Case Series

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Changes in Left Ventricle Mechanics in Patients with Anderson - Fabry Disease under Enzyme Replacement Therapy

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Abstract

Background: Sixty percent of patients with Fabry disease (FD) have cardiovascular involvement at the time of diagnosis. Among patients with heart failure of all causes, about 50% show normal or preserved left ventricular systolic function. We reported the evolution and echocardiographic findings of five patients with Fabry disease before undergoing enzyme replacement therapy and after 48 months of follow-up.

Method: Systolic and diastolic functions were assessed in 5 patients with FD using transthoracic echocar- diography. They were matched with echocardiography performed between 36 to 48 months after treatment was started.

Results: At initial evaluation, heart failure symptoms were positive in 3 patients. No history of fainting or cardiac arrhythmia was found on the initial approach. The mean LVEF before ERT was 57.25 ± 3.3. After 48 months of follow-up we observed a significant change increased on the LVEF to 68.7 ± 4.2 (p=0.04). All patients had increased interventricular septum thickness (IVT). The mean relative parietal thickness decreased from 0.63 to 0.59, after 48 months. Patients with mutation c.971T>A were more likely to increase the RPT. If the patient was free of dialysis the RWT tends to decrease. Diastolic function assessment revealed significantly higher E velocities, E wave increase from 73.6 to 81 m sec (p=0.04). But E/A ratio did not change after 48 months of ERT (1 *vs.* 1.1, p=NS). Two patients had diastolic dysfunction before ERT. After 2 years, four patients have diastolic dysfunction grade II. Before starting enzyme replacement therapy, all strain measures were abnormal. However, it was observed that their measurements did not worsen after ERT was started. The left ventricular twist was assessed, finding a decrease in it with a mean pre-ERT of 10º ± 4 *vs.* 13.7º ± 2.5 at 48 months (normal value 20 ± 7.3°), this was not significant.

Conclusion: After 2 years of follow-up, we found an improvement in LVEF, a decrease in the ventricular septum. We found no progression in diastolic dysfunction. Even though enzyme replacement therapy in Fabry has proven efficacy, there are very few evaluation and monitoring tools to assess its effects at the cardio- vascular level.

Systolic function is affected only in the late stages of the disease, although the diastolic function is affected earlier, it does not vary greatly over time once ERT has started. We found that conventional parameters, ven- tricular mass and septum diameter are useful as a baseline evaluation.

Keywords: Fabry-disease; Cardiovascular-disease; Agalsidase; Echocardiography; Heart failure; Enzyme replacement

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Introduction

Fabry disease, a rare inborn error of the enzyme α-galactosidase A (α-Gal A) metabolism, also called Anderson-Fabry disease, is the most prevalent lysosomal storage disorder. It is X-linked causing alterations on glycosphingolipid metabolic pathway which results in lysosomal accumulation of globotriaosylceramide (GL-3) and associated metabolites in a wide variety of cells, thereby leading to the protean manifestations of the disease [1]. Prevalence of FD in male populations is reported in a wide range, approximately 1:17,000 to 1:117,000. Classic Fabry disease mutations are seen in approximately 1:22,000 to 1:40,000 males and atypical presentations are associated with about 1:1000 to 1:3000 males and 1:6000 to 1:40,000 females [2]. Cardiovascular involvement in classic FD, is over 60%. Cardiac involvement in affected males occurs around the second decade of life and tends to increase with age, both in incidence and severity. This represents, along with untreated renal failure, the first cause of death among patients with Fabry disease [3]. As the disease progresses, lysosomes are saturated with GL-3 because of absent or partial α-Gal A activity. This results in heart conduction disorders, valvular disease, alterations of intima arterial, in its early years [4]. Morphological changes such as left ventricular concentric hypertrophy leads to systolic and diastolic dysfunction, hypertrophic and restrictive cardiomyopathies after several years [5]. The GL-3 deposits occur in only 3% of the myocardium, and the increased wall thickness is also due to hypertrophy of cardiomyocytes [6]. This could be explained because of the accumulation of Gb3 (often observed in the endothelial cells of patients with FD) which can lead to poor organ perfusion. These abnormalities can be explained through Gb3-induced impairment of endothelium-dependent vasodilation since Gb3 induces the lysosomal degradation of calcium (Ca^{2+})-activated K+-channels [7]. Cardiac involvement must be considered when patients have family history of heart disease, unexplained early death and/or premature stroke. Heterozygous females may be affected and can express FD phenotypes ranging from asymptomatic to major involvement of different organs; disease progression in females usually occurs later in life (as opposed to males) [8]. If after an evaluation, the patient with a positive genotype does not have phenotypic manifestations an annual clinical evaluation must be followed [9]. Identifying the early signs of cardiac involvement is very important, as younger patients will benefit the most from enzyme replacement therapy (ERT) [10]. Here, we report the evolution and echocardiographic findings of five patients with Fabry disease before undergoing enzyme replacement therapy and after 48 months of follow up.

Case Series

Case 1

A 38-year-old male, diagnosed in 2012 (88 months of follow-up), started at 8 years-old with a peripheral neurological condition, which persisted until adulthood; currently with paresthesias, kidney disease with renal replacement therapy and gastrointestinal manifestations; no kidney biopsy was performed. Treated with beta agalsidase at 1 mg/kg/dose, 170 cumulative doses.

Case 2

A 45-year-old male, diagnosed in 2014 (62 months of follow-up), started symptoms from childhood with a pre- dominance of neurological manifestations (headache and paresthesias), his diagnosis was secondary to family screening carried out by initial diagnosis of his brother (index case). At the time of diagnosis he was on hemodialysis already, no kidney biopsy was performed. Treated with beta agalsidase at a dose of 1 mg/kg/, 118 cumulative doses.

Case 3

A 41-year-old male, diagnosed in 2014 (68 months of follow-up), systemic arterial hypertension since 2013. He started at 7 years-old with headache, anxiety and paresthesias. He made her debut with nephrotic syndrome and sudden deterioration in renal function. A renal biopsy was performed, podocytes showed vacuolization of the cytoplasm, with a foamy appearance, some glomeruli with proliferation of podocytes, forming crescents like lesions, interstitial fibrosis in 15 percent of the sample. Electron microscopy showed severe damage to the visceral epithelial cells with diffuse obliteration of the processes, "zebroid" bodies were not observed. The kidney function was lost rapidly. He's currently on hemodialysis. Treated with beta agalsidase (1 mg/kg/dose), 136 cumulative doses.

Case 4

A 47-year-old male, diagnosed in 2014 (70 months follow-up), with a history of systemic arterial hypertension prior to diagnosis and left ventricular hypertrophy. Symptoms onset 6 months prior to diagnosis with intolerance to cold and heat; Uremic syndrome in July 2014 required hemodialysis for 2 years, a kidney transplant was performed in 2016, continuing to date with a functional graft. Treated with beta agalsidase (1 mg/kg/ dose) since October 2015 in a biweekly periodic infusion, 102 cumulative doses.

Case 5

A 54-year-old female, diagnosed in 2016 by screening her family (48 months follow up). Previously with systemic arterial hypertension. She started at 40 years old with paresthesias, headache, abdominal pain, angiokeratomas and albuminuria (1.3 gr/day). Due to the intense headache, an MRI was performed, reporting bilateral frontoparietal small vessel disease. Kidney function preserved, no biopsy was performed. Beta agalsidase was started at 1 mg/kg, so far 62 doses administered.

Methodology

We performed a retrospective comparison using echocardiographic reports of patients with Fabry disease diagnosed at "20 de Noviembre" Medical Center, in Mexico City. Once the patient is referred to our center with a suspected or diagnosed Fabry disease, an initial evaluation is carried out to decide if the patient will be a candidate for enzyme replacement therapy; a baseline transthoracic echocardiography is performed and afterwards is done annually. The first available complete echocardiographic report from each patient was selected, and

these were matched with echocardiography performed between 36 to 48 months after treatment was started. Echocardiography was performed using Phillips EPIQ 7 ultrasound machines. Left ventricular dimensions were measured by M mode at long axis parasternal view. Left ventricular ejection fraction (LVEF) was calculated using bidimensional Simpson method. The wall thickness was defined as the dimension of septal and posterior walls at end-diastole. Hypertrophy was defined as left ventricle mass index (LVMI) greater than 95 g/m^2 in females and greater than 115 g/m^2 in males. Ventricular geometry was calculated with the LVMI (normal<95 g/m^2 in females and<115 g/m^2 in males) and the relative parietal thickness (RPT, normal<0.46). Concentric remodeling was determined with LVMI<95 g/m^2 in females and<115 g/m^2 in males; and RPT greater than 0.46. Left ventricle hypertrophy concentric if LVMI>95 g/m^2 in females and> 115 g/m^2 in males; and RWT>0.46. Left ventricle hypertrophy eccentric if LVMI>95 g/m^2 in females and> 115 g/m^2 in males; and RPT<0.46. Left ventricle diastolic dysfunction (DD) was defined following Nagueh algorithm (11), which includes E/e ratio>14; septal e' velocity<7 cm/s or lateral e' velocity<10 cm/s; Tricuspid regurgitation velocity (TRV)>2.8 m/s; and Left atrial volume index (LAVI)>34 ml/m^2. If the score was>50% positive we concluded diastolic dysfunction.

Statistical analysis

Categorical variables are presented as counts and percentages while continuous variables are expressed using median [25th-75th percentile] and compared using the nonparametric Mann–Whitney– Wilcoxon test when they had nonnormal distribution and using the nonpaired t-test if otherwise. Categorical variables were compared using the chisquare test. Continuous variables' normal distribution was tested using the Shapiro Wilk test and plot analysis. All statistical test results were calculated with 95% confidence interval and P values<0.05 were considered significant. The statistical analysis was performed using SPSS.

Results

General characteristics of study patients are presented in **Table 1**. The mean age of the group was 48 (41-51.5) years. Most of the patients were males (80%), one patient was female. Enzymatic activity of a- Gal A on dried blood spot was measured in all male patients. This activity was below cutoff value (2.0 µmol/L blood/h) in all cases. The levels of Plasma GL-3 were 5.02 ± 2.18, and Lyso-GL3 were 30.24 ± 9.22. The media of months on therapy was 61.28 ± 18.5 months, with 105 ± 40 doses administered. No adverse effects were reported during that time. Three patients were positive for antibodies against the enzyme. During the follow up, only one patient was swichted from α to β agalsidase because the patient requested it. At initial evaluation, we found that acroparesthesias and headache was a particular symptom in- formed by all of them. Heart failure symptoms were positive in 3 patients. No history of fainting or cardiac arrhythmia was found on the initial approach. Renal involvement was observed in 5/5 patients, only one had kidney biopsy (Case 3). All men were under renal replacement therapy, two of them in hemodialysis, one in peritoneal dialysis and another one on kidney transplant. None of the general characteristics were significantly different between the patients. The mean LVEF before ERT was 57.25 ± 3.3 **(Table 2)**. After 48 months of follow up we observed a significative increase to 68.7 ± 4.2 (p=0.04). We did not find a significant correlation between GL3 levels and LVEF before ERT (r=0.635, p=0.09) and Lyso-GL3's levels and LVEF at 48 months (r=0.301, p=ns). All patients had increased interventricular septum thickness (IVT). When comparing the two measurements of each patient, they had significant changes, decreasing an average of 15 to 13 mm at 48 months, however, this still is septum's hypertrophy. The greatest decrease was seen in the female patient, who also showed no plasma GL-3 levels detected after the first year with ERT. The mean relative parietal thickness decreased from 0.63 to 0.59, after 48 months, this was not significant. Patients with mutation c.971T>A were more likely to increase the RPT. If the patient is free of dialysis the RWT tends to decrease **(Table 3)**. The

Table 1 General characteristics of the patients.

Variables	Echocardiography (baseline)	Echocardiography (24 months on ERT)	*p-value*
Left ventricular ejection fraction (%)	57.2 (5 –64)	68.7 (61.5–76)	0.04
Interventricular septum (mm)	15 (12.5–18)	13 (11–17)	0.05
Relative parietal thickness ( )	0.63 (0.49–1.1)	0.59 (0.55 –0.7)	0.89
Left ventricular mass index (gm/m^2)	153 (86.5–201.5)	185 (99.5–206)	0.08
Ventricular geometry			
• Remodeled	1 (20%)	1 (20%)	
• Concentric hypertrophy	3 (60%)	4 (80%)	0.09
• Normal	1 (20%)	0	
E Wave (msec)	73.6 (59.5–124.5)	81 (72–131)	**0.04**
A Wave (msec)	74 (55.5–133)	64 (50–110)	0.6
E/A ratio (msec)	1 (0.66–1.4)	1.1 (0.8–2.4)	0.5
E/E' ratio (msec)	11.2 (8.3–16.5)	16.2 (11.4–28.4)	0.2
Pulmonary vein flow	1(1–1.5)	2 (1–2)	0.3
Tricuspid regurgitation velocity (m/s)	2.4(2.3–2.6)	2.81(2.8–2.9)	0.2
Isovolumetric relaxation time (ms)	90 (70–92.5)	100 (68.5–130)	0.1

Abbreviations: ERT: Enzyme Replacement Therapy.

Table 2 Comparison between baseline echocardiography and after 48 months on ERT.

Variables	Case 1	Case 2	Case 3	Case 4	Case 5
Age at diagnosis	31	43	40	44	52
Mutation	c.107T>G	c.971T>A	c.971T>A	c.44C>A	c.1156C>T
Plasma a-Gal A activity* (nmol/h/ml)	0.2	0.3	0.22	0.7	NA
Plasma GL3 (ug/mL)*	4.8	8.7	7	5.1	3
Lyso-GL3 (ng/mL)*	42.4	36.7	21.1	29.4	BQL
Antibodies **	(-)	(-)	(+)	(+)	(+)
Cerebrovascular damage*	(+)	(-)	(-)	(-)	(+)
Angiokeratoma*	(+)	(-)	(-)	(-)	(+)
Acroparesthesias*	(+)	(+)	(+)	(+)	(+)
Dyspnea *	(+)	(-)	(+)	(+)	(-)
Palpitations*	(+)	(+)	(+)	(+)	(-)
Edema*	(+)	(-)	(+)	(-)	(-)
Arterial hypertension*	(+)	(+)	(+)	(+)	(+)
NYHA class *	II	I	III	II	I
Cardiac arrhythmia*	(-)	(-)	(-)	(-)	(-)
Albuminury (gr/day)*	1.3	0.71	NA	0.09	1.3
Chronic renal disease	(+)	(+)	(+)	(+)	(+)
Renal replacement therapy	PD	HD	HD	KT	(-)
Duration of ERT (months)	88	49	72	51	32
Type of enzyme	β	α → β	β	β	β

* Values before starting replacement therapy.
** Determination at 24 months on therapy.

Abbreviations: PD: Peritoneal Dialysis; HD: Hemodialysis; KT: Kidney Transplant; ERT: Enzyme Replacement Therapy.

echocardiographic characteristics and left ventricular geometry were evaluated, sixty percent of patients displayed concentric left ventricular hypertrophy (LVH). Before ERT only the female patient was within normal geometry. At 48 month of follow up to 80% of patients displayed concentric left ventricular hypertrophy. Currently none of them have a normal geometry. Diastolic function assessment revealed significantly higher E velocities, E wave increase from 73.6 to 81 msec (p=0.04). But E/A ratio did not change after 48 months of ERT (1 *vs.* 1.1, p=NS). Two patients had diastolic dysfunction before ERT. After 2 years, four patients have DD grade II **(Table 4)**. After initiating enzyme replacement therapy the NYHA class was better. Controlled atrial fibrillation is present in patient #1. The left ventricular mechanics of each case was assessed at the beginning and compared with the echocardiograms at 48 months **(Table 5)**. Before starting enzyme replacement therapy, all strains measures were abnormal. However, it was observed that their measurements did not worsen after ERT was started. Left ventricular twist was assessed, finding a decrease in it with a mean pre ERT of 10º ± 4 *vs.* 13.7º ± 2.5 at 48 months (normal value 20 ± 7.3°), this was not significant. Increased LV mass (defined as LVMI>95 g/m^2 for females and>115 g/m^2 for males) [11,12]. The mean LVMI for the study population is shown in **Table 2**. The LVMI tends to increase in 3/5 patients. But patients with decrease in this measure have a 50% reduction in plasma GL3 levels at second year of ERT (**Table 3**). Pearson's correlation between GL3 levels and LVMI (before ERT) was positive (r=0.635), but not significant, this could be explained because of the small sample. Changes in diastolic function in patients 3, 4 and 5, who tested positive for antibodies, did not improve according to Nagueh criteria, in fact they worsened. But we found an improvement in systolic function. We must mention that patients 4 and 5 were the two free of dialysis.

Discussion

The main manifestation of cardiac involvement in FD is the progressive thickening of the heart walls and therefore may be expressed as a hypertrophic cardiomyopathy [4]. As FD progresses patients also report symptoms related to the degree of cardiovascular impairment. The main symptoms reported between our patients were dyspnea and palpitations. When we compare the symptoms before and after ERT, all of them reported improvement in symptoms and functional class. Studies have reported that up to 56% of male patients present manifestations such as palpitations and chest pain at the onset of symptoms, however, effects of ERT on cardiological clinical manifestations have not been reported [13,14]. In a study by Wu Justina et Al, they found in a Fabry cohort that 60.4% of patients had a history of cardiovascular signs and symptoms: hypertension and edema were the most prevalent, followed by murmur, dyspnea, and angina [15]. A normal LVEF was observed in our patients before starting ERT. An increase in LVEF was observed after 48 months of follow up. On a study of sixteen patients with Fabry disease who were treated in an open- label study with 1.0 mg/kg body weight of recombinant α-Gal A (agalsidase β) they showed normal LVEF at baseline (Fabry: 62 ± 1%, controls: 64 ± 1%), and there was no significative change during ERT (Fabry: 64 ± 1%) [16]. In our study the change in the LVEF was significative. A case report of a man with angina and dyspnea on mild effort and at rest described marked improvement with intravenous infusions of galactose (as chaperone therapy to enhance residual alpha-galactosidase A

Table 3 Diastolic dysfunction at baseline echocardiography and 48 months of follow up.

Case 1	Baseline	6.6	6	7	3	73.6	83	0.88	1	Yes	I
	Follow up	16.2	5	5	3	81	101	0.8	2	Yes	II
Case 2	Baseline	19.8	4	5	2.8	89	61	1.45	1	Yes	II
	Follow up	14	3	4	3	92	119	0.77	2	Yes	II
Case 3	Baseline	13.3	4	8	2.4	160	160	1	1	No	NA
	Follow up	17.8	4	5	2.8	170	155	3.4	2	Yes	III
Case 4	Baseline	20	6	7	2.9	130	102	1.2	1	Yes	I
	Follow up	8.8	7	9	2.8	70	50	1.4	1	Yes	II
Case 5	Baseline	10	6	7	2.2	63	74	0.85	1	No	NA
	Follow up	14	5	5	2.8	74	64	1.15	1	Yes	II

Table 4 Cardiac involvement at baseline and 48 months of follow up.

Variables		Plasma GL3 (ug/mL)	Lyso-GL3 (ng/mL)	NYHA (Class)	Arritmia	Anti-hypertensive agent (#)	IVS (mm)	RPT	LVMI (gm/m2)
Case 1	Baseline	4.8	42.4	II	No	4	15	0.45	88
	Follow up	3.8	6.3	II	Atrial fibrillation	3	15	0.56	224
Case 2	Baseline	8.7	36.7	I	No	3	15	0.74	169
	Follow up	4.4	31.7	I	No	2	13	0.64	188
Case 3	Baseline	7	21.1	III	No	4	14	0.53	153
	Follow up	3	13.6	I	No	3	13	0.76	116
Case 4	Baseline	5.1	29.4	II	No	3	20	0.82	161
	Follow up	2.5	BQL	I	No	1	19	0.55	185
Case 5	Baseline	3	BQL	I	No	2	12	0.63	85
	Follow up	BQL	BQL	I	No	2	9	0.59	83

Abbreviations: IVS, inter ventricular septum. RPT, relative parietal thickness. LVMI, Left ventricular mass index. BQL, Below quantifiable level.

Table 5 Left ventricular mechanical function at baseline echocardiography and 48 months of follow up.

Variables		LV E F (%)	Twist	Strain 4c (%)	Strain 3c (%)	Strain 2c (%)	Circ-Ap strain (%)	Circ-Bas Strain (%)	Strain IB (%)	Rot apical (º)	Rot basal
Case 1	Baseline	55	13	-15	-14.6	-14.6	-14	-13.7	-27	5	4.5
	Follow up	68	8	-14	-15	-15	-14	-14.2	-28	6	4.8
Case 2	Baseline	64	14	-19	-16.2	-15.9	-22	-24	-39	8	9
	Follow up	62	16	-21	-18	-17	-21	-25	-41	9	11
Case 3	Baseline	55	10	-16	-18	-15	-18	-17	-37	5	4
	Follow up	61	8	-15.2	-18	-14.9	-12	-14	-36	4	2
Case 4	Baseline	78	10	-16	-15	-16	-25	-20	-40	5.2	5
	Follow up	76	11.5	-18	-17.5	-18	-27	-21	-40	5.7	6
Case 5	Baseline	55	6	-15.8	-14	-14	-14	-14	-40	4.8	3.9
	Follow up	70	6.9	-16.4	-15.5	-17	-15	-15	-42	5	4.1

activity), with left ventricular ejection fraction increasing from 32 to 51 percent after three months of therapy and to 55 percent after two years of therapy [17]. It is important to note that among patients with heart failure of all causes, about 50% show normal or preserved left ventricular systolic function [18]. When it comes to Fabry disease this could be because the earliest cardiovascular manifestations are pathophysiological changes involving the microvasculature, with arterial remodeling and intima-media thickening of the small and medium arterioles [19]. In these cases, in order to rule out if there is a cardiological condition, we can use other studies such as cardiac Magnetic Resonance Imaging (MRI), this is an excellent method to guide the diagnosis, and it is one of the useful tools available to predict treatment response [4]. Cardiac MRI is a great method to unveil the presence of fibrosis in FD [20]. Historically, LVEF has been used to assess cardiac function as a mechanical pump whose objective is the ejection of blood through the gradient of the aorta, however, in recent years we know that this reality is distant, since contractile function is dependent, not only the strength of the fiber, but also the pre-load and post-load conditions, therefore, to talk about this stability, other parameters such as the cardiac power index are needed, which allows us to properly evaluate this integrity, likewise in heart failure, despite having preserved LVEF, it is important to assess cardiac output and cardiac index, which have been widely correlated by echocardiography as part of non-invasive hemodynamic monitoring, since these last measures

tend to be reduced in early stages [21]. Increased left ventricle mass is a finding very common between Fabry patients, there are reports were the 84.9% of the subjects have an abnormal increase [15]. In this study four patients met the criteria for increased left ventricle mass at 48 months of follow up. The patients with the higher increase in ventricular mass were those who had the most time in renal replacement therapy. We found that patients with decrease in this measure have a 50% reduction in plasma GL3 levels this findings in the LVMI demonstrate a decrease in wall stress in myocardial fibers, which can translate the clearance of GL3 in the fibers. In the ATTRACT study, it was shown that in patients treated with migalastat (an oral pharmacological chaperone), LVMI decreased significantly from baseline over 18 months (−6.6 g/m^2; 95% CI −11.0 to −2.2); a smaller, non-significant change was observed in patients who remained on ERT (−2.0 g/m^2 (−11.0, 7.0)) [22]. It is known that in forms of cardiomyopathies such as hypertrophic, a ventricular mass> 150 g/m^2 demonstrated by magnetic resonance imaging, is associated with a worse prognosis and a high rate of arrhythmias [23]. After 48 months of follow up that the vast majority (80%) of this Fabry population had concentric LVH. This agrees with the previously published bibliography. Kampmann found that concentric hypertrophy was the most prevalent cardiomyopathy in his cohort [24]. A discovery also found by Justina et al. [15]. The analysis of ventricular mechanics is a novel tool for the evaluation and distribution of the contractile fiber. The main evaluation tools take into account 3 components when evaluating the left ventricle: longitudinal, circumferential and radial fibers, the first; has a great role in the stability of systolic function. The circumferential fibers are compensatory and tend to fall ill later in almost any pathology, although they denote a significant component of damage to the myocardial fiber. In the case of entities with a genetic component, such as hypertrophic cardiomyopathies, such as those of the apical type, an early pattern of affection has been found, the same that we observed in our patients and its compensatory rotational parts (twist and torsion) that were reduced in all patients, this speaks of an earlier condition in the myofibril, the result of abnormal enzymatic processing [25]. Diastolic function assessed by Nagueh algorithm was found in 80% of patients. In Frank Weidemann's cohort, when evaluating diastolic function in 16 patients with FD, they observed deceleration time (DT) and E/A ratio did not differ between patients and controls (Fabry: DT=242 ± 11, E/A=1.3 ± 0.2; controls: DT=217 ± 13, E/A=1.3 ± 0.1) and did not change after 12 months of ERT (DT=258 ± 12, E/A=1.4 ± 0.1) [16]. Of note is that it may not be an improvement, however the damage does not seem to get worse once ERT is started as we can observe in our study when we assess the LV mechanism. We found that strains abnormal at baseline did not change after 48 months of ERT. Shanks et al, their 16 showed reduced longitudinal early diastolic strain rate (P=.001), strain rate IVR (P<.001), and E/ SR IVR (P<.001), while radial and circumferential diastolic function was not affected. Of the conventional diastolic function indices, reductions were seen in E (P=.006), E' (P=.021), and E/e' ratio (P<.001) [24]. They also found that both conventional and novel diastolic indices were impaired in patients with FD compared with controls, and after controlling for LVH, only Strain rate during the isovolumic relaxation period and E/SRIVR ratio remained significantly different between FD and controls [26]. It is important to mention that although a couple of patients remained with diastolic dysfunction, and the E/A improvement was not statistically significant, there was no progression in filling pressures (E/e' ratio). The degree of diastolic dysfunction was stable during follow-up. Diastolic dysfunction corresponds to a poorly advanced heart disease. However, this finding reveals an alteration in the titin protein, which is the main contractile protein, and which is involved in almost all diastolic function, altering in these patients due to the inefficient function of alpha-Gal [27]. We found a noticeable improvement in the torsion mechanism, this refers to an interaction in which a suction mechanism is generated (such as a vortex) capable of generating suction and opening the aortic valve. When this mechanism is lost, contractile function can decrease up to 50%, even in the presence of normal LVEF. In multiple studies, it is affected only in the final forms of myocardial disease (post-infarction with advanced heart failure and greatly reduced LVEF) [28] but given the intrinsic damage caused by GL3 deposition, we can find it earlier. In patients with heart failure, it is not reported that there is improvement in this mechanism with the progression of the disease. Finding an improvement in the torsion mechanism in patients with Fabry is a great finding since it speaks of the recovery of the integrity of the myocardial fiber after the enzyme replacement.

Conclusion

After 2 years of follow-up, we found an improvement in LVEF, a decrease in the ventricular septum. We found no progression in diastolic dysfunction. Even though enzyme replacement therapy in Fabry has proven efficacy, there are very few evaluation and monitoring tools to assess its effects at the cardiovascular level. Systolic function is affected only in late stages of the disease, although diastolic function is affected earlier it does not vary greatly over time once ERT has started. We found that conventional parameters, ventricular mass and septum diameter, are useful as a baseline evaluation. For follow-up we must take into ac- count new tools, such as longitudinal and circumferential strain, which, although they are dependent on the acoustic window, provide us with information that is less observer and operator dependent. The initial evaluation must be clinical, based on functional class, and then on diastolic function. During follow up, we must integrate the evaluation of ventricular mechanics, giving us a tool to easily evaluate contractile function and the status of the cardiac myofibrilla, at an affordable cost.

Study Limitation

A limitation of this study is the small sample and the lack of a control group consisting of individuals without Fabry disease.

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