmol/L/h, Lyso-GL-3 6.92 ng/ml). The patient presented a 24-h urine protein level of 159.6 mg (slightly elevated), a left ventricular mass index of 39.8 g/m$^{2.7}$ (left ventricular hypertrophy: >38 g/m$^{2.7}$). Vision and hearing were normal. Renal biopsy was performed to further confirm FD. The deposition of toluidine blue-stained particles was determined by toluidine blue staining (Fig. 1A). Electron microscopy showed vacuolar degeneration of podocytes, with a large number of myeloid bodies; and vacuolar degeneration of tubular epithelial cells, indicating Fabry nephropathy (Fig. 1B). Aquaporin-2 (AQP2) and Na/K-ATPase on renal tissue was detected by immunohistochemistry and tubular epithelial cells were counted in each section. Decreased tubular cell number and AQP2 expression and increased Na/K-ATPase were observed (Fig. 1C,D,E,F,G). The patient started ERT with agalsidase β 1 mg/kg, q2w. Of course, since N215S is an amenable mutation, ERT and pharmacological chaperone migalastat are both options if they are available. Fortunately, after more than 12-months of treatment, although the boy's urine volume remained at 3–5 ml/kg/hour, the urine specific gravity increased from 1.002 to 1.005–1.008 (Fig. 1H), which was a reliable sign reflecting the

efficacy of ERT. Serum potassium levels remain stable after reduced potassium supplement (Fig. 1H). Laboratory results after one year treatment are shown in Table 1. We will continue to monitor the patient's renal tubular function and urine output.

3. Discussion

Early renal symptoms of FD may include disorders of urine concentration, polydipsia, polyuria, increased nocturia, and tubular dysfunction. In this report, the patient presented polydipsia and polyuria as the initial manifestation, which was diagnosed as hereditary nephrogenic diabetes insipidus. However, the patient had no mutations in nephrogenic diabetes insipidus-related genes such as AVPR2 or AQP2, and no secondary causative factors, such as drugs, electrolyte imbalance, or urinary tract obstruction. The patient experienced no dehydration or elevated sodium over the next 7 years. His physical growth and development were normal, although he required oral potassium chloride tablets to maintain a normal blood potassium level. These signs and symptoms were inconsistent with the common symptoms of nephrogenic diabetes insipidus. Low plasma potassium levels were never observed in patients with AVPR2 or AQP2 mutations who were not treated with hydrochlorothiazide. And the association of hypokalemia is suggesting of a Bartter-like polyuric syndrome. But in Bartter's patients the urine osmolality is not as low as compared to patients bearing AVPR2 or AQP2 mutations and the return of plasma potassium to normal will not improve the polydipsia and polyuria signs and symptoms.

The improvement of urine specific gravity observed after 12 months of enzyme treatment suggested that GL-3 deposition in the medulla was involved in the abnormal urinary concentration and dilution. Urinary concentration and dilution depend on the presence of a discrete segmental distribution of transport properties along the renal tubule, and urinary concentration depends on 2 factors [3, 4]: Firstly, the hypertonic medullary interstitium, which is generated by active NaCl reabsorption as a consequence of countercurrent multiplication in water-impermeable nephron segments. In present study, renal tubular expression of Na+/K + -ATPase is upregulated, which might be the compensatory mechanism for re-absorption more Na + to medullary interstitium. Secondary, the high water-permeability (constitutive or vasopressin regulated) in other renal tubular segments for osmotic equilibration, which chiefly depends on aquaporins (AQPs). In present study, AQP2 expression is down-regulated which may reflecting the dysfunction of the high water permeability in renal tubular epithelial cell after accumulation of GL-3.

Excessive thirst, polydipsia, and polyuria have been reported in FD-like cases [5]. However, only two pediatric cases in which nephrogenic diabetes insipidus was the initial manifestation of FD have been reported. In 1978, Parchoux et al. reported a pediatric FD patient whose initial manifestation was nephrogenic diabetes insipidus [6]. In 2006, Wornell [7] reported the clinical data of a boy with confirmed FD. The patient developed polyuria, excess thirst, hypertension, hypokalaemia, and proteinuria at the age of 7. A vasopressin test (after fasting from water) confirmed nephrogenic diabetes insipidus. Renal biopsy showed lamellar structures in podocytes, distal tubular epithelial cells, and endothelial cells. Unfortunately, no results of α-gal A activity, Lyso-GL-3 and genetic testing reported in this study.

In addition to polydipsia and polyuria, our patient presented with hypokalaemia one year after onset of disease, although his serum sodium remained normal, without marked hypertension or proteinuria. Wornell reported only relevant symptoms, which improved after short-term oral lisinopril treatment, and did not mention whether the symptoms of diabetes insipidus were resolved or whether any subsequent treatment was provided. This is the first report indicating that children with FD taking N215S variation may initially present nephrogenic diabetes insipidus as an early sign of renal involvement and that ERT may improve the function of renal tubules in present study. We will continue to observe the effect of ERT during further treatment.

The *GLA* N215S variation is recognized as a mutation in patients with late-onset FD, which mainly affects the heart. Mild renal involvement has been reported in a few cases [8], with occasional reports of the classic presentation as severe renal involvement. N215S variation was reported in a pedigree involving two brothers, one of whom presented early limb pain with rapid progression to end-stage renal failure and hypertrophic cardiomyopathy; the other presented only mild left ventricular hypertrophy, suggesting that patients with this variation may present the classic phenotype [9]. N215S variation has also been reported in two Chinese adults with FD, in whom kidney damage was the main manifestation. One of the patients was a 40-year-old man who had nephrotic range proteinuria, and a creatinine clearance of 27 ml/min/1.73m^2. His renal function continued to deteriorate despite ERT, and received a kidney transplant 5 months later [10]. His 48-year-old sister, a carrier, also had moderate proteinuria. Renal biopsy showed zebra bodies in podocytes, and echocardiography showed no sign of left ventricular hypertrophy. In a French FD screening study of chronic renal failure patients on long-term hemodialysis, a 49-year-old man was found to have N215S variation. He had left ventricular hypertrophy, and a brain MRI showed multiple lacunar infarcts [11]. These data suggested that although this variant primarily affects the heart, kidney involvement varies between individuals and races and may be the initial manifestation.

Unexpectedly, electron microscopy mainly showed a large number of myeloid bodies in podocytes, which is consistent with previous reports on childhood FD. However, our patient mainly presented renal tubular involvement, including polyuria and hypokalaemia, without the expected evidence of a large number of myeloid bodies in renal tubular cells. In the report by Wornell [7], electron microscopy showed accumulations of lamellated membrane structures in podocytes and distal tubular epithelial cells, but the abundance of myeloid bodies in tubular cells was not reported, possibly because tubular cells are prone to involvement but shed and regenerate quickly. This is also evidenced by the significant reduction in the number of tubular cells in this case. The origin of urinary mulberry cells may offer an explanation [12]. Further research is needed for clarification.

In short, this case shows that nephrogenic diabetes insipidus may be the initial manifestation in FD children with N215S variation.

Authors' contributions

LZH and WY were the major contributors to in writing the manuscript and reviewing the literature. GLP, LL, LD, and MJH provided

valuable comments. All authors listed have significantly contributed to the investigation, development and writing of this article. All authors revised the manuscript and approved the final version.

Ethics approval and consent to participate

The study was approved by Ethics committee of The Children's Hospital, Zhejiang University School of Medicine (2020-IRB-187).

Consent for publication

All images, clinical data and other data included in this manuscript were published with the consent of the boy's parents.

Data availability statement

No data was used for the research described in the article.

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The authors confirm independence from the sponsors; the content of the article has not been influenced by the sponsors.

Additional information

Supplementary content related to this article has been published online at [URL].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Abbreviations

FD	Fabry disease
ERT	Enzyme replacement therapy
α-gal A	α-galactosidase A
HIV	human immunodeficiency virus
ANA	antinuclear antibody
ECG	Electrocardiogram
MRI	Magnetic resonance imaging

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