Clinical report

Comprehensive clinical evaluation of a large Spanish family with Anderson-Fabry disease, novel GLA mutation and severe cardiac phenotype

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A R T I C L E   I N F O

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A B S T R A C T

Background and objective: Fabry disease is an X-linked multisystemic lysosomal-storage condition. We describe a large family with a novel GLA mutation: p.M187R/g7219 T > G.

Patients and methods: Anamnesis/physical-exam, blood/urine analysis, α-Gal-A activity and/or genetic study of at-risk individuals and multidisciplinary evaluation in confirmed cases.

Results: 4 males and 13 heterozygous-females displayed the mutation. Cardiac/renal/neurological disease was diagnosed at a mean age of 41/29/39 years in males and 51/56/46 years in females. Onset mean age was 20 years versus 42 years. 9/15 had cardiomyopathy. Delta wave suggestive of accessory pathway was identified in 1 male and 2 females. 1 female had cardiac arrest (ventricular fibrillation, 61 years). 2 females and 1 male died suddenly (63, 64 and 57 years). Cardiac-subscore of Mainz Severity-Score-Index was severe for males and females over 40 years. 4/15(26%) developed early renal disease. 2 males needed dialysis. 1 male died at 69 years in spite of kidney-heart transplant.

Conclusion: We describe the largest genetically confirmed Spanish family using multidisciplinary evaluation and MSSI calculation. The novel mutation p.M187R/g7219 T > G is associated with a particularly malignant cardiac phenotype in males and females over 40 years. Severity was higher than that of the largest Spanish FOS-cohort. Short-PR with delta is being reported for the first time.

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Evaluación clínica detallada de una familia española con enfermedad de Anderson-Fabry, nueva mutación en GLA y fenotipo cardiaco grave

R E S U M E N

Fundamento y objetivo: La enfermedad de Fabry es un trastorno sistémico por depósito lisosomal ligado a X. Describimos una familia grande con una mutación nueva en GLA: p.M187R/g7219 T > G.

Palabras clave:
Fabry
Gravedad
Mutación

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Introduction

Anderson-Fabry disease (AFD) is an X-linked recessive condition due to the deficiency of the enzyme α-galactosidase (α-GAL-A), which is caused by GLA gene mutations. It leads to progressive and multisystemic intralysosomal accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb3). Typical signs and symptoms of AFD include angiokeratoma, neuropathic pain, hypohidrosis, gastrointestinal symptoms and corneal opacities. Progressive glycosphingolipid deposition in the microvasculature leads to kidney failure, cardiac involvement, and cerebrovascular disease.1,2

For a long time women were considered to be asymptomatic carriers of the disease.1,3 However, recent data indicate that females are also affected and their phenotype is attributed to non-random X-chromosome inactivation (Lyonisation) and the incapacity of cells to cross-correct metabolic defect.3

More than 370 mutations causing AFD have been reported in the GLA gene (Xq22). Most mutations are missense and private (unique to each family), with the exception of a few ones found in known hotspots (at CpG dinucleotides).1 The disease is phenotypically heterogeneous with classic and variant phenotypes. Several studies have previously analyzed the molecular heterogeneity and defined some genotype/phenotype correlations.4

We report on the clinical characteristics of a large Spanish AFD family with a novel GLA gene mutation, p.M187R/g7219 T > G, which seems to be associated with a particularly malignant cardiac phenotype.

Methods

After index case diagnosis, cascade familial screening was performed on 24 individuals (informed consent was obtained) (Fig. 1). The study was approved by local ethical committee. A retrospective analysis of medical records was also performed in deceased obligate carriers.

All family members were offered clinical evaluation. α-Gal-A activity measurement was performed in males (M). Females were directly offered a genetic study. If there was low α-Gal-A activity and a positive genetic study result for males or a positive genetic study result in females, genetic counseling was provided and comprehensive multidisciplinary evaluation was requested. Cardiologic, nephologic and ophthalmologic evaluations were included. Dermatologic, neurologic and Ear-Nose-Throat (ENT) consultation were requested if there were suggestive signs (Table 1).

Mainz Severity Score Index (MSSI) in its classical/FOs versions was calculated.20 MSSI of individuals older than 40yrs was taken for comparisons between genders. In deceased patients, estimation of MSSI was calculated at the age of death. Previously proposed MSSI cut-offs were used. Arbitrary cut-offs for MSSI subscores were defined (Table 1). We defined “systemic involvement” as two or more subscores of MSSI over 0 (Table 1).

GLA genetic study

DNA was extracted from peripheral blood samples. All seven GLA exons were sequenced in the proband, including intron/exon boundaries. Only exon4 was amplified in the proband’s relatives

Fig. 1. Family tree. Squares represent males, circles represent females. Diagonal lines across squares or circles mean a deceased individual. (+) represents a carrier of the M187R mutation. Vertical lines inside a circle represent an obligate carrier. (−) represents a wild type individual. A black arrow indicates proband. (?) represents individuals without available data.
Table 1
Study protocol.

<table>
<thead>
<tr>
<th>Study protocol.</th>
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<tbody>
<tr>
<td><strong>Anamnesis and physical exam</strong></td>
<td>Complete per systems anamnesis and physical exam</td>
</tr>
<tr>
<td><strong>Basic complementary exams</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Blood tests</strong></td>
<td>Glycemia, Urea, Creatinine, Uric Acid, Sodium, Potassium, Chloride, Phosphorus, Albumin, Proteins, Bilirubine, AST, ALT, GGT, AP, LDH, GSR, Hemoglobin, erythrocyte volumes, Platelets, WBC counts, INR, Prothrombin Activity. Tria-ratio. Thyroid Hormone determination (TSH, FT4)</td>
</tr>
<tr>
<td><strong>Urine tests</strong></td>
<td>Basic urine sediment: pH, Density and Osmolality, nitrites, spot proteinuria and glucosuria, Microscopic examination (hematia, piuria, urinary crystals)</td>
</tr>
<tr>
<td><strong>α-Gal A activity determination</strong></td>
<td>Serum and Lymphocitc α-Gal A activity determination</td>
</tr>
<tr>
<td><strong>Cardiological evaluation</strong></td>
<td>ECG and echocardiogram&lt;br&gt;<strong>If indicated by ECG or echocardiogram abnormalities:</strong>&lt;br&gt; Gadolinium Cardiac Magnetic Resonance 24 h Holter Treadmill exercise test</td>
</tr>
<tr>
<td><strong>Nephrological evaluation</strong></td>
<td>Kidney Ultrasonography Spot urine analysis (3 determinations along 6 months): urinary protein/creatinine ratio, albumin/creatinine ratio, 24 h proteinuria and 24 h albuminuria. CKD-EPI eGFR MDRD eGFR&lt;br&gt;<strong>If indicated by clinical picture:</strong> Renal biopsy</td>
</tr>
<tr>
<td><strong>Ophthalmological evaluation</strong></td>
<td>Fundoscopy&lt;br&gt;Slit Lamp examination&lt;br&gt;<strong>If indicated by previous tests:</strong> Fluorescein angiography Ocular CT</td>
</tr>
<tr>
<td><strong>Neurological-ENT evaluation if symptoms</strong></td>
<td>Brain CT/MRI&lt;br&gt;Supra-aortic vessels US&lt;br&gt;Audiometry</td>
</tr>
<tr>
<td><strong>Dermatologic evaluation if signs/symptoms</strong></td>
<td>Dermatologic oriented anamnesis and physical exam&lt;br&gt;<strong>If indicated by clinical picture:</strong> Skin biopsy</td>
</tr>
<tr>
<td><strong>Genetics Evaluation</strong></td>
<td>Genetics oriented anamnesis and physical exam&lt;br&gt;Genetics counselling&lt;br&gt;<strong>If indicated by clinical picture:</strong>&lt;br&gt; GLA gene genetic study (see text)&lt;br&gt;Prenatal diagnosis (chorionic villey biopsy amniotic cells culture)</td>
</tr>
<tr>
<td><strong>Mainz Severity Score Index (MSSI)</strong>&lt;br&gt;(classical and FOS versions)</td>
<td><strong>Global classical MSSI:</strong>&lt;br&gt; mild &lt;20/76, moderate 20–40/76, severe &gt;40/76 points&lt;br&gt;<strong>Global FOS MSSI:</strong>&lt;br&gt; mild ≤18/64/5, moderate 19–38/64/5, severe &gt;38/64/5 points&lt;br&gt;<strong>Severe classical or FOS MSSI subscores:</strong>&lt;br&gt;Severe MSSI cardiac &gt;10/20 or 9/18, severe MSSI neuro &gt;9/18 or 7/5/15, severe MSSI renal &gt;9/18 or 9/18, severe MSSI general &gt;9/18 or 6/75/13</td>
</tr>
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</table>


for identification of the detected mutation. The results were confirmed using a second blood sample in all participants.

**Results**

**Index-case**

A 50-year-old male was admitted after stroke. Electrocardiogram (ECG) demonstrated atrial fibrillation (AFib) with abnormal repolarization and echocardiogram showed a 16 mm concentric hypertrophy. He had a 15 year (yr) history of hypertension (AHT) and mild chronic renal impairment. Brain-MRI demonstrated small right anterior hemisubar infarction (Fig. 2e–f). Abdominal ultrasound reported normal size kidneys with numerous bilateral parayecystic cysts (Fig. 2g–h). His mother and 2 maternal uncles had died at 64, 52 and 70 years (yrs) after a long course of either severe heart failure, renal impairment or both. His grandmother (F1), mother (F2), and youngest uncle (M2) suffered sudden death. 2uncles required hemodialysis (HD), and one of them died aged 69 yrs, 12 yrs after a heart + kidney transplant (M3). Like in the index case, the facies of one uncle (M2) was reported as “pseudoacro-megalic”. CT scan (October 1979) ruled out a hypersecreting hypophysis tumor. Suspcion of AFD was confirmed by reduced plasma αGalA activity (9%). Genetic testing identified a novel hemizygous missense mutation in GLA (exon4): p.M187R/g7219 T > G.

He also referred dyspnea, occasional vertigo, chronic achropar-esthesia, painful abdominal crisis and episodic bronchospasm. Lips angiokeratoma, periubimbilical telangiectasia, hypoacusia and typical AFD ophthalmologic findings were elicited. Enzyme replacement therapy (ERT) was started.

**Family study**

After familial screening, 17 individuals [average (av) age 44 ± 19.6, 4 males (M), 13 females (F)] displayed c.7219T > G/p.M187R mutation (Fig. 1).

**General involvement**

12/15 (80%) carriers (3 males, 9 females) had signs/symptoms consistent with AFD. 9/15 (60%, 3 males, 6 females) had
Stroke was diagnosed in 3/15 (20%, 2 males, 1 female, 3/3 over 40 yrs).

Mean age of cardiac disease diagnosis was 41 ± 14 yrs in males and 53 ± 8 yrs in females (p = 0.3). Renal involvement was also an earlier finding in males (29 ± 4 yrs) than in females (57 ± 12 yrs) (p = 0.04). Neurological involvement was also earlier in males: 39 ± 13 yrs vs. 46 ± 16 yrs (p = 0.5).

Cardiac involvement

ECG was abnormal in 7/11 (64%, all over 40 yrs). Repolarization abnormalities with negative lateral T-waves and ST segment depression were most common findings. High voltage QRS (Sokolov > 3.5 mV) was present in 2/7 (28%). 2/7 (28%) had AFb (2/2. 100% paroxysmal) and 8/14 had AHT (3 males, 4 females). Short PR with delta wave was identified in three cases (M2, F2, F3) (Fig. 2i–j). A pacemaker was implanted in one patient with symptomatic sinus bradycardia (SB) of 36 bpm. SB was frequent in carriers over 40 yrs (6/7, 86%). Advanced AV-blocks were not demonstrated. First degree AV-block (PR 0.24 ms) and left bundle branch block were recorded in F4.

5/7 (71%) had left ventricular hypertrophy (LVH). Maximal hypertrophy for male1 was 12 mm (M2/M3 not available). Mean maximal LVH for females was 16.6 ± 5.9 mm. The pattern was concentric in 4/5 (80%). 1/5 (20%) (F4) presented septal hypertrophy. None had obstruction. Systolic impairment was present in 3/7 (43%).

Late gadolinium enhancement, transmural at lateral wall, was found in all 3/3 patients who underwent cardiac-MRI (Fig. 2k–l). One woman (F5) with minor ECG abnormalities and normal echocardiogram displayed MRI late gadolinium enhancement as the only cardiac finding.

Mitroaortic sclerosis with/without regurgitation was recorded in 2/7 (28%, 2 females). Ischemic disease was recorded or highly suspected in 5/9 individuals (55%, 2 males, 3 females).

Ventricular arrhythmia was evidenced in one patient (F2). Three patients (F1, F2, M2) died suddenly from cardiac causes. M3 died (69 yrs) from cardio-renal end-stage disease and multiorgan failure after cardio-renal transplant.

Renal involvement

4/15 individuals (27%, 3 males, 1 female) had chronic kidney disease (CKD) with Glomerular Filtration Rate (GFR) of 47.8 ml/min and 48 ml/min in M1 and F3 respectively (moderate CKD, stage3). M2 and M3 had GFR below 15 ml/h (stage5, HD).

Less than 1gram (g) proteinuria was found in a 24 h urine measurement of M1 and F3, M2 had 1.6 g proteinuria. Microalbuminuria with normal GFR was found in one 24-h urine measurement of F7 (1/15, 7%), pending confirmation. HD initiation age was 48 yrs for M2 and 45 yrs for M3.

Multiple bilateral renal parapelic cysts (2–3 cm diameter) with normal sized kidneys were identified in M1 ultrasonography (Fig. 2g–h). Heart and kidney transplant was performed in M3 (57 yrs, stage IV cardiac failure and end stage CKD).

Ophthalmological involvement

All examined individuals (6/6, 100%) displayed AFD's opthalmopathy, 6/6 (100%) presenting bilateral cornea verticillata (CV) (Fig. 2a/b). 5/6 (83%, 1 male, 4 females) had vascular winding: bilateral conjunctival and retinal arterio-venous tortuosity in 2/5 individuals (40%, M1, F3, Fig. 2c–d), and 3/5 (60%, F5, F6 and F7) with isolated retinal arterio-venous winding (Fig. 2d). Cristalline deposits/opacities, aneurysmal dilatations, vascular angulations and retinal pigmentation were described. Senile cataracts were described in M1/F7. No typical “spoke-like” Fabry cataracts.
were reported, nor were there rarer findings [22,24]. As an accidental finding, small retinal detachment was identified in F6 (successful photococagulation).

Neuropsychiatric involvement

Cerebrovascular clinical/subclinical ictal ischemic-disease was found in 6/15 individuals (40%, 3 males and 3 females, all over 40 yrs).

Affected arterial brain territory was “posterior” or in conjunction with other territories in 2/3 individuals (67%, 2 males) and “anterior” in 1/3 (33%, 1 female). Neither hemorrhagic ictal episodes nor vascular abnormalities (aneurysms/dolichoectasia), were found.

Different forms of AFD-neuropathy were observed in 12/15 (80%). All individuals over 40 yrs had neuropathy. Painful achroparesthesia was identified in 7/12 cases (58%, 3 males, 4 females). M2 had right pedal motor-axonal-neuropathy on electromyography. 40% displayed multiple types of neuropathy (such as achroparesthesia, heat intolerance, gastrointestinal and ENT affection in male 1).

F2, F4 and F10 displayed chronic anxious symptoms, exacerbated by appearance of AFD.

Ear-Nose-Throat involvement

Results are summarized in Table 2.

<table>
<thead>
<tr>
<th>Table 2: Other organs and systems involvement.</th>
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<tbody>
<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Colicky abd pain-diarrhea</td>
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<tr>
<td>Constipation-Hemorrhoids</td>
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<tr>
<td><strong>ENT area</strong></td>
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<tr>
<td>Tinnitus</td>
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<tr>
<td>Vertigo</td>
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<tr>
<td>Hypoacusia/Audiometry</td>
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<tr>
<td><strong>Pneumological</strong></td>
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<tr>
<td>Bronchospasm</td>
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<tr>
<td><strong>Rheumatological</strong></td>
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<tr>
<td>Arthralgia (large joints)</td>
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<tr>
<td>Osteoporoic fractures</td>
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<tr>
<td><strong>Endocrinological</strong></td>
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<tr>
<td>2 HyperPTH CKD* confirmed</td>
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<tr>
<td>2 HyperPTH CKD* probable</td>
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<tr>
<td>Thyroid</td>
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<tr>
<td>DM-2</td>
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<tr>
<td>Fasting impaired glycemia</td>
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<tr>
<td><strong>Neoplastic disease</strong></td>
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<td>Breast carcinoma</td>
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<tr>
<td><strong>Infectious disease</strong></td>
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<tr>
<td>Lower respiratory tract infs.</td>
</tr>
<tr>
<td>Hepatitis B</td>
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<tr>
<td>Acute Pyelonephritis</td>
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<tr>
<td>Acute repetition tonsililitis</td>
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<tr>
<td>Costal Zoster-Herpes (P)</td>
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<tr>
<td>Mumps</td>
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<tr>
<td><strong>Comments</strong></td>
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<tr>
<td>Missdiagnosis of irritable bowel syndrome in F2</td>
</tr>
<tr>
<td>Occasional/Episodic tinnitus</td>
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<tr>
<td>Occasional Rotatory vertigo</td>
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<tr>
<td>With lower respiratory tract infs mainly during third to fourth decade.</td>
</tr>
<tr>
<td>ankles, knees, wrists, shoulders</td>
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<tr>
<td>No osteoporotic fractures identified until the date.</td>
</tr>
<tr>
<td>No PTH available data of M2 and M3 (deceased).</td>
</tr>
<tr>
<td>Thyroid nodule excised to F9 (third decade, no AP available).</td>
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<tr>
<td>On oral antidiabetics. Male 3 (deceased)</td>
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<tr>
<td>On diet, Female 3.</td>
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<tr>
<td>F3: Ductal SLQ R breast ca (surgery + RT Aug’05). Remission. F9/F3’s daughter): Breast ca + MTS deceased 38y</td>
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<tr>
<td>With bronchospasm, mainly during third to fourth decade. Community acquired pneumonia M2 (35y)</td>
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</tbody>
</table>

Dysmorphic/dermatological involvement

Dysmorphic/dermatological signs were found in 1/7 (28%, M1). He displayed marked coarse facies with prominent supraciliary archi and inferior maxilar. He presented angiokeratoma in lips. Relatives reported that 2 uncles had a similar facies in adulthood. M1 also had episodes of rashes with angiokeratoma (on groins/genitals/inferior abdomen) at youth. Periumbilical telangiectasia was elicited.

Other organ/system involvement

Results are summarized in Table 2.

Evaluation of severity: MSSI results

MSSI was calculable in 12/15 (80%, 3 males, 9 females). Results are summarized in Table 3 (individual data not shown).

Discussion

Previous studies have reported different mutations in GLA gene showing allelic heterogeneity. However, genotype-phenotype correlation knowledge is scarce.

We present the clinical phenotype of a family with a novel missense mutation that affects methionine in position 187...
Table 3
Clinical characteristics of M187R+ AFD members of family split up by gender and MSSI subscores (Nov 2012).

<table>
<thead>
<tr>
<th>n &gt; 40</th>
<th>Average age of debut (y)</th>
<th>Cardiovasc</th>
<th>Renal</th>
<th>Neurol</th>
<th>General</th>
<th>Total</th>
</tr>
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<tr>
<td>40</td>
<td></td>
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<tr>
<td>(M, 3; F, 6)</td>
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<tr>
<td>n comparisons with [29]</td>
<td>12 (M: 3; F: 9)</td>
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</table>

**Male (%)**
- **cl MSSI av**: 20
- **FOS MSSI av**: 17.2/20
- **Median FOS MSSI av**: 18 (2-6)

**Female (%)**
- **cl MSSI av**: 42
- **FOS MSSI av**: 13.6/18
- **Median FOS MSSI av**: 12 (0-9)

**Male + Female**
- **cl MSSI av**: 36
- **FOS MSSI av**: 15.5/20
- **Median FOS MSSI av**: 14.5/18

**Bold type: main results and gender comparisons. Times New Roman: Classic MSSI comparisons. Alldhaby: FOS MSSI comparisons [Medians from Barba Romero et al’s study [29] in brackets]. For comparison with Barba Romero et al’s study all age individuals have been considered. For gender comparisons between family members only individual older than 40 years of age have been considered (n = 5, M: 3; F: 6).**

[p.M187R/g7219 T > G]. Its absence in 100 healthy-population chromosomes was checked. Predictive study confirmed high probability of pathogenicity. Clinical co-segregation was concordant. There are 3 other reported missense mutations related to classic phenotype in this position (M187V, M187L, M187T), suggesting a “hot spot” in GLA gene.4

The heart was the main organ involved, with early and severe forms. Patients were frequently admitted to hospital with heart failure/arrhythmias. Heart failure was the most frequent mode of death, with sudden deaths (SD) and 1 resuscitated cardiac arrest.

Progressive conduction disease due to AV-node fibrosis and malignant ventricular arrhythmias favored by anatomic reentrant-circuits around fibrotic areas are associated with SD in AFD.3–8 In this context, occurrence of syncope deserves careful examination. Linhart et al. found a 3.2% syncope prevalence in a FOS population (2% vs. 4% females vs. males)9 and 4% vs. 6% pacemaker implantation in females vs. males.27 AFB/non-sustained ventricular tachycardia (NSVT) as markers of atrial/ventricular electrical instability are frequently found.1 In late AFD phases, almost all adult men show NSVT on Holter, unspecific intraventricular conduction disturbances and QRS prolongation.9

Almost every individual over 40 yrs displayed sinus-bradycardia. This lends support to the concept of “AFD cardio-neuropathy”. Autonomic cardiac dysfunction leads to depressed heart-rate variability and chronotropic incompetence. Direct involvement of conduction system in AFD appears as short PR interval or delayed AV/ventricular conduction.10 Both dyssynaptic and direct involvement can at least partially explain not only fatigue/syncope but also ominous events. In fact, combination of conduction disease, fibrosis and ischemia might trigger ventricular arrhythmias.9

Our study is the first to hint at the role of accessory pathways, demonstrating delta-waves in 3 patients with advanced disease. Diagnosis was achieved by medical records review since electrophysiological study was not available. Development of accessory pathways during disease progression has been reported in other heart storage-diseases such as those caused by PRKAG2 mutations.11 Infiltration of AV-annulus could cause abnormal pathways between atria and ventricles also in AFD.

We highlight the value of cardiac-MRI for early identification of heart disease and diagnostic stratification.7,12 All carriers with available cardiac-MRI had typical late gadolinium enhancement.

With regard to gender differences, we have found that all heterozygous females over 40 yrs had cardiomyopathy. This is consistent with previous studies8 but, contrary to others, in our study, women showed a moderate to severe cardiac involvement similar to that of males.

With regard to kidney disease, we highlight: Renal disease caused severe morbidity and was the second cause of death in males after cardiac death. Isolated microalbuminuria was not frequent in our family. Nevertheless, the importance of clinical renal-biomarkers for early diagnosis, such as microalbuminuria, urinary albumin to creatinine ratio, has been emphasized.13 Another important diagnostic clue is identification of characteristic paracalyptic cysts, as happened in M1.14 Nonetheless, perhaps the most important clue is being aware of AFD as cause of uncertain-origin CKD. Besides ERT, renal-AFD must be managed according to CKD standards (cardiovascular risk-factors control, introduction of IECAS/ARBs, transplant) as our individuals receive.15–18

With regard to gender differences, we confirm less severe renal involvement in females. However, females can display severe phenotypes, often with a 10 yr onset-delay compared to males, as observed in our family.19–21

Several issues may be considered about ophthalmological involvement: high prevalence of AFD ophthalmopathy is in line with previous studies.22 Nevertheless, we have noted a higher frequency of arterial/venous winding in our family. In previous studies,23 vascular tortuosity in females was a relatively rare finding, reported in 21.9%, as opposed to 60% of our females. In Sodi’s study “for all age groups FOS-MSSI was higher in patients with vessel tortuosity”. We think the higher prevalence of vessel tortuosity in our patients indicates the higher severity in family, including the females. High MSSI of proband and several females with vascular winding support this hypothesis. Lastly, prominent corneal involvement, with striking CV images as compared to subtle ones in other families, might suggest higher severity. Therefore, ophthalmological evaluation is crucial for AFD early diagnosis, and vascular winding may be considered as a potential marker of systemic severity.24,25

Neurologic involvement is also remarkable: NP symptoms are a frequent debut in childhood/adolescence, being also an important clue for early diagnosis. A less frequent but more devastating consequence of neurologic AFD is cerebralvascular ictus. In our family clinical ictus was identified in a high percentage of individuals (20%) who were preferentially affected in the posterior territory, as previously described. Subclinical disease was also
frequent. Clinicians should keep AFD in mind as cause of 0.5–4% of cryptogenic strokes.\textsuperscript{23} Neurological symptoms/signs revealing a compromised patient indicate ERT. Antigli/projective-anticoagulants, statins and ACEI-ARBs should be used for non-AFD-ictus.\textsuperscript{26}

With regard to ENT involvement, in line with previous research, males and elderly patients displayed higher progressive hearing-loss, with largest deficits at high frequencies.\textsuperscript{27} Tinnitus and vertigo were common, as in other families. Slowly progressive sensorineural hearing-loss predominates over sudden or conducive/mixed loss. Hearing aids are frequently required, even at early ages, as proband exemplifies.

With regard to gender differences, our results confirm previous findings: AF ictal disease is present in females with a later onset than males.\textsuperscript{19,21} With regard to ENT area, severe findings in both males and females are confirmed.

Other organ and system involvement was also identified, confirming systemic character of AFD and highlighting importance of a coordinated and multidisciplinary approach to this disorder.

We also remark on some features related to severity, debut-age and systemic involvement (Table 3; p.M187R carriers over 40 yrs are severely affected by AFD (av-MSSI:38.7/76). We found a high av cardiac-global-subscore (15.5/20) and intermediate renal (8/18). MSSI from males vs. females was 55.3/76 vs. 30.5/76. Nevertheless, the differences were probably not so significant: scarce retrospective female data favored a higher infraestimation of females’ MSSI, and several females died (SD/neoplastic disease) at a younger age than males. This may preclude development and verification of their severity. Analyzing gender and subscores high male renal-subscore was notable, and, particularly, both males and females cardiac-MSSI subscores were high (17.3/20 and 14’6/20 respectively). This underlines high cardiac severity not only in the males in the family but also in females (classically considered mere “carriers” of AFD).\textsuperscript{3,19,20}

Av age of debut was 36 yrs. Previous studies\textsuperscript{19,20} observed a delay of 6–10 yrs between earlier Fabry male and female debut. Our greater delay (22 yrs) might be accounted for by the fact that, having no access to some retrospective female data, we arbitrarily designated them a particularly late age of debut. Finally, we have found that the level of systemic involvement was also high (66% have 2 or more affected systems).

We also compare our patients with those from the Fabry Outcome Survey (FOS) Spanish Cohort (Table 3; overall, cardiac, neurological and general severity of our males and females is greater than that in the largest FOS-Spanish cohort.\textsuperscript{26,28,29} Confirmation of 3 sudden deaths plus 1resuscitated cardiac arrest, besides the first identification of short PR with delta-waves are other remarkable differences.\textsuperscript{28,29} Renal severity was also higher in our males and we identified 3females with CKD, apart from one female with TIA (both absent in FOS-02-03 Spanish females). For future comparisons we consider including ABO blood-group, urinary GB3, Fabry International Prognostic Index\textsuperscript{30} and specific X-chromosome inactivation genetic studies in females.

Therefore, as a final summary, we conclude that the novel c.7219T > G/p.M187R mutation in GLA gene is associated with a particularly malignant phenotype. Severity is higher than that in the previous largest Spanish FOS cohort. Individuals over 40 yrs, regardless of gender, have severe cardiac manifestations, including 3 sudden cardiac deaths, 2 of them in females. Delta waves have been identified for the first time. Finally, the systemic involvement of AFD individuals is high, underlining the need for a coordinated multidisciplinary approach.

Conflict of interest

The authors declare no conflicts of interest.

References


