

Exceptional Case

Renal variant of Fabry disease with sporadic *GLA* gene mutation: role of early renal biopsy

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Abstract

Fabry disease (FD) is a rare, X-linked inherited disease of glycosphingolipid metabolism due to deficiency of lysosomal α -galactosidase A activity. Scarce activity of lysosomal α -galactosidase A results in progressive accumulation of globotriaosylceramide (Gb3) within lysosomes, believed to trigger a flow of cellular changes that lead to the clinical manifestation of the disease. We present a 23-year-old male with renal variant of FD who was born from non-affected parents, which, to the best of our knowledge, has not been reported in the literature so far. In conclusion, FD can occur due to sporadic *GLA* gene mutation. Pure renal involvement might be associated with progressive disease which leads to end-stage renal disease within a short period. Physicians should have a high index of suspicion for FD especially in male cases with unexplained renal failure that are slowly progressive in nature, even in the absence of a clear hereditary component. Early renal biopsy is recommended in any progressive renal impairment.

Keywords: Fabry disease; renal variant; sporadic

Introduction

Fabry disease (FD) is a rare, X-linked inherited disease of glycosphingolipid metabolism due to deficiency of lysosomal α -galactosidase A activity [1]. FD is pan-ethnic and the reported annual incidence of 1 in 100 000 may underestimate the true prevalence of the disease [2]. Classically, affected hemizygous males, with no residual α -galactosidase A activity, may exhibit all the characteristic, cutaneous (angiokeratoma), cardiovascular (cardiomyopathy, arrhythmia, ischaemia), neurologic (pain, transient ischaemic attacks, strokes), renal (proteinuria, kidney failure), ear (hearing loss, tinnitus, vertigo) and eye (cataract, cornea verticillata) features of the disease, while heterozygous females have features ranging from very mild to severe. Reduced activity of lysosomal α -galactosidase A results in progressive accumulation of globotriaosylceramide (Gb3) within lysosomes, believed to trigger a flow of cellular changes that lead to the systemic manifestations of the disease. Demonstration of marked deficiency of α -galactosidase A is the definitive method for the diagnosis of hemizygous males [3]. Enzyme analysis may occasionally help to detect heterozygotes but is often inconclusive due to random X-chromosomal inactivation; hence, molecular testing of females is obligatory [3]. We present a 23-year-old male having FD with pure renal involvement and born from

non-affected parents which, to the best of our knowledge, has not been reported in the literature before.

Case report

A 23-year-old male presented with nephrotic range proteinuria (4.5 g/24 h), haematuria and persistent high serum creatinine (190 μ mol/L) for more than 6 months. Estimated glomerular filtration rate (GFR) was 39 mL/min. Kidney ultrasound showed bilateral normal-size echogenic kidney. All serologic markers were negative. On examination, the patient looked well and not in any respiratory distress. He was normotensive and had no peripheral or periorbital oedema. The patient had no hearing or vision problems. The heart and lung examinations were normal. The abdomen was soft with no organomegaly. The extremities were normal. The neurologic examination was unremarkable. No skin lesion was identified. He had a past medical history of urethral meatal stenosis with multiple dilatations.

The serum creatinine continued to rise (Figure 1) and the patient's family decided to take him to Germany for medical treatment. At that time, his creatinine reached 380 μ mol/L with a GFR of only 16 mL/min. He underwent renal biopsy which revealed focal and segmental glomerulosclerosis with advanced global glomerulosclerosis and



Fig. 1. Serum creatinine curve, showing progressive renal insufficiency.

marked interstitial fibrosis. Based on initial results of renal biopsy, he was treated with steroid and mycophenolate mofetil for a short period. The electron microscopic result was consistent with FD. Subsequently, the patient represented to us and his recent work-up showed creatinine 517 mmol/L, bicarbonate 25 mmol/L, potassium 5.3 mmol/L, calcium 2.29 mmol/L, albumin 43 g/L, phosphorus 1.4 mmol/L, alanine transaminase 0.2 mkat/L, cholesterol 5 mmol/L, low density lipoprotein 3.5 mmol/L, parathyroid hormone 29.9 ng/L, fasting blood sugar 5.2 mmol/L, 24-h urine protein 4.26 g/day, haemoglobin 151 g/L, white blood cell count $5.5 \times 10^9/L$ and platelets $145 \times 10^9/L$. Serology markers for hepatitis B, hepatitis C, HIV, ANA, C-ANCA, P-ANCA, anti-double stranded DNA, anti-rheumatoid factor were negative. Anti-streptolysin-O-titer was 77. Cardiac evaluation including ECG, Holter monitor and ECHO were all normal. Hearing and eye tests were normal. Brain magnetic resonance imaging was normal. Molecular and biochemical studies confirmed the diagnosis of FD.

Methods and results

Kidney biopsy

The light and electron microscopic studies of the kidney biopsy were diagnostic of FD as shown in Figures 2 and 3, respectively.

The 'light microscopic study' revealed renal tissue with the cortex and medulla showing focal and segmental glomerulosclerosis (Figure 2). Many globally sclerosed glomeruli with residuals of PAS-positive vacuolated podocytes were noticed. The interstitium showed quite a large number of foam cells. Foam cells were also seen in the wall of the small blood vessel. There was moderate tubular atrophy with thyroidization. Moderate interstitial mixed inflammatory cells mainly consisting of lymphocytes, and moderate interstitial fibrosis were also identified (Figure 2).

The 'electron microscopic study' demonstrated many enlarged lysosomes packed with lamellated membrane structures filling the whole podocyte cytoplasm. There

was also podocyte enlargement and focal fusion of the podocyte foot process (Figure 3).

Biochemical study

The α -galactosidase enzyme activity on leukocytes was undetectable (0.0 nmol/h/mg, reference value ≥ 23.1), which confirmed the diagnosis of FD.

Molecular genetics study

The patient is hemizygous in the *GLA* gene (located on the X chromosome) for a mutation defined as c.1277-1278delAA, which is predicted to result in frameshift and premature protein termination p.Lys426ArgfsStop24. The carrier testing of the proband's mother was negative (no mutation in the *GLA* gene). No other member of his family is known to be affected by the disease.

Discussion

We present a case of FD with pure renal involvement that was born from non-affected parents, a finding that has not been reported previously. Molecular studies of our patient show a mutation in the *GLA* gene which is predicted to result in frameshift and premature protein termination p.Lys426ArgfsStop24. This mutation has been reported to be causative of FD [4]. Biochemical studies confirm the absence of α -galactosidase A enzyme activity. Molecular studies from the patient's mother confirmed the absence of *GLA* gene mutation and that she is not heterozygous for the *GLA* gene. No other family member is affected or shows any feature of FD. The absence of *GLA* mutation in the patient's mother and the non-affected father suggest a possible sporadic mutation of the *GLA* gene. This is a remarkable novel finding which has not been reported previously.

The other interesting finding is the pure renal involvement in this patient. Systemic work-up failed to identify any involvement outside his kidneys. Besides, renal involvement was very progressive and led to renal failure

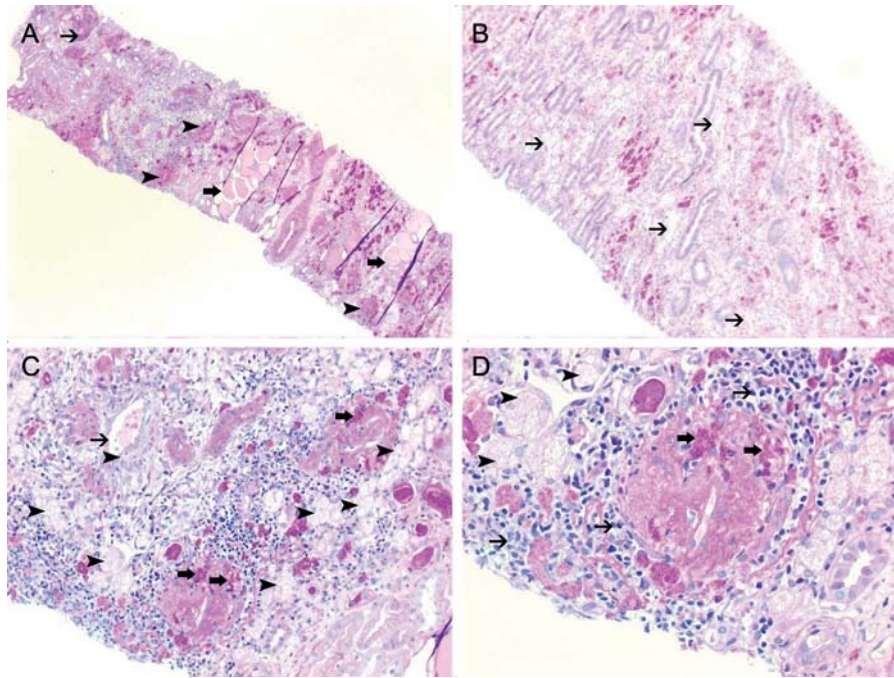


Fig. 2. Representative light microscopic findings. (A) Focal and segmental glomerulosclerosis (thin arrows), global glomerulosclerosis (arrowheads) and tubular atrophy with intratubular protein (thyroidization) (thick arrows); PAS, $\times 5$. (B) Large number of foam cells in the interstitium (thin arrows); PAS, $\times 10$. (C) Clusters of foam cells in the interstitium (arrowheads). A foam cell (arrowheads) is seen in the wall of a blood vessel (thin arrows). Podocytes contain PAS-positive material (thick arrows) consistent with Gb3 accumulation; PAS, $\times 20$. (D) Clusters of foam cells in the interstitium (arrowheads) and podocytes containing PAS-positive material (thick arrows) consistent with Gb3 accumulation. Many lymphocytes (thin arrows) are seen in the renal interstitium; PAS, $\times 40$.

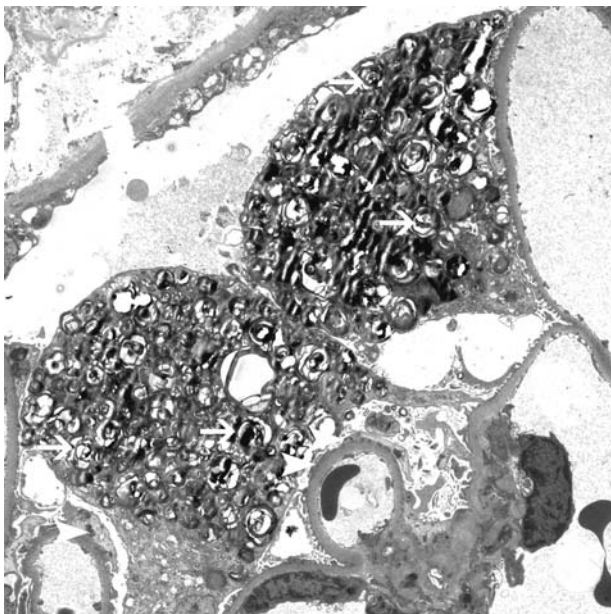


Fig. 3. Electron microscopic analysis shows many enlarged lysosomes packed with lamellated membrane structures filling the whole podocyte cytoplasm (thin arrows). There is focal fusion of podocyte foot processes (arrowheads).

within a relatively short period (1 year) when compared with previous reports of FD.

We think that physicians should be aware and consider FD in any rapidly progressive renal failure especially when it does not respond to the routine medical treatment. There are few reports on the renal variant of FD and most

of them were discovered when performing α -galactosidase A activity among haemodialysis patients with end-stage renal disease (ESRD) [5].

Moreover, we show that the diagnosis of FD was first made by renal biopsy with light and electron microscopic studies, a diagnosis that can hardly be made by light microscopy only. The finding of foamy vacuolated cells within the glomeruli is diagnostic in addition to the electron microscopic finding of many enlarged lysosomes packed with lamellated membrane structures filling the whole podocyte cytoplasm. We believe that early renal biopsy is recommended in any patient with progressive renal impairment, since early diagnosis and subsequent treatment of FD with enzyme replacement therapy will end the progression of the disease and save renal function.

Three mechanisms might explain the segmental and global glomerulosclerosis that characterizes FD, including microvascular disease, podocyte injury and tubulointerstitial injury. The progressive renal pathologic changes in the glomeruli and tubulointerstitium may be related to ischaemic change due to accumulation of Gb3 within the arterial wall and subsequent vascular narrowing. These changes include glomerulosclerosis, tubular atrophy, interstitial fibrosis and vascular thickening [6]. Toxic accumulation of Gb3 within the podocyte may constitute a second important mechanism of glomerular injury. Podocytes are highly differentiated cells; their foot processes and slit-diaphragms constitute a critical portion of the glomerular filtration barrier that prevents the entry of large molecules into the urinary space [7]. These cells are post-mitotic and fail to undergo proliferation under most pathologic circumstances, which means that they generally are not replaced when they are lost due to toxic

injury. Kriz and Lemley [8] proposed that when podocytes are lost, the denuded glomerular basement contacts the parietal epithelial cells and forms a synechia. Within the synechia, there is activation and proliferation of cells, especially mesangial cells with entry of immune cells, including macrophages, and accumulation of extracellular matrix protein. This repair response may partly be driven by leakage from the circulation into the synechia of cytokines, chemokines and growth factors, via the impaired glomerular filtration barrier. Matrix expansion and subsequent collapse of the capillary loop appears as the focus of solidification. This constitutes the lesion of segmental glomerulosclerosis, which progresses to global glomerulosclerosis. On the other hand, deposition of Gb3 within tubular epithelial cells may lead to focal tubular atrophy and interstitial fibrosis [7].

Although our patient had advanced chronic renal failure, his haemoglobin level was within normal range. This finding is very surprising since anaemia is a common finding in patients with ESRD. Data from Fabry Registry show mild peripheral blood cytopenias and anaemia is prevalent among patients with FD [9, 10]. The mechanism of having normal haemoglobin in FD with ESRD is obscure and needs to be investigated. A hypothetical mechanism can be drawn in relation to the accumulation of Gb3 in endothelial cells and smooth muscle cells in blood vessels which may lead to longstanding ischaemia. Ischaemia can lead to overexpression of hypoxia-inducible factor-1 α (HIF-1 α) [11]. Erythropoietin gene is a known target for HIF-1 α [11, 12]; hence, overexpression of HIF-1 α may lead to an increase in erythropoietin mRNA and erythropoietin production, hence maintaining the normal red blood cell mass and haemoglobin level. This, however, is entirely speculative and needs to be confirmed by future studies.

In conclusion, FD can be due to sporadic *GLA* gene mutation. Pure renal involvement might be associated with progressive disease which leads to ESRD within a short period. Physicians should have a high index of suspicion for FD especially in male cases with unexplained renal failure that are slowly progressive in nature, even in the absence of a clear hereditary component. Early renal biopsy is recommended in any progressive renal impairment.

Conflict of interest statement. None declared.

(See Editorial comment by Torra and Ortíz. Fabry disease: the many faces of a single disorder. *Clin Kidney J* 2012; 5: 379–382; and related article by Lukas *et al.* Broad spectrum of Fabry disease manifestation in an extended Spanish family with a new deletion in the *GLA* gene. *Clin Kidney J* 2012; 5: 395–400)

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