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Non-invasive evaluation of arterial involvement in patients affected with Fabry disease

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EDITOR—Fabry disease (FD) (OMIM 301500) is an X linked recessive disease resulting from deficiency of the lysosomal hydrolase α-galactosidase A.[1] The enzymatic defect leads to the widespread deposition of uncleaved neutral glycosphingolipids in the plasma and lysosomes, especially in vascular endothelial and smooth muscle cells. Initial clinical signs include skin lesions (angiokeratoma), excruciating acral pain, and benign corneal opacities. Progressive glycosphingolipid deposition in the microvasculature of hemizygous males subsequently leads to failure of target organs and to ischaemic complications involving the kidneys, heart, and brain.[2 3] Much interest is currently shown in emerging therapies for FD and recent studies have reported that genetic engineering has removed many of the obstacles to the clinical use of enzyme replacement and that infusions of purified α-galactosidase A are safe and biochemically active.[4 5] However, clinical and laboratory indicators of benefit are lacking, given the slow course of the disease. This emphasises the need for non-invasive surrogate endpoints to delineate target organ damage and to monitor the efficacy of enzyme replacement therapies.

Methods and results

In the present study, we determined intima-media thickness (IMT) at the site of the radial artery, a distal, muscular, medium sized artery, in a cohort of 21 hemizygous male FD patients, with a mean age of 32 years (SD 13, range 13-56 years), compared with 21 age and sex matched normal controls. All patients were diagnosed with FD by the presence of both clinical signs and a markedly decreased α-galactosidase A activity in leucocytes (<4 nmol/h/mg protein, normal values 25-55 nmol/h/mg protein). No patient had end stage renal disease. Measurements of the radial artery parameters were obtained with a high precision echotracking device (NIUS 02, SMH, Bienne, Switzerland) as previously described.[6 7] Briefly, the radiofrequency signal was visualised and the peaks corresponding to the blood-intima and media-adventitia interface were electronically tagged and followed over several cardiac cycles. Internal diameter and wall thickness were then measured with a precision of about 10 μm. Four to six measurements were averaged.[6 7] Radial artery IMT was measured 2 cm upstream from the wrist.

Compared to controls, FD patients had considerably higher IMT values at the site of the radial artery (fig 1). IMT was twice as high in

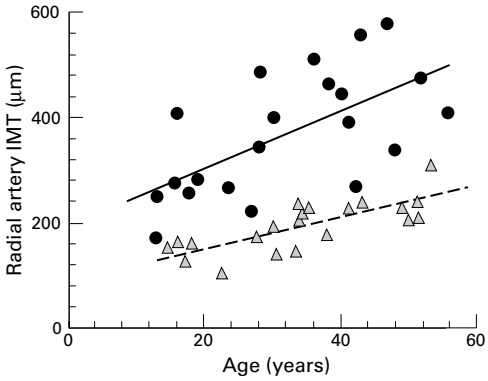

Figure 1 Correlation between radial artery intima-media thickness and age in patients with Fabry disease (circles) and in control subjects (triangles). Correlations are significant (p<0.001) in both populations and slopes differ significantly (59 (SD 14) v 25 (SD 4) μm per 10 years, p<0.001).

FD patients than in controls, even after adjustment for body surface area, age, and mean blood pressure (p<0.001). Radial artery IMT increased significantly with age in each group. However the slope was 2.3-fold higher in FD patients than in controls (p<0.001) (fig 1).

Discussion

In the present study, we describe evidence of a major, accelerated hypertrophy of the wall of a medium sized artery in a cohort of patients with FD. The magnitude of the difference in radial artery IMT was very large, with virtually no overlap between FD patients and controls. With age, the radial artery wall thickening was 2.3-fold faster in FD patients than in controls. The high definition echotracking system used in the present study has been previously validated in large subsets of patients with various diseases, and its accuracy and reproducibility are well accepted.[6 7]

The most commonly proposed explanation for the pathogenesis of cardiovascular lesions in FD patients is the slow deposition of uncleaved neutral glycosphingolipids within the arterial and cardiac tissues. However, the hypothesis of

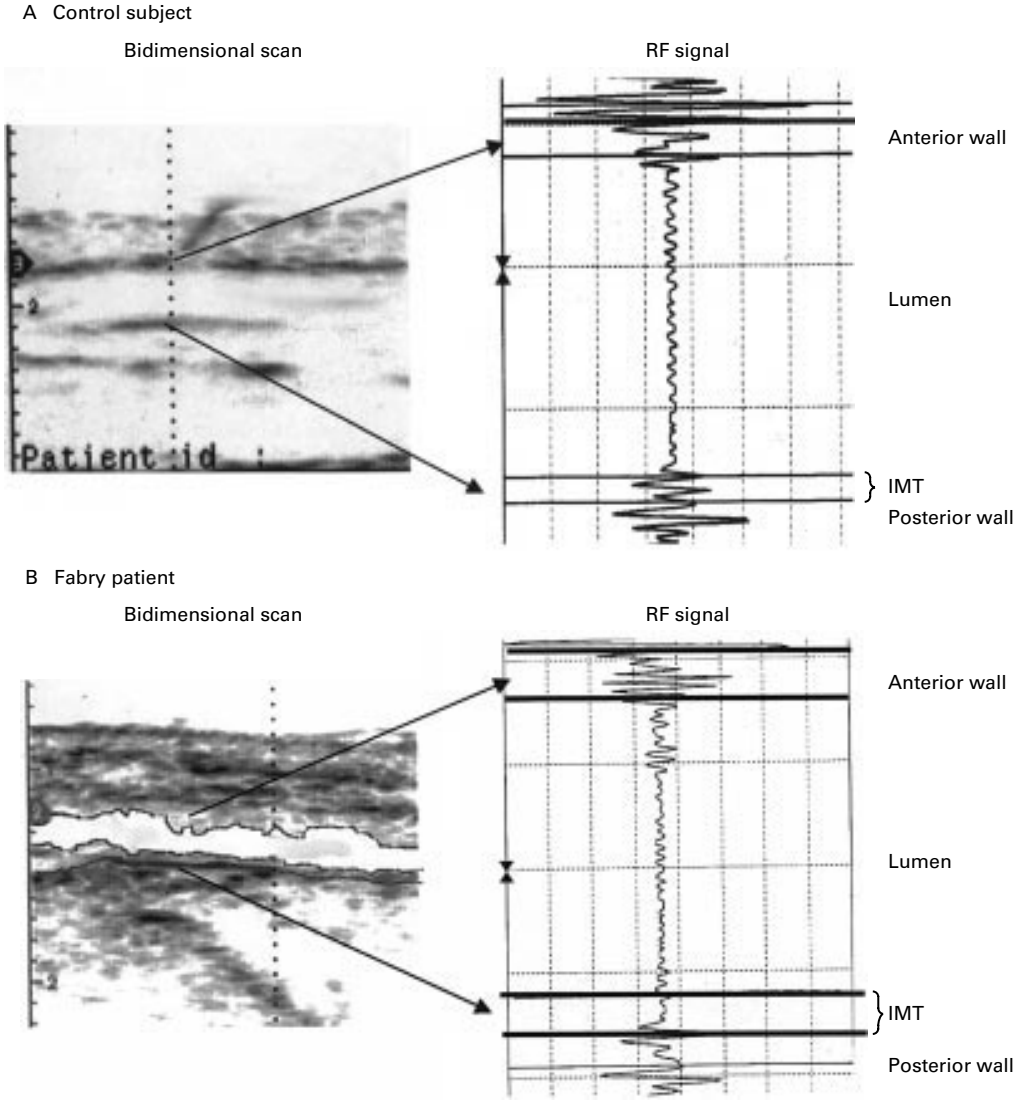

Figure 2 Bidimensional scans and radiofrequency signals (RF) of the right radial artery from a control (A) and a patient with Fabry disease (B). Lumen and posterior wall contours have been emphasised. Intima-media thickness (IMT) was measured from the distance between the RF peaks corresponding to the blood-intima and media-adventitia interfaces. Note the irregularity and the prominent thickening of the arterial wall in the Fabry patient.

a sole lysosomal accumulation of sphingolipids is somewhat simplistic since in the most advanced reported cases of left ventricle hypertrophy in FD patients, the amount of uncleaved glycosphingolipids found in the cardiac tissue did not exceed 1.6% of tissue weight (10-20 mg/g wet weight).[8] Other mechanisms are thus probably involved. First, although accumulation of globotriaosylceramide is the main mechanism in FD, the metabolism of other glycosphingolipids may also be disregulated.[9] Among them, lactosylceramide, which mimics the biological function of cytokines, growth factors, and stress signalling molecules[10 11] and accumulates in vascular tissues of FD patients,[8 9] could act as a second messenger and potentiate the hypertrophy of the arterial wall. Second, the smaller internal diameter of the radial artery in FD patients may be the result not only of wall hypertrophy encroaching the lumen (fig 2), but also endothelial dysfunction. Deposition of glycosphingolipids occurs predominantly in the lysosomes of endothelial and smooth muscle cells, with consequent cellular dysfunction.[3] An altered endothelium dependent relaxation of arterial smooth muscle could occur at the site of the radial artery or downstream, in arterioles, influencing the tonic flow dependent vasodilatation. The mechanism of flow dilatation is known to occur physiologically at the site of the radial and brachial arteries,[12] and has been related to changes in basal and stimulated nitric oxide (NO) release.[12] Finally, both in the media and intima, smooth muscle cells with glycosphingolipid inclusions secrete important quantities of extracellular matrix, notably elastic fibres.[8] Proliferation of smooth muscle cells and extracellular matrix deposition may thus contribute to the hypertrophy of the radial artery observed in FD patients.

In conclusion, this study presents the first non-invasive demonstration of a major increase in arterial wall thickness at the site of the radial artery in a cohort of patients with confirmed FD. The assessment of the involvement of the large arteries, through non-invasive procedures, could prove useful in monitoring new therapies for FD in providing an intermediate phenotype or a surrogate marker. However, the prognostic significance of the radial artery wall hypertrophy and its ability to regress with emerging treatments, such us enzyme replacement[4 5 13 14] or gene therapy,[15] remains to be determined during follow up studies.

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