Asymmetric septal hypertrophy and hypertrophic cardiomyopathy

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SUMMARY Nineteen families were selected for study in which hypertrophic cardiomyopathy and/or isolated asymmetric septal hypertrophy occurred in successive generations. All 19 probands had hypertrophic cardiomyopathy proven by cardiac catheterisation and angiocardiology (eight), operation (four), or necropsy (seven). These 19 families consisted of the 19 probands and their 39 siblings, 38 parents, and 23 children. Of these 119, 114 were examined or, if dead before the study, there was sufficient evidence from necropsy or operation reports to establish the diagnosis. In five (four parents and one sibling) who had died before the study there was insufficient evidence to establish the presence or absence of heart disease. These 19 families were selected from over one hundred cases of familial cardiomyopathy with a minimum follow up of five years. The main points leading to selection were the presence of the disease in two successive generations and the availability of the first degree relatives for examination.

The families were divided into two subsets. One consisted of 12 families where not only the proband had all the clinical manifestations of hypertrophic cardiomyopathy but so did one of the parents. In the second subset of seven families, the proband had proven hypertrophic cardiomyopathy, but one of the parents had isolated asymmetric septal hypertrophy, with no other manifestation of cardiovascular disease. For the purpose of this study differentiation was made between relatives with clinical, radiological, electrocardiographic, and echocardiographic signs of hypertrophic cardiomyopathy, and those in whom the only abnormality was in the interventricular septum and detected solely by echocardiography. The term isolated asymmetric septal hypertrophy was applied to the latter if the interventricular septal:posterior left ventricular wall (IVS/PLVW) ratio was 1.3 or more, when allowance had been made for the thickening of the interventricular septum which occurs with age.

In the 12 families (subset I) where both the proband and one parent had hypertrophic cardiomyopathy, there were the 12 probands with 22 siblings. Nineteen of these 34 were found to have hypertrophic cardiomyopathy and one had isolated asymmetric septal hypertrophy; thus there were 20 affected. In the seven families (subset II) in which the proband had proven hypertrophic cardiomyopathy and one of the parents had isolated asymmetric septal hypertrophy, there were the seven probands with 17 siblings. Eleven of these 24 had hypertrophic cardiomyopathy and one had isolated asymmetric septal hypertrophy; thus 12 were affected. Applying Smith's method of analysis, the expected number affected if the condition was inherited as a dominant characteristic was 20.1 in subset I and 13.4 in subset II. These figures did not differ significantly from those actually found, that is 24 and 12, respectively.

The conclusions are that in familial hypertrophic cardiomyopathy isolated asymmetric septal hypertrophy is part of the clinical spectrum and has the same genetic implications as hypertrophic cardiomyopathy. Thus parents with clinical hypertrophic cardiomyopathy can produce offspring with either isolated asymmetric septal hypertrophy or clinical hypertrophic cardiomyopathy. Con-

versely, parents with isolated asymmetric septal hypertrophy can produce children with either anomaly. In all circumstances other than hypertrophic cardiomyopathy, asymmetric septal hypertrophy does not appear to be an inherited characteristic.

Asymmetric septal hypertrophy can no longer be considered the "unifying link" in hypertrophic cardiomyopathy.¹ It occurs in a small percentage of normal adults, is common in infants,^{2,3} may be present in athletes,⁴ and it is also seen in cases of congenital heart disease, particularly where the right ventricle is involved.⁵⁻⁹ It is not uncommon in fixed aortic valve stenosis^{7,10} and it also occurs in hypertension¹¹ and coronary artery disease, especially with inferior infarction.^{12,13} Conversely, it is occasionally absent in cases of hypertrophic cardiomyopathy where the disarrayed muscle involves the free wall of the left ventricle as extensively as the interventricular septum.¹⁴⁻¹⁶

Confusion will arise if the term asymmetric septal hypertrophy is used synonymously with hypertrophic cardiomyopathy. It is suggested that the latter should be used to describe cases with clinical, radiological, electrocardiographic, and echocardiographic evidence of the disease, which will include asymmetric hypertrophy of the interventricular septum. The term asymmetric septal hypertrophy, qualified by the word isolated, should be confined to those cases where the sole abnormality is in the interventricular septum, detected only by echocardiography, and where there is no clinical, radiological, or electrocardiographic evidence of cardiovascular disease.

The problem is exemplified by Clark *et al.*¹⁷ who referred to 44 first degree relatives with asymmetric septal hypertrophy. In 77% there were abnormalities in the history, physical examination, or electrocardiogram, but in the remaining 23% the abnormalities were confined to the interventricular septum. Similarly, in 27 first degree relatives reported by Van Dorp *et al.*¹⁸ and referred to as having asymmetric septal hypertrophy, 83% were clinically affected, but in 17% the abnormality was confined to the interventricular septum. The same was the case with the first degree relatives reported by Ten Cate *et al.*¹⁹ where only the minority had abnormalities confined to the interventricular septum.

In this study a differentiation has been made between relatives with clinical, radiological, electrocardiographic, and echocardiographic evidence of hypertrophic cardiomyopathy and those in whom the only abnormality was in the interventricular septum, detected solely by echocardiography. The term isolated asymmetric septal hypertrophy has been confined to the latter. An interventricular septum to posterior left ventricular wall (IVS/PLVW) ratio of 1.3 or more was considered abnormal when allowance

had been made for the thickening of the interventricular septum which occurs with age.²⁰⁻²²

The purpose of this study was to examine the association of isolated asymmetric septal hypertrophy and its relation to hypertrophic cardiomyopathy in selected families.

Subjects and methods

Nineteen families were selected for study in which the proband had hypertrophic cardiomyopathy proven by cardiac catheterisation and angiocardiology (eight), operation (four), or necropsy (seven). These were divided into two subsets. In the first there were 12 families where not only the proband but also one of the parents had all the clinical, radiological, electrocardiographic, and echocardiographic manifestations of hypertrophic cardiomyopathy. In the second group of seven families the proband had proven hypertrophic cardiomyopathy but one parent had isolated asymmetric septal hypertrophy without any other manifestation of cardiovascular disease. These 19 families consisted of the 19 probands and their 39 siblings, 38 parents, and 23 children. Of these 119 first degree relatives, 114 were examined or, if dead before the study, there was sufficient evidence available from previous medical examinations or from necropsy or operation reports to establish the presence or absence of heart disease. There were five exceptions, four parents (54.I.1, 72.I.1, 73.I.1, and 93.I.1) and one sibling (72.II.4) who died before study and without adequate information available for a diagnosis to be made.

As in previous studies,²³⁻²⁷ arrangements were made to interview the proband or a close relative at home and a family pedigree was drawn up which included all first, second, and third degree relatives. Because of the problem of availability the analysis was confined to first degree relatives as by so doing it was possible to examine or obtain reliable information on 95.8% of the sample. During the interview, specific questions were asked to ascertain whether any relative was known to have a cardiac abnormality. Parents, siblings, and children of the proband who were willing to co-operate were examined at the National Heart Hospital, The Middlesex Hospital, or a convenient regional hospital. Examination involved physical examination, chest radiography, electrocardiography, and echocardiography. If the examination was done at a regional hospital, all the chest radiographs

Table 1 Analysis of propoiti and siblings from 19 families

	No. of offspring*	No. with HC	No. with IASH	Expected No. affected	Variance
12 families in which propoitus and one parent had hypertrophic cardiomyopathy	34	19 +	1	20.1	5.5
Seven families in which propoitus had hypertrophic cardiomyopathy and one parent had isolated aymmetric septal hypertrophy	24	11 +	1	13.4	4.4

In 12 of the families both propoitus and one parent had hypertrophic cardiomyopathy; in the remaining seven the propoitus had hypertrophic cardiomyopathy and one parent isolated asymmetric septal hypertrophy. Figures for the expected number affected, assuming a dominant inheritance (Smith²⁸), are also shown. *Offspring=propoiti and their siblings.

and electrocardiograms were sent to one of us (RE). All echocardiograms were done by JM at The Middlesex Hospital using a Smith Kline Ekoline 20A and a 2.25 MHz Transducer focused at 7.5 cm coupled to a Cambridge six channel fibreoptic recorder. Recordings were made with the subject lying on the left side. The mitral valve echocardiogram was recorded from a transducer in the third, fourth, or fifth intercostal space, perpendicular to the chest wall. Aortic valve echoes were identified by tilting the transducer medially and superiorly from the mitral valve position. The interventricular septal and free posterior left

ventricular wall echoes were recorded at both mitral and submitral levels, measurements being made at the Q wave inscription of the electrocardiogram.

Results

The 19 families were divided into two groups. In the 12 families where both the propoitus and one parent had hypertrophic cardiomyopathy there were 12 propoiti with their 22 siblings. Nineteen of these 34 (one of the siblings (72.II.4) was not examined) were found to have hypertrophic cardiomyopathy and one

Fig. 1 Pedigrees of 12 families in which the propoitus and one parent had hypertrophic cardiomyopathy. The doubtful cases (72.III.1 and 89.II.1) have been considered normal for the purposes of the statistical analysis. In the three relatives who may have additional congenitally bicuspid aortic valve (BAV) diagnostic details are given in Table 2. HC, hypertrophic cardiomyopathy. IASH, isolated asymmetric septal hypertrophy. PMV, prolapsed mitral valve.

had isolated asymmetric septal hypertrophy; thus there were 20 affected. Analysing these figures according to Smith,²⁸ who allowed for the inevitable truncate selection of this type of material, if the condition was inherited as a dominant characteristic the predicted number affected would be 20.1 which was not significantly different from our findings of 19 or 20 if the one sibling with isolated asymmetric septal hypertrophy was included. Considering the seven families in which the propositus had proven hypertrophic cardiomyopathy and one of the parents isolated asymmetric septal hypertrophy, there were the seven propositi and their 17 siblings. Examination showed 11 of these 24 had hypertrophic cardiomyopathy and one had isolated asymmetric septal hypertrophy; thus 12 were affected. Again applying Smith's²⁸ analysis, if the inheritance was dominant the expected number of affected would be 13.4 which again did not differ significantly from our findings of 11 or 12 if the sibling with isolated asymmetric septal hypertrophy was included; thus in neither subgroup was there a significant difference between our results and those expected for a dominant mode of inheritance (Table 1). Pedigrees of the 19 families are given in Fig. 1 and 2. In three siblings (32.II.3, 89.II.1, and 93.II.1) the diagnosis was uncertain. In the pedigrees they have

been shown as "doubtful hypertrophic cardiomyopathy" but have been considered unaffected for the purpose of the above analysis. The clinical details of the 12 parents, 11 siblings (seven in subset I; four in subset II), and three children with hypertrophic cardiomyopathy are given in Table 2.

The echocardiographic data leading to the diagnosis of isolated asymmetric septal hypertrophy in the two siblings and seven parents are given in Table 3. Henry *et al.*²⁹ have examined 92 normal persons using M-mode echocardiography and have produced regression equations with limits for septal thickness and posterior ventricular wall thickness. Using these equations for the two siblings and seven parents we find that the interventricular septal measurements fall outside the 95% prediction interval for normal subjects, whereas the posterior left ventricular wall thicknesses are well within normal limits, thus confirming the diagnosis of isolated asymmetric septal hypertrophy (Table 3). It should be noted that Marcomichelakis *et al.*²² in their analysis of 100 normal male subjects, found that there was not only an increase in the IVS/PLVW ratio with age, but also an increase in the scatter of the ratios after the age of 40 years. Assuming the same is true for female subjects, the two siblings and seven parents had an IVS/PLVW ratio at or

Table 2 Clinical findings in 12 parents, 11 siblings, and three children with hypertrophic cardiomyopathy

Pedigree No.	Sex	Age	Murmurs	Electrocardiogram
7.I.2	F	57	—	—
13.I.1	M	53	—	SR and SVT LV+ AF, ST and T↓ I II V5-7
54.I.2	F	66	—	—
54.II.1	M	16	—	—
72.I.2	F	71	LSM:3rd	SR, Q II III avF
72.II.1	M	37	—	—
73.I.2	F	65	EJSM	SR, Q I avL:ST and T↓ I avL V4-6
73.II.5	F	38	EJSM	SR, N
73.III.1	M	18	EJSM: 3rd	SR, Q II III avF V5-6
77.I.1	M	51	EJSM	SR, T↓ I II avL V4-6
77.II.2	M	47	EJSM:LSM	SR, Q I avL
80.I.1	M	64	EJSM	SR, T↓ I II V2-6:V+
80.II.2	F	45	EJSM	SR, T↓ I avL V4-6
80.III.2	F	10	EJSM	SR, RV+Axis+140, P pul
89.I.1	M	31	—	—
90.I.1	M	47	PanSM:4th	SR, T↓ avL
91.I.1	M	56	None	SR, T↓ avL avF V4-6
91.II.3	F	28	EJSM	SR, Q II III avF V4-6
93.II.4	M	45	EJSM	SR, Q I avL:Dim R V1-4
93.II.5	M	40	EJSM:LSM	SR, Q I II avL, V4-6
96.II.1	M	47	EJSM	SR, LBBB
96.II.4	M	36	EJSM:LSM	SR, T↓ II III avF V6
96.III.1	M	17	LSM	SR, T↓ I II avL V3-6: Q avL
98.I.1	M	46	EJSM:4th	SR, T↓ I avL V4-6
99.I.1	M	47	EJSM:PanSM	SR, AV dis, LBBB
99.II.1	M	22	EJSM	SR, Q I avL V6

Note: The 19 propositi have been omitted. Doubtful cases (32.II.3, 33.III.4, 72.III.1, 89.II.1, and 93.II.1, see Fig. 2) have also been omitted. Abbreviations used are as follows: 3rd, third heart sound; 4th, fourth (atrial) heart sound; EJSM, ejection systolic murmur; LSM, late systolic murmur; PanSM, pansystolic murmur; SR, sinus rhythm; SVT, supraventricular tachycardia; AF, atrial fibrillation; AV dis, atrioventricular dissociation; increased voltage (S V2 or V3+R V5 or V6>35 mm); P pul, P pulmonale; Dim R V1-4, diminishing R wave V1-4; LBBB, left bundle-branch block; x-ray+, enlarged heart; Im IVS, impaired movement of interventricular septum; EC AV CL, eccentric aortic valve closure; SAM, systolic anterior motion.

By definition in all cases of isolated asymmetric septal hypertrophy the sole abnormality was in the interventricular septum. All nine cases in Table 3 were considered normal after clinical examination which included an electrocardiogram and chest radiograph, but after the echocardiogram had been found abnormal these data were reviewed. In two relatives there were minor abnormalities which had previously been accepted as normal, mainly on account of the patients' ages, but in retrospect these findings were probably related to the abnormal interventricular septum. In one man aged 67 (33.I.2), there was a soft (grade 1/6) apical late systolic murmur, and in one woman, aged 65 (96.I.2), the electrocardiogram showed a partial right bundle-branch block.

When considering the thickness of the interventricular septum as a specific measurement or comparing it with the thickness of the posterior left ventricular wall as a ratio, it is important to appreciate that both become thicker with age, particularly the interventricular septum. More relevant, perhaps, is the scatter in the IVS/PLVW ratios, which occurs above the age of 40 years, and great caution must be exercised

1st x-ray	Echocardiogram		Catheter	Dead/Alive	Other information
	IVS/PLVW	Other observations			
—	—	—	—	+57	Sudden+PM
—	—	—	—	+53	Sudden+PM
R	R	—	LV++ No Grad	A	—
—	—	—	—	+16	Sudden+PM Ht wt 340 g
—	—	—	—	+73	Sudden+PM
—	—	—	—	+37	Sudden+PM Ht wt 410 g
2:0	—	—	—	+69	Sudden+
1:6	EC AV CL	—	—	A	? BAV
1:5	Im IVS	—	—	A	? BAV
—	—	—	—	+59	PM
1:7	Im IVS:PMV	—	—	A	—
—	—	—	—	+64	—
1:5	SAM	—	—	A	—
1:5	—	—	—	A	—
—	—	—	LV++ Grad 50 mm	+31	Sudden+PM
—	—	—	—	+53	Sudden+PM Ht wt 510 g
1:7	Im IVS	—	—	A	—
1:5	EC AV CL	—	—	A	? BAV
1:7	Im IVS	—	—	A	—
1:6	Im IVS	—	—	A	—
1:4	—	—	—	A	—
1:5	SAM	—	—	A	—
1:7	Im IVS	—	—	+21	Sudden+PM Ht wt 900 g
1:5	SAM:	—	LV++ Grad 60 mm	A	Confirmed at surgery
—	EC AV CL	—	—	—	AV normal
—	Mid Sys CL	—	—	—	—
—	—	—	LV++ Grad 10 mm	+53	PM
1:2	—	—	—	A	(see text)

Table 3 Echocardiographic findings in two siblings and seven parents with isolated asymmetric septal hypertrophy

Pedigree No.	Sex	Age	BSA	IVS (mm)	Predicted IVS at 95% interval	PLVW (mm)	Predicted PLVW at 95% interval	Other findings
<i>Two siblings</i>								
73.II.2	F	46	1.70	12	11.74	9	11.26	Im IVS
82.II.2	M	18	1.76	13	10.95	9	10.47	Im IVS
<i>Seven parents</i>								
24.I.2	F	78	1.60	16	12.61	10	12.12	Im IVS
32.I.1	M	53	1.87	15	12.42	10	11.96	Im IVS
33.I.1	M	67	1.94	15	13.06	10	12.57	Im IVS
82.I.1	M	51	1.88	18	12.37	10	11.87	Im IVS
93.I.1	F	74	1.42	15	12.02	10	11.53	—
96.I.2	F	65	1.68	17	12.45	10	11.92	—
97.I.1	M	66	1.96	19	13.10	—	12.60	PM Ht wt 602 g

*Actual measurements of IVS and PLVW obtained, compared with the 95% predicted limits from 92 normal subjects. **Henry *et al.*²⁹ The following abbreviations have been used: Im IVS, impaired movement of interventricular septum; PM, post-mortem examination; Ht wt, heart weight at necropsy.

before accepting ratios of 1.3 or more above this age as being abnormal.

In the 12 families where not only the proband but one parent had hypertrophic cardiomyopathy, one of the siblings had isolated asymmetric septal hypertrophy. Conversely, in the seven families where the proband had hypertrophic cardiomyopathy and one of the parents isolated asymmetric septal hypertrophy, the seven probands and six of their siblings had hypertrophic cardiomyopathy and only one sibling had isolated asymmetric septal hypertrophy. Therefore, a parent with either clinical hypertrophic cardiomyopathy or isolated asymmetric septal hypertrophy may produce an offspring with either manifestation of the disease, that is hypertrophic cardiomyopathy or isolated asymmetric septal hypertrophy.

In these 19 families there were 23 children. Assuming a dominant inheritance the expected number affected would be 11.5, but only three were found to have hypertrophic cardiomyopathy and two isolated asymmetric septal hypertrophy both of whom may also have bicuspid aortic valves as the echocardiograms showed eccentric aortic valve closure and in one (77.III.2) there was also a soft aortic diastolic murmur. (In 33.III.4 and 72.III.1 the diagnosis was doubtful and these children have therefore been considered normal in the statistical analysis.) The figure of five (three with hypertrophic cardiomyopathy and two with isolated asymmetric septal hypertrophy) does not differ significantly from the expected number ($\chi^2 = 2.8$), though it is low, which may be because of underdiagnosis. The explanation for this in the younger age group is discussed elsewhere³⁰ but we have increasing evidence that, though the disease is genetically determined, its clinical manifestations may not be evident until adolescence, or even early adult life. A good example of this was Family 99. When first seen 99.II.1 and 99.II.2 were aged 11 and 9 years. They were asymptomatic, the cardiovascular findings

were normal, in particular there were no murmurs, and both the electrocardiograms and chest radiographs were normal. Echocardiography was not available. When examined eight years later because the younger (99.II.2) had had a syncope attack while playing football, both had developed ejection murmurs. The electrocardiograms had become abnormal; in the younger (99.II.2) there was T wave inversion in the left chest leads and equivalents, and in the elder (99.II.1) pathological Q waves had developed in I, aVL, V5, and 6. Their chest radiographs had remained normal. The echocardiograms, previously unrecorded, were abnormal; in both there was a thickened immobile interventricular septum and the younger also showed systolic anterior movement of the mitral valve. The IVS/PLVW ratio was 1.4. Five years after this examination he died suddenly at the age of 22 years. The diagnosis of hypertrophic cardiomyopathy was confirmed at necropsy, the heart weighing 430 g. The interventricular septum measured 33 mm compared with the free wall of the left ventricle which was 20 mm. The echocardiogram in the elder (99.II.1) when aged 19 years showed an immobile and abnormally thick interventricular septum measuring 13 to 14 mm. There was also thickening of the posterior left ventricular wall 11 to 12 mm giving an IVS/PLVW ratio of 1.2 which was within normal limits. After the inhalation of amyl nitrate, however, there was systolic anterior movement of the mitral valve. In this case the thickening of the posterior left ventricular wall tended to make the ventricular hypertrophy more symmetrical than usual, which is known to occur in some cases of hypertrophic cardiomyopathy. All causes of symmetrical hypertrophy such as hypertension and aortic valve stenosis had been excluded and the diagnosis of hypertrophic cardiomyopathy was strongly supported in this case by the development of murmurs between the ages of 11 and 19 years, the changes in the electrocardiograms during the same period, and the

strongly positive family history: his brother, father, and father's sister all had proven hypertrophic cardiomyopathy.

It is uncertain whether some genetically determined cases of isolated asymmetric septal hypertrophy, that is those occurring in families in which there are no known cases of hypertrophic cardiomyopathy, progress and develop the full clinical picture of hypertrophic cardiomyopathy. There is some evidence that this may occur in children and in young adults, but after the age of 20 we have not seen isolated asymmetric septal hypertrophy alter with the years.

GENETICS

The fundamental problem is the genetic relation between asymmetric septal hypertrophy and hypertrophic cardiomyopathy. A survey of the published reports on the inheritance of asymmetric septal hypertrophy^{18 19 31} showed that the data have been ascertained through families in which there were proven cases of hypertrophic cardiomyopathy. Only Maronichelakis *et al.*²² studied the normal population and looked at asymmetric septal hypertrophy in those subjects who were at the extreme of the distribution of septal thickness when allowance had been made for their age. Their findings confirmed that asymmetric septal hypertrophy was non-specific for hypertrophic cardiomyopathy.

The simplest genetic concept would be a single autosomal dominant gene which could be expressed in a mild (isolated asymmetric septal hypertrophy) or severe (hypertrophic cardiomyopathy) form. The problem, however, of the variation of expression within a family would remain unanswered. It could be postulated that there was either a gene for asymmetric septal hypertrophy which with genetic or environmental modifiers could be expressed as hypertrophic cardiomyopathy or, conversely, that there was a gene for hypertrophic cardiomyopathy which, with other genetic or environmental modifiers, could be expressed as isolated asymmetric septal hypertrophy. Whichever is the case the net effect is that the hypertrophic cardiomyopathy expression behaves like an autosomal dominant condition. Until a genetic study of asymmetric septal hypertrophy is done in its own right nothing can be said about its mode of inheritance. The suggestion that more than one factor is involved would fit the threshold model proposed by a number of authors in other conditions.^{32 33} Indeed there is evidence that part of the underlying liability for hypertrophic cardiomyopathy might be related to the HLA-DRW4 antigen linkage.³⁴

The delayed clinical expression of hypertrophic cardiomyopathy in many cases and the fact that there is some evidence that isolated asymmetric septal hypertrophy may progress to hypertrophic car-

diomyopathy suggest that the liability to asymmetric septal hypertrophy may be part of the underlying predisposition. It also suggests that the threshold for asymmetric septal hypertrophy is just below that for hypertrophic cardiomyopathy. Under these conditions such a complex genetic aetiology may simulate dominance.

By definition all patients with hypertrophic cardiomyopathy had asymmetric septal hypertrophy. If hypertrophic cardiomyopathy represents the increased severity of liability then both isolated asymmetric septal hypertrophy and hypertrophic cardiomyopathy may occur in the same family. This was the case in both the subsets studied and it would also explain the much greater incidence of hypertrophic cardiomyopathy than isolated asymmetric septal hypertrophy in any affected generation.

Our conclusion is that when a patient presents with isolated asymmetric septal hypertrophy if there is hypertrophic cardiomyopathy in the family, then either of them may be expected in 50% of the offspring. Any minor deviations from 50% are what one might expect from a complex trait simulating dominance.

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