

Case Report

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Fabry's nephropathy: A man with progressive proteinuria

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Abstract

Fabry's nephropathy is an X-linked lysosomal storage disease, commonly seen in patients with undetermined proteinuria. Herein, we describe a 35-year-old male who was diagnosed with Fabry's nephropathy. The patient presented with a progressive decline in his renal function, and the diagnosis was confirmed by a serum alpha-galactosidase level. This case demonstrates the disease's entire course and various treatment options.

Introduction

Fabry disease, also called Anderson-Fabry disease, is an X-linked error of the glycosphingolipid metabolic pathway resulting in lysosomal accumulation of globotriaosylceramide (Gb3) in a variety of cells. In the absence of significant alpha-Gal A activity, Gb3 accumulates in various cells and tissues, which has cytotoxic, proinflammatory, and profibrotic effects [1].

Patients with Fabry disease may present with a range of clinical features, ranging from the severe classic phenotype in males to asymptomatic disease in some females. Approximately 80 percent of males have neurologic, dermatologic, renal, or cardiac manifestations by the second to fifth decades of life [2].

Progressive accumulation of Gb3 in podocytes, epithelial cells, and tubular cells of the distal tubule and loop of Henle contribute to the renal symptoms of Fabry disease. Fabry's nephropathy manifests as proteinuria and declined Glomerular Filtration Rate (GFR) leading to Chronic Kidney Disease (CKD) and progression to End-Stage Renal Disease (ESRD) [3]. Fabry's nephropathy manifesting as proteinuria occurs in more than 80 percent of untreated male patients with a mean age of diagnosis of 35 to 40 years. Fabry's nephropathy is underdiagnosed among patients with ESRD and should potentially be screened for patients on dialysis or undergoing transplantation. It has

been shown that CKD progression is faster in Fabry's patients with more advanced kidney disease [4]. Hypertension is not a common early finding in Fabry's patients but becomes more prevalent with the progression of the disease [5].

Case report

A 24-year-old man with no significant past medical history initially presented to his PCP with swelling in his legs and tingling in his hands and feet. Vital signs were within normal limits. Upon further questioning, the patient noted that his deceased paternal grandfather had "some sort of kidney problem in his thirties." Given the patient's acroparesthesias, rheumatological tests, including PPD, RPR, ANA, rheumatoid factor, monospot, and Lyme titers, were obtained and unremarkable. The patient was given routine labs, including CBC, CMP, and urinalysis which showed serum creatinine of 2.4 mg/dl (normal 0.74-1.35 mg/dl) and urinary protein of 1.6 g/day (normal <150 mg/day).

Given the peripheral edema, the patient's family history, and labs, he was given a referral to nephrology, who obtained a renal biopsy. The biopsy revealed Focal Segmental Glomerulosclerosis (FSGS). The patient was prescribed corticosteroids, which were tapered and discontinued after ten weeks due to no improvement in his proteinuria.

In a routine nephrology follow-up at age 33, the patient was determined to be in stage four CKD (GFR 24), and in anticipation of dialysis, an arteriovenous fistula was placed. Five months later, the patient developed status epilepticus and was admitted to the ICU. The ensuing MRI Brain with and without contrast showed nonspecific findings.

While admitted, the patient developed cortical blindness. In the setting of multi-system organ failure and decreased renal function (GFR 18), a serum alpha-galactosidase level was obtained and was markedly low at 25 nmol/h/mg (normal >60 nmol/h/mg). The patient was started on Fabrazyme (alfa galactosidase beta; 1 mg/kg) infusions every two weeks for life. During a routine follow-up nine months later, the patient showed improved renal function (GFR 53) and had no further seizures (on anti-epileptic therapy).

Discussion

Due to the non-specific nature of early signs of Fabry disease, diagnosis is often delayed—commonly for more than 15 years after the onset of the first clinical symptoms. The degree of albuminuria/proteinuria and GFR are useful non-invasive markers of severity in Fabry's nephropathy. Measuring the alpha-Gal enzyme activity in leukocytes using the fluorogenic substrate 4-methylumbelliferyl- α -D-glucopyranoside (4-MUGal) has become the gold standard enzyme assay for diagnosing Fabry's in males. A renal biopsy can be useful in all patients with any level of proteinuria or renal dysfunction, as it assesses the degree of glomerulosclerosis and interstitial damage, which are markers of chronicity with high prognostic significance. A renal biopsy also assumes greater importance when clinical and laboratory markers of renal impairment are absent in women [6]. As recommended by the National Society of Genetic Counselors in the USA and others, pedigree analysis in families of Fabry's disease patients should be used to identify relatives that need Fabry's disease diagnostic testing.

The treatment recommendations for Fabry's nephropathy include controlling proteinuria to <0.5 g/day, controlling blood pressure and hyperlipidemia, and initiating Enzyme Replacement Therapy (ERT) at the first sign of kidney involvement (or at the time of diagnosis for patients with little or no residual α -gal A activity) [7]. The recommended therapeutic strategy for patients receiving ERT is to also receive Angiotensin-Converting Enzyme Inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs) to reduce proteinuria.

The initiation of ERT before the development of significant proteinuria is considered essential to prevent future kidney disease. ERT initiated prior to CKD stage 5 was shown to be associated with stability in cardiac and renal disease. ERT could be provided by agalsidase alfa or agalsidase beta, by intravenous infusion at 0.2 mg/kg EOW and 1.0 mg/kg EOW, respectively. In patients with ESRD undergoing dialysis, ERT, can slow the progression or development of extra-renal signs and symptoms of the disease and improve the quality of life.

As part of the therapeutic strategies for Fabry's nephropathy, pharmacological chaperones have shown great promise for patients with specific mutations resulting in misfolded or unstable enzymes and, among them, migalastat has recently been approved for the treatment. Migalastat hydrochloride is an analog

of the terminal galactose of Gb3 that binds and stabilizes wild-type and mutant forms of α -Gal A [7].

Fabry's nephropathy should be considered in the differential diagnosis of proteinuria of uncertain origin. Proteinuria is a risk factor for the progression of the disease and should be managed appropriately. CKD is faster in Fabry's nephropathy patients; therefore, initiating ERT at a younger age is crucial. As early diagnosis is pivotal, implementing approaches for quick detection is needed to prevent long-term adverse results.

ERT is the standard of care, effectively reducing symptoms and slowing progression. However, ERT is not a cure and requires lifelong treatment. Several new therapies including chaperone therapies as discussed above aim to increase the activity of the deficient enzyme rather than just replace it. These therapies are still in the infancy stage, and therefore developing new treatments is vital to provide patients with more effective and convenient options.

In families known to have Fabry disease, screening at-risk or symptomatic male relatives of an affected individual, at-risk female relatives of an affected individual, females with a family history of Fabry disease, and females with symptoms suggestive of Fabry disease are vital.

Statements and declarations

Consent: Written informed consent was taken from the patient for publication of this case report.

Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Germain DP. Fabry disease. *Orphanet journal of rare diseases.* 2010; 5: 30.
2. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *European journal of clinical investigation.* 2004; 34: 236-242.
3. Waldek S, Feriozzi S. Fabry nephropathy: A review- how can we optimize the management of Fabry nephropathy?. *BMC Nephrol.* 2014; 15: 72.
4. Schiffmann R, Warnock DG, Banikazemi M, et al. Fabry disease: Progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. *Nephrol Dial Transplant.* 2009; 24: 2102-2111
5. Torra, Roser. Renal Manifestations in Fabry Disease and Therapeutic Options. *Kidney International.* 2008; 74.
6. Silva CAB, Moura-Neto JA, Dos Reis MA, Vieira Neto OM, Barreto FC. Renal Manifestations of Fabry Disease: A Narrative Review. *Canadian journal of kidney health and disease.* 2021; 8: 2054358120985627.
7. Del Pino MD, Andrés A, Bernabéu AA, de Juan-Rivera J, Fernández E, et al. Fabry Nephropathy: An Evidence-Based Narrative Review. *Kidney Blood Press Res* 2018; 43: 406-421.