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## A renal variant of Fabry disease: A case with a novel Gal A hemizygote mutation

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### ABSTRACT

**Background:** Fabry disease is caused by an X-linked recessive inborn error of glycosphingolipid metabolism with deficient activity of a lysosomal enzyme, alpha-galactosidase A ( $\alpha$ -GalA).

**Case Presentation:** A 46 year-old man with progressive kidney disease showed on kidney biopsy electron microscopic evidence of Fabry disease. The patient had no systemic manifestations of Fabry disease, despite residual  $\alpha$ -GalA activity, therefore genetic testing was done by direct DNA sequencing, demonstrating a new GAL A gene mutation (C174G-exon 3). After three years of enzyme replacement therapy (agalsidase beta) treatment, a second biopsy was done. Although there was demonstrable clearance of intracellular inclusions, remarkable podocyte activation was evident.

**Conclusions:** This report represents an unusual renal variant of Fabry disease and provides histologic data on long-term follow up after enzyme replacement therapy.

*Implication for health policy/practice/research/medical education:*

There are forms of Fabry disease in which renal involvement is most prominent and together with the cardiac variant, represent single disorder extreme phenotypes. It is important for nephrologists to recognize this atypical clinical presentation, because it lacks classical signs and symptoms of Fabry disease.

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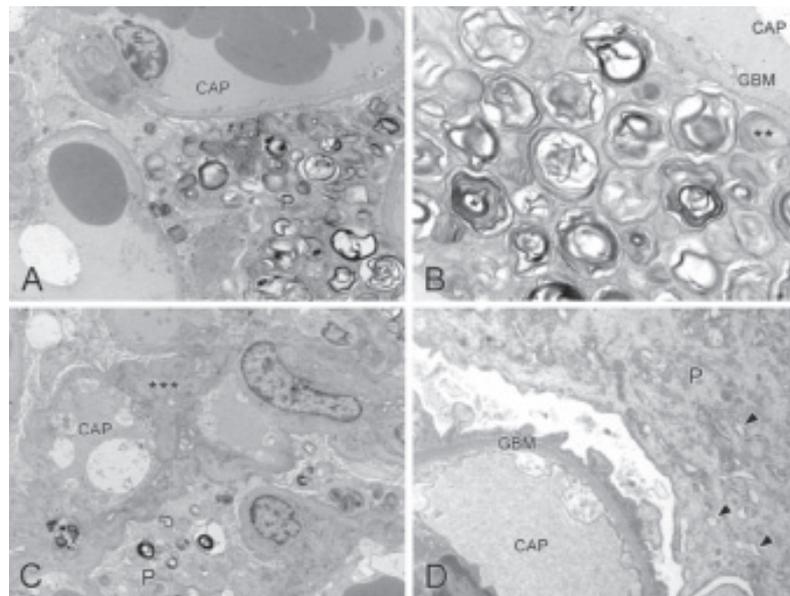
## 1. Introduction

**F**abry disease is caused by an X-linked recessive inborn error of glycosphingolipid metabolism with deficient activity of a lysosomal enzyme, alpha-galactosidase A ( $\alpha$ -GalA). The enzymatic defect causes progressive accumulation of neutral glycosphingolipids, predominantly globotriaosylceramide (GL-3), particularly in renal and cardiac vascular endothelial cells (1). The true prevalence is underestimated as many patients go undiagnosed due to a diverse symptom complex. A 'renal variant' phenotype was recently described in male patients who developed end-stage renal disease without classic extra-renal symptoms (2-3). Another male patient with progressive kidney disease and renal limited Fabry disease on renal biopsy is presented.

## 2. Case presentation

A 46 year-old white male presented to his primary physician in 2001 with lower extremity edema. He reported good health, had a negative review of systems and family history was negative for kidney disease. Blood pressure was 130/80 mmHg and laboratory tests showed 1.05 mg/dL (92.82  $\mu$ mol/L) creatinine and proteinuria of 1300 mg/day with unremarkable urine sediment. Serology was negative for hepatitis B and C, HIV-1 and HIV-2 anti-DNA, ANA, ANCA, and anticardiolipin antibodies. Complement was normal. Treatment began with enalapril 5 mg/day. Two years later serum creatinine was 1.07 mg/dL (95.5  $\mu$ mol/L). Proteinuria increased to 2800 mg/day. Renal ultrasound revealed normal sized kidneys and cortical medullary differentiation. In 2004, routine labs were significant for 1.29 mg/dL (114  $\mu$ mol/L) creatinine, 4000 mg/day proteinuria and urine sediment still unremarkable. A renal biopsy was unsuccessful and the patient was lost to follow-up. One year later, he was re-

ferred to Sanatorio Allende Renal Service for kidney biopsy. Blood pressure was 150/90 mmHg, 2.35 mg/dL (207  $\mu$ mol/L) creatinine and 8500 mg/day proteinuria. On light microscopy, one of two glomeruli showed segmental sclerosis and swollen podocytes with vacuolated cytoplasm. Tubulo-interstitium had fibrosis and moderate tubular atrophy. Immunofluorescence was negative. Electron microscopy (EM) semi-thin sections showed prominent and numerous podocyte myelin-like inclusions, without tubular, mesangial or small artery and arteriole endothelial cell inclusions. Podocyte ultra-structure demonstrated numerous lamellated myelin-like inclusions, which distended cytoplasm markedly (figure 1A). Zebra body inclusions were also present (figure 1B). Finally, there was prominent podocyte foot process effacement. EM findings prompted Gal A level testing, 0.90 (ref 2.0-14.6 umol/1/h), Gal B 25.7 (normal 16.1-42.1 umol/h) and  $\alpha$ -galactosidase leukocyte levels ( $\alpha$ -GalA) 2.9 (normal 30.5-57.7 nmol/h/mg). Because the patient lacked other clinical findings consistent with Fabry disease, direct DNA sequencing confirmatory testing was done. A novel Gal A hemizygote mutation, C174G in exon 3, was identified. Enzyme replacement therapy (ERT) was started in 2006 with agalsidase beta (90 mg every 2 weeks) and administered continuously for three years in addition to enalapril 10 mg/day and losartan 50 mg/day. Pre-treatment creatinine was 1.72 mg/dL (152 umol/L) and proteinuria 8.9 g/day; after three years of therapy, creatinine was 1.99 mg/dL (175.9 umol/L) and proteinuria 5.8 g/day. A final kidney biopsy was performed. Three of five glomeruli were globally sclerosed with intense tubular atrophy and fibrosis seen on light microscopy. On EM, remaining glomeruli showed a moderate reduction of podocyte lamellar inclusions (figure 1C), and numerous cytoplasmic



**Figure 1: A-D:** Pre-treatment baseline biopsy, showing in A GL-3 as multiple, tight scroll-like figures that fill podocyte cytoplasm (Original magnification x 3597). In B: at higher magnification podocyte cytoplasm shows the typical structure of glycosphingolipid deposits, arranged in onion-like or zebra-like-figures (\*\*). (Original magnification x 7953). C-D: Long-term agalsidase beta therapy. In C a podocyte contains discrete number of scroll-like GL-3 forms. Early mesangial sclerosis is characterized by heterogeneous enhancing of matrix electron density (\*\*\*) (Original magnification x 3597). In D podocyte cytoplasm show prominent lysosomal architecture suggesting GL-3 enzymatic hydrolysis. (Original magnification x7953). P: podocyte. End: endothelium. CAP: glomerular capillary. GBM: glomerular basement membrane.

organelles with prominent nuclei and loose chromatin (figure 1D). There was moderate podocyte foot process effacement.

### 3. Discussion

This case is note worthy because it represents one of the less common variants of Fabry disease, the renal variant, and also because there is histologic material obtained before and 3 years into ERT. To our knowledge, this represents one of the longer intervals of therapy with before and after biopsies in the literature and helps define the long-term effect of ERT on the kidney at an ultra-structural level. Additionally, we have identified a new gene mutation associated with renal-limited Fabry disease.

We find it interesting that our patient had none of the early manifestations of Fabry and yet his renal disease developed in the fifth decade of life as would be anticipated in classical Fabry

and it progressed at a similar tempo. A natural history review of classical Fabry disease demonstrated renal involvement in 105 males and, reported that 50% of patients had proteinuria by age of 35 years and end stage renal disease by age of 47 years (4). To date, nearly 400  $\alpha$ -GalA gene mutations have been described (5). This patient had a novel Gal A exon 3, C to G mutation that is associated with a “renal limited variant” and expands the genotypic spectrum of Fabry with residual  $\alpha$ -GalA activity. Despite of no cytoplasmic scroll-like myelin figures in tubular, mesangial and small artery and arteriole endothelial cells, there was segmental or global glomerulosclerosis observed in more than half of the glomeruli, which has been associated with progressive decline in GFR despite ERT (6). Furthermore, EM usually reveals lysosomal accumulation of typical myelin figure-like concentric lamellar inclusions, that may be mimicked by various drugs, such as amio-

darone (7) and chloroquine (8), which this patient did not take. Other studies have also shown that after three years of ERT there was low-level intracellular podocyte inclusion clearance (9) that is possibly attributed to the slow renal cell turnover rate. Nevertheless, an interesting ultra-structural finding in this case was podocyte activation characterized by mitochondrial hyperplasia and hypertrophy, important lysosomal development and lax nuclear chromatin. This could be associated with ERT, but similarly as in this case, a group of patients with proteinuria greater than 1 g/day showed marked disease progression despite effective clearance of GL-3 from vascular endothelial cells (10).

#### 4. Conclusions

In summary, there are forms of Fabry disease in which renal involvement is most prominent and together with the cardiac variant, represent single disorder extreme phenotypes. It is important for nephrologists to recognize this atypical clinical presentation, because it lacks classical signs and symptoms of Fabry disease.

#### Financial Disclosure

The author declared no competing interests.

#### Conflict of interest

Authors declare that the results presented in this paper have not been published previously in whole or part.

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