

Original article

Clinical Appearance and Management of Fabry Nephropathy in Greece

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Abstract

Introduction. Fabry disease is a rare, X-linked sphingolipidosis caused by an insufficient activity of the lysosomal enzyme alpha-galactosidase-A. Renal involvement is a major cause of morbidity and mortality in these patients.

Methods. We performed a multi-center study, in which almost the entire population of Fabry patients in Greece (20 patients (15 men and 5 women) from 10 independent families) participated and we assessed the clinical manifestations of the disease in our country, focusing on renal involvement. In addition we studied the clinical course of the disease during enzyme replacement therapy (ERT).

Results. The mean age at diagnosis was 37.6 (ranging between 11 and 67) years for males and 38.6 (ranging between 21 and 70) years for females. The diagnosis of the disease was made late, within approximately 18 years after the onset of the symptoms. Almost all patients showed renal involvement upon referral (90% of them presented with albuminuria, 50% with decreased glomerular filtration rate (GFR) and 25% in end-stage renal disease (ESRD). Three years after the initiation of ERT the renal function, as well as proteinuria levels remained stable.

Conclusion. Renal involvement represents one of the most common and particularly serious complications of Fabry disease. Timely diagnosis and early beginning of ERT may provide greater clinical benefit.

Key words: agalsidase beta, alpha-galactosidase-A, Fabry nephropathy, chronic kidney disease, proteinuria

Introduction

Fabry disease is a rare disorder of glycosphingolipids (GSLs) metabolism [1]. It is caused by complete or partial deficiency of the lysosomal enzyme alpha-galactosidase-A (α -Gal A), which leads to gradual accumulation of GSLs in the tissues and the plasma of patients [2]. Clinical diagnosis in affecting hemizygotes is confirmed by demonstrating very low or undetectable α -Gal A enzyme activity in plasma or leucocytes. Identification of disease-causing mutation rather than enzyme activity testing is required in females with either a positive family history or symptoms suggesting Fabry disease [3].

Renal involvement is a major cause of morbidity and mortality in Fabry patients and typically starts during the 2nd-3rd decade of patients life [4]. Urinary concentration defects may be the earliest sign of renal functional abnormalities leading to polyuria and nocturia. Proteinuria, lipiduria and GFR deterioration could also be the initial manifestations [5]. Gradually, the progressive accumulation of GSLs in nearly all renal cell types causes deterioration in renal function; [6] ESRD is usually apparent between the 4th and 5th decade of life, leading to the initiation of renal replacement therapy (RRT) [7,8].

Renal involvement occurs almost in all hemizygotes men, but often in heterozygotes women, too. The clinical manifestation of Fabry nephropathy in males shows increased diversity regarding the degree and the intensity of symptoms: the type of the patient's mutation and the α -Gal A residual activity seem to be related to the clinical expression of the renal involvement [9]. In female patients, variable X-inactivation within renal tissue, as well as the other tissues, along with different thresholds of α -Gal A enzyme required for normal tissue function, may be responsible for the observed phenotypic heterogeneity [10,11].

Aim of the present study was to assess the clinical manifestations of Fabry disease in our country, focusing on

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the renal involvement and to study its clinical course after the initiation of enzyme replacement therapy (ERT).

Patients and Methods

The disease has been already diagnosed in 10 families. The total number of documented patients is 20 (15 males and 5 females). Diagnosis was based on residual enzyme's activity measurement and genetic control-identification of the responsible mutations. Initial symptoms, clinical and biochemical evaluation and disease progression were also recorded. Patient's age at the time of diagnosis ranged between 11 and 70; mean age for males was 37.6 (ranging between 11 and 67) and for females 38.6 (ranging between 21 and 70) years. No statistically significant difference noted in age between males and females ($p=0.89$). The diagnosis of Fabry disease was made approximately 18 years after the onset of the symptoms.

Currently, 16 patients (3 females and 13 males) are on ERT. Half of them started ERT within the last two years, whereas 2 out of 16 are at the treatment initiation stage. Eight patients have completed three years of follow-up and treatment results have been recorded based on a proposed protocol. Clinical evaluations were performed every 2 months and all adverse reactions were assessed for the degree of severity, in relation to the treatment regimen. Renal function was evaluated on monthly basis by serum creatinine and eGFR calculated by the Modification of Diet in Renal Disease Study equation [12]. Proteinuria (24 hours urine protein) was evaluated every 6 months of

follow-up. Blood chemistries, which also included mass spectrometric quantification of GL-3 in the plasma, using standardized method [13], were performed every 6 months. Serum samples for recombinant human α -Gal A, IgG antibody testing were collected at baseline and every 6-month after ERT initiation.

We have studied the outcome of eight patients in ERT, who have completed three years of follow-up, receiving a common treatment regimen [intravenous administration of 1mg/kg of body weight agalsidase beta (Fabrazyme[®], Genzyme Corp) every 2 weeks] in accordance to international guidelines.

Results

Renal involvement

In the vast majority of our patients the diagnosis was made when renal complications occurred. With the exception of two teenagers, a boy and a girl, to whom the disease was diagnosed via the investigation of the respective pedigree trees, the rest 18 patients had already developed clinical and laboratory manifestations of renal involvement upon disease diagnosis. The most common finding was proteinuria (90%), which usually did not exceed 1g/24h (Figure 1). Only one patient was reported with nephrotic syndrome at the time of diagnosis. Kidney biopsies were performed in four patients and were useful to document the diagnosis in three of them.

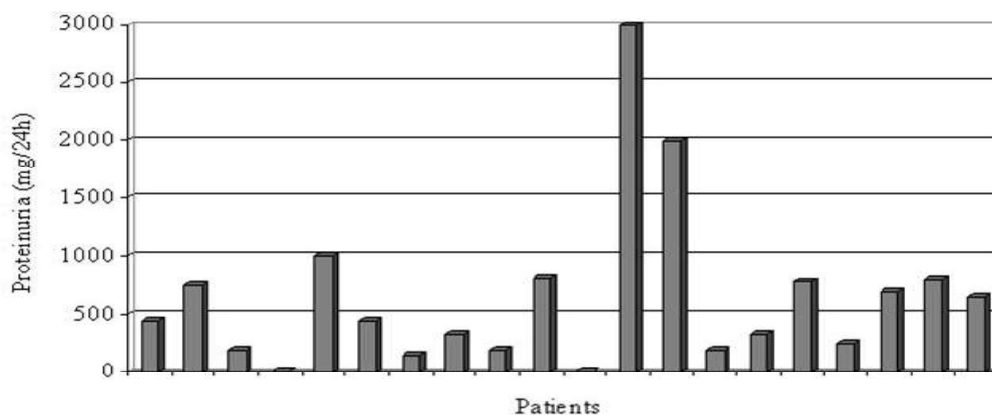


Fig. 1. Levels of Proteinuria of Greek patients at the time of diagnosis of Fabry disease

We have to underline that, 50% of patients, at the time of diagnosis, had already deterioration of GFR at a relatively young age (39 ± 9 years); three patients presented with stage II CKD, while in other three patients the renal disease had already progressed significantly (stages III-IV) and four male patients presented with ESRD (Figure 2). Three of the ESRD patients were on chronic haemodialysis program (one underwent a successful kidney transplant), whereas the fourth was on peritoneal dialysis.

Enzyme replacement therapy

ERT was invariable during the whole study period and the patients follow up was completed in accordance with the current protocol. No patient withdrawals were reported during the follow up period. Mean plasma GL-3 levels showed a decrease to normal levels (≤ 7.03 $\mu\text{g/ml}$) within 6 months of treatment with recombinant α -Gal A in all patients included in the study and these levels remained stable throughout the three years of follow-up (Figure 3).

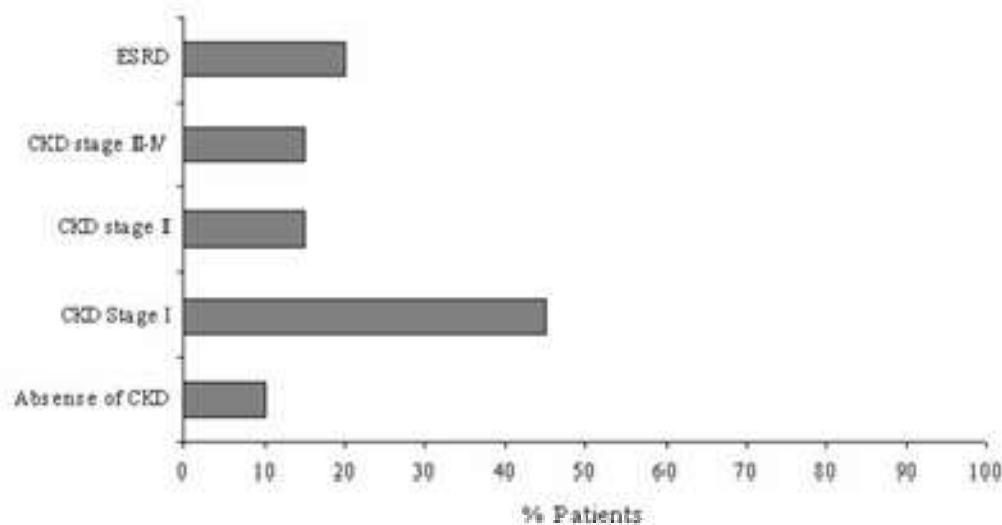


Fig. 2. CKD at the time of diagnosis of Fabry disease in Greece

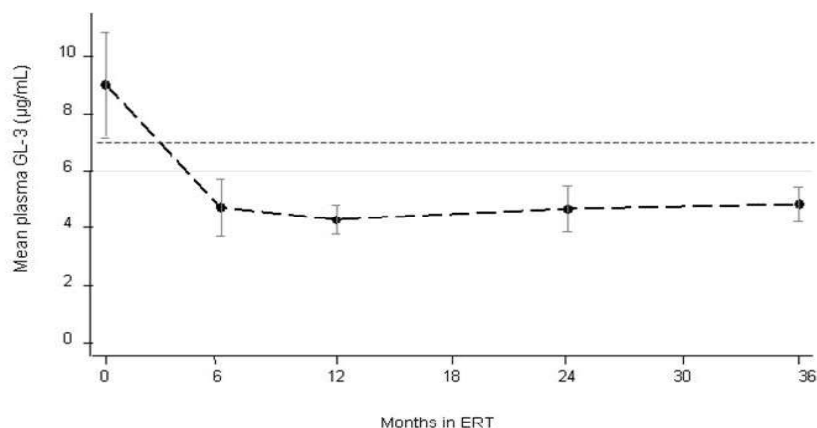


Fig. 3. Mean (\pm SD) plasma GL-3 concentration ($\mu\text{g}/\text{mL}$), at baseline and at 6, 12, 24, and 36 mo, showing normalization ($\leq 7.03 \mu\text{g}/\text{mL}$) after ERT

Mean serum creatinine and 24 hours mean proteinuria levels remained stable from baseline in patients receiving ERT during the 3 years of follow-up as shown in figure 4 (A) and (B), respectively. Interestingly in one 51-years-old man patient in ERT, renal function was ameliorated. He was about 39 years old when mild CKD was diagnosed (serum creatinine: 1.3 mg/dL). At the same time, he presented with microalbuminuria ($\approx 150 \text{ mg}/24\text{h}$), which remained unchanged during the years of follow-up. During a follow-up of about 10 years his creatinine clearance (Ccr) decreased at a rate of 2.4 mL/min/year. At the initiation of ERT his Ccr was 45 mL/min and rose gradually during the 36 months of treatment and reached 65 mL/min; microalbuminuria remained stable at 150mg/24hours.

In our cohort, ERT was well tolerated; the adverse reactions were mild (fever, rigors, headache) and the majority of them was observed during the treatment and was ma-

naged by increasing the infusion time. The development of specific IgG antibodies (seroconversion) against agalsidase beta, as expected [14], occurred in 7 out of 8 patients during the first semester of treatment. However it did not alter the rate of adverse effects during enzyme administration.

Only one patient was reported with significant hypersensitivity reaction despite the pre-medication treatment (antihistamines and corticosteroids). We decided to modify the enzyme administration schedules: for the following-after the reaction-period of six months, the patient received the treatment every week instead of every 15 days with a particularly slow infusion rate (about 12 hours). This modification was absolutely effective and six months later the patient returned to the initial schedule of ERT without developing any other complication ever since.

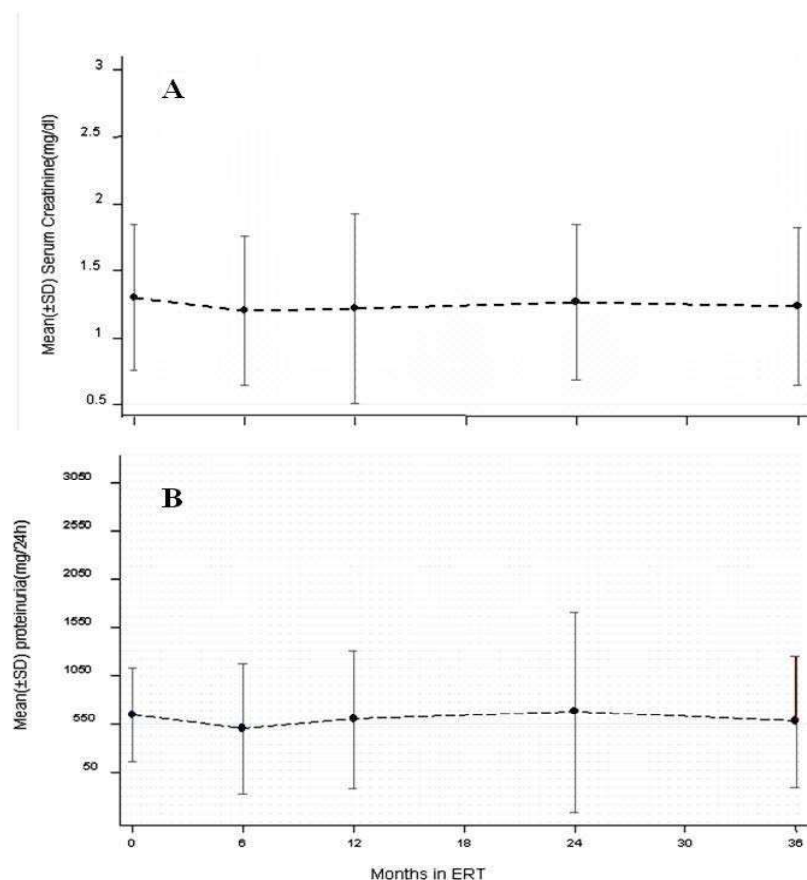


Fig. 4. (A) Stabilization of renal function (serum creatinine) during ERT-three years follow-up
(B) Stabilization of proteinuria (mg/24h) during ERT-three years follow-up

Discussion

Fabry disease is a rare inherited metabolic disorder which, if not treated appropriately and timely, could cause multiple organ failure, leading to death during the 4th-5th decade of patients' life [1,3]. The correlation between the genotype and phenotype of the disease is an important field of medical research and every report to this direction could contribute to the deeper understanding of the underlying pathogenesis of Fabry disease [15,16].

Conducting an epidemiological study on Fabry disease in the Greek territory is a challenging attempt given that prior to 2000 only 2 or 3 cases of Fabry disease were identified in our country. The ERT approval resulted in raising the awareness about this rare disease among the medical community in our country, which led to an increased rate of Fabry diagnosis: during the following 6-7 years about 20 new cases were diagnosed in Greece; in other words, every year a new family with Fabry disease is added [17]. Current data indicate a prevalence of about 1 case per 500,000 inhabitants, which is significantly higher than the respective rate at the beginning of 2000, but yet much lower compared to the rest of the world. Based on the significantly increasing rate of new cases, the increasing disease awareness and the better educational level of differ-

ent medical specialties concerning the disease, we are quite optimistic that, very shortly, Hellenic prevalence of Fabry disease is going to reach the levels of the other developed world.

The diagnosis in our country was mainly based on the established significant complications in the course of the disease and despite the fact that the clinical manifestations were apparent very early: the vast majority had the classical symptoms already during the childhood-adolescence period (mean age of symptoms onset: 15.6 years, ranging between 9-20 years). It is noteworthy that the definite diagnosis was delayed approximately 18 years (mean age at diagnosis 36 years, ranging between 15-60 years) [17].

Only two cases in our country were diagnosed based on a typical initial clinical manifestation of the disease such as acroparesthesias or angiokeratomas and without having any known family member with Fabry disease. Nevertheless, at the time of initial diagnosis, even these two patients had already established kidney or heart involvement, suggesting that the diagnosis was delayed. In the rest of the cases, nephrologists made the initial diagnosis during investigation of proteinuria or deterioration of GFR. In some of these cases renal biopsy confirmed the diagnosis. Four patients were presented with ESRD at the time of diagnosis. Fifty percent of Fabry cases in our country (and all the cases of women) were diagnosed through

pedigree trees. Nevertheless, there is no statistically significant difference in terms of the age at which the diagnosis is confirmed between males and females.

Renal involvement constitutes one of the most common and serious complications of the disease. In our study, almost all patients were presented with renal involvement, consisting of proteinuria, and impaired renal function (GFR<80 mL/min/1.73 m²) at the time of diagnosis. Renal damage is caused by diffuse deposition of GSLs in glomeruli, the tubular system and vasculature and development of structural changes including glomerular sclerosis, tubular atrophy, and interstitial fibrosis [18-20]. Progressive kidney failure develops at a comparable rate as in diabetic nephropathy [21]. However, the pathogenesis of progressive chronic kidney disease in Fabry nephropathy is not yet completely understood; also the renal response to ERT is largely unknown.

Enzyme replacement therapy constitutes the most rational, effective and safe treatment for Fabry patients [22-25]. Exogenous administration of recombinant α -Gal A results in a significant reduction of the deposits of GSLs by all renal cells [26]. The encouraging results of ERT have already been shown in the first clinical trials. Indeed, the renal function in these patients seemed to stabilize in long-term and this finding was more obvious in those starting the treatment at the early stages of renal disease. Moreover, patients who presented with moderately impaired renal function at the initiation of treatment demonstrated significant improvement regarding the rate of loss of their renal function, resulting in a significant delay of renal disease progression [27-30]. In our study, after three years of ERT, patients did not increase the initial proteinuria levels preserving at the same time their renal function stable.

Conclusions

In conclusion, renal involvement constitutes one of the most common and particularly serious complications of Fabry disease. Patients with unexplained chronic renal disease at any stage or albuminuria should be examined for Fabry disease. Timely diagnosis and early initiation of ERT are the most effective ways to prevent further renal deterioration due to Fabry disease.

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Conflict of interest statement. None declared.

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