


References

We thank Professors Stollberger and Finsterer for their interest in our report and note the questions raised. We confirm that the echocardiographic features of left-ventricular hypertrabeculation/non-compaction (LVHT), as defined by the widely used criteria of Jenni et al., were only present in the twin siblings. The female sibling also demonstrated mild echocardiographic changes of LVHT, but these did not fulfill the diagnostic criteria. Echocardiographic images of one of the twins and the female sibling from approximately 2 years earlier were available for review, and demonstrate normal left ventricular systolic function in both cases. In the short-axis view, there was a degree of hypertrabeculation apparent in both cases, but more pronounced in the twin. However, the images were not of sufficient quality to make accurate measurements of the thickness of myocardial layers, and it is unclear whether the criteria for left ventricular non-compaction (LVNC) would have been met. Nevertheless, these findings suggest that the hypertrabeculation preceded the onset of iron-overload-induced systolic dysfunction.

One might hypothesize that all three siblings carried a genetic predisposition for LVHT, but that the phenotype was more overtly expressed in the twins. These three siblings are the only sufferers of thalassaemia major in their known family, although multiple family members including both parents carried the gene for beta-thalassaemia trait. Echocardiographic screening of relatives has not taken place; however, no apparent cardiac or neurological abnormalities are manifest within their family. There is no known consanguinity in the family.

The cardiac MR (CMR) scan was concordant with the echocardiographic findings. Myocardial iron overload demonstrated by CMR was not confirmed by myocardial biopsy in these cases. Hepatic iron deposition assessed by liver biopsy has been shown to correlate well with T2* time assessed by magnetic resonance imaging of the liver, and similarly cardiac iron levels assessed by T2* imaging correlate with cardiac function. Mavrogeni et al. have compared myocardial biopsy findings with myocardial iron levels assessed by T2* imaging in 25 patients, and showed significant correlation. Myocardial biopsy was not performed in our patients as the procedural risk, and possibility of false-negative findings given the patchy distribution of myocardial iron deposition, was felt not to be justifiable. MR imaging confirmed moderate-to-severe hepatic iron overload in the three siblings; however, no investigations for iron overload of skeletal muscle, brain, or endocrine organs have been performed to date. In terms of iron chelation therapy, desferrioxamine dosing was not significantly different between the siblings. All had been prescribed 3 g desferrioxamine on 5 days per week for several years, prior to intensification of their chelation regimes following the results of CMR imaging. The siblings did not report any specific side-effects, but adherence to the chelation regime was reported to be variable during early teenage life. In recent years compliance had improved, although remained suboptimal in one of the twins, which explains the higher ferritin levels noted. Transferrin levels were not measured.

No neurological abnormalities were noted in any of the siblings. All siblings suffered from hypothyroidism and hypogonadotrophic hypogonadism, and received appropriate replacement therapy. The twins had also been treated for growth hormone deficiency in the past.

None of the siblings received oral anticoagulation, and none had any evidence of embolic events. Pharmacotherapy was prescribed to one of the twins in the form of an ACE-inhibitor and digoxin following his admission with an arrhythmia. All siblings received intensified iron chelation therapy with plans to reassess cardiac iron load and cardiac function prior to further consideration of specific heart failure therapy. The results of these reassessments are awaited.

We agree that the noted association between LVHT and myocardial iron overload is interesting, although it remains unclear whether a causal relationship exists or whether these findings were coincidental. The presence of more pronounced abnormalities within twins, with less evident abnormalities in a sibling suggests a genetic component to these findings. Unanswered questions obviously remain regarding the link between LVNC and other pathologies.