Prevalence of Cardiac Abnormalities in Fabry Disease: a large CMR study in Argentina

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Fabry disease (FD) is a X-linked lysosomal storage disorder, caused by mutations in the gene encoding for alpha-galactosidase A, which results in progressive lysosomal accumulation of sphingolipids (predominantly globotriaosylceramide) in multiple organs [1-2]. The disease phenotype seems to follow different patterns in male (hemizygous) and female (heterozygous) patients [3,4]. Left ventricular hypertrophy (LVH), progressive fibrosis and impaired ventricular function with arrhythmia and sudden death are characteristic of FD cardiomyopathy [3,4,5]. Cardiac involvement is a major contributor to mortality in Fabry disease [2], thus its detection is crucial. In addition to this, there is growing evidence suggesting early enzyme replacement therapy (ERT) may delay the progression of LVH and preserves exercise capacity [6, 7, 21].

Cardiovascular magnetic resonance (CMR) is the gold-standard tool to measure cardiac structure and function, but its strength is the ability to characterize myocardial tissue – a particular utility in cardiomyopathies [8]. In FD, characteristic CMR findings include increased left ventricular mass (LVM), and late gadolinium enhancement (LGE) in a typical location starting in the basal infero-lateral wall [9-11]. More recently, there is evidence of low...
T1 values (longitudinal relaxation) in FD patients, even in the absence of LVH [9-11]. Our aim was to assess the clinical utility of CMR at detecting and classifying cardiac involvement in a mixed cohort of FD patients.

**Methods**

**Study Population**
A retrospective observational study of CMR scans performed in 99 unique FD patients from 2 tertiary care hospitals in Buenos Aires between April 2005 and October 2013.

The inclusion criterion was FD disease, with no age, gender or time from diagnosis restrictions. Diagnosis of FD was confirmed by measurement of alpha-galactosidase A activity on plasma and peripheral leukocytes (males) or genetic testing (females). Patients under 18 years old (n=14) at the first visit were considered pediatric cases.

**Ethics**
The study was approved by the local ethics committee of both sites and performed according to local clinical research guidelines.

**Cardiovascular magnetic resonance**
CMR was performed on a 1.5T Scanner (Avanto Siemens-Erlangen®, Germany). Standard protocols were used (based on Society of CMR Image Acquisition Protocols [8]) including: 1) Scouts; 2) Axial half Fourier single shot turbo spin echo (HASTE) images; 3) Pilots to line up cines; 4) steady state free precession (SSFP) image; 5) LGE imaging with inversion times set to null the normal myocardium, at least 10 minutes after contrast administration (0.2 mmol/kg gadolinium (Dotarem, gadoterate meglumine, Guerbert), using inversion recovery GRE imaging during diastole in the same views as cines (slice thickness 8 mm, 2 mm interslice gap).

**CMR analysis**
All short axis cine images were evaluated using ARGUS (Siemens) with manual planimetry of endocardial/epicardial borders at end-diastole and end-systole to derive the CMR parameters including LV wall thickness (LVWT), LVM, and LV ejection fraction (LVEF). LVM excluded papillary muscles from the myocardial mass. LVH was defined as LV wall thickness (LVWT) ≥ 12mm or increased LVM index according to previously published age and gender matched references [12]. Myocardial fibrosis was defined as the presence of LGE in at least one myocardial segment and confirmed on at least one additional acquisition (cross-cut, same view repeated). LV dysfunction was defined as a reduced LVEF according to age and gender as previously published for CMR [12]. FD cardiomyopathy was defined as the presence of LVH and/or myocardial fibrosis and/or LV dysfunction.

**Statistical Analysis**
All continuous variables were summarized as mean, standard deviation, maximum and minimum. Categorical variables were summarized using percentages and 95% confidence intervals (CI). One way ANOVA was used for continuous variable analysis. Chi square, with continuity correction or Fisher’s exact test as applicable, was used for categorical variables. Statistical significance was considered at p < 0.05. All statistical analyses were performed using SPSS 17 (IBM, Armonk, NY).

**Results**
A total of 99 patients were identified (61 females and 38 males), including 14 pediatric cases (14%, 9 females and 5 males), with a mean age 35 SD 15 years (range 9-73).

**Fabry Cardiomyopathy**
Cardiac involvement was present in (54/99) 55% of this Fabry disease cohort; 44 patients with LVH (26/44 with LGE and 5/44 with LV dysfunction) and 10 patients without LVH (7/10 with LGE and 3/10 with LV dysfunction). Greater prevalence was observed in males compared to females (76% vs 41%). Table 1 summarises the main CMR findings.

**Cardiac mass and function**
LVH was present in (44/99) 44% of patients (Figure 1). More males had LVH than females (68% vs 30%, p<0.01), with increased LVWT (14 SD 5mm vs 11 SD 4mm, p<0.001), and greater LVM index (115 SD 35 vs 65 SD 27, p<0.001). Older FD patients also had increased LVWT (r=0.65 age vs wall thickness, p<0.01) in both males (r=0.80, p<0.01) and females (r=0.67, p<0.01). The cohort in general had good LV function (LVEF 63 SD 8%), with no significant differences between genders. However, there was global LV impairment present in 8 patients - 4 females and 4 males; mean age 25 years (range 11-37 years), mean LVEF 49% (range 40-54%).

**Myocardial characterization**
All participants received gadolinium. Myocardial fibrosis (as detected by LGE) occurred in 33% (33/99) of cases – 16 males and 17 females, and was more common with age, and when LVH was present. Of the LVH patients, 59% (26/44) had LGE, compared to 13% (7/55) of patients without LVH (p<0.001). When there was LVH, LGE was classical – basal inferolateral wall – in 75% (Figure 2), but in 25% the LGE was more extensive involving other areas (Figure 3). There was also LGE in non-hypertrophied patients and occurred in both males and females – 25% (3/12) of men without LVH and 9% (4/43) of females without LVH (Figure 4). The incidence of LGE in patients with LV impairment was 25% (2/8 cases) suggesting some impairment (compared to reference ranges) without scar.[7] However, only 3 had LVEF <50%, only one of which had no LGE, (Figure 5).

**Discussion**
The current study is one of the largest in FD to assess cardiac involvement. These results are consistent with previous studies [4, 13], showing a significant prevalence of cardiac involvement (55%) due to LVH, LGE and LV dysfunction. Like this study, others [4,13], found a higher prevalence of LVH in males (65 to 67%) than females (17 to 25%), reflecting the known phenotypic gender differences in Fabry disease.
differences [4,11,14,15]. Overall, in this study, LGE was detected in 33% of the patients, with a similar proportion of males and females. This moderate prevalence has been previously reported [11,13]. LGE was more prevalent as LVH increases and with age. LGE was thought to be ubiquitous where LV impairment was present – with this “final common pathway” of fibrosis and dysfunction occurring in both males and females [7, 16, 17], but we observe 1 patient with significant (<50%) LV impairment and no LGE, this could be due to a diffuse myocardial process, which could be tested with T1 mapping. This raises the possibility of a non fibrosis related Fabry impairment mechanism, such as toxic metabolites, although dual pathology with another unidentified disease could be occurring. The cascade of myocardial changes in FD is only beginning to be understood in the heart and other organs with a broad range of pathological mechanisms increasingly recognized, such as toxic metabolites, cytokine activation and autophagy [13, 18]. LGE correlates with histologic presence of fibrosis and is considered a marker of advanced disease [16, 19], particularly in males, and appears to be a tipping point after which enzyme replacement therapy does not work [20]. Here, LGE is seen on multiple occasions early – before LVH has occurred. Although there is evidence that early enzyme replacement therapy (ERT) may delay the progression of LVH and preserves exercise capacity [6, 7, 21], the response to therapy of patients with scar but no LVH is unknown [20]. Interestingly, the presence of myocardial fibrosis before the onset of hypertrophy is well documented in females [4], but has not been remarked upon in males. In our study, myocardial fibrosis was detected in both females and males without hypertrophy (9% and 25% respectively), although the number of cases was small (n=7). The added value of CMR imaging in detecting 13% (7/52) of the patients with LGE but without LVH or LV dysfunction deserves to be further investigated and will depend on the potential impact of early ERT on the evolution of these patients (something that is not known at this moment) that will need to be balanced with the extra cost implied in the CMR studies.

Recently, T1 mapping has emerged as a potential tool in FD. The T1, a magnetic property of tissue, falls in FD patients. This is thought to be a direct measurement of myocardial (and likely myocyte) sphingolipid accumulation – storage [9-11]. It may be present in almost all LVH positive patients and around half of LVH negative subjects as an early marker complementing LGE and providing insights for the early diagnosis of FD cardiomyopathy [9-11].

Although large in numbers, this study has limitations including its retrospective observational design, no control group, a relative lack of complementary methods (eg advanced myocardial mechanics by CMR or echocardiography), and no T1 mapping (which did not exist in clinical practice when the study started).

Conclusions
CMR is a useful diagnostic tool in FD patients in detecting and classifying cardiac involvement. Gender differences can be clearly detected with greater prevalence of FD cardiomyopathy in males. A small proportion of both female and male patients can present with LGE before LVH occurs. Future work including a wider range of techniques and serial follow-up may unpick the biology of differential fibrosis rates, its underlying pathophysiology, and the significance for therapy.

Table 1. CMR Variables in the total cohort, and males and females

<table>
<thead>
<tr>
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<th>Total (n = 99)</th>
<th>Males (n = 38)</th>
<th>Females (n = 61)</th>
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<tr>
<td>Mean age (years)</td>
<td>35 ± 15</td>
<td>34 ± 15</td>
<td>35 ± 16</td>
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<tr>
<td>LVH</td>
<td>44 (44%)</td>
<td>26 (68%)*</td>
<td>18 (30%)*</td>
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<tr>
<td>LVM index (g/m2)</td>
<td>84 ± 39</td>
<td>115 ± 35**</td>
<td>65 ± 27**</td>
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<tr>
<td>LVWT (mm)</td>
<td>12 ± 4.6</td>
<td>14± 5.3**</td>
<td>11 ± 3.6**</td>
</tr>
<tr>
<td>Myocardial fibrosis</td>
<td>33 (33%)</td>
<td>16 (42%)</td>
<td>17 (28%)</td>
</tr>
<tr>
<td>LV systolic dysfunction</td>
<td>8/99 (8%)</td>
<td>4/38 (11%)</td>
<td>4/61(7%)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>63± 8</td>
<td>61± 9</td>
<td>65± 8</td>
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<tr>
<td>LVEDV (ml/m2)</td>
<td>80 ± 18</td>
<td>97 ± 17**</td>
<td>70 ± 10**</td>
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LV: left ventricle; LVWT: LV wall thickness; EF: ejection fraction; EDV: end diastolic volume. (*) p < 0.01; (**) p < 0.001

Figure 2 Myocardial characterization - Male Fabry patient with left ventricular hypertrophy and classic late gadolinium enhancement in basal and inferolateral wall 4-chamber and short axis late enhancement images.

Figure 3 Male Fabry patient with LVH and more extensive Late gad enhancement involving other areas (medial and basal septal segments).

Figure 4 Female Fabry patient without LVH but classical LGE but with in addition an apical aneurysm (coronary angiography normal; Chagas disease).
Acknowledgements

The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [22].

Declarations of Interest

James C Moon has investigator led research funding from Genzyme and has given talks for Shire (both of whom make enzyme for Fabry). Rebecca Kozor was sponsored by Heart Research Australia, and has received investigator led research funding from Genzyme and Shire, and honoraria for presenting from Genzyme.

References