Left ventricular non-compaction in identical twins with thalassaemia and cardiac iron overload

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Cardiac disease in patients with transfusion-dependent beta-thalassaemia major is well described. Cardiac manifestations may include left ventricular wall thickening and both systolic and diastolic dysfunctions. We describe a group of family members, including a pair of identical twins, each of whom suffered from thalassaemia major requiring multiple transfusions. Cardiac magnetic resonance demonstrated myocardial iron overload, and impairment of systolic function. Echocardiography confirmed both significant left ventricular systolic and diastolic impairment, along with features consistent with left ventricular non-compaction. This finding has not been noted in association with thalassaemia-related cardiac disease before. We then review the cardiac manifestations which occur in association with thalassaemia major.

KEYWORDS
Left ventricular non-compaction; Thalassaemia major; Heart failure

Case report
A group of three siblings were referred for echocardiography as part of their routine annual follow-up. The group consisted of a female aged 19 years, and two male identical twins aged 20 years. All had a diagnosis of beta-thalassaemia major, and had been transfusion-dependent since early childhood. All were asymptomatic at the time of echocardiography; however, one of the twins had suffered a lower respiratory tract infection a few months previously which had precipitated episodes of supra-ventricular tachycardia and resulted in admission to hospital. The arrhythmias had required a combination of digoxin and amiodarone to control.

Each member of the group was receiving iron chelation therapy in the form of desferrioxamine, although all had prior evidence of poor iron chelation. The ferritin levels of one of the twins and the female tended to run between 2000 and 3000 μg/L, and those of the second twin between 1000 and 1500 μg/L.

Echocardiography of the female demonstrated normal cardiac chamber dimensions, with normal left ventricular systolic function (Table 1). The echocardiographic studies of both twins demonstrated left ventricular cavities at or just above the upper limit of normal dimensions with globally reduced systolic function. Moderate cardiac iron overload was confirmed in all three cases by cardiac magnetic resonance (MR) imaging (Figure 1). However, in both twins, the apical posterolateral segments of the left ventricle demonstrated a hypertrabeculated appearance with intertrabecular recesses on echocardiography (Figure 2A); this appearance was confirmed using microbubble contrast. The appearance and ratio of the hypertrabeculated to normal myocardium were consistent with a diagnosis of left ventricular non-compaction (Figure 2B).

Left ventricular non-compaction is now a well-established cause of left ventricular dysfunction and dilated cardiomyopathy both in children and in adults. Features consistent with non-compaction have not been described previously in association with thalassaemia or cardiac iron overload.

Discussion
Beta-thalassaemia major is an inherited disorder of haemoglobin synthesis, which results in severe anaemia due to chronic haemolysis. Patients require regular, lifelong transfusions to prevent anaemia; the high volume of transfusions required over many years may result in iron overload and deposition of excess iron within tissues (haemosiderosis). Haemosiderosis can result in liver cirrhosis, endocrinopathies such as diabetes, and cardiac disease; indeed, cardiac complications remain the major cause of death in thalassaemia major, despite recent improvements in the treatment of the condition.
Cardiac disease occurs predominantly via two mechanisms:

1. **Haemosiderosis.** Iron excess within cells leads to free radical formation, causing damage to membrane lipids and proteins, and resulting in cellular injury. Excess intracellular iron also impairs calcium release from the sarcoplasmic reticulum, impairing cardiac contractility, and myocardial performance. Genetic variations in iron handling affect the individuals’ susceptibility to these adverse effects of iron overload.

2. **Chronic anaemia.** This results in reduced tissue oxygen delivery and marrow expansion, demanding an increased cardiac output and leading to volume overload.

Cardiac disease tends to become more prevalent with age, as the effects of chronic volume overload and iron deposition become apparent. Comparison of a group of 197 thalassaemia patients receiving regular transfusion and iron chelation therapy and without clinical evidence of cardiac disease (mean age 25.7 years) with a group of healthy controls confirmed a significantly lower ejection fraction in the thalassaemia group (56.1 vs. 61.3%). Thirty-three of these patients (16.7%) had an ejection fraction <50%.

### Systolic dysfunction

Echocardiographically, the effects of chronic volume overload are manifested by an increase in left ventricular volumes and dimensions, and increased LV mass index and stroke volume. Progression of the myocardial dysfunction due to both ongoing volume overload and myocardial iron deposition becomes apparent in the later stages of the disease, with evidence of myocardial contractile dysfunction, and abnormalities of diastolic function. The differential cardiac effects of both chronic anaemia and transfusion-related iron overload are demonstrated by comparison between patients with thalassaemia major and those with thalassaemia intermedia (a phenotypically milder form of disease characterized by persistent mild anaemia not requiring regular transfusions). In those patients with thalassaemia intermedia, the cardiac effects of chronic anaemia are seen, without the occurrence of iron overload. This comparison demonstrates that those

### Table 1 Echocardiographic dimensions of the three patients

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<thead>
<tr>
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<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVIDd (cm)</td>
<td>4.1</td>
<td>5.5</td>
<td>5.9</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>2.5</td>
<td>4.4</td>
<td>4.2</td>
</tr>
<tr>
<td>IVSd (cm)</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>PWd (cm)</td>
<td>0.8</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>LA (cm)</td>
<td>3.2</td>
<td>3.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>39</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>64</td>
<td>47</td>
<td>42</td>
</tr>
<tr>
<td>Mitral E wave (m/s)</td>
<td>1.3</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Mitral A wave (m/s)</td>
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<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Tricuspid plane excursion (cm)</td>
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<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Mean E’ (cm/s)</td>
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<td>17.2</td>
<td>13.8</td>
</tr>
<tr>
<td>Mean A’ (cm/s)</td>
<td>9.25</td>
<td>3.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Mean S’ (cm/s)</td>
<td>9.95</td>
<td>8.4</td>
<td>6.8</td>
</tr>
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Figure 1 Cardiac magnetic resonance (1.5 T, Siemens Avanto) using a single breath-hold, multi-echo T2* pulse sequence showing a mid-ventricular short-axis slice. Both the left ventricular myocardium and the liver appear very dark, indicating moderate cardiac and severe liver iron loading. T2 imaging allows quantification of the myocardial and liver iron deposits using T2* time; in this case, cardiac T2* was 9.0 ms, liver T2* 1.3 ms (normal >20 ms).

Figure 2 (A) Parasternal short-axis image demonstrating the hypertrabeculated and non-compacted myocardial layer. The appearance was predominantly towards the apex of the left ventricle affecting the posterolateral walls, a typical appearance of left ventricular non-compaction. (B) Parasternal short-axis image confirming that the ratio of the compacted to non-compacted myocardial layers at end-systole is >2:1—a key diagnostic criteria in left ventricular non-compaction.
with thalassaemia major have significantly lower left ventricular mass and volumes, along with lower ejection fraction and fractional shortening, suggesting that increases in left ventricular mass, wall thickness, and volumes are driven primarily by anaemia, whereas reduction in contractile function occurs because of myocardial iron overload.

**Diastolic dysfunction**

Abnormalities of diastolic function in asymptomatic thalassaemia patients were first reported many years ago. Initial reports demonstrated changes in peak E wave velocity, E wave deceleration slope, and E/A ratio in patients with normal cardiac dimensions and systolic function, the authors suggesting that restrictive diastolic filling may be a precursor to systolic impairment. Subsequent reports were conflicting, however, with further data, suggesting that in a similar cohort of patients, only minor diastolic abnormalities consistent with the effects of volume overload were seen. In this study, restrictive filling patterns were only seen in a very small number of patients who were older, with high serum ferritin, and presumably severe myocardial iron overload. These relatively mild abnormalities in diastolic function in asymptomatic patients were confirmed in subsequent reports.

**Right heart dysfunction**

Pulmonary hypertension and right ventricular impairment are a relatively common finding in thalassaemia patients. Pulmonary hypertension may result from several mechanisms:

- chronic tissue hypoxia;
- pulmonary iron deposition;
- abnormalities of endothelial function.

Endothelial dysfunction appears to be a consequence of chronic haemolysis, and is also seen in other disorders such as sickle cell anaemia and hereditary spherocytosis. Right ventricular dysfunction was previously thought to occur secondary to pulmonary hypertension; however, a primary right ventricular cardiomyopathy is now known to occur.

**Other cardiac manifestations**

Pericarditis was a common feature of transfusion-dependent thalassaemia before the advent of regular chelation therapy, seen in up to 50% of cases, although it is rare today. Additionally, arrhythmias may complicate iron overload. Paroxysmal atrial arrhythmias and atrial or ventricular extrasystoles are most common. More rarely, non-sustained or sustained ventricular arrhythmias may occur.

**Investigation of cardiac disease**

Echocardiography remains the primary investigation to determine cardiac dimensions, as well as systolic and diastolic function. The presence of systolic dysfunction should prompt further investigations in order to quantify myocardial iron deposition, and guide changes in iron chelation therapy.

Ferritin measurement can give an idea of total body iron, but ferritin is also an acute phase reactant, and its blood level correlates poorly with tissue iron levels. Liver biopsy gives a more accurate assessment of total body iron burden, but is invasive, and hepatic iron overload is not necessarily a reliable estimate of cardiac iron levels. Magnetic resonance imaging protocols initially developed for the assessment of hepatic iron levels, have been adapted for cardiac use, and MR is now the first-line investigation for quantification of myocardial iron deposits.

**Treatment**

Treatment of thalassaemia major is directed at achieving a balance between the effects of anaemia and those of iron overload. Chelation therapy has been very successful in improving the outlook for patients with this condition, and ideally should be guided by MR assessment of cardiac iron loading. Where cardiac MR is not available, therapy is typically guided by serum ferritin levels, liver biopsy, and echocardiography. Once chelation therapy is commenced, the target ferritin level should be <1500 ng/L. Intense chelation therapy in patients with iron overload and evidence of cardiac impairment can improve and even normalize cardiac function over time, although improvement in cardiac function once iron-related myocardial dysfunction has occurred is not universal.

**Left ventricular non-compaction and thalassaemia**

Left ventricular non-compaction is now a well-described condition associated with left ventricular systolic dysfunction and other clinical and echocardiographic features. Specific diagnostic criteria have been formulated. The abnormality is thought to represent a congenital defect in myocardial development, resulting in an uncompacted, highly trabeculated layer of myocardium, typically towards the apex of the posterolateral walls of the left ventricle. The condition may be isolated, or may occur in conjunction with other congenital cardiac defects such as pulmonic stenosis or hypoplastic left ventricle.

Genetic abnormalities have been identified, and the condition is generally thought to be transmitted in an autosomal dominant fashion in adults, although penetrance of the genetic mutation may be variable. Many cases appear to be sporadic, and most likely due to a new genetic mutation, rather than familial. However, familial occurrences have been reported both in siblings and in parent and child, although never in twins.

The echocardiographic features of left ventricular non-compaction have not been reported in association with cardiac disease due to thalassaemia major.

**Summary**

Cardiac disease occurs in thalassaemia major due to a combination of long-standing anaemia and myocardial iron deposition related to the requirement for recurrent transfusion. We present a family group of similar age, with similar transfusion history, and who each had evidence of moderate myocardial iron overload as measured by MR imaging. However, two of the family members, who are identical twins, had evidence of more severe cardiac disease than their sibling in association with these findings. On the basis of the echocardiographic appearances, we hypothesize that both twins also suffered from left ventricular non-
compaction cardiomyopathy. Non-compaction may be the primary cause of the myocardial dysfunction noted; however, it is possible that the presence of both non-compaction and myocardial iron overload makes myocardial dysfunction more likely. Additionally, the increased thickness of the myocardium in non-compaction may render the myocardium capable of increased iron storage.

All our patients have now been treated with intensification of their iron chelation regime, and await re-assessment of both their myocardial iron levels and their cardiac function. The presence of left ventricular non-compaction may limit the improvement in myocardial function that would otherwise be anticipated with any reduction in myocardial iron overload.

Conflict of interest: none declared.

References