Original Article

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Congenital Heart Defects and Non-Cardiac Malformations in Patients with Normal Karyotype

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Abstract

Context: Present study is based on the available data on patients with heart defects. *Aim:* The presence of non-cardiac malformations in patients with heart defects and normal karyotype is reported. *Settings and Design:* Division of Human Genetics, St John's Medical College, Bangalore is a referral centre for genetic counseling. *Methods and Material:* Information was gathered from 10 male and 8 female patients. Their age ranged from neonates to 16 years. *Statistical analysis:* Percentage analysis is calculated. *Results:* A total of 26 CHDs were noted and 38 NCMs were observed in 5 systems (skeletal, central nervous, digestive, urogenital, respiratory system). Malformations noted in male were 22 (58%) and in female 16 (42%). Heart defects observed in male were 16 (61.5%) and in female 10 (38.5%). Malformations in 2 systems have occurred 9 times (50%); in which skeletal anomalies were 15 (39.5%). Single heart defects have occurred 12 times and in that ventricular septal defects were 7 times (27%). In male patients, skeletal anomalies (9), ventricular septal defects (4) and malformations in 2 systems (5) were prevalent. The association between the types of heart defects versus malformations showed that in male atrial septal defects were associated to 5 system anomalies and in female dextrocardia to 4 system anomalies. *Conclusions:* The study has reported the presence of 38 malformations in 18 patients with 26 heart defects and normal karyotype. Two system anomalies; defects in skeletal system and associations of malformations to ventricular septal defects were found to be frequent. Patients and families were counseled and were recommended for medical and surgical management of malformations and heart defects.

Keywords: Non-Cardiac Malformations; Congenital Heart Defects; Normal Karyotype; Genetic Counseling.

Introduction

The incidence of the congenital abnormalities in the newborns is reported to be around 2 to 3%. The reported overall prevalence of congenital heart defects (CHDs) is around 8 to 10 in 1000 births (Turnpenny and Ellard 2012). CHDs account for around 1/3rd of all congenital anomalies and are considered to be the major causal factor to infant mortality attributed to birth defects (Reller et al 2008).

Based on the method of ascertainment, the reported overall frequency of non-cardiac malformations (NCMs) among the individuals with CHDs is from 9 to 42% (Belisario et al 1981). For birth defects, such as CHDs and or NCMs, genetic etiology (chromosomal abnormalities or single gene disorder-Mendelian inheritance) and multifactorial mode of inheritance (genetic and or environmental factors) are the contributing factors (Rajangam et al 2015).

The present study is designed to include only those CHD patients with normal genetic profile. CHD patients in whom genetic causes have been identified as chromosomal abnormality and syndromes with Mendelian or sporadic occurrence are excluded.

It is Aimed to Assess

i. The presence of NCMs in CHD patients with normal karyotype;
ii. The occurrence of NCMs as per the systems of the body;
iii. The association between the types of NCMs and the types of CHDs.

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Material and Method

Eighteen patients with CHDs out of 65, referred consecutively for genetic analysis and genetic counseling to Division of Human Genetics, St.John's Medical College, Bangalore were selected for the study. They had CHDs, NCMs and normal karyotype. There were 10 male and 8 female patients and their age ranged from neo-nates to 16 years. From the available records, retrospectively, information on the presence of the types of CHDs and NCMs were gathered. Percentage analysis is calculated.

Results

The observed features in the patients were grouped under 5 major systems (central nervous/ skeletal/digestive/uro-genital/respiratory) of the body (developmental delay, poor weight gain, tired, mental retardation, hypotonia, spasticity, not attained head control, open mouth, high arched palate, large tongue, poor feeding, low set ears, clinodactyly, syndactyly, polydactyly, club foot, barrel chest, conical fingers, breathlessness, pulmonary hypopalsia, vesico-urethral reflex, hypoplastic genitalia).The findings from the 18 patients are tabulated.

Table 1: A total of 26 CHDs were noted in these patients. 38 NCMs were observed in 5 systems (SS-skeletal system, CNS-central nervous system, DS-digestive system, UGS: urogenital system, RS-Respiratory system). 22 NCMs (22/38, 58%) were noted in male and 16 (16/38, 42%) in female patients. 16 (16/26, 61.5%) CHDs were noted in male and 10 (10/26, 38.5%) in female patients.

Table 2: The affected systems in NCMs in male patients were 5 (SS, CNS, DS, UGS, RS) and in females were 4 (SS, CNS, DS, UGS). Likewise, the observed CHDs in male patients were 8 (VSD, ASD, PFO, PAH, murmur, double outlet right ventricle, PDA, pulmonary valve stenosis) and in female were 6 (murmur, VSD, ASD, dextrocardia, PAH, mitral valve stenosis). It is seen, that CHDs such as VSD, ASD, PAH and murmur were present in both sexes.

The distribution of NCMs were: skeletal system-SS:15 (15/38, 39.5%) (male 9; female 6); central nervous system-CNS:10 (10/38, 26.3%) (male 4; female 6); urogenital system-UGS:6 (6/38,15.8%) (male and female 3 each); digestive system-DS:6 (6/38, 15.8%) (male 5; female 1); respiratory system-RS:1 (1/38,2.6%) (male 1). In males, SS defects were found 9 times (9/22, 41%); whereas in females SS and CNS defects have occurred in equal numbers (6/16, 37.5%). In total SS anomalies have occurred 15 times (15/38, 39.5%).

Types of CHDs and their occurrence: VSDs: 7 times (7/26, 27%); murmur 4 times (4/26, 15.4%); ASD (3 times (3/26, 11.5%); PDA/dextroxardia/ mitral valve prolapsed/pulmonary valve stenosis/

Table 1: CHDs, NCMs, Normal karyotype

Serial No.	Male: CHDs	Karyotype/ NCMs
1	Ventricular septal defects (VSD)	46,XY,CNS/ SS
2	Atrial septal defects(ASD), patent foramen ovale (PFO)	46,XY,CNS/SS/DS
3	Murmur	46,XY,CNS/SS
4	ASD	46,XY,SS/RS/DS/UGS
5	Murmur	46,XY,SS/DS/UGS
6	Murmur	46,XY,SS/UGS
7	Double outlet right ventricle, VSD, pulmonary artery hypoplasia (PAH)	46,XY,SS/DS
8	Pulmonary valve stenosis, VSD	46,XY,CNS
9	PDA	46,XY,SS
10	Pulmonary tricuspid stenosis, VSD, PDA	46,XY,SS/ DS
Total	16 (61.5%)	22 (58%)
Serial No.	**Female: CHDs**	**Karyotype**
1	Murmur	46,XX,CNS/SS/UGS
2	Dextrocardia	46,XX,CNS/SS/DS
3	VSD	46,XX,CNS
4	VSD,ASD	46,XX,CNS/SS
5	Dextrocardia	46,XX,SS/UGS
6	VSD, PAH	46,XX,SS/UGS
7	Mitral valve prolapse	46,XX,CNS/SS
8	Mitral valve prolapse	46,XX,CNS
Total	10 (36.5%)	16 (42%)
Grand Total	26	38

Table 2: Systemic NCMs and CHDs in male and female

Systems	Male (n)	Female (n)	Total (n & %)
SS	9	6	15, 39.5
CNS	4	6	10, 26.3
DS	5	1	6, 15.8
RS	1	-	1, 2.6
UGS	3	3	6, 15.8
Total (n & %)	22 (58%)	16 (42%)	38
CHDs	Male (n)	Female (n)	Total (n & %)
VSD	4	3	7, 27
ASD	2	1	3, 11.5
PFO	1	-	1, 3.8
Murmur	3	1	4, 15.4
Double outlet right ventricle	1	-	1, 3.8
PAH	1	1	2, 7.7
Pulmonary valve stenosis	2	-	2, 7.7
PDA	2	-	2, 7.7
Dextrocardia	-	2	2, 7.7
Mitral valve prolapse	-	2	2, 7.7
Total (n & %)	16 (61.5)	10 (38.5)	26

pulmonary artery hyperplasia: 2 times each (2/26, 7.7%) and PFO/ double outlet right ventricle: one time each (1/26, 3.8%). It is VSD which has occurred 7 times (27%).

Table 3:It is seen, that NCMs in 2 systems have occurred 9 times (9/18, 50%) and in male 5 times (5/10, 50%) times.

It is single CHDs which have occurred 12 times (12/18, 66.7%).

Number of CHDs to Number of systems in Male and Female patients: In 5 patients one CHD each has affected 2 systems (3 males: VSD:CNS/SS, Murmur: CNS/SS; Murmur: SS/UGS); (2 females: dextrocardia: (SS/ UGS, mitral valve prolapse: CNS/SS). It is also seen in a male patient that one CHD has affected 4 systems (ASD-SS/RS/DS/ UGS).

Table 3: Association:CHDs and NCMs

Number and names of CHDs	Number of affected systems	Number of male patients	Number of female patients
One CHD: One system: One male/ 2 females: 3			
PDA	SS	1	-
VSD	CNS	-	1
Mitral valve prolapsed	CNS	-	1
One CHD: 2 systems : 3 males/ 2 females: 5			
VSD	CNS/ SS	1	-
Murmur	CNS/SS	1	-
Murmur	SS/UGS	1	-
Dextrocardia	SS/UGS	-	1
Mitral valve prolapse	CNS/SS	-	1
One CHD: 3 systems: 1 male/ 2 females: 3			
Murmur	SS/DS/UGS	1	-
Murmur	CNS/SS/UGS	-	1
Dextrocardia	CNS/SS/DS	-	1
One CHD: 4 systems: 1 male: 1			
ASD	SS/RS/DS/UGS	1	
2 CHDs: One system: 1 male: 1			
Pulmonary valve stenosis, VSD	CNS	1	-
2 CHDs: 2 systems: 2 females: 2			
VSD,ASD	CNS/SS	-	1
VSD, PAH	SS/UGS	-	1
2 CHDs: 3 systems: 1 male: 1			
ASD,PFO	CNS/SS/DS	1	-
3 CHDs: 2 systems: 2 males: 2			
Double outlet right ventricle, VSD, PAH	SS/DS	1	-
Pulmonary tricuspid stenosis, VSD, PDA	SS/ DS	1	-
26	38	10	8

Table 4: Association: Systems and types of CHDs

Systems versus number of CHDs	Types of CHDs	
	Male patients	Female patients
SS: 14 + 8= 22	VSD-3,ASD-2, PDA-2, Murmur-3, PFO, double outlet right	Murmur,Dextrocardia- 2, VSD-2
8+6=14	ventricle, PAH, Pulmonary tricuspid stenosis,	,ASD, Mitral valve prolapse,PAH
CNS: 6 + 7= 13	VSD-2 ,ASD, PFO, Murmur, Pulmonary valve stenosis	Murmur,Dextrocardia, VSD- 2,ASD,
5+5=10		Mitral valve prolapse-2
DS: 8 +1= 9	ASD- 2, PFO, VSD-2, Murmur,double outlet right ventricle, PAH, Pulmonary tricuspid stenosis, PDA	Dextrocardia
RS: 1	ASD	-
UGS: 3+ 4= 7	ASD,Murmur-2	Murmur,Dextrocardia,
2+4=6		VSD,PAH
34+20= 54	34	20
24+16=40	24	16

Table 4: Defects in SS were associated to 14 types of CHDs; defects in CNS were associated to 10 types of CHDs; defects in DS were associated to 9 types of CHDs; defects in UGS were associated to 6 types of CHDs and defect in RS to one type of CHD. SS (5 times) and CNS (4 times) were associated to VSDs (9 times).

The association between the types of CHDs versus NCMs showed that in male ASD was associated to 5 system anomalies and in female dextrocardia to 4 system anomalies.

Discussion

Review of literature showed that studies on non-cardiac or extra-cardiac malformations and CHDs have been carried out on live births or still births and as necropsy and autopsy studies.

Cardoso et al (2013) reviewed the association between CHDs and extracardiac malformations.

Scientific articles were searched in the Medline, Lilacs, and SciELO databases and all case series that specifically explored the association between CHDs and extracardiac malformations were included. CHDs were found to be responsible for about 40% of birth defects, being one of the most common and severe malformations. Extracardiac malformations were observed in 7 to 50% of the patients with CHDS, bringing a greater risk of co-morbidity and mortality and increasing the risks related to heart surgery. Different studies have attempted to assess the presence of extracardiac abnormalities in patients with CHDs and among the changes described, those of the urinary tract were more often reported.

In India, Karande et al (2014) have assessed the proportion and pattern of extracardiac birth defects in children with CHDs. They have found that out of 560 with CHDs, 98 (17.5%) had extracardiac birth defects. Fifty-six had multiple congenital defects; 36 were syndromic cases and 6 had laterality defects. A total of 386 extracardiac birth defects (103 major and 283 minor) were documented, with craniofacial and skeletal birth defects being the commonest.

From literature, it is seen that exactly matching the observations of the present study, articles could not be traced. The present study differs, because it is an attempt on NCMs in patients with CHDS without any genetic profile; such as chromosomal abnormalities or single gene disorders. Moreover, in spite of the sample size, the present study has tried to associate the types of NCMs with the types of CHDs. Of course, the high percentage of NCMs in skeletal system was similar to the reports by Greenwood et al (1975) and Karande et al (2014). Any differences may be attributed to the sample size and the method of assessment. With each discovery, knowledge on genes is becoming explosive. Nowadays, genes involved during development are also investigated. Some of them are segment polarity genes, homeo-box containing genes and paired-box containing genes. Examples are: Transcription factor β super family, Sonic hedgehog-Gli pathway, T-box genes, Zinc finger genes, SOX genes). They act as transcription factors in regulating sequentially the developmental processes and in cell signaling. Mutations in these genes resulting in malformations of the various systems of the body are also reported.(Turnpenny and Ellard 2012)

Genetic counseling (GC): During GC, diagnosis/ incidence/ risk assessment/ medical and surgical options/ support are communicated. In general, one in 20 (5%) or less is considered to be a low risk; whereas one in 10 (10%) or high is high risk. In case a definite genetic etiology could not be detected (chromosomal abnormalities, single gene disorders) then multifactorial inheritance could account for most of the congenital abnormalities. Based on

family and population studies for malformations, the observed or empirical risks are derived. For example: CHD: incidence is 8 in 1000 births; male to female sex ratio is 1: 1; parents unaffected; then the risk is around 1 to 4% for a second child to be affected; father is affected then it is 2%; mother is affected then it is 6%. (Turnpenny and Ellard 2012).

Conclusion

The primary outcome of the study is reporting the presence of 38 non-cardiac malformations and 26 CHDs in 18 patients with normal karyotype. 22 malformations were seen in 10 male and 16 in 8 female patients. The secondary outcomes are the frequent occurrence of the: 2 system anomalies (9 times); skeletal system defects (15 times) and associations of malformations to ventricular septal defects (9 times). Genetic counseling was provided to patients and families and they were recommended for medical and surgical management of CHDs and non-cardiac malformations.

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