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ORIGINAL ARTICLE

Early cardiovascular remodelling in Fabry disease

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Abstract
Aims Fabry disease (FD) is a rare X-linked genetic disorder caused by the deficiency or absent activity of lysosomal α-galactosidase A. Cardiovascular remodelling is a hallmark of FD. The present study aimed to comprehensively evaluate the cardiac, vascular and microvascular status in a population of patients with genetic mutations for FD without left ventricular hypertrophy (LVH).
Methods and results This study includes subjects carrying genetic mutations for FD (Fabry disease mutation-carrier, FDMC) without LVH (n=19). A group of control subjects (n=19) matched for age, sex, body mass index and cardiovascular risk factors were also included. All subjects underwent echocardiography, carotid ultrasound scan, endothelial flow-mediated dilatation (FMD) and nailfold capillaroscopy (NFC) assessment. When compared to the subjects in the control group, FDMC patients showed significantly lower mean values of systolic myocardial velocity (7.33±1.28 vs. 10.08±1.63 cm/s, p<0.0001), longitudinal systolic strain (−18.07±1.72 vs. −21.15±2.22 %, p<0.0001), significantly higher E/E' mean values (7.15±1.54 vs. 5.98±1.27, p=0.016) and intima-media thickness mean values (0.80±0.20 vs. 0.61±0.19 mm, p=0.005), significantly lower FMD (8.3±4.6 vs. 12.2±5.0 %, p=0.02), more atypical capillaries and irregular NFC architecture in FDMC than control subjects (52.6 vs. 0 %, p<0.0001; 78.9 vs. 36.8 %, p=0.02 respectively).
Conclusions FD progressively involves cardiac, macrovascular and microvascular systems in an early stage. These features are present even in asymptomatic mutation carriers without LVH.

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Introduction

Fabry disease (FD) (OMIM 301500) is a rare X-linked genetic disorder caused by the deficiency or absence of lysosomal α-galactosidase A (α-Gal A) due to mutations in the GLA gene. These mutations may lead to a complete deficiency or to a dysfunctional enzyme with a lower activity and different manifestations: in males who carry the mutation (1/40,000), a severe multisystem disease develops in childhood or adolescence, conversely, women who are heterozygous for the GLA gene may be free of symptoms or can develop moderate to severe disease related to uneven chromosome X inactivation (Maier et al 2006). Therefore, among women mutation carriers, enzymatic levels are not compelling as most affected females have normal α-Gal A activity (Linthorst et al 2008). The absent or deficient activity of α-Gal A leads to inability to efficiently catabolize lipids, causing progressive accumulation of globotriaosylceramide (Gb3) and other neutral glycosphingolipids in a variety of cell types (Germain 2010). In particular, cardiovascular remodelling is a hallmark of FD and occurs both in male and female patients, even if men are more severely affected than age-matched women (Barbey et al 2006a). Cardiac functional abnormalities, accelerated increase in

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intima-media thickness (IMT), decreased flow-mediated dilatation (FMD) and morphological and functional capillaries alterations have been widely reported in the literature (Barbey et al 2006a; Linhart et al 2000; Boutouyrie et al 2002; Kalliokoski et al 2006; Wasik et al 2009; Pieroni et al 2003). Currently, studies assessing the cardiovascular function in FD patients without left ventricular hypertrophy (LVH) are limited (Toro et al 2009). In addition, studies on FD patients with and without LVH have focused only on either cardiac or vascular involvement (Kalliokoski et al 2006; Pieroni et al 2003; Zamorano et al 2011; Puccio et al 2005). The present study aimed to comprehensively evaluate the cardiac, vascular and microvascular status in patients with genetic mutations for FD without LVH.

Methods

Study population

This was a prospective observational study including all consecutive subjects carrying genetic mutations for FD (Fabry disease mutation-carrier, FDMC) who referred to our Department after the genetic evaluation between January 2008 and December 2011. The study complied with the Declaration of Helsinki. A written informed consent was achieved from all subjects. The local Ethical committee approved this study. A group of control subjects was primarily recruited from our department (personnel or family members) as volunteers and matched for age, sex, body mass index (BMI) and cardiovascular risk factors. All subjects underwent transthoracic echocardiography (TTE), carotid ultrasound scan, FMD and nailfold capillaroscopy (NFC) to evaluate cardiac, macrovascular, endothelial and microvascular functions. Subjects with LVH were excluded. Patients with Raynaud phenomenon, systemic sclerosis and systemic lupus erythematosus have been excluded according to the criteria of American Rheumatism Association (Lonzetti et al 2001). All evaluations were compared between FDMC subjects and control volunteers.

Echocardiography

Standard TTE examination was performed using a GE Vivid 7 Ultrasound system (GE Healthcare, Horten, Norway) equipped with S3 multifrequency probe. Measurements were made by a level III-certified echocardiologist blinded to all clinical data and according to the current recommendations (Galderisi et al 2011). LV mass was calculated according to Devereux's formula (Devereux and Reicheck 1997) and indexed for body surface area to obtain the left ventricular mass index (LVMI). LV hypertrophy was defined as a diastolic left ventricular wall thickness (LVWT) greater than 12 mm. The two-dimensional TTE parameters evaluated were: left atrium volume indexed (LAVi) and LV ejection fraction by using modified 2D Simpson's formula. Pulsed-wave Doppler imaging was performed placing the sample volume at the tip level of the mitral leaflets in the apical 4-chamber view in order to obtain peak mitral inflow early diastolic velocity (E), atrial filling velocity (A), their ratio (E/A) and the E wave deceleration time. Tissue Doppler imaging (TDI) was applied in pulsed Doppler mode to record mitral annulus velocities at the septal and lateral corners to evaluate the following averages measures (Nagueh et al 2009): systolic (S'), early (E') and late diastolic (A') myocardial velocity, myocardial performance index (MPI) according to Tei formula (Lakoumentas et al 2005); the ratio between E and E' (E/E') was used as a surrogate of LV filling pressure (Nagueh et al 1997). Global longitudinal strain of left ventricle (GLS) was obtained by 2D-speckle tracking analysis from apical 4-chamber view (frame rate 60–80 fps) using a speckle tracking software (Echo Pac, GE Healthcare, ver. 110.0.0). The operator set the endocardial border at end-diastole and the software automatically detected the region of interest analysing speckle movement frame by frame. The tracking was visually controlled to avoid pericardial inclusion and validated.

Flow-mediated dilatation and vascular ultrasound assessment

All studies were performed using GE Vivid E Ultrasound system (GE Healthcare, Horten, Norway) equipped with 8 L-RS linear array transducer by an independent experienced vascular sonographer, blinded to the clinical features of subjects. For every examination, subject's conditions were standardized and endothelium-dependent FMD of the brachial artery was evaluated as previously described and recommended (Corretti et al 2002). Mean IMT, upper limit of normality and carotid plaque were defined and assessed as previously described (Stein et al 2008).

Nailfold capillaroscopy

NFC was performed as previously described (Bollinger and Fagrell 1990). The nailfold capillaries have been visualized by a video microscopy system (Charm View, Moritex Corporation, Tokyo, Japan). The morphology of capillaries was independently assessed according to the previously reported patterns observed in FD (Wasik et al 2009) by two expert operators. In case of disagreement, consensus between the two operators was obtained. Six parameters were then evaluated: 1) Irregular capillaries architecture; 2) avascular fields; 3) atypical capillaries (bushy and ramified capillaries); 4) abnormal capillary density; 5) haemorrhages; 6) apical capillary dilatation.

Statistical analysis

Categorical variables are expressed as frequencies and percentages while continuous variables are presented as mean±standard deviation. A total of 19 FDMC subjects were evaluated and compared to a matched control group. Data were compared using Student's *T*-test or chi-square test, as appropriate. In case of a non-normal distribution, appropriate non-parametric tests were performed. Intra- and inter-observer variability is expressed as coefficient of variability (COV) and intra-class correlation coefficient (ICC) with 95 % confidence interval. COV was calculated as the absolute difference of paired measurements in percentage of their mean. We tested for several correlations among different parameters by Pearson's or Spearman's test, as appropriate. All tests were two-tailed. A p value<0.05 was considered statistically significant.

Results

Clinical characteristics

No significant differences with regards to clinical characteristics were observed between the two groups (Table 1). The mean age of the included population was 32.6±12.4 years. The majority of evaluated subjects were below the age of 40 (73.7 % in FDMC, 63.2 % in control group, p=0.49). Common cardiovascular risk factors were overall poorly represented in the included population. However 50 %, 47.4 %, 57.9 % of patients were overweight (BMI >25 Kg/m^2) in the whole population, FDMC group and the control group, respectively (p=0.74, FDMC vs. control group). Raynaud phenomenon was referred by five subjects in the FDMC group and by one subject in the control group (p=0.075). Pain and acroparaesthesias were present in four subjects in the FDMC group and in none of the control group (p=0.034). *Echocardiographic findings* (Table 1).

All subjects, except one in the FDMC group, showed normal LVEF. However, in the FDMC group significantly lower mean values of S' and GLS were observed compared to the control group (7.33±1.28 vs. 10.08±1.63 cm/s and −18.07± 1.72 vs. −21.15±2.22 % respectively, both p<0.0001). LVMi was normal. Diastolic function parameters were normal in all subjects, although significantly higher E/E' mean values were found in the FDMC group (7.15±1.54 vs. 5.98± 1.27, p=0.016). Distributions of S', longitudinal strain and E/E' in FDMC and control group are shown in Fig. 1.

Figure 2a and b show GLS values in a control subject and in one patient of FDMC group.

Vascular findings (Table 2)

Carotid plaques were not found in any subject. In the FDMC group significantly higher mean IMT values (0.80±0.20 vs. 0.61±0.19 mm, p=0.005) and a lower mean FMD were found compared to the control group (8.3±4.6 vs. 12.2± 5.0, p=0.02) (Fig. 3). Also, stratifying the population for age according to the upper interquartile range (≥43 years), FDMC group showed significantly higher mean IMT values (data not shown). No significant difference in the mean

Table 1 Clinical and TTE results

Findings			FDMCs (n=19)	Control group (n=19)	p value
Clinical	Gender (male)	*n* (%)	3 (15.8)	6 (31.6)	0.44
	Age	mean±SD	30.1±14.8	35.1±9.1	0.23
	Hypertension	*n* (%)	2 (10.5)	1 (5.3)	1.00
	Hyperlipidemia	*n* (%)	2 (10.5)	3 (15.8)	1.00
	Diabetes	*n* (%)	0 (0.0)	1 (5.3)	1.00
	Smoking	*n* (%)	6 (31.6)	6 (31.6)	1.00
	Family history of CAD	*n* (%)	2 (10.5)	2 (10.5)	1.00
	Acrosyndromes	*n* (%)	8 (42.1)	8 (42.1)	1.00
	BMI	mean±SD	25.5±6.4	24.8±3.8	0.67
TTE	LVMi (g/m^2)	mean±SD	62.22±15.69	62.25±16.10	1.00
	LVEF (%)	mean±SD	65.14±7.40	61.58±5.57	0.11
	S' (cm/sec)	mean±SD	7.33±1.28	10.08±1.63	<0.0001
	MPI	mean±SD	0.49±0.10	0.47±0.06	0.61
	LV GLS (%)	mean±SD	−18.07±1.72	−21.15±2.22	<0.0001
	E/A	mean±SD	1.71±0.57	1.55±0.61	0.42
	LAVi (ml/m^2)	mean±SD	18.72±6.33	17.20±3.50	0.38
	E/E'	mean±SD	7.15±1.54	5.98±1.27	0.016

FDMCs Fabry disease mutation carriers patients; *CAD* coronary artery disease; *BMI* body mass index; *TTE* transthoracic echocardiography; *LVMi* left ventricular mass indexed for body surface area; *LVEF* left ventricular ejection fraction; *S'* systolic myocardial velocity; *MPI* myocardial performance index; *LV GLS* left ventricular global longitudinal strain; *LAVi* left atrium volume indexed for body surface area; *E/A* early diastolic filling velocity/late diastolic filling velocities; *E/E'* early diastolic filling velocity/early diastolic myocardial velocity

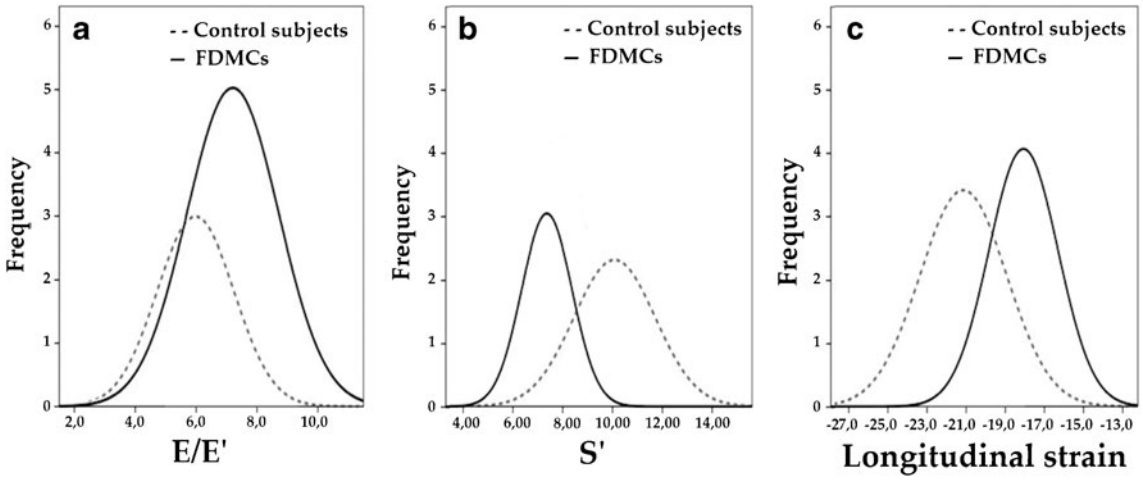

Fig. 1 **a** Distributions of ratio (E/E') between peak mitral inflow early diastolic velocity (E) and early diastolic myocardial velocity (E'); **b** systolic myocardial velocity (S'); **c** global longitudinal strain of left ventricle, in Fabry disease mutation-carrier patients (FDMCs) and control group

baseline brachial diameter was detected between the two groups (0.36±0.08 vs. 0.36±0.07, p=0.86).

Nailfold capillaroscopy findings (Table 2)

The proportion of patients with irregular capillaries architecture was two-fold higher in FDMC subjects compared to the control group with statistically significant difference. None of the patients in the control group had atypical capillaries (Fig. 4a–b). Unlikely, this latter aspect was detected in about half of the FDMC subjects (52.6 %). There was a trend toward a higher proportion of patients showing avascular fields in the FDMC group. Prevalence of apical capillary dilatation did not differ between the groups. Micro-haemorrhages were an infrequent pattern in the overall population with no case found in the control group and only three cases in the FDMCs group. At least three of the six evaluated capillaroscopic features were not found in the control group subjects, while they were present in two-thirds of patients in FDMC group (Fig. 4c).

Reproducibility analysis

Reproducibility data for both echocardiographic and vascular parameters has been obtained in a subgroup of ten subjects. To test for intra-observer variability, the first operator repeated measurements. In order to test the inter-observer variability, a second operator, blinded to the previous measurements, performed analysis on the same group of subjects. A good agreement, both in terms of intra- and inter-observer variability, was found for all evaluated parameters (Table 3).

Correlations

No statistically significant correlations among relevant variables related on theoretical pathophysiological bases were found.

Discussion

Several studies have assessed the cardiovascular involvement in patients with FD. However, currently, there are limited data on the early cardiovascular impairment in FDMC without LVH (Pieroni et al 2003). In an attempt to fill this gap and to expand the knowledge of early signs of cardiovascular involvement, we aimed to comprehensively evaluate cardiac, macrovascular and microvascular functions in patients carrying FD mutation without LVH.

Main findings of the present analysis are the following: 1) TDI parameters and longitudinal strain were able to show pre-clinical cardiac function impairments in FDMC patients; 2) FDMC patients had more pronounced early macrovascular involvement, as evaluated by the IMT and FMD, and more often microvascular alterations, as assessed by NFC. These findings suggest that, in FDMC patients, it is possible to detect early abnormalities of myocardial function with involvements of macrovascular and microvascular systems before the development of LVH.

Cardiac evaluation

Our TDI and strain results are in line with those observed in previous studies involving patients with genetic mutations of FD and no LVH (Pieroni et al 2003; Toro et al 2009).

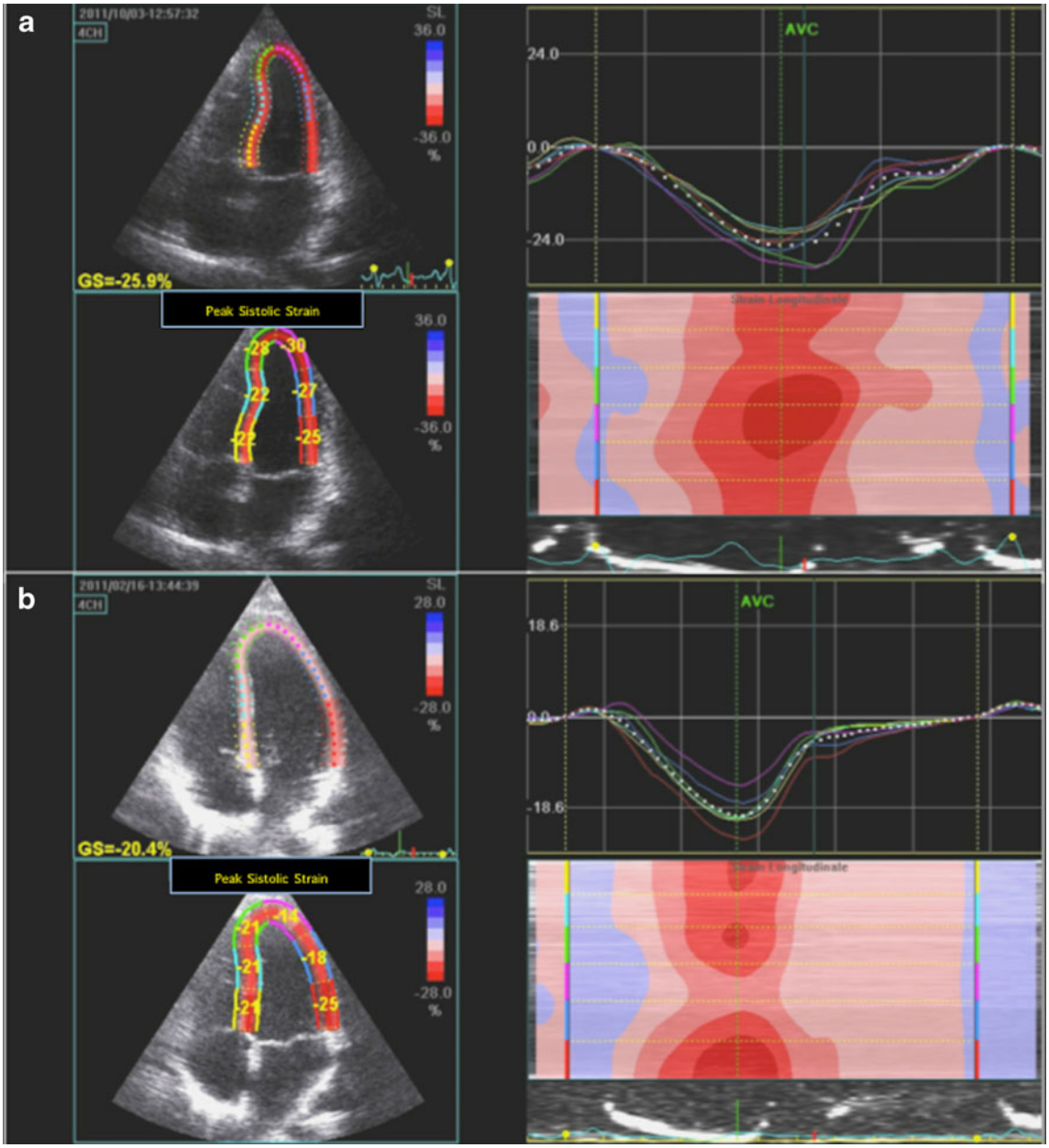

Fig. 2 Left ventricular global longitudinal strain in a control patient (**a**) and in a Fabry disease mutation-carrier patient (**b**)

Table 2 Vascular and NFC results

Findings			FDMCs (n=19)	Control group (n=19)	p value
Vascular	IMT (mm)	mean±SD	0.80±0.20	0.61±0.19	0.005
	FMD (%)	mean±SD	8.3±4.6	12.2±5.0	0.02
NFC	Irregular K architect	n (%)	15 (78.9)	7 (36.8)	0.02
	Avascular fields	n (%)	11 (57.9)	5 (26.3)	0.099
	Atypical K	n (%)	10 (52.6)	0 (0)	<0.0001
	Abnormal K density	n (%)	1 (15.8)	0 (0)	0.23
	Hemorrhagies	n (%)	3 (15.8)	0 (0)	0.23
	Apical K dilatation	n (%)	12 (63.2)	8 (42.1)	0.330

FDMCs Fabry disease mutation carrie patients; *IMT* intima-media thickness; *FMD* flow mediated dilatation. *NFC* nailfold capillaroscopy. *K* capillaries

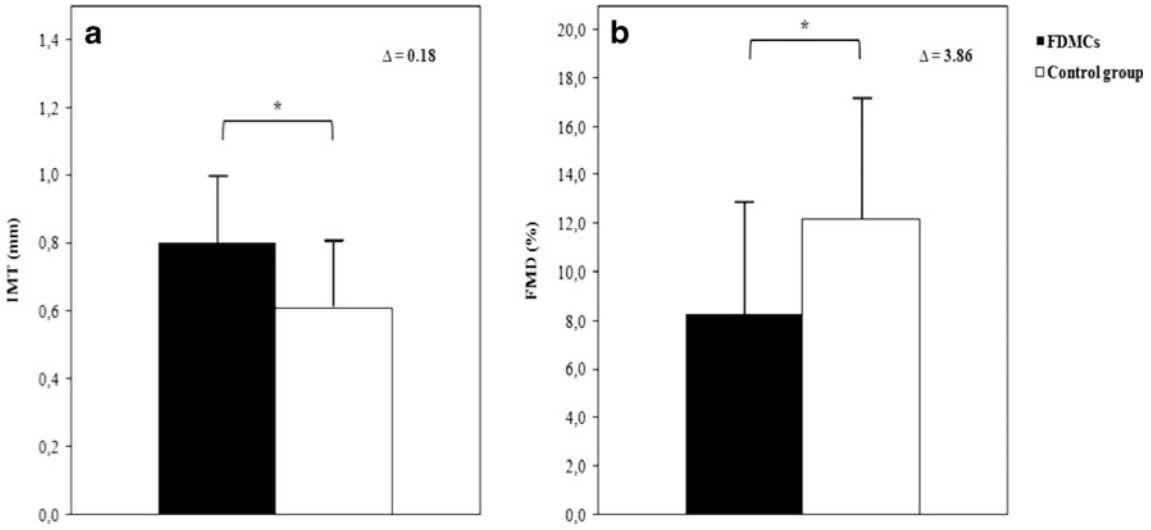

Fig. 3 **a** Intima-media thickness (IMT) values in the Fabry disease mutation-carrier patients (FDMCs) and in control group. **b** Flow-mediated dilatation (FMD) in the FDMC group and in control group

Functional interference of initially stored glycosphingolipids, manifesting with alterations of the relaxation-contraction cycle and myofilament structure, may explain TDI and strain abnormalities before overt LVH. Bioptic studies in FD hypertrophied myocardium showed ultrastructural evidence of myofibrillolysis associated with degradation of myofilament proteins and that the extent of myofibrillolysis correlated with a far lower active tension coupled with higher resting tension (Chimenti et al 2008). It may be supposed that these changes can even be present in the not yet hypertrophied myocardium and be responsible for functional impairments before morphological ones.

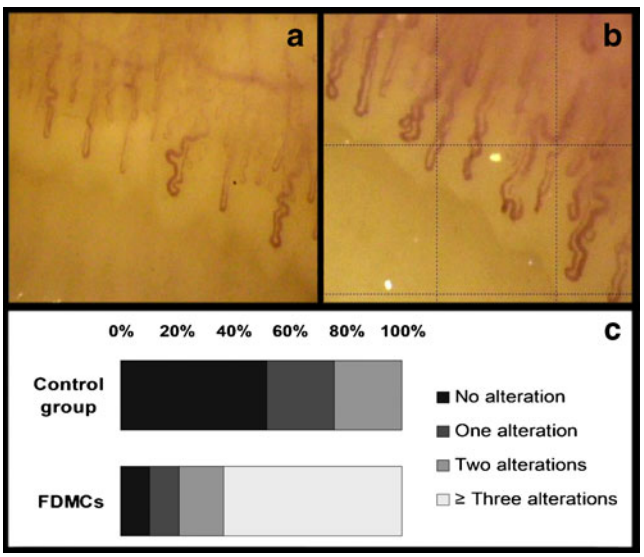

Fig. 4 Nailfold capillaroscopy in Fabry disease mutation-carrier patients. **a** Isolated atypical capillary. **b** Diffuse atypical and tortuous capillaries. **c** Distribution of capillaroscopic alterations in Fabry disease mutation-carrier patients (FDMCs) and in control group

Moreover, tiny areas of fibrosis have been identified in FD patients without LV hypertrophy (Pieroni et al 2003) and could lead to increased myocardial stiffness having a negative effect on contraction velocity and deformation. Additionally, increased myocardial stiffness can be responsible for the initial tendency to increased LV filling pressures in FDMC. TDI analysis represents a sensible tool, able to identify early myocardial function impairment and may be useful especially in female FDMC, who often present atypical clinical manifestations. Therefore, in patients with abnormal TDI values a closer follow-up may be advisable due to the risk of developing LVH in future years (Zamorano et al 2011).

Vascular evaluation

We have shown that FDMC patients have increased IMT in the carotid arteries in absence of plaques and decreased brachial artery FMD compared to the controls. These results confirm those from previous reports (Kalliokoski et al 2006; Barbey et al 2006b).

Glycosphingolipid deposition in the vessel wall can explain the increased vascular IMT found in FD. A predominant globotriaosylceramide accumulation in the intima and smooth muscle of the media of arterial walls has been shown, and this may lead to the thickening of the extracellular matrix and calcifications (Desnick et al 1976). Furthermore, glycosphingolipid has a particular affinity for vascular endothelium. The reduced FMD in FD patients may be caused by down-regulation of the endothelial nitric oxide pathway, thus allowing dominance of the non-nitric-oxide pathways (Altarescu et al 2001). Moreover, the accumulation of Gb3 in the autonomous nervous system (Seino et al 1983) and the consequent neuropathy that

Table 3 Reproducibility analysis

	Intra-observer		Inter-observer	
	COV (%)	ICC (95 % CI)	COV (%)	ICC (95 % CI)
E/A ratio	7.8±3.7	0.96 (0.78–0.99)	10.9±6.6	0.97 (0.91–0.99)
E' (cm/sec)	2.3±3.4	0.97 (0.85–0.99)	4.7±6.6	0.96 (0.88–0.99)
E/E' ratio	2.5±3.0	0.96 (0.78–0.99)	5.9±4.9	0.98 (0.95–0.99)
S' (cm/sec)	3.6±2.7	0.98 (0.88–0.99)	6.5±5.9	0.84 (0.59–0.95)
GLS (%)	5.2±4.5	0.87 (0.41–0.98)	7.6±6.5	0.78 (0.48–0.93)
IMT (mm)	2.8±3.2	0.97 (0.94–0.99)	4.9±2.9	0.97 (0.89–0.99)
FMD (%)	3.9±4.5	0.97 (0.90–0.99)	5.1±5.1	0.99 (0.97–0.99)

COV coefficient of variability; *ICC* intra-class correlation coefficient; COV is expressed as mean±SD

E/A early diastolic filling velocity/late diastolic filling velocities; *E'* early diastolic myocardial velocity; *S'* systolic myocardial velocity; *GLS* left ventricular global longitudinal strain; *IMT* intima-media thickness; *FMD* flow mediated dilatation

predominantly affects small peripheral and autonomic nerve fibres (Stemper and Hilz 2003; Dütsch et al 2002) may also influence vasomotor function in FD patients.

Microvascular evaluation

Although some NFC alterations were also found in the control group, a significantly higher number was found in FD patients. The majority of FD patients showed atypical capillaries while none were found in control subjects. Moreover, irregular capillary architecture was more frequently encountered in FD subjects than controls. Interestingly, of the six evaluated NFC features, more than three alterations were present in two-thirds of patients in the FDMC group, conversely no subject in the control group showed this pattern. Wasik and coworkers (Wasik et al 2009) previously described morphological and functional microangiopathy of nailfold capillaries in FD patients. Similarly to their findings, we identified higher prevalence of atypical capillaries and a more frequent presence of irregular capillary architecture.

A possible explanation of the NFC alterations might be the altered endothelial function due to the intracellular accumulation of glycosphingolipids (Barbey et al 2006a; Linhart et al 2000; Boutouyrie et al 2002; Kalliokoski et al 2006). Stemper and Hilz (Stemper and Hilz 2003) also postulated an alteration of end-organ perfusion, most likely with arterio-venous shunting and inadequate perfusion of capillaries. This might result not only in structural lesions at the level of the shunts but also in compromised sympathetic vasomotor control due to the small fibres neuropathy (Dütsch et al 2002). In addition, important physiologic control of smooth muscle activity is indirectly mediated by endothelial cells (Furchgott and Zawadzki 1980) with the release of vasodilator prostaglandins (prostacyclin) and potent vasoconstrictor like endothelin-1. In FD, the accumulation of sphingolipids may cause an imbalance of these regulatory mechanisms. the clinical significance of these findings is unclear, however, a high number of NFC alterations may suggest early microvascular involvement in FD before the development of macrovascular impairment.

Study limitations

The small cohort of patients limited the observations in this study. Moreover, based on selections' criteria, our study population was mostly composed of female patients. We reckon that this selection bias may probably be a consequence of the natural course of the disease; generally, at a similar age male patients are more severely affected and more frequently show the features of advanced disease. Therefore, our findings could not be fully representative of a male population with FD without LVH. Additional studies with larger samples are needed to establish definitively data regarding the preclinical diagnosis of FC. Furthermore, because TDI velocities decrease with age, the application of age-specific values is needed to achieve maximum accuracy. The identification of FD can be problematic and may introduce ascertainment bias, particularly in females. For ethical reasons, we did not undertake myocardial biopsies in patients to confirm myocardial involvement.

Conclusions

FD progressively involves the cardiovascular system and is present even in asymptomatic mutation carriers. A global evaluation of the cardiovascular system should be carefully performed in FD patients to identify initial alterations and to correctly stratify patients' risk. The detection of TDI and strain abnormalities coupled with vascular alterations even in female carriers can represent a hint for invasive assessment of cardiac involvement and therefore for a possible enzymatic therapy. Furthermore, nailfold capillaroscopy might be used as an additional diagnostic tool in patients

with FD to assess microvascular function. Therefore, we recommend a close follow up with instrumental and laboratory testing in presence of early abnormalities even without any clinical impairment. Further studies are needed to identify if enzymatic replacement therapy (ERT), started even in such early phases, could improve patients' survival and prognosis. It is known indeed that response to therapy is strongly dependent on the status of organ involvement and that in the future organ functional preservation should become the main therapeutic strategy.

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Conflict of interest None.

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