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Characteristics, associations and outcome of absent pulmonary valve syndrome in the fetus

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KEYWORDS: 22q11 microdeletion; absent pulmonary valve syndrome; fetal/neonatal outcome

ABSTRACT

Objectives *To assess in a population of 21 fetuses diagnosed with absent pulmonary valve syndrome (APVS) the accuracy of prenatal diagnosis, the incidence of extracardiac and chromosomal anomalies and the perinatal outcome.*

Methods *This was a retrospective observational study of 21 fetuses with a confirmed diagnosis of APVS. All of them underwent fetal echocardiography and a detailed anatomical scan. Karyotyping was performed in 20/21 cases, with fluorescent* in-situ *hybridization analysis to detect the 22q11 microdeletion performed in 16/21 cases. The following variables were retrieved from databases and evaluated: indication for referral, gestational age at diagnosis, presence of cardiomegaly, branch pulmonary dilatation, associated anomalies or intrauterine growth restriction, and fetal/neonatal outcome. Autopsy reports and postnatal surgical/medical files were available for confirmation in all cases.*

Results *Prenatal diagnosis of APVS proved correct in all cases, with only three cases occurring not in association with tetralogy of Fallot. Additional cardiovascular anomalies were present in five cases (24%). Extracardiac anomalies were found in nine cases (42.8%), and were associated with chromosomal anomalies in five cases (24%). The 22q11 microdeletion was present in 4/16 cases (25%). Fetal/neonatal outcome was as follows: nine terminations of pregnancy, three intrauterine deaths, six postnatal deaths. The remaining three (14.3%) neonates were alive after surgery. Cardiomegaly and marked branch pulmonary dilatation were present in 16 and 15 cases, respectively, and were associated with bronchomalacia in virtually all cases.*

Conclusions *APVS can be reliably diagnosed and characterized prenatally. The association with major chromosomal anomalies or 22q11 microdeletion is consistent with previous findings. The relatively poor survival rate is due to the high rate of terminations, associated genetic anomalies and bronchomalacia. Bronchomalacia is present in the overwhelming majority of cases featuring cardiomegaly and marked branch pulmonary dilatation. Copyright © 2004 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Absent pulmonary valve syndrome (APVS) is a rare cardiac abnormality characterized by the existence of a dysplastic or rudimentary pulmonary valve, associated in most instances with severe dilatation of the pulmonary trunk and its branches due to the concurrent occurrence of valve stenosis and regurgitation[1–4]. The condition is generally associated with tetralogy of Fallot (TOF) and absence of the arterial duct, though cases with a patent ductus arteriosus and/or it occurring as an isolated anomaly have been reported[5–10].

The postnatal incidence of APVS is estimated at 3–6% of all patients with TOF[1,5,8]. However, its prenatal incidence is probably higher due to a significant rate of fetal wastage. Prenatal diagnosis of APVS is feasible and has been reported in two case series and/or as part of larger series of heart defects[7,9–12].

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The objective of this study was to assess the degree of accuracy of the prenatal diagnosis and to describe the characteristics, associations and outcome of APVS when diagnosed in the fetus.

METHODS

This was a retrospective study performed at three referral centers for prenatal diagnosis of congenital anomalies, over a 10-year period (1993–2003). Twenty-one cases satisfying the definition of APVS were retrieved and evaluated. The following variables were assessed: indication for referral, gestational age at diagnosis, associated cardiac, extracardiac and chromosomal abnormalities, presence of intrauterine growth restriction (IUGR), pregnancy and fetal/neonatal outcome. In addition, the following quantitative echocardiographic parameters were retrieved from recorded videotapes and/or measured on an offline computer, and analyzed: cardiothoracic ratio, maximum diameter of the main pulmonary artery (measured just above the valve annulus), maximum diameter of pulmonary branches (measured distal to the bifurcation) and pulmonary trunk Doppler velocity. These measurements were compared with established normal sizes[13,14].

All cases underwent fetal echocardiography and detailed anatomical scan was performed with high-quality ultrasound equipment (Pro-Sound 5000, Aloka, Tokyo, Japan; Voluson 730, General Electric, Zipf, Austria; Sonos 550, Hewlett Packard, Andover, MA, USA). Karyotyping was performed in all but one case. Chromosomes were analyzed with G- or Q-banding and fluorescent *in-situ* hybridization (FISH) for the DiGeorge syndrome critical region (22q11). This was carried out with the following probes: N25 (D22S75 within 22q11.2)/WI-941 (within 22q13), ONCOR, Gaithersburg, MD, USA), and TUPLE 1 (within 22q11.2)/ARSA (arysulfatase A within 22q13.31qter), Vysis, Downers Grove, IL, USA).

Necropsy reports and postnatal surgical/medical files were available for confirmation of the prenatal diagnosis in all cases.

RESULTS

Among 2270 cases of fetal heart defects detected in the referral centers during the observation period, APVS was diagnosed in 21 fetuses (0.9%), with only three cases occurring not in association with TOF. In all cases the diagnosis was confirmed at autopsy or at postnatal echocardiography/surgery. There were neither false-positive nor incorrect diagnoses. The mean gestational age at diagnosis was 24 (range, 18–31) weeks, with 10/21 cases diagnosed prior to 24 weeks of gestation (Table 1). Reasons for referral were: suspected heart malformation in 14 cases (67%), extracardiac anomaly in six cases (28%), and a positive family history in one case (5%) (Table 1).

In four of the 21 fetuses with APVS, other cardiovascular anomalies were identified on fetal echocardiography (Table 1): right aortic arch ($n = 3$) and ostium primum atrial septal defect with left persistent superior vena cava ($n = 1$). In one of the fetuses already diagnosed with APVS and right aortic arch, the existence of an aberrant left subclavian artery was overlooked. In another fetus, a type II atrial septal defect remained unrecognized.

Pulmonary valve stenosis (with a peak systolic velocity >1.8 m/s in 16/21 cases) and regurgitation were present in all cases. In 15/21 cases, the main and branch pulmonary arteries were markedly dilated, being only slightly dilated in the remaining six cases (Cases 2, 12, 15, 19, 20, 21) (Figure 1). All but five fetuses (Cases 2, 15, 19, 20, 21) had a cardiothoracic ratio $> 95^{th}$ centile.

Extracardiac anomalies were detected in nine cases and were associated with chromosomal anomalies in five of them (Table 1). These included two cases of triploidy, one case of trisomy 13, one case of trisomy 21 and one case of chromosome 18 short arm deletion. Targeted examination for the 22q11 microdeletion using the FISH technique was performed in 16 of the 21 cases. This approach allowed detection of the 22q11 microdeletion in four fetuses (25%), two of them also showing extracardiac anomalies. IUGR was present in six fetuses, four of them being affected by genetic anomalies.

As for pregnancy outcome, there were nine terminations of pregnancy, among 10 fetuses diagnosed before 24 weeks (90%), and three (14.3%) intrauterine deaths, two cases with cytogenetic aberrations and IUGR, and one with severe heart failure (Table 1). However, as previously mentioned, an increased cardiothoracic ratio was present in most of the fetuses (16/21) with APVS, consistent with an increased central venous pressure[12,15]. Of the nine newborns, five (55%) died in the neonatal period: one (Case 1) immediately after birth and the remaining neonates within 2 weeks prior to (Cases 11 and 17), or after (Cases 8, 10), surgery (Figure 2). Another infant (Case 15), who was prematurely delivered at 32 weeks, was discharged, and died of viral infection at 2 months. The remaining three babies (33%) underwent complete surgical repair beyond the neonatal period. At the time of writing two of them (Cases 2 and 19), at 10 and 28 months of age, respectively, were doing well. The remaining one (Case 4), who required ventilation in the neonatal period, had a full repair at 4 months of age and a month later was still hospitalized for respiratory distress.

DISCUSSION

In the present and two previous case series[9,10] two variants of APVS were recognized in the fetus: the more frequent one is characterized by an absent pulmonary valve with ventricular septal defect (TOF) and ductal agenesis, while the rarer variant is defined by the presence of an intact ventricular septum and a lower degree of pulmonary artery dilatation, associated in most instances with a patent ductus arteriosus. The differential role of the duct developmental derangement in the pathogenesis of the two variants and in the degree of pulmonary artery dilatation is still to be defined. Some authors have suggested that the

Table 1 Study subjects with absent pulmonary valve syndrome

Case	*GA (weeks)*	*Referral diagnosis*	*Diagnosis*	*Arterial duct*	*Extracardiac anomalies*	*Cyt/FISH aberrations*	*IUGR*	*Outcome*
1	30	Extracardiac anomalies	TOF + APV	Absent	Diaphragmatic hernia	Triploidy	Yes	Neonatal death
2	28	Abnormal heart	TOF + APV	Absent			No	Alive after surgery
3	21	Abnormal heart	TOF + APV	Absent	Cleft lip and palate, polydactyly	Trisomy 13	No	TOP
4	21	Abnormal heart	TOF + APV	Absent			No	Alive after surgery
5	22	Abnormal heart	TOF + APV + ASD	Absent	Neural tube defects, hydrocephalus	Triploidy	No	TOP
6	20	Abnormal heart	TOF + APV	Absent		22q11 microdeletion	No	TOP
7	20	Extracardiac anomalies	TOF + APV	Absent	Diaphragmatic hernia	22q11 microdeletion	No	TOP
8	28	Abnormal heart	TOF + APV	Absent		*	No	Neonatal death
9	25	Extracardiac anomalies	TOF + APV + ASD + LSVC	Absent	Duodenal atresia	Trisomy 21	Yes	Died *in utero*
10	30	Abnormal heart	TOF + APV	Absent			No	Neonatal death
11	31	Abnormal heart	TOF + APV	Absent			Yes	Neonatal death
12	27	Extracardiac anomalies	TOF + APV	Present	Hydrops		Yes	Died *in utero*
13	18	Positive family history	TOF + APV	Absent		*	No	TOP
14	20	Abnormal heart	TOF + APV + RAA	Absent		*	No	TOP
15	25	Abnormal heart	TOF + APV	Present		*	No	Infant death
16	26	Abnormal heart	TOF + APV + RAA	Absent	Hydrops, hydronephrosis	22q11 microdeletion	Yes	Died *in utero*
17	30	Extracardiac anomalies	TOF + APV + RAA + ALSA	Absent		22q11 microdeletion	No	Neonatal death
18	21	Abnormal heart	TOF + APV	Absent		ND	No	TOP
19	30	Abnormal heart	APV + intact ventricular septum	Present	Mild hydronephrosis		No	Alive after surgery
20	21	Extracardiac anomalies	APV + intact ventricular septum	Present	Megacisterna magna	18p deletion	Yes	TOP
21	19	Abnormal heart	APV + intact ventricular septum	Present			No	TOP

*Fluorescent *in-situ* hybridization (FISH) was not performed. ALSA, aberrant left subclavian artery; APV, absent pulmonary valve; ASD, atrial septal defect; Cyt, cytogenetic; GA, gestational age; IUGR, intrauterine growth restriction; LSVC, left superior vena cava; ND, not detectable; RAA, right aortic arch; TOF, tetralogy of Fallot; TOP, termination of pregnancy.

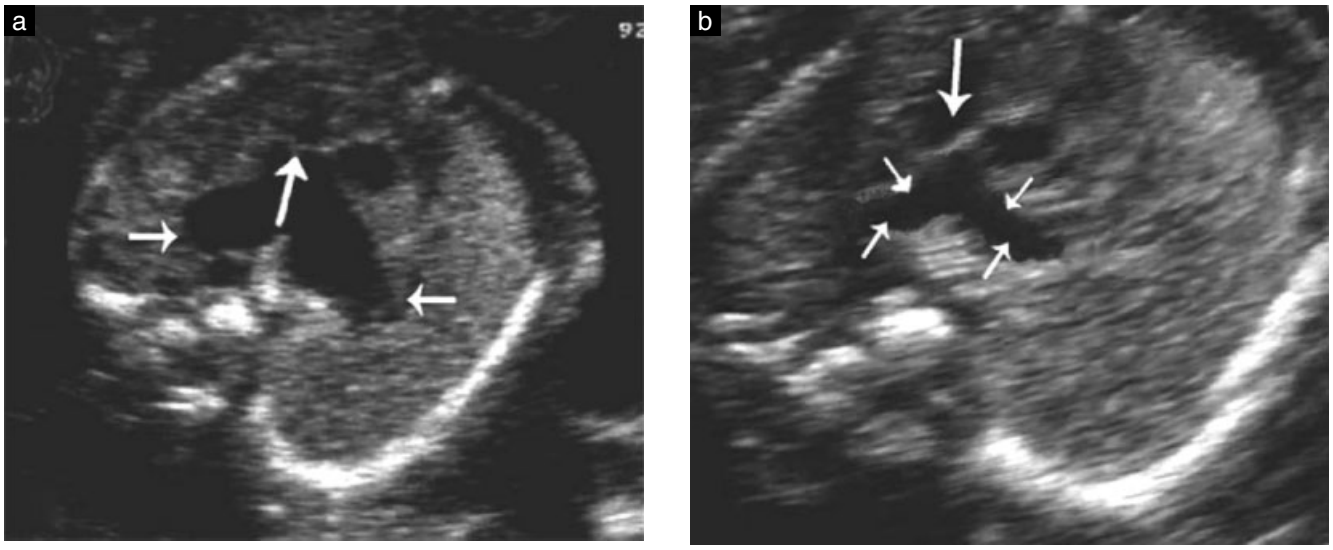

Figure 1 Ultrasound images of the right ventricular outflow tract showing dysplastic valve leaflets (big arrows), and different degrees of dilatation of the main and branch pulmonary arteries. The branch pulmonary arteries were severely dilated (small arrows) in most (15/18) cases of variants of absent pulmonary valve syndrome (APVS) with tetralogy of Fallot (a); a lower degree of the branch pulmonary arteries dilatation was present in the remaining cases, including the three cases of APVS-intact ventricular septum variants (b).

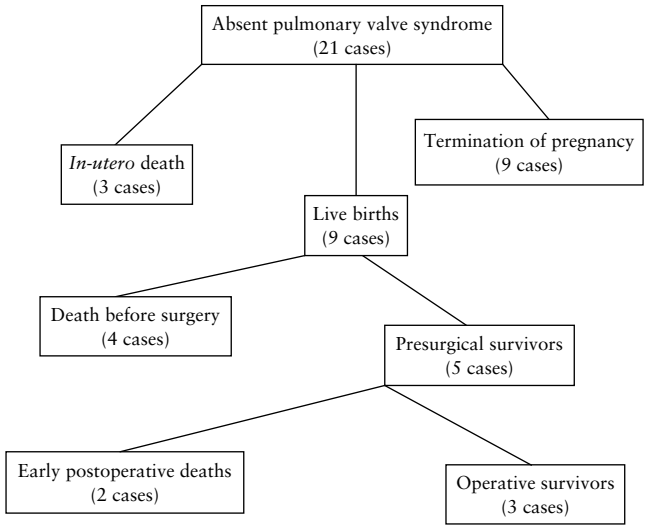

Figure 2 Flow diagram of outcome of absent pulmonary valve syndrome diagnosed prenatally.

extent of pulmonary artery dilatation is a mere by-product of the valve lesion causing stenosis and insufficiency[7,10]. Others believe that in APVS associated with TOF and ductal agenesis the consequent unavailability of the ductal pathway for runoff into the systemic circulation would play a key role in the development of volume overload and engulfment of the pulmonary arteries[3,9,16]. Our finding that mean pulmonary trunk and branch diameters are significantly greater in the case of arterial duct agenesis compared with in the five cases of patent ductus arteriosus seems, in part, to support this hypothesis, though some degree of pulmonary vessel dilatation was present in all cases. Interestingly, both in this series and in that of Razavi *et al.*[10], all cases with intact ventricular septum had a patent ductus arteriosus, lower branch pulmonary dilatation and were not associated with a 22q11 microdeletion. If we consider the different hemodynamics and the differential association with extracardiac and chromosomal anomalies of the two APVS variants (with TOF or with intact ventricular septum), it could be speculated that these may represent completely different pathological entities; furthermore, only the former shows the anterior displacement of the interventricular septum typical of conotruncal lesions.

Another issue to take into consideration concerns the screening and the diagnostic performance of ultrasound with respect to APVS. In this regard, our study demonstrates that the characterization of APVS in referral centers is straightforward and accurate, with no false positives, no inaccurate diagnoses, and additional cardiac lesions being overlooked in few cases. The distribution of cases featuring a right aortic arch, an intact ventricular septum and a patent ductus arteriosus is in close agreement with the data of Razavi *et al.*[10] (3 vs. 4 cases, 3 vs. 2 cases and 5 vs. 4 cases, respectively), as is overall survival (3/21 and 3/20 cases, respectively). Our findings also indicate that, unlike most conotruncal malformations, APVS can be suspected at routine second-trimester ultrasound since the four-chamber view is clearly abnormal in most instances, due to evident cardiomegaly and the fact that the pulmonary trunk is so dilated as to become visible (Figure 3). As for chromosomal anomalies, our figures are consistent with those reported by others[17–19]. Of the 21 cases, five (24%) had major chromosomal anomalies, and four (of 16 tested; 25%) had the 22q11 microdeletion, the latter condition being associated with APVS-TOF only (Figure 4). These findings strengthen once more the concept that in conotruncal anomalies, chromosomal aberrations and especially the 22q11 microdeletion should be directly ruled out.

With regard to outcome, most fetuses with APVS showed at autopsy or after birth signs of bronchomalacia

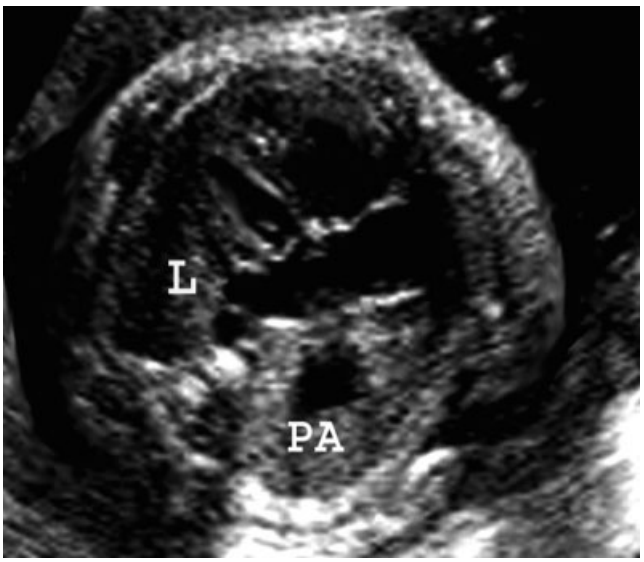

Figure 3 Ultrasound image of a case in which the cardiothoracic ratio was increased and the pulmonary artery (PA) was so dilated it was visible in the four-chamber view. L, lung.

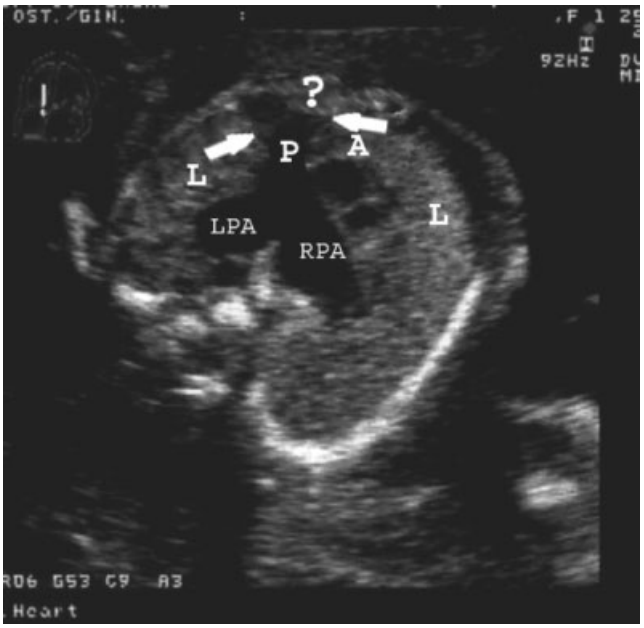

Figure 4 Ultrasound image of a fetus affected by 22q11 microdeletion associated with the variant absent pulmonary valve syndrome with tetralogy of Fallot. No thymus was seen (arrows) and the great vessels are directly behind the sternum. A, aorta; L, lungs; LPA, left pulmonary artery; P, pulmonary trunk; RPA, right pulmonary artery.

due to the compression exerted by the dilated pulmonary vessels. In particular, of the nine newborns, one died immediately after birth and five required ventilation support because of upper airway obstruction (Cases 4, 8, 10, 11 and 17), ultimately leading to death in three of them (Cases 8, 11 and 17). Furthermore, two of the three surviving children showed no signs of bronchomalacia (Cases 2 and 19). Therefore, the occurrence of bronchomalacia seems to represent, at least in newborns, a significant indicator of bad prognosis, being associated with neonatal death in most cases as previously demonstrated[10,12]. Although the identification of prenatally detectable prognostic indicators would have been of some interest, no definite conclusion could be drawn in this regard: the fact that cardiac size was within the normal range in five cases only, and pulmonary branch diameters were only slightly dilated in six cases makes any statistical analysis unfeasible. In addition, the direct causal relationship between dilatation of the pulmonary vascular tree up to the distal arteries and the occurrence of bronchomalacia has already been described[20]. Therefore, the only prognostic finding, though of limited value due to its common occurrence, at least in this series, is that when cardiomegaly and marked branch pulmonary dilatation are present in a fetus with APVS, the occurrence of bronchomalacia is highly probable. As is the case for other congenital heart defects, the prognosis for APVS is poorer when it is diagnosed in the fetus; this is probably related to the fact that less severe forms of the lesion are more likely to be overlooked during routine second-trimester screening ultrasound than are the more critical ones, since they do not alter the four-chamber view[10,12,21].

In conclusion, we have reported on an additional large series of fetuses with APVS, to be added to the few already available on this rare anomaly[9,10,12]. We have confirmed that APVS can be exhaustively characterized in the fetus and that the outcome is poor due the severity of the defect, the frequent association with genetic and extracardiac anomalies and the common occurrence of bronchomalacia. We have also shown that the occurrence of bronchomalacia is highly probable if cardiomegaly and marked branch pulmonary dilatation are detected *in-utero*.

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