Cardiology in the Young

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Crossed pulmonary arteries and DiGeorge syndrome: case reports and literature review

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Abstract

DiGeorge syndrome has heterogeneous clinical presentation, and for this reason, its diagnosis can be challenging and may be missed. Since CHDs are very common in this patients, they can be considered pillars of clinical diagnosis of the syndrome. Therefore, accurate echocardiography is needed to detect even minor cardiac anomalies, as some specific malformation like crossed pulmonary arteries can be associated with 22q11 syndrome. We report two cases of newborns where the diagnosis of DiGeorge syndrome was suspected after finding crossed pulmonary arteries on echocardiography. In order to reach a timely diagnosis of DiGeorge syndrome, we suggest a careful echocardiographic examination of the pulmonary arteries position in all patients and genetic analysis for 22q11.2 microdeletion in patients in whom malposition has been detected.

Review

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DiGeorge syndrome can be hard to identify especially in the absence of major clinic manifestation, so patients sometimes escape the diagnosis until adulthood. Nevertheless, the presence of specific minor cardiac anomalies could help to raise suspicion of this syndrome. Therefore, a cardiological evaluation including accurate echocardiography is required in all newborn with facial abnormalities or mild symptoms.

We report two cases of neonates born at full term with no complications or risk factors, where the postnatal echocardiographic finding of crossed pulmonary arteries led to the diagnosis of DiGeorge syndrome.

Case presentation

The first case refers to a newborn girl who presented in second day of life dysphonic crying, stridor, and perioral cyanosis. Therefore, the patient was admitted to the Neonatal ICU under continuous monitoring. Transthoracic echocardiography was performed to exclude CHD and revealed a short pulmonary trunk with branch pulmonary arteries arising from two different imaging planes; mild bilateral proximal stenosis of the pulmonary arteries (3 mm diameter, Parameterz z-score, Detroit −2.86 right pulmonary artery, and −2.36 left pulmonary artery) was also observed. The day after the girl developed hypocalcaemia (serum calcium 6.5 mg/dl). Both these findings, crossed pulmonary arteries and especially hypocalcaemia, were considered warning signs for DiGeorge syndrome. The genetic diagnosis of 22q11.2 deletion syndrome (22q11.2 DS) was then confirmed with Array-CGH. Further investigations revealed also thymic aplasia with decreased lymphocyte count and a subglottic membrane that required tracheostomy and tracheoplasty.

The second case concerns a 19-day-old girl referred to our Cardiology Service from the Pediatric Emergency Department for poor feeding, hypotonia, perioral cyanosis, and low blood oxygen saturation during an episode of inflammation of the upper airways. Physical examination revealed a grade II systolic heart murmur with radiation to the scapula and weak femoral pulses. Transthoracic echocardiography showed systolic dysfunction of the left ventricle with an ejection fraction of 56% and septal dyskinesia and crisscrossed branch pulmonary arteries with moderate left pulmonary artery stenosis (diameter at the origin of 3 mm). Considering the left ventricular dysfunction, myocarditis was suspected, and specific blood exams were performed: cardiac enzymes were slightly elevated (troponin-HS peak 246 ng/L with a cut-off value of 58 ng/L), respiratory pathogen test showed the presence of rhino-enterovirus, and blood cultures resulted in later positive for *Haemophilus influenzae*. The newborn was then transferred to the Pediatric ICU, where angiotensin converter enzyme inhibitor therapy was immediately started. On cardiological re-evaluation, the 12-lead electrocardiogram revealed prolonged QT interval and the echocardiogram showed worsening of left ventricle dysfunction (ejection fraction 51%), although

cardiac enzymes normalised. Alternative diagnoses were therefore considered: sepsis was excluded due to negativity of phlogosis indices (PCR 0,0 and PCT 0,15), while analysis of blood electrolytes, initially normal, when repeated indicated severe hypocalcaemia (serum calcium 5.8 mg/dl), and hypomagnesemia (magnesium 1.74 mg/dl); subsequent examination confirmed the hypoparathyroidism (parathyroid hormone 12.7 pg/ml). As for the first case, the association between crossed pulmonary arteries and hypoparathyroidism raised the suspicion of 22q11.2 deletion syndrome (22q11.2DS), later confirmed by genetic analysis.

Discussion

DiGeorge syndrome or, more properly, 22q11.2 deletion syndrome (22q11.2DS) is the most common chromosomal microdeletion syndrome with a prevalence of 1 case per 3.000–6.000 live births.[1] Because of its heterogenous clinical presentation, 22q11.2 deletion syndrome is not so simple to diagnose. However, since CHDs appear in about 75–80% of patients with 22q11.2 deletion, they can be considered pillars of clinical diagnosis of the syndrome.[1–4] In particular, conotruncal defects, including tetralogy of Fallot, truncus arteriosus, interrupted aortic arch (mainly type B), pulmonary atresia, and ventricular septal defect, are the most common heart anomalies observed in these patients.[1–5] This characteristic involvement of the outflow tract is due to the deletion of specific genes (TBX1, CRKL, ERK2) localised on chromosome 22q11.2 that are involved in the anterior heart field cells differentiation and in the neural crest cells migration.[1–3,6]

Major CHDs are symptomatic since the neonatal period, which allow early diagnosis of DiGeorge syndrome. However, 22q11.2 DS may also be related to minor heart anomalies without evident manifestation and therefore may remain undetected until adulthood.[2]

A peculiar type of cardiovascular congenital defect associated with 22q11 deletion is crossed pulmonary arteries. Crisscross or crossed pulmonary arteries is a rare anomaly of pulmonary artery branches where the ostium of the left pulmonary artery is above and to the right of the right pulmonary artery origin; the branches then cross each other directing to each respective lung.[7–12] This malposition of pulmonary arteries may occur isolated or associated with other CHDs, especially conotruncal and aortic arch abnormalities.[10,13,14] Crossed pulmonary arteries are commonly related also to extracardiac congenital malformations and chromosomal abnormalities, and in particular to DiGeorge syndrome with a reported frequency ranging from 50%[10,14] to 10%[13] of cases. Nevertheless, limited reports concerning crossed pulmonary arteries are available in the literature and some authors[13] suggest a probable higher prevalence in the general population, and in particular in patients with a genetic syndrome (e.g. DiGeorge-, Noonan-, Costello-, trisomy 18, or VACTERL anomalies).

The crossed pulmonary arteries, despite the abnormal position of pulmonary branches, if not associated to congenital heart disease, does not cause neither hemodynamic compromission nor airway obstruction, and therefore is always asymptomatic.

Accurate evaluation of pulmonary artery branches is crucial during echocardiography, as the finding of crossed pulmonary arteries can be a clue to associated cardiac and extracardiac anomalies and to genetic syndromes such as DiGeorge. Therefore, a careful echocardiographic examination of the pulmonary arteries position is suggested in all patients, especially when facial dysmorphisms are present, as well as genetic analysis for 22q11.2 microdeletion is required in all patients in whom malposition has been detected.[14]

Conclusions

Timely diagnosis of DiGeorge syndrome, particularly in the newborn period, is of utmost importance to permit identification and treatment of associated medical problems. Patients with mild clinical form may be undiagnosed until adulthood; therefore, it is necessary to recognise even minor cardiac abnormalities that can be crucial markers of this syndrome.

We want to highlight the importance of identifying an uncommon cardiac malformation such as the crossed pulmonary arteries, in order to allow the diagnosis of an important multisystemic condition like the 22q11.2 deletion syndrome.

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