Clinical research

Gadolinium enhanced cardiovascular magnetic resonance in Anderson-Fabry disease

Evidence for a disease specific abnormality of the myocardial interstitium

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Aims Anderson-Fabry Disease (AFD), an X-linked disorder of sphingolipid metabolism, is a cause of idiopathic left ventricular hypertrophy but the mechanism of hypertrophy is poorly understood. Gadolinium enhanced cardiovascular magnetic resonance can detect focal myocardial fibrosis. We hypothesised that hyperenhancement would be present in AFD.

Methods and results Eighteen males (mean 43±14 years) and eight female heterozygotes (mean 48±12 years) with AFD underwent cine and late gadolinium cardiovascular magnetic resonance. Nine male (50%) had myocardial hyperenhancement ranging from 3.4% to 20.6% (mean 7.7±5.7%) of total myocardium; in males, percentage hyperenhancement related to LV mass index (r=0.78, P=0.0002) but not to ejection fraction or left ventricular volumes. Lesser hyperenhancement was also found in four (50%) heterozygous females (mean 4.6%). In 12 (92%) patients with abnormal gadolinium uptake, hyperenhancement occurred in the basal infero-lateral wall where, unlike myocardial infarction, it was not sub-endocardial. In two male patients with severe LVH (left ventricular hypertrophy) and systolic impairment there was additional hyperenhancement in other myocardial segments.

Conclusion These observations suggests that myocardial fibrosis occurs in AFD and may contribute to the hypertrophy and the natural history of the disease.

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KEYWORDS Cardiomyopathy; Hypertrophy; Magnetic resonance imaging; Anderson-Fabry disease

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Introduction
Anderson-Fabry Disease (AFD), an X-linked disorder of lysosomal metabolism, has recently become the subject of increased clinical interest with the demonstration that it is a relatively common cause of left ventricular hypertrophy in middle aged men. Most of the cardiovascular manifestations of AFD are attributed to the deposition of glycosphingolipid (GB3) within myocytes, valves and vascular endothelium, but there are data suggesting that GB3 storage alone is insufficient to account for the extent of myocardial abnormalities seen in AFD patients.

Other diseases characterized by myocardial hypertrophy are associated with expansion of the cardiac interstitium and variable degrees of myocardial fibrosis. If this were to be the case in AFD, then the efficacy of new treatment strategies based on enzyme replacement therapy may be limited. In order to investigate the extent of any myocardial interstitial abnormalities in AFD, we performed contrast enhanced CMR (cardiovascular magnetic resonance) in individuals with AFD using the interstitial tracer Gadolinium-DTPA.

Methods
Patients
This study complies with the Declaration of Helsinki and was approved by the local research ethics committees; and all patients gave written informed consent before entry. Eighteen male patients (43±14 years, range 12–67) with AFD and eight female heterozygotes (48±12, range 31–59 years) were studied. Patients were recruited from the cardiomyopathy clinic at St. George’s Hospital and the Royal Free Hospital, London, United Kingdom. Patients had a variety of AFD symptoms including acroparaesthesia (n=17); hypohidrosis (n=7); abdominal pain (n=6); tinnitus (n=5) and angiokeratoma (n=9). The diagnosis of AFD in males was based on a plasma α-galactosidase A (α-Gal) activity of <1.0 mmol/h/ml (0.3±0.3, range 0.1–0.9, normal range 4.0–21.9). Of the eight females, four were obligate carriers, two had disease-causing mutations and in two the diagnosis was based on a renal biopsy. The females had a mean α-Gal activity of 4.2±1.3 (range 2.7–6.6). All patients underwent 12-lead electrocardiography and 2-D/Doppler echocardiography prior to CMR. For the patient baseline characteristics, left ventricular wall thickness was determined as the greatest diastolic wall thickness in any segment when the heart was divided into four basal, four mid and two apical segments.

Cardiovascular magnetic resonance
The technique has been described in detail. In brief, a short axis stack of cine images was quantified by planimetry to determine myocardial mass. A bolus of 0.1 mmol/kg gadolinium-DTPA was administered intravenously and late contrast enhanced imaging using inversion recovery acquired. All images were taken twice with a phase swap to exclude artefact. The location of any regions of hyperenhancement was noted by consensus of two observers using a standard 17 segment model. The extent of hyperenhancement was quantified by planimetry and expressed as a percentage of the total myocardial mass.

Table 1 Patient baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male (n=18)</th>
<th>Female (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years</td>
<td>43±14 (range 12–67)</td>
<td>48±12 (range 31–59)</td>
</tr>
<tr>
<td>ECG abnormal</td>
<td>16 (89%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>T wave changes</td>
<td>14 (78%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>LVH</td>
<td>12 (67%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Short PR</td>
<td>2 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>atrial fibrillation</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>LVWTb (mm)</td>
<td>15.3±5 (range10–29)</td>
<td>11.3±4 (range7–18)</td>
</tr>
<tr>
<td>Max LVWT &gt;13mm</td>
<td>12 (67%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>NYHAa Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (56%)</td>
<td>7 (88%)</td>
</tr>
<tr>
<td>II+</td>
<td>8 (44%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>6 (33%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5 (28%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>3 (17%)</td>
<td>0</td>
</tr>
</tbody>
</table>

aLVH=left ventricular hypertrophy.
bLVWT=left ventricular wall thickness.
cNYHA=New York Heart Association.

Statistics
All continuous values are shown as mean±SD. Non-Parametric Wilcoxon rank comparisons were made to compare measures of LV function and mass in the presence/absence of hyperenhancement. Linear correlations coefficients were assessed between extent of hyperenhancement and parameters of LV function using SPSS v 9.0 (SPSS Inc, Chicago, Illinois). A P value of <0.05 was considered significant.

Results
Patient baseline characteristics

Patient baseline data are displayed in Table 1. Eight patients (seven male) had undergone coronary angiography on clinical grounds which was normal (no narrowing greater than 30%) in all cases. These patients included the 6 patients with the most hypertrophy and the highest percentage gadolinium hyperenhancement. 14 (53%) had LVH (left ventricular hypertrophy) with maximum LV wall thickness >13 mm. There was mild mitral regurgitation (n=4), mild TR (n=1), mild AR (n=1) and rest outflow tract obstruction (n=2).

CMR
Myocardial hyperenhancement was present in nine males and four females, one of whom had a normal echo (2D, M-mode and colour flow) and ECG. The mean percentage of myocardium involved was 6.7%±5.1, (range 1.2 to 20.6%) with more hyperenhancement in males (mean 7.7% males vs 4.6% females). Percentage hyperenhancement in males related to LV mass index (r=0.78,
$P=0.0002$, Fig. 1, and patients with hyperenhancement had a higher mass than those without (188 vs 100 g/m², $P=0.001$). There were no relationships between hyperenhancement and end-diastolic, end-systolic left ventricular diameters or to ejection fraction.

In 12 of the 13 (92%) patients with abnormal gadolinium uptake, the hyperenhancement occurred in basal infero-lateral wall. The subendocardium was not involved in 8 patients, Fig. 2, unlike the hyperenhancement associated with myocardial infarction that always involves the subendocardium. In three males, extensive hyperenhancement in this region was associated with a wall motion abnormality and wall thinning, Fig. 3. The two patients with the most severe LVH (maximum wall thickness of 29 mm and 28 mm) had hyperenhancement elsewhere in the myocardium, Fig. 4. One male patient did not follow the typical pattern and had hyperenhancement in the inferior wall but not the basal lateral wall.

**Discussion**

Hyperenhancement during gadolinium CMR occurs because gadolinium chelated to DTPA diffuses into the interstitial space between cells but not across cell
membranes. In fibrosis and interstitial expansion, there is a greater extracellular space and distribution kinetics are slower compared with normal myocardium. In myocardial infarction, these two effects result in a higher relative concentration of gadolinium in areas of the heart where extracellular tissue is abnormal. Recent studies have demonstrated focal gadolinium enhancement in a number of non-ischemic cardiac diseases including hypertrophic cardiomyopathy, and glycogen storage disease type IIIa, where it is thought to represent myocardial fibrosis. In one case of HCM, the relationship between fibrosis and myocardial enhancement has been confirmed. The few studies that have examined cardiac histology in AFD have focussed on the classical intra-myocyte concentric lamellar inclusions bodies within lysosomes, but at least one study has suggested that sphingolipid accumulation alone is insufficient to account for the extent of myocardial abnormalities seen in patients with AFD, whilst myocardial fibrosis has been demonstrated in isolated case reports and exertional angina and thallium perfusion defects can occur despite complete epicardial revascularisation. The demonstration of myocardial hyperenhancement in this study suggests that, in addition to the accumulation of sphingolipid within myocytes, interstitial expansion is also a prominent pathological feature of AFD.

The underlying mechanism for interstitial expansion in AFD is unknown. In other myocardial diseases characterised by myocardial hypertrophy, interstitial expansion and fibrosis are caused by activation of various neurohormones and growth factors, as well as cell loss and necrosis. AFD may be similar with intracytoplasmic storage being the trigger for pathway activation resulting in a similar end phenotype with myocardial fibrosis and its associated clinical manifestations of diastolic and systolic dysfunction and arrhythmia. To the best of our knowledge, the curious predilection for the basal infero-lateral segments of the left ventricle that was seen in over 50% of the patients has not been described previously in any other cardiac disease. This region of the heart is usually supplied by the circumflex and or right coronary arteries, but in this study, of the 7 out of 12 patients with basal hyperenhancement studied by angiography, none had angiographic evidence of epicardial coronary artery disease. It is possible that factors such as regional wall mechanics or microvascular anatomy may influence enzyme deficiency with the myocardium, but this too seems unlikely given the fact that all myocardial cells in male patients should be equally affected by a deficiency of α-Gal. Whatever the explanation, the presence of myocardial hyperenhancement suggests that fibrosis plays an important role in disease progression in AFD, potentially contributing to the clinical manifestations. It also has important implications for the treatment of AFD, as enzyme replacement therapy may be less effective in patients with extensive areas of myocardial scarring, thereby providing an argument for the early initiation of therapy before fibrosis has developed.

The limitations of this study include a lack of histological correlations and an incomplete exclusion of coronary artery disease. Although only 8 (31%) patients underwent coronary angiography, this was skewed towards patients with hyperenhancement. Seven out of the eight (88%) catheters were in patients with myocardial hyperenhancement. So over half (53%) of the patients with hyperenhancement were studied angiographically. The distribution of hyperenhancement also suggests a disease specific phenomenon and it seems improbable that is
related to unrecognised epicardial coronary artery disease. The behaviour of gadolinium-DTPA is well described in coronary artery disease where it acts as an extra-cellular tracer. It is possible that myocytes in AFD behave differently and allow intracellular accumulation of gadolinium-DTPA, but is unlikely. Further study will be required to determine the clinical correlates of myocardial enhancement in Anderson-Fabry disease.

Conclusions

Patients with AFD have focal enhancement during gadolinium CMR which is evidence that interstitial abnormalities, including myocardial fibrosis may be important in the natural history of cardiovascular disease in AFD. Prospective studies are required to determine the relevance of these findings to the treatment of AFD with enzyme replacement therapy.

Acknowledgements

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References

9. Reimer KA, Jennings RB. The ‘wavefront phenomenon’ of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest 1979;40:633–44.