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ORIGINAL ARTICLE

Pulmonary Valve Atresia in the Kingdom of Bahrain: Early Outcomes and Genetic Associations

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Abstract

Background: Pulmonary atresia is a congenital heart defect that results from failure in the formation of the pulmonary valve that leads to right ventricular outflow obstruction, preventing the right heart ejection of blood to the lungs. It is also associated with a high incidence of chromosomal anomalies.

Methods: A retrospective study of all infants diagnosed with pulmonary in Bahrain was undertaken. Pulmonary atresia was classified into pulmonary atresia with intact ventricular septum, pulmonary atresia in Tetralogy of Fallot, and pulmonary atresia in complex cyanotic heart defects**.** Short-term outcomes, survival, and associated genetics were analyzed.

Results: 84 patients were diagnosed. 57 (67.9%) were males and 27 (32.1%) were females ($p = 0.204$). The median age at diagnosis was 25 days. Patients diagnosed with pulmonary atresia and complex cyanotic heart defects had the highest early survival rate. The early survival rate of patients diagnosed with pulmonary atresia with intact ventricular septum was lowest ($p = 0.0179$).

Twenty-two patients (26.19%) had chromosomal anomalies. The DiGeorge syndrome was found in 18 patients, and 2 with Down Syndrome and other dysmorphisms in 2. 19 (86.36%) with chromosomal anomalies had pulmonary atresia and Tetralogy of Fallot, and 3(13.64%) with pulmonary atresia and complex cyanotic heart defects ($p = 0.027$).

Conclusions: Pulmonary atresia is a rare but serious congenital heart defect. The lowest short-term survival is in those with intact intraventricular septum. There is a high incidence of chromosomal deletion of 22q11 leading to DiGeorge syndrome in those with Tetralogy of Fallot with pulmonary atresia. Early catheterization and surgical techniques are effective palliation for short-term survival.

Keywords: Atresia, Genetic, Outcomes, Pulmonary, Valve

Introduction

Pulmonary Atresia (PA) is a congenital heart defect resulting from a failure to form the pulmonary valve that leads to right ventricular outflow obstruction, preventing the right heart from providing blood to the pulmonary circulation. This results in lung perfusion dependent on the shunt from the aorta to the pulmonary arteries. PA is classified into pulmonary atresia with intact ventricular septum (PA/IVS), pulmonary atresia in Tetralogy of Fallot (TOF/PA), and PA in complex cyanotic heart defects (CCHD/PA).[1,2] In most cases of PA surgery or a cardiac catheterization, intervention will be required soon after birth.[3-5]

Genetic and chromosomal defects, mainly 22q11 deletions (as seen in DiGeorge Syndrome), are commonly seen in patients having PA[6] and are known to have a more complex disease.[7]

The incidence of PA is approximately 0.15 per 1000 live births, and the incidence of PA in the Kingdom of Bahrain is lower at 0.04 per 1000 live births.[8] We present a study of PA in the Kingdom of Bahrain of short-term outcomes and associated genetic anomalies.

Materials & methods

A retrospective study using a comprehensive computerized database retrieved all patients diagnosed and referred with PA from 1998 to 2021 was conducted at the only tertiary congenital heart unit in the country performing congenital cardiac interventions. All patients born in Bahrain who received treatment inside or outside the Kingdom of Bahrain and returned to Bahrain were included. They were divided into three categories based on the diagnosis: PA/IVS, TOF/PA, and CCHD/PA for comparative analysis.

Patient characteristics of age, gender, associated comorbidities, genetic syndromes, surgical or catheterization early interventions, overall short-term outcomes, and survival were analyzed.

A descriptive analysis of the three classifications of PA patients was conducted. Shapiro–Wilk test was used to test the normality of data. Categorical variables were summarized as frequencies and percentages and analyzed with the Chi-square test. Normal data were described as mean with standard deviations and analyzed with one-way ANOVA.

The short- and long-term survival probability was analyzed using the Kaplan–Meier survival analysis method, and differences between groups were calculated using the log-rank test.

All statistical analyses were conducted using Stata 17 software (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC), and graphs were generated using GraphPad Prism 9.

Approval to conduct the study was obtained from the Mohammed bin Khalifa Cardiac Centre ethical committee.

Results

A total of 84 patients were diagnosed with PA. Demographics and surgical data are summarized in Table 1. 11 patients (13.1%) were diagnosed with PA /IVS, 54 patients (64.3%) had TOF/PA, and 19 (22.6 %) had CCHD/PA. 57 (67.9%) were males, 27 (32.1%) were females (p = 0.204) Median age at diagnosis was 25 days old. Patients diagnosed with CCHD/PA had an older median age (105 days) at diagnosis than patients diagnosed with PA / IVS (6 days) and TOF/PA (25 days). This was not statistically significant (p = 0.8797).

Table 1: Demographics and surgical data

	Total	PA with intact IVS (n =11)	PA in complex cyanotic heart defect (n = 19)	TOF +PA (n = 54)	*p-value*
Median age at diagnosis	**25 days**	**6 days**	**105 days**	**25 days**	**0.8797**
Gender					
Male	57 (67.9%)	9/57 (15.8%)	15/57 (26.3%)	33/57 (57.9%)	0.204
Female	27 (32.1%)	2/27 (3.5%)	4/27 (14.8%)	21/27 (36.8%)	
Comorbidities					
Patent ductus arteriosus	35 (41.7%)	7/35 (20%)	7/35 (20%)	21/35 (60%)	0.281
Atrial Septal Defect	32 (38.1%)	6/32 (18.8%)	5/32 (15.6%)	21/32 (65.6%)	0.302
Major aortopulmonary collateral arteries	31 (36.9%)	0/31 (0%)	3/31 (9.7%)	28/31 (90.3%)	0.000
Aortic arch syndrome	16 (19.1%)	0/16 (0%)	3/16 (18.7%)	13/16 (81.3%)	0.165
Dextrocardia	7 (8.3%)	0/7 (0%)	5/7 (71.4%)	2/7 (28.6%)	0.005
Patients with syndromes (total)	22 (26.19%)	0/22 (0%)	3/22 (13.64%)	19/22 (86.36%)	0.027
DiGeorge syndrome	18 (21.4%)	0/18 (0%)	3/18 (16.7%)	15/18 (83.3%)	0.098
Dysmorphism	2 (2.4%)	0/2 (0%)	0/2 (0%)	2/2 (100%)	0.566
Down Syndrome	2 (2.4%)	0/2 (0%)	0/2 (0%)	2/2 (100%)	0.566
Non- Syndromic patients	62 (73.8%)	11/62 (17.7%)	16/62 (25.8%)	35/62 (56.5%)	0.027
Interventions					
Catheterization	35 (41.7%)	5/35 (14.3%)	11/35 (31.4%)	19/35 (54.3%)	0.217
Blalock-Taussig (BT) Shunt	33 (39.3%)	3/33 (9.1%)	3/33 (9.1%)	27/33 (81.8%)	0.022
Modified Blalock-Taussig shunt	6 (7.1%)	3/6 (50%)	3/6 (50%)	0/6 (0%)	0.001
Binding of large major aortopulmonary collateral artery	2 (2.4%)	0/2 (0%)	0/2 (0%)	2/2 (100%)	0.566
Right Ventricular Outflow Tract Reconstruction	1 (1.6%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	0.035
Septectomy	1 (1.2%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	0.177

PA= pulmonary atresia, IVS= intact intraventricular septum, TOF = Tetralogy of Fallot

The most common associated cardiac defects were patent ductus arteriosus (PDA) (35, 41.7 %), atrial septal defect (ASD) (32, 38.1%), major aortopulmonary collateral arteries (MAPCA's) (31, 36.9%), aortic arch syndrome (16, 19.1%), and dextrocardia (7, 8.3%).

PDA in TOF/PA (21, 60%) was higher compared to patients diagnosed with PA / IVS (7, 20%) and with CCHD/PA in complex cyanotic heart defects (7, 20%) but with no statistical significance (p = 0.281). ASD was also higher in TOF/PA (21, 65.6%) compared to patients diagnosed with PA/ IVS (6,

18.8%) and with CCHD/PA infants (5, 15.6%) but with no statistical significance ($p = 0.302$)

The number of patients with MAPCAs was statistically higher in patients diagnosed with TOF/PA (28, 90.3%) when compared with patients diagnosed with CCHD/PA defect (3, 9.7%) and PA / IVS (0, 0%) ($p = 0.0003$). Aortic Arch syndrome was also higher in TOF/PA (13, 81.3%) compared to patients diagnosed with CCHD/PA (3, 18.7%) and PA/IVS (0, 0%) and also with no statistical significance ($p = 0.165$). Dextrocardia was diagnosed, i.e., CCHD/PA (5, 71.4%) and was significantly higher compared with patients diagnosed with TOF/PA (2, 28.6%) and with PA / IVS (0, 0%) ($p = 0.0043$).

A total of 22 patients (26.19%) were found to have chromosomal anomalies. DiGeorge syndrome 22q11 deletions were found in 18 patients (21.4%), 2 had Down Syndrome (2.4%), and other dysmorphism without proven genetic diagnoses was noted in 2 additional patients (2.4%). Between the three groups of patients who had the 22 chromosomal abnormalities, 19 patients (86.36%) had TOF/PA, which is significantly higher than patients with combined PA/IVS and CCHD/PA (3, 13.64%) ($p = 0.027$).

A total of 61(72.6%) underwent early interventions. The most common of which were cardiac catheterization (n = 35; 41.7%) and Blalock-Taussig (BT) shunt placement (n =33; 39.3%). The number of patients undergoing BT shunt procedures was statistically the highest among patients diagnosed with TOF/PA group 27 (81.8%) ($p = 0.022$).

A smaller number of patients underwent types of surgery, including unifocalisation of large MAPCAS, right ventricular outflow tract reconstruction, and septectomy (Table 1.) Thirteen patients were still waiting for surgery (15.5%) and two died before surgery (2.4%).

Survival analysis

The median 2-year survival of the study population was 260 days (9.5 - 730). Eight patients were lost to long-term follow-up. The PA survival probability for males was higher than for females (Figure 1) ($p = 0.0179$). Patients diagnosed with PA/CCHD defects had the highest early survival outcome, followed by those with TOF/PA. The survival rate of patients diagnosed with PA/ IVS was the lowest ($p = 0.0179$) (Figure 2).

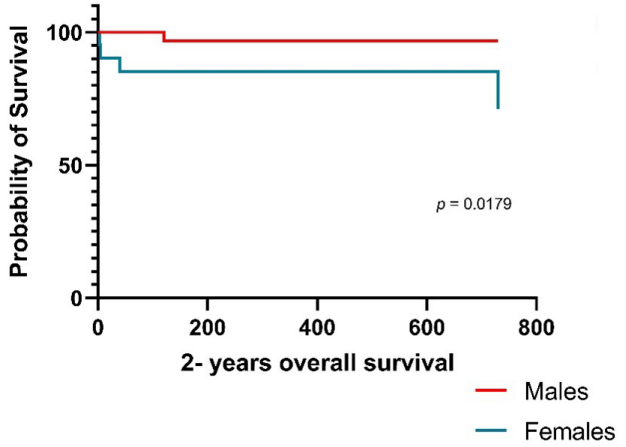

Figure 1: Kaplan-Meir curve comparing probability of survival between male and female patients

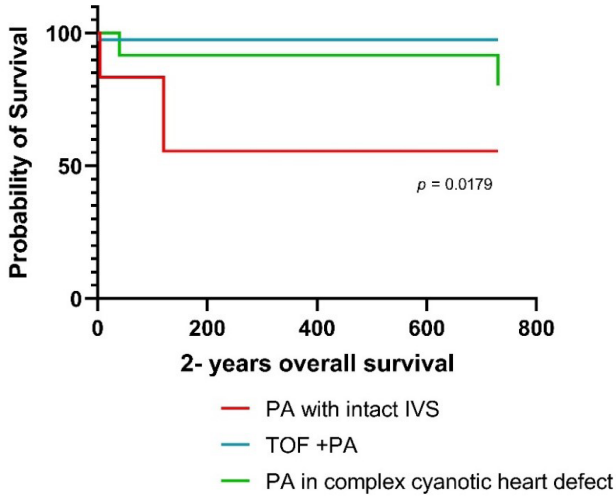

Figure 2: Kaplan-Meir curve comparing probability of survival between patients diagnosed with PA with intact IVS, PA with TOF, and PA in complex cyanotic heart defect

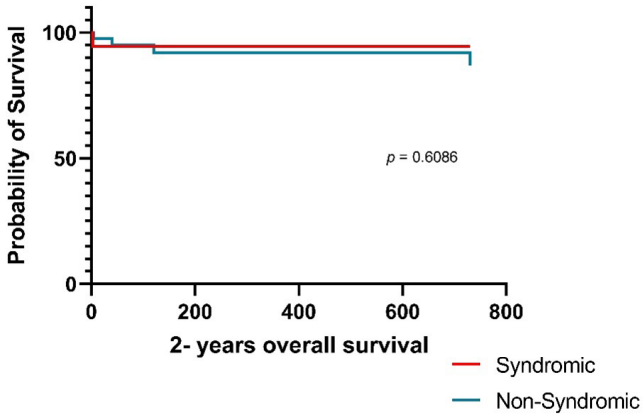

Figure 3: Kaplan-Meir curve comparing probability of survival between syndromic and non-syndromic patients

The early survival rates between syndromic and non-syndromic patients were comparable, with no significant difference ($p = 0.6086$) (Figure 3).

Discussion

We present the first study in the Kingdom of Bahrain investigating the characteristics of early survival outcomes of PA of different types and associated genetic anomalies. The exact cause of PA is unclear. The prognosis of PA depends on many variables, such as the size and connections of the pulmonary arteries and associated other cardiac congenital defects. It is extremely poor without intervention.[9] Even those surviving to adulthood have a 21.6% mortality due to heart failure and sudden cardiac death.[10]

Patients with pulmonary atresia can be either symptomatic or asymptomatic. They can present with cyanosis, poor feeding, or extreme sleepiness.[11,12] PA is confirmed with different modalities such as Chest x-ray, echocardiogram, Electrocardiogram (ECG), CT angiogram, or heart catheterization.[13] Until surgical intervention is undertaken, PA patients are often treated using prostaglandin E1 to facilitate blood flow to the lungs through a PDA.[14] The treatment modalities for those patients were by catheterization 35 (41.7%) or Blalock-Taussig (BT) shunts 33 (39.3%).

PA/IVS is rare, resulting from varying degrees of underdevelopment of the right ventricle that range from mild to severe.[12,15,16] In this study, 11 patients (13.1%) were diagnosed with PA/IVS, of which 9 were males. It was most associated with PDA and ASD. PA/IVS can be treated by either surgical or catheterization techniques.

TOF/PA is considered one of the most severe forms of TOF.[17] In our study, most patients with PA were diagnosed with TOF / PA (54, 64.29%). PA/ CCHF is less common than TOF/PA. In this study, 19 patients had PA / CCHD (22.62%). It still represents a major source of mortality among pediatric age groups.[18]

The 22q11 deletions (as seen in DiGeorge Syndrome) are commonly seen in patients with PA.[19] Patients with 22q11 deletions have more complex disease than those without, as they present with small pulmonary arteries and are dependent on MAPCAs.[20] In this study, 21.4% of the patients had this chromosomal abnormality. 36.9% of patients were dependent on MAPCAs for pulmonary perfusion. TOF/PA is often associated with the deletion of chromosome 22qll, leading to DiGeorge syndrome.[20] Similarly, in our study, 83.3% of patients with a 22q11 chromosome deletion were diagnosed with TOF /PA.

The occurrence of PA in patients with other dysmorphisms is uncommon.[20] In this study, only two patients were dysmorphic, and those were patients with TPF/PA.

In this retrospective study, the short follow-up duration is one of the limitations. The small number of patients in our center also was a limitation. Diagnostic methods, technology, indications, and interventions have changed over the study period, which could also have influenced our results.

Conclusions

PA is a severe but rare congenital heart defect. PA with IVS has the lowest probability of short-term survival. PA w is associated with a high incidence of chromosomal deletion 22q11, leading to DiGeorge syndrome in TOF with PA. Blalock-Taussig (BT) or other shunts and catheterization techniques are effective palliative interventions for short-term survival in PA. Early pre or neonatal referral and genetic screening are recommended for all infants with PA.

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