Evolution of Fabry disease in male patients: The Greek experience

E. Andrikos¹, C. Iatrou², J.N. Boletis³, A. Diamandopoulos⁴, C. Katsinas⁵, K. Kalaitzidis⁶, A. Galinas⁷, A. Xaidara⁸, M. Pappas¹ and K.C. Siamopoulos⁹

¹General Hospital “G. Hatzikosta”, Ioannina, ²General Hospital, Nikea-Piraeus, ³Genener Hospital “Laiko”, Athens, ⁴General Hospital “Agios Andreas”, Patras, ⁵General Hospital, Ptolemaida, ⁶General Hospital, Kavala, ⁷251 General Aeronautic Hospital, Athens, ⁸Pediatric Hospital “Aghia Sophia”, Athens and ⁹University Hospital, Ioannina, Greece

Abstract. Fabry disease is a progressive metabolic disorder with a clinical course characterized by different phases and a variety of disease manifestations. The first symptoms generally appear in childhood or early adolescence and are followed by late life-threatening complications involving vascular, renal, cardiac, and cerebral systems. We report the clinical and biochemical characteristics of 16 male patients from 10 unrelated families who represent almost the entire cohort of known Fabry patients in Greece. Despite the presence of early symptoms in almost every patient (mean age at onset of symptoms 15.6 years), the diagnosis was delayed for a mean of about 18 years (mean age of diagnosis 36 years). Patients are currently monitored and the majority (15 out 16 patients) treated with Enzyme Replacement Therapy.

Introduction

Fabry disease (OMIM 301500) is a progressive, life-threatening metabolic disorder resulting from a defect in the gene encoding the enzyme α-galactosidase A (α-Gal A, EC 3.2.1.22) [3]. Due to incomplete metabolic breakdown of glycosphingolipids, predominantly of globotriaosylceramide (GL-3), substrate progressively accumulates within the lysosomes of a variety of cell types, particularly in vascular endothelial cells. The clinical phases of classical Fabry disease range from manifestation of early symptoms at young age [9], to late life-threatening complications involving vascular, renal, cardiac, and cerebral systems [8].

In this prospective study the clinical and biochemical characteristics of all known male Fabry patients in Greece are reported. The study was initiated as a multi-centre effort to record the clinical presentation of Fabry Disease in Greece in order to enable provision of optimal standardized care to these patients in our country.

Materials and Methods

The medical histories and clinical characteristics of sixteen male Fabry patients from 10 unrelated families are reported. The assessment of renal involvement was tested by measurements of glomerular filtration rate (GFR) and 24 h urine protein. In 4 patients kidney biopsy was also performed. The diagnosis of Fabry disease was biochemically confirmed by measurement of the residual α-Gal A activity in plasma [13] and by full sequence or PCR mutation analysis [11]. GL-3 plasma levels were also determined in most patients [22].

Results

Patients’ clinical characteristics

In most cases, it was a challenge to clinically suspect the diagnosis, as seen in Table 1. In five families, an index case led to identification of other family members affected by
<table>
<thead>
<tr>
<th>Patient</th>
<th>Early symptoms – age at presentation</th>
<th>Age at diagnosis</th>
<th>Renal involvement</th>
<th>Cardiac involvement</th>
<th>Valvular Abnormalities</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>GFR (ml/min/1.73 m²)</td>
<td>Proteinuria (mg/24 h)</td>
<td>Renal Biopsy</td>
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<tr>
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<td>ESRD in CAPD</td>
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<tr>
<td>3</td>
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<tr>
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<tr>
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<td>31</td>
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<tr>
<td>6</td>
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<td>22</td>
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<td>8</td>
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<td>None</td>
<td>58</td>
<td>ESRD in HD</td>
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</table>
The disease. Debilitating early symptoms reported by our patients (Table 1) included severe episodic pain crises (3 patients) and chronic acroparesthesias in the extremities (9 patients). Further symptoms resulting from progressive damage to the peripheral neurologic system included hypo- or anhidrosis with heat, cold and exercise intolerance (7 patients), and abdominal pain with episodic diarrhea (4 patients). Characteristic cutaneous and mucosal angiectasis (angiokeratomas) were seen in 12 patients. Slit-lamp examination revealed Fabry corneal dystrophy in 7 patients, while 5 patients were documented to have high frequency hearing loss and vestibular abnormalities. Two patients, aged 60 and 52 years old, had clinical history or signs of stroke, as judged by magnetic resonance imaging.

Plasma α-Gal A activity level was indicative of classical Fabry disease (Healthy control range > 4 nmol/h/ml of plasma) in all except one patient (Table 2). The youngest patient’s residual enzyme activity level was remarkably high, particularly if compared to his uncle who has an identical genotype, and may point at a variant phenotype of Fabry disease. At age 15, this patient was still free of overt clinical signs or symptoms of the disease.

Although GL-3 may not be the most ideal biomarker for monitoring disease status, plasma GL-3 levels were elevated in all patients tested (Table 2). Mutation analysis successfully identified the α-Gal A gene mutation in patients from 9 families. For one patient, the mutation remained unknown.
Discussion

It has been suggested that the severity of the clinical course of Fabry disease, and particularly the extend of renal involvement, at least partly, depends on the amount of residual α-Gal A activity [1]. Twelve of our patients had minimum residual enzyme activity, as is typical in classically affected Fabry patients [5]. “Cardiac variant” patients with predominant or exclusive cardiac involvement may have marginal residual enzyme activity and it cannot be excluded that our youngest patient may have such an atypical form of Fabry disease [6, 16].

The 16 cases presented herein illustrate that the progression of pathology initially results in symptoms in childhood or early adolescence reflecting involvement of the somatosensory and autonomous nervous systems [8]. The insidious process of progressive GL-3 accumulation in vascular endothelial cells, kidney cells and cardiomyocytes leads to irreversible damage to tissues and organs.

With regard to the kidneys, storage in epithelial cells of the Henle’s loop and distal tubule induces an early impairment in renal concentrating ability, while Fanconi’s syndrome results from involvement of proximal tubuli [18]. Various glomerular cells are involved, particularly podocytes, and glomerular proteinuria may occur at a young age [4]. Kidney involvement with proteinuria and/or GFR reduction was evident in 13 out of the 16 patients.

Patients with Fabry disease are bound to develop chronic kidney disease in most patients around the age of 30 years due to progressive glomerulosclerosis, tubular atrophy, and renal tissue remodeling fibrosis [2, 8]. These irreversible changes led to ESRD 4 in patients of our cohort (0.04% of all Greek dialysis patients, personal communication), aged 49 – 60 years. In the USRDS analysis, among 250,352 American patients who began RRT between April 1995 and July 1998, 42 patients were identified as having ESRD due to Fabry disease, which corresponds to 0.0188% of all causes of ESRD [21]. Although the prevalence rates reflects comparison of Fabry patients with all other patients with ESRD, the prevalence among young males who initiate dialysis before the age of 40 year, for example, may be higher. In FOS group 336 patients with Fabry disease, 201 males and 165 females ESRD was present in 17% of males and in 1% of females [15]. Progressive renal disease is commonly treated with the dietetic and therapeutic strategies aiming to delay the progression of CKD [4, 19]. This strategy is currently suggested in all patients with renal dysfunction. In ESRD patients, dialysis and renal transplantation are life-saving treatments, which unfortunately do not modify the progression of Fabry-related cardiovascular lesions. Therefore, the survival rate of patients with Fabry disease on dialysis is even worse as compared to patients with other renal diseases, mainly due to increased risk of potentially lethal cardiovascular and cerebrovascular complications [19].

Cardiac hypertrophy was present in all patients aged 38 years which suggests that cardiac pathology increases in severity with age. The pathology may involve all cardiac tissues and results in arrhythmias, left ventricular hypertrophy, heart failure, myocardial ischemia or infarctions [8].

Brain abnormalities were found only in two patients in our cohort but early stroke and transient ischemic attacks in Fabry patients are not uncommon [10].

The profound and life-threatening clinical consequences from vital organ pathologies described above may lead to premature death around the fifth decade of life. The last 10 years a cause-specific treatment for Fabry disease in the form of enzyme replacement therapies (ERT) with purified α-Gal A produced by using a genetically engineered human cell line and Chinese hamster oocytes is available. The products are very similar with comparable specific activities per mg [14]. Phase III clinical studies have shown that GL-3 can be partially [17], or in the case of agalsidase β, completely cleared from various target cells [7]. Longer-term follow-up data, as reported for agalsidase β-treated patients, have confirmed that this therapy also prevents GL-3 re-accumulation and may stabilize renal function [12, 19]. In addition,
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References


