CASE REPORT

Cardiac transplant in a family pedigree of hypertrophic cardiomyopathy secondary to a mutation in the AMP gene

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SUMMARY

The phenotype of this unique condition comprises left ventricular hypertrophy (LVH), accessory pathways, atrial arrhythmia and premature failure of the atrioventricular node. At age 11, his ECG showed marked voltage criteria for LVH but his echocardiography was negative. He declined further screening but was reassessed at 21 years of age. By this time he had developed significant LVH. He had an implantable cardioverter defibrillator (ICD) in 2001. He developed atrial flutter and fibrillation which was initially treated with medical therapy and then radiofrequency ablation. Unfortunately, his condition deteriorated. He was New York Heart Association (NYHA) class 3–4 for most of 2011 and spent the latter part of the year and most of 2012 as an in-patient. An attempt to upgrade his ICD to a cardiac resynchronisation therapy-defibrillator was unsuccessful. In March 2012 he was placed on the transplant waiting list. He received an organ in June. He is now NYHA class 1 and has returned to work part-time.

BACKGROUND

Mutations in the AMP gene signalling for AMP-activated protein kinase are an uncommon cause for hypertrophic cardiomyopathy.¹

The disease was first described in 1992. A familial hypertrophic cardiomyopathy with associated conductive tissue disease including Wolff-Parkinson-White syndrome and atrioventricular block was identified in a family in Ireland.

Twenty-two members of the family underwent genetic testing; all tested positive for the $\gamma 2$ subunit of the adenosine monophosphate activated protein kinase gene (PRKAG2) ($\gamma 2$ regulatory subunit) mutation in the AMP kinase gene.² Follow-up of this family has provided a unique insight into the natural history and the clinical expression of this genetic disease.

We present a case of the second member of the family to have a cardiac transplant for severe left ventricular dysfunction. The histology of the explanted organ provides new information as to the aetiology of the left ventricular hypertrophy in this condition.

Figure 1 12 Lead ECG age 12 years showing pronounced voltage criteria for Left Ventricular Hypertrophy and abnormal ventricular repolarisation.

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Figure 2 Age 21 years Transthoracic Echocardiogram showed severe Left Ventricular Hypertrophy. IVSd >3cm.

CASE PRESENTATION

At age 11 our patient was invited for familial screening with a 12 lead ECG and echocardiogram.

His ECG showed a short PR interval and abnormal ventricular repolarisation. A year later his ECG showed pronounced voltage criteria for hypertrophy and significant repolarisation abnormalities (figure 1). His echocardiogram at this time showed normal left ventricular wall size. His genetic screening confirmed he was positive for PRKAG2 mutation in the AMP kinase gene.

He did not wish to be routinely followed but in March 2001 age 21 years he developed chest pains and he was seen again. At this time he has significant left ventricular hypertrophy (LVH) demonstrable on echo (figure 2). His intraventricular septal diameter in diastole (IVSd) measured >3 cm (figures 3–6). During the intervening period, two members of his family, including his brother, had sudden cardiac deaths. For these reasons he was assessed for an implantable cardioverter defibrillator (ICD). Given the size of his IVSd and family history he was felt to be at high risk and a Medtronic Gem ICD was implanted.

Two years later he developed problems with paroxysmal atrial flutter and fibrillation with rapid decompensation requiring

Figure 4 Histology from explanted heart with PRKAG2 mutation. Sections from the left ventricle showing marked and interstitial fibrosis and vacuolar degeneration (arrows).

urgent DC cardioversion. He was started on amiodarone, which unfortunately led to amiodarone-induced hypothyroidism.

In 2009 he had pulmonary vein isolation. This was repeated in 2011 with radiofrequency ablation including a left atrial roof ablation given his history of atypical atrial flutter. The procedures were difficult with the right inferior pulmonary vein being difficult to isolate.

Despite the improvement in his arrhythmia's he remained New York Heart Association (NYHA) class 3–4 for most of 2011 and spent the latter part of the year and most of 2012 as an inpatient. His ICD was upgraded to a cardiac resynchronisation therapy-defibrillator device in November 2011. Unfortunately the left ventricular lead pacing caused diaphragmatic pacing and remained turned off.

Echocardiography at this time showed a reduction in his intra-ventricular septal wall diameter and dilation of the left ventricle. IVSd 2.5 cm, ejection fraction 50%, elevated right heart pressures 45–50 mm Hg. The elevated right heart pressure on echo was further assessed with a 'right heart catheter': right atrium mean 8, right ventricle 36/12, pulmonary artery 35/12, Mean 24, Wedge 15, cardiac output 4 L/min, pulmonary vascular resistance 2.4 Wood units. He did not have a left heart catheter.

As an inpatient in February 2012, his medical therapy at this time included losartan 25 mg, aldactone 50 mg, bumetanide 1 mg twice daily, metoprolol 50 mg twice daily, amiodarone 200 mg, lipitor 40 mg and intravenous milirone at 6.25 µg/kg/h.

Figure 3 Histology from explanted heart with PRKAG2 mutation. Sections from the left ventricle showing marked and interstitial fibrosis and vacuolar degeneration (arrows).

Figure 5 Histology from explanted heart with PRKAG2 mutation. Periodic acid Schiff stain showing vacuolar fibre debris.

Figure 6 Histology from explanted heart with PRKAG2 mutation. Desmin stain demonstrates very focal normal myocyte fibres with intercalated disc (arrow, top left). In contrast the background shows extensive tangles of fibrils some forming dots/aggregates seen in vacuoles (thick arrow, bottom right).

In March he was transferred to Dublin for transplant workup. He was also assessed by psychiatric services for anxiety.

He received his transplant in June. He is now NYHA class 1 and has returned to part-time work.

INVESTIGATIONS

Histology

The explanted heart was examined histologically using H&E, Masson.

Trichrome, desmin, Miller's elastic, periodic acid Schiff (PAS) and PAS plus diastase stains.

Macroscopic evaluation of the fixed explanted heart demonstrated marked left ventricular hypertrophy; maximum left ventricular thickness of 35 mm, right ventricle 5 mm and septum 20 mm. Light microscopy showed myocyte hypertrophy and marked subendocardial, transmural and interstitial fibrosis with extensive myofibre disarray. Severe coronary artery atherosclerotic disease (>70% stenosis) was also evident.

Prominent cytosolic vacuoles were present within cardiomyocytes, containing finely granular eosinophilic material, which are PAS negative and diastase-resistant, best represent degenerate fibre debris. These granules are desmin positive confirming that these vacuolar 'inclusions' are degenerative in nature not glycogen accumulation.

The histology from the first explanted heart in this family shows an almost identical pattern of vacuolar alteration, interstitial fibrosis and myofibre disarray.

DISCUSSION

Hypertrophic cardiomyopathy is a polygenic autosomal dominant disease characterised by myocyte hypertrophy and disarray and interstitial fibrosis.

Previous studies of this family pedigree lead to the discovery of a non-sarcomeric gene mutation. This was felt, initially, to

cause hypertrophy secondary to glycogen storage abnormality with pronounced vacuole formation within myocytes and deposition of amylopectin.²

Histological examination of the explanted hearts in this pedigree has shown interstitial fibrosis with extensive myofibre disarray. There were no histological findings to support the hypothesis that the LVH in this pedigree is secondary to a glycogen storage disease. In this case there was also evidence of premature coronary artery disease. This has not been previously described.

Although the genetic mutation in this family is known, how this results in the phenotype of the disease is not fully understood. The exact cause of the cardiac abnormalities in this family is still to be determined.

The presence of ECG abnormalities well ahead of echocardiographically detectable hypertrophy in this case may suggest that cellular abnormalities in ATP handling and signalling may be the initial insult with myocyte cell death and fibrosis occurring as a result of energy mismatch. The progression of LVH in this case occurred during puberty.

Further study of this family is planned.

Learning points

- ▶ In cases of familial hypertrophic cardiomyopathy, ECG abnormalities may predate true left ventricular hypertrophy assessed by transthoracic echo.
- ▶ Continued screening of first-degree relatives with a 12-lead ECG and echocardiogram every 1–2 years is recommended into late adolescence.
- ▶ Structural cardiomyopathies can often coexist with electrophysiological conditions.
- ▶ Transplantation should be considered in patients with significant heart failure symptoms not remediable with conventional measures.

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Contributors RSS, KMG and CLM wrote the case report; KOH was involved in histology reports and provided slides. KMG originally diagnosed and cared for the patient.

Competing interests None.

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