Congenital heart defects in Down syndrome patients from western Saudi Arabia

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ABSTRACT

الأهداف: تحديد نوع العيوب الخلقية في القلب لدى مرضى متلازمة داون في المنطقة الغربية بالمملكة العربية السعودية، ومقارنتها بالدراسات التي أُجريت في المناطق الأخرى بالمملكة وكذلك بالدراسات العالمية.

الطريقة: أُجريت هذه الدراسة الاستطلاعية على مرضى متلازمة داون الذين تم فحصهم في عيادة متلازمة داون بمستشفى جامعة الملك عبد العزيز، جدة، المملكة العربية السعودية وذلك خلال الفترة من أكتوبر 2007م إلى أكتوبر 2011م. وقد قامت الدراسة على تقييم التاريخ المرضي والعائلي للحالات، مع الفحص السريري الشامل. كما تم عمل تحليل للكروموسومات الذي أكد التشخيص السريري، بالإضافة إلى إجراء فحص بالموجات الصوتية للقلب للمرضى الذين تضمنتهم الدراسة.

النتائج: شملت هذه الدراسة 130 حالة من متلازمة داون (59% من الذكور، و41% من الإناث) تتراوح أعمارهم ما بين 0-33 (متوسط العمر=5±4.9). لقد تبين أن معظم المشاركين (90.9%) يعانون من التثلث الصبغي، حيث كان 21 بسبب عدد الانفصال، و5.05% بسبب إزفاء روبرنسوني، و4% بسبب التزيق. وظهرت العيوب الخلقية في القلب لدى 86.8% من المرضى المشاركين في الدراسة. وأوضحت الدراسة أن الغالبية العظمى 71/92 (77%) كانوا مصابين بعيوب خلقية متعددة بالقلب، بينما 21/92 (23%) منهم كانوا مصابين بعيوب خلقية مفردة بالقلب. ولقد كانت أكثر العيوب الخلقية في القلب والتي كانت شائعة بين المرضى الذين شملتهم الدراسة كالتالي: القناة الشريانية المفتوحة لدى 44/92 (47.8%) وعيوب الحاجز الأذيني لدى 38/92 (41.3%) وتهريب في صمامات القلب لدى 31/92 (33.7%) وعيوب الحاجز البطيني 27/92 (29.3%) وبقاء الثقب البيضاوي لدى 26/92 (28.3%).

خاتمة: أظهرت هذه الدارسة أن نسبة حدوث عيوب القلب الخلقية لدى مرضى متلازمة داون في المنطقة الغربية من المملكة العربية السعودية كانت عالية وذلك بالمقارنة مع المناطق الأخرى بالمملكة، وكذلك بمقارنتها مع الإحصاءات العالمية. كما أننا لاحظنا ظهور العيوب الخلقية المتعددة في القلب لدى هؤلاء المرضى، بالإضافة إلى أنماط توزيعية مختلفة.

Objectives: To characterize congenital heart defects in individuals with Down syndrome (DS) in the Western Region of Saudi Arabia, and compare with studies from other regions of Saudi Arabia and with international figures.

Methods: We conducted a prospective study including all patients attending the DS clinic at King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia between October 2007 and October 2011. All patients underwent full history and physical evaluations, dysmorphologic assessment, chromosomal studies, and echocardiography.

Results: A total of 130 individuals (59% males and 41% females) with ages ranging between 0-33 years (mean=5±4.9) were included. Most individuals (90.9%) had trisomy 21 due to non-disjunction, 5.05% due to Robertsonian translocation, and 4% had mosaicism. Congenital heart defects were found in 86.8% of patients. The majority 71/92 (77%) showed combined cardiac defects, while 21/92 (23%) of DS patients had isolated congenital heart defects (CHD). The most frequent CHDs detected in this study were: patent ductus arteriosis in 44/92 (47.8%), atrial septal defect in 38/92 (41.3%), trivial tricuspid regurge in 31/92 (33.7%), ventricular septal defect in 27/92 (29.3%), and patent foramen oval in 26/92 (28.3%).

Conclusion: We found a higher incidence of CHDs among DS individuals from the Western Region, compared to national and international figures. We detected more combined CHD and a different pattern of distribution.

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Down syndrome (DS) is a genetic disorder due to a numerical chromosomal abnormality, which results in extra genetic material from chromosome 21.[1] It is the most common and best known chromosomal disorder in humans. There are no known behavioral or environmental factors that cause DS. Its incidence in Saudi Arabia is reported to be 1 in 554 live births.[2] There are 3 types of DS according to chromosomal analysis: non-disjunction trisomy 21, Robertsonian translocation, and mosaic DS. Phenotypically, all individuals with DS have common dysmorphic features and a wide range of congenital anomalies that may affect almost any body system.[3,4] Frequencies of congenital heart defects (CHD) in DS ranging from 16-65% have been reported.[5] A thorough literature review by the authors using common electronic databases including PubMed did not yield any studies reporting the prevalence of DS in the Western Region of Saudi Arabia. The current study was carried out to prospectively report the prevalence and the pattern of CHD associated with DS in the local population, and to characterize and compare the findings of CHD in DS patients in the western region with other studies from both central and south regions of Saudi Arabia, as well as with that of international figures.

Methods. We performed this prospective case study on 130 DS patients attending and being followed up at the DS clinic of the Genetic Medicine Unit at King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia (KSA) between October 2007 and October 2011. The DS clinic at KAUH is a specialized clinic managing patients affected with trisomy 21. It provides a comprehensive multidisciplinary service, which includes anticipatory clinical guidance, parental genetic counseling, and prenatal testing for DS. It is the largest genetic tertiary care referral unit accepting patients from all major cities in the Western region of Saudi Arabia. Inclusion criteria included all patients cytogenetically diagnosed as having trisomy 21 on chromosomal analysis. The initial clinical evaluation for each patient included: complete medical history taking and physical examination. The medical history focused on: antenatal, natal, and postnatal history, pedigree analysis, parental age at delivery, and developmental history. The physical examination included: dysmorphologic assessment, growth parameters, which were plotted on DS specific charts, cardiovascular and neurological examinations, gastrointestinal evaluation, and other systemic examination. Echocardiography was requested for each patient, and a cardiologist followed up those with abnormal findings. Patients who did not undergo echocardiography were excluded from the study. At birth or on the first visit, chromosomal analysis was requested to confirm the clinical diagnosis of DS and provide genetic counseling of the family. The data of each patient were recorded in a specifically designed data base collection sheet. The statistical analysis was carried out utilizing MegaStat® for Microsoft® Excel® version 14. The recruitment and experimental protocols for the study were conducted in compliance with the Declaration of Helsinki, and approved by the KAUH Biomedical Ethics Committee.

Results. A total of 130 patients were examined and investigated in the 4-year period, either after delivery in our hospital or after referral from other facilities. Out of 130 patients seen in our clinic, 33 were born in KAUH. Therefore the incidence of DS in our center is 1:740. There were 53 (40.8%) females and 77 (59.2%) males, and their age ranged between 0-33 years (mean 5+4.9 years). The average maternal age at birth of the affected child was 35 years. Sixty percent of the mothers were aged 35 years or older. The clinical diagnosis of DS was confirmed by chromosomal studies: classic trisomy 21 (non-disjunction) was present in 90/99 (90.9%) of cases, translocation was detected in 5/99 (5.05%) of patients and 4/99 (4%) of patients were mosaics. No phenotypic differences were detected between non-disjunction, translocation, and mosaic patients.

Cardiac abnormalities were screened in 106/130 patients using echocardiography. Twenty-four patients were excluded from the study because they did not undergo echocardiography evaluation. Congenital heart defects were detected in 92/106 (86.8%). Seventy-one patients showed combined CHD (77%), while only 21 (23%) DS patients included in the current study showed isolated CHD.

The most frequent CHDs detected in our study either in combination or isolated are summarized in **Table 1**. Patent ductus arteriosis (PDA) in 44/92 (47.8%), atrial septal defect (ASD) in 38/92 (41.3%), trivial tricuspid regurge (TTR) in 31/92 (33.7%), ventricular septal defect (VSD) in 27/92 (29.3%), and patent foramen ovale (PFO) in 26/92 (28.3%) were found in order of frequency. **Table 2** classifies the types of CHD found and compares them with the 2 other main regions in the Kingdom of Saudi Arabia. The most common combinations detected in DS patients in the current study were ASD with PDA + VSD in 16/92 (17.4%), followed by AVSD with ASD, VSD, PDA as well as PH in 12/92 (13%). The frequency of associated CHD in DS patients in the current study compared to international figures is summarized in **Table 3**.

Discussion. The Kingdom of Saudi Arabia is a large country with a population of 25 million people. It is divided into 5 main provinces.[6] This study was conducted in the city of Jeddah in the Makkah province. Jeddah is the second largest city of the Kingdom and harbors a population of over 3.5 million.[7] It has a multicultural society of diverse ethnicity due to its proximity to the Holy Islamic cities and its location on the Red Sea. The frequency and type of heart defects among DS patients in published studies differ according to study design and population characteristics. Frequencies of CHD in DS ranging from 16-65% have been reported from different parts of the world.[5-16] Unal et al,[8] reported CHD in 35.9%, and Ayanci et al,[9] in 71.4% of DS patients from different regions of Turkey. In another study carried out by Bertelli et al,[10] in the Brazilian population, CHD in DS were present in 56.5% of the cases with a greater frequency of PDA (34.3%), followed by ASD in 17.1% of cases. A similar frequency was also reported by other Brazilian studies, which range from 51.1-62.2%.[11,12] Congenital heart defects were diagnosed in 35/71 (49.2%) DS patients from Malaysia, where it was found that the most common anomalies were PFO (22.8%), VSD (20%), AVSD (20%), followed by ASD (17.1%).[13] Afifi et al,[14] reported CHD in 40% of Egyptian DS patients with a greater frequency of ASD (8.9%), VSD (8.9%), and PDA (4%). The prevalence of DS with CHD in our study (86.8%) is higher than the rates found by other authors both locally,[17-20] and internationally. In a previous study looking at the incidence of congenital

Table 1 - Frequency of congenital heart defects in 92 patients.

Congenital heart defect	No of patients	(%)
Patent ductus arteriosis	44	(47.8)
Atria septal defect	38	(41.3)
Trival tricuspid regurge	31	(33.7)
Ventricular septal defect	27	(29.3)
Patent foramen ovale	26	(28.3)
Atrioventricular septal defect	11	(12.0)
Mitral regurge	10	(10.8)
Pulmonary hypertension	9	(9.7)
Pericardial effusion	6	(6.5)
Dilated atrium/ventricle	5	(5.4)
Tetralogy of Falot	2	(1.5)
Pulmonary stenosis	2	(1.5)
Hypertrophic cardiomyopathy	2	(1.5)
Double outlet right ventricle	1	(0.77)
Right sided aortic arch	1	(0.77)
Aneurysmal interatrial septum	1	(0.77)
Total	**92/106**	**(86.8)**

Table 2 - Frequency of congenital heart defects in Down syndrome patients from different regions of Saudi Arabia.

Congenital heart defect	(Current study) Jeddah		Abbag, 2006 Aseer[18]		Al-Jarallah, 2009 Riyadh[19]	
	n=92 patients	(%)	n=57 patients	(%)	n=54 patients	(%)
Patent ductus arteriosis	44	(47.8)	8	(14.0)	4	(7.4)
Atria septal defect	38	(41.3)	12	(21.1)	14	(26.0)
Trival tricuspid regurge	31	(33.7)				
Ventricular septal defect	27	(29.3)	19	(33.3)	23	(42.6)
Patent foramen ovale	26	(28.3)				
Atrioventricular septal defect	11	(12.0)	13	(22.8)	8	(14.8)
Mitral regurge	10	(10.8)				
Pulmonary hypertension	9	(9.7)				
Pericardial effusion	6	(6.5)				
Dilated atrium/ventricle	5	(5.4)				
Tetralogy of Falot	2	(1.5)	3	(5.3)	2	(3.7)
Pulmonary stenosis	2	(1.5)	1	(1.8)	1	(1.9)
Hypertrophic cardiomyopathy	2	(1.5)				
Double outlet right ventricle	1	(0.77)			1	(1.9)
Right sided aortic arch	1	(0.77)				
Aneurysmal interatrial septum	1	(0.77)				
Tricuspid atresia			1	(1.8)		
Bicuspid aortic valve					1	(1.9)

Table 3 - Frequency of combined CHD in DS in Jeddah compared to different international studies.

Combined CHD	Current study		Afifi et al,[14] 2011 Egypt		Mihci et al,[5] 2010 Antalya		Kava et al,[21] 2004 Malaysia		Venugopalan,[15] 2003 India	
	71/92 patients	77%	15/36 patients	41.7%	59/136 patients	43.4%	20/58 patients	34.5%	22/58 patients	37.9%
ASD+VSD	1	(1.4)	3	(20.0)	20	(33.9)	4	(20.0)	4	(18.2)
ASD+PDA	8	(11.3)	4	(26.7)	8	(13.6)	4	(20.0)	4	(18.2)
ASD+VSD+PDA	8	(11.3)			4	(6.8)				
AVSD+PH	3	(4.2)								
AVSD+ASD+VSD	4	(5.6)								
AVSD+PDA	3	(4.2)			8	(13.6)				
AVSD+VSD+PDA	1	(1.4)								
AVSD+ASD+PDA	1	(1.4)			1	(1.7)				
TTR+PFO	7	(9.9)								
TTR+PFO+PDA	5	(7.0)					1	(5.0)		
TTR+MR	4	(5.6)								
TTR+VSD+PDA	2	(2.8)								
TTR+AVSD	2	(2.8)								
TTR+ASD+PDA	2	(2.8)								
TTR+ASD	2	(2.8)								
TTR+ASD+VSD	2	(2.8)								
TTR+PDA	1	(1.4)								
TTR+VSD	1	(1.4)								
TTR+ others	3	(4.2)								
PS+ASD	1	(1.4)			1	(1.7)	1	(5.0)	1	(4.5)
VSD+PDA	1	(1.4)			1	(1.7)	2	(10.0)	2	(9.1)
DORV+VSD+ASD+PDA	1	(1.4)					2	(10.0)		
Other combinations	8	(11.3)	8	(53.3)	16	(27.1)	6	(30.0)	11	(50.0)

CHD - congenital heart defects, DS - Down syndrome, ASD - atrial septal defect, VSD - ventricular septal defect, PDA - patent ductus arteriosis, AVSD - atrioventricular septal defect, TTR - trivial tricuspid regurge, PFO - patent foramen ovale, MR - Mitral regurge, DORV - double outlet right ventricle, PS - pulmonary stenosis

malformations among live births (LB) in Jeddah, we found CHD to have a higher prevalence (7.1/1000 LB) and to be more common in the general population than other defects as compared with other studies from the region.[17] Although the high incidence of CHD found may be due to the fact that this study was performed in a referral center for genetics, these findings together with this current study raise the possibility that genetic polymorphisms predisposing to CHD are higher in this population. This may also explain the findings of a higher incidence of combined heart defects (77%) compared to single ones in our population. The higher prevalence of ASD also supports this hypothesis. The pattern of differences cannot be attributed to the cytogenetic subtypes of DS since more than 90% of cases were due to non-disjunction, making comparison irrelevant.

On review of literature from other parts of the KSA, we found that Abbag[18] conducted a study in the Aseer region (Southwest of Saudi Arabia), to determine the frequency and types of CHD in DS patients. Congenital heart defects were found in 57 out of 98 of their study group (61.3%), and the most frequent was VSD (35.3%) followed by atrioventricular septal defect (22.8%), ASD (21.1%), and PDA (14%) in descending order of frequency. In another study conducted on 110 DS patients by Al-Jarallah,[19] in Riyadh, which is located in the central region of Saudi Arabia, it was found that CHD were detected in 49% of patients with a prevalence of VSD of 42.6% followed by ASD at 26%.

Al-Mesned et al,[20] screened severe CHD in the province of Al-Qassem, and found that the incidence of severe CHD is 5.4/1000 live births. Of these, 15% had an underlying genetic syndrome and the most common was DS. Our study, conducted in the western region of Saudi Arabia, showed a difference in the frequency of CHD in DS patients as well as the distribution of the different forms of CHD detected in the current study from the 2 studies performed in the central and south region of Saudi Arabia. The most frequent CHDs detected in our study were PDA (47.8%), followed by ASD (41.3%), and TTR (33.7%).

The study was limited by the fact that it was carried out on a relatively small number of patients. It is also considered as a single center experience representing a sample of the total population. As the incidence of CHD in DS patient is high, all patients with DS should be evaluated with complete examination and investigations. It is well known that echocardiography offers an excellent non-invasive tool to diagnose cardiac malformations in infants with DS, especially during the newborn period. Early diagnosis in the neonatal period offers the best chance for effective intervention.[21]

In conclusion, we conducted this study to define the incidence of CHD in DS in the Western Region of KSA. It showed a higher rate of CHD, multiple cardiac defects, and ASD than in individuals with DS in other parts of the KSA and internationally. Further studies to confirm these findings and explore the underlying cause of such variation are needed. A registry for CHD in KSA is essential to further study the difference in prevalence and the relevant contributing factors.

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