Original article

Dysmorphic Features, Consanguinity and Cytogenetic Pattern of Congenital Heart Diseases: a pilot study from Mansoura Locality, Egypt

Ahmad Settin, Hala AlMarsafawy, Ahmad AlHussieny, Moataz Dowaidar
Genetics and Cardiology Unit, Mansoura University Hospital, Mansoura, Egypt

Abstract

Background: Congenital heart diseases (CHD) constitute a common cause of birth defects with a multifactorial inheritance background.

Objectives: to check for the dysmorphic features, consanguinity and cytogenetic pattern that may be associated with congenital heart disease in Egyptian cases from Mansoura, Egypt.

Methods: This work is a pilot prospective controlled study including randomly selected 69 cases affected with congenital heart disease recruited from the Pediatric Cardiology Department, Mansoura University, Egypt. These cases were compared to 500 normal children of matched age and sex taken from the same locality serving as a control group. Complete history taking, clinical examination for dysmorphic features as well as cardiac examination were carried out for all subjects. Furthermore, cases were evaluated by Echocardiography and cytogenetic studies.

Results: Egyptian children affected with CHD were significantly associated with positive family history of CHD, perinatal history of maternal diseases or drug intake during pregnancy and positive parental consanguinity (odds ratio = 10.5, 7.6 and 3.1 respectively). Significant associated dysmorphic features included ear anomalies, eye anomalies, cleft lip, polydactyly and cleft palate (odds ratio = 217.6, 176.6, 68.7 and 37.07 respectively). Seven cases (10.1%) had chromosomal aberrations and were associated with dysmorphic features.

Conclusion: Risk of CHD increased with positive family history and consanguinity. Cytogenetic studies added to dysmorphic features seem to have an important clue for early diagnosis of CHD.
Key words: Heart disease, risk factors, dysmorphism, Egypt

Correspondence:
Prof. Ahmad Settin
Professor of Pediatrics and Genetics
Qassim University, College of Medicine
BO 6040 Buraydah 51432, Saudi Arabia
e-mail : settin@mans.edu.eg,
http://uk.360.yahoo.com/settin60

Introduction

Congenital heart diseases (CHD) refer to structural or functional abnormalities that are present at birth even if discovered much later. [1] These comprise many forms of cardiovascular diseases in young including cardiac malformations, cardiomyopathies and cardiac arrhythmias. [2]

Congenital heart malformations constitute a common cause of birth defects with the prevalence of confirmed defects ranging from 5 to 10 per 1000 live birth. [3] The prevalence of CHD in 1998 at the school age in Alexandria, Egypt, was 10.01 per 1000 school children. [4]

The etiology of the majority of congenital heart diseases is still unexplained, with the progress in molecular and developmental biology our understanding of the factors that influence cardiac development is likely to increase. Cardiac development is regulated by complex mechanisms involving interaction between genetic and environmental factors. [5]

About 30% of the all congenital heart disease cases are associated with extracardiac malformations. The presence of facial dysmorphic features and associated extracardiac malformations should alert the pediatricians to an underlying syndrome diagnosis, for example: 22q11 deletion syndrome, Williams syndrome, Down syndrome, Kabuki syndrome. [6]

Epidemiologic studies and reports of familial disease suggest that inherited traits contribute to the development of CHD. Recent studies demonstrate that isolated or syndromic CHD can be associated with single gene defects. Evidence suggests that genetic factors play a critical role in the development of CHD, even in sporadic cases. [7]

Correlation of underlying genetic background of cases with congenital heart diseases with external phenotype seems to be an important step in early detection and prevention of the disorder. [8]

The aim of this work is to check for various factors (social, environmental and genetic) that may be associated with congenital heart disease among Egyptian cases. External dysmorphic features are also analyzed and tested for association with congenital heart diseases.

Methods

This prospective case controlled study included randomly selected 69 Egyptian cases affected with congenital heart disease. They were recruited at their presentation to the Pediatric Cardiology Unit of Mansoura University Children Hospital, Egypt. Their sex was in the form of 38 males and 31 females with an age ranging between 15 days and 10 years with the mean age was 16.2±23.9 months.

In addition, 500 Egyptian normal children were taken as a control group. They were in the form of 223 males and 277 females. Their age ranged between 0.5 and 15 years with a mean age of 62.4±67.7 months. All cases as well as controls were subjected to complete history taking including name, age, sex, parental consanguinity, family history and pedigree pattern as well as perinatal history Maternal disease like hypertension, renal and cardiac diseases and maternal work, congenital infections,, pregnancy complication as hemorrhage, fever, pre-eclampsia and diabetes, use of ovulatory drugs.

All cases and control were also subjected to complete clinical examination including external dysmorphic features related to skull, face, neck, chest, abdomen and extremities and cardiac examination.[9] In addition all cases were subjected to 2D echocardiography (HB5500, Philips) and cytogenetic study using conventional method of karyotyping with G-and C-banding technique. [10,11] On the basis of Echocardiography done by an expert Pediatric Cardiologist, cases were classified according to American Heart Association, 1994 [12] (Table 1), into cases having cyanotic heart disease (28 cases), left to right shunt (33 cases), obstructive lesion (8 cases). On the other hand, cases having congenital cardiomyopathy, rheumatic heart disease, and secondary heart disease were excluded from the study.

Statistical analysis

Data were analyzed using SPSS version 10.0 (SPSS, 1999). Statistical tests included descriptive data as Mean± SD, Frequency distribution, Chi square ($\chi 2$) test, Fisher test and Odds ratio for testing of association.

Results

Important items of the history were positive family history of congenital heart disease (OR=10.5, p<0.0001), and positive maternal diseases and/or intake of drugs during pregnancy (OR= 7.6 p=0.0095). (Table 2)

Frequency of total positive parental consanguinity among the studied cases was significantly higher compared to control children (18.8% vs 8% respectively, p=0.015, OR=2.4). Frequency of 1st cousin consanguinity was the most prominent pattern in cases compared to controls (11.6% vs 4% respectively, p=0.013, OR=3.1) (Table 3).

Cases have shown a significant higher frequency of external dysmorphic features compared to controls (34.8% vs 16%, OR=2.6, p=0.0009). Among the dysmorphic features, a significant high frequency were observed with ear anomalies (OR=217.6, p<0.0001), eye anomalies (OR=176.6, p<0.0001), polydactyly (OR=68.7, p=0.0002), and cleft lip and palate (OR=37.07, p=0.0145) (Table 4).

Among the cases with dysmorphism, 7 cases had chromosomal aberrations. These aberrations were in the form of: four cases with trisomy 21 (3 affected with VSD and one with an ASD), one case with trisomy 14 (had ASD), one case with trisomy 15 (had ASD) and one case with iso-chromosome10 (had double outlet right ventricle DORV). All the studied cases with chromosomal aberrations had positive perinatal history and had dysmorphic features as well. These cases had an earlier presentations than others (9.7±17.2 vs 17±24.5 months).

On the other hand, no significant difference was shown related to sex, consanguinity or positive family history of CHD. Analysis of subgroups related to various types of congenital heart diseases showed no significance related to age, sex, family history, consanguinity and cytogenetic background (data not shown).

Discussion

This study is another proof of the genetic background of CHD. Studied cases have shown high significant association with positive family history of similar conditions and also of positive consanguinity particularly for first cousin parental consanguinity. Also, Bassili et al. (2000), in a study in Egypt, have reported a higher rate of positive family history and parental consanguinity in their studied sample in Alexandria. [4] Similarly, Becker et al. (2001), in a study in Saudi Arabia, have reported that first cousin consanguinity was significantly higher than in the general population that was also associated with certain types of CHD. [13]

The relatively elevated risk of congenital heart disease associated with consanguineous marriage may warrant more health education sessions to transfer this information to the public.

The presence of significant higher frequency of external dysmorphic features among studied cases with congenital heart disease than general population is probably indicative of the importance of these landmarks for early diagnosis of these cases. We recommend giving training courses to all junior doctors how to pick and or interpret these features for disease diagnosis.

Interestingly, in this study, cases with face dysmorphic features particularly with depressed nasal bridge and high arched palate significantly high constituted more than one third of the studied cases. Other important features included skull shape like brachcephaly, dermatoglyphic lines as simian crease and sandal line, polydactyly and clefting of lips or palate.

Nevertheless, cases did not show a particular stigma pertaining to various forms of congenital heart disease in terms of their dysmorphism.

Similarly, Schellberg et al. (2004), in a study in Germeny, have reported that more than (90%) of the patients having extracardiac malformations. [14] However, Bassili et al. (2000), in a study in Egypt and Stephensen et al. (2004), in a study in Iceland, have reported that extracardiac malformations in their cases were often genitourinary and gastrointestinal malformations, while skull and face malformations were less common. [4,15]

This study has included 7 cases i.e 10.1% of all studied cases with chromosomal aberrations detected by conventional cytogenetic study. Down syndrome was diagnosed among 4 of them i.e 5.7% of total cases. These cases presented at an earlier age and were noted to have positive perinatal history of maternal diseases or drug intake during pregnancy. Moreover, all these cases had various dysmorphic features. Stephensen, et al. (2004), have also reported that their cases with cardiac defects had other congenital malformations, chromosomal defects and syndromes; of them, Down syndrome constituted 3.8% of cases. [15] Furthermore, Meberg, et al. (2000), in a study in Norway, have found that chromosomal disorders, syndromes and associated extracardiac malformations occurred in 20% of the CHD cases. [16]

We can come to the conclusion that orientation should be given to high risk factors of congenital heart disease like consanguinity and maternal health during pregnancy and also to the importance of external dysmorphic features for early diagnosis and management of these disorders.

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Table 1. Descriptive data of all studied congenital heart disease subjects related to the American heart association classification.

	Total n=69	**Cyanotic n=28**	**Lt to Rt Shunt n=33**	**Obstructiv n=8**
Age				
Mean+SD (Mos)	16.2± 23.9	10.3±12.9	19.0±25.4	25.8±40.9
Range	3ds-10ys	9ds-4ys	3ds-10ys	9ds-10ys
Sex				
Male (n,%)	38(55.1)	14(50.0)	17(51.5)	7(87.5)
Female (n,%)	31(44.9)	14(50.0)	16(48.5)	1(12.5)

Type of Lesion (n)	TGA(3)	VSD(18)	CoArc(2)
	TOF(5)	ASD(4)	AS(2)
	DORV(11)	PDA(3)	PS(4)
	TAPVD(1)	PFO(1)	
	HLHS(2)	ConMR(1)	
	CAVC(6)	ASD+VSD(6)	

***TGA**: Transposition of great arteries **VSD**: Ventricular septal defect **CoArc**: Coarctation of the aorta **TOF**:Tetralogy of Fallot **ASD**:atrial sepatal defect **AS**: aortic stenosis **DORV**:double outlet right ventricle **PDA**:patent ductus arteriosus **PS**:pulmonary stenosis **TAPVD**:total anomalous pulmonary venous retrun disease **PFO**: patent formaen ovale **HLHS**: hypertrophic left heart syndrome **ConMR**: congenital mitral regurge **CAVC**: common atrio-ventricular canal*

Table 2. Distribution of CHD cases (frequency and frequency %) related to positive family history, positive perinatal history and maternal work.

	Cases n=69(100%)	**Control n=500(100%)**	**Fisher test**	**OR(95%CI)**
Positive family history	9(13.0%)	7(1.4%)	<0.0001**	10.5(3.7-29.4)
Positive Perinatal history	15(22.0%)	20(4.0%)	<0.0001**	6.6(3.2-13.7)
Congenital infection	3(4.3%)	8(1.6%)	0.1331	2.7(0.7-10.8)
Maternal disease	4(5.9%)	4(0.8%)	0.0095*	7.6(1.8-31.2)
Pregnancy complication	4(5.9%)	2(0.4%)	0.0025*	15.3(2.7-85.3)
Drugs	4(5.9%)	4(0.8%)	0.0095*	7.6(1.8-31.2)
Maternal work	23(35.5%)	91(18.0%)	0.0058*	2.2(1.2-3.8)

* $p < 0.05$ ** $p < 0.001$ OR (95% CI)= Odds ratio (95% confidence interval).

Table 3. Distribution of CHD cases (frequency and frequency %) related to parental consanguinity.

Consanguinity	Cases n=69(100%)	Control n=500(100%)	Fisher p	OR(C.I)
1st cousin	8(11.6%)	20(4.0%)	0.0131*	3.1(1.3-7.4)
2nd cousin	1(1.4%)	6(1.2%)	0.5975	1.2(0.1-10.2)
1st cousin once removed	0(0.0%)	6(1.2%)	1.0000	0.5(0.03-9.8)
Remote	4(5.8%)	11(2.2%)	0.0961	2.7(0.8-8.8)
Total	13(18.8%)*	43(8.0%)	0.0153*	2.4(1.2-4.8)

* $p < 0.05$ ** $p < 0.001$ OR (95% CI)= Odds ratio (95% confidence interval).

Table 4. Distribution of CHD cases (frequency and frequency %) related the presence or absence of dysmorphic features (minor or major).

Dysmorphism	**Cases n(%)**	**Control n(%)**	**Fisher P**	**OR(95% CI)**
Skull Dysmorphism				
Brachycephaly	11(15.9)	7(1.4)	<0.0001**	13.3(4.9-35.8)
Microcephaly	3(4.4)	6(1.2)	0.0838	3.7(0.9-15.3)
Frontal bossing	1(1.4)	7(1.4)	1.0000	1.01(0.12-8.5)
Box-shaped skull	1(1.4)	12(2.4)	1.0000	0.5(0.07-4.6)
Total skull dysmorphism	**16(23.1)**	**32(6.4)**	**<0.0001****	**4.4(2.2-8.5)**
Face Dysmorphism				
Nasal depression	22(31.9)	22(4.4)	<0.0001**	10.1(5.2-19.7)
Eye anomalies	10(14.5)	0(0)	<0.0001**	176.6(10.2-3055.2)
Ear anomalies	812(17.1)	0(0)	<0.0001**	217.6(12.7-3726.6)
Micrognathia	15(21.7)	15(3)	<0.0001**	8.9(4.1-19.3)
Cleft lip and palate	2(2.9)	0(0)	0.0145*	37.07(1.7-781.06)
High arched palate	23(33.3)	16(3.2)	<0.0001**	15.12(7.4-30.6)
Total face dysmorphism	**24(34.5)**	**53(10.6)**	**<0.0001****	**4.4(2.5-7.9)**
Neck dysmorphism	9(13)	11(2.5)	0.0002**	6.6(2.6-16.7)
Chest dysmorphism	4(5.8)	11(2.5)	0.0961	2.7(0.8-8.8)
External Genitourinary dymorphism	5(7)	14(3)	0.0678	2.7(0.9-7.7)
Simian crease	8(11.6)	8(1.8)	0.0002**	8.06(2.9-22.2)
Polydactyly	4(5.8)	0(0)	0.0002**	68.7(3.6-1292.8)
Sandal line	8(11.6)	7(1.5)	0.0001**	9.2(3.2-26.3)
Bow legs	6(8.6)	23(4.5)	0.1471	1.9(0.7-5.03)
Total dysmorphism	**24(34.8)**	**84(16 %)**	**0.0009****	**2.6(1.5-4.5)**

** $p < 0.05$ ** $p < 0.001$ OR (95% CI)= Odds ratio (95% confidence interval).*