ECRONICON OPEN ACCESS

EC CARDIOLOGY
Research Article

Complete Atrioventricular Septal Defect: Impact of Down Syndrome on Atrioventricular Valve Morphology and Haemodynamics and Clinical Outcomes

Meryem Haboub*, Abdenasser Drighil and Hanane Mechal

Cardiology Department, Hospital University Ibn Rochd, Casablanca, Morocco

***Corresponding Author**: Meryem Haboub, Cardiology Department, Hospital University Ibn Rochd, Casablanca, Morocco.

Received: April 18, 2020; **Published:** May 14, 2020

Abstract

Background: Other cardiac malformations might be associated with complete atrioventricular septal defect (CAVSD) such as abnormalities of the left atrioventricular valve. Down syndrome is known to affect the natural history of complete atrioventricular septal defect but associations between Down syndrome and outcomes remain to be established. The purpose of this study was to investigate the impact of Down syndrome on atrioventricular valve morphology and haemodynamics as well as on outcomes in children with CAVSD.

Methods: We performed a single-centre, retrospective and descriptive study with a prospective follow-up in the Congenital Heart Disease Unit of cardiology department over a 9-year period. We compared 2 groups of patients with CAVSD: Down syndrome patients (group 1) and non-Down syndrome patients (group 2). Demographic variables, echocardiographic features and outcomes were studied.

Results: 225 were diagnosed with CAVSD, 121 (54%) in group 1 and 104 (46%) in group 2. Atrioventricular valve annulus was hypoplastic in 6 patients (5.8%) of group 2 whereas all patients in group 1 had a normally developed atrioventricular valve annulus (p = 0.024). Papillary muscles were abnormal in 8 patients (6.6%) in group 1 versus 15 patients (14.4%) of group 2 (p = 0.048). Significant preoperative left atrioventricular valve regurgitation was lower in group 1 patients: 11 (9.1%) versus 23 (22.1%) (p = 0.02). Mortality rate was lower in group 1; 14 (11.5%) versus 23 (22.1%) (p = 0.03).

Conclusion: Down syndrome patients have a better atrioventricular valve anatomy, fewer preoperative left atrioventricular valve regurgitation and a lower long-term mortality rate after surgery.

Keywords: *Complete Atrioventricular Septal Defect; Down Syndrome; Left Atrioventricular Valve Dysplasia; Left Atrioventricular Valve Regurgitation; Mortality*

Abbreviations

CAVSD: Complete Atrio-Ventricular Septal Defect; LAVVR: Left Atrio-Ventricular Valve Regurgitation

Introduction

Complete atrioventricular septal defect (CAVSD) is a complex cardiac malformation characterised by a variable deficiency of the atrioventricular area (crux cordis) in the developing heart. CAVSD accounts for about 3% of all cardiac malformations. It occurs in two out of

every 10,000 life births. Both sexes are equally affected, with a slightly higher frequency in female (female/male ratio: 1.3) and a striking association with Down syndrome (DS) was found [1,2]. Transthoracic echocardiogram within the first month of life is recommended in DS patients [3].

We know that DS affects the natural history of CAVSD especially in relation with the occurrence of obstructive pulmonary disease but associations between DS and atrioventricular valve disease and outcomes remain to be established. There are very few studies that have made a head-to-head comparison of DS children with non-DS children with regard to anatomical, haemodynamic features and outcomes in CAVSD and controversies remain concerning the impact of DS on atrioventricular valve and outcomes.

Purpose of the Study

The purpose of this study was to investigate the impact of DS on atrioventricular valve morphology and haemodynamics as well as on outcomes in children with CAVSD.

Materials and Methods

Study design: We performed a single-centre, retrospective and descriptive study with a prospective follow-up in the Congenital Heart Disease Unit of cardiology department over a 9-year period (from December 2008 to September 2017).

Study population: Among children followed-up for CHD in our Unit, those with complete atrioventricular septal defect were collected. The diagnosis was based on echocardiographic findings. We compared 2 groups of patients: Group 1 (DS patients defined as characteristic facial features associated with physical growth delays and mild to moderate intellectual disability) and Group 2 (non-DS patients).

Data collection: Demographic variables at the time of diagnosis, echocardiographic features before surgery (Situs, ventricular imbalance, atrioventricular valve abnormalities, associated cardiac anomalies, pulmonary hypertension), occurrence of Eisenmenger syndrome, treatment and outcomes (atrioventricular valve regurgitation, residual defects and mortality) were studied. All echocardiograms were performed by the same operator (AD) at initial evaluation and at follow-up.

Data collection and statistical analysis were performed on IBM SPSS statistics Inc., IL, Chicago, USA, version 20.0. Quantitative variables are expressed as means ± standard deviation or as medians with intervals, and qualitative variables are expressed as percentage. The results were statistically significant when the p value < 0.05.

Results

Among the 2778 patients registered in our CHD Unit during the study period, 225 (8%) were diagnosed with CAVSD, 121 (54%) in group 1 and 104 (46%) in group 2.

Median follow-up duration was 3 years [0 - 9 years].

Demographic variables, clinical and haemodynamic features are reported in table 1.

Median age at diagnosis was 5 months [0 - 17 years] in group 1 versus 5 months [1month - 10 years] in group 2 (p = 0.856), sex-ratio = 1 was similar in both groups (p value = 0.790). The situs was solitus in all group 1 patients. However, in group 2, the situs was inversus in 4 (3.8%) and ambiguous in 17 (16.3%) (p < 0.001). Ventricles were unbalanced in 4 patients (3.3%) in group 1 versus 30 patients (28.8%) in group 2 (p < 0.001). Atrioventricular valve annulus was hypoplastic in 6 patients (5.8%) of group 2 whereas all patients in group 1 had

	Group 1 (n = 121)	Group 2 (n = 104)	P value
	n (%)	n (%)	
Demographic variables			
Median age at diagnostic	5 months [0 - 17 years]	5 months [0 - 10 years]	0,836
Sex			
Male	58 (47,9)	52 (50)	0,790
Female	63 (52,1)	52 (50)	
Echocardiographic data			
Situs			
Solitus	121 (100)	81 (77,9)	< 0,001
Inversus	0 (0)	4 (3,8)	
Ambiguous	0 (0)	17 (16,3)	
Unbalanced ventricles	4 (3.3)	30 (28.8)	< 0,001
Sufficient valvular tissue	110 (90,9)	90 (86,5)	0,204
Hypoplastic atrioventricular valve annulus	0 (0)	5,8 (6)	0,024
Abnormal papillary muscles	8 (6,6)	15 (14,4)	0,048
Atrioventricular leaflets dysplasia	2 (1,7)	3 (2,9)	0,0192
Chordae dysplasia	2 (1,7)	3 (2,9)	0,0192
Preoperative LAVVR			
No LAVVR	43 (35,5)	39 (33,5)	0,02
Non-significant LAVVR	67 (55,3)	42 (40,4)	
Significant LAVVR	11 (9,1)	23 (22,1)	
Significant pulmonary stenosis	12 (9,9)	24 (23,1)	0,011
Tetralogy of Fallot	7 (6)	4 (3.8)	0.043
Double outlet right ventricle	0 (0)	16 (15%)	<0.001
Associated defects			
Other atrial septal defects	40 (33)	30 (28,8)	0,205
Other ventricular septal defects	0 (0)	35 (29)	
Pulmonary hypertension	120 (84,3)	75 (72,1)	0,039
Eisenmenger syndrome	5 (4,3)	5 (5)	1

Table 1: *Demographic variables, clinical and haemodynamic features of CAVSD in DS patients and non-DS patients. LAVVR: Left Atrioventricular Valve Regurgitation.*

a normally developed atrioventricular valve annulus (p = 0.024). Papillary muscles were abnormal in 8 patients (6.6%) of group 1 (apically displaced in 7 and single in 1 patient) versus 15 patients (14.4%) of group 2 (apically displaced in 7 and single in 8 patients) (p = 0.048). Preoperative left atrioventricular valve regurgitation was significant in 11 patients (9.1%) of group 1 versus 23 patients (22.1%) of group 2 (p value = 0.02). Significant pulmonary stenosis was associated in 12 patients (9.9%) of group 1 versus 24 patients (23.1%) of group 2 (p = 0.011). Double outlet right ventricle was associated in 16 (15%) patients of group 2 versus none of group 1 (p < 0.001). Pulmonary hypertension was significant in 102 patients (84.3%) in group 1 versus 75 patients (72.1%) of group 2 (p = 0.039). Eisenmenger syndrome was diagnosed in 5 patients (4.3%) of group 1versus 5 patients (5%) in group 2 (p = 1).

Median age at surgery was 6 months [1 month - 7 years] in group 1 versus 7 months [1 month - 11 years] in group 2 (p = 0.023). Surgical techniques and results are reported in table 2.

	Group 1 (n = 40)	**Group 2 (n = 26)**	**P value**
	n (%)	**n (%)**	
Age at surgery	6months [1 month - 7 years]	7months [1 month - 11 years]	0,023
Surgical procedure			
Palliative surgery	14 (35)	5 (19,2)	0,041
PA banding	14 (35)	2 (7,7)	
Blalock	0 (0)	1 (3,8)	
Fontan	0 (0)	1 (3,8)	
Glenn	0 (0)	1 (3,8)	
Complete repair	26 (65)	19 (73,1)	0,07
Post-operative results			
Post-operative LAVVR			
No LAVVR	29 (72,5)	15 (57,7)	0,345
Non signifiant LAVVR	9 (22,5)	6 (23)	
Signifiant LAVVR	2 (5)	5 (19,2)	
Residual atrial septal defect	14 (35)	8 (30,7)	0,162
Residual ventricular septal defect	13 (32,5)	7 (26,9)	0,280

Table 2: *Surgical procedures and outcomes in operated patients.*

Mortality rates are lower in group 1 and are reported in table 3.

	Group 1 (N = 121)	Group 2 (N = 104)	P value
	n (%)	n (%)	
Orerall mortality	14 (11,5)	22,1	0,03
Mortality before surgery	4 (3,3)	10,6	0,004
Operated patients	40 (33%)	24 (23%)	0.098
Global mortality	10 (25%)	12 (50%)	0.041
At discharge mortality	1 (2,5)	3 (11,5)	0,036
Long term mortality	9 (22,5)	9 (34,6)	0,042

Table 3: *Mortality rates.*

The overall mortality was 14 (11.5%) in group 1 versus 23 (22.1%) in group 2 (p = 0.03). The number of patients who underwent surgery was 40 (33%) in group 1 versus 24 (23%) in group 2 (p = 0.098). The low income status explains the lack of access to surgery in our country. However, 4 patients (3.3%) died before surgery in group 1 versus 11 (10.6%) in group 2 (p = 0.004).

The mortality rate after surgery was 10 (25%) in group 1 versus 12 (50%) in group 2 (p = 0.041).

Discussion

The prevalence of Down syndrome among children with CAVSD is high: 54% in our study population. The prevalence reported in Japan (53%) by Munetaka., *et al*. [4] is similar to our study, whereas those reported in United Kingdom (63%) by Ajay., *et al.* [5], in Italy (64%) by Formigari., *et al*. [6] or in North-America (80%) by Atz., *et al.* [7] are higher.

Given this fact, a head-to-head comparison of anatomical, haemodynamic features and clinical outcomes of DS and non-DS patients is of biggest interest, especially that there are very few studies making this comparison.

It is known that CAVSD represents 30% of CHD in Down syndrome children [8], but in children without chromosomal and genetic anomalies, CAVSD represents 10 - 40% of CHD cases [8,9]. In patients with DS, CAVSD occurs in 82.3% of all the anomalies of atrioventricular septal defect, and in those having a normal set of chromosomes, it occurs in 74% of cases [10].

In our study, echocardiogram wasn't performed systematically in DS children as recommended by international guidelines [4], reason why the diagnosis wasn't made earlier in DS children compared to non-DS.

Regarding abnormalities of the atrioventricular valve and according to a cohort study performed by Al Hay., *et al*. [11], there was a very high prevalence of dysplasia of the AV valve in children without chromosomal anomalies (24 vs 3%). This finding has not been validated in a later study conducted in the same institution between 2004 and 2009, as it shows no difference between DS and non DS children regarding the prevalence of atrioventricular valve regurgitation or dysplasia [5], but is confirmed in our study population as hypoplastic atrioventricular valve annulus was seen in non-DS children but not in DS children and abnormalities of papillary muscles, dysplasia of atrioventricular leaflets and chordae and significant left atrioventricular valve regurgitation are significantly more prevalent in non-DS children. Moreover, in patients with Down-syndrome valve tissue is more abundant and allows for an easier reconstruction. It suggests that patients without Down syndrome would have a higher risk of worse surgical outcomes regarding left atrioventricular valve regurgitation (LAVVR) [6,11,12].

A study by Miller., *et al.* in 2010 in Atlanta in the USA [13] have reported no effect of DS on postoperative long term survival after CAVSD repair. However, four different studies in four different institutions have outlined the protective influence of Down syndrome on outcomes in CAVSD patients with significantly lower incidence of LAVV anomalies (double orifice mitral valve, single papillary muscle, dysplastic valve), lower overall hospital mortality, fewer major complications, and fewer reoperations with bypass before discharge: Al-Hay., *et al.* in the UK in 2003 [11], by Formigari., *et al.* in Italy in 2004 [6], by Lange., *et al.* in Munich in 2007 [12] and by St Louis., *et al.* in North America in 2014 [14]. This is confirmed in our study as the high prevalence of atrioventricular valve abnormalities in the non-DS group of our population is associated with a non-significant increase of the risk of post-operative left atrioventricular valve regurgitation and a significant increase in mortality rates before and after surgery, at discharge and long term.

Unbalanced complete atrioventricular septal defect was more prevalent in non-DS group confirming the results of the cohort study performed by Meena., *et al* [15]. Nevertheless, univentricular repair in DS children is difficult to perform due to persistent pulmonary vascular obstructive disease in this population [16].

CAVSD in patients with Down syndrome has been reported to be associated with an unusually high incidence of pulmonary hypertension and pulmonary vascular obstructive disease [17-21]. On the basis of histologic specimens from patients with and without Down syndrome, Yamaki and associates [18] reported a more severe form of pulmonary vascular disease in patients with Down syndrome, with significant differences in the amount of intimal lesions and medial thickness of the small pulmonary arteries. Down syndrome have a higher degree of pulmonary vascular resistance in the 1st year of life. They go through a quicker transition to progressive lung disease as compared with children with the same CHD but without Down syndrome. Clapp and associates [22] found that 10 of 81 children (12%) with Down syndrome had fixed pulmonary vascular disease that developed well before 1 year of age. They suggested that cardiac catheterization with measurement, of pulmonary vascular resistance should be performed in all children with a complete AVSD even younger than 6 months of age, especially in Down syndrome. In our study, pulmonary hypertension was more prevalent in DS children but, surprisingly, Eisenmenger syndrome occurs in a same proportion as non DS children. This could be explained by delayed surgery in non-DS patients. On the basis of these findings, early surgical correction (within the first 6 months of life) of patients with DS prior to increasing pulmonary vascular resistance is a good surgical decision and is recommended.

Knowing the risk of earlier development of pulmonary hypertension in DS patients, probably, led to earlier surgical intervention of the children in the DS group. According to literature, it is important that surgery to repair CAVSD be done earlier in life, before the first year of life [4], as it is normally associated with a higher risk of operative mortality and less hope for hemodynamic improvement as compared with analogous children without DS when performed after the first year of life [10]. Comparative analysis of the morphometrics of the heart chambers [10] showed that regardless of DS, during the first 3 months of life, there is an increase in ventricular volumes and dilation of the pulmonary artery. At the same time, in spite of the same age, in patients with CAVSD and associated with DS, by the end of the neonatal period, heart failure progresses faster in comparison with infants having the same defect and a normal karyotype. We assume that this is due to diffused hypotonic muscle, which is characteristic of DS and not with the hemodynamic characteristics of CHD. The surgical repair of complete AVSD should be performed during infancy, although no consensus has been reached regarding the ideal timing to balance the risk of congestive heart failure symptoms against the greater technical operative risks.

Conclusion

Down syndrome patients have a better atrioventricular valve anatomy, fewer preoperative left atrioventricular valve regurgitation, with a lower long-term mortality rate after CAVSD surgery. This finding should be confirmed in larger, prospective and multicentric case-control studies comparing CAVSD outcomes in DS versus non DS patients.

Conflict of Interest

Nothing to declare.

Bibliography

1. Flyer DC. "Endocardial cushion defects". In Nadas' Pediatric Cardiology Edited by: Fyler DC. Hanley and Belfus, Inc., Philadelphia (1992): 577-589.

2. Ferencz C., *et al.* "Genetic and Environmental Risk Factors of Major Cardiovascular Malformations: The Baltimore-Washington Infant Study 1981-1989 Edited by: Anderson RH Armonk N". Futura Publishing Co Inc (1997).

3. Thankavel PP and Ramaciotti C. "Isolated mitral cleft in trisomy 21: an initially silent lesion". *Pediatric Cardiology* 37.2 (2006): 405-408.

4. Munetaka M. "Does Down syndrome affect the long-term results of complete atrioventricular septal defect when the defect is repaired during the first year of life?" *European Journal of Cardio-Thoracic Surgery* 27.3 (2005): 405-409.

5. Ajay R Desai. "Early Postoperative Outcomes Following Surgical Repair of Complete Atrioventricular Septal Defects: Is Down Syndrome a Risk Factor? (2013)". *Pediatric Critical Care and Medicine* 15.1 (2014): 35-41.

6. Formigari R., *et al.* "Better surgical prognosis for patients with complete atrioventricular septal defect and Down's syndrome". *The Annals of Thoracic Surgery* 78.2 (2004): 666-672.

7. Andrew M Atz. "Surgical management of complete atrioventricular septal defect: Associations with surgical technique, age, and trisomy 21, 2011". *The Journal of Thoracic and Cardiovascular Surgery* 141.6 (2011): 1371-1379.

8. Pierpont ME., *et al.* "Genetic basis for congenital heart defects: current knowledge: a scientific statement from the American Heart Association Congenital cardiac defects committee, council on cardiovascular disease in the young: endorsed by the American Academy of Pediatrics". *Circulation* 115 (2007): 3015-3038.

9. Shin M., *et al.* "Prevalence of Down syndrome among children and adolescents in 10 regions of the United States". *Pediatrics* 124.6 (2009): 1565-1571.

10. Margarita R Tumanyan. "Repair of Complete Atrioventricular Septal Defect in Infants with Down Syndrome: Outcomes and Long-Term Results". *Pediatric Cardiology* 36.1 (2015): 71-75.

11. Al-Hay AA., *et al.* "Complete atrioventricular septal defect, Down syndrome, and surgical outcome: risk factors". *The Annals of Thoracic Surgery* 75.2 (2003): 412-421.

12. Lange R., *et al*. "The presence of Down syndrome is not a risk factor in complete atrioventricular septal defect repair". *The Journal of Thoracic and Cardiovascular Surgery* 134.2 (2007): 304-310.

13. Miller A., *et al.* "Long-term survival of infants with atrioventricular septal defects". *The Journal of Pediatrics* 156 (2012): 994-1000.

14. James D. "Contemporary outcomes of complete atrioventricular septal defect repair: Analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database". *The Journal of Thoracic and Cardiovascular Surgery* 148.6 (2014): 2526-2531.

15. Meena Nathan. "Mid-term outcomes in unbalanced complete atrioventricular septal defect: role of biventricular conversion from single-ventricle palliation". *European Journal of Cardio-Thoracic Surgery* (2017): 1-8.

16. Naoki Wada. "Single ventricle repair in children with Down's syndrome". *The General Thoracic and Cardiovascular Surgery* 56 (2008): 104-108.

17. Chi TPL and Krovetz LJ. "The pulmonary vascular bed in children with Down syndrome". *The Journal of Pediatrics* 86 (1975): 533-538.

18. Yamaki S., *et al.* "Pulmonary vascular disease and operative indications in complete atrioventricular canal defect in early infancy". *The American Journal of Cardiology* 51 (1983): 1503-1506.

19. Fudge JC Jr., *et al*. "Congenital heart surgery outcomes in Down syndrome: analysis of a national clinical database". *Pediatrics* 126 (2010): 315-322.

20. Suzuki K Yamaki Sh MimoriSh., *et al*. "Pulmonary vascular disease in Down's syndrome with complete atrioventricular septal defect". *The American Journal of Cardiology* 86 (2000): 434-443.

21. Margarita R Tumanyan. "Repair of Complete Atrioventricular Septal Defect in Infants with Down Syndrome: Outcomes and Long-Term Results". *Pediatric Cardiology* 36.1 (2015): 71-75.

22. Clapp SK., *et al*. "Surgical and medical results of complete atrioventricular canal: a ten year review". *The American Journal of Cardiology* 59 (1987): 454-458.

Volume 7 Issue 6 June 2020