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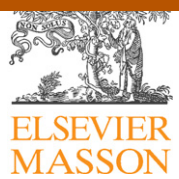

CLINICAL RESEARCH

Conotruncal defects associated with anomalous pulmonary venous connections

Cardiopathies intéressant la région conotroncale et retour veineux pulmonaire anormal associés

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KEYWORDS
Conotruncal defects;
Anomalous pulmonary venous connection;
Second heart field

Summary
Background. — Conotruncal defects constitute one of the major categories of congenital heart disease. Our understanding of how these defects develop has been derived from knowledge of the role of neural crest cells in heart development. However, recent studies have revealed a role for the myocardium in the formation of both the arterial and venous poles of the heart.
Aim. — To identify congenital heart defects that associate anomalies of the arterial and venous poles.
Methods. — From a database spanning 27 years, we identified those patients with conotruncal defects associated with an anomalous pulmonary venous connection (APVC; total or partial). Patients with atria isomerism or atrioventricular septal defects were excluded. Patient files were reviewed for clinical presentation, family history, diagnostic and surgical procedures, and outcome.
Results. — We identified 23 patients with conotruncal defects and APVC. Conotruncal defects were as follows : common arterial trunk, $n = 7$; tetralogy of Fallot, $n = 5$; discordant ventriculoarterial connections, $n = 4$; interrupted aortic arch, $n = 2$; subarterial ventricular septal defect, $n = 2$; double outlet right ventricle, $n = 2$; and right pulmonary artery from ascending aorta, $n = 1$. Nine patients had total APVC and 14 patients had partial APVC. Recurrence of the cardiac defects in siblings was observed in three families.

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Conclusion. — Our findings suggest that congenital heart defects that associate anomalies of the arterial and venous poles may have a common embryology, which results from a myocardial defect.

MOTS CLÉS
Cardiopathies conotroncales ;
Retour veineux pulmonaire anormal ;
Second champ cardiaque

Résumé
Introduction. — Les cardiopathies conotroncales constituent un des principaux groupes de cardiopathies congénitales. Leur origine embryologique a longtemps été attribuée à des anomalies des cellules de la crête neurale. Plus récemment, le rôle du myocarde dans le développement des pôles artériel et veineux du cœur a été mis en exergue.
But. — Identifier les patients ayant une cardiopathie congénitale affectant les pôles artériels et veineux simultanément.
Méthodes. — Les patients ayant une cardiopathie conotroncale et une anomalie du retour veineux pulmonaire (RVPA) ont été identifiés à partir d'une base de données couvrant une période de 27 ans. Les patients ayant un isomérisme ou un canal atrioventriculaire ont été exclus. La présentation clinique, l'histoire familiale, les méthodes diagnostiques et thérapeutiques ainsi que le devenir des patients ont été analysés.
Résultats. — Vingt-trois patients ayant une cardiopathie conotroncale et un RVPA ont été identifiés. Les cardiopathies conotroncales étaient les suivantes : tronc artériel commun, $n = 7$; tétralogie de Fallot, $n = 5$; discordance ventriculo-artérielle, $n = 4$; interruption de l'arche, $n = 2$; communication interventriculaire conoventriculaire, $n = 2$; ventricule droit à double issue, $n = 2$; et artère pulmonaire droite aberrante, $n = 1$. Neuf patients avaient un RVPA total et 14 un RVPA partiel. Une récurrence de cardiopathies congénitales était notée dans trois familles.
Conclusion. — Notre étude suggère que les cardiopathies congénitales complexes associant des anomalies des pôles artériel et veineux puissent avoir une origine embryologique commune dérivée du myocarde embryonnaire.

Abbreviations

Ao	aorta
APVC	anomalous pulmonary venous connection
CAT	common arterial trunk
IV	innominate vein
PA	pulmonary trunk (artery)
PAPVC	partial anomalous pulmonary venous connection
TAPVC	total anomalous pulmonary venous connection
Tbx1	T-box transcription factor 1

Background

Congenital heart disease affecting the arterial pole is often described as a conotruncal defect [1]. Ablation of premigratory neural crest cells from chick embryos has shown that conotruncal defects (such as tetralogy of Fallot, CAT and double outlet right ventricle) are caused by cardiac neural crest defects [2]. However, abnormal migration of neural crest cells may not be the sole cause of abnormal conotruncal development. In clinical practice, conotruncal defects are often observed in patients with DiGeorge syndrome, who have deletions on the long arm of chromosome 22 (specifically at region 22q11), which include the Tbx1 locus [1,3]. Studies indicate that DiGeorge syndrome and conotruncal defects share common embryological perturbations, although the resultant anatomical abnormalities are different. Tissue-specific ablation of Tbx1 in the pharyngeal mesoderm named the second heart field [4] was found to cause severe defects in the conotruncal region, identical to those seen in DiGeorge syndrome [5]. The second heart field provides most of the myocytes for the arterial pole, and for a portion of the venous pole [6]. These observations suggest that conotruncal defects have multiple embryological origins — an idea that is supported by the genetic heterogeneity of the malformations [7]. Conotruncal defects can be associated with a wide variety of other cardiovascular defects [2]. For example, abnormal development of the conotruncal region is a regular feature in patients with isomerism, univentricular heart, and atrioventricular canal defects [8]. Several isolated examples of an association between a conotruncal defect and an APVC have been described [9—12]. In this study, we report on a series of 23 patients displaying this rare association.

Methods

We extracted all patients with conotruncal defects and APVC from our database, which has had retrospective ascertainment from January 2006 to May 1979. We excluded patients with atria isomerism and atrioventricular septal defects. We included patients with total or partial APVC (TAPVC and PAPVC, respectively). With regard to conotruncal defects, the following abnormalities were considered: CAT, tetralogy of Fallot, tetralogy of Fallot with pulmonary atresia or absent pulmonary valve, discordant ventriculoarterial connections, subarterial ventricular septal defect, double outlet right ventricle, right pulmonary artery from ascending

Table 1 Type of outflow tract defects and abnormal pulmonary venous connections in 23 patients.

Common arterial trunk	$n=7$
PAPVC to the superior caval vein ($n=4$)	
PAPVC to the inferior caval vein	
PAPVC to the coronary sinus	
PAPVC mixed to both inferior caval and innominate veins (+ IAA)	
Tetralogy of Fallot	$n=5$
TAPVC to the coronary sinus	
PAPVC to the superior caval vein	
PAPVC to the inferior caval vein	
PAPVC to the inferior caval vein (pulmonary atresia)	
PAPVC to the innominate vein (absent pulmonary valve)	
Discordant ventriculoarterial connections IVS	$n=4$
TAPVC to the coronary sinus	
TAPVC to the inferior caval vein	
PAPVC to the right atrium	
TAPVC to the coronary sinus (+ coarctation)	
Interrupted aortic arch	$n=2$
TAPVC to the coronary sinus	
TAPVC to the innominate vein	
Subarterial ventricular septal defect	$n=2$
TAPVC to the innominate vein	
TAPVC to the portal vein (+ coarctation)	
Double outlet right ventricle	$n=2$
TAPVC to the superior caval vein	
PAPVC to the innominate vein	
Right pulmonary artery from ascending aorta	$n=1$
PAPVC to the right atrium	

IAA: interrupted aortic arch; IVS: intact ventricular septum; PAPVC: partially anomalous pulmonary venous connection; TAPVC: totally anomalous pulmonary venous connection.

Ao, interrupted aortic arch, and aortopulmonary window. Nomenclature was based on the European Paediatric Cardiac Code [13]. We reviewed patient files for clinical presentation, family history, diagnostic and surgical procedures and outcome.

Results

We identified 23 patients with conotruncal defects and APVC in our database. The types of defects are shown in Table 1, and two examples of the association are shown in Fig. 1.

Diagnosis of the conotruncal defect was made during fetal life in five patients (CAT, $n=2$; tetralogy of Fallot, $n=1$; discordant ventriculoarterial connections, $n=1$; interrupted aortic arch, $n=1$). APVC was detected during fetal life in four patients. The presenting symptoms were as follows:

- cyanosis, $n=20$;
- heart failure, $n=1$;
- cardiac murmur, $n=1$;
- failure to thrive, $n=1$.

Complete echocardiographic assessment of the conotruncal defect and the abnormal pulmonary veins was possible before repair in 16 patients, and the diagnosis was confirmed either by computerized tomography scan (Fig. 2) or by catheterization. The diagnosis was incomplete before surgery in the remaining seven patients, but the APVC was diagnosed during surgery in three of these patients and during follow-up in two patients. A TAPVC was diagnosed during autopsy in one patient who had undergone an arterial switch for discordant ventriculoarterial connections, and a subarterial ventricular septal defect was diagnosed (and subsequently repaired) in the final patient after repair of an abnormal venous connection.

Of the 23 patients, 17 had both the conotruncal defect and the APVC repaired. No treatment was proposed for three patients (in the early 1980s). Eight of nine TAPVC were

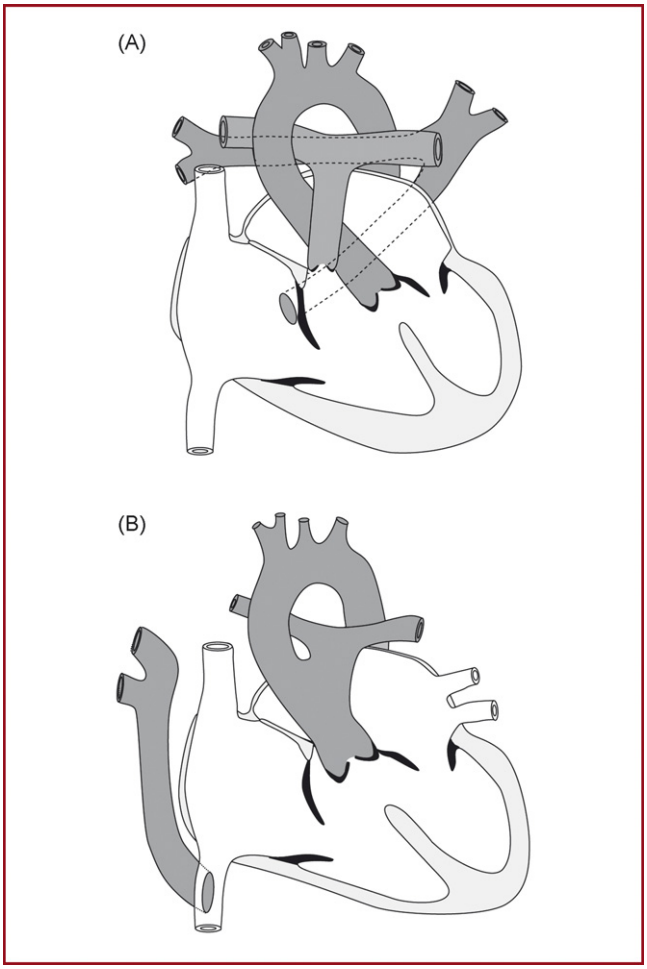

Figure 1. Schemes of conotruncal defects with associated anomalous pulmonary venous connections. A. Tetralogy of Fallot and totally anomalous pulmonary venous connection to the coronary sinus. B. Common arterial trunk and partially anomalous pulmonary venous connection of both right pulmonary veins to the inferior caval vein.

Schémas de malformations complexes associant une cardiopathie conotroncale et un retour veineux pulmonaire anormal (RVPA). A. Tétralogie de Fallot et RVPA total au sinus coronaire. B. Tronc artériel commun et RVPA partiel des veines pulmonaires droites à la veine cave inférieure.

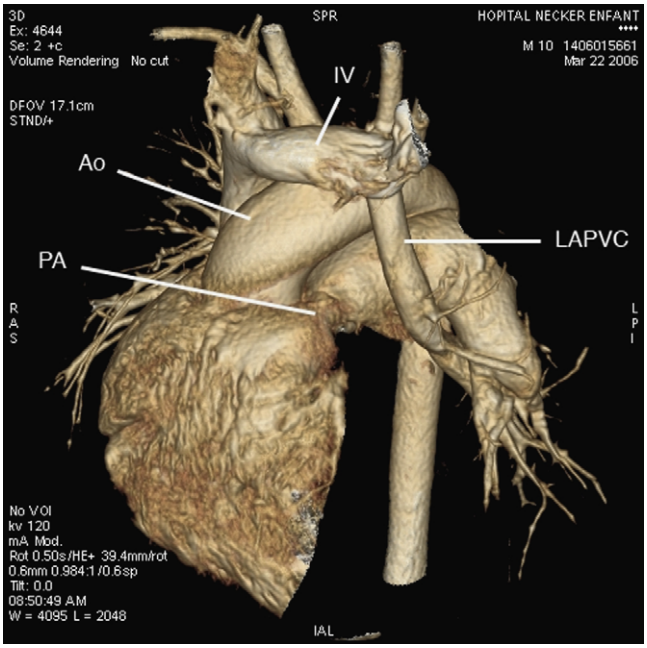

Figure 2. Computerized tomography scan of a patient with tetralogy of Fallot with absent pulmonary valve and APVC of the left lung to the innominate vein. Note the pulmonary stenosis and the dilated pulmonary artery branches. The left ventricle has been removed. Ao: aorta; PA: pulmonary trunk; LAPVC: left partially anomalous pulmonary venous connections; IV: innominate vein.
Scanner 3D d'un patient ayant une agénésie des valves pulmonaires avec communication interventriculaire et RVPA partiel du poumon gauche au tronc veineux innominé. Notez la sténose pulmonaire et la dilatation des artères pulmonaires. Le ventricule gauche a été enlevé numériquement.

repaired and nine of 14 PAPVC were repaired. At the last follow-up, 12 patients were still alive; two patients died before repair, two during surgery and seven after surgery.

Associated extracardiac anomalies were present in five patients (holoprosencephalia, $n=1$; anal imperforation, $n=1$; Pepper syndrome, $n=1$; Hirschsprung disease, $n=1$; plane angioma, $n=1$). Recurrence of cardiac defects in siblings was noted in three families (Fig. 3); none of these patients had a 22q11 deletion confirmed either by fluorescence in situ hybridization or according to the files.

Discussion

A recent study has suggested that conotruncal defects have multiple embryological origins [5]. Although the cardiac neural crest is known to contribute to the morphogenesis of the conotruncal region (aorticopulmonary septum), the fact that both poles of the heart are affected suggests that a myocardial abnormality may have a critical role to play in the development of conotruncal defects. Furthermore, alterations in the cardiac neural crest have been shown to have no involvement in venous anomalies such as TAPVC or PAPVC [14,15]. In addition, four patients had discordant ventriculoarterial connections, which are not associated with neural crest defects [16].

Studies with Pitx2δc mutant mice have shown that discordant ventriculoarterial connections can be caused by laterality defects [17,18], which can affect rotation of the myocardial wall during outflow tract remodeling. Indeed, a rotation defect in the conotruncal myocardium has been linked specifically to discordant ventriculoarterial connections [17]. Mice with mutations in the Smad2 and Nodal genes can also display discordant ventriculoarterial connections [19]. In Perlecan mutant mice, discordant ventriculoarterial connections have been associated with the existence of an abnormal extracellular matrix throughout the common trunk [18]. Finally, in humans, mutations in the Cryptic gene have been associated with left-right malformations and with some discordant ventriculoarterial connections [19,20].

In a similar manner, CAT and double outlet right ventricle are often observed in animal studies involving ablation of the neural crest, but are also associated with myocardial defects, as seen in Pitx2δc mutant embryos [17]. In fate-mapping studies with a Pitx2 Cre knock-in allele, Pitx2 daughter cells were observed in the pharyngeal mesoderm (the second heart field) and the pulmonary veins, but were severely reduced in Pitx2δc mutant embryos [21]. These findings suggest that different mechanisms can produce the same congenital heart defect.

Recent studies have identified a novel source of cardiac progenitor cells in the pharyngeal mesoderm (the second heart field), which give rise to the arterial and venous poles of the heart [4]. This new concept led us to scan our database to find patients with defects affecting both poles, which until now had been thought to be the consequence of independent events. Twenty-three patients were identified with this rare association — a prevalence of 0.18% in our total cohort of patients with conotruncal defects. We identified three families with recurrences in siblings, which suggest that familial forms of this association may occur more frequently than familial forms of isolated conotruncal defects or APVC, although the sample size was small. Our study underlines the different factors that contribute to the development of the conotruncal region and opens the way for the testing of candidate genes that may play a role in the second heart field. A clinical, pathogenetic approach to congenital heart defects remains important, as recurrence in siblings is relatively rare. Undeniably, the classification proposed by Clark, in 1996, clarified our knowledge of heart formation at that time, and made an important contribution to congenital cardiology, particularly prenatal diagnosis [22]. However, the time has now come to revisit this classification, to ensure that it reflects our current understanding of how the heart develops.

Congenital cardiovascular malformations give rise to high neonatal morbidity and mortality. There is a strong incentive, therefore, to improve prevention and accuracy of diagnosis of these conditions. Greater understanding of normal and abnormal cardiac development is crucial if these clinical goals are to be achieved. While molecular insight into cardiac development has undergone major advances during the last decade, the clinician remains a key contributor in terms of observation and informed interpretation. The causes and pathogenesis of congenital heart defects will only be revealed through careful analysis of clinical syndromes together with elucidation of developmental pathways in normal and abnormal animal models.

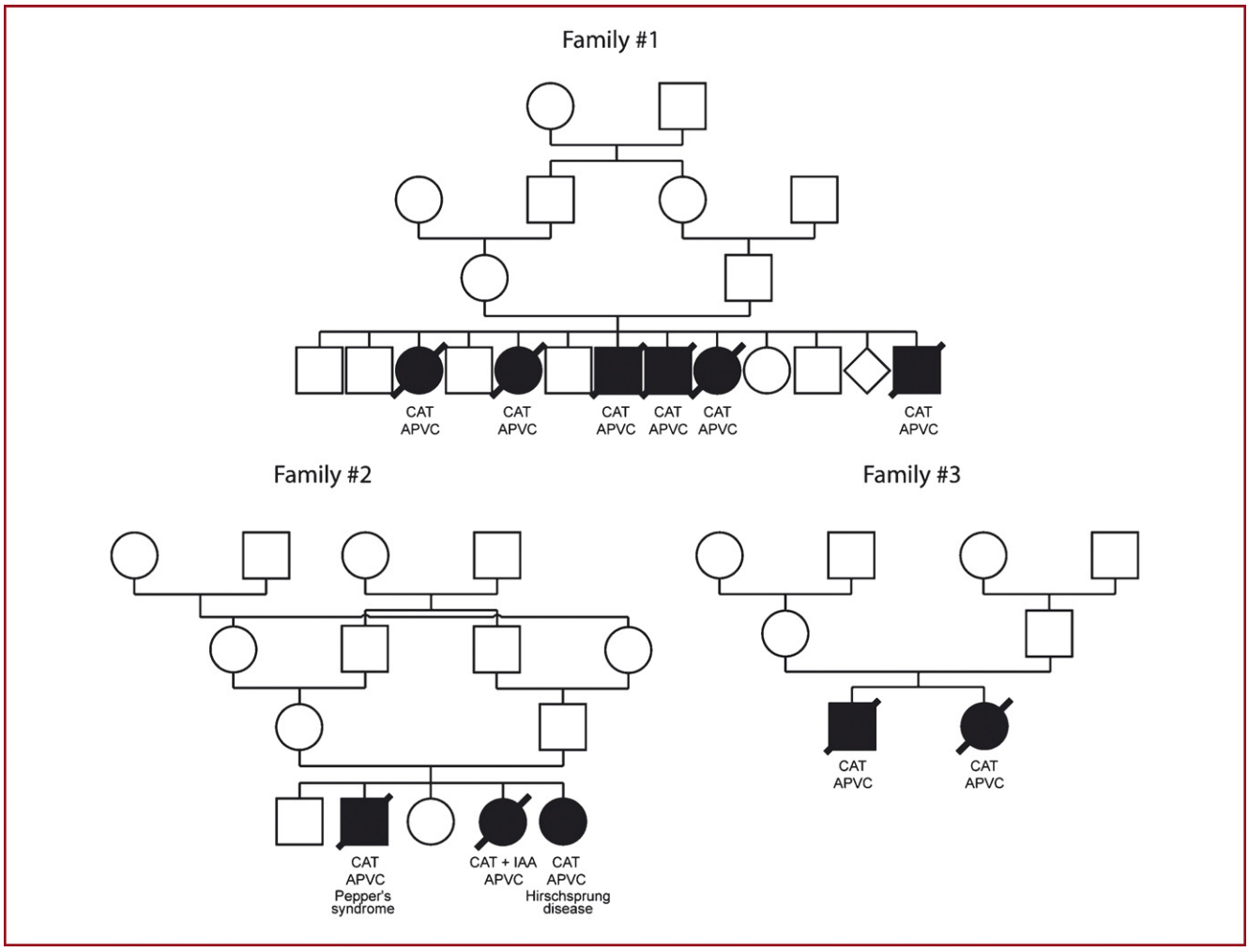

Figure 3. Pedigrees of three families with malformations at both arterial and venous poles. All patients had common arterial trunk with an associated APVC. CAT: common arterial trunk; IAA: interrupted aortic arch; APVC: anomalous pulmonary venous connection.
Arbres généalogiques de trois familles avec cardiopathies intéressant les pôles artériel et veineux. Tous les patients avaient un tronc artériel commun et un retour veineux pulmonaire anormal associé.

Conflict of interest

None declared.

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