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Prenatal diagnosis of tetralogy of Fallot with an absent pulmonary valve: is this malformation still associated with a poor prognosis? A 5-year single-center experience

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Abstract

Objective: This study sought to assess the prenatal features and clinical outcomes of cases with a fetal diagnosis of tetralogy of Fallot (TOF) with an absent pulmonary valve (APV) at our maternal-fetal medicine unit.

Methods: Twelve cases of TOF and APV prenatally diagnosed at Kanuni Sultan Süleyman Training and Research Hospital between 2015 and 2020 were retrospectively reviewed. Prenatal characteristics, additional cardiac and extracardiac anomalies, and postnatal outcomes of the cases were examined.

Results: The median gestational age at diagnosis was 22 weeks (range: 18–24 weeks). The absence of ductus arteriosus was found in all cases (100%). Karyotype analysis was performed in 5 cases. A chromosomal abnormality was detected in 3 of these cases (60%); 2 cases with 22q11 microdeletion, and 1 case with trisomy 21. Parents opted for termination of pregnancy in two of these cases; 1 case with 22q11 microdeletion, and 1 case with trisomy 21. Two patients experienced spontaneous intrauterine fetal demise. Finally, 8 live-born fetuses underwent total correction surgery during the postnatal period. Four (33.3%) out of 12 cases survived at the end of the 4-years follow-up period.

Conclusion: While TOF with APV cases were predominantly associated with poor prognoses in the past, more promising results have been obtained in recent years in parallel with the developments in surgery and postnatal care. For this reason, we think that the prognosis will be even better in the coming years as the developments in surgical technique and care continue.

Keywords: Tetralogy of Fallot, absent pulmonary valve, prenatal diagnosis.

Introduction

The tetralogy of Fallot (TOF) with an absent pulmonary valve (APV) was first defined by Chevers in 1847 presenting with pulmonary regurgitation and aneurysmal dilatation of the pulmonary trunk and two primary branch pulmonary arteries.[1,2] APV syndrome (APVS) is an unusual congenital heart defect (CHD) featured by rudimentary, absent, or dysplastic pulmonary valve leaflets in association with diverse cardiac abnormalities. This syndrome has a frequency of 3–6% in patients with TOF and 0.2–0.4% in live-born neonates with CHDs. It is a congenital abnormality that shows similar features to TOF, but with either a complete absence of a pulmonary

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valve or only a rudimentary ridge of the valve. The APV causes the dilatation of the main pulmonary artery visible as a paracardiac, pulsatile cystic lesion on prenatal ultrasound (US) examination.[2] In most patients, the ductus arteriosus is absent; concurrently, the pulmonary annulus is stenotic and restrictive with to-and-from blood flow over the dysplastic pulmonary valve. Severe enlargement of the pulmonary trunk and branches were also observed.[3]

Significant pulmonary artery dilatation is its pathognomonic feature, which is important in prenatal diagnosis. Dilatation of the pulmonary branch and accompanying cardiomegaly might cause bronchomalacia secondary to bronchial compression, causing respiratory failure early in life and chronic obstructive pulmonary disorder in later years of life. The majority of researchers divide APVS into two subgroups: APV with ventricular septal defect (VSD), which was labeled as Fallot type APVS, and APV with an intact ventricular septum and probable tricuspid atresia, labeled as non-Fallot type APVS.[3,4]

Although there are many publications and opinions in the literature regarding the pulmonary stenosis subtype of TOF, which is the most common subtype, the absence of the pulmonary valve subtype has not been clarified much due to the low number of cases.[2,3] APVS was strongly connected with neonatal morbidity and mortality as the dilated branch pulmonary arteries might end in bronchomalacia as a consequence of bronchial compression with compromise in respiration after delivery, and in patients with effective surgical treatment of the cardiac defects, with chronic obstructive lung disease. However, recent studies reported improving perinatal outcomes with the early repair of TOF with APV, including cases with severe tracheomalacia.[5,6]

This study sought to assess the prenatal characteristics and clinical outcomes of patients with a prenatal diagnosis of TOF with APVS at our maternal-fetal medicine unit.

Methods

In this retrospective study, we included all singleton pregnant women who were referred to the maternal-fetal medicine of Kanuni Sultan Süleyman Training and Research Hospital with a fetal diagnosis of TOF with an APV between the years of 2015 and 2020. We performed this study consistent with the Declaration of Helsinki Ethical Principles. After obtaining Institutional Ethics Committee approval (approval number: 2022.03.57), our medical records were reviewed retrospectively. Fetal echocardiograms, clinical records, and surgical records of cases were collected. The diagnosis of TOF with APVS was made by observing anterior subaortic VSD, right ventricular hypertrophy, overriding aorta, pulmonary annular stenosis with the non-existence of a functional pulmonary valve leading to pulmonary regurgitation and aneurysmal dilatation of the pulmonary trunk and two main branch pulmonary arteries.[3] Observing to-and-from blood flow in the pulmonary trunk on colored Doppler US examination with dysplastic or rudimentary pulmonary valve leaflets has also been evaluated for the diagnosis. Voluson E 6 (GE healthcare Ultrasound, Milwaukee, WI, USA) US machine equipped with a RAB 6D (2–7 MHz) probe was utilized for routine second-trimester detailed anatomical scan and fetal echocardiography. Prenatal counseling was given to the patients about the probability of intrauterine congestive cardiac failure and fetal hydrops in the fetus due to APVS, neonatal complications, including postpartum respiratory distress, and the requirement of multi-stage surgery. We offered pediatric cardiology counseling to all pregnant patients whose fetuses suffered from TOF with APV. We performed serial echocardiography in all cases with active pregnancy management. We assessed all cases with serial, two-dimensional, color, and pulsed wave Doppler echocardiography until delivery. The pediatric cardiologist re-performed echocardiography in all newborns with TOF with APV after birth. Necessary decisions were made by consulting the pediatric cardiologist again before and within 12 hours of delivery for all newborn fetuses. Demographic data, diagnosis week, maternal age, birth week, associated fetal abnormalities, extracardiac anomalies, chromosomal anomalies, age at surgical repair, surgery type, and postoperative complications were followed up for a maximum of 4 years. Genetic karyotype analysis was offered in all cases. In all surviving cases, the APVS diagnosis was verified by postnatal preoperative two-dimensional transthoracic echocardiography after delivery. Our prenatal diagnosis was also confirmed by examining the surgical notes of cases who survived and underwent surgery.

Statistical analysis

We performed the statistical analysis utilizing IBM SPSS Statistics for Windows, version 21.0 (IBM Corp.,

Table 1. Characteristics of study group with 12 cases.

Case	Gestational age at diagnosis	Gender	Karyotype	Outcome	Ductus arteriosus
1	21 weeks	Male	Not done	Alive, reoperation	Not seen
2	22 weeks	Male	Not done	Postnatal death after surgery	Not seen
3	23 weeks	Female	Not done	Alive, reoperation	Not seen
4	19 weeks	Female	Not done	Alive, complete repair	Not seen
5	18 weeks	Female	Trisomy 21	Termination	Not seen
6	24 weeks	Male	DiGeorge	Termination	Not seen
7	21 weeks	Female	DiGeorge	Intrauterine fetal demise	Not seen
8	22 weeks	Male	Not done	Alive, complete repair	Not seen
9	23 weeks	Male	Not done	Alive, complete repair	Not seen
10	24 weeks	Female	Normal karyotype	Intrauterine fetal demise	Not seen
11	21 weeks	Male	Not done	Alive, complete repair	Not seen
12	22 weeks	Female	Normal karyotype	Postnatal death after surgery	Not seen

Armonk, NY, USA). We performed a descriptive statistical analysis. We expressed continuous variables as median values and categorical variables as numbers and percentages.

Results

A total of 12 cases participated in this study. These cases were identified from 48,746 total deliveries over 5 years. A total of 149 TOF cases were detected during this period, of which 12 cases were APVS subtypes. All cases in our study cohort were singleton pregnancies, and half of the fetuses were male. Only one case had a family history of cardiomyopathy. The median gestational age at diagnosis was 22 (range: 18–24) weeks. **Tables 1** and **2** show the details of the anomalies and outcomes of these 12 cases. During the antenatal period, 4 cases out of 12 cases did not survive. Parents opted for termination of pregnancy in two cases because of genetic disorders; one case had a fetus with trisomy 21, and the other had a fetus with 22q11 microdeletion. The other 2 patients experienced spontaneous intrauterine fetal demise. Although the genetic examination was recommended in all cases for further evaluation, karyotype analysis was performed in 5 cases. A chromosomal abnormality was detected in 3 of these cases (60%); two of them were diagnosed with

Table 2. Prenatal abnormalities and outcomes after birth.

Case	Extracardiac diseases	Follow-up	Operation time	Family history about congenital heart disease
1		4 years	1 month, 2 years (two operations)	-
2	Polyhydramnios	-	2 months, death	-
3		4 years	2 months,1 year (two operations)	-
4		2 years	1 month	-
5	Pyelectasis, nasal bone hypoplasia		-	Cardiomyopathy
6	Thymus hypoplasia	-	-	-
7	Thymus hypoplasia, fetal hydrops	-	-	-
8		3 years	2 months	-
9	Choroid plexus cysts	Lost to follow-up	1 month	-
10	Fetal hydrops	-	-	-
11		Lost to follow-up	2 months	-
12	Polyhydramnios	-	1 month, death	-

DiGeorge syndrome, and one case was diagnosed with trisomy 21. During the postnatal period, 8 live-born fetuses underwent total correction surgery. The median surgery time was two months after delivery (ranging between one month and two years). Postoperative death occurred in 2 cases within a week after surgery. During the follow-up period, 2 cases underwent reoperation. Four cases in our study group did not receive additional surgery and experienced a single operation. Ductus arteriosus could not be visualized in any case in our study group. Although the follow-up period of postpartum cases changed to a maximum of 4 years, in some cases, follow-up could not be performed. Two cases in our study group were lost to follow-up after a certain period after a successful postpartum surgery. The overall survival rate of our study cohort was 33.3% (n=4) following the 2–4-years follow-up period.

Discussion

TOF with APV syndrome is an unusual CHD related to severe neonatal morbidity and mortality, with a recorded survival rate following initial diagnosis between 14% and 68%.[2,6,7] In the presence of an abnormality of 4-chamber view with pulmonary trunk aneurysmal dilatation, this uncommon CHD should be considered regarding differential diagnosis. Estimation of outcomes of APVS in the prenatal period is challenging. The clinical manifestation is notably unstable. Cases might experience intrauterine fetal demise, fetuses might manifest with severe neonatal hemodynamic and respiratory distress, or be born with no respiratory symptoms, with a comparatively benign neonatal period, and experience elective surgery later in infancy.[6] Despite the advanced era of prenatal diagnosis, it remains challenging to accurately estimate the prognosis of a case that is antenatally diagnosed. This uncertainty restricts both prenatal counseling and delivery planning.[7,8]

In past case series with more than 10 fetuses recorded fetal and postnatal survival rates of <20%.[2,6,9,10] The low survival rate was associated with pregnancy termination, chromosomal abnormalities, respiratory disorders, and fetal heart failure. **Table 3** shows some of the previously published case series and our study.[2,6,9,10]

Our 5-year single-center experience delineates the characteristics and outcomes of cases prenatally diagnosed with APVS. We found a survival rate of 50% with a maximum follow-up duration of 4 years. This rate in our study was similar to the study of Cheliah et al.[8] Also, Wertaschnigg et al. reported a 50% survival rate in their study of 12 cases in 2013, which was comparable to our study.[6] However, Razavi et al. found a 15% of overall survival rate in their study.[9] Moreover, Volpe et al. in their study in 2004 and Galindo et al. in 2006 found a survival rate of 14%, which was quite low compared to the rate in our study.[2,10]

Unlike other studies, in our study, we diagnosed all cases in the second trimester.[2,6] The clinical outcomes of APVS include termination of pregnancy, intrauterine fetal demise, perinatal demise, severe postpartum respiratory distress, or a milder course requiring further surgery, as seen in our study.[2,6,9]

We detected genetic disorders in 60% of the cases that underwent karyotype analysis in our study, while this rate was 45% in the study of Volpe et al.[10] Also, the nonexistence of the ductus arteriosus is an ordinary but not a persistent feature of this syndrome.[11] In our study, we did not see ductus arteriosus in any case. However, Razavi et al. stated in their study that the incidence of ductus arteriosus in APVS was 20%.[9]

Table 3. Features of previous studies regarding an absent pulmonary valve syndrome.

	Razavi et al.[9]	Volpe et al.[10]	Galindo et al.[2]	Wertaschnigg et al.[6]	Our study
Number of cases	20	21	14	12	12
Study period, years	1988–2000	1993–2003	1998–2004	2000–2010	2015–2020
Single or multicenter	Single	Multicenter	Multicenter	Single	Single
Survival rate	15%	14%	14%	50%	33%
Genetic disorder	2/9 (22%)	9/20 (45%)	3/14 (21%)	6/12 (50%)	3/5 (60%)
Fallot type APVS – non-Fallot type APVS	18 (90%) – 2 (10%)	18 (86%) – 3 (14%)	13 (93%) – 1 (7%)	10 (83%) – 2 (17%)	12 (100%) – 0
Ductus arteriosus	4 (20%)	5 (23%)	3 (21%)	2 (17%)	0 (not seen)

Of 149 fetuses with TOF diagnosed at our unit during the last five years, 8% had APVS. This rate is comparable with 2–6% of cases with neonatally diagnosed TOF.[12] The number of cases with APVS was very low in most of the previous studies on this subject,[2,6,9] and also, in our study, the number of the study group was small because of the low incidence of APVS.

Concerning previous studies, including our study, the most frequent karyotype abnormality was 22q11 deletion (DiGeorge syndrome), supporting the evidence that fetal karyotype with chromosomal microarray analysis should be always suggested.[2,6,9,10]

Prenatally, anatomic details emerged by a detailed examination of the fetal heart are essential in orienting prenatal counseling and perinatal management. As a result, we can potentially reduce perinatal deaths. While not very satisfactory results were obtained after surgery in the past, with the development of surgical techniques in recent years, the preferred treatment is a whole surgical treatment in all cases, including symptomatic newborns.[13–16]

Cases presenting with serious respiratory compromise in the early period of life frequently need ventilatory support followed by urgent surgery.[13,14] In recent years, clinicians have reported very promising results with different surgical techniques.[15,16] Chen et al. reported low postoperative morbidity and a total survival rate of 89% in newborns and infants by utilizing a valveless right ventricle pulmonary artery connection with a transannular patch.[13] Moreover, Godart et al. suggested treatment with pulmonary arterioplasty without pulmonary valve insertion and declared that they achieved an overall survival rate of 92%.[14] In our study, there were 8 cases alive postnatally but only 6 cases were alive after postnatal surgery, and 2 cases were lost to follow-up. So, a total of four cases (50%) of eight live births who received active postnatal care were followed up for 2–4 years without any residual respiratory symptoms after a successful surgical approach.

Improvement in perioperative care and the development of new surgical techniques have led to a decrease in APVS mortality, improving the prognosis of affected children.[13,14] However, it remains difficult to control infants and cases with persistent respiratory symptoms.[13] The operative treatment of this CHD has developed over the last several decades. Unfortunately, there is presently no common concurrence on the technique of repairing dilated pulmonary arteries. Moreover, the optimum method for right ventricular outflow tract reconstruction is still questionable.[15,16]

Conclusion

While APVS cases were predominantly associated with poor prognoses in the past, more promising results have been obtained in recent years in parallel with the developments in surgery and postnatal care. For this reason, we think that the prognosis will be even better in the coming years as the developments in surgical technique and care continue.

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References

1. Cheevers N. Retrecissement congenital de l orifice pulmonaire. Arch Med Fourth Ser 1847;15:488.
2. Galindo A, Gutiérrez-Larraya F, Martínez JM, Del Rio M, Grañeras A, Velasco JM, et al. Prenatal diagnosis and outcome for fetuses with congenital absence of the pulmonary valve. Ultrasound Obstet Gynecol 2006;28:32–9. [PubMed] [CrossRef]
3. Grewal DS, Chamoli SC, Saxena S. Absent pulmonary valve syndrome – antenatal diagnosis. Med J Armed Forces India 2014;70:198–200. [PubMed] [CrossRef]
4. Mivelaz Y, Lim KI, Templeton C, Campbell AI, Potts JE, Sandor GGS. Population-based review of tetralogy of Fallot with absent pulmonary valve: is prenatal diagnosis really associated with a poor diagnosis? Ultrasound Obstet Gynecol 2012; 40:536–41. [PubMed] [CrossRef]
5. Tanaka Y, Miyamoto T, Naito Y, Yoshitake S. Surgical treatment of tetralogy of Fallot with absent pulmonary valve syndrome. Asian Cardiovasc Thorac Ann 2016;24:470–2. [PubMed] [CrossRef]
6. Wertaschnigg D, Jaeggi M, Chitayat D, Shannon P, Ryan G, Thompson M, et al. Prenatal diagnosis and outcome of absent pulmonary valve syndrome: contemporary single-center experience and review of the literature. Ultrasound Obstet Gynecol 2013;41:162–7. [PubMed] [CrossRef]
7. Gottschalk I, Jehle C, Herberg U, Breuer J, Brockmeier K, Bennink G, et al. Prenatal diagnosis of absent pulmonary valve syndrome from first trimester onwards: novel insights into pathophysiology, associated conditions and outcome. Ultrasound Obstet Gynecol 2017;49:637–42. [PubMed] [CrossRef]
8. Chelliah A, Moon-Grady AJ, Peyvandi S, Chiu JS, Bost JE, Schidlow D, et al. Contemporary outcomes in tetralogy of

Fallot with absent pulmonary valve after fetal diagnosis. J Am Heart Assoc 2021;10:e019713. [PubMed] [CrossRef]

9. Razavi RS, Sharland GK, Simpson JM. Prenatal diagnosis by echocardiogram and outcome of absent pulmonary valve syndrome. Am J Cardiol 2003;91:429–32. [PubMed] [CrossRef]
10. Volpe P, Paladini D, Marasini M, Buonadonna AL, Russo MG, Caruso G, et al. Characteristics, associations and outcome of absent pulmonary valve syndrome in the fetus. Ultrasound Obstet Gynecol 2004;24:623–8. [PubMed] [CrossRef]
11. Ettedgui JA, Sharland GK, Chita SK, Cook A, Fagg N, Allan LD. Absent pulmonary valve syndrome with ventricular septal defect: role of the arterial duct. Am J Cardiol 1990;66:233–4. [PubMed] [CrossRef]
12. Emmanouilides GC, Thanopoulos B, Siassi B, Fishbein M. "Agenesis" of ductus arteriosus associated with the syndrome of tetralogy of Fallot and absent pulmonary valve. Am J Cardiol 1976;37:403–9. [PubMed] [CrossRef]
13. Chen JM, Glickstein JS, Margossian R, Mercando ML, Hellenbrand WE, Mosca RS, et al. Superior outcomes for repair in infants and neonates with tetralogy of Fallot with absent pulmonary valve syndrome. J Thorac Cardiovasc Surg 2006;132:1099–104. [PubMed] [CrossRef]
14. Godart F, Houyel L, Lacour-Gayet F, Serraf A, Sousa-Uva M, Bruniaux J, et al. Absent pulmonary valve syndrome: surgical treatment and considerations. Ann Thorac Surg 1996;62:136–42. [PubMed] [CrossRef]
15. Nair AK, Haranal M, Elkhatim IM, Dillon J, Hew CC, Sivalingam S. Surgical outcomes of absent pulmonary valve syndrome: an institutional experience. Ann Pediatr Cardiol 2020;13:212–9. [PubMed] [CrossRef]
16. Hu R, Zhang H, Xu Z, Liu J, Su Z, Ding W. Late outcomes for the surgical management of absent pulmonary valve syndrome in infants. Interact Cardiovasc Thorac Surg 2013;16:792–6. [PubMed] [CrossRef]