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Fabry disease in Spain. Description of Spanish patients and a comparison with other European countries using data from the Fabry Outcome Survey (FOS)

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ABSTRACT

Aims: Fabry disease (FD) is an X chromosome-linked transmitted lysosomal storage disorder due to the deficient activity of enzyme α -galactosidase A. This leads to accumulation of neutral glycosphingolipids associated with organ involvement and premature death. We report the clinical characteristics of Spanish patients enrolled on the Fabry Outcome Survey (FOS; an international multicentre registry for the disease) and also compare these data with those from the rest of Europe.

Methods: Baseline clinical data of 92 patients (41 males and 51 females) are described and analyzed globally and according to sex. We compare the data of Spanish patients with those previously published from the rest of Europe patients in FOS.

Results: Mean age of onset of symptoms in males was 20, and 24 years in females, with a mean delay to the diagnosis in both sexes of 11 years. The predominant clinical involvement in males was renal (69%), cardiac (66%) and neurological (60%). For females, was neurological (42%), cardiac (33%), keratopathy (30%) and nephropathy (28%). Disease severity was significantly higher in males. On comparing with the rest of European FOS-patients, Spanish patients were diagnosed at an earlier age with a smaller proportion of disease-related involvement for most organ irrespective of sex, though not is global severity in males.

Conclusions: We present the largest cohort of Spanish patients diagnosed with FD. The pattern of involvement (though not its global severity) could be different in Spanish patients in comparison with others from Europe. Expanding the knowledge of FD will permit early diagnosis as well as the possibility of starting the specific treatment.

KEY WORDS: Fabry disease; Fabry Outcome Survey; Spain; Europe.

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INTRODUCTION

Fabry disease (FD; Online Mendelian Inheritance in Man (OMIM) 301500) is a rare hereditary disease with X chromosome-linked transmission involving lysosomal deposits of sphingolipids originating from deficient activity of the lysosomal enzyme α -galactosidase A (*GLA*, Enzyme Commission (EC) 3.2.1.22) [1]. The deficient activity of this enzyme leads to the accumulation of its main substrate, globotriaosylceramide (Gb3), in the lysosomes of practically all tissues and organs. The main clinical traits include: cutaneous lesions (angiokeratomas); progressive renal damage with proteinuria; painful neuropathy predominantly affecting the hands and feet (acroparesthesias); myocardial hypertrophy; gastrointestinal manifestations; corneal dystrophy; and hypohidrosis. This entails severe progressive multi-system involvement leading to premature death [1,2].

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The gene encoding *GLA*, which is located in position Xq 22.11, was identified in 1989 [3]. More than 600 mutations have been described worldwide (Human Genetic Mutation Database (HGMD) Professional 2010.4) [4], most of which are private or particular mutations of a single family. Owing to its mode of inheritance, male hemizygotes normally present marked enzyme activity deficit expressing a severe disease phenotype. Heterozygous females, however, had been classically considered to be "carriers" of the disorder, with the appearance of a mild phenotype in a minority of heterozygous females. However, recent investigations have clearly shown that most female heterozygotes present manifestations of the disease, some of them as incapacitating as those of hemizygous males [5,6,7,8,9,10]. This heterogeneity in the clinical expression of the disease in females has been attributed partly to lyonization (random inactivation of one of the two X chromosomes) which takes place in the precocious stages of embryogenesis. Along with this, other factors such as the existence of different thresholds of enzyme activity in each tissue required for their normal functioning and, probably, absence of correction of the enzyme deficit by the activity of the closest cells may explain such heterogeneity in female patients. All of this results in patchy enzyme activity in each organ or tissue, with expression of the mutated gene in some cells and the normal gene in others [11,12].

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Owing to the existence of atypical or oligosymptomatic forms, the precise incidence and prevalence of FD are not known. Publications based on our geographical setting have described an incidence of 1 case per 476,000 inhabitants (1 per 230,000 males) [13], and a prevalence of up to 1 case per 3,100 newborn males, with predominance of mutations responsible for a later-onset form of the disease [14].

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A specific enzyme-replacement treatment (ERT) for FD has been available since 2001 [15,16]. Such therapy has been effective with respect to lessening most of the signs and symptoms of the disease, which in turn will enhance the quality-of-life and may extend the survival of those suffering from FD. To improve our knowledge and the management of FD, international multicentre registries have been set up [17,18].

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The Fabry Outcome Survey (FOS) is an international multicentre registry of patients with a confirmed diagnosis of FD receiving ERT with agalsidase-alfa (Replagal®) or who are candidates for such treatment. We detail below the baseline clinical characteristics of the Spanish patients included in the FOS, without ERT, or before initiating ERT. We also compared the clinical characteristics of Spanish patients with those previously published from other European patients included in the FOS [2].

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PATIENTS AND METHODS

PATIENTS

The FOS registry has been approved by the ethics committees of all the participating centres. All patients provided written informed consent to be included in the FOS. At the time of conducting this analysis (January 2009), there were data for 92 (41 males, 51 females) Spanish patients from 29 hospitals.

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DATA COLLECTION

The data in the FOS are collected from the clinical records of patients as well as those stemming from different routine clinical visits. These data comprise information on: demographic aspects; familial history; symptoms and their evolution over time; physical examination; general and specific analytical studies of FD; supplementary examinations needed in accordance with disease evolution; concomitant therapies; and appearance of adverse events. The data are recorded at admittance to the FOS and subsequently on a periodic basis. All of them are forwarded by electronic means to the centralized database. All persons over 18 years of age are considered to be adult patients and those under that age as pediatric population. For the genetic analyses, index cases were considered to be the first patient of each family included in FOS with a molecular confirmed diagnosis of FD.

The estimated glomerular filtration rate (eGFR) was calculated for adults by means of the abbreviated Modification of Diet in Renal Disease (MDRD) study [19], with the serum creatinine values adjusted (if necessary) by the analytical method used at each centre to achieve their uniformity. Left ventricular mass (LVM) index was determined by standard M-echocardiography at each participating centre and adjusted for height using the Devereux formula [20]. In males, left ventricular hypertrophy (LVH) was considered if the LVM index was $> \text{ or } = 51 \text{ g/m}^{2.7}$; the corresponding value in females was $48 \text{ g/m}^{2.7}$. Pain was evaluated by the patient by means of the Brief Pain Inventory (BPI) questionnaire [21]. This questionnaire rates pain intensity at the time of being completed and its retrospective evaluation in the previous week by assigning a score to the maximum, minimum and mean pain using a visual analog scale ranging from 0 (no pain) to 10 (worst pain imaginable). Patient health-related quality of life (HRQoL) was assessed by means of the European Five-Dimension Quality of Life Questionnaire (EQ-5D) [22]. A score of 1 represented full health, whereas 0 was equivalent to death. Both questionnaires had been validated in different European countries and languages.

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Disease severity was estimated using a slight modification of the Mainz Severity Score Index (MSSI) [23] so as to be able to adapt it to the FOS data input binary format (FOS-MSSI). The MSSI consists of four sections covering the various signs and symptoms of the disease (general, neurological, cardiovascular and renal), weighted in accordance with their contribution to its morbidity. Hence, a global score was obtained that enabled patients to be classified according to disease severity.

STATISTICAL ANALYSES

Qualitative variables are expressed as a percentage, and quantitative variables as a mean (standard deviation (SD)) or median (10–90 percentile), according to their distribution. Variables regarding time are expressed as whole numbers.

Paired *t*-tests were used to compare the mean value and Wilcoxon-ranked sign tests were used to compare the medians of one-sample data. The latter test was used if the data were not normally distributed.

For two-sample comparisons, the two-sample *t*-test was used to compare the two means for normally distributed data and the Wilcoxon rank sum test used to compare the two medians if the data were not distributed normally.

For categorical data, the Fisher's exact test and chi-square tests were used to test if there was an association. Approximation of the chi-squared tests for 2×2 tables may not be valid if the sample sizes are small. Hence, the Fisher's exact test was used if the following two conditions were met: the overall total of the table was <20 or the overall total was between 20 and 40; and the smallest of the four expected numbers was <20.

RESULTS

In January 2009, there were recorded in FOS data from 92 Spanish patients. Of those, 78 (35 males and 43 females) comprised of the adult population, and 14 (6 boys and 8 girls) belonged to the paediatric population. The patients came from 29 hospital centres. Of the adult patients, 94 % of the males (mean starting age, 38 years; SD, 13), and 48% of the females (mean starting age, 44 years; SD, 13) were receiving ERT. For the pediatric population, 4 patients were receiving ERT (3 boys; mean starting age, 13 years; SD 2).

In adult patients, the mean age of males at symptom onset was 20 years (SD 16) and 32 years (SD 15) at the diagnosis, with a mean delay in the diagnosis of 11 (SD 12). For females, the mean age at symptom onset was 24 years (SD 15) and 34 years (SD 14) at the diagnosis, with a mean delay of 11 years (SD 13). There were not significant differences upon comparing the foregoing parameters.

In the pediatric population, the mean age of symptom onset was 6 years (SD 2) in boys and 8 (SD 4) for girls, with a delay in the diagnosis of 1 year (SD 2) for boys, and 0.3 (SD 0.58) for girls.

Of the global set of patients, 35% of males and 20% of females had received different prior diagnoses other than FD, but this difference was not significant. In females, the diagnosis of FD was first suspected by the family (with an already diagnosed member) in 46% of cases, whereas it was 20% in males. In both sexes the nephrologist was the specialist who made the diagnosis most often, followed by the internal medicine specialist and the dermatologist.

The predominant clinical involvement (Table 1) in adult males was renal (69%), followed by cardiac (66%), neurological (60%), angiokeratomas (57%), heat intolerance (57%) and hypohidrosis (31%). The predominant involvement in adult females was neurological (42%), followed by cardiac (33%), cornea verticillata (30%), renal (28%) and angiokeratomas (23%).

In both sexes, except for cardiac and renal involvement, the classical clinical manifestations of the disease appeared before the second decade of life, with no statistically significant differences. In males, the earliest symptoms were neuropathic pain bouts (mean age 14 years; SD 12) and cold intolerance (17 years; SD 19), followed by sweat disturbances (anhidrosis, 19 years -SD 21-; hypohidrosis 19 -SD 18-) and recurrent fever (19, SD 15). In females, the earliest symptoms were hypohidrosis (16 years; SD 8) and cold intolerance (17, SD 1), followed by chronic neuropathic pain (18 years; SD 15) and abdominal pain (23 years; SD 1). Myocardial involvement (LVH) appeared in males at a mean age of 40 years (SD 12) and at 49 years (SD 5) in females, but this difference was not significant.

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Seven males (mean age at starting 42 years; SD 16) and one female (45 years) were on dialysis. Four males had required kidney transplantation at a mean age of 28 years (SD 3). All of them had high (>30) individual FOS-MSSI scores (total, and its subcomponents). One female had received a kidney transplant at the age of 48 years. Two males had experienced a stroke at a mean age of 44 years (SD 20). No sex-related differences were observed with regard to the body mass index (BMI), mean blood pressure (systolic and diastolic) values, or in the percentage of patients with good control of either of these values defined as systolic blood pressure (SBP) <135 and/or diastolic blood pressure (DBP) <85 mmHg (70% for males and 84.4% for females) (Table 2).

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Disease severity was significantly greater in males than in females (Table 3) (FOS-MSSI total median, 14.5 [inter-quartile range 8.5–27.5] vs. 7.0 [4.5–11.5] – $p < 0.001$ - in the total score and in the various subcomponents (except in the neurological subcomponent)). There was only information on the QoL of 10 patients, 2 of whom were males (with a mean EQ5D score of 0.92; SD 0.107), and 8 were females (with a mean EQ5D score of 0.75; SD 0.24), with no significant differences.

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Male patients had significantly lower enzyme activity for GLA in plasma or leucocytes (expressed as a percentage value compared with healthy controls) than female patients (Table 2). Forty-two percent of males with enzyme-activity data had almost undetectable activity ($\leq 1\%$). However, in 38% of females enzyme activity was considered to be in the normal range ($\geq 35\%$).

The results of the molecular study of the GLA gene conducted in patients considered to be index cases for this purpose (first case of a family enrolled in the registry) showed the existence of 34 exonic mutations found in 30 patients. Twenty-one of the mutations were missense, 4 were nonsense, 6 were deletions (one of which affected 3 exons), 2 were insertions and 1 was a splice site type. Two patients had 2 missense mutations, and one patient was also carrying an insertion and a deletion. No mutation was found in one patient.

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In the results of the supplementary examinations (Table 2), a significantly lower eGFR was found in males than in females, and a greater level of proteinuria, along with a higher value of the interventricular septum in diastole (IVSd) measurement, but with no differences in LVM index. There were data relating to renal ultrasound scans undertaken on 6 adult patients, but information was available on the existence of cysts in only 4 of them (3 males). Of those, cysts in a para-pelvic location were observed in 2 subjects (1 male and 1 female).

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Eleven kidney biopsies had been carried out (6 in females and 5 in males) before the start of ERT except in 1 case. All the biopsies showed abnormal results: 8

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2 with typical changes due to FD; 2 with glomerulosclerosis; and 1 with findings
3 compatible with chronic nephropathy of the transplanted kidney.
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5 Twenty-nine percent of males and 26% of females needed to take analgesic
6 medication. The most commonly used analgesics in males were anticonvulsants,
7 whereas in females were non-steroidal anti-inflammatory drugs (NSAIDs). Thirty-one
8 percent of males were taking angiotensin-converting enzyme inhibitors (ACEIs) or
9 angiotensin receptor blockers (ARBs) vs 14% of females ($p=0.03$ for ACEIs). The most
10 frequent concomitant treatment was ACEIs in males, followed by anticonvulsants. For
11 females, the most common concomitant treatment was NSAIDs, followed by ARBs.
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13 Since their inclusion in the FOS, 3 males and 2 females with FD had died. All
14 except 1 male were under ERT or had received ERT. The mean age of males at death
15 was 57 years (SD 4) and the cause of death was sepsis, cholecystitis and multiorgan
16 failure, respectively. The females had died at a mean age of 58 years (SD 9). One died
17 due to a disseminated neoplasm (peritoneal carcinomatosis), whereas the other died
18 suddenly at her home and an autopsy was not carried out. The patients who died
19 presented greater clinical involvement (total median FOS-MSSI in males, 33.5 (30.5-
20 46.5); total median FOS-MSSI in females 13.0 (9.0-17.0)) than those who were still
21 alive (total median FOS-MSSI in males 14.0 (7.5-23.5); total median FOS-MSSI in
22 females 6.0 (4.0-11.5)), $p < 0.05$ for the comparison in males.
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24 Comparison of our cohort of patients with the data of other European patients
25 included in FOS in December 2007 [2] showed, in our patients, a significantly smaller
26 proportion of disease-related organ involvement irrespective of gender except for
27 cardiac and renal involvement in males and psychiatric involvement in females (Table
28 4). In addition, Spanish male patients were diagnosed at an earlier age than those of
29 the rest of Europe, with no difference in the age at which females were diagnosed. No
30 significant differences were found between alive Spanish patients and those from the
31 rest of Europe regarding to the severity of disease (FOS-MSSI) in males, but in
32 females the severity was significantly lower than in their European peers. On
33 comparing the severity of involvement of deceased patients and the age at which death
34 occurred, there were not significant differences.
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DISCUSSION

FD belongs to the group of “rare” or “low-prevalence” diseases. Hence, registries or databases (such as the FOS) are particularly useful when carrying out an in-depth study of the physiological, pathologic, clinical, and response to treatment aspects, which would be hard to obtain through individual clinical practice. The data collected in the FOS are not obtained by questionnaires, but rather through routine clinical visits (albeit with limitations that may stem from different clinical procedures between the various participating centres).

The present study presents the baseline clinical characteristics of untreated Spanish patients included in the FOS database up to January 2009. The multi-system nature of FD and its reputation as a “great imposter” [24] makes the role of the Internal Medicine specialist or Pediatrician vitally important with respect to the diagnosis and management of FD. The role of the family with a member already diagnosed of FD as an active “disease seeker” in the search for the diagnosis, in our opinion is reflected by a shorter delay in the diagnosis of other symptomatic children and females.

Moreover, it is also beyond doubt that FD significantly affects females. This is observed in our cohort and has been extensively described [5–10]. In both sexes, the age of onset of symptoms characteristics of FD in our patients appeared before the second decade of life, and there were no differences in the age at which myocardopathy appeared. LVH in FD appears to be the herald of involvement in other organs or systems [25]. Its early detection (before full development) could be improved using cardiac tissue Doppler imaging [26], thereby permitting treatment of FD in a more favorable situation. Painful neuropathy, a classic symptom of involvement in male hemizygous, is also a fundamental manifestation in females, with no difference in its prevalence compared with males.

Noteworthy is the low frequency of keratopathy observed in our patients, a classical hallmark of the disease mainly for heterozygous women. Further investigations are necessary to determine if this low frequency of corneal dystrophy in Spanish patients is related with the observed lower proportion for other disease-related organ involvement.

In Spanish patients, FD was a major cause of end-stage renal insufficiency (20% on dialysis, 11.4% with a kidney transplant) at a premature age, very similar to that obtained by other authors [27,28], with a significant association with morbidity and mortality. Our male patients required a renal transplant at a young age, but this fact it is not so uncommon. In the largest series of Fabry patients with a renal transplant, derived from the US national registry, Shah T et al [29] reported that 67.5% of patients needed the procedure in the range of 22 to 45 years old. In addition to this, all of them

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2 had very high scores in the FOS-MSSI indicating a more severe phenotype of the
3 disease that would have led to an end-stage renal insufficiency earlier than the rest. FD
4 was also the cause of premature stroke in Spanish patients, as described in other
5 cohorts [17,30].
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8 Measurement of enzyme activity may prove useful for diagnostic purposes in
9 male patients showing reduced values in all of them. However, more than one-third of
10 our female patients had activity values that could lie within the normal range. This
11 reinforces the concept that the first-line diagnostic method in women should be
12 molecular study of the GLA gene. This has been proved to be invaluable in family
13 screening studies for FD. The distribution of the mutations of the GLA gene found in
14 the index cases of our patients followed the same pattern as obtained in the HGMD [4],
15 with a clear predominance of nonsense and missense mutations.
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18 The literature shows a prevalence of renal cysts detected by ultrasonography
19 from 20% (in heterozygous females) [31] up to 50% (in symptomatic males) and some
20 authors postulate that multiple parapyelic cysts could be a possible marker of FD [32].
21 With the limited data of the present study, we can only suggest that the finding of renal
22 cysts in a parapyelic location may be a distinctive trait of FD. Variability in completion of
23 the data is one of the weak points of these registries. This is because this examination
24 was probably done on most patients within the context of a nephropathy study, and
25 such alterations are evaluated on a systematic basis.
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28 Drawing conclusions on the impact of FD on the QoL of our patients was
29 difficult due to the few baseline questionnaires available. There was a tendency to
30 perceive a greater impact of FD on females that is not in keeping with the data of an
31 earlier study with a larger number of patients [33]. However, the fact that more
32 questionnaires came from females may be the explanation for our finding because
33 women usually have a poorer perception of their health status than men [34].
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39 Owing to the high prevalence of neuropathic pain in men and women, it is not
40 surprising that more than one-quarter of patients had an ongoing need to take
41 analgesics. First-line treatment for Fabry-related neuropathic pain is NSAIDs. The
42 preferential use of anticonvulsants in men compared to women may suggest that
43 typical neuropathic pain is more severe or worst perceived in men. Unfortunately, we
44 couldn't obtain enough information on quantitative pain scores (Brief Pain Inventory,
45 BPI) from our patients to confirm this fact or not.
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49 Our attention is drawn, however, to the low proportion of males treated with
50 ACEIs or ARBs. Despite this finding, the high percentage of our patients with
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2 appropriate control of their BP (much higher than in the general population) has been
3 shown to be a potential protective factor in the deterioration of the GFR observed in FD
4 [35].
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6 Obviously, comparison of our Spanish patients with FD with those of other
7 European countries [2] should be taken with caution, particularly on account of the
8 difference in the number of individuals. **The fact that only 6% of our patients were first**
9 **diagnosed by a paediatrician and that the proportion of the paediatric population was**
10 **quite similar in both cohorts (15% of our cases and 17% from other European**
11 **countries), in our opinion excludes a potential source of bias in the differences found**
12 **regarding the age of diagnosis in males.** Nevertheless, the generally lower prevalence
13 of organ involvement in our patients compared to those from the rest of Europe is
14 noteworthy. This is reflected in the disease severity (FOS-MSSI) in females but not in
15 males, as has previously observed in women living in the southern countries of Europe
16 [36]. Like the patients from the rest of Europe, the patients of our cohort who died were
17 more severely affected by FD and died at a premature age. However, the fundamental
18 cause of death in our patients was of infectious origin and not of cardiac origin, as
19 reported in the rest of Europe [2]. This could be related to a lower incidence of coronary
20 heart disease in our country.
21

22 In summary, we detailed the largest series of Spanish patients diagnosed with
23 FD. FD is a multi-system disease which mimics other processes, with an onset of
24 symptoms affecting both sexes at an early age. The morbidity and mortality associated
25 with FD is significant and predetermines ongoing drug administration in a large
26 proportion of patients. The pattern of involvement of FD, though not its global severity,
27 could be different in our patients in comparison with other subjects in Europe. The
28 causes of death seem to be different as well. It will be necessary to continue to expand
29 our knowledge of FD, not only among the scientific community, **but also among the**
30 **families with a proband already diagnosed with the disease.**
31

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28 **AUTHORS' CONTRIBUTIONS**

29 M-Á B-R: concept, research design, data analysis and interpretation, drafting.

30 A R-G: concept, critical review of article and statistics.

31 G P-M: concept and critical review of article.
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Table 1 .- Frequency of Symptoms by gender. Spanish adult Fabry patients.

SYMPTOMS	Frequency		p
	Males (n=35)	Females (n=43)	
NEUROLOGICAL	60%	42%	n.s.
Chronic pain	26%	21%	n.s.
Pain Attacks	43%	28%	n.s.
CEREBROVASCULAR	9%	2%	n.s.
AUDITORY	34%	16%	n.s. (0.06)
Tinnitus	6%	9%	n.s.
Vertigo	9%	12%	n.s.
CARDIAC	66%	33%	0.0035
LV Hypertrophy	54%	19%	0.001
Hypertensión	20%	14%	n.s.
Palpitations	23%	12%	n.s.
RENAL	69%	28%	0.0003
Microalbuminuria	23%	19%	n.s.
Proteinuria	54%	16%	0.0004
EYE	43%	37%	n.s.
Cornea Verticillata	26%	30%	n.s.
Tortuous Vessels	20%	9%	n.s.
GASTROINTESTINAL	40%	28%	n.s.
Abdominal pain	31%	12%	0.03
Constipation	11%	5%	n.s.
Diarrhoea	17%	5%	n.s. (0.07)
DERMATOLOGICAL	57%	23%	0.003
Angiokeratoma	57%	23%	0.0022
Anhidrosis	17%	0	0.0047
Hypohidrosis	31%	9%	0.013
GENERAL	74%	16%	<0.0001
Cold intolerance	11%	5%	n.s.
Heat intolerance	57%	2%	<0.0001
Fever Attacks	20%	0	0.0021
Body pain	14%	9%	n.s.
Joint pain	14%	14%	n.s.
Depresión	20%	16%	n.s.

Values are expressed as percentages (frequencies)

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Table 2.- Anthropometric parameters (BMI), laboratory, Electrocardiogram and Echocardiography data at baseline, in Spanish adult Fabry patients, by gender.

	Males	Females	p
BMI	25.2 (3.69) n= 23	25.7 (5.94) n= 27	n.s.
SBP < 135 and DBP < 85 mmHg	70% (21/30)	84.4% (27/32)	n.s.
AGA activity (% normal)	5.1 (9.71) n= 37	31.9 (20.36) n= 37	< 0.001
eGFR (ml/min/1.73m ² bsa)	67.16 (40.40) n= 16	89.38 (14.97) n= 23	0.049
Proteinuria (mg/24h)	1257 (1362.57) n= 12	286.9 (343.58) n= 16	0.008
PR interval (msec)	160 (120-180) n= 8	160 (120-200) n= 12	n.s.
PWTd (mm)	14 (8-29) n= 9	11 (8-16) n=17	n.s. (0.08)
IVSd (mm)	14 (10-20.5) n= 10	10 (8-16) n= 15	0.01
LVM index (g/m ^{2.7})	65.82 (32.9-150) n= 8	42.03 (21.4-118) n=10	n.s.

Values are expressed as Mean (SD), Medians (10th-90th percentiles), Percentage for BP control and AGA activity.

BMI: body mass index. SBP: systolic blood pressure. DBP: diastolic blood pressure. AGA: alfa-galactosidase A. eGFR: estimated glomerular filtration rate. Bsa: body surface area. PWTd: posterior wall thickness in diastole. IVSd: interventricular septum in diastole. LVM: left ventricular mass.

Table 3.- FOS-MSSI. Spanish adult patients, by gender

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	Males	Females	p
FOS-MSSI	n= 37	n= 34	
Total	14.5 (8.5-27.5)	7 (4.5-11.5)	<0.001
General	3.5 (1.5-5.5)	1 (0-3.5)	0.007
Neurological	4 (0-6)	1 (0-6)	0.341
Cardiovascular	6 (0-7)	0 (0-6)	0.015
Renal	4 (0-8)	0 (0-4)	0.001

Values are expressed as Medians (Quartile1-Quartile3)

FOS-MSSI: Mainz severity score index adapted to FOS (Fabry Outcome Survey)

Table 4.- SPANISH FOS-PATIENTS COMPARED TO EUROPEAN FOS-PATIENTS*

	Male			Female		
	Spanish Patients (n= 41)	Mehta et al Patients* (n= 699)	P	Spanish Patients (n= 51)	Mehta et al Patients* (n= 754)	p
Age at diagnosis	18.5 (15.68) n= 39	23.5 (15.4)	0.005	30.1 (16.54) n= 47	30.8 (17.6)	ns
Organ Involvement	%	%		%	%	
NEUROLOGICAL	61	75	0.001	41	61	0.000
CARDIAC	56	60	ns	27	50	0.000
OCULAR	39	58	0.000	37	49	0.001
GASTROINTESTINAL	39	57	0.000	27	45	0.000
DERMATOLOGICAL	49	66	0.025	24	37	0.007
GENERAL**	71	59	0.015	16	44	0.000
AUDITORY	29	56	0.000	17	44	0.000
RENAL	59	59	ns	24	38	0.004
MUSCULO-SKELETAL	29	39	0.004	20	34	0.003
VASCULAR	19	35	0.001	10	25	0.001
PSYCHIATRIC	17	27	0.024	18	23	ns
RESPIRATORY	19	29	0.028	8	21	0.001
CEREBROVASCULA	7	25	0.000	0.4	21	0.000
ENDOCRINOLOGICAL	5	5	ns	0.4	8	0.010
GENITAL	5	6	ns	0	1	ns
FOS-MSSI						
Alive patients	16.2 (10.09) n= 31	17.9 (10.1) n= 497	ns	8.4 (6.42) n= 35	11.8 (9.0) n= 558	P<0.005
Dead patients	36.8 (8.5) n= 3	30.7 (12.1) n= 33	ns	13 (5.66) n= 2	26.4 (14.5) n= 7	ns
Age at dead	56.7 (4.04) n= 3	51.8 (9.3) n= 35	ns	58.5 (9.19) n= 2	64.4 (10.0) n= 7	ns

Values are expressed as Mean (SD) or percentages (frequencies)

FOS-MSSI: Mainz severity score index adapted to FOS (Fabry Outcome Survey)

(*) Reference 2

(**)Typical Fabry's facies, heat-cold intolerance, fatigue or fever attacks.

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