Familial spontaneous complete heart block in hypertrophic cardiomyopathy

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SUMMARY Two siblings with hypertrophic cardiomyopathy developed spontaneous complete heart block requiring permanent pacemaker implantation at similar ages (29 and 33 years). The clinical, morphological, and haemodynamic expressions of hypertrophic cardiomyopathy differed considerably in these two patients. The sister had severe functional limitation due to dyspnoea, pronounced and diffuse left ventricular hypertrophy (maximum ventricular septal thickness of 41 mm), and left ventricular outflow obstruction (peak subaortic gradient of 75 mm Hg under basal conditions). In contrast the brother was symptom free, had only modest left ventricular hypertrophy which was confined to the anterior ventricular septum (maximal thickness of 16 mm), and had no echocardiographic evidence of subaortic obstruction. These dissimilar findings in siblings with hypertrophic cardiomyopathy suggest that the predisposition to develop complete heart block was probably genetically transmitted, although it was unrelated to the phenotypic and clinical expression of the disease.

Hypertrophic cardiomyopathy is a primary myocardial disease, usually genetically transmitted as an autosomal dominant trait.¹⁻³ This disease is characterised by great heterogeneity in the patterns of left ventricular hypertrophy⁴ that are present even among closely related patients.⁵ Complete heart block is rare in patients with hypertrophic cardiomyopathy, and its aetiology has not been defined. Sporadic examples, however, have been reported at all ages including those in a neonate in whom the abnormality was congenital⁶ and in several young adults.⁷⁻¹² Complete heart block that was apparently unrelated to acquired cardiac disease has also been reported in older adults¹³⁻¹⁶ and in elderly patients¹⁷⁻²¹ with hypertrophic cardiomyopathy.

Recently, we have evaluated a sister and brother with hypertrophic cardiomyopathy who both developed complete heart block as young adults. We believe that such an occurrence is particularly unusual and represents an opportunity to assess and discuss

the potential aetiology of complete heart block in this disease. Hence, the present report describes and compares the clinical and morphological features identified in a sister and brother with hypertrophic cardiomyopathy and complete heart block.

Case reports

Sister—The sister had experienced exertional dyspnoea and fatigue attributed to hypertrophic cardiomyopathy for seven years and also had a history of mild systemic hypertension (165/100 mm Hg while off medications and normal blood pressure on alpha methyl dopa (1 g per day) and propranolol (30 mg per day)). At initial evaluation at the National Institutes of Health, a grade 3/6 systolic ejection murmur which increased during the Valsalva manoeuvre was present at rest; the electrocardiogram showed normal sinus rhythm (65 beats per minute) and left bundle branch block pattern. At cardiac catheterisation under basal conditions, pull-back recordings from the left ventricular apex to the ascending aorta showed systolic pressures of 240 mm Hg in the distal left ventricular cavity and 165 mm Hg in the outflow tract. A 75 mm Hg peak to peak systolic pressure gradient was apparently localised to the

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Fig. 1 Electrocardiogram confirming persistence of complete heart block (18 months after its onset) in the sister. At the left the tracing shows normal pacemaker function (atrial sensing and ventricular pacing with 100% capture). Subsequently (arrow) the pacemaker output was programmed to subthreshold levels; this resulted in pacemaker spikes which failed to capture the ventricles and unmasked P waves which do not conduct to the ventricles. A seven second period of ventricular asystole ensued before the appearance of a ventricular escape beat (asterisk).

mid-ventricular cavity level distal to the tips of the mitral valve leaflets (and not associated with systolic anterior motion of the mitral valve on angiogram or M mode echocardiogram); during the Valsalva manoeuvre the pressure gradient increased to 120 mm Hg. Left ventricular end diastolic pressure was 26 mm Hg.

Subsequently (at 33 years of age) the patient experienced a prolonged episode of lightheadedness and was found to have a heart rate of 20 beats per minute. Electrocardiogram showed complete heart block with sinus P waves which failed to conduct to the ventricles and a slow idioventricular escape rhythm that was different from her previously identified left bundle branch block pattern. These electrocardiographic findings are consistent with an infranodal conduction block; however, in the absence of intracardiac His potential recordings a higher level of block cannot be excluded. Serum electrolyte, calcium, and creatine kinase concentrations were normal.

Permanent pacing was started with a Cordis 233 F pacemaker. At follow up one and a half years later the electrocardiogram showed ventricular pacing with 100% capture; complete heart block was confirmed by programming the rate of the pacemaker to subthreshold levels. This uncovered the sinus P waves that failed to conduct to the ventricles

and resulted in a seven second period of ventricular asystole (Fig. 1).

Brother—The brother had not been evaluated for cardiovascular disease before the onset of complete heart block. He was symptom free until the age of 29 years when he fainted four times within a two week period. After the fourth episode of syncope he was found to have pronounced bradycardia (30 beats per minute). The electrocardiogram showed complete heart block. As in his sister's case an infranodal level of block was indicated by the failure of sinus P waves to conduct to the ventricles and the presence of a slow idioventricular escape mechanism, though a more proximal level of block cannot be excluded. Serum electrolyte, calcium, and creatine kinase concentrations were normal.

Permanent pacing was started with an Intermedics 253-04 pacemaker. At follow up two and a half years later the electrocardiogram showed ventricular pacing with 100% capture; complete heart block was confirmed by programming the rate of the pacemaker to 30 beats per minute. This uncovered sinus P waves which failed to conduct to the ventricles.

On physical examination a grade 1/6 systolic ejection murmur was heard along the left sternal border which did not change appreciably with the Valsalva manoeuvre; blood pressure was 150/90 mm Hg. The

Table Echocardiographic findings in siblings with hypertrophic cardiomyopathy and complete heart block

Variable	Sister	Brother
Ventricular septal thickness (mm)	41 (8–12)*	16 (8–11)
Posterior free wall thickness (mm)	8 (8–11)	9 (8–11)
Septal to free wall ratio	3.9 (<1.3)	1.8 (<1.3)
% Systolic thickening of septum	0 (>30%)	25 (>30%)
LV end diastolic dimension (mm)	42 (42–53)	50 (41–52)
LV end systolic dimension (mm)	26 (25–36)	30 (24–35)
% Fractional shortening	38 (28–44%)	40 (28–44%)
RV end diastolic dimension (mm)	18 (9–26)	21 (9–26)
Left atrial dimension (mm)	48 (30–44)	41 (30–43)

*Normal values or range are shown in parentheses.^{25–27}

LV, left ventricle; RV, right ventricle.

Fig. 2 Stop frames of short axis echocardiograms obtained during diastole showing contrasting morphological features in the sister and brother. Each echocardiogram is accompanied by a schematic illustration (below). (a) Pronounced ventricular septal thickening and substantial hypertrophy in the contiguous anterolateral free wall in the sister. (b) Mild anterior ventricular septal thickening in the brother; other areas of the left ventricular wall are of normal thickness. FW, free wall; VS, ventricular septum. Calibration dots are 10 mm apart.

absence of both an important heart murmur and of systolic anterior motion of the mitral valve on echocardiographic studies suggests the absence of a sub-aortic pressure gradient under basal conditions. The patient did not undergo cardiac catheterisation.

Echocardiographic findings in siblings

The M mode echocardiographic findings in the two siblings are compared in the Table. In each patient the left ventricle was not dilated and the pattern of left ventricular hypertrophy was asymmetric (ventricular septal to posterior free wall ratios were 3.9 in the sister and 1.8 in the brother). Cross sectional echocardiography showed the magnitude and distribution of hypertrophy to be markedly different in

the siblings (Fig. 2). The sister had pronounced diffuse hypertrophy affecting the entire ventricular septum (maximum thickness of anterior septum 41 mm) as well as the contiguous portion of the anterolateral left ventricular free wall (thickness of 22 mm). In contrast the brother showed only mild wall thickening (16 mm) (Fig. 3) which was confined to the anterior ventricular septum; the posterior septum and the left ventricular free wall appeared normal in thickness. Neither patient demonstrated systolic anterior motion of the mitral valve (Fig. 3).

Echocardiographic analysis of other family members

Genetic transmission of hypertrophic cardiomyopathy was demonstrated in relatives of the two

Fig. 3 M mode echocardiogram at the mitral valve level obtained in the brother. The ventricular septum is slightly thickened whereas the posterior wall is of normal thickness, resulting in a septal to free wall ratio of 1.8. There is no systolic anterior motion of the mitral valve. MV, mitral valve; PW, posterior wall; RV, right ventricle; VS, ventricular septum. Calibration dots are 10 mm apart.

siblings (Fig. 4). Their mother (who is symptom free) showed an increased ventricular septal thickness of 20 mm, left ventricular posterior free wall

Fig. 4 Family pedigree for the two siblings (arrows) with hypertrophic cardiomyopathy and complete heart block. Patient's ages (in years) at most recent follow up or at death are shown in parentheses. Solid symbols, sudden death presumed to be due to hypertrophic cardiomyopathy; half-filled symbols, alive with hypertrophic cardiomyopathy identified by echocardiography; stippled, alive with no evidence of hypertrophic cardiomyopathy on echocardiographic studies; clear symbols, individuals not studied with echocardiography; squares, males; circles, females.

thickness of 10 mm, and a septal to free wall thickness ratio of 2.0; the left ventricle was non-dilated and the end diastolic transverse dimension was 42 mm. Systolic anterior motion of the mitral valve was absent. She had no evidence of systemic hypertension or other cardiac diseases that could produce left ventricular hypertrophy.

In addition the siblings' maternal uncle and maternal grandmother died suddenly at 28 and 38 years of age respectively. While we assume that these two relatives had hypertrophic cardiomyopathy, this diagnosis could not be confirmed in either individual because neither clinical evaluation during life nor necropsy examination of the heart were performed.

Discussion

This report describes the unusual occurrence of spontaneous complete heart block in two youthful siblings with hypertrophic cardiomyopathy. Onset of heart block was accompanied in each patient by syncope or lightheadedness and pronounced bradycardia necessitating the implantation of a permanent pacemaker. Neither patient had evidence of other cardiovascular abnormalities or metabolic alterations that could have been responsible for the development of complete heart block. While both siblings had a history of mild systemic hypertension, it is highly unlikely that this condition could have produced complete heart block in such youthful in-

dividuals. Propranolol, which was taken by the sister, is not known to prolong the HV interval or produce infranodal heart block at usual therapeutic dosages.¹⁴ The mother of these two siblings with hypertrophic cardiomyopathy and complete heart block had no evidence of clinically overt connective tissue disease.²²

The precise mechanism by which complete heart block occurred in our patients has not been defined. Previous histopathological analyses of the conduction system in two patients with hypertrophic cardiomyopathy and advanced conduction system disease (one with HV prolongation and split His potentials and the other with complete heart block) identified alterations of potential pathophysiological importance, including interstitial fibrosis or myocardial necrosis and abnormal small intramural coronary arteries with thickened walls and luminal narrowing.^{12 23}

Whereas both our patients had hypertrophy affecting the basal septum in the region of the conduction system, the magnitude of septal thickening did not appear to be an important aetiological factor in producing complete heart block. The sister had pronounced and diffuse left ventricular hypertrophy with substantial ventricular septal thickening (in excess of 40 mm); however, the brother showed only mild localised anterior septal thickening (of about 15 mm). Indeed, these patients illustrate the heterogeneity and dissimilarity of patterns of left ventricular hypertrophy that are characteristic of first degree relatives with hypertrophic cardiomyopathy.⁵

Obstruction of the left ventricular outflow tract does not appear to be necessary for the spontaneous development of complete heart block in hypertrophic cardiomyopathy. The sister had a pronounced intraventricular pressure gradient at rest which appeared to be confined to the mid-cavity region of the left ventricle and was not associated with mitral systolic anterior motion,²⁴ while the brother (who did not undergo cardiac catheterisation) had no echocardiographic evidence of basal subaortic obstruction.

The sister had had complete left bundle branch block pattern on electrocardiogram for at least six years before the occurrence of complete heart block. It is tempting to speculate¹⁶ that her left bundle branch block was indicative of pre-existing disease of the conduction system and was a forerunner of the subsequent complete heart block.

The dissimilar clinical, morphological, and haemodynamic expressions of hypertrophic cardiomyopathy in our two siblings suggest that the predisposition to develop complete heart block was genetically transmitted but was largely unrelated to the phenotypic and clinical expression of the disease.

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