Foot Process Effacement with Normal Urinalysis in Classic Fabry Disease

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Abstract Fabry disease is an X-linked glycosphingolipidosis caused by deficient synthesis of the enzyme α -galactosidase A, which results in glycosphingolipidosis, predominantly globotriaosylceramide, progressively accumulating in systemic tissue. A dominant complication of Fabry disease is nephropathy. The average age for the development of clinical nephropathy is 27 years in male patients, with up to half of all patients developing end-stage renal failure by their 50s. A recent study revealed podocytes play important roles in antiproteinuria. Podocyte injury leads to foot process effacement and proteinuria. The foot process effacement induces podocyte depletion from the glomerular wall, glomerulosclerosis, and results in end-stage renal failure. We report on a 13-year-old boy with classic Fabry disease, who developed foot process effacement *and podocyte depletion* even before proteinuria appeared. At the time, his only symptom of Fabry disease was acroparesthesia. He was administered Agalsidase β (1 mg/kg/dose

div) every other week and *14 months after treatment*, his renal function *remained normal*. This is the first report of a patient with classic Fabry disease, with only acroparesthesia, who had normal urinalysis but manifested foot process effacement and podocyte depletion. Podocytes are highly differentiated cells with a limited capacity for cell division and replacement. The large individual variation and often progressive nature of this disease raises concerns about the appropriate timing for initiating enzyme replacement therapy (ERT). Recent data have shown a limited effect of ERT on progressive organ damage. In our case, ERT was initiated before proteinuria appeared, with good outcome.

Keywords Enzyme replacement therapy · Fabry disease · Foot process effacement · Proteinuria · Renal pathology

Introduction

Fabry disease (MIM ID #301500) is an X-linked glycosphingolipidosis caused by deficient synthesis of the enzyme α -galactosidase A (EC 3.2.1.22). Glycosphingolipids, predominantly globotriaosylceramide (GL-3), progressively accumulate in systemic tissue (Eng et al. 2006). Nephropathy is a dominant complication of Fabry disease, and the average age for the development of clinical nephropathy is 27 years in male patients, with up to half of all patients developing end-stage renal failure by their 50s (Branton et al. 2002). GL-3 accumulation begins during fetal development, and cellular inclusions of GL-3 have been detected in fetal kidney podocytes (Desnick 2007). However, it remains unclear when cellular inclusion of GL-3 triggers foot process effacement from podocyte injury, causing *podocyte depletion from the glomerular wall* and end-stage renal failure (Wiggins 2007). We present a case of classic Fabry disease with foot process effacement *and podocyte depletion*, but with normal urinalysis results and acroparesthesia the only symptom of the disease.

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Case Report

A 13-year-old boy consulted at our hospital for fever- or exercise-associated burning pain on the soles and palms that had persisted for 3 years. His maternal grandfather, who had not received a diagnosis of Fabry disease, died of multi-organ failure when he was 45 years old. His mother and maternal grandfather had acroparesthesia when they were young. His father and maternal grandmother had not experienced any signs or symptoms of Fabry disease.

Physical Examination and Laboratory Data

The patient's height was 159.7 cm; body weight, 47.6 kg; blood pressure, 106/66 mmHg; and body temperature, 36.8°C. He had no rash or angiokeratomas. It was determined that he had a point mutation of C382Y on exon 7 of the α -galactosidase A gene. Examination of blood revealed extremely low α -galactosidase A activity [0.1 nmol/mg protein/h; reference level, 50–110 nmol/mg protein/h, *measured using a fluorogenic substrate* (Mayes et al. 1981)], elevated GL-3 level [17.5 μ g/mL; reference level, less than 7.0 μ g/mL, *measured by liquid chromatography/tandem mass spectrometry* (Roddy et al. 2005)], normal creatinine level (0.46 mg/dL) and blood urea nitrogen level (11 mg/dL), and no acidemia (pH 7.346; HCO_3^- , 23 mEq/L). Repeated urinalysis showed negative proteinuria [less than 4 mg/dL and 50–80 mg/day, *measured by a pyrogallol red-molybdate complex* (Watanabe et al. 1986)], no hematuria (less than 5 per high-power field), and no hyposthenuria (specific gravity, 1.025–1.030 on the morning samples), but a slightly elevated β_2 -microglobulin level (544.0 μ g/L). His glomerular filtration rate was 144 mL/min/1.73 m². He presented with no other signs or symptoms of Fabry disease (e.g., hypohidrosis, gastrointestinal disturbances, thermal sensation loss, or cornea verticillata by slit-light examination). Echocardiography demonstrated normal function and structure. Cerebral involvement could not be detected by magnetic resonance imaging.

Renal Pathologic Findings with Normal Urinalysis

After receiving informed consent from the patient and his parents and approval from the Ethics Committee of Jichi Medical University, we performed a renal biopsy for renal damage assessment. Twenty-six glomeruli were observed, demonstrating diffuse global vacuolated podocytes by light

microscopy, and diffuse global whorled inclusions in podocytes and focal segmental foot process effacement by electron microscopy (Fig. 1). The podocytes with whorled inclusions had foot processes and foot process effacement was detected where there were no podocytes. We observed no vacuolated endothelial cells or mesangial cells. No deposits were observed based on immunofluorescent studies (IgA, IgG, IgM, C3, C4, and C1q), and there was no glomerular sclerosis. Tubular cells were also vacuolated by light microscopy and included whorled inclusions diffusely and globally. Although there was no tubulointerstitial fibrosis, the tunica media of the small arteries were vacuolated.

Agalsidase β (1 mg/kg/dose div) was administered every other week, which decreased the GL-3 level and provided relief from the acroparesthesia. *Fourteen months after treatment, the patient maintained a normal GL-3 plasma level (less than 7.0 μ g/mL), normal renal function, normal urinalysis, and was free of other signs and symptoms of Fabry disease.*

Discussion

Foot process effacement and podocyte depletion had already developed in our classic Fabry disease case, in a patient who only presented with acroparesthesia, a first symptom of Fabry disease (Desnick and Brady 2004). This is the first report of a patient with classic Fabry disease, with only acroparesthesia, who had normal urinalysis but manifested foot process effacement from podocyte injury. Previous studies reported several patients with detectable proteinuria and renal damage such as foot process effacement and glomerular sclerosis (Gubler et al. 1978; Tondel et al. 2008).

The findings of diffuse global whorled inclusions in podocytes, focal segmental foot process effacement, podocytes with both whorled inclusions and foot processes, and foot process effacement without podocytes indicate that depletion of podocytes with whorled inclusions was induced by foot process effacement. Foot process effacement depends on disruption of the actin cytoskeletal network, which forms the slit membrane in the podocytes (Asanuma et al. 2007). This disruption results in proteinuria (Kawachi et al. 2009) and is thought to cause podocyte depletion (Wiggins 2007). Podocytes are highly differentiated cells with a limited capacity for cell division and replacement (Wiggins 2009), and podocyte injury and loss from the glomerulus result in end-stage renal failure by glomerular sclerosis (Wiggins 2009). In our case, progression of podocyte injury would have caused proteinuria, severe podocyte depletion, and ultimately end-stage renal failure.

Fig. 1 (a) Vacuolated podocytes (original magnification $\times 400$; periodic-methenamine silver stain). (b) Diffuse global whorled inclusions in podocytes and focal segmental foot process effacement (original magnification $\times 1,200$). The podocytes with whorled inclusions had foot processes and foot process effacement was detected where there were no podocytes. (c) Whorled inclusions (*zebra body*) in podocytes with foot processes (original magnification $\times 6,000$). (d) Foot process effacement that we observed where there were no podocytes (original magnification $\times 10,000$). (e) and (f) Normal foot process at the remission phase of minimal change nephrotic syndrome (original magnification $\times 2,500$ and $\times 10,000$) in a 13-year-old female

The large individual variation and often progressive nature of this disease raise concerns about the appropriate timing for initiation of enzyme replacement therapy (ERT). Recent data have shown a limited effect of ERT on progressive organ damage when treatment is initiated at a later stage (Breunig et al. 2006). The findings in our case are informative for establishing the optimal ERT initiation time. Our patient showed no proteinuria, but already had foot process effacement resulting from podocyte injury and podocyte depletion that would lead to glomerular sclerosis. Therefore, in our case, ERT was appropriately initiated before proteinuria appeared, with good outcome.

Conclusions

Foot process effacement resulting from podocyte injury and podocyte depletion from the glomerular wall had already manifested when acroparesthesia developed in this patient.

Although urinalysis was normal, it was a case of classic Fabry disease. Therefore, normal urinalysis does not necessarily indicate normal renal tissue. Accumulated data are needed for a better understanding of when to initiate ERT.

Synopsis

Normal urinalysis does not always indicate normal kidney tissue in Fabry disease.

Details of the Contributions of Individual Authors

Dr. Kanai, the author of this article and the doctor of this patient; Prof Yamagata and Prof Momoi, advisors for this article; Dr. Ito, Dr. Odaka, Dr. Saito, and Dr. Aoyagi,

assisted in treating this patient and writing this article; Dr. Kobayashi and Prof Ohashi, detected the gene abnormality; and Prof Ueda, reported the pathologic findings.

Name of One Author Who Serves as Guarantor for This Article

Dr. Takahiro Kanai.

A Competing Interest Statement

We declare that the answers to all questions on the JIMD competing interest form are NO; therefore, we have nothing to declare.

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

Details of Ethics Approval for This Study

This study was approved by The Ethics Committee of Jichi Medical University with the patient consent statement.

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