

# Fabry Disease: Why suspect it in patients on dialysis?



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**Abbreviations:** FD: Fabry Disease;  $\alpha$ -galA: Alpha-Galactosidase A; Gb3: Globotriaosylceramide; DBS: Dried Blood Spot; GFR: Glomerular Filtration Rate; ERT: Enzyme Replacement Therapy; r-haGalA: Recombinant human A-Galactosidase A; ESRD: End-Stage Renal Disease

## Introduction

Fabry disease (FD, OMIM #301500) is an X-linked lysosomal storage disorder caused by deficiency of the enzyme alpha-galactosidase A ( $\alpha$ -galA, EC 3.2.1.22) [1]. This defect leads to the systemic accumulation of complex glycosphingolipids, mainly globotriaosylceramide (Gb3) and its metabolites. The GLA gene, which encodes  $\alpha$ -galA, is located on the X-chromosome (Xq22.1), whereby practically all men carrying a genetic mutation (hemizygous) develop the disease, while women (heterozygotes) exhibit a wide variability in the severity of their phenotype, mainly due to the random X-chromosomes inactivation in each of their cells (Lyon hypothesis) [2]. The dosage of  $\alpha$ -galA in Dried Blood Spot (DBS) on filter paper is useful in males and a decrease activity confirms the disease, while in females the molecular study is required because of the possibility of false negatives.

FD manifestations are multisystemic and begin in childhood. The main signs and symptoms of the disease are acroparesthesias in hands and feet, gastrointestinal disorders, angiokeratomas, dyshidrosis, intolerance to exercise and heat, hearing loss, arrhythmias, hypertrophic cardiomyopathy, cerebrovascular accidents, and renal failure [3,4]. Nephropathy is one of the major complications of FD and mainly includes reduced Glomerular Filtration Rate (GFR) and proteinuria [5]. Gradual deterioration of renal function and development of azotemia usually occur in the third to fifth decades of life [6]. A significant proportion of patients with FD are treated by dialysis or kidney transplantation [7]. Kidney transplantation is a viable

option and recipients with FD have a lower risk of functional graft loss compared with all other recipients with other causes of End-Stage Renal Disease (ESRD) [8].

Although FD has been a known pathology for more than 100 years, over the last decade the prognosis has changed significantly due to the possibility of Enzyme Replacement Therapy (ERT). Administration of Recombinant human  $\alpha$ -galactosidase A (r-haGalA) during hemodialysis not associated with a reduced activity of r-haGalA therapy in patients with FD. ERT may therefore be performed during hemodialysis without apparent loss of enzyme into the dialysate [9].

FD is panethnic and, given its low incidence, there is no accurate information regarding its prevalence, ranging from 1:40,000 men to 1:117,000 live births [10]. Due to the great phenotypic and symptoms variability, it is difficult to perform a precise diagnosis, which is reached in adult ages when the organic involvement is already installed. The targets for FD screening have been newborns, patients who have suffered early-onset stroke, patients undergoing dialysis for ESRD, and patients developing left ventricular hypertrophy at a young age, among others. Thanks to systematic studies of FD detection in dialysis centers, it has been possible to advance in the determination of the prevalence in the dialysis population. In dialysis patients to date, prevalence rates are between 0.16 and 1.2% [11], showing that screening is a useful strategy in patients with chronic kidney damage. Renal variants have been identified among Japanese chronic dialysis patients whose ESRD had been misdiagnosed

as chronic glomerulonephritis [12]. These findings suggest that cases of FD may be under diagnosed among dialysis and transplant patients.

Why suspect Fabry disease in patients on dialysis? The main causes of ESRD with dialysis requirement in the world are diabetes and arterial hypertension, but unknown or not identified causes are also relevant. Knowing that FD continues to be a low suspicion pathology, we believe it is important to consider it in patients with ESRD who are on or will require dialysis with unknown etiology. According to our study group, in 72 follow-up patients (30 males and 42 females) with FD, 5 were detected in hemodialysis (all males). It is important to remember that DBS screening is a useful tool that can be used in male dialysis patients, but this method fails to detect one third of female patients with FD. In women the molecular study may be required.

### Conclusion

In summary, FD should be considered in the differential diagnosis of chronic kidney disease with unknown etiology. Screening programs for FD in high risk populations as dialysis or transplant patients are important as FD is a treatable multi systemic disease, which is frequently overlooked in patients without classical manifestations. Once the diagnosis has been made, it is possible to work on the family screening, which will allow the identification of affected relatives, thus detecting patients at an earlier age.

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