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Case Report

Two related Chinese Fabry disease patients with a p.N215S pathological variant who presented with nephropathy

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ABSTRACT

Fabry disease is an X-linked lysosomal storage disease resulting from a mutation in the *GLA* gene that encodes α-galactosidase A. The p.N215S (c.644A > G [p.Asn215Ser]) genotype is the most common later-onset variant reported in individuals of European or North American descent. It is usually referred to as a cardiac variant, although manifestations in other organ systems have been observed. In this report, we describe a nephropathy presentation in two related Chinese Fabry disease patients with p.N215S.

1. Introduction

Fabry disease (OMIM #301500) is a lysosomal storage disease of X-linked inheritance that emerged from a mutation in the *GLA* (OMIM #300644; NCBI reference sequence NM_000169.2) gene, which encodes α-galactosidase A (α-Gal A, EC 3.2.1.22). The resulting deficiency of α-Gal A causes the accumulation of glycolipids, particularly globotriaosylceramide (Gb3) and globotriaosylsphingosine (Lyso-Gb3), in a wide range of cell types, including smooth muscle cells, kidney podocytes and cardiomyocytes [1]. The clinical spectrum can be divided into classic Fabry disease, a multisystem disorder characterized by angiokeratoma, painful neuropathy, progressive nephropathy and hypertrophic cardiomyopathy at a young age that leads to premature death if untreated, usually seen in hemizygous males with severe mutations and very low residual α-Gal A activity, and later-onset variants with a higher residual α-Gal A activity [2]. The phenotype of the latter is heterogeneous. Overall, variant Fabry disease is a milder form, and the prognosis is variable. The missense mutation c.644A > G (p.Asn215Ser), also known as p.N215S, is associated with a later-onset cardiac phenotype, but many also have disease manifestations outside the cardiovascular system [3]. p.N215S is the most common later-onset variant among individuals of European or North American descent but is rarely reported in other ethnic populations. We describe two related Chinese patients with p.N215S, who initially presented with proteinuria.

2. Cases

The proband was a 40-year-old man who presented with frothy urine and progressive lower limb edema for 1 month. Initial investigations revealed nephrotic range proteinuria at 12.9 g/d and renal impairment with the serum creatinine level elevated to 325 μmol/l and a creatinine clearance (CrCl) of 27 ml/min. A kidney biopsy was performed. Histology showed the presence of 14 glomeruli with 6 global and 2 segmental sclerosis, and spikes were noted. Immunofluorescent study revealed global and diffuse deposits of 3 + IgG and 2 + C3 along the capillary loops with some segmental mesangial, 1–2 + IgM. The pattern pointed to membranous glomerulonephritis (MGN), which was confirmed by the presence of numerous subepithelial electron-dense deposits with scanty mesangial and no subendothelial deposits on electron microscopy. In addition, numerous myelin-like inclusion bodies characteristic of Fabry disease were found in the podocytes, with very scant findings in tubular cells and none in endothelial cells (Fig. 1). Subsequent investigations confirmed α-Gal A deficiency with α-Gal A

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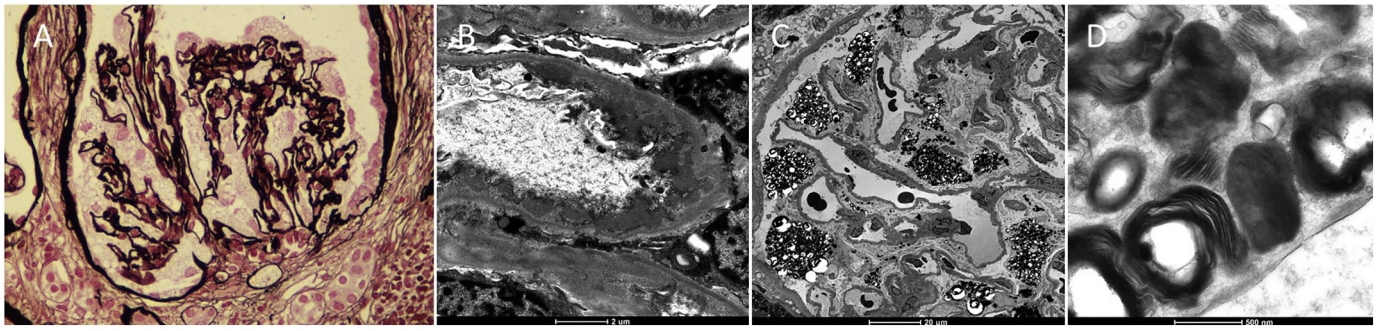
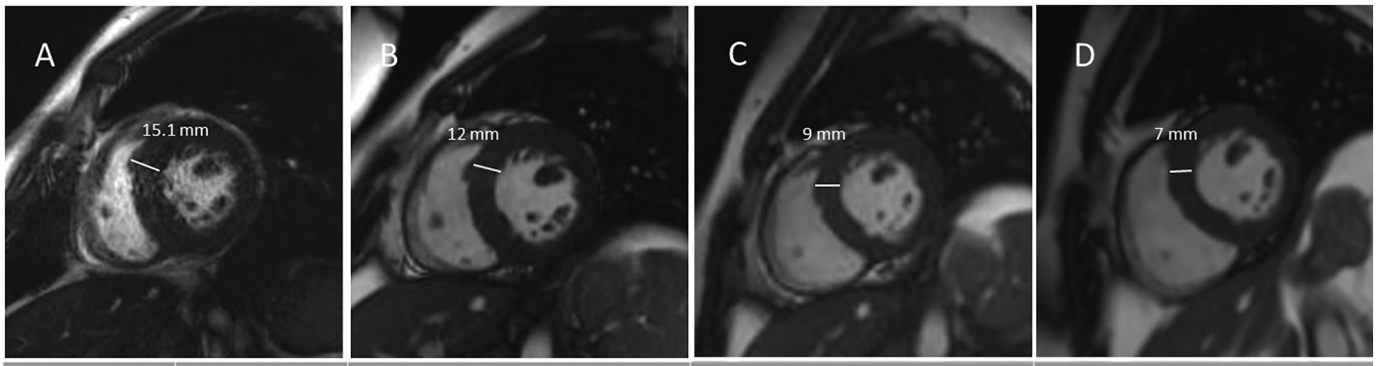


Fig. 1. (A) Glomerulus showing fine vacuolization of podocytes and focal spiky basement membrane (PASM stain, x 400). (B-D) Electron micrograph showing (B) subepithelial electron-dense deposits (x 8000) (C) markedly enlarged podocytes that are filled with dark-lamellated structures (x 3200), (D) characteristic myelin figures and zebra bodies (x 40,000).



	Baseline	12 m	24 m	36 m
IVS (mm)	15.1	12	9	7
LVPW (mm)	12	11	10	6
LVM (g)	182.6	180.3	163.8	155.7

Fig. 2. Cardiac MR imaging at baseline (A) and 12 m (B), 24 m (C) and 36 m (D) after ERT revealed continuous regression of the interventricular septum and left ventricular wall thickness. (IVS, interventricular septum; LVPW, left ventricular posterior wall; LVM, left ventricular mass.)

activity at 0.27 μmol/l/h (ref. 4.75 +/− 1.80 μmol/l/h) and a plasma Lyso-Gb3 level of 1.17 ng/ml (ref. < 0.8 ng/ml). A genetic study identified the hemizygous missense mutation p.N215S in the *GLA* gene. The patient also had hypertrophic cardiomyopathy upon presentation, with a thickened wall measuring 15.1 mm and 12 mm at the interventricular septum (IVS) and left ventricular posterior wall (LVPW), respectively. The left ventricular systolic function was normal. Enzyme replacement therapy (ERT) with agalsidase beta at a dose of 1 mg/kg once every two weeks was started at approximately 3 months after his initial presentation of nephrotic syndrome. The patient's kidney function further deteriorated, and he received a cadaveric kidney transplant 5 months later. Serial cardiac magnetic resonance imaging (CMR) performed at 12 m, 24 m and 36 m post-ERT revealed continuous regression of the ventricular wall thickness and left ventricular mass (LVM), and there was no late gadolinium enhancement (Fig. 2). The Lyso-Gb3 level improved to 0.576 ng/ml.

His 48-year-old older sister was subsequently identified through cascade screening as having heterozygous p.N215S. Her α-Gal A activity was slightly reduced at 1.07 μmol/l/h, and the Lyso-Gb3 level was not elevated (0.133 ng/ml). Investigations revealed that the patient had proteinuria up to 1.25 g/d, her creatinine clearance was normal (127 ml/min), and echocardiogram did not show left ventricular hypertrophy. Kidney biopsy was performed, and histology revealed cytoplasmic vacuolation in the podocytes and mild expansion of the mesangial matrix, while ultrastructural examination demonstrated zebra bodies in the cytoplasm of podocytes and mild effacement of foot processes. There was no glomerulosclerosis, and the cytoplasmic inclusions were inconspicuous in other cell types. In reviewing past medical records, it was found that the patient previously had mild proteinuria of 0.37 g/d at age 35. She was treated with agalsidase beta and an angiotensin-converting enzyme inhibitor, and the proteinuria gradually decreased to 0.42 g/d four years after ERT.

3. Discussion

The p.N215S pathological variant, with an A to G transition in codon 215 of exon 5 of *GLA* that causes the substitution of an asparagine by a serine, is the most commonly reported later-onset Fabry mutation in Western countries and among individuals of European or North American descent [4]. Hemizygous males with p.N215S typically retain approximately 5% to 25% of residual α-Gal A activity in various tissues [5]. Characteristically, p.N215S in males presents as a cardiac phenotype, with ventricular hypertrophy starting in their 20s or 30s and becoming severe in their 60s [6]. Chronic kidney disease (CKD) and proteinuria also occur in p.N215S patients, usually at a later age when compared to classic Fabry disease. Germain et al. reported that 17% of p.N215S patients had CKD upon first assessment in an international Fabry registry, and most of them were older than 65 [6]. Kidney disease could also be the first presentation. In a case series, via kidney biopsy, Oder et al. diagnosed three p.N215S patients who presented with proteinuria, and in another report, Lavalle et al. described the exceptional presentation of end stage kidney disease in two p.N215S men at ages 25 and 38 [7,8]. As expected, female patients are more heterogeneous, with delayed clinical manifestations. The overall prognosis of patients with the p.N215S variant is more favourable than that of classic Fabry patients, with less decline in kidney function, later development of

proteinuria, and better survival [8].

Later-onset Fabry disease with the p.N215S variant among Chinese individuals or in Asians is rarely reported. We could only identify one case report of this variant in the Chinese literature. That patient was a 51-year-old man with proteinuria at 0.3 g/d, and kidney biopsy confirmed Fabry nephropathy. He also had ventricular hypertrophy with IVS measured at 13 mm [9]. The same mutation has also been identified in a large Japanese Fabry disease cohort, but the phenotypic details were not provided [10].

Our index patient presented with nephrotic syndrome. Overt nephropathy in p.N215S at his age is uncommon, and even with proteinuria, nephrotic syndrome is not a usual phenomenon. In the Fabry registry, only 33 out of 287 Fabry patients with overt proteinuria had nephrotic syndrome at diagnosis [11]. The histological hallmark of Fabry nephropathy is the intracellular accumulation of Gb3 in glomerular and tubular epithelial cells, while immunofluorescence microscopy is usually negative [12,13]. In our patient, the histological findings of diffuse subepithelial electron-dense immune complex deposits suggested that MGN was the main contributor to his kidney impairment. The identification of dual kidney disease in our patient also demonstrated that kidney biopsy would still be indicated in Fabry patients with atypical renal presentations since any superimposed kidney disease would modify treatment and prognosis. Nevertheless, our patient had already developed moderate ventricular hypertrophy at the time of diagnosis, which is consistent with the natural disease history of p.N215S-associated later-onset Fabry disease in male patients [6–8]. Fabry cardiomyopathy at this early stage of ventricular hypertrophy, without myocardial fibrosis, responds well to ERT [14]. Our patient exhibited good regression of ventricular wall thickness after treatment. His older sister has high residual α-Gal A activity. Despite having proteinuria for 13 years, her kidney biopsy only showed a mild histological abnormality associated with Fabry disease, and there was no ventricular hypertrophy at age 48. She also had a good treatment response to ERT. Significant proteinuria greater than 1 g/d is associated with disease progression in both natural history and ERT-treated patients [15], but with mild histological grading, she still responded well. ERT is the mainstay treatment for Fabry disease [16]. Migalastat, a pharmacological chaperone, has also been successfully used in patients with amendable mutations [17]. p.N215S is a migalastat-amendable variant, but only ERT could be offered to our two patients because migalastat is not available locally.

The second patient was diagnosed through cascade screening. Her symptoms were mild at the time of confirmation and would not be suspected to have Fabry disease otherwise. With proper genetic counselling and cascade screening, patients can be identified early, allowing for better reproduction plans and early effective treatments to improve long-term morbidity.

4. Conclusion

We reported two Chinese Fabry disease patients with a p.N215S pathological variant who presented with nephropathy. Fabry patients with atypical nephropathy presentations can have superimposed acquired kidney disease that modifies the disease progression and prognosis. Diagnosing patients at an early stage through cascade screening allows for early treatment and potentially a better outcome.

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