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Original article

Enzyme replacement therapy in paediatric patients affected by Anderson-Fabry disease leads to improvement in arterial elasticity, but not normalization

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Abstract

Introduction: Increase in blood pressure, probably due to an impairment in arterial elasticity, is frequent in patients affected by Anderson-Fabry disease (FD). The purpose of this study was to evaluate arterial distensibility in a group of children or adolescent with FD before and after enzyme replacement therapy and compare after enzyme replacement therapy findings with those of healthy controls (C).

Material and methods: Sixteen FD patients were recruited (87.5% male; mean age at diagnosis: 13.5 ± 1.5 years; mean age at study: 15.7 ± 2.1 years; mean treatment length: 2.2 ± 0.6 years). Arterial distensibility was evaluated by means of the previously validated non-invasive $QKd_{100\text{-}60}$ method, coupled with a 24-h ambulatory blood pressure monitoring (ABPM).

Results: FD subjects before therapy vs after therapy – systolic ABPM: $p < 0.05$; diastolic ABPM: $p < 0.05$; mean ABPM: $p < 0.05$; $QKd_{100\text{-}60}$: $p < 0.009$. FD subjects after therapy vs C – systolic ABPM: $p < 0.01$; diastolic ABPM: $p < 0.03$; mean ABPM: $p < 0.02$; $QKd_{100\text{-}60}$: $p < 0.04$.

Conclusions: Impaired arterial distensibility in paediatric FD patients implies an early vascular involvement even in these still so young subjects. Enzyme replacement therapy resulted in a significant improvement in arterial elasticity when compared with before treatment findings, but was not able to normalize it. It may explain the differences in ABPM levels.

Keywords

Arterial compliance, QKd interval, blood pressure, prognostic tests, Anderson-Fabry disease.

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Introduction

Fabry disease (FD), also known as Anderson-Fabry disease, is a rare X-linked, multisystem disorder caused by a deficiency of the lysosomal enzyme alpha-galactosidase A. The progressive accumulation of glycosphingolipids, specially globotriaosylceramide, may also lead to cardiovascular diseases, such as hypertrophic cardiomyopathy, arterial hypertension, valvular abnormalities, and arrhythmias. FD predominantly affects males, and – as a general rule – becomes manifested in the third-fourth decade of life. In addition, also heterozygous females may have variable manifestations of FD, ranging from asymptomatic to as severe as a male with classic FD [1-5]. However, a cardiac involvement in children and adolescent with FD is not rare and may be evident even at young age [6].

High blood pressure (BP) in FD patients may depend on glycosphingolipids accumulation in the lysosomes of arterial smooth muscle and endothelial cells, with consequent systemic vasculopathy [7]. A study about biophysical characteristics of FD patients' carotid arteries in adulthood revealed structural anomalies, implying that the elastic properties of the carotid wall were not preserved [8]. Previous reports in the literature showed marked alterations in adult FD patients' brachial arteries, which were related to both reduced secretion of endothelium-derived nitric oxide, and thickened intima-media layer [9, 10]. An increased vascular oxidative stress was certainly present in these FD patients' arteries, as shown by impaired flow-mediated vasodilatation, an early marker of atherosclerosis [9].

On the other hand, a loss of the natural aortic elasticity may be responsible for a rise in BP values of FD patients [3]. However, the cellular pathophysiological mechanism responsible for high BP remains not clearly identified [11]. The hypothesis of an increased arterial stiffness, which could be responsible for this complication, was proposed. Up to now, there is still a considerable debate about the exact mechanism responsible for persistent hypertension in FD and no one of the published explanations of this complication can be considered fully convincing [12].

The QKd interval is the time (measured in milliseconds) between the onset of the depolarization on the electrocardiogram (Q) and the detection of the last Korotkoff sound (K) at brachial artery during cuff deflation, corresponding to diastolic blood pressure (d). The clinical validation and the prognostic value of QKd index in providing valuable information about arterial compliance were established by several previously published studies, even in paediatric age [13-17].

The QKd technique was previously validated in comparison with pulse wave velocity as well [15, 17]. As this interval is inversely related to pulse wave velocity, QKd measurement provides valuable information about arterial distensibility [17]. The latter is calculated on an arterial segment, including the ascending aorta and a portion of the subclavian and brachial arteries.

The aims of the present study were: 1) to evaluate arterial compliance before and after enzyme replacement therapy, in patients who were children or adolescent at the time of the diagnosis of FD; 2) to compare after enzyme replacement therapy data with those of a control group (C) of healthy subjects.

Methods

Selection of study participants

FD, as a cause of hypertrophic cardiomyopathy, is relatively common in Sardinia, a wide island in the Italian sea with a relatively small number of inhabitants [18].

Sixteen Sardinian paediatric patients with a previous diagnosis of FD, aged between 11 and 18 years (14 male and 2 female; mean age at diagnosis: 13.5 ± 1.5 years; mean age at study: 15.7 ± 2.1 years; mean treatment length: 2.2 ± 0.6 years) were included in this study. All of them were examined before and after undergoing the enzyme replacement therapy. Due to the rarity of the FD manifestations in paediatric age, the patients' enrolment required

about 15 years (from 2001 to 2016). The diagnosis of FD was on the basis of the early signs and/or symptoms (involving the heart, brain, kidney, eye, skin, peripheral nerves, and gastrointestinal tract) or familial history and confirmed at genetic test (*GLE* gene) or biochemical screening (alpha-galactosidase A activity). The most commonly involved organs was the heart. The treatment was administered as soon as the diagnosis was confirmed at laboratory tests.

These patients were compared with a control group of 16 healthy subjects paired with respect to gender and age. Criteria of exclusion were the conditions increasing pre-ejection period and those which might impair interpretation of the QKd interval (such as severe subvalvular aortic stenosis, hyperthyroidism, presence of a pacemaker, left bundle branch block, and atrial fibrillation) [17].

A 24-hour ambulatory blood pressure monitoring (ABPM) coupled with QKd interval measurement, a 12-lead surface ECG, and a transthoracic echocardiographic examination were performed for each patient in the study. In the FD group, no one of the patients was suffering from arterial hypertension, according with paediatric population specific nomograms [19, 20].

All patients' parents gave their informed written consent to the study, which was conducted according to Helsinki's declaration.

QKd measurement

The authors undertook a 24-hour ABPM in the auscultatory mode coupled with measurement of the QKd interval, in order to evaluate the rigidity of the large arteries. In practice, a microphone was located in the cuff on the brachial artery and three electrodes were placed on the chest to detect the QRS complexes. The QKd interval was measured along with concomitant cardiac frequency, and BP values every 15 minutes over a 24-hour period (approximately 96 values for each patient). The variations of QKd interval were automatically performed by a monitoring device with a specific software (Diasys Integra from Novacor, Rueil Malmaison, France). This index gives an estimate of arterial distensibility derived from the pulse wave velocity, so that a reduction in arterial compliance results in a reduction of the QKd interval.

The device allowed to automatically derive the $QKd_{100\text{-}60}$ index, which is the value of QKd for a systolic BP of 100 millimetres of mercury and a heart rate of 60 beats for a minute, which is totally independent of the BP levels. It reduces the influence of the pre-ejection time (which is linearly correlated to the heart rate) and makes the comparison among subjects who have different levels of BP easier [17]. In fact, as known, many FD patients develop hypertension [3]. Values of $QKd_{100\text{-}60}$ higher than 200 milliseconds are usually considered normal [17].

As any movement and physical activity often result in invalid readings in machines that rely on detection of Korotkoff sounds with simultaneous ECG recording, our device was programmed to get additional readings if a likely erroneous reading is recorded. We followed the generally accepted rule that an ABPM recording is not acceptable if less than 85% of readings are suitable for use in the analysis [21]. In this respect, it was necessary to repeat the 24-hour ABPM in 3 out of 20 cases.

Electrocardiography and echocardiography

A 12-lead surface ECG (Cardioline ar2100view 12-channel electrocardiograph, Cardioline, Milan, Italy) was performed in each patient in the study. A transthoracic echocardiographic study (Toshiba Artida™ ultrasound machine, Toshiba Medical Systems Corporation, Tochigi, Japan) was performed by the same trained physician. The left ventricular mass was calculated using Devereux's formula and indexed by height to the power of 2.7 [22].

Statistical analysis

The results involving the entire study population (n = 16) were compared to those of controls (n = 16) by using the two-tailed Student's t-test. As for QKd index, there is no difference in the genders. QKd analysis was performed with respect to the reference values obtained in previous studies conducted on subjects who had either normal or high BP [23]. Values of $p < 0.05$ were set as the minimum level of statistical significance throughout the paper.

The relationships among the various parameters were studied by using the univariate analysis. Multivariate analysis was not applied because the sample size was not large enough for this statistic test.

For all the analyses, commercially available computer software (SPSS® version 22.0, SPSS Inc., Chicago, Illinois, USA) was used.

Results

Tab. 1 shows the main clinical characteristics of the 16 FD patients, compared to controls. Regarding

these basal findings, heart rate was measured by means of a 12-lead surface ECG, whilst BP with a mercury sphygmomanometer. By contrast, the measurements reported in the other tables derived from 24-hour ABPM coupled with QKd evaluation. In this respect, **Tab. 2** shows the patients divided into two groups: a) subjects affected by FD before enzyme replacement therapy; b) subjects affected by FD after enzyme replacement therapy. The before enzyme replacement therapy FD group showed some significantly disadvantageous differences for 24-hour ABPM and heart rate values in comparison with after therapy data. In **Tab. 3** the patients are divided into two other groups: a) subjects affected by FD after enzyme replacement therapy and b) control group. Even after therapy, FD patients had higher BP values and lower heart rate in comparison with the control group.

The echocardiographic data are shown in **Tab. 4**. Among the groups there were significant differences in left ventricular mass as well as septal and posterior wall thicknesses. On the contrary, no statistically significant differences were detected at basal ECG between the two groups.

The results of the $QKd_{100\text{-}60}$ index are summarized in **Tab. 5**. There were significant differences between the values of the $QKd_{100\text{-}60}$ index before and after enzyme replacement therapy ($p < 0.001$). Furthermore,

Table 1. Basal clinical characteristics (mean values ± standard deviation) of the 16 Fabry disease (FD) patients compared with those of the 16 healthy subjects of the control group.

	FD patients (n = 16)	Control group (n = 16)	Statistical significance p
Age (years)	14.2 ± 3.5	14.9 ± 3.1	ns
Height (cm)	167.7 ± 5.8	164 ± 6.4	ns
Weight (kg)	63.6 ± 3.8	65.2 ± 3.7	ns
Systolic BP at rest (mmHg)	120.4 ± 2.9	116.9 ± 3.3	< 0.01
Diastolic BP at rest (mmHg)	77.2 ± 3.5	74.4 ± 3.0	< 0.02
Heart rate at rest	62.6 ± 3.1	78.3 ± 7.4	< 0.001

Heart rate was measured by means of a 12-lead surface ECG, whilst blood pressure with a mercury sphygmomanometer.
FD: Fabry disease; BP: blood pressure; ns: not significative.

Table 2. Data from 24-hour ambulatory blood pressure monitoring (ABPM): Fabry disease (FD) patients before and after enzyme replacement therapy.

	FD patients before enzyme replacement therapy (n = 16)	FD patients after enzyme replacement therapy (n = 16)	Statistical significance p
24-hour SBP	118 ± 4	113 ± 5	< 0.05
24-hour DBP	73 ± 7	68 ± 6	< 0.05
24-hour MAP	88 ± 6	83 ± 5	< 0.05
Heart rate	65 ± 3	72 ± 4	< 0.05

Mean values ± standard deviation.
FD: Fabry disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure.

Table 3. Data from 24-hour ambulatory blood pressure monitoring (ABPM): Fabry disease (FD) patients after enzyme replacement therapy vs control group.

	FD patients after enzyme replacement therapy (n = 16)	Control group (n = 16)	Statistical significance p
24-hour SBP	113 ± 5	104 ± 6	< 0.01
24-hour DBP	68 ± 6	62 ± 3	< 0.03
24-hour MAP	98 ± 5	90 ± 5	< 0.02
Heart rate	72 ± 4	82 ± 5	< 0.04

Mean values ± standard deviation.
FD: Fabry disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure.

Table 4. Echocardiographic findings (mean values ± standard deviation).

	FD patients before enzyme replacement therapy (n = 16)	FD patients after enzyme replacement therapy (n = 16)	Statistical significance p
IVS (mm)	11.6 ± 0.9	8.5 ± 0.7	< 0.0001
PW (mm)	10.1 ± 0.7	8.4 ± 1.1	< 0.001
LVDD (mm)	45.5 ± 1.9	44.4 ± 1.7	ns
LVSD (mm)	30.6 ± 2.6	31.0 ± 2.7	ns
LVM index (g/m$^{2.7}$)	52.5 ± 5.5	45.0 ± 3.8	< 0.005
	FD patients after enzyme replacement therapy (n = 16)	**Control group (n = 16)**	**Statistical significance p**
IVS (mm)	8.5 ± 0.7	9.3 ± 0.6	< 0.05
PW (mm)	8.4 ± 1.1	8.2 ± 1.3	ns
LVDD (mm)	44.4 ± 1.7	46.1 ± 1.2	ns
LVSD (mm)	31.0 ± 2.7	30.5 ± 2.2	ns
LVM index (g/m$^{2.7}$)	45.0 ± 3.8	47.3 ± 3.3	ns

FD: Fabry disease; IVS: interventricular septum; PW: posterior wall; LVDD: diastolic diameter of the left ventricle; LVSD: systolic diameter of the left ventricle; LVM: left ventricular mass; ns: not significative.

Table 5. Observed $QKd_{100\text{-}60}$ interval values (milliseconds).

	Control group (n = 16)	FD patients before enzyme replacement therapy (n = 16)	FD patients after enzyme replacement therapy (n = 16)
$QKd_{100\text{-}60}$ (msec)	203 ± 2 [a]	183 ± 5 [b]	196 ± 3 [a,b]

[a] $p < 0.04$ (patients after therapy vs control group); [b] $p < 0.009$ (patients before therapy vs patients after therapy).
FD: Fabry disease.

there was also a significant statistical difference in the after enzyme replacement therapy $QKd_{100\text{-}60}$ index in comparison with the same index in the control group ($p < 0.01$). Individual findings about systolic and diastolic BP, interventricular septum thickness, and $QKd_{100\text{-}60}$ are reported in **Tab. 6**.

At 24-hour ABPM, the nocturnal decline in BP values was reduced in the FD patients (with no statistically significant difference between before and after enzyme replacement therapy groups), whereas the nocturnal decline in BP values was normal in most controls, but reduced in most of the after therapy FD patients (non-dipper patients: 10/16 FD patients vs 1/16 control group patients, $p < 0.0008$). In univariate analysis, we observed a significant relationship between the QKd interval and the increased BP values, the interventricular septum, and the left ventricular mass ($r = 0.57$, $p = 0.02$; $r = 0.61$, $p = 0.01$; $r = 0.54$, $p = 0.03$, respectively). No other significant relationships were found. In particular, due to the marked disproportion between genders in our sample size, a statistical comparison was not possible.

Discussion

At the best of our knowledge, no other studies were conducted to evaluate the profile of arterial stiffness in patients who were children or adolescent at the time of the diagnosis of FD. Our findings confirm the previous hypothesis of increased rigidity of the large arteries in patients affected by FD, also when the disease appeared at a very young age [9]. Increased arterial stiffness may be just the predisposing cause of higher 24-hour ABPM values in these patients, although as told these values were still considered normal for paediatric age standards.

Moreover, in the present study arterial compliance was lower in FD subjects than in controls even after enzyme replacement therapy, being the QKd values, based upon pulse wave velocity measurement, lower in these patients than in controls. That outlines a deterioration in the arterial physical properties in the FD patients. Until now, differences in arterial distensibility among FD subjects under enzyme replacement therapy were evaluated only in adult subjects

Table 6. Individual findings derived from echocardiography and 24-hour ambulatory blood pressure monitoring (ABPM), pre- and post-treatment.

	Gender		IVS (mm)	SBP (mmHg)	DBP (mmHg)	QKd_{100-60} (msec)
1	M	pre-treatment	11.0	118	73	183
		post-treatment	8.5	113	62	194
2	M	pre-treatment	11.4	114	74	188
		post-treatment	9.2	110	74	196
3	M	pre-treatment	11.5	122	80	181
		post-treatment	7.8	115	68	193
4	M	pre-treatment	9.6	118	72	178
		post-treatment	7.5	113	65	189
5	M	pre-treatment	12.2	125	63	185
		post-treatment	9.2	123	61	198
6	M	pre-treatment	11.3	122	73	195
		post-treatment	8.0	118	69	193
7	M	pre-treatment	11.8	115	73	183
		post-treatment	7.9	111	67	197
8	M	pre-treatment	11.6	118	73	186
		post-treatment	8.2	116	75	202
9	M	pre-treatment	12.4	119	70	178
		post-treatment	9.1	113	67	203
10	M	pre-treatment	11.6	111	73	189
		post-treatment	9.0	111	71	196
11	M	pre-treatment	11.9	118	66	188
		post-treatment	9.5	114	65	196
12	M	pre-treatment	11.7	121	72	177
		post-treatment	7.3	113	69	196
13	M	pre-treatment	10.8	118	77	183
		post-treatment	7.8	108	71	190
14	M	pre-treatment	13.6	128	83	171
		post-treatment	9.7	118	72	199
15	F	pre-treatment	10.9	108	74	188
		post-treatment	8.5	103	64	199
16	F	pre-treatment	12.3	114	73	180
		post-treatment	8.8	108	68	196

IVS: interventricular septum; SBP: systolic blood pressure; DBP: diastolic blood pressure.

calculating carotid to femoral artery pulse wave velocity by means of tonometry [24]. However, this method provided an evaluation only at the moment of the examination, while the QKd interval technique provided a complete profile of circadian variations in pulse wave velocity that would be more appropriate than a single measurement in assessing arterial elasticity.

The evaluation of arterial distensibility by the QKd measurement has advantages of being non invasive, completely automated, reproducible, and for avoiding interoperator variability. It is a useful ancillary to 24-hour ABPM, without any extra discomfort for the patients. In our opinion, it should be taken into account when studying the development and prognosis of cardiovascular complications in FD, such as BP rises. Our data indicate disadvantageous differences in arterial rigidity of patients affected by FD that could explain the differences in BP values. The vascular damage induced by sphingolipids storage, especially in endothelial cells, may be responsible of this issue [25].

According to previous studies conducted on hypertensive patients, we found a relationship

between the QKd interval value reduction and the increased BP values, confirming the already well-established importance of BP in arterial compliance [26, 27]. Regarding the cardiac consequences of the reduction in arterial compliance, we found a significant relationship between the QKd interval and interventricular septum, and left ventricular mass, according to previous reports in essential hypertension [28].

Heart rate analysis revealed that FD young patients had a significantly lower heart rate in comparison with controls, that might reflect a reduction in parasympathetic stimulation of their heart [6]. In addition, our echocardiographic findings are in accordance with previous reports about cardiac structural manifestations of FD in children and adolescents [6, 29].

The main limitation of this study was the small number of patients, with the consequent need to implement it. This will probably be complicated by the rarity of this disease in young age. However, it should be pointed out that the selected FD patients represented a very homogeneous population.

In addition, going on with the QKd monitoring for a long time to investigate a possible correlation with atherosclerosis, which develops as time passes, would be very interesting. Other most frequently used methods to evaluate arterial stiffness, such as pulse wave velocity, could be considered [30]. Again, other factors potentially contributing to the reduction in arterial compliance in FD should be considered (for example, over-expression of the renin-angiotensin system) [31].

In conclusion, our data show that FD patients have an increased arterial stiffness also in childhood, and even after enzyme replacement therapy. This is in accordance with previous reports about the effect of the enzyme replacement therapy in adult patients [32]. It might signify a poor future outcome even in those FD patients with apparently not yet severe cardiovascular involvement. So, a careful follow-up is requested. In addition, although a consensus opinion about medical treatment in paediatric FD is still far from being ready, we suggest to use all the current therapies whenever possible (i.e. enzyme replacement therapy, low doses of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers) to preserve the natural arterial elasticity as long as possible and delay the consequent complications that can contribute to early cardiovascular morbidity in these patients [6, 33]. In the future, a more in-depth knowledge of the biochemical mechanisms involved in FD development – by means of new technologies such as metabolomics – may lead to a more personalized therapy with novel approaches, such as stem cells [34-36].

Declaration of interest

The Authors declare that there is no conflict of interest.

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