Govern de les Illes Balears
Conselleria de Salut

II JORNADA DE L'ESTRATÈGIA MALALTIES MINORITÀRIES I COMPLEXES DE LES ILLES BALEARS

23 i 24 de maig de 2024

Sala d'actes de l'Hospital Universitari Son Espases, Palma.

Enfermedad de Fabry en la mujer ♀

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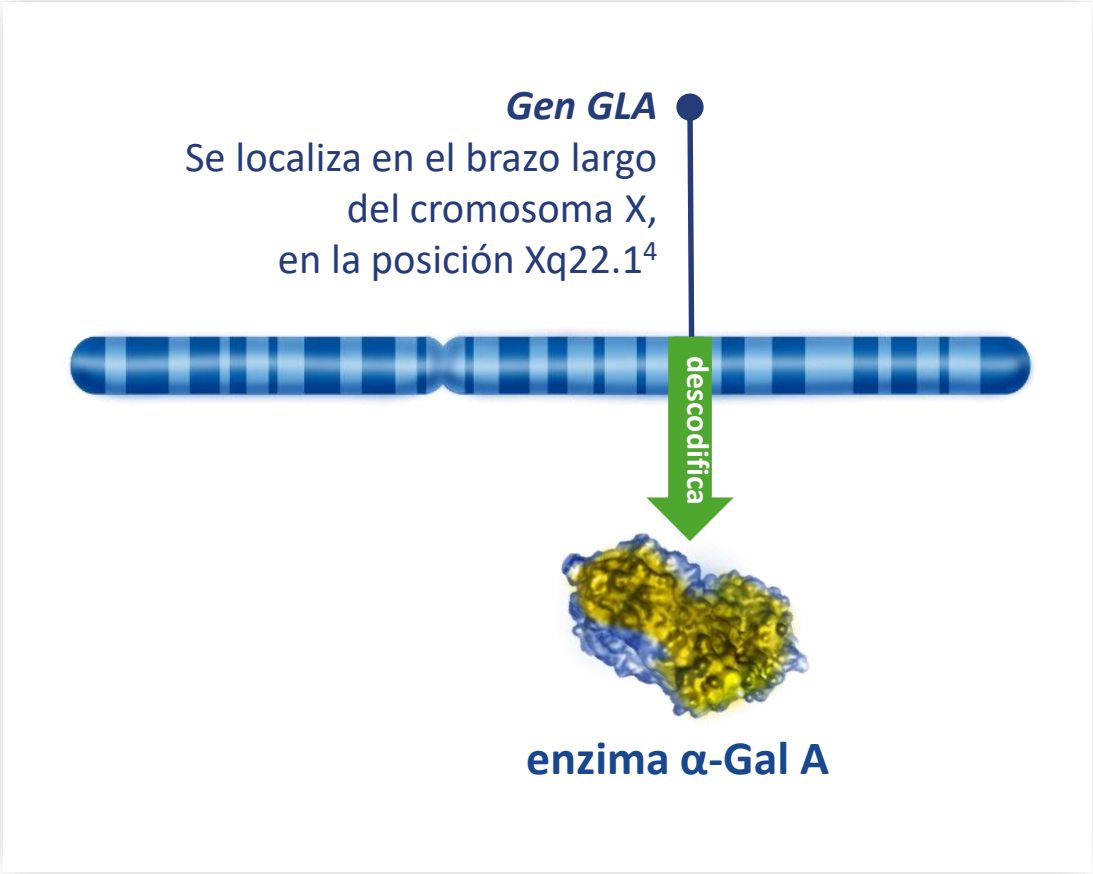
Cardiología Hospital Universitario Son Espases

Son Espases hospital universitari

Institut d'Investigació Sanitària Illes Balears
IdISBa

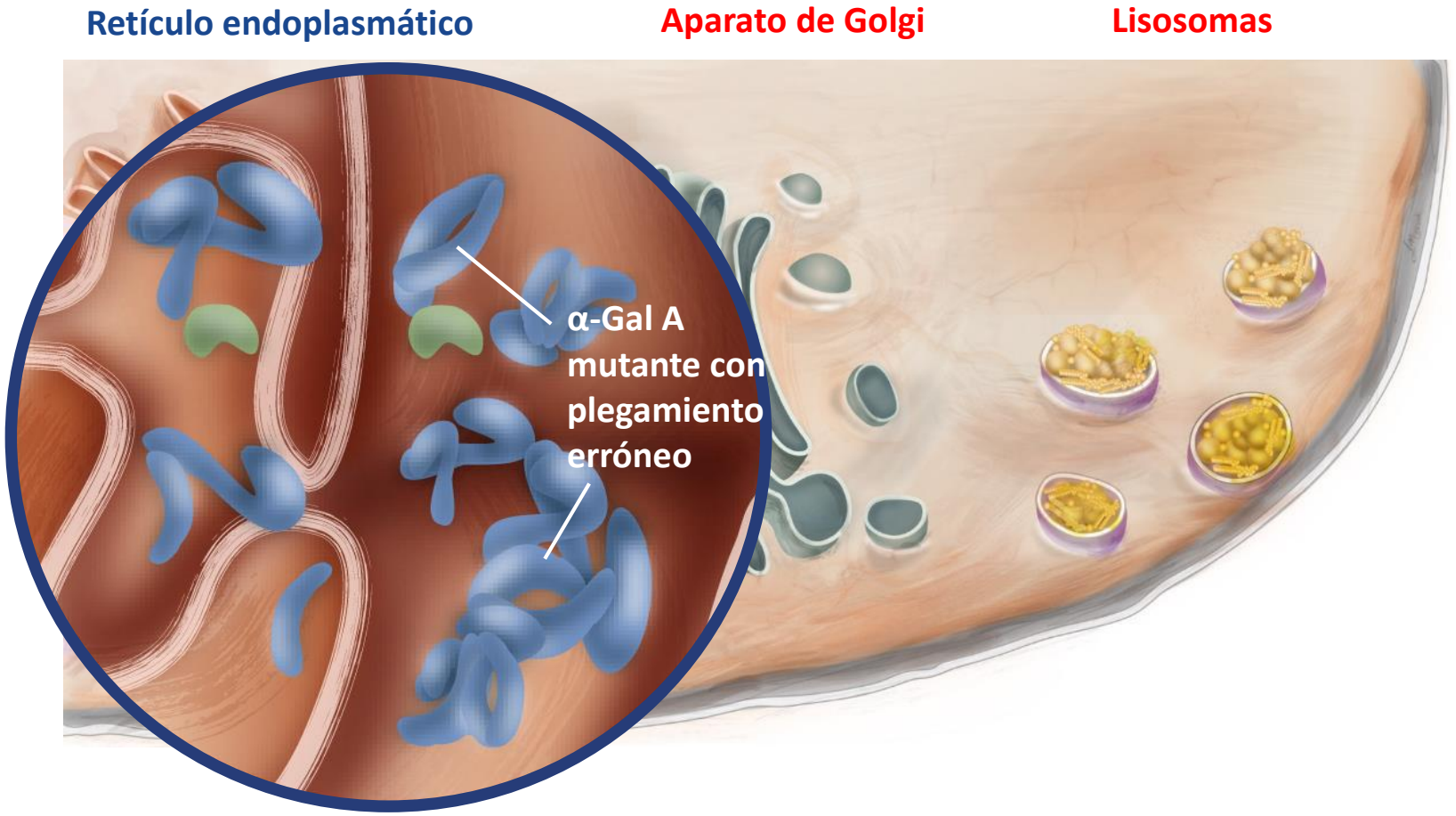
Enfermedad de Fabry

- La enfermedad de Fabry es un **trastorno de depósito lisosomal multisistémico** originado por una **mutación en el gen *GLA***[1, 2]
- Las mutaciones en el gen *GLA* producen una ausencia o deficiencia de **la enzima α-Gal A**, que degrada los glucolípidos en los lisosomas[1-3]



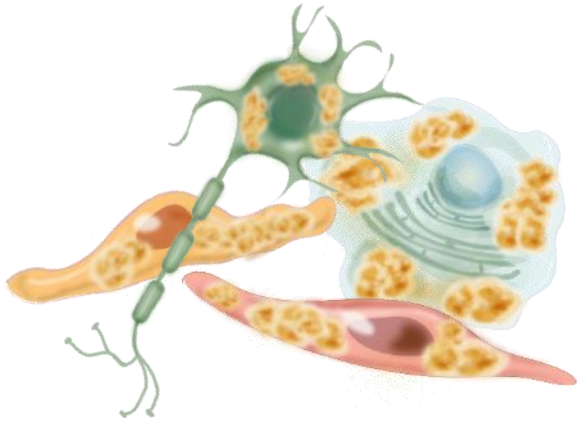
α-Gal A: α-galactosidasa A, GLA: gen galactosidasa A.

1. Ortiz A et al. *Mol Genet Metab.* 2018;123(4):416-427; **2.** El-Abassi R et al. *J Neurol Sci*. 2014;344(1-2):5-19; **3.** Martins AM et al. *J Pediatr*. 2009;155(suppl 4):S18-S31; **4.** Schiffmann R and Ries M. *Pediatr Neurol*. 2016;64:10-20.



La α-Gal A mutante con plegamiento erróneo queda retenida o se degrada en el RE, lo que da lugar a una pérdida de función.

Parenti G et al. *Mol Ther*. 2015;23(7):1138-1148.



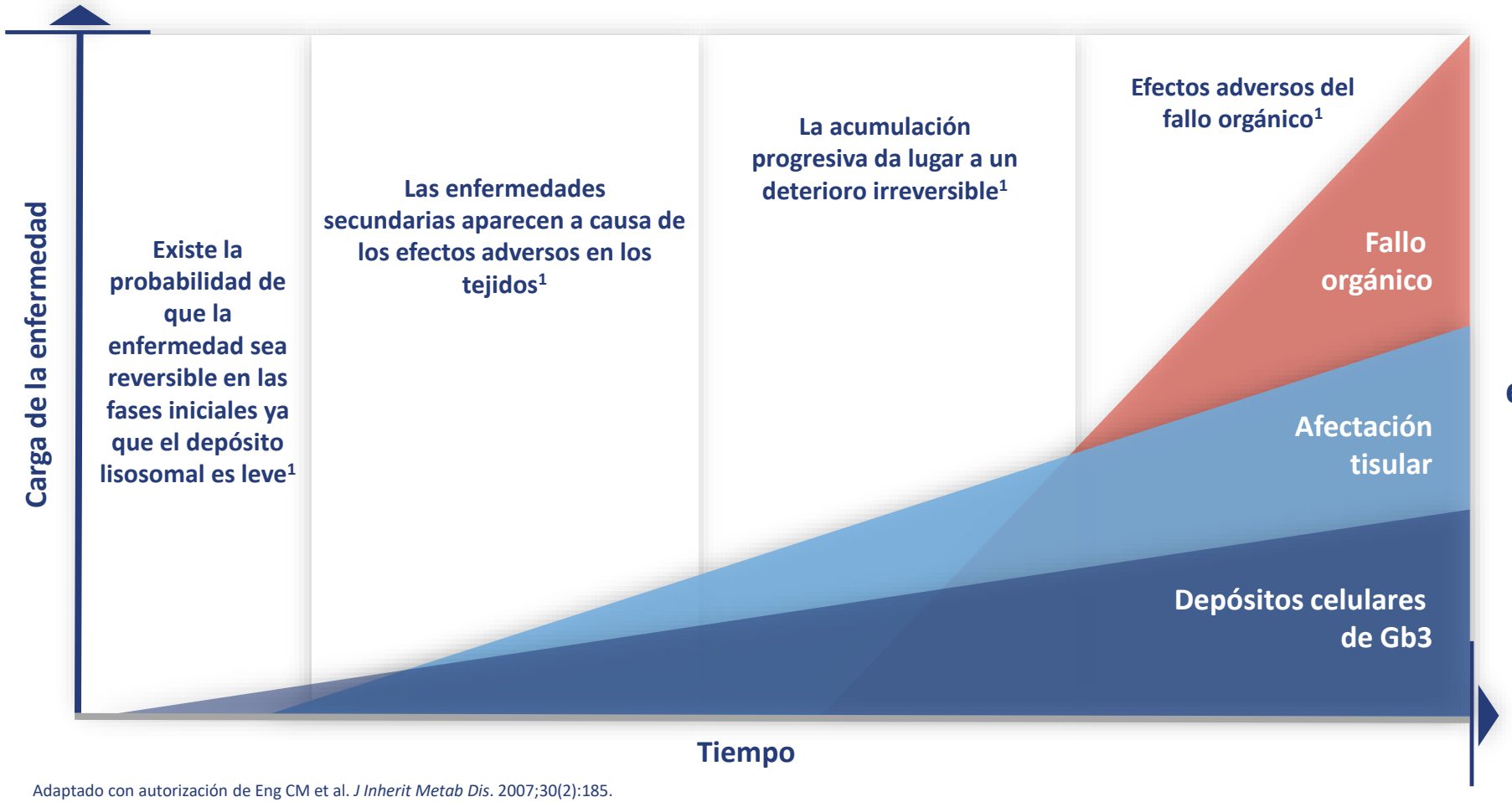
Acumulación de Gb3 y liso-Gb_3 en distintos tejidos y células[1,2]

- Lesiones de vasos pequeños
- Inflamación
- Isquemia tisular
- Estrés oxidativo
- Muerte celular
- Disfunción de células endoteliales
- Alteración del metabolismo energético
- Deterioro de la maduración del autofagosoma

→ **Fibrosis tisular irreversible** → **Fallo orgánico[3]**

1. Germain DP. *Orphanet J Rare Dis*. 2010;5:30. doi:10.1186/1750-1172-5-30; **2.** Ortiz A et al. *Mol Genet Metab.* 2018;123(4):416-427; **3.** El-Abassi R et al. *J Neurol Sci.* 2014;344(1-2):5-19.

Evolución clínica de la enfermedad de Fabry



La acumulación de Gb3 se inicia en el útero y evoluciona durante toda la vida[2,3]

Adaptado con autorización de Eng CM et al. *J Inherit Metab Dis*. 2007;30(2):185.

1. Eng CM et al. *J Inherit Metab Dis*. 2007;30(2):184-192; **2.** Vedder AC et al. *J Inherit Metab Dis*. 2006;29(1):106-111; **3.** Thurberg BL and Politei JM. *Hum Pathol*. 2012;43(4):610-614.

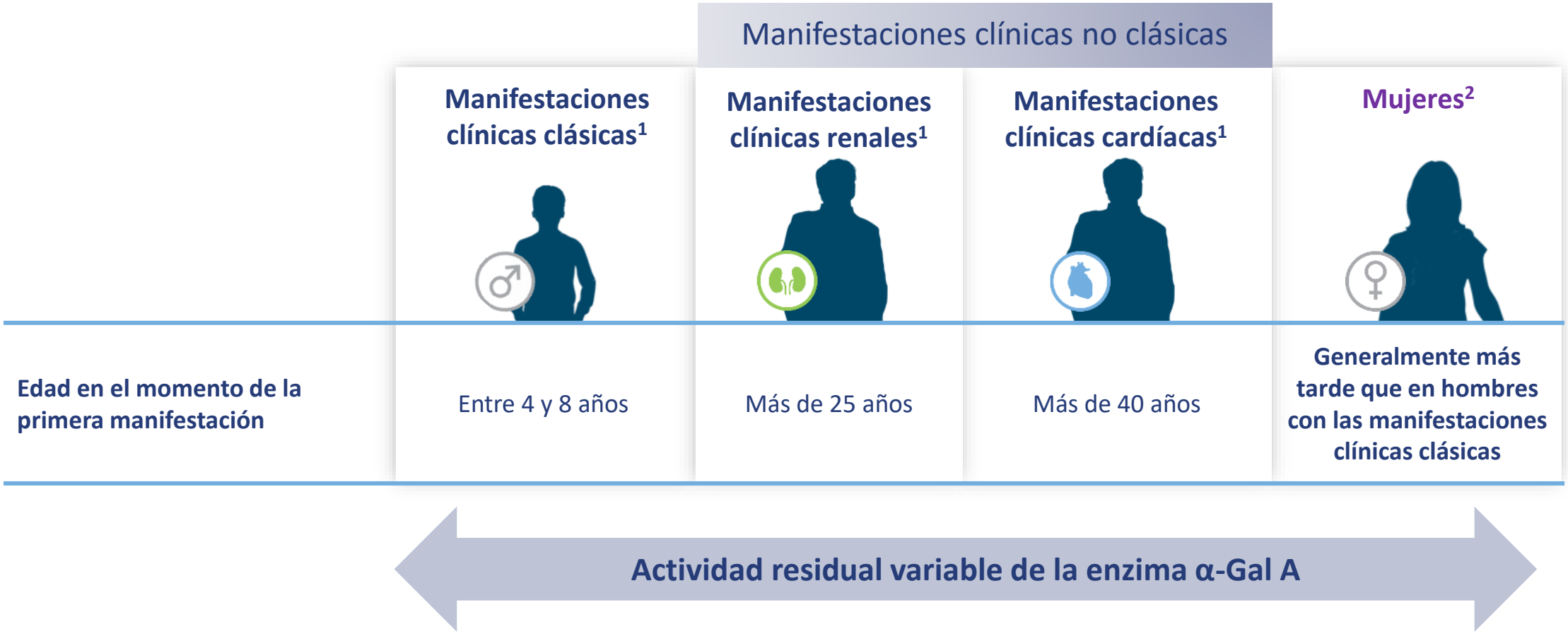
La enfermedad de Fabry es un trastorno multisistémico y progresivo[1-3]

Adaptado con autorización de la Sociedad Japonesa de Nefrología.

GI: gastrointestinal, HVI: hipertrofia ventricular izquierda, ICC: insuficiencia cardiaca congestiva, ERT: enfermedad renal terminal

1. Schiffmann R and Ries M. *Pediatr Neurol*. 2016;64:10-20; **2.** Kusano E et al. *Clin Exp Nephrol*. 2014;18(2):269-273; **3.** Schiffmann R et al. *Kidney Int.* 2017;91(2):284-293.

La enfermedad de Fabry tiene manifestaciones clínicas heterogéneas



1. Mehta A and Hughes DA. In: Adam MP, Ardinger HH, Pagon RA, eds. *GeneReviews®*. Seattle, WA: University of Washington, Seattle;1993-2018. At: www.ncbi.nlm.nih.gov/books/NBK1292/. Último acceso el 11 de mayo de 2018; **2.** Ortiz A et al. *Mol Genet Metab.* 2018;123(4):416-427.

La enfermedad de Fabry posee manifestaciones clínicas variables

	Manifestaciones clínicas clásicas[1]	Manifestaciones clínicas no clásicas: Manifestaciones clínicas renales[1]	Manifestaciones clínicas no clásicas: Manifestaciones clínicas cardíacas[1]	Mujeres[2]
				
Angioqueratoma	++	–	–	–/+
Acroparestesia	++	–/+	–	–/+
Hipohidrosis/anhidrosis	++	–/+	–	–/+
Opacidad corneal/lenticular	+	–	–	–/+
Cardiopatía	HVI/isquemia	HVI	HVI/miocardiopatía	–/+
Enfermedad cardiovascular	AIT/ictus	–	–	–/+
Enfermedad renal	ERT	ERT	Proteinuria	–/+

HVI, hipertrofia ventricular izquierda; AIT, accidente isquémico transitorio; ERT, enfermedad renal terminal.

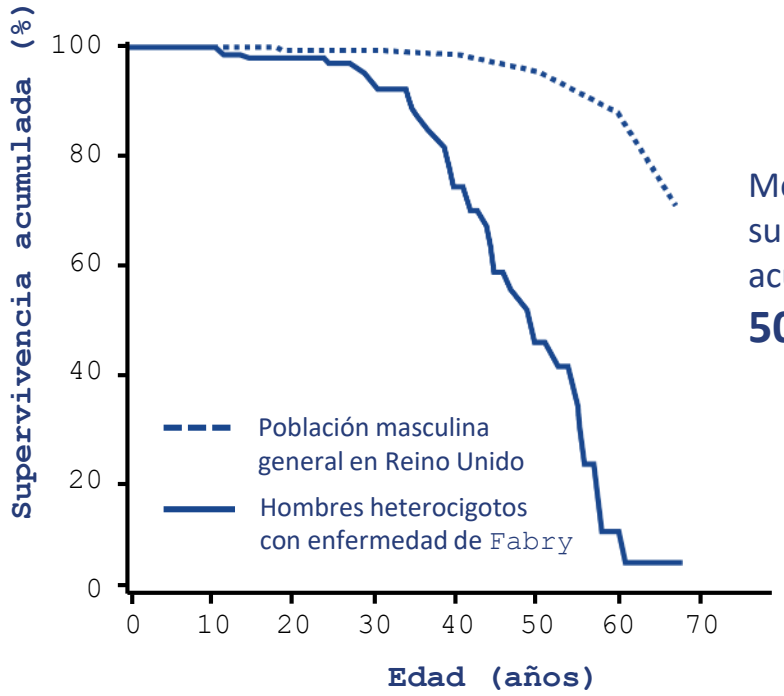
Complicaciones embarazo
Infertilidad
QoL/ Psicológicos

1. Mehta A and Hughes DA. In: Adam MP, Ardinger HH, Pagon RA, eds. *GeneReviews®*. Seattle, WA: University of Washington, Seattle;1993-2018. At: www.ncbi.nlm.nih.gov/books/NBK1292/. Último acceso el 11 de mayo de 2018; **2.** Ortiz A et al. *Mol Genet Metab.* 2018;123(4):416-427.

La esperanza de vida se reduce en estos pacientes

Probabilidad acumulada de muerte en pacientes con enfermedad de Fabry

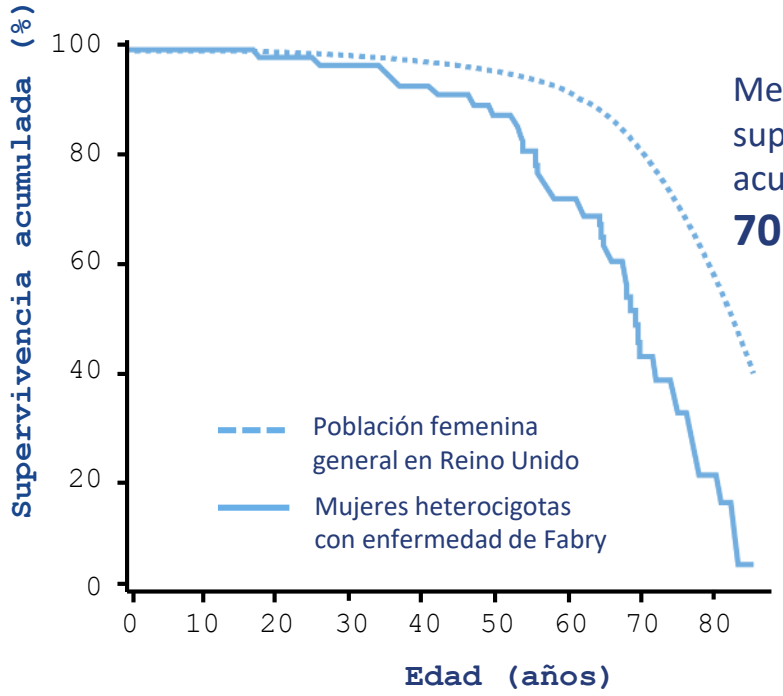
Hombres (N = 98)[1]



Mediana de la supervivencia acumulada
50 años

Extraído de BMJ Publishing Group Limited. *J Med Genet*., MacDermot K et al., 38, 752, 2001.

Mujeres (N = 60)[2]



Mediana de la supervivencia acumulada
70 años

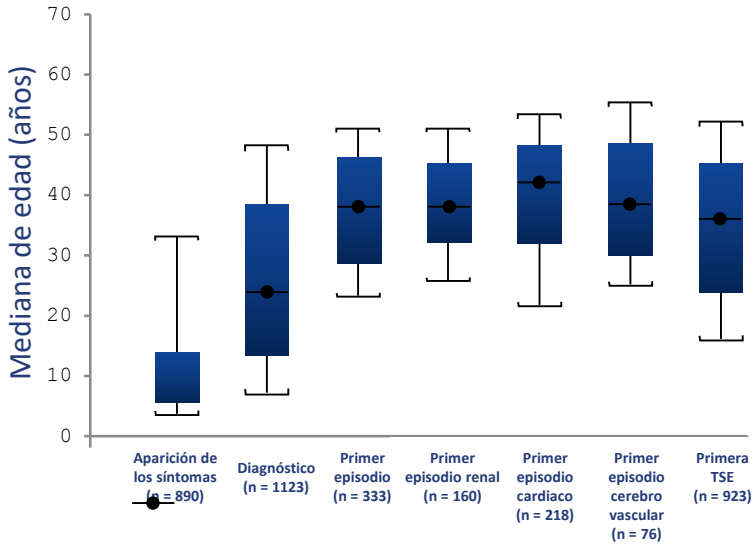
Extraído de BMJ Publishing Group Limited. *J Med Genet*., MacDermot K et al., 38, 770, 2001.

1. MacDermot KD et al. *J Med Genet*. 2001;38(11):750-760; **2.** MacDermot KD et al. *J Med Genet*. 2001;38(11):769-807.

Retraso diagnóstico/otros diagnósticos

Mediana de la edad en el momento de la aparición de los síntomas, diagnóstico, primer evento clínico e inicio de TSE

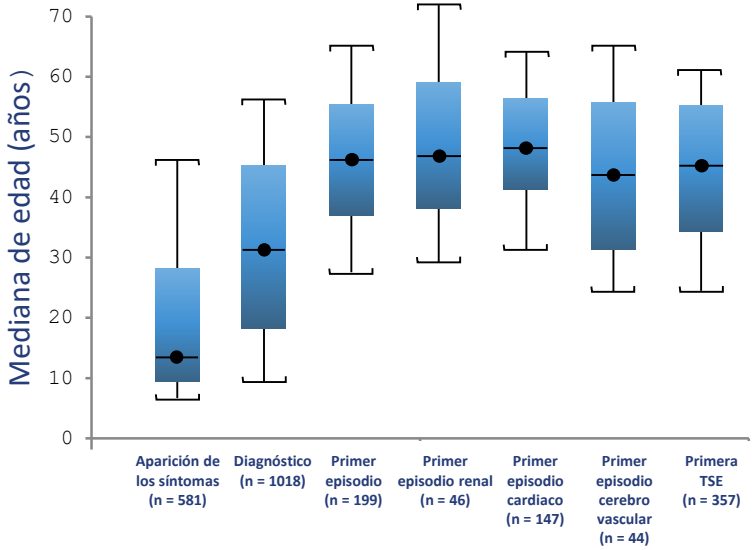
Hombres



Hombres (n = 778)

14,2 años
Media del tiempo desde la aparición de los síntomas hasta el diagnóstico

Mujeres



Mujeres (n = 473)

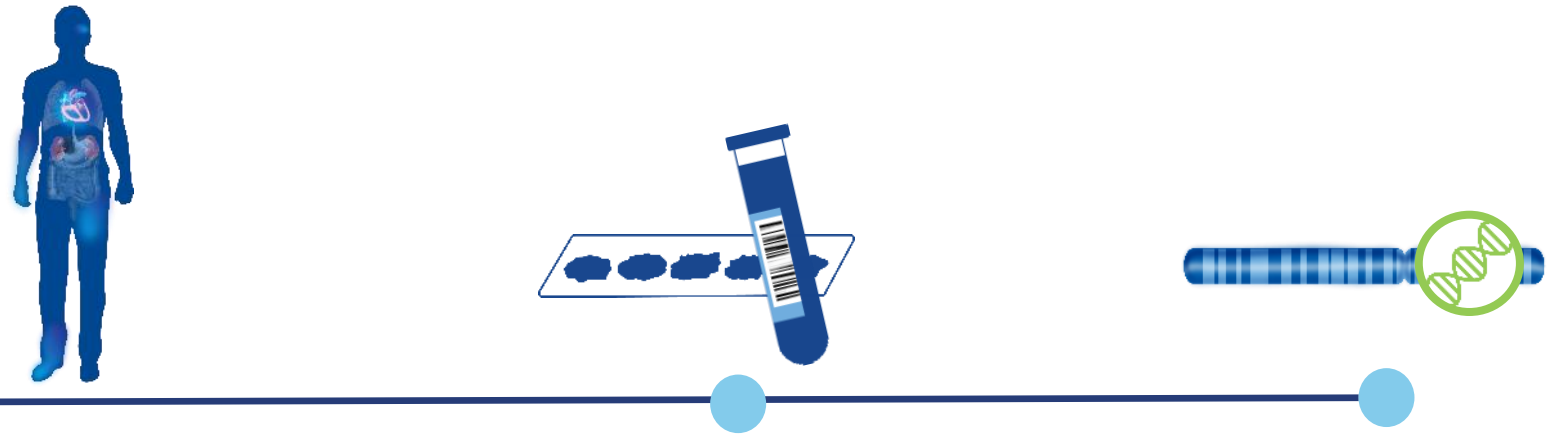
15,7 años
Media del tiempo desde la aparición de los síntomas hasta el diagnóstico

Extraído de de Wilcox WR et al. *Mol Genet Metab.* 2008;93(2):119.

TSE: terapia de sustitución enzimático.

Wilcox WR et al. *Mol Genet Metab.* 2008;93(2):112-128 .

¿Cómo diagnosticar?



Clínicos[1]

- **Características principales**
  - Angioqueratomas
  - Acroparestesias
  - Córnea verticilada
  - Anhidrosis o hipohidrosis
  - Insuficiencia renal
  - Intolerancia al ejercicio, al frío o al calor
  - Hipertrofia cardiaca
- **Antecedentes familiares de enfermedad de Fabry**

Bioquímicos[1,2]

- **Nivel de α-Gal A en el plasma, leucocitos o GSC**
- **Liso-Gb_3 en el plasma, orina o leucocitos**
- **Gb3 en el plasma o la orina**

Genéticos[1-3]

- **Secuenciación completa o selectiva del *GLA***

Gb-3: globotriaosilceramida, liso-Gb3: globotriaosilesfingosina, GSC: gota de sangre seca.

1. Laney DA et al. *J Genet Couns*. 2013;22(5):555-564; **2.** Ortiz A et al. *Mol Genet Metab.* 2018;123(4):416-427; **3.** Mehta A and Hughes DA. In: Adam MP, Ardinger HH, Pagon RA, eds. *GeneReviews®*. Seattle, WA: University of Washington, Seattle;1993-2018. At: www.ncbi.nlm.nih.gov/books/NBK1292/. 11 de septiembre de 2018.

¿Cómo diagnosticar?

Nivel de α-Gal A en el plasma, leucocitos o GSC[1-3]

Análisis de la mutación del *GLA*[1,2,4]

Hombres

- La actividad de la α-Gal A muy reducida o indetectable en los leucocitos se considera el criterio de referencia para el diagnóstico[1, 2]
- La actividad residual es significativa en los pacientes que no presentan manifestaciones clínicas clásicas[1, 2]

- Confirma el diagnóstico[2, 4]
- Contribuye a establecer el fenotipo de la enfermedad[4]
- Descarta polimorfismos benignos que provoquen una disminución de la actividad de la α-Gal A[4]
- Ofrece información adicional para el pronóstico y tratamiento de la enfermedad[2]
- Proporciona información para la realización de pruebas a familiares en riesgo[4]

Mujeres

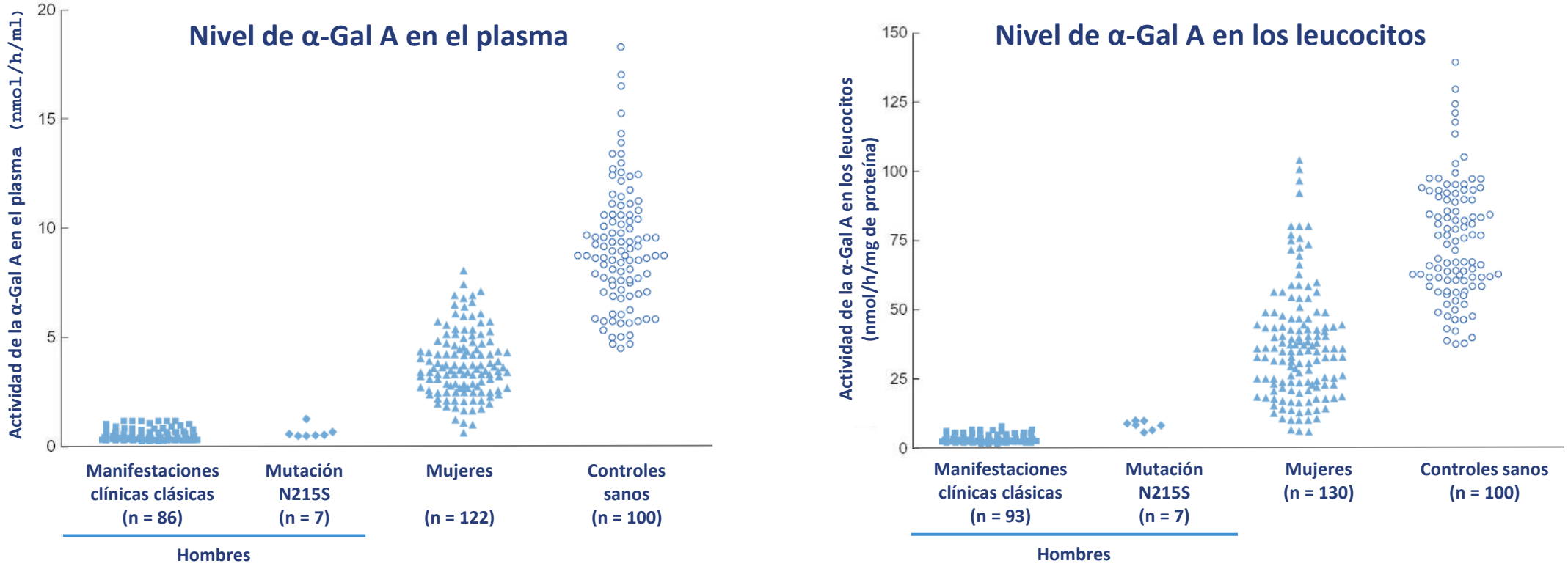
- Va desde el nivel reducido detectado en hombres al normal[3]
- **No sirve para el diagnóstico[2, 3]**

- **Necesario para el diagnóstico[1,2,4]**
- Contribuye a establecer el fenotipo de la enfermedad[4]
- Descarta polimorfismos benignos que provoquen una disminución de la actividad de la α-Gal A[4]
- Ofrece información para el pronóstico y tratamiento de la enfermedad[2]
- Proporciona información para la realización de pruebas a familiares en riesgo[4]

1. Gal A et al. *J Inherit Metab Dis*. 2011;34(2):509-514; **2.** Laney DA et al. *J Genet Couns*. 2013;22(5):555-564; **3.** Winchester B and Young E. In: Mehta A, Beck M, Sunder-Plassmann G, eds. *Fabry DIsease: Perspectives From 5 Years of FOS*. Oxford, UK: Oxford PharmaGenesis; 2006. At: www.ncbi.nlm.nih.gov/books/NBK11601/. Último acceso el 11 de septiembre de 2018; **4.** Ortiz A et al. *Mol Genet Metab.* 2018;123(4):416-427.

La actividad residual de la α-Gal A varía de un modo considerable en los pacientes con enfermedad de Fabry

Nivel de α-Gal A en pacientes con enfermedad de Fabry y controles sanos



Extraído de Winchester B and Young E. En: Mehta A, Beck M, Sunder-Plassmann G, eds. *Fabry Disease: Perspectives From 5 Years of FOS*. Oxford, UK: Oxford PharmaGenesis; 2006:3. En: www.ncbi.nlm.nih.gov/books/NBK11601/. Último acceso el 11 de septiembre de 2018.

Winchester B and Young E. In: Mehta A, Beck M, Sunder-Plassmann G, eds. *Fabry DIsease: Perspectives From 5 Years of FOS*. Oxford, UK: Oxford PharmaGenesis; 2006. At: www.ncbi.nlm.nih.gov/books/NBK11601/. Último acceso el 11 de septiembre de 2018.

La enfermedad de Fabry tiene tratamiento

- **Tratamiento enzimático sustitutivo**
- **Chaperonas farmacológicas (migalastat)**
- **Enfermedad de depósito→ factor tiempo es importante**

- **Tratamiento en la mujer:**
  - ✓ **Recomendaciones europeas de inicio de tratamiento específico separadas para hombres y mujeres.**
  - ✓ **Para mujeres, independientemente de si la mutación es clásica o no clásica, es necesario demostrar la presencia de signos o síntomas de EF (descartando otras causas).**
  - ✓ **Las mujeres están infratratadas (recomendaciones de consenso españolas de 2011).**

Sanchez *et al. Orphanet Journal of Rare Diseases (2023) 18:8* (https://doi.org/10.1186/s13023-022-02599-w)

Evidencia previa

International Journal of *Molecular Sciences*

MDPI

Article

Gender Differences in the Application of Spanish Criteria for Initiation of Enzyme Replacement Therapy for Fabry Disease in the Fabry Outcome Survey

Miguel-Ángel Barba-Romero [1,*] and Guillem Pintos-Morell [2] on behalf of The Spanish FOS Investigators [†]

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† Membership of The Spanish FOS Investigators is provided in the Acknowledgments.

Academic Editor: Ritva Tikkanen

Received: 2 August 2016; Accepted: 18 November 2016; Published: 24 November 2016

Abstract: Both male/female patients with Fabry disease (FD) may receive enzyme replacement therapy (ERT). Previously published analyses of the Fabry Outcome Survey (FOS; Shire-sponsored) database suggested gender differences in timing of ERT initiation. We assessed alignment of criteria for ERT initiation in the Spanish adult population included in FOS with recommendations of a Spanish national consensus. This retrospective analysis examined baseline clinical data of 88 adults (49 females) enrolled in the FOS database up to August 2014. Thirty-five (39.8%) patients were not receiving ERT: five (12.8%) males and 30 (61.2%) females. Baseline disease severity on the FOS-derived Mainz Severity Score Index was lower in untreated males (median (interquartile range), 0.0 (0.0–1.0)) than treated males (TM; 15.0 (7.5–26.5)), and was similar in untreated and treated females. The percentage of untreated females with at least one criterion for treatment initiation was 76.7% versus 100.0% of treated females ($p = 0.0340$) and 97.1% ($p = 0.0210$) of TM. In discordance with Spanish consensus recommendations, a substantial number of females with evidence of FD who might benefit from ERT have not yet initiated treatment. These results suggest unequal gender perceptions with respect to ERT initiation in Spain.

Keywords: agalsidase alfa; enzyme replacement therapy; Fabry disease; Fabry Outcome Survey (FOS); gender differences; Spain; women

1. Introduction

Fabry disease (FD) is a rare inherited X-linked metabolic disease secondary to reduction/absence of lysosomal α-galactosidase A activity. As a result, a progressive accumulation of globotriaosylceramide (Gb_3) and related glycosphingolipids within lysosomes is believed to produce cellular changes that progressively affect multiple organ systems, determining a natural disease evolution ranging from an asymptomatic status in the first years of life to different clinical presentations with increasing age. FD in adults has a wide variety of phenotypes, from the "classical" severe form in males to a seemingly asymptomatic course in some females. Owing to the X-linked nature of the disease and the potential for skewed X-chromosome inactivation, females can have normal α-galactosidase A activity in plasma/leukocytes with variable signs and symptoms of FD [1,2]. Most heterozygous females develop symptoms with vital organ involvement, usually later than males [1]. FD manifestations may include neuropathic pain, gastrointestinal disturbances, angiokeratomas, hypohidrosis, kidney dysfunction,

Lenders *et al. Orphanet Journal of Rare Diseases* (2016) 11:88
DOI 10.1186/s13023-016-0473-4

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Multicenter Female Fabry Study (MFFS) - clinical survey on current treatment of females with Fabry disease

Malte Lenders[1], Julia B. Hennermann[2], Christine Kurschat[3], Arndt Rolfs[4], Sima Canaan-Kühl[5], Claudia Sommer[6,7], Nurcan Üçeyler[6,7], Christoph Kampmann[2], Nesrin Karabul[2,8], Anne-Katrin Giese[4], Thomas Duning[9], Jörg Stypmann[10], Johannes Krämer[7,11], Frank Weidemann[7,12], Stefan-Martin Brand[13], Christoph Wanner[7] and Eva Brand[1*]

Abstract

Background: The aim of the present study was to assess manifestations of and applied treatment concepts for females with Fabry disease (FD) according to the current European Fabry Guidelines.

Methods: Between 10/2008 and 12/2014, data from the most recent visit of 261 adult female FD patients from six German Fabry centers were retrospectively analyzed. Clinical presentation and laboratory data, including plasma lyso-Gb3 levels were assessed.

Results: Fifty-five percent of females were on enzyme replacement therapy (ERT), according to recent European FD guidelines. Thirty-three percent of females were untreated although criteria for ERT initiation were fulfilled. In general, the presence of left ventricular hypertrophy (LVH) seemed to impact more on ERT initiation than impaired renal function. In ERT-naïve females RAAS blockers were more often prescribed if LVH was present rather than albuminuria. Affected females with missense mutations showed a similar disease burden compared to females with nonsense mutations. Elevated plasma lyso-Gb3 levels in ERT-naïve females seem to be a marker of disease burden, since patients showed comparable incidences of organ manifestations even if they were ~8 years younger than females with normal lyso-Gb3 levels.

Conclusion: The treatment of the majority of females with FD in Germany is in line with the current European FD guidelines. However, a relevant number of females remain untreated despite organ involvement, necessitating a careful reevaluation of these females.

Keywords: Fabry disease, Females, Lyso-Gb3, Enzyme replacement therapy, Guidelines

Background

Fabry disease (FD; OMIM #301500) is an X-linked (Xq22.1) inborn error of glycosphingolipid degradation resulting from deficient α-galactosidase A activity (GLA; 300644) due to mutations in the *GLA* gene. Fabry-specific manifestations result from systemic lysosomal accumulation of mainly globotriaosylceramide (Gb3) [1]. Gb3 accumulation in cells of different tissues is accompanied by a high risk of early onset of stroke, life-threatening arrhythmia, myocardial infarction, or cardiac and renal failure, leading to a reduced life expectancy [1]. Enzyme replacement therapy (ERT) with recombinant GLA, including agalsidase-alfa (Replagal, Shire) and agalsidase-beta (Fabrazyme, Genzyme) results in subcellular Gb3 clearance, leading to stabilization or at least slowing of disease progression in males and females [2–11]. While the onset of first symptoms (Fabry-associated pain, angiokeratoma, abdominal pain, cornea verticillata, hypo- or anhidrosis) in affected hemizygous males with low or absent enzymatic GLA activity starts in early childhood, heterozygous female

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Received: 15 January 2019 | Revised: 9 July 2019 | Accepted: 12 July 2019
DOI: 10.1002/jmd2.12071

RESEARCH REPORT

JIMD Reports | SSIEM WILEY

The clinical profiles of female patients with Fabry disease in Latin America: A Fabry Registry analysis of natural history data from 169 patients based on enzyme replacement therapy status

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[5]Instituto de Genética Humana, Facultad de Medicina, Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Bogota, Colombia

[6]National Dialysis Coordinator of Social Security of Panama, Panama City, Panama

[7]Sanofi Genzyme, Cambridge, Massachusetts

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Communicating Editor: Roberto Giugliani

Funding information
Sanofi Genzyme

Abstract

Background: Fabry disease is an X-linked lysosomal storage disorder with heterogeneous clinical expression in female patients ranging from asymptomatic to severe clinical presentations as in classic males. We assessed clinical profiles and compared natural history data of female patients eventually initiated on enzyme replacement therapy ("ERT-recipients") with those remaining untreated ("ERT-naïve").

Methods: We analyzed Fabry Registry data from 93 ERT-recipients, collected prior to ERT initiation, and 76 ERT-naïve females with classic or unclassified phenotypes from four Latin American countries and evaluated Fabry symptoms, interventricular septum thickness, left ventricular posterior wall thickness, estimated glomerular filtration rate, and severe clinical events.

Results: For 169 patients with available data, median age of first Fabry symptom manifestation was 12.7 years with peripheral pain as predominant first symptom, and diagnostic delay of 10.3 years from the first reported symptom. Female patients had high symptomatic burden during natural history follow-up, with 83% reporting peripheral pain, 69%-79% cold/heat intolerance or abnormal sweating, and 32% gastrointestinal symptoms. ERT-recipients reported similar age at first symptom as ERT-naïve patients but they were older at diagnosis (median 39.2 vs 24.4 years, $P < .01$) and last follow-up (median 43.4 vs 28.2 years, $P < .01$). Reported Fabry symptom frequencies and abnormal echocardiography findings were higher in ERT-recipients. Functional renal assessments were normal and similar.

Conclusions: Female patients from Latin America have notable diagnostic delays and high symptomatic burden. ERT was prescribed late in females with advanced age at diagnosis and advanced disease. There remained many female patients who had been diagnosed at younger age, had substantial Fabry manifestations, but did not receive disease-specific treatment.

ESTUDIO MUJER FABRY

ESTUDIO OBSERVACIONAL RETROSPECTIVO PARA DESCRIBIR EL FENOTIPO DE MUJERES CON VARIANTES GENÉTICAS ASOCIADAS A ENFERMEDAD DE FABRY EN ESPAÑA

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The Spanish Fabry women study: a retrospective observational study describing the phenotype of females with GLA variants

Rosario Sánchez, Tomas Ripoll-Vera, Manuel López-Mendoza, Joaquín de Juan-Ribera, Juan Ramon Gimeno, Alvaro Hermida, María Aurora Ruz-Zafra, José Vicente Torregrosa, Antonia Mora, José Manuel García-Pinilla, Elena Fortuny, Ana Aguinaga-Barrilero and Roser Torra. The Spanish Fabry women study: a retrospective observational study describing the phenotype of females with *GLA* variants.

Orphanet Journal of Rare Diseases (2023) 18:8

Diseño del estudio

- Retrospectivo

- 97 mujeres (≥16 años) con variante *GLA*.
- 12 hospitales en España
- Multidisciplinar

HUSE actualmente 24 pacientes con E de Fabry **(12 mujeres)**

Objetivos

- Principal

  - Describir retrospectivamente una cohorte española de mujeres con variante del gen GLA.

- Secundarios

  - Determinar las diferencias clínicas entre subgrupos en función de características como edad, tipo de variante genética, actividad α-Gal A y nivel de liso-Gb3 plasmática.

  - Diferencias por inicio de tratamiento específico o no, y factores que conducen al inicio de tratamiento.

LPE, last Patient evaluation

Sanchez *et al. Orphanet Journal of Rare Diseases (2023) 18:8* (https://doi.org/10.1186/s13023-022-02599-w)

Características basales

Table 1 Demographic and baseline disease characteristics

Patient characteristics	Overall N = 97	Type of variant regarding associated phenotype			Treatment status		
		Classic N = 39	Non-classic N = 52	*P* value	Treated N = 33	Untreated N = 64	*P* value
Age at study inclusion, years				0.683[b]			0.127[b]
Median (range)	50.0 (16–84)	51.0 (16–81)	50.5 (19–84)		52.0 (16–79)	45.5 (16–84)	
Mean (SD)	50.1 (17.2)	49.3 (17.2)	50.8 (17.6)		53.8 (14.8)	48.2 (18.1)	
Identification of the mutation, n (%)				0.071[c]			**0.016[c]**
Family screening	68 (70.1)	24 (61.5)	41 (78.9)		18 (54.6)	50 (78.1)	
Clinical signs/symptoms	29 (29.9)	15 (38.5)	11 (21.2)		15 (45.5)	14 (21.9)	
Type of variant regarding associated phenotype, n (%)				**< 0.001[d]**			< 0.001[d]
Classic	39 (40.2)	39 (100.0)	0 (0.0)		23 (69.7)	16 (25.0)	
Non-classic	52 (53.6)	0 (0.0)	52 (100.0)		8 (24.2)	44 (68.8)	
VUS	6 (6.2)	0 (0.0)	0 (0.0)		2 (6.1)	4 (6.3)	
Plasma Lyso-Gb3 levels, n (%)	48 (49.5)	12 (30.8)	33 (63.5)		14 (42.4)	34 (53.1)	
Median (range), ng/mL	2.4 (1–11)	6.5 (3–11)	1.8 (1–11)	**< 0.001[a]**	6.5 (1–11)	1.8 (1–5)	**< 0.001[a]**
Mean (SD), ng/mL	3.4 (2.6)	6.4 (2.2)	2.5 (1.8)		6.1 (3.0)	2.3 (1.2)	
Elevated, n (%)	24 (50.0)	12 (100.0)	12 (36.4)	**< 0.001[c]**	13 (92.9)	11 (32.4)	**< 0.001[c]**
α -Gal A activity, n (%)	29 (29.9)	10 (25.6)	16 (30.8)		14 (42.4)	15 (23.4)	
Decreased[a], n (%)	15 (51.7)	6 (60.0)	9 (56.3)	1.000[d]	9 (64.3)	6 (42.9)	0.256[c]
Any comorbidity, n (%)	53 (54.6)	19 (48.7)	30 (57.7)	0.395[c]	23 (69.7)	30 (46.9)	**0.032[c]**
Most frequent comorbidities, n (%)							
Arterial hypertension	25 (25.8)	11 (28.2)	13 (25.0)		14 (42.2)	11 (17.2)	
Diabetes mellitus	7 (7.2)	3 (7.7)	4 (7.7)		1 (3.0)	6 (9.4)	
Obesity	6 (6.2)	1 (2.6)	4 (7.7)		3 (9.1)	3 (4.7)	
Fibromyalgia	3 (3.1)	2 (5.1)	1 (1.9)		2 (6.1)	1 (1.6)	
Genetic variant, n (%)				**< 0.001[d]**			**< 0.001[d]**
Nonsense	7 (7.2)	5 (12.8)	2 (3.9)		6 (18.2)	1 (1.6)	
Missense	84 (86.6)	28 (71.8)	50 (96.2)		23 (69.7)	61 (95.3)	
Deletion	1 (1.0)	1 (2.6)	0 (0.0)		1 (3.0)	0 (0.0)	
Frameshift	5 (5.2)	5 (12.8)	0 (0.0)		3 (9.1)	2 (3.1)	

Tiempo medio de seguimiento desde identificación de *GLA* hasta la última visita o muerte fue 52,9 (47,9) meses (mediana 36,1 [3–226])

- 70% de mujeres con variante *GLA* se identificaron por **cribado familiar**
- De las mujeres que recibieron tratamiento, 54,6% se diagnosticaron por **cribado familiar**. Curiosamente, de las mujeres identificadas por **sospecha clínica,** 48,3% no recibieron tratamiento.

Sanchez *et al. Orphanet Journal of Rare Diseases (2023) 18:8*

Características basales

Table 1 Demographic and baseline disease characteristics

Patient characteristics	Overall N = 97	Type of variant regarding associated phenotype			Treatment status		
		Classic N = 39	Non-classic N = 52	*P* value	Treated N = 33	Untreated N = 64	*P* value
Age at study inclusion, years				0.683[b]			0.127[b]
Median (range)	50.0 (16–84)	51.0 (16–81)	50.5 (19–84)		52.0 (16–79)	45.5 (16–84)	
Mean (SD)	50.1 (17.2)	49.3 (17.2)	50.8 (17.6)		53.8 (14.8)	48.2 (18.1)	
Identification of the mutation, n (%)				0.071[c]			**0.016[c]**
Family screening	68 (70.1)	24 (61.5)	41 (78.9)		18 (54.6)	50 (78.1)	
Clinical signs/symptoms	29 (29.9)	15 (38.5)	11 (21.2)		15 (45.5)	14 (21.9)	
Type of variant regarding associated phenotype, n (%)				**< 0.001[d]**			< 0.001[d]
Classic	39 (40.2)	39 (100.0)	0 (0.0)		23 (69.7)	16 (25.0)	
Non-classic	52 (53.6)	0 (0.0)	52 (100.0)		8 (24.2)	44 (68.8)	
VUS	6 (6.2)	0 (0.0)	0 (0.0)		2 (6.1)	4 (6.3)	
Plasma Lyso-Gb3 levels, n (%)	48 (49.5)	12 (30.8)	33 (63.5)		14 (42.4)	34 (53.1)	
Median (range), ng/mL	2.4 (1–11)	6.5 (3–11)	1.8 (1–11)	**< 0.001[a]**	6.5 (1–11)	1.8 (1–5)	**< 0.001[a]**
Mean (SD), ng/mL	3.4 (2.6)	6.4 (2.2)	2.5 (1.8)		6.1 (3.0)	2.3 (1.2)	
Elevated, n (%)	24 (50.0)	12 (100.0)	12 (36.4)	**< 0.001[c]**	13 (92.9)	11 (32.4)	**< 0.001[c]**
α -Gal A activity, n (%)	29 (29.9)	10 (25.6)	16 (30.8)		14 (42.4)	15 (23.4)	
Decreased[a], n (%)	15 (51.7)	6 (60.0)	9 (56.3)	1.000[d]	9 (64.3)	6 (42.9)	0.256[c]
Any comorbidity, n (%)	53 (54.6)	19 (48.7)	30 (57.7)	0.395[c]	23 (69.7)	30 (46.9)	**0.032[c]**
Most frequent comorbidities, n (%)							
Arterial hypertension	25 (25.8)	11 (28.2)	13 (25.0)		14 (42.2)	11 (17.2)	
Diabetes mellitus	7 (7.2)	3 (7.7)	4 (7.7)		1 (3.0)	6 (9.4)	
Obesity	6 (6.2)	1 (2.6)	4 (7.7)		3 (9.1)	3 (4.7)	
Fibromyalgia	3 (3.1)	2 (5.1)	1 (1.9)		2 (6.1)	1 (1.6)	
Genetic variant, n (%)				**< 0.001[d]**			**< 0.001[d]**
Nonsense	7 (7.2)	5 (12.8)	2 (3.9)		6 (18.2)	1 (1.6)	
Missense	84 (86.6)	28 (71.8)	50 (96.2)		23 (69.7)	61 (95.3)	
Deletion	1 (1.0)	1 (2.6)	0 (0.0)		1 (3.0)	0 (0.0)	
Frameshift	5 (5.2)	5 (12.8)	0 (0.0)		3 (9.1)	2 (3.1)	

- **Liso-Gb3 plasmática** aumentada en todas las mujeres con variante clásica, y en la mayoría de tratadas.
- Diferente de las no clásicas y no tratadas (P<0,001)
- No hubo diferencias en actividad enzimática (N 29)

Los hallazgos apuntan al tipo de variante como influyente en el inicio de tratamiento

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Variantes *GLA (29 diferentes)*

Table 2 Genetic variants

	Genetic mutation	Variant	Associated phenotype	n (%)
	p.Ala143Thr (c.427G>A)	Missense	VUS	2 (2.1)
	p.Asp313Gly (c.938A>G)	Missense	Classic	4 (4.1)
	p.Asp313Tyr/p.Gly411Asp (c.937G>T; 1232G>A)	Missense	Classic	1 (1.0)
	p.Gly147Glu (c.440G>A)	Missense	Classic	1 (1.0)
	p.Gly373Asp (c.1118G>A)	Missense	Classic	1 (1.0)
	p.Gly411Asp (c.1232G>A)	Missense	Classic	1 (1.0)
	p.Ile270Thr (c.809T>C)	Missense	Classic	1 (1.0)
	p.Lys185* (c.553A>T)	Nonsense	Classic[a]	1 (1.0)
3	p.Met187Arg (c.560T>G)	Missense	Classic	9 (9.3)
	p.Met187Thr (c.560T>C)	Missense	Classic	1 (1.0)
	p.Met290Ile (c.870G>A o c.870G>C o c.870G>T)	Missense	Non-classic[a]	3 (3.1)
	p.Met290Thr (c.869T>C)	Missense	Classic[a]	2 (2.1)
	Other: c.9_19del	Frameshift	Classic[a]	3 (3.1)
	Other: p.Gly163* (c.487 G>T)	Nonsense	Non-classic[a]	2 (2.1)
	p.Gln119* (c.355C>T)	Nonsense	Classic	1 (1.0)
	p.Gln250Pro (c.749A>C)	Missense	Classic	5 (5.2)
	p.Arg118Cys (c.352C>T)	Missense	VUS	3 (3.1)
	p.Arg227* (c.679C>T)	Nonsense	Classic	1 (1.0)
2	p.Arg301Gln (c.902G>A)	Missense	Non-classic	10 (10.3)
	p.Arg363His (c.1088G>A)	Missense	Non-classic	1 (1.0)
	p.Ser126Gly (c.376A>G)	Missense	VUS	1 (1.0)
1	p.Ser238Asn (c.713G>A)	Missense	Non-classic	36 (37.1)
	p.Trp162Gly (c.484T>G)	Missense	Classic	1 (1.0)
	p.Trp262* (c.785G>A o c.786G>A)	Nonsense	Classic	1 (1.0)
	p.Trp81Ser (c.242G>C)	Missense	Classic	1 (1.0)
	p.Trp95* (c.284G>A o c.285G>A)	Nonsense	Classic	1 (1.0)
	p.358delGlu (c.1072_1074del)	Deletion	Classic	1 (1.0)
	p.Ala368delinsFYfs*23 (c.1102delGinsTTATAC)	Frameshift	Classic[a]	1 (1.0)
	p.Lys426Argfs*23 (c.1277_1278del)	Frameshift	Classic	1 (1.0)

Excluidas mujeres con VUS (n=6)

Variantes más frecuentes

1. pSer238Asn (37,1%)
2. pArg301Gln (10,3%)
3. pMet187Arg (9,3%)

Sanchez *et al. Orphanet Journal of Rare Diseases (2023) 18:8* (https://doi.org/10.1186/s13023-022-02599-w)

Afectación clínica

Sugiere que mujeres con variante patogénica de EF, independientemente del tipo, desarrollarán enfermedad probablemente en un alto porcentaje de los casos.

Table 3 Female signs and symptoms at diagnosis or at last assessment (females with VUS excluded)

Type of signs or symptoms	Total N = 91	Type of variant regarding associated phenotype			Treatment status		
		Classic N = 39	Non-classic N = 52	*P* value	Treated N = 31	Untreated N = 60	*P* value
Any[a]	76 (83.5)	36 (92.3)	40 (76.9)	0.050[d]	30 (96.8)	46 (76.7)	**0.014**[d]
Peripheral nervous system	32 (35.2)	22 (56.4)	10 (19.2)	**< 0.001**[d]	15 (48.3)	17 (28.3)	0.058[d]
Neuropathic pain	21 (23.1)	18 (46.2)	3 (5.8)		8 (25.8)	13 (21.7)	
Acroparesthesia	21 (23.1)	16 (41.0)	5 (9.6)		13 (41.9)	8 (13.3)	
Heat/cold intolerance	6 (6.6)	6 (15.4)	0 (0.0)		5 (16.1)	1 (1.7)	
Sickness	8 (8.8)	6 (15.4)	2 (3.9)		2 (6.5)	6 (10.0)	
Dizziness	4 (4.4)	2 (5.1)	2 (3.9)		0 (0.0)	4 (6.7)	
Tinnitus	3 (3.3)	3 (7.7)	0 (0.0)		1 (3.2)	2 (3.3)	
Hypoacusia	9 (9.9)	8 (20.5)	1 (1.9)		4 (12.9)	5 (8.3)	
Ophthalmological	35 (38.5)	25 (64.1)	10 (19.2)	**< 0.001**[d]	20 (64.5)	15 (25.0)	**< 0.001**[d]
Cornea verticillata	27 (29.7)	24 (61.5)	3 (5.8)		18 (58.1)	9 (15.0)	
Retinal vasculopathy	5 (5.5)	4 (10.3)	1 (1.9)		3 (9.7)	2 (3.3)	
Cataracts	6 (6.6)	0 (0.0)	6 (11.5)		1 (3.2)	5 (8.3)	
Dry eyes	3 (3.3)	1 (2.6)	2 (3.9)		2 (6.5)	1 (1.7)	
Cardiac	45 (49.5)	24 (61.5)	21 (40.4)	**0.046**[d]	23 (74.2)	22 (36.7)	**0.001**[d]
LVH	35 (38.5)	19 (48.7)	16 (30.8)		20 (64.5)	15 (25.0)	
Dyspnoea	10 (11.0)	7 (18.0)	3 (5.8)		4 (12.9)	6 (10.0)	
Reduced exercise tolerance	9 (9.9)	6 (15.4)	3 (5.8)		2 (6.5)	7 (11.7)	
Syncope	5 (5.5)	5 (12.8)	0 (0.0)		1 (3.2)	4 (6.7)	
Gadolinium retention on MRI[b]	2 (2.2)	1 (2.6)	1 (1.9)		1 (3.2)	1 (1.7)	
Heart failure	8 (8.8)	6 (15.4)	2 (3.9)		4 (12.9)	4 (6.7)	
Bradycardia	5 (5.5)	4 (10.3)	1 (1.9)		2 (6.5)	3 (5.0)	
Auricular fibrillation	2 (2.2)	1 (2.6)	1 (1.9)		1 (3.2)	1 (1.7)	
Ventricular tachycardia	4 (4.4)	2 (5.1)	2 (3.9)		1 (3.2)	3 (5.0)	
Sudden cardiac death	1 (1.1)	1 (2.6)	0 (0.0)		0 (0.0)	1 (1.7)	
Gastrointestinal	13 (14.3)	7 (18.0)	6 (11.5)	0.387[d]	7 (22.6)	6 (10.0)	0.122[e]
Dermatological (i.e., angiokeratoma)	11 (12.1)	7 (18.0)	4 (7.7)	0.195[d]	7 (22.6)	4 (6.7)	**0.041**[e]
Renal	18 (19.8)	8 (20.5)	10 (19.2)	0.879[d]	7 (22.6)	11 (18.3)	0.630[d]
Alburninuria	5 (5.5)	3 (7.7)	2 (3.9)		1 (3.2)	4 (6.7)	
Proteinuria	10 (11.0)	5 (12.8)	5 (9.6)		5 (16.1)	5 (8.3)	
Decreased GFR	7 (7.7)	2 (5.1)	5 (9.6)		2 (6.5)	5 (8.3)	
Dialysis	2 (2.2)	1 (2.6)	1 (1.9)		1 (3.2)	1 (1.7)	
Kidney transplant	1 (1.1)	1 (2.6)	0 (0.0)		1 (3.2)	0 (0.0)	
Cerebrovascular	10 (11.0)	8 (20.5)	2 (3.9)	**0.017**[e]	7 (22.6)	3 (5.0)	**0.028**[e]
White matter lesion on MRI[c]	2 (2.2)	2 (5.1)	0 (0.0)		2 (6.5)	0 (0.0)	
TIA	2 (2.2)	2 (5.1)	0 (0.0)		1 (3.2)	1 (1.7)	
Stroke	3 (3.3)	2 (5.1)	1 (1.9)		2 (6.5)	1 (1.7)	

- Un total de 76 (83,5%) pacientes tuvieron signos o síntomas clínicos.
- **Mujeres con variante clásica** tuvieron mayor carga de enfermedad.
- Mujeres del subgrupo **no clásico** también tuvieron alta prevalencia de signos y síntomas.

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Afectación clínica

Específicamente en mujeres:

- ✓ Dificultad para demostrar de manera objetiva estos síntomas
- ✓ Dificultad para atribuirlos específicamente a E de Fabry (comorbilidades, edad)
- ✓ Sesgo histórico de género

Afectación clínica

Table 3 Female signs and symptoms at diagnosis or at last assessment (females with VUS excluded)

Type of signs or symptoms		Total N = 91	Type of variant regarding associated phenotype			Treatment status		
			Classic N = 39	Non-classic N = 52	*P* value	Treated N = 31	Untreated N = 60	*P* value
Any[a]		76 (83.5)	36 (92.3)	40 (76.9)	0.050[d]	30 (96.8)	46 (76.7)	**0.014**[d]
Peripheral nervous system	3	32 (35.2)	22 (56.4)	10 (19.2)	**< 0.001**[d]	15 (48.3)	17 (28.3)	0.058[d]
Neuropathic pain		21 (23.1)	18 (46.2)	3 (5.8)		8 (25.8)	13 (21.7)	
Acroparesthesia		21 (23.1)	16 (41.0)	5 (9.6)		13 (41.9)	8 (13.3)	
Heat/cold intolerance		6 (6.6)	6 (15.4)	0 (0.0)		5 (16.1)	1 (1.7)	
Sickness		8 (8.8)	6 (15.4)	2 (3.9)		2 (6.5)	6 (10.0)	
Dizziness		4 (4.4)	2 (5.1)	2 (3.9)		0 (0.0)	4 (6.7)	
Tinnitus		3 (3.3)	3 (7.7)	0 (0.0)		1 (3.2)	2 (3.3)	
Hypoacusia		9 (9.9)	8 (20.5)	1 (1.9)		4 (12.9)	5 (8.3)	
Ophthalmological	2	35 (38.5)	25 (64.1)	10 (19.2)	**< 0.001**[d]	20 (64.5)	15 (25.0)	**< 0.001**[d]
Cornea verticillata		27 (29.7)	24 (61.5)	3 (5.8)		18 (58.1)	9 (15.0)	
Retinal vasculopathy		5 (5.5)	4 (10.3)	1 (1.9)		3 (9.7)	2 (3.3)	
Cataracts		6 (6.6)	0 (0.0)	6 (11.5)		1 (3.2)	5 (8.3)	
Dry eyes		3 (3.3)	1 (2.6)	2 (3.9)		2 (6.5)	1 (1.7)	
Cardiac	1	45 (49.5)	24 (61.5)	21 (40.4)	**0.046**[d]	23 (74.2)	22 (36.7)	**0.001**[d]
LVH		35 (38.5)	19 (48.7)	16 (30.8)		20 (64.5)	15 (25.0)	
Dyspnoea		10 (11.0)	7 (18.0)	3 (5.8)		4 (12.9)	6 (10.0)	
Reduced exercise tolerance		9 (9.9)	6 (15.4)	3 (5.8)		2 (6.5)	7 (11.7)	
Syncope		5 (5.5)	5 (12.8)	0 (0.0)		1 (3.2)	4 (6.7)	
Gadolinium retention on MRI[b]		2 (2.2)	1 (2.6)	1 (1.9)		1 (3.2)	1 (1.7)	
Heart failure		8 (8.8)	6 (15.4)	2 (3.9)		4 (12.9)	4 (6.7)	
Bradycardia		5 (5.5)	4 (10.3)	1 (1.9)		2 (6.5)	3 (5.0)	
Auricular fibrillation		2 (2.2)	1 (2.6)	1 (1.9)		1 (3.2)	1 (1.7)	
Ventricular tachycardia		4 (4.4)	2 (5.1)	2 (3.9)		1 (3.2)	3 (5.0)	
Sudden cardiac death		1 (1.1)	1 (2.6)	0 (0.0)		0 (0.0)	1 (1.7)	
Gastrointestinal		13 (14.3)	7 (18.0)	6 (11.5)	0.387[d]	7 (22.6)	6 (10.0)	0.122[e]
Dermatological (i.e., angiokeratoma)		11 (12.1)	7 (18.0)	4 (7.7)	0.195[d]	7 (22.6)	4 (6.7)	**0.041**[e]
Renal	4	18 (19.8)	8 (20.5)	10 (19.2)	0.879[d]	7 (22.6)	11 (18.3)	0.630[d]
Albuminuria		5 (5.5)	3 (7.7)	2 (3.9)		1 (3.2)	4 (6.7)	
Proteinuria		10 (11.0)	5 (12.8)	5 (9.6)		5 (16.1)	5 (8.3)	
Decreased GFR		7 (7.7)	2 (5.1)	5 (9.6)		2 (6.5)	5 (8.3)	
Dialysis		2 (2.2)	1 (2.6)	1 (1.9)		1 (3.2)	1 (1.7)	
Kidney transplant		1 (1.1)	1 (2.6)	0 (0.0)		1 (3.2)	0 (0.0)	
Cerebrovascular		10 (11.0)	8 (20.5)	2 (3.9)	**0.017**[e]	7 (22.6)	3 (5.0)	**0.028**[e]
White matter lesion on MRI[c]		2 (2.2)	2 (5.1)	0 (0.0)		2 (6.5)	0 (0.0)	
TIA		2 (2.2)	2 (5.1)	0 (0.0)		1 (3.2)	1 (1.7)	
Stroke		3 (3.3)	2 (5.1)	1 (1.9)		2 (6.5)	1 (1.7)	

Prevalencia de afectación de órganos

Tipo de signos y síntomas	%
Cardiaco	49,5%
Oftalmológico	38,5%
SNP	35,2%
Renal	19,8%
Gastrointestinal	14,3%
Angioqueratoma	12,1%
Cerebrovascular	11,0%

Sanchez *et al. Orphanet Journal of Rare Diseases (2023) 18:8* (https://doi.org/10.1186/s13023-022-02599-w)

Afectación clínica

Table 3 Female signs and symptoms at diagnosis or at last assessment (females with VUS excluded)

Type of signs or symptoms		Total N = 91	Type of variant regarding associated phenotype			Treatment status		
			Classic N = 39	Non-classic N = 52	*P* value	Treated N = 31	Untreated N = 60	*P* value
Any[a]		76 (83.5)	36 (92.3)	40 (76.9)	0.050[d]	30 (96.8)	46 (76.7)	**0.014**[d]
Peripheral nervous system	3	32 (35.2)	22 (56.4)	10 (19.2)	**< 0.001**[d]	15 (48.3)	17 (28.3)	0.058[d]
Neuropathic pain		21 (23.1)	18 (46.2)	3 (5.8)		8 (25.8)	13 (21.7)	
Acroparesthesia		21 (23.1)	16 (41.0)	5 (9.6)		13 (41.9)	8 (13.3)	
Heat/cold intolerance		6 (6.6)	6 (15.4)	0 (0.0)		5 (16.1)	1 (1.7)	
Sickness		8 (8.8)	6 (15.4)	2 (3.9)		2 (6.5)	6 (10.0)	
Dizziness		4 (4.4)	2 (5.1)	2 (3.9)		0 (0.0)	4 (6.7)	
Tinnitus		3 (3.3)	3 (7.7)	0 (0.0)		1 (3.2)	2 (3.3)	
Hypoacusia		9 (9.9)	8 (20.5)	1 (1.9)		4 (12.9)	5 (8.3)	
Ophthalmological	2	35 (38.5)	25 (64.1)	10 (19.2)	**< 0.001**[d]	20 (64.5)	15 (25.0)	**< 0.001**[d]
Cornea verticillata		27 (29.7)	24 (61.5)	3 (5.8)		18 (58.1)	9 (15.0)	
Retinal vasculopathy		5 (5.5)	4 (10.3)	1 (1.9)		3 (9.7)	2 (3.3)	
Cataracts		6 (6.6)	0 (0.0)	6 (11.5)		1 (3.2)	5 (8.3)	
Dry eyes		3 (3.3)	1 (2.6)	2 (3.9)		2 (6.5)	1 (1.7)	
Cardiac	1	45 (49.5)	24 (61.5)	21 (40.4)	**0.046**[d]	23 (74.2)	22 (36.7)	**0.001**[d]
LVH		35 (38.5)	19 (48.7)	16 (30.8)		20 (64.5)	15 (25.0)	
Dyspnoea		10 (11.0)	7 (18.0)	3 (5.8)		4 (12.9)	6 (10.0)	
Reduced exercise tolerance		9 (9.9)	6 (15.4)	3 (5.8)		2 (6.5)	7 (11.7)	
Syncope		5 (5.5)	5 (12.8)	0 (0.0)		1 (3.2)	4 (6.7)	
Gadolinium retention on MRI[b]		2 (2.2)	1 (2.6)	1 (1.9)		1 (3.2)	1 (1.7)	
Heart failure		8 (8.8)	6 (15.4)	2 (3.9)		4 (12.9)	4 (6.7)	
Bradycardia		5 (5.5)	4 (10.3)	1 (1.9)		2 (6.5)	3 (5.0)	
Auricular fibrillation		2 (2.2)	1 (2.6)	1 (1.9)		1 (3.2)	1 (1.7)	
Ventricular tachycardia		4 (4.4)	2 (5.1)	2 (3.9)		1 (3.2)	3 (5.0)	
Sudden cardiac death		1 (1.1)	1 (2.6)	0 (0.0)		0 (0.0)	1 (1.7)	
Gastrointestinal		13 (14.3)	7 (18.0)	6 (11.5)	0.387[d]	7 (22.6)	6 (10.0)	0.122[e]
Dermatological (i.e., angiokeratoma)		11 (12.1)	7 (18.0)	4 (7.7)	0.195[d]	7 (22.6)	4 (6.7)	**0.041**[e]
Renal	4	18 (19.8)	8 (20.5)	10 (19.2)	0.879[d]	7 (22.6)	11 (18.3)	0.630[d]
Albuminuria		5 (5.5)	3 (7.7)	2 (3.9)		1 (3.2)	4 (6.7)	
Proteinuria		10 (11.0)	5 (12.8)	5 (9.6)		5 (16.1)	5 (8.3)	
Decreased GFR		7 (7.7)	2 (5.1)	5 (9.6)		2 (6.5)	5 (8.3)	
Dialysis		2 (2.2)	1 (2.6)	1 (1.9)		1 (3.2)	1 (1.7)	
Kidney transplant		1 (1.1)	1 (2.6)	0 (0.0)		1 (3.2)	0 (0.0)	
Cerebrovascular		10 (11.0)	8 (20.5)	2 (3.9)	**0.017**[e]	7 (22.6)	3 (5.0)	**0.028**[e]
White matter lesion on MRI[f]		2 (2.2)	2 (5.1)	0 (0.0)		2 (6.5)	0 (0.0)	
TIA		2 (2.2)	2 (5.1)	0 (0.0)		1 (3.2)	1 (1.7)	
Stroke		3 (3.3)	2 (5.1)	1 (1.9)		2 (6.5)	1 (1.7)	

Signos y síntomas predominantes

- Hipertrofia ventricular izquierda (38,5%)
- Córnea verticillata (29,7%)
- Dolor neuropático (23,1%)
- Acroparestesias (23,1%)

- Más % de afectación en las variantes clásicas y en las tratadas

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Afectación clínica

- Para demostrar **HVI**, papel FUNDAMENTAL de la RM cardiaca
  - ✓Evidencia creciente de que especialmente la mujer puede desarrollar fibrosis miocárdica sin HVI detectable
  - ✓RM parámetros de afectación precoz: VEC, T1 mapping, RGE
- A nivel **SNC** papel de la RM cerebral
- Otras afectaciones **(SNP, GI)** ¿cómo monitorizarlas?→subestimadas

Genes 2024, 15, 37. https://doi.org/10.3390/genes15010037

Eventos clínicos

- **11 (11,3%) de pacientes tuvieron eventos clínicos durante el seguimiento:**

  ✓Cerebrovascular → 4 ictus; 1 AIT; 1 nueva lesión de sustancia blanca

  ✓Cardiaco → 1 arritmia; 1 insuficiencia cardiaca congestiva; 2 intervenciones cardiacas

  ✓Renal → 1 empeoramiento de TFGe

- **3 pacientes murieron (3,1%)** (1 pancreatitis, 2 insuficiencia cardiaca).

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Factores de inicio de tratamiento

Table 4 Factors leading to treatment initiation (females with VUS excluded)

Factors	N = 31 n (%)
Neuropathic pain	6 (19.4)
Proteinuria	1 (3.2)
GFR decreased	1 (3.2)
Stroke	2 (6.5)
TIA	1 (3.2)
Cardiac disease	12 (38.7)
GI symptoms	1 (3.2)
Exercise intolerance and hypohidrosis	2 (6.5)
Lyso-Gb3 increased	1 (3.2)
Angiokeratoma	3 (9.7)
Other[a]	17 (54.8)

[a]Principalmente: detección de variante GLA (n=3), biopsia renal confirmatoria (n=3) y acroparestesias (n=2); otros factores seleccionados por los médicos incluyeron acceso al fármaco, α-Gal A disminuida, presencia de cornea verticillata, insuficiencia venosa crónica o microalbuminuria

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- La enfermedad cardiaca fue la causa más frecuente de inicio de tratamiento

Para reflexionar...

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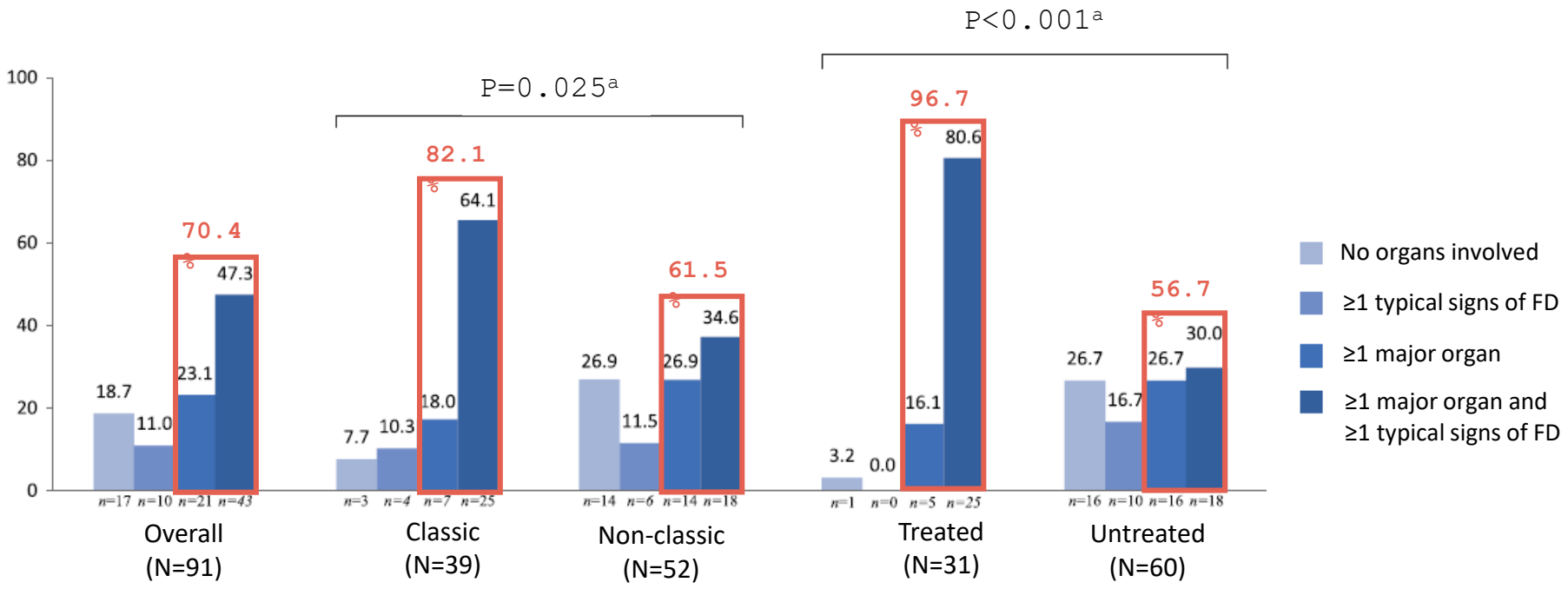

- ✓ 27 pacientes no tratadas presentaban al menos afectación renal, cardiaca o cerebrovascular, órganos resaltados en las recomendaciones europeas como indicativos de un potencial inicio de tratamiento específico

- ✓ No hubo diferencias en edad (p=0,8) o comorbilidades (p=0,8) entre tratadas y no tratadas con al menos un órgano principal afectado.

Mensajes para llevar a casa

1. Las mujeres con E. Fabry **no son simples transmisoras** de la enfermedad
2. Un alto porcentaje **desarrollará enfermedad** (independientemente clásico/no clásico)
3. Afectación a nivel **cardiaco, oftalmológico y SNP**
4. La actividad enzimática no es útil. **Diagnóstico mediante genética**. Valores LysoGB3 elevados 50% (+ clásica).
5. Importancia de **diagnóstico precoz**. Cribado familiar
6. Seguimiento **estrecho** y evaluación **exhaustiva**
7. Nuevas **pruebas complementarias** para mejor detección de afectación
8. La enfermedad de Fabry tiene **tratamiento específico**→enfermedad de depósito
9. Para inicio de tratamiento en mujeres se debe **demostrar signos o síntomas de la E. Fabry**
10. Si bien se ha avanzado en el diagnóstico, hay **mucho margen de mejora** en el **tratamiento** de las mujeres con E. Fabry

Govern de les Illes Balears
Conselleria de Salut

II JORNADA DE L'ESTRATÈGIA MALALTIES MINORITÀRIES I COMPLEXES DE LES ILLES BALEARS

23 i 24 de maig de 2024

Sala d'actes de l'Hospital Universitari Son Espases, Palma.

Enfermedad de Fabry en la mujer ♀

GRACIAS

Son Espases
hospital universitari

Institut d'Investigació Sanitària Illes Balears
IdISBa