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Familial Hypertrophic Cardiomyopathy: New Insight on Mode of Inheritance among Egyptian Children

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Abstract

Background: No single mode of Inheritance is typical of Hypertrophic cardiomyopathy (HCM). Although autosomal dominant (AD) transmission is most common yet the existence of a recessive form of hypertrophic cardiomyopathy could neither be established nor disproved. This work aims to report the most common mode of inheritance among children with familial HCM who were recruited from the biggest tertiary referral hospital for young age cardiomyopathy in Egypt.

Methodology and Results: This study included ten cases (7 families) with Familial HCM (8 males and 2 females; their mean age was 5.07 ± 2.36 years, ranging from 0.75 to 8.25 years). Each case subjected to three-generation pedigree construction. Echocardiography was documented in all our cases and their families. In our study AD inheritance could be suspected in 30% of cases who had an affected parent. However, 70% of our cases had an affected relative (same generation), this fact together with the fact that 90% of our cases had positive Consanguinity of their parents support the existence of autosomal recessive (AR) inheritance. Penetrance of HCM is incomplete and age related as most of the cases showed more extensive phenotype and earlier age of presentation compared to their diseased parents. Asymmetrical septal hypertrophy (ASH) is considered the most common form of HCM in children.

Conclusions and Recommendations: Autosomal recessive inheritance is the most common mode of inheritance among Egyptian patients with familial hypertrophic cardiomyopathy. Predictive genetic screening of family members of HCM patient is a must, on an attempt to decrease the risk of SCD.

Keywords: Familial hypertrophic cardiomyopathy; Hypertrophic cardiomyopathy; Mode of inheritance; Left ventricular hypertrophy

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary cardiac disease of the myocardium of autosomal dominant inheritance [1,2]. It is characterized by left ventricular hypertrophy without chamber dilatation, in the absence of either a systemic or other cardiac disease which may cause a similar magnitude of hypertrophy [2,3]. HCM is a complex and confusing disorder that has been a subject of intense scrutiny for the past 50 years and of great interest to cardiologists, geneticists and pathologists. This is attributed to its diverse pathological, clinical and molecular heterogeneity [4].

The estimated prevalence of HCM in young adults is 1:500 and comprising about 30-40% of cardiomyopathies in children [5]. One of the challenging problems in HCM world is the sporadic occurrence of HCM in children. Gene mutations previously known to cause adult onset HCM are detected in about half of childhood- onset sporadic HCM cases and in nearly two thirds of familial cases [6]. Moreover, many children with positive HCM genotype can't be disclosed before puberty as they may remain asymptomatic for years [7].

The occurrence of HCM in the cardiac clinic of Cairo University Children Hospital (CUCH) is 50/10,000. And over a period of 10 years HCM cases represent 180 cases out of 36,229 cardiac patients. HCM represents 20% of cases presenting to cardiomyopathy clinic (180/923). Generally it accounts for 2-3 cases/year while in CUCH 18 new cases/year [8]. Echocardiography is the cornerstone in diagnosis of HCM, which is diagnosed by the presence of primary cardiac hypertrophy and a preserved or enhanced left ventricular ejection fraction [9,10].

No single mode of inheritance is typical of HCM, although autosomal dominant transmission is most common; a variety of phenotypic expressions occur that appear to have genetic as well as non-genetic causes, suggesting that HCM may not be a single etiologically distinct disease entity. Hence, individualized genetic counselling is recommended as it should be influenced by the particular pattern of inheritance demonstrated in each family [11].

This work aims to report the most common mode of inheritance among children with familial HCM who were recruited from the biggest tertiary referral hospital of young age cardiomyopathy in Egypt.

Patients and Methods

All Egyptian children referred to Cardiomyopathy Clinic in Cairo University children hospital (CUCH) for suspected cardiomyopathy from September 2003 to October 2013 were screened. Patients aged

<12 years likely to have isolated familial HCM by history were included. Infants of diabetic mother, hypertensive patients, patients with renal impairment, and patients with valvular stenosis or aortic coarctation and dysmorphic syndromes were excluded, as well as neuro-metabolic disorders like Pompe disease, myotonic dystrophy, Duchene muscle dystrophy.

Included cases were subjected to the following:

1) Three-generation pedigree construction including consanguinity, similar conditions in the family and other genetic disorders.

2) Complete history including parents' occupation, pregnancy and delivery histories, exposure to drug intake, fever, trauma, irradiation, or any maternal chronic illness. Parental ages at birth of the child, family history and developmental milestones were also recorded.

3) Detailed history of cardiac symptoms such as; dyspnea, palpitations, arrhythmias, syncope, attacks of cardiac arrest and family history of sudden cardiac death (SCD).

4) Detailed clinical examination with special emphasis on cardiac examination, dysmorphic features and examination of different body systems.

5) Anthropometric measurements including height, weight and head circumference to evaluate the proband growth state. Measurements were compared to Egyptian growth curves [12].

6) Blood pressure was measured to exclude hypertension as a cause of HCM.

7) Plain chest X-rays, electrocardiogram (ECG) were performed.

8) Echocardiography (M-mode and Doppler) was performed. Echocardiographic evidence was obtained of either concentric left ventricular hypertrophy (LVH) or asymmetric septal hypertrophy (ASH) defined as median septal thickness 1.4 times that of the posterior wall or Z-score>2 of the diastolic septal thickness or left ventricular diastolic wall thickness (Z score: wall thickness >2 SD above the normal population mean for (BSA) body surface area) [13]. Z scores were applied to overcome the variability of echo measurements in the paediatric age group (due to variable age, weight and height).

9) Other investigations to rule out non-isolated HCM cases were performed when needed; as karyotyping for diagnosis of syndromic cases and extended metabolic screening for inborn errors of metabolism.

10) Predictive genetic and cardiac screenings were performed to the probands' 1st degree relatives.

Results

In the present study, 10 cases (7 families) with familial HCM (8 males and 2 females) fulfilled the inclusion criteria. The cases age ranged from 9 months to 8.25 years with mean age 5.07 ± 2.36 years.

80% of patients were diagnosed after the age of two years. Only a single case (case 5) was diagnosed during the 1st year of life. Female patients represent 20% of our cases, unlike male patients who represent the majority of cases (80%). Other congenital disorders were reported in 20% of cases; case 8 gave history of two cousins with growth hormone deficiency and a cousin with hydrocephalus while, case 10 had a cousin with short stature as illustrated in Table 1.

Case no.	Age at diagnosis	Sex	Similarly affected family members	Family members affected with other congenital disorders
1	6.6 yrs	M	A sibiling (case: 2)	-
2	1.6 yrs	M	A sibiling (case: 1)	-
3	4.25 yrs	M	1)A cousin (case:4) 2)Son of another cousin	-
4	yrs	M	1)A cousin (case: 3) 2)Son of another cousin	-
5	9 m	M	A sib (case: 6)	-
6	4.6 yrs	F	A sib (case: 5)	-
7	4.08 yrs	M	The mother	-
8		F	The father's cousin	1) Two cousins with growth hormone deficiency 2) A cousin with hydrocephlus
9	3.3 yrs	M	The father	-
10	8.25 yrs	M	1)The father 2)Grandmother (paternal) 3)Father's uncle (maternal)	A cousin with short stature

			4)Father's anut maternal)	

Table 1: Demographic and family history data of the cases

Positive consanguinity was reported in 9 out of 10 cases as shown in Figures 1,2,3,5 and 6.

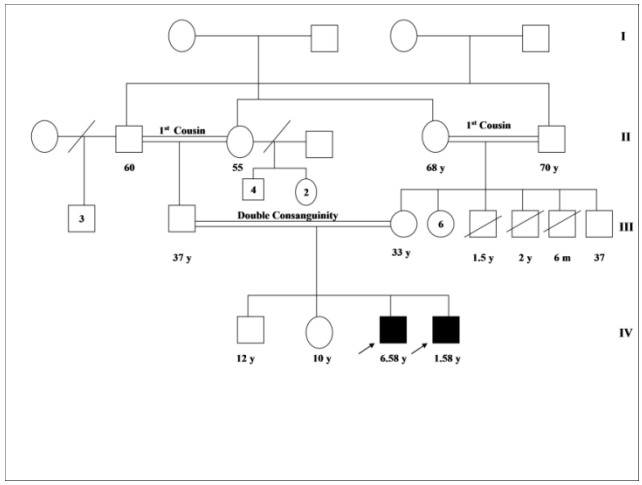

Figure 1: Family pedigree of cases 1 and 2 showing parental double consanguinity and + ve consanguinity in generation no. II (maternal and paternal)

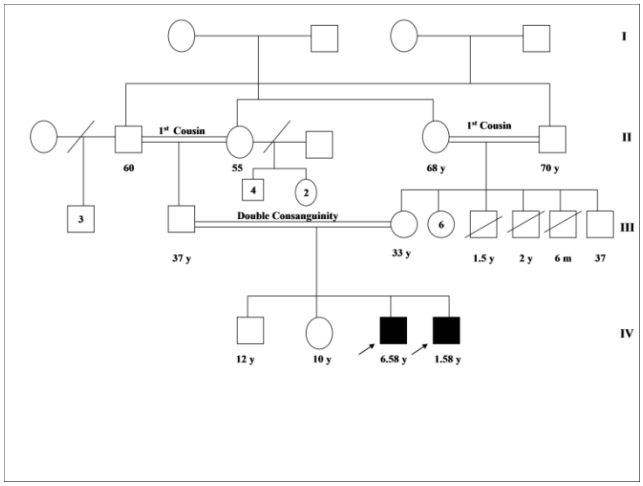

Figure 2: Family pedigree of cases 3 and 4 showing affection of 3 family members, 2 are of the same generation (IV)

Family history of SCD per se was proved in only one case as shown in Figure 5. Thirty percent of our patients had an affected parent; 2 cases (9 and 10) had an affected father and one case (case 7) had an affected mother. Forty percent had an affected sibling (cases 1,2,5 and 6), while two cases were second cousins (cases 3 and 4) and only one case gave history of an affected parent's cousin (case 8).

The Figures 1 and 2 demonstrate affection of individuals within the same generation as well as positive parental consanguinity.

HCM patients among successive generations were found in 30% of cases (cases 7, 9 and 10) as shown in Figures 4, 6 and 7. While, in70% of cases (cases 1-6 and 8) the disease was detected among individuals within the same generation (Figures 1, 2, 3 and 5).

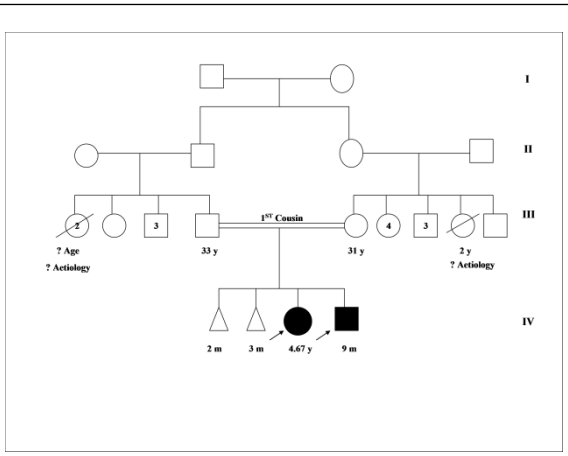

Figure 3: Family pedigree of 2 sibs; cases 5&6

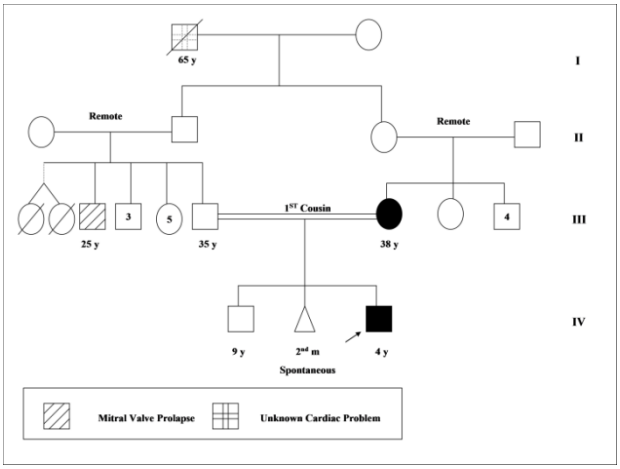

Figure 4: pedigree of case 7 showing affection of 2 successive generations

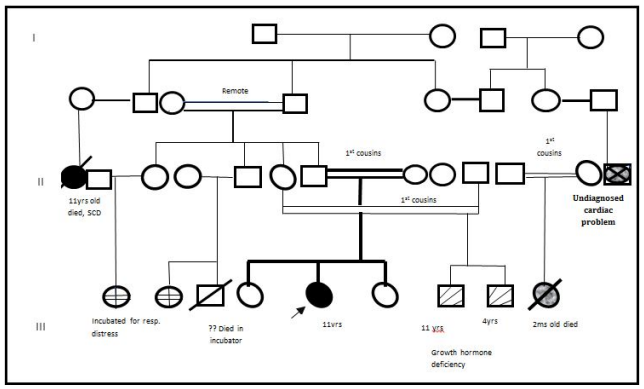

Figure 5: Family pedigree of case 8 showing affection of the proband and the parents' cousin who died from SCD

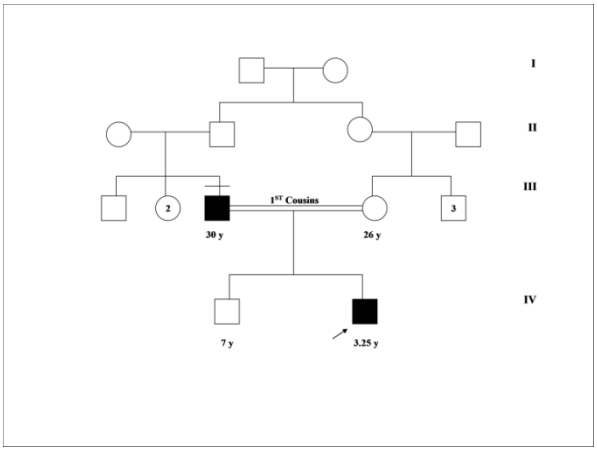

Figure 6: family pedigree of cases 9 and his father showing affection of 2 generations (III, IV)

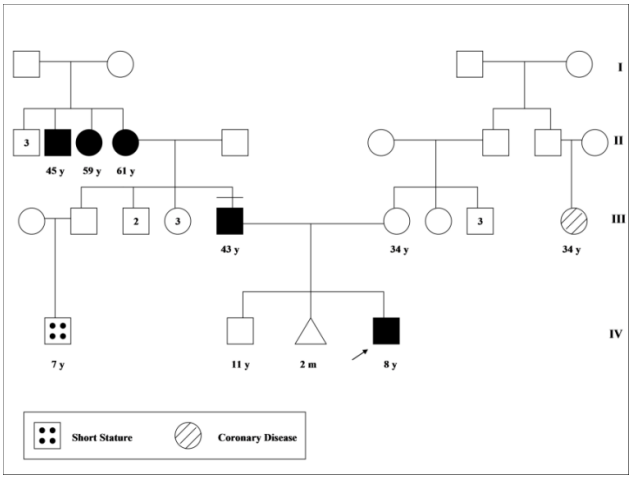

Figure 7: Pedigree of case 10 demonstrating affection of 3 successive generations

Affection of individuals within the same generation as well as successive generations was proved in only one case, illustrated in the family pedigree of case 10 as shown in Figure 7.

In the majority of our patients, their condition was initially asymptomatic; 20% of them were discovered on family screening (cases 2 and 6) and in 50% of cases a cardiac murmur was discovered during an attack of pneumonia that necessitated hospital admission, the patients were referred to the cardiology clinic for cardiological evaluation (Table 2).

Echocardiographic findings are presented in Table 2. Left ventricular outflow obstruction was present in 5 cases with peak gradient ranging from 35 mmHg to 100 mmHg. Right ventricular outflow tract obstruction was absent in all cases.

Isolated septal hypertrophy was found in all the study population: it was massive (equal to or even exceeding 3.0 Z-score for age) in 4 cases, limited to the outflow tract in 2 more patients. Two cases showed other types of ASH like mid cavitary obstruction or butterfly shape of interventricular septum. A single patient had concentric hypertrophy involving both the septum and posterior wall. The majority of patients showed abnormal ECG findings, which were absent in 30% of cases.

Discussion

Hypertrophic cardiomyopathy is a primary myocardial disease in which part of the left ventricular muscle becomes hypertrophied unjustifiably. Its importance lies in being one of the most dangerous silent killers, as it causes sudden cardiac death especially in young apparently healthy individuals, including athletes. The prevalence of HCM is about 0.2% to 0.5% of the general population [2,5,6].

Unfortunately, the occurrence of HCM in children is sporadic explaining the rarity of familial HCM cases in paediatric age. HCM is genetically transmitted mainly by autosomal dominant (AD) inheritance though autosomal recessive (AR) form cannot be denied, particularly in populations were positive consanguinity is so prevalent [6-8].

This study included 10 familial HCM cases (7 families); 80% were males similar to the study of Greaves et al. [14]. However, a gender-related difference was not confirmed by Maron et al. who highlighted the HCM being misdiagnosed in females and in developing countries [15].

Case no	Inheritance	Consanguinity	Presentation	Echocardiography findings					
				LVED DZ	IVS Z	PW Z	LVOTO PG	Pathologic phenotype	IVS/PW
1	AR	Positive	Cardiac murmur	-0.52	2.2	2.37	Absent	ASH sparing PW	3.76
2	AR	Positive	On family screening	-1.7	1.8	2.2	80	Mid cavity obstruction	1.1
3	AR	Positive	Cardiac murmur	0.05	3.2	0.98	80	Subaortic ms. hypertr	2.43
4	AR	Positive	Cardiac murmur	6	1.1	0.8	40	Subaortic ms. hypertr	1.67
5	AR	Positive	Failure to thrive	0.05	5.9	1.29	Absent	Concentric	2.48
6	AR	Positive	On family screening	1.75	1.8	-1.2	Absent	Butterfly IVS	2.17
7	AD	Positive	Dyspnea	1.1	3.2	3.1	100	Concentric	1.18
8	AR	Positive	Dyspnea	0.96	5.5	0.96	35	ASH sparing PW	2.25
9	AD	Positive	Cardiac murmur	1.37	2.7	1.07	Absent	ASH sparing PW	2.3
10	AD	Negative	Cardiac murmur	1.8	2	1.29	Absent	ASH sparing PW	2.43

Table 2: Presents the different studied parameters in the ten cases. AR: Autosomal Recessive; AD: Autosomal Dominant; LVEDD: Left Ventricular End Diastolic Dimension; IVS: Interventricular Septum; PW: Posterior Wall; LVOTO: Left Ventricular Outflow Obstruction; PG: Pressure Gradient; ASH: Assymetric Septal Hypertrophy; Subaortic Ms. Hypertr: Subaortic Muscle Hypertrophy

The age of our study population ranged from 9 months to 8 years, emphasizing the fact that HCM can be detected in infancy, during childhood or adolescence according to previous studies [16,17].

AD inheritance in HCM is agreed upon in most studies, since the study done by Pare et al. in the year 1961who described this disorder in 30 out of 87 members of French-Canadian kindred [18]. The survey was carried back to the original emigrant from France in the seventeenth century. The pattern of its occurrence in five generations and over 160 years indicated autosomal dominant inheritance [18]. The family study on HCM using echocardiography indicated that 28 of 30 probands (93%) had an affected parent supporting AD inheritance [19]. Also Maron in his systematic review of HCM stated that HCM is transmitted in an AD fashion [10].

Another study stated that the existence of a recessive form of hypertrophic cardiomyopathy could neither be established nor disproved [20]. However, Branzi et al. reported the existence of an autosomal recessive form because of a family they found with two affected sisters and both parents were normal [21]. It is worth mentioning that we have the same situation in our study where two families each had 2 children with HCM and their parents were normal. However, both of them had positive consanguinity supporting AR inheritance.

In our study AD inheritance could be suspected in 30% of cases who had an affected parent. However, 70% of our cases had an affected relative (same generation), this fact together with the fact that 90% of our cases had positive consanguinity of their parents support the existence of AR inheritance especially in communities like ours were positive consanguinity is so prevalent. Studies of parental consanguinity in the general population in Egypt throughout the last 40 years showed an average consanguinity rate above 30% [22].

Penetrance of HCM is incomplete and age related and that agrees with our study in which most of the cases showed more extensive phenotype and earlier age of presentation compared to their diseased parents (anticipation phenomenon) [17].

Cardiac murmur was the main presenting sign in most cases (50%) which was discovered during an attack of chest infection that necessitated hospitalization. Dyspnoea was the second common presenting sign in 20% of our cases and this is in accordance with previous studies [10,23]. Twenty percent of our patients were discovered accidently on family screening of HCM emphasizing the importance of predictive genetic screening of family members of HCM patient even if they were asymptomatic; on a trial to decrease the risk of SCD. That resembles the study carried out by Christians et al. about the uptake of genetic counselling and predictive DNA testing in HCM [24].

In the current study, two of our cases showed more extensive phenotype compared to their affected fathers as in an American study conducted by Maron et al. they studied a group of 237 adult HCM patients, an inverse relation was identified between age and maximal LV wall thickness (P=0.007) [25]. This relation is more statistically significant in females (P=0.002). Hence, there was a decrease in LV wall thickness with increasing age, so younger patient in that study showed substantially more severe and diffuse LVH than older ones.

Current perspectives underline the growing importance of genetic testing in early identification of asymptomatic relatives of HCM patients, in an attempt to avoid the occurrence of SCD [11]. Only analyses of genes encoding sarcomere-protein mutations may help physicians to identify the individuals who are at risk of HCM and, then, sudden cardiac death [6].

Conclusion

Autosomal recessive was the most common modality of HCM inheritance in our Egyptian study population. Asymmetrical septal hypertrophy was the most common phenotype. Providing advanced genetic counselling may help family members at risk for HCM to discover their affected children, as well as those who are at risks of major complications. All children from HCM families are encouraged to undergo regular ECG- and ultrasound-based screening, even if asymptomatic. Facilities to access genetic laboratories should be endorsed by National Care Systems.

Recommendations

Molecular diagnosis of gene mutations responsible for AR type of HCM is highly recommended. Additionally, identification of homozygous diseased patients and heterozygous carriers for accurately diagnosing HCM is a must, hence preventing this disorder through individualized genetic counselling and prenatal genetic testing. Further studies must include genetic analysis of sarcomere protein genes that may precisely define the cause and help to identify family members at risk.

Study Limitations

This study, although conducted in the biggest tertiary hospital for paediatrics in Egypt, still represents a single centre study. The main limitation was the inability to evaluate genetic contribution as a causative factor. Furthermore, the observation reached could not be extrapolated to patterns of inheritance in the Egyptian population and remain in the category of interesting observation.

Acknowledgement

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