

# TOTAL ANOMALOUS PULMONARY VENOUS RETURN IN SIBLINGS

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Total anomalous pulmonary venous return (TAPVR) is a rare and critical congenital vascular anomaly that requires an early operation. However, initial symptoms of TAPVR may be non-specific, and cardiovascular findings may be minimal. The heart may not be enlarged and there is often no cardiac murmur. Without cardiac murmur, these symptoms are similar to those of respiratory distress syndrome in newborns. Therefore, a high degree of suspicion and an early diagnosis of TAPVR are important. This condition generally occurs without a family history and has a low recurrence rate, but several familial cases, including siblings, have been reported worldwide. Additionally, several chromosomal or gene abnormalities associated with TAPVR have been reported. In the case presented here, two brothers with a 6-year age gap were diagnosed with TAPVR. Surgery was performed without cardiac or neurological complications. This is the first report on TAPVR in siblings in Korea.

**KEY WORDS:** Total anomalous pulmonary venous return · TAPVR · Sibling.

## INTRODUCTION

Total anomalous pulmonary venous return (TAPVR) is a rare and critical congenital vascular anomaly in which the pulmonary veins drain into the right atrium or one of its venous tributaries.<sup>1,2)</sup> TAPVR is not a problem during fetal development because of the high pulmonary vascular resistance and shunting blood flow through the foramen ovale.<sup>2)</sup> However, the heart of a patient with TAPVR has no direct pulmonary connection to the left atrium; thus, severe pulmonary congestion and pulmonary hypertension can occur after closing the ductus arteriosus. Without surgery, 80% of all children with TAPVR die due to progressive congestive heart failure after birth, usually within the first few weeks of life.<sup>1)</sup> In contrast, undergoing early TAPVR repair can produce a good outcome. Advances in surgical techniques and medical management, particularly since 2000, have increased the post-operative survival rate from TAPVR to 97%. Therefore, a high degree of suspicion and an early diagnosis of TAPVR are important.<sup>3)</sup> However, initial symptoms of TAPVR may be non-specific and include dyspnea, poor oral feeding, and cardiorespiratory failure. Moreover, the cardiovascular findings may be mini-

mal. The heart may not be enlarged and there is often no cardiac murmur. Without cardiac murmur, these symptoms are similar to those of respiratory distress syndrome in newborns. Therefore, misdiagnosis and a delayed operation can increase mortality and morbidity in infants with TAPVR.<sup>1)</sup>

The mechanism of transmission of TAPVR has not been elucidated. Although it has no known definitive genetic transmission pattern to date, a monogenic pattern of inheritance has been suggested from the numbers of reported family cases of TAPVR, including siblings.<sup>1)</sup> This is the first recorded report on TAPVR in siblings in Korea. The type of TAPVR of the elder brother, diagnosed at 6 days after birth, was the supracardiac type, and that of the younger brother, aged 1 month, was the cardiac type. Both had undergone surgical correction successfully without cardiac or neurological complications.

## CASE

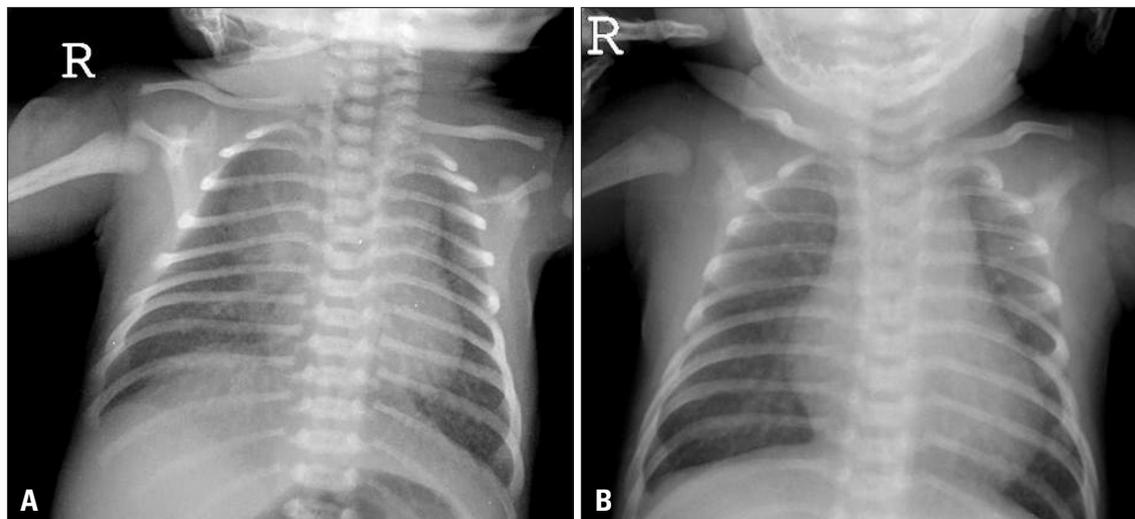
### CASE 1

A male infant was born at term to a 30-year-old mother following an uncomplicated pregnancy. This was the mother's

• Received: May 12, 2014 • Revised: August 12, 2014 • Accepted: November 27, 2014

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**Fig. 1.** Chest X-rays of the patients. A: Chest X-ray shows a normal size and configuration of the heart and increased pulmonary vascular markings. B: Chest X-ray shows mild cardiomegaly with a cardiothoracic ratio of 0.60 and increased pulmonary vascular markings.

third pregnancy; the first and the second pregnancy terminated in spontaneous abortions due to an unknown etiology. There was no familial history of congenital heart disease, including TAPVR. The labor and delivery were normal, and the birth weight of the baby was 3400 g. The infant was admitted to a hospital at 6 days of age due to tachypnea and chest retraction. In a physical examination, cardiac murmur was inaudible. At admission, his growth profile showed a body weight of 3380 g (50–75th percentile) and height was 51.5 cm (75–90th percentile). Heart rate was 168 beats per min, and respiratory rate was 88 times per min. Body temperature was 37.1°C. The arterial blood gas analysis results were pH, 7.285;  $p\text{CO}_2$ , 53.4 mm Hg;  $p\text{O}_2$ , 40.3 mm Hg; and  $\text{HCO}_3^-$ , 24.8 mmol/L. Electrocardiography (ECG) showed right ventricular hypertrophy and right axis deviation. A chest X-ray showed a normal heart size and configuration with increased pulmonary vascular markings (Fig. 1A). The echocardiogram revealed supracardiac type TAPVR. It showed dilatation of the right atrium (RA) and right ventricle (RV) and severe tricuspid regurgitation due to right heart volume overload and pulmonary hypertension on a parasternal four-chambered view (Fig. 2A). The common venous chamber (CVC) from the four pulmonary veins was not connected with the left atrium (LA), and a patent foramen ovale (PFO) with a right to left shunt was revealed on the subcostal view (Fig. 2B). An ascending vertical vein from the CVC drained into the enlarged innominate vein secondary to the superior vena cava (SVC) (Fig. 2C).

An operation was performed the day after admission. The vertical vein was ligated, and an anastomosis was made between the common pulmonary venous chamber and the LA. Additionally, the PFO was closed.

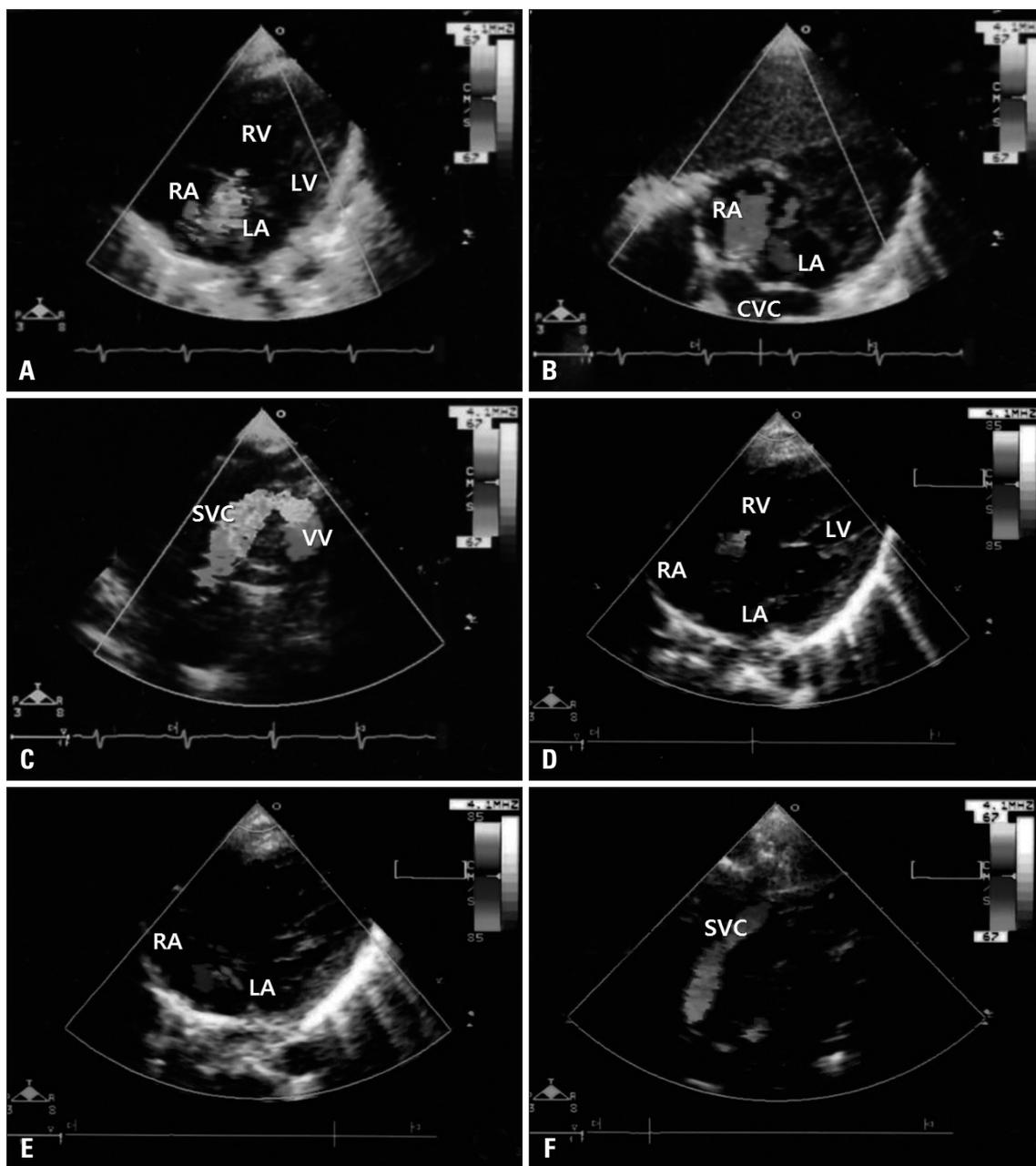
After surgical repair, the follow-up ECG showed a decreased amount of tricuspid regurgitation and normalized sizes of the RA and RV (Fig. 2D). No flow obstruction was detected be-

tween the common pulmonary venous chamber and the LA (Fig. 2E). Blood flow and size of the SVC were normalized after ligating the ascending vertical vein (Fig. 2F). He is now alive and well at 10 years of age.

## CASE 2

A male infant was born 6 years after his brother. The pregnancy and delivery were uncomplicated. He was born at 37 weeks gestation with a birth weight of 3300 g at a local hospital. At 1 month of age, he was admitted to the hospital due to irritability. No murmur was audible. Body weight was 3.99 kg (< 3rd percentile = 4.1 kg), height was 52.5 cm (25th percentile), and head circumference was 38.5 cm. Heart rate was 148 beats per min, respiratory rate was 36 breaths per min, and systolic blood pressure was 90 mm Hg. Body temperature was 36.4°C. The venous blood gas analysis results were pH, 7.396;  $p\text{CO}_2$ , 37.3 mm Hg; and  $\text{HCO}_3^-$ , 22.4 mmol/L. A chest X-ray showed cardiomegaly with a cardiothoracic ratio of 0.60 and an increased vascular marking in both lung fields (Fig. 1B). ECG showed right ventricular hypertrophy with right axis deviation.

The echocardiogram revealed cardiac type TAPVR. It showed a common pulmonary venous chamber from four pulmonary veins that were not connected with the LA and a PFO with a right to left shunt in the subcostal four-chambered view (Fig. 3A). It also showed severe pulmonary hypertension, a severe amount of tricuspid regurgitation with peak velocity of 4.4 m/s, and RA and RV enlargement (Fig. 3B). A common pulmonary venous chamber drained to the dilated coronary sinus secondary to the RA (Fig. 3C). An operation was performed the following day. An incision was made in the anterior wall of the coronary sinus, and the ostium of the coronary sinus was closed with a patch. After surgical repair, the echocardiogram showed a normalized RA and RV (Fig. 3D).



**Fig. 2.** Echocardiogram of the case 1 patient. A: A parasternal four-chambered view echocardiogram shows dilatation of the right atrium (RA) and right ventricle (RV) and severe tricuspid regurgitation due to right heart volume load and pulmonary hypertension. B: The subcostal view shows that a common venous chamber (CVC) was not connected with the left atrium (LA), and a patent foramen ovale is seen with a right to left shunt. C: The suprasternal view show an ascending vertical vein (VV) draining into the enlarged innominate vein secondary to the superior vena cava (SVC). D: Follow-up echocardiogram after surgical repair shows decreased amount of tricuspid regurgitation and normalized sizes of the RA and RV. E: No flow obstruction was detected between the CVC and the LA. F: Blood flow and size of the SVC were normalized.

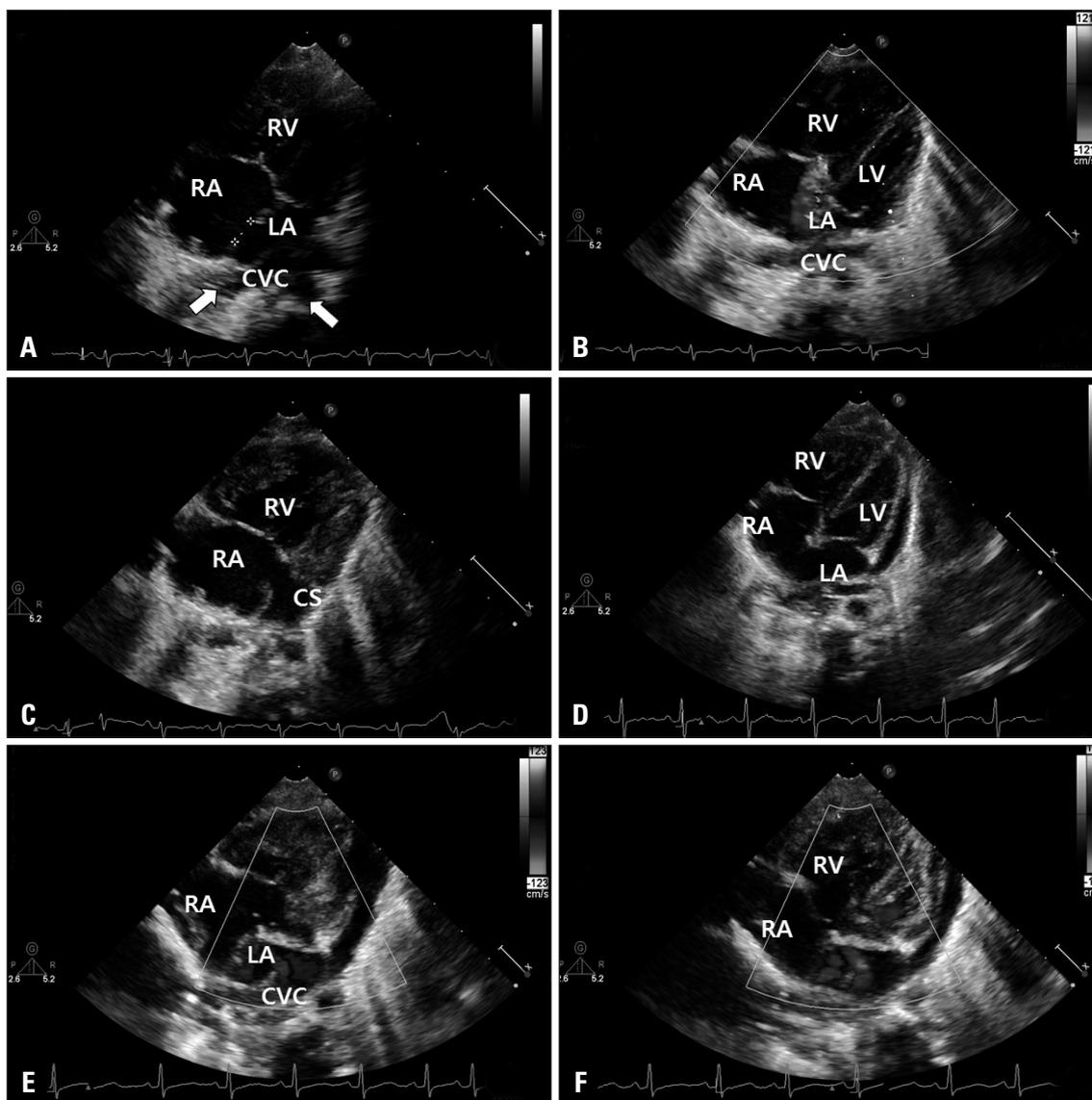
It also showed no tricuspid regurgitation and a common pulmonary venous chamber that opened to the LA without flow disturbance (Fig. 3E and F).

No other abnormalities suggesting a specific genetic disorder were detected (e.g., Holt-Oram syndrome, Noonan syndrome, Ivemark syndrome, chromosomal aberrations, or 22 partial trisomies)<sup>4)</sup> such as abnormal facial, hand, or foot appearance, developmental delay, or growth delay. We recommended a study

to determine the relevance of this rare recurrence of TAPVR. Despite our suggestion of a genetic investigation for counseling, the parents did not consent. The patient is now alive and well at 4 years of age.

## DISCUSSION

Patients with TAPVR have occasionally been reported with known single gene disorders such as Holt-Oram syndrome,



**Fig. 3.** Echocardiogram of the case 2 patient. Parasternal four-chambered view echocardiogram shows a common pulmonary venous chamber (CVC) from pulmonary veins (arrows) not connected to the left atrium (LA) and a patent foramen ovale (A). It also shows severe pulmonary hypertension, a severe amount of tricuspid regurgitation with peak velocity of 4.4 m/s, right atrial (RA) and right ventricle (RV) enlargement (B), and a CVC draining into the dilated coronary sinus (CS) secondary to the RA on the subcostal view (C). The follow-up echocardiogram after surgical repair shows the normalized RA and RV (D), no tricuspid regurgitation, and a CVC opened to the LA without flow disturbance (E and F).

Noonan syndrome, Ivemark syndrome, and chromosomal aberrations (22 partial trisomies),<sup>4</sup> but the majority of cases have insufficient data from which to draw conclusions about hereditary predisposition. Several familial cases have been reported, but no notable pedigree has been announced, except in the case of a Utah-Idaho family in 1994.<sup>2</sup> Until now, 42 sibling patients have been reported with TAPVR including the two cases presented herein. Seale et al.<sup>5</sup> reported that six of 422 (1.4%) live births with TAPVR had a sibling. Table 1 shows the characteristics of the other 36 sibling patients with TAPVR.<sup>2</sup> Among these 36 sibling pairs with TAPVR, 22 (61%) were male, 11 (31%) were female, and the remainder were not indicated. Excluding 12 of the patients whose outcomes were not men-

tioned, 16 of the 24 patients died, so the overall fatality rate was 67%. However, the majority of the patients who died did not undergo surgery. The most common type of TAPVR was the infracardiac type, which was found in 12 cases (33%). One pair of siblings was diagnosed with Holt-Oram syndrome. Seven patients had associated cardiac anomalies that included a hypoplastic left heart, atrial septal defect, patent ductus arteriosus, and mitral atresia. In our cases, TAPVR included the supracardiac and cardiac types. Although case 2 had significant pulmonary hypertension due to TAPVR at diagnosis, both patients recovered completely after surgical correction.

Several chromosomal or gene abnormalities associated with TAPVR have been reported. Bleyl et al.<sup>18</sup> described a 4P13-

**Table 1.** Demographics and clinical characteristics of siblings with TAPVR

References	Affected siblings (birth order)	Age at hospital visit	Age at diagnosis	TAPVR type	Associated cardiac anomaly	Involved other family
Le-Tan-Vinh et al. (1968) <sup>6)</sup>	Brother	Unknown	Unknown	IC	Unknown	
	Sister	Unknown	Unknown	IC	Unknown	
Gathman and Nadas (1970) <sup>7)</sup>	Unknown	Unknown	Unknown	Unknown	Unknown	
	Unknown	Unknown	Unknown	Unknown	Unknown	
Paz and Castilla (1971) <sup>8)</sup>	Brother (1st)	15 days	Autopsy	SC	None	Cousin
	Brother (2nd)	15 days	1 month	SC	None	
Kaufman et al. (1972) <sup>9)</sup>	Sister (1st)	6 weeks	2.5 years	SC	HLHS, CoA	Cousin
	Sister	1 day	2 days	SC		
Clarke et al. (1973) <sup>10)</sup>	Brother (2nd)	Unknown	Unknown	IC	Unknown	Cousin
	Brother (3rd)	Unknown	Unknown	IC	Unknown	
Delisle et al. (1976) <sup>11)</sup>	Unknown	Unknown	Unknown	IC	Unknown	
	Brother	Unknown	Unknown	C	Unknown	
Milner et al. (1977) <sup>12)</sup>	Brother (1st)	2 months	3 months	SC	None	
	Brother (3rd)	3 months	4 months	SC + C	None	
Baron et al. (1982) <sup>13)</sup>	Brother (3rd)	1 day	2 days	IC	None	
	Sister (4th)	1 day	2 days	SC + IC	None	
Solymer et al. (1987) <sup>14)</sup>	Brother (1st)	8 days	12 days	IC	CoA	
	Brother (4th)	1 day	5 days	SC	ASD, PDA	
Solymer et al. (1987) <sup>14)</sup>	Brother (3rd)	1 day	15 days	IC	PFO	
	Sister (4th)	1 day	3 days	IC	None	
Solymer et al. (1987) <sup>14)</sup>	Sister (2nd)	1 day	4 days	IC	CoA, PDA, mitral atresia hypoplastic left ventricle, ASD	
	Brother (4th)	1 day	1 day	SC		
Gleason (1989) <sup>15)</sup>	Brother (twin 1)	1 day	Autopsy	C	None	
	Brother (twin 2)	1 day	8 days	SC	None	
Raisher et al. (1991) <sup>16)</sup>	Brother (1st)	7 weeks	7 weeks	C	None	Father
	Sister (2nd)	3 weeks	3 weeks	SC + C	None	
Correa-Villaseñor et al. (1991) <sup>17)</sup>	Brother	Unknown	Unknown	Unknown	Holt-Oram	
	Sister	Unknown	Unknown	Unknown	Holt-Oram	
Bleyl et al. (1994) <sup>2)</sup>	Sister (1st)	Unknown	Unknown	Unknown	Unknown	Familial case
	Brother (3rd)	Unknown	Unknown	Unknown	Unknown	
Bleyl et al. (1994) <sup>2)</sup>	Sister (3rd)	Unknown	Unknown	Unknown	Unknown	Familial case
	Brother (4th)	2.5 months	2.5 months	Unknown	Unknown	
Bleyl et al. (1994) <sup>2)</sup>	Sister (5th)	5 days	1 week	IC	None	Familial case
	Brother (6th)	1 day	1 day	SC	Unknown	
This cases	Brother (1st)	6 days	6 days	SC	None	
	Brother (2nd)	1 month	1 month	C	None	

TAPVR: total anomalous pulmonary venous return, SC: supracardiac type, IC: infracardiac type, C: cardiac type, HLHS: hypoplastic left heart syndrome, CoA: coarctation of the aorta, ASD: atrial septal defect, PDA: patent ductus arteriosus, PFO: patent foramen ovale, Holt-Oram: Holt-Oram syndrome

q12 chromosomal abnormality in the aforementioned Utah-Idaho family with TAPVR. The authors speculated that the *PDGFRA* gene is related to inflow tract anomalies that include TAPVR in mouse and chick models. In these models, knocked-down expression of *PDGFRA* may play a role in pulmonary vein development and the developing venous pole resulted in the occurrence of intermediate inflow tract anomalies, suggesting that TAPVR occurs at one end of a spectrum

of defects.<sup>19)</sup> Ramer et al.<sup>20)</sup> reported five children with del (2)(q31q33) and one individual with dup (2)(q31q33) from a single family. Wu et al.<sup>21)</sup> suspected a deletion of 11q24.2-qter was related to TAPVR. Harris et al.<sup>22)</sup> reported a neonate with isolated TAPVR, respiratory distress syndrome, and cyanosis associated with a mosaic ring 12p. Cinquetti et al.<sup>23)</sup> suspected that a balanced 10;21 translocation and the *ANKRD1/CARP* gene are related to TAPVR. Degenhardt et al.<sup>24)</sup> reported that

the *SEMA3D* gene is associated with TAPVR or partial anomalous pulmonary venous return. They identified semaphorin 3D as playing a crucial role in pulmonary venous patterning. Although no other abnormality was associated with a congenital disorder in our case, we proposed a genetic study for this sibling. The limitation of these cases was that a genetic investigation could not be performed because the parents did not desire further evaluation. We suspected that a larger genetic study was needed to determine the genetic background of TAPVR recurrence in siblings in Korea.

Earlier detection and correction of TAPVR improves patient outcome.<sup>25</sup> However, it is difficult to make a differential diagnosis between TAPVR and other neonatal respiratory diseases, such as respiratory distress syndrome, in newborns because initial symptoms or signs may be non-specific and cardiac murmur can be inaudible in TAPVR.<sup>1</sup> Therefore, a high degree of suspicion is essential for an early diagnosis of TAPVR. In the cases presented herein, TAPVR was recognized in the younger brother at 1 month of age. Upon his hospital admission, his symptoms of congestive heart failure and pulmonary hypertension had already progressed. As in this case, early manifestations in TAPVR were nonspecific; thus, diagnosis of this critical congenital heart disease can be delayed. Echocardiography is the diagnostic mode of choice; thus, if the younger brother had received routine echocardiography, TAPVR could have been diagnosed and operated on earlier.

Routine echocardiographic screening of siblings or first relatives is recommended in those with an LV outflow obstruction or a bicuspid aortic valve (BAV).<sup>26</sup> Hales and Mahle<sup>26</sup> reported that BAV was diagnosed in 10% of siblings screened and might lower the risk of complications such as dissection. Furthermore, the cost to screen this disease is less expensive than the cost to avert a single aortic dissection in the third or fourth decade of life.

Screening of all siblings with TAPVR is a burden to patients due to psychological stress or financial problems on the parents; thus, not all siblings will present for screening. However, these consequences are outweighed by the benefit of diagnosing this critical disease so the patient can be taken for surgery before severe congestive heart failure develops. Therefore, if a genetic background is detected in a case of TAPVR, routine fetal echocardiography or cardiography immediately after birth is reasonable to screen for TAPVR.

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