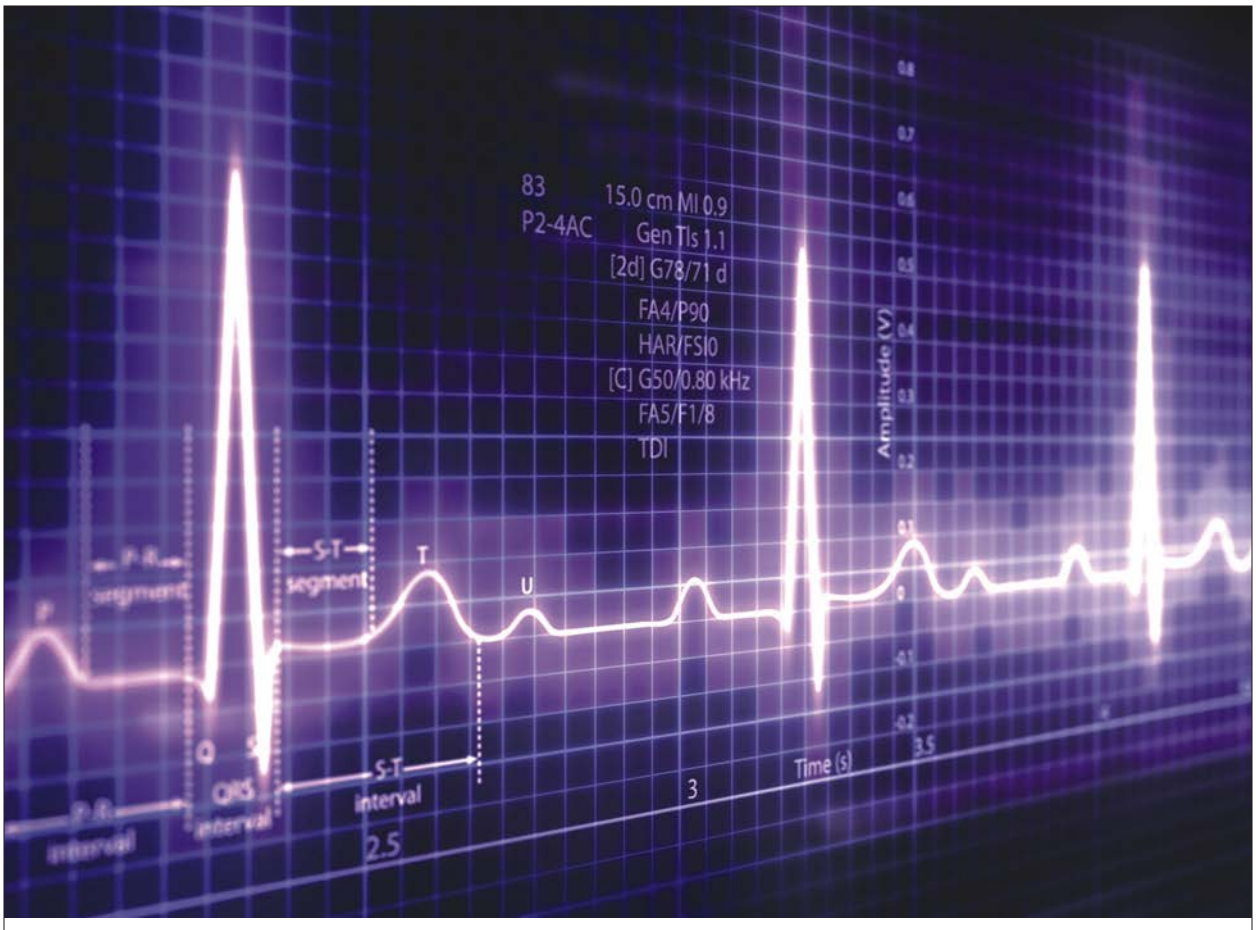

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Congenital Heart Diseases in Saudi Down Syndrome Children: Frequency and Patterns in Almadinah Region

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ABSTRACT

Congenital Heart Diseases (CHDs) occur in about 40-50% of neonates born with Down syndrome. Increased incidence of CHDs in children with Down syndrome in certain populations has been associated with widespread consanguinity. Up till now there is no explanation for why some Down syndrome patients are susceptible to CHDs. This study aims to evaluate the frequency and patterns of CHDs in Down syndrome children at Almadina province in the west of Saudi Arabia and compare it with other previously reported studies. The study included Down syndrome children referred to the pediatric cardiology clinic for screening of CHDs. Full history taking, pedigree analysis and clinical examination were done to all cases. Parental consanguinity was documented and echocardiography was done to assess the cardiac lesions. Out of 110 Down syndrome children, 45 (40.9%) had CHDs were selected. Parental consanguinity was present in 26/45 (57.8%). The most frequent lesion was AVSD (33.3%), followed by VSD (22.2%), then ASD (13.3%), PDA was present in 8.8% and TOF was diagnosed in one case. The most common combination of cardiac lesions in Down syndrome cases included in this study was ASD with VSD. Conclusion: The frequency of CHDs in Down syndrome children from Almadina province in the west of Saudi Arabia was similar to those reported worldwide. The most frequent lesion diagnosed in this study was AVSD. The CHDs were slightly more frequent in Down syndrome children born to consanguineous parents.

Key words: Down syndrome, congenital heart diseases, Saudi children, AVSD

INTRODUCTION

Chromosomal aneuploidy is one of the major causes of fetal abnormalities that cause fetal and neonatal morbidity and mortality. Down syndrome is the most frequent chromosomal anomaly diagnosed in neonates. The worldwide incidence of Down syndrome is reported to be 1 in 650-1,000 live births (Hook, 1982). Its incidence in Saudi Arabia is 1 in 554 live births (Niazi *et al*., 1995).

Down syndrome children are clinically diagnosed by the presence of a characteristic phenotype including brachycephaly, hypotonia, upslanting palpebral fissures, relatively large protruding tongue, short neck with the presence of skin fold and short stubby hands with simian creases. The clinical diagnosis is confirmed by chromosome analysis. There are three types of Down syndrome according to karyotype result: Trisomy 21 which represents the majority of cases (95%) in which there is an extra copy of chromosome 21, translocation Down syndrome and mosaicism (Tolmie and MacFadyen, 2007).

Children with Down syndrome are prone to have multiple birth defects and health problems. Congenital Heart Diseases (CHD) is the most frequent and the greatest cause of death in Down syndrome children during the first two years of life (Stoll *et al*., 1998) Great advances in the surgical treatment of CHD with improved postoperative care helped in the treatment of congenital heart defects in Down syndrome children and improved their quality of life. Early diagnosis and management is required to achieve good results (Kabbani *et al*., 2005; Roussot *et al*., 2006).

The aim of this study was to determine the frequency and patterns of CHDs in Down syndrome children at Almadina region in the west of Saudi Arabia and compare it with other previously reported studies.

MATERIALS AND METHODS

Down syndrome children referred to the pediatric cardiology clinic at Children and Maternity Hospital, AlMadinah, seen between April, 2013 and March, 2015 were included in this study.

Selected cases were subjected to detailed genetic history regarding the age, sex, consanguinity, developmental history and family history with special emphasis on maternal age, paternal age and presence of a previous child with Down syndrome or any chromosome anomaly present in the family or other relatives. Pedigree analysis was done to all cases. All cases were subjected to full clinical assessment looking for phenotypic features that suggesting Down syndrome as hypotonia, brachycephaly, small low set ears, upslanting palpebral fissures, brushfield spots of iris, short stubby hands and feet, simian creases and gap between first and second toes. Down syndrome diagnosis was confirmed by chromosome analysis using trypsin G-banding technique on Peripheral blood lymphocytes with some modifications (Seabright, 1971). All probands included were examined by plain X-ray chest and ultrasound of the heart (2-Dechocardiography) with Doppler study. Down syndrome children aged above 12 years with ethnic background outside almadinah or any other congenital or chromosomal anomalies were excluded from the study. The study was approved by the ethical committee of the Child and Maternity Hospital, AlMadina, Saudi Arabia where the study was done and it was in agreement with declarations of Helsinki. The obtained data were analyzed using descriptive statistics (range, mean±SD, proportions) using direct counting and Microsoft excel 2010. p-value was calculated using chi square test.

RESULTS

As shown in Table 1 the study included 110 Down syndrome children screened for congenital heart anomalies by echocardiography. Congenital Heart Diseases (CHDs) were diagnosed in 45/110, 40.9% and 65/110, 59.1% had normal echocardiography findings. Consanguinity rate was 54/110, 49.1%. In CHD affected Down syndrome cases, consanguineous parents were documented in 26/45, 57.8% and non-consanguineous parents were seen in 19/45, 42.2%, while among Down syndrome children without CHDs, 28(43.1%) were offspring of consanguineous parents and 37 (56.9%) had non-consanguineous parents. There were no statistical significant difference between both groups regarding consanguinity (p-value 0.05).

Table 2, illustrates the clinical characteristics of the selected Down syndrome cases having CHD. The age of Down syndrome children affected with CHD ranged from 0-12 years (mean = 3.22±3.61). Females were 21(46.6%) and males were 24 (53.4%). Down syndrome children with CHD born to consanguineous parents were 26 (57.8%) and absent consanguinity was seen in 19 (42.2%). The diagnosis of Down syndrome was confirmed by chromosome analysis done to all

Table 1: Distribution of CHDs in Down syndrome children included in the study

	Down syndrome without CHD		Down syndrome with CHD	
Characteristics	No.	%	No.	%
Frequency	65.00	59.1	45	40.9
Consanguinity				
Present	28.00	43.1	26	57.8
Absent	37.00	56.9	19	42.2
p-value	0.129			

Table 2: Clinical characteristics of the studied Down syndrome cases

Characteristic	No.	Percent
Number	45	100
Age range		
2 years	25	55.6
2-5 years	15	33.3
5-12 years	11.1	
Mean±SD	3.22±3.61	
Sex		
Female	21	46.6
Male	24	53.4
M/F ratio	1.14:1	
Consanguinity		
Present	26	57.8
Absent	19	42.2
Chromosome analysis		
Trisomy 21	44	97.8
46, XX, t(14q; 21q)	2.2	

Table 3: Frequency and patterns of CHD in the studied Down syndrome cases

Cardiac lesion	No.	%	Non-consanguineous parents	Consanguineous parents
Isolated	36	80.0	17/36 (47.2%)	19/36 (52.8%)
ASD	6	13.3	4	2
VSD	10	22.2	6	4
AVSD	15	33.3	5	10
PDA	4	8.8	2	2
TOF	1	2.2	0	1
Combined	9	20.0	2/9 (22.2%)	7/9 (77.8%)
ASD+VSD	5	11.1	2	3
ASD+PDA	1	2.2	0	1
VSD+PDA	2	4.4	0	2
TOF+PDA	1	2.2	0	1

selected cases, where trisomy 21 was detected in 97.8% of cases, while translocation Down syndrome was seen in one girl with karyotype 46, XX, t (14q; 21q). Chromosome analysis was done to parents; the mother was carrier for robertsonian translocation between chromosome 14 and chromosome 21{45, XX, t (14q; 21q)} while the father had normal karyotype {46, XY}.

Table 3, shows frequency and patterns of cardiac lesions detected in the selected cases. Isolated cardiac lesions were present in 36 (80%) of cases, descendants from consanguineous matting were19/36; 52.8%. Nine cases (20%) had combined cardiac lesions and consanguinity was present in 7/9; 77.8%.

The most frequent isolated cardiac lesion detected in our study was AVSD which was found in 15/45, 33.3%, followed by VSD in 10/45, 22.2% and ASD in 6/45, 13.3% cases. The PDA was detected in 4/45, 8.8% and TOF was diagnosed in one case. The most common combination of cardiac lesions in Down syndrome cases included in this study was ASD with VSD (5/45,11.1%) followed by VSD with PDA (2/45, 4.4%) and ASD with PDA in 1/45, 2.2%. A rare combination between TOF and PDA was diagnosed in one case.

DISCUSSION

Down syndrome is the most frequently observed autosomal chromosome anomaly among live births and is the main genetic cause of mild to moderate mental retardation in children (Nussbaum *et al*., 2007).

In the present study, the frequency of CHD among Down syndrome children was 40.9%. This matches with the internationally reported Fig. 1, where 30-65% of Down syndrome children were

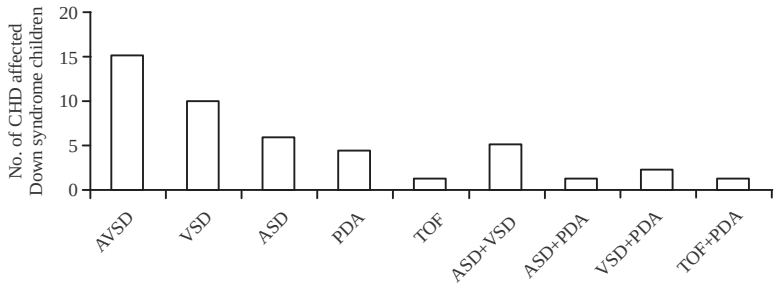

Fig. 1: Frequency and distribution of CHDs in studied Down syndrome children

found to have CHD (Murthy *et al*., 2007; Van der Linde *et al*., 2011; Zhu *et al*., 2013). Afifi *et al*. (2011) reported CHDs in 40% of Egyptian Down syndrome children, Elmagrpy *et al*. (2011) found that approximately 50% of Down syndrome children in Libya had CHD which is near to Malayza (Azman *et al*., 2007). On the other hand, the frequency of CHD in Down syndrome observed in this study is less than that reported in Oman (60%) (Venugopalan and Agarwal, 2003), Turkey (78%) (Nisli *et al*., 2008) and Guatimala (80%) (Vida *et al*., 2005). In comparison to local studies done in Saudi Arabia, Al-Jarallah (2009) reported that CHD was diagnosed in 49% of Down syndrome children in Riyadh region, the capital of Saudi Arabia. While, Abbag (2006) found that 61.3% of the studied group of Down syndrome in Aseer region at the south of Saudi Arabia had CHD.

In the current study, consanguinity rate was 49.1% which is near to the overall consanguinity rate in Saudi Arabia (57.7%) (Teebi and Faraag, 1997). The frequency of CHD was slightly higher among Down syndrome children of consanguineous parents (57.8%) than non- consanguineous. An important feature in our study is that the frequency of isolated and combined cardiac defects were slightly higher in Down syndrome children, who were born to consanguineous parents (52.8 and 77.8%, respectively). The statistically non-significant association between consanguinity and CHD in Down syndrome cases involved in our study can be attributed to the small sample size in which all cases included were from one hospital.

The high frequency and severity of CHD among Down syndrome children who are the offspring of consanguineous matting were reported in certain populations like Oman (Venugopalan and Agarwal, 2003), Turkey (Aynaci *et al*., 1998), india (Ashraf *et al*., 2010) and Qatar (Wahab *et al*., 2006). Al-Jarallah (2009) reported that the frequency of CHD was slightly higher in Down syndrome children of consanguineous parents from Riyadh population. El Mouzan *et al*. (2008) found that there was no significant association between first-cousin consanguinity and Down syndrome. However, there was a significant association between CHD and parental consanguinity, mostly for septal defects. Such a finding was reported by Becker *et al*. (2001) in Saudi Arabia and Khalid *et al*. (2006) from Lebanon.

Consanguineous marriage is common in the Middle East and Arab countries especially in small and rural areas. In many parts of the Saudi Arabia like Al Madinah, the society is still tribal with families descended from a common ancestors which makes the congenital and genetic disorders more complicated. We can propose a possible role of an autosomal recessive gene involvement in CHD development.

In the present study, septal cardiac lesions were found in Down syndrome cases with absence of stenotic lesions and the frequency of isolated lesions were more than combined ones that can be explained by the severity of combined lesions which may cause fetal and neonatal death before the diagnosis. The AVSD was the most frequent cardiac lesion in CHD affected Down syndrome

Table 4: Frequency and distribution of CHDs in Down syndrome patients from different regions of Saudi Arabia

	Abbag (2006) Aseer		Al-Jarallah (2009) Riyadh		Al-Aama (2012) Jeddah	
CHD pattern	No. = 57	%	No. = 54	%	No. = 92	%
CHD frequency in down syndrome	57/90	61.3	54/110	49	92/106	86.8
PDA	8	14.0	4	7	44	47.8
ASD	12	21.1	14	25	38	41.3
VSD	19	33.3	23	43	27	29.3
AVSD	13	22.8	8	15	11	12.0
TOF	3	5.3	2	4	2	1.5
Tricuspid regurge					31	33.7
Mitral regurge					10	10.8
Patent foramen ovale					26	28.3
Pulmonary stenosis	1	1.8	1	1.9	2	1.5
Pulmonary hypertension					9	9.7
Dilated atrium/ventricle					5	5.4
Right sided aortic arch					1	0.77
Pericardial effusion					6	6.5

children (33.3%), followed by VSD (22.2%), then ASD (13.3%) cases. This matches with most of the European countries, USA, Sudan, Turkey and Egypt (Freeman *et al*., 1998; Ali, 2009; Mokhtar and Fattah, 2001).

In comparison to locally published studies in Saudi arabia, Al-Jarallah (2009) reported that VSD was present in 13% of Down syndrome children followed by ASD (7%), while AVSD was present in 4% of cases. In another study conducted in Aseer region, Abbag (2006) found that VSD was the most frequent lesion (35%) followed by AVSD (22%), then ASD (21.1%). These data differs from that reported by Al-Aama *et al*. (2012), who found that the most frequent cardiac lesion diagnosed among Down syndrome patients in Jeddah, at the west of Saudi Arabia was PDA with high frequency of CHD (86.8%) in Down syndrome cases. Table 4 summarizes the results obtained by different studies done in Saudi Arabia to analyze the frequency and distribution of CHD among Down syndrome children.

We can notice that the frequency and distribution of CHDs in Down syndrome vary in different geographical regions locally and internationally, The exact genetic, epigenetic and/or environmental causes of CHD in Down syndrome children remains unclear and variations between different studies may be caused by many factors, one of which could be the genetic make-up of each nation; gene-gene interaction and gene-environment interactions that may disturb specific molecular pathways of embryogenesis during fetal life.

CONCLUSION

The frequency of CHDs in Down syndrome children from Almadina province in the west of Saudi Arabia was similar to those reported worldwide. The most frequent lesion diagnosed in this study was AVSD. The CHDs were slightly higher in Down syndrome children of consanguineous parents. The main limitations of this study were small sample size and the dependence on patients referred to one hospital. The high rate of consanguinity and the tribal structure in Saudi Arabia population can be put into consideration as risk factors for CHDs in Down syndrome which need further studies with large population samples. Further studies on Down syndrome patients with and without CHD are recommended to evaluate the additional genetic differences that might add to the CHD risk in Down syndrome on the basis of why some Down syndrome children are susceptible to CHDs than others, which will help in developing better strategies for genetic counseling and proper management.

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