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Original Article

Parental consanguinity and congenital heart defects in Afghan children with Down's syndrome

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Abstract

Background Parental consanguinity affects the pattern of congenital heart defects (CHDs). The association between Down's syndrome (DS) and congenital heart defects has long been known. Parental consanguinity may affect the pattern of CHDs. Some communities in Afghanistan have a high consanguineous marriage rate, possible affecting the types of CHDs in children with DS.

Objective To determine the frequency and distribution of CHDs in children with Down's syndrome in Afghanistan, where the community had a high consanguineous marriage rate.

Methods This prospective cross-sectional study was conducted in Maiwand Hospital, a pediatric teaching hospital in Kabul, Afghanistan. Subjects were children with DS shown by clinical and cytogenetic studies, and referred to the Pediatric Cardiology Service from September 2018 - September 2020. Parental consanguinity was documented. Subjects underwent 2D echocardiography and Doppler studies performed by two experienced pediatric cardiologists after physical examination, ECG, and chest X-ray.

Results During the two-year study period, 120 DS patients were identified, 78 (65%) of whom had CHDs. The prevalences of isolated and multiple CHD in the 78 children with DS were 35.8% (43 patients) and 29.1% (35 patients), respectively. The most common isolated defects were ventricular septal defect (21.7%) and atrial septal defect (15.3%). The most com-mon CHD associations were VSD + PDA (20.5%) and VSD + ASD (10.2%). Consanguinity was found in 69.2% of all parents.

Conclusion A higher frequency of CHD is documented in DS children from parents with a high consanguineous marriage rate. The frequencies of specific lesions are similar to those reported locally and internationally; VSD is the most frequently detected in our study. The predominance of left-right shunt lesions and the relative rarity of cyanotic and complex CHD are notable in this DS population. **[Paediatr Indones. 2021;61:306-10 ; DOI: 10.14238/pi61.6.2021.306-10].**

Keywords: *congenital heart disease; atrioventricular septal defect; Down's syndrome; Afghanistan*

Down's syndrome (DS), a common chromosomal aberration compatible with life,[1] has an incidence of 1: 700 live births.[2] The association between DS and congenital heart disease (CHD) has been well established since 1950, when the incidence and types of CHD present in newborns and infants with DS were thoroughly described.[3]

Cardiovascular malformations constitute the single most important cause of death in infants and young children with DS,[4] with rates ranging from 48-55.9%.[2,5-7] The incidence of AV canal occurrence ranges from 18.7-22.8%.[2,5] Despite advances in the surgical management of CHD, their presence remains a significant predictor of mortality in patients with DS.[8] This analytic, cross-sectional study aimed at identifying the frequency and distribution of CHDs in Afghan children with DS in a community with a high consanguineous marriage rate, and comparing such CHDs with those in children without DS in regional countries,[9-11] and populations with low prevalence of consanguinity. We expected a higher and possibly different CHD distribution due to the genetic influence.[12]

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Methods

Patients ≤14 years of age, referred to the Pediatric Cardiology Department of Maiwand Hospital, a teaching hospital of Kabul University of Medical Science, and admitted between September 2018 - September 2020 were included in this study. Children above 14 years of age were seen by adult cardiology services, according to Ministry of Health policy. The Maiwand Hospital is a tertiary, open-access teaching hospital serving a wide, community-based population from the central and other regions of Afghanistan. Down's syndrome patients were included, irrespective of the presence or absence of any cardiac symptoms, physical signs, ECG, or chest X-ray abnormality suggesting congenital heart disease. Patients with chromosomal anomalies (other than DS) or congenital infections were excluded. The diagnosis of DS was confirmed by clinical manifestations and chromosomal analysis of the peripheral blood lymphocytes. After detailed history-taking, including parental consanguinity and its degree, and physical examination, subjects underwent two-dimensional (2D) echocardiographic examination and Doppler studies using a *SonoAce X6* echocardiographic scanner. Children below 3 years of age, except for neonates in the first 4 weeks of life, were sedated with chloral hydrate (50 mg/kg orally) given 30 minutes before the procedure; no sedation was used in older children or neonates. The 2D-echocardiographic images were recorded in the standard parasternal long axis, short axis, apical 4-chamber, subcostal, and suprasternal views. Color Doppler as well as pulse and continuous wave Doppler were also performed in all patients.

The presence and severity of any cardiac malformation were analyzed in accordance with the recommendations of the *American Society of Echocardiography*.[13] The presence of atrioventricular septal defect (AVSD) was determined to be complete, if a single common atrioventricular valve was present, or to be partial, if both atrioventricular valves (mitral and tricuspid) were seen with a primum atrial septal defect, inlet ventricular septal defect, or cleft anterior leaflet of the mitral valve. Persistent foramen ovale and patent ductus arteriosus (PDA) separately or combined in premature and full-term babies were not included in the analysis. However, these were included if they persisted beyond the first six weeks of life.

Data analysis was done with *Statistical Package for Social Sciences (SPSS)* software, using simple descriptive statistics such as ratios, proportions, and percentages. Chi-square and Fisher's exact tests were used for analyses, with statistical significance defined for P values ≤ 0.05. This study was approved by the Ethics Committee of the Pediatric Cardiology Department, Kabul University of Medical Science, Afghanistan.

Results

A total of 120 patients satisfied the inclusion criteria. Their mean age was 2 (SD 3) years (range 0-14 years), with 28 (23.3%) <1-week olds and 35 (29.2%) <1-month olds. There were 62 males and 58 females (M:F = 1:0.9). Forty percent of the children were from Kabul City and 60% were from other provinces of Afghanistan.

All the children had clinical features of DS, while 65 patients had heart murmur at presentation, 42 presented with ejection systolic murmur, and 23 with pan-systolic murmur. The prevalences of isolated and multiple CHDs in the 78 DS subjects with CHDs were 35.8% (43 patients) and 29.1% (35 patients), respectively. There were 42 (35%) DS patients without CHD. Ventricular septal defect (20.5% of CHDs) and atrial septal defect (15.3% of CHDs) were the most common isolated defects. The most com¬mon associations of CHD were VSD + PDA (20.5% of CHDs) and VSD + ASD (10.2% of CHDs) (**Table 1**).

Consanguinity was found in 45% of parents of all DS patients and in 54 (69.2%) of those with CHDs. The heart defects of children from consanguineous and non-consanguineous parents are shown in **Table 2**. Children from consanguineous parents had significantly more total CHDs than the non-consanguineous group, as revealed by Chi-square test (P=0.026). Fisher's exact test comparison of single defects revealed significantly more ASDs (P=0.001), COA (P=0.001), AVSD (P=0.002), PDA (P=0.045), VSD+PDA (P=0.046) and ToF (P=0.003) in the consanguineous group than in the non-consanguineous group.

Table 3 shows that percentage of CHDs were not significantly different according to sex. In addition, there were no significant differences in age or birth weight in those with and without CHDs, as shown on **Table 4**.

Table 1. Prevalence and types of CHDs in children with DS

Congenital heart disease	Type of CHD	Number	% of CHD	% of children with DS
Isolated CHD	Total	423	53.9	35
	VSD	167	20.5	13.3
	ASD	12	15.3	10
	AVSD	4	5.12	3.33
	PDA	5	6.41	4.16
	COA	3	3.84	2.5
	PS	2	2.56	1.66
Multiple CHD	Total	36	46.1	30
	VSD+ PDA	16	20.5	13.33
	VSD + ASD	8	10.25	6.66
	VSD + PFO	4	5.2	3.33
	TOF	6	7.69	5
	ASD + PDA	2	2.56	1.66

ASD=atrial septal defect, AVSD=atrioventricular septal defect, CHD=congenital heart disease, COA=coarctation of aorta, PDA=patent ductus arteriosus, PFO=patent foramen oval, PS=pulmonary stenosis, TOF=tetralogy of Fallot, VSD=ventricular septal defect.

Table 2. Comparison of heart defects in subjects with consanguineous and non-consanguineous parents

CHD	Consanguineous parents	Non-consanguineous parents	P value
VSD	9	8	0.654
ASD	10	2	0.001
AVSD	4	0	0.002
PDA	3	2	0.045
COA	3	0	0.001
PS	1	1	0.783
VSD+ PDA	10	6	0.046
VSD + ASD	6	2	0.56
VSD + PFO	2	2	0.954
TOF	5	1	0.003
ASD + PDA	1	0	0.05
Total	54 (69.2%)	24 (30.7%)	0.026

Chi-square test

Table 3. Gender distribution of DS children with and without CHDs

	Male (n=62)	Female (n=58)	Total (N=120)	P value
CHD, n (%)	42 (35)	36 (30)	78 (65)	0.38
No CHD, n (%)	204 (16.6)	22 (18.3)	42 (35)	0.47

Table 4. Analysis of age and birth weight of 120 DS children with and without CHDs

	CHD (n=78)	No CHD (n=42)	P value
Mean age (SD), months	14.7 (16.34)	13.9 (15.6)	0.57
Mean birth weight (SD), kg	3.8 (0.74)	3.89 (0.4)	0.69

Discussion

The frequency of congenital heart disease in our DS subjects was higher than results from regional studies, but similar to those of previously published, international historical cohorts,[13-21] which ranged from 35-65%. Our hospital-based, prospective study revealed a 65% frequency of CHD in children with DS, which was similar to many studies in the West.[2-5,11,14-20,22-23] Since all our DS patients underwent echocardiographic screening, even in the absence of symptoms, physical signs, ECG, or chest X-ray abnormalities (as per hospital policy), we are reasonably confident that our observation accurately represents the frequency of CHD in children with DS in our population. A similar prevalence of CHDs has been reported in larger studies, such as one from California.[2] However, the frequency was not that much higher than those of local[9] and regional studies with higher rates,[13,24] which may suggest other factors, such as a high consanguineous marriage rate and environmental effects.

The exact rate of consanguinity in the Afghan population is not known, but in regional countries like Saudi Arabia, a 1995 study reported the rate to be 57.7%,[25] while the rate in our study in children with DS was 45%. The lower consanguinity rate may be due to our small sample size .

In our study, VSD (21.7%) was the most common isolated CHD in DS children, similar to many other reports.[6,9,26-28] VSD + PDA was the most common multiple CHD in our study, similar to other countries.[9-11] Another finding which this report brought to light was the lower frequency of stenotic lesions and an absence of certain CHDs (AS, TGA, and complex CHD) in DS subjects. Such evidence suggests that trisomy 21 does not have any significant role in the pathogenesis of these anomalies, but further investigation with a large sample size is needed. Larger studies have, however, shown evidence of these anomalies, although less frequently in DS children.[15,19]

Consanguineous marriage is common in Islamic countries, exceeding 50% in some communities, especially in rural areas and small towns.[12,24] Comparison with published studies showed that the 65% frequency of CHD in our DS patients was slightly higher than that reported in France (46.2%), Atlanta (44%), Australia (33%), Dallas (38%), and Chile (30%), which are regions with low prevalence of consanguinity.[6,8,9,26-28]

A high frequency of CHD with DS has also been reported in Turkey (65%) and Oman (60%).[17] A similar study from the southwestern region in Saudi Arabia revealed a prevalence of 60% CHD in DS.[9] The rate of consanguinity is slightly higher in these countries, which may explain the relatively higher rates of CHDs in patients with DS.[10,11]

In our study children from consanguineous parents had significantly more total CHDs than the non-consanguineous group, as revealed by Chi-square test (P=0.026). Fisher's exact test comparison of single defects revealed significantly more ASDs (P=0.001), COA (P=0.001), AVSD (P=0.002), PDA (P=0.045), VSD+PDA (P=0.046) and ToF (P=0.003) in the consanguineous group than in the non-consanguineous group, similar to many other reports.[6,9,26]

In conclusion, a higher frequency of CHD is documented in DS children from a population with a high rate of consanguineous marriages, but with similar proportions for specific lesions. Ventricular septal defect (VSD) is the most frequent lesion, with a predominance of left-to right shunt lesions and relative rarity of cyanotic and complex CHDs in the DS population studied. The rate of CHD in DS children is significantly higher in consanguineous parents. Further detailed genetic-clinical correlation studies are needed.

Conflict of Interest

None declared.

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