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Original Article

The role of modern imaging techniques in the diagnosis of malposition of the branch pulmonary arteries and possible association with microdeletion 22q11.2

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Abstract Malposition of the branch pulmonary arteries is a rare malformation with two forms. In the typical form, pulmonary arteries cross each other as they proceed to their respective lungs. The "lesser form" is characterised by the left pulmonary artery ostium lying directly superior to the ostium of the right pulmonary artery, without crossing of the branch pulmonary arteries. Malposition of the branch pulmonary arteries is often associated with other congenital heart defects and extracardiac anomalies, as well as with 22q11.2 microdeletion. We report three infants with crossed pulmonary arteries and one adolescent with "lesser form" of the malformation. The results suggest that diagnosis of malposition of the branch pulmonary arteries could be challenging if based solely on echocardiography, whereas modern imaging technologies such as contrast computed tomography and magnetic resonance angiography provide reliable establishment of diagnosis. In addition, we performed the first molecular characterisation of the 22q11.2 region among patients with malposition of the branch pulmonary arteries and revealed a 3-megabase deletion in two out of four patients.

Keywords: Cardiac; contrast computed tomography; magnetic resonance angiography; molecular

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MALPOSITION OF THE BRANCH PULMONARY arteries is a rare congenital heart disease with two forms. Crossed pulmonary arteries are a classic form of this anomaly, characterised by an abnormal ostium of the left pulmonary artery that lies to the right of and above the right pulmonary artery. Because of this abnormal positioning, the pulmonary arteries cross each other as they proceed to their respective lungs.[1–3] In the second form, the left pulmonary artery ostium lies directly superior to the ostium of the right pulmonary artery. From these origins, the branch pulmonary arteries proceed to their respective lungs without crossing. This variant of malposition of the branch pulmonary arteries, first reported by Becker et al,[2] is considered as the "lesser form" of such anomaly. To the best of our knowledge, since 1966 when Jue et al[1] provided the first description of crossed pulmonary arteries, no more than 28 cases of crossed pulmonary arteries and 7 cases of "lesser form" – malposition of the branch pulmonary arteries without crossing – have been reported in the literature.[1–16]

Malposition of the branch pulmonary arteries is often associated with other congenital heart defects and extracardiac anomalies,[10,12–14] as well as with 22q11.2 microdeletion.[3,17–19] The 22q11.2 deletion syndrome is the most common deletion disorder in humans, with an incidence of ~1/4000 per live

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birth.[11,20] The syndrome is characterised by a broad spectrum of features, including conotruncal heart anomalies, craniofacial dysmorphism, cleft palate, aplasia or hypoplasia of the thymus, hypoparathyroidism, and developmental delay.[11,13,17–21] Moreover, recent reports imply psychiatric disorders as the main medical and social burden for adult patients with 22q11.2 deletion syndrome.[18]

The recognition of malposition of the branch pulmonary arteries in four children within 1 year prompted us to perform a multidisciplinary assessment of these patients, including comprehensive clinical evaluation and molecular characterisation of this rare anomaly.

Materials and methods

Diagnostic imaging techniques

Transthoracic two-dimensional and Doppler echocardiography was applied with Philips Sonos 7500, followed by cardiac catheterisation in two patients. Thoracic contrast computed tomography scan was performed with Siemens Somatom Emotions (Siemens AG, Forchheim, Germany) in transverse planes with 3-millimetre slice thickness. Magnetic resonance angiography was carried out using Philips Achieva (Philips Healthcare, DA Best, The Netherlands) 1.5T.

Karyotyping and fluorescence in situ hybridisation

Lymphocytes were cultured for 72 hours in RPMI 1640 medium containing 25% foetal calf serum at 37°C, with phytohemagglutinin stimulation. G-banding cytogenetic analysis was performed on patients following standard protocol. Fluorescence in situ hybridisation was performed on metaphase spreads from cultivated lymphocytes, with the probe covering the common deletion interval (TUPLE1, 22q11.2, SpectrumOrange) and control probe (ARSA, 22q13.3, SpectrumGreen) following the manufacturer's protocol (Abbott). Briefly, slides were immersed in denaturation solution (70% formamide/2 × saline sodium citrate) for 5 minutes at 75°C, dehydrated through an ethanol series (70%, 85%, and 100% ethanol, 1 minute each), and air-dried. Probe mixture, containing TUPLE1 and control ARSA probes, hybridisation buffer and purified water, was denatured for 5 minutes in 73°C, cooled on ice, applied to the slide, sealed under a coverslip with a rubber cement, and incubated in a humidified box at 37°C overnight. Following hybridisation, the coverslips were removed by rinsing in 0.4 × saline sodium citrate/0.3% NP-40 at room temperature. The slides were washed in 0.4 × saline sodium citrate/0.3% NP-40 at 73 ± 1°C for 2 minutes, then washed in 2 × saline sodium citrate/0.1% NP-40 for 30 seconds at room temperature, and air-dried in darkness. The slides were mounted in 0.4 milligram per millilitre diamidino phenylindole, counterstain in Vectashield Antifade Buffer, viewed under an Olympus BX51 fluorescent microscope with appropriate filters for detection of SpectrumGreen, SpectrumOrange, and diamidino phenylindole, and analysed using Cytovision 3.1 software (Applied Imaging Corporation, Santa Clara, CA, United States of America). In total, 30 metaphases were scored for the microdeletion by fluorescence in situ hybridisation, except for patient 4 where 50 interphase nuclei were analysed.

Multiplex ligation-dependent probe amplification

In order to better characterise the size and position of 22q11.2 deletion, we performed multiplex ligation-dependent probe amplification using Kit P250-A1 DiGeorge (MRC-Holland, Amsterdam, The Netherlands). The kit comprises 57 probes, including a subset of 30 different probes that corresponds to 22q11.2 region – 14 probes covering the most common deletion interval. An additional five regions (4q35, 8p23, 9q34.3, 10p15, and 17p13.3), associated with features resembling 22q11.2 deletion syndrome, are covered by 18 probes. The reaction set also covers nine control fragments. The kit was used according to the instructions of the manufacturer, with some modifications. Briefly, genomic deoxyribonucleic acid was extracted from peripheral blood lymphocytes using the QIAamp DNA Mini Kit (QIAGEN Hilden, Germany), precipitated with ethanol, and 150 nanograms of deoxyribonucleic acid was used for further analysis. Probe hybridisation, ligation, and amplification reactions were carried out in a standard thermal cycler (GeneAmp PCR System 2700, Applied Biosystems, Foster City, CA, USA). Amplification products were run on 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) with the following modules: capillaries 36 centimetres Polymer POP-7, oven temperature 60°C, poly Fill Vol 4840 steps, pre-run voltage 15 kilovolts, pre-run time 180 seconds, injection voltage 1.6 kilovolts, injection time 20 seconds, voltage number of steps 20, voltage step interval 15 seconds, date delay time 60 seconds, run voltage 15 kilovolts, run time 1200 seconds. The obtained data were analysed using the GeneMapper Software Version 4.0 (Applied Biosystems, Foster City, CA, USA) and Coffalyser v9.4 (MRC-Holland, Amsterdam, The Netherlands).

Results

In all, three infants, that is, patients 1–3, received a diagnosis of classical form of malposition of the branch pulmonary arteries, so called crossed pulmonary arteries, whereas one adolescent, that is, patient 4, was diagnosed with lesser form of malposition of the

Table 1. Summary of clinical data of the four patients with malposition of the branch pulmonary arteries.

Patient	1	2	3	4
Additional cardiac malformations	+	+	+	+
Extracardiac malformations	−	−	−	−
Growth deficiency	+	−	−	−
Cognitive/speech/motor delay	−	+	−	−
Facial dysmorphism	+	−	−	−
Cleft palate	−	−	−	−
Hypocalcaemia	−	−	−	−
Low T-cell number	+	+	−	+
Microdeletion 22q11.2	+	+	−	−

branch pulmonary arteries known as malposition of the branch pulmonary arteries without crossing. All were Caucasian, born from healthy and unrelated parents, having unremarkable family history. History of pregnancy revealed normal intrauterine growth for all patients, and no data suggest aetiological impact of environmental factors.

Clinical characteristics of patients

Table 1 summarises the clinical data of the patients analysed in this study. This section provides more detailed clinical information for the individual cases.

Patient 1: a 1.5-month-old female infant, with diagnosis of ventricular septal defect, was referred to our hospital because of tachypnoea and feeding difficulties. Echocardiography showed large perimembranous ventricular septal defect, dilated left ventricle, and crossed pulmonary arteries (Fig 1a and b), which were subsequently confirmed by thoracic computed tomography scan (Fig 1c and d). The result of peripheral blood lymphocyte immunophenotyping (CD4 lymphocyte count 1.41×10^9/litre) was suggestive of thymic hypoplasia, without other features of 22q11.2 deletion syndrome – for example, facial dysmorphism, hypocalcaemia, and overt cleft palate. Neither thoracic computed tomography scan nor median thoracotomy revealed thymic aplasia.

Owing to the fact that crossed pulmonary arteries did not cause any haemodynamic consequences, the surgery was focused on ventricular septal defect closure. At present, at the age of 3 years, clinical follow-up reveals mild growth retardation – body length on the third centile; mild facial dysmorphism – anteverted ears and Darwin tuberculum; and normal motor, speech, and cognitive development.

Patient 2: a 2-month-old male infant with diagnosis of ventricular septal defect was admitted because of signs of cardiac failure and persistent cough. The first physical assessment revealed moderate failure to thrive, tachypnoea, dyspnoea, enlarged liver, and wheezing. Echocardiography revealed a large perimembranous ventricular septal defect with double-chambered right ventricle and possible crossed pulmonary arteries, which were later confirmed by thoracic computed tomography scan. Computed tomography scan also demonstrated a compression of the main bronchus by enlarged lymph nodes. Immunophenotyping of peripheral blood lymphocytes suggested thymic hypoplasia (CD4 lymphocyte count 0.47×10^9/litre), although neither thoracic computed tomography scan nor median thoracotomy revealed thymic aplasia.

Follow-up at the age of 3 years showed speech delay with normal voice quality, as well as borderline achievement during psychological assessment of cognitive and motor development. Physical examination and nasopharyngoscopy did not reveal overt or submucosal cleft palate. The patient underwent a successful surgical closure of ventricular septal defect. Presently, the main clinical problem is persistent asthma.

Patient 3: a 1.5-month-old male infant was referred because of cardiac decompensation and echocardiographic diagnosis of aortopulmonary window. Cardiac catheterisation confirmed this diagnosis with additional findings of pulmonary valve and branch stenosis and right aortic arch. During the surgical correction, crossed pulmonary arteries were disclosed. No facial dysmorphism was noticed. Brain ultrasound, as well as abdominal, did not reveal associated malformations. The number of T-cells and levels of serum calcium were normal. No overt cleft palate was observed during physical examination. However, abnormalities of the aortic arch and pulmonary arteries indicated the possibility of microdeletion 22q11.2. After successful surgical repair, the infant is not facing any significant clinical problem, having normal growth and development.

Patient 4: a 13-year-old boy suffering from heterotaxy syndrome – isomerism of the right atrial appendage – type B interrupted aortic arch, severe aortic valve stenosis, and atrial septal defect was admitted to the hospital for reevaluation. Interrupted aortic arch had been surgically corrected at the age of 3 months. At the age of 6 years, he had a second surgical intervention because of severe aortic valve stenosis, with small aortic annulus. Aortic valve commissurotomy was performed with enlargement of a small annulus with a bovine pericardium patch. At the age of 10 years, balloon dilatation of severe valvular aortic restenosis was performed. At that time, moderate left pulmonary artery stenosis was recognised for the first time. During hospitalisation at the age of 13 years, echocardiography showed reappearance of severe aortic stenosis (100 millimetres of mercury pressure gradient) and the presence of severe left pulmonary artery stenosis (64 millimetres of mercury), which were confirmed by magnetic resonance angiography.

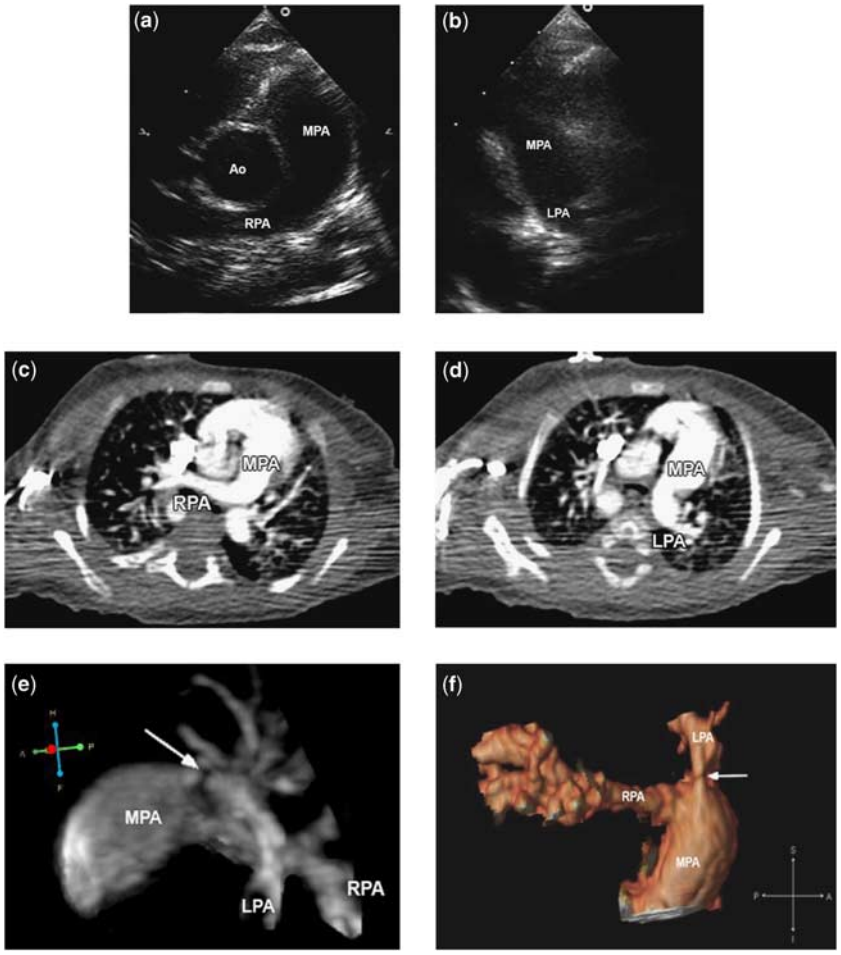

Figure 1.
*Echocardiography, contrast computed tomography, and magnetic resonance angiography of the patients with crossed pulmonary arteries and malposition of the branch pulmonary arteries without crossing. (**a**) High left parasternal short-axis echocardiographic view in patient 1 demonstrates the RPA originating from the MPA. (**b**) Superior sweep of transducer demonstrates LPA arising from the right of the MPA and crossing towards the left lung. (**c**, **d**) Contrast-enhanced cardiac computed tomography in patient 1. Transverse images show the relationship of crossing pulmonary arteries in inferior to superior progression. (**e**) Magnetic resonance angiography of pulmonary arteries (MIP) in patient 4. (**f**) Volume-rendered magnetic resonance angiogram in patient 4. Ostium of the LPA lies above and slightly to the right of the RPA. LPA stenosis is marked by an arrow. RPA = right pulmonary artery; MPA = main pulmonary artery; Ao = aorta; LPA = left pulmonary artery; MIP = maximum intensity projection.*

In addition, magnetic resonance angiography revealed malposition of the branch pulmonary arteries without crossing (Fig 1e and f). At the age of 14 years, left pulmonary artery stenosis has been surgically corrected with a pulmonary homograft patch, whereas aortic valve stenosis has been corrected with replacement of the hypoplastic annulus and aortic valve with St. Jude valved conduit, together with posterior aortic annular enlargement. Speech is normal and no overt cleft palate was observed. Growth, as well as cognitive and motor development, is normal.

Diagnostic imaging

For patients 1 and 2, diagnosis of crossed pulmonary arteries was suspected during echocardiography. Anatomy of the pulmonary artery was best visualised on parasternal short-axis and high left parasternal transverse views. The branch pulmonary arteries could not be visualised in the single planar image because of their abnormal spatial relationship, and thus serial superior–inferior sweeps were necessary (Fig 1a and b). Colour Doppler echocardiography enabled confirmation of abnormal direction of pulmonary artery branches, as well as assessment of haemodynamics, which was normal. In both infants, diagnosis of crossed pulmonary arteries was confirmed by cardiac computed tomography scan (Fig. 1c and d) and during surgery.

In patient 3, echocardiography and cardiac catheterisation did not allow recognition of anomalous origins and positions of pulmonary artery branches. Diagnosis of crossed pulmonary arteries was established during surgery.

In patient 4, malposition of the branch pulmonary arteries without crossing was detected on magnetic resonance angiography (Fig 1e and f). Three-dimensional reconstruction – magnetic resonance volume rendering – clarified this finding and allowed accurate analysis of spatial relationship of pulmonary artery branches (Fig 1f). Left pulmonary artery stenosis near the ostium was clearly visualised. After a detailed review of the previous pulmonary angiography performed at the age of 10 years, the anomalous position of the pulmonary artery branches was revealed (Fig 2).

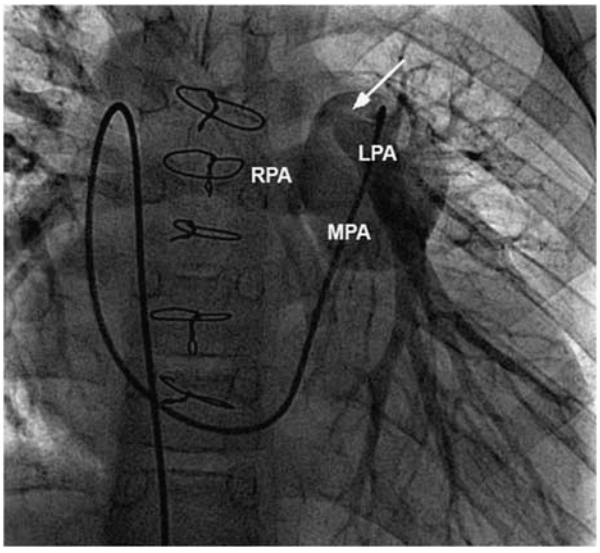

Figure 2.
Pulmonary angiogram in patient 4. The origin of the LPA from the MPA lies superior to the RPA. There is no crossing of the pulmonary artery branches. LPA stenosis is marked by an arrow. LPA = left pulmonary artery; MPA = main pulmonary artery; RPA = right pulmonary artery.

Cytogenetic and molecular diagnostics

Considering observed clinical findings, 22q11.2 deletion syndrome was suspected in all patients. In order to assess the presence of chromosomal rearrangement(s), classic cytogenetic, fluorescence in situ hybridisation, and multiplex ligation-dependent probe amplification analyses were performed. The cytogenetic analysis of peripheral blood lymphocytes revealed normal karyotypes (data not shown). Fluorescence in situ hybridisation analysis (Fig 3a) demonstrated 22q11.2 deletion in patients 1 and 2, whereas no deletion of this region was detected in patients 3 and 4.

To define more precisely the deletion region in patients 1 and 2, we performed multiplex ligation-dependent probe amplification analysis. Results revealed deletion spanning the 14-probe region, between proximal *CLTCL1* and distal *LZTR1* probe (Fig 3b). This region represents the most common deletion interval in patients with deletion 22q11.2.[22] The same analysis was performed in

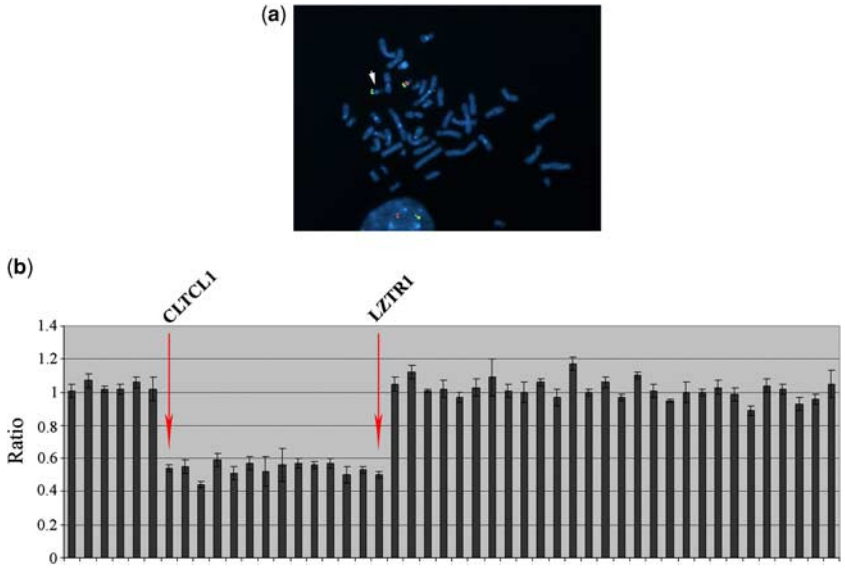

Figure 3.
*Fluorescence in situ hybridisation and multiplex ligation-dependent probe amplification analyses of the 22q11.2 region in patient 2. (**a**) Fluorescence in situ hybridisation with TUPLE1 probe (22q11.2, orange) and ARSA control probe (22q13.3, green) revealed 22q11.2 deletion. The arrow designates the chromosome 22 carrying the microdeletion (green signal only). (**b**) Diagram of the results obtained by multiplex ligation-dependent probe amplification analysis. Results revealed a 3-megabase deletion spanning the 14-probe region, between proximal* CLTCL1 *and distal* LZTR1 *probe (indicated with red arrows). X-axis represents various probes, whereas Y-axis represents probe–height ratio.*

patients 3 and 4 for further characterisation of the 22q11.2 region and assessment of five additional regions involved in phenotype resembling 22q11.2 deletion syndrome.[23–26] In both patients, multiplex ligation-dependent probe amplification assay did not disclose rearrangements in any of the analysed regions.

Discussion

Malposition of the branch pulmonary arteries is a rare congenital anomaly reported in limited number of studies.[1–16] The typical form of this disease is the entity called crossed pulmonary arteries, with anomalous origins and positions of pulmonary artery branches crossing each other. There are only two reports describing a "lesser form" of malposition, so called malposition of the branch pulmonary arteries without crossing, in which ostia are abnormally positioned on the posterior wall of the pulmonary artery, but the branches are not crossed.[2–3] Malposition of the branch pulmonary arteries is often associated with other cardiac and extracardiac anomalies, including features of 22q11.2 deletion syndrome.[1,6,14] According to available literature data, the most commonly associated cardiac defects are conotruncal anomalies – interrupted aortic arch, double outlet right ventricle, tetralogy of Fallot – and ventricular septal defects (Supplementary Table S1).

A single case of crossed pulmonary arteries with ventricular septal defect as the only additional cardiac anomaly has been reported worldwide so far.[9] To the best of our knowledge, our patients 1 and 2 are the second and third ever described patients with such association. Initially, both patients were diagnosed only with ventricular septal defect in a local paediatric hospital. The presence of crossed pulmonary arteries was suspected during examination in a tertiary healthcare centre, requiring confirmation with computed tomography scan. Ventricular defects were located in the perimembranous part of the septum and had no conotruncal characteristics in two patients presented in this study, as well as in the patient described by Siwik et al.[9] Notably, these three patients had 22q11.2 microdeletion. Taken together, we suggest careful assessment of pulmonary artery branch position in all patients with ventricular septal defect, both conotruncal and nonconotruncal, as well as testing for 22q11.2 microdeletion in all patients with disclosed malposition.

Patient 3 had an association of aortopulmonary window and crossed pulmonary arteries, which was not previously described in the literature. The presentation was typical for aortopulmonary window, with cardiac decompensation and without any haemodynamic repercussion of crossed pulmonary arteries. Growth and development were normal, and no extracardiac malformations were detected. The presence of right aortic arch in this patient additionally prompted us to perform molecular testing for 22q11.2 microdeletion; however, no deletion has been found.

Among previously described patients with malposition of the branch pulmonary arteries, only seven had lesser form, so called malposition of the branch pulmonary arteries without crossing (Supplementary Table S2). Of these, five had anomalies of the aortic arch – two interrupted aortic arch – in conjunction with other anomalies. In the present study, we describe one patient with malposition of the branch pulmonary arteries without crossing, that is, patient 4. The leading problem for this patient was type B interrupted aortic arch, as a part of unusual heterotaxy syndrome. He underwent numerous echocardiographies, cardiac catheterisations, and two cardiac surgeries, and none of them recognised this rare variant of malposition of the branch pulmonary arteries without crossing. In our opinion, this pulmonary artery anomaly could not be recognised in patient 4 without use of magnetic resonance angiography. We presume that a substantial number of patients remain unrecognised because of limitations of standard diagnostic procedures. Thus, this condition may be more common than previously suspected. Accordingly, by introducing new powerful imaging techniques, diagnostics of this anomaly could become more feasible.

The developmental mechanism of malposition of the branch pulmonary arteries is not fully recognised. However, Jue et al[1] proposed that this form of malposition could occur because of counterclockwise rotation of the normally formed main and branch pulmonary arteries. The recognition of two variants of malposition of the branch pulmonary arteries, classical and "lesser form", indicates probable spectrum of rotational anomalies, creating different positions of origins and branches of pulmonary artery. In both variants, it seems that there are no haemodynamic consequences,[3,13] which is in concordance with results of investigation of patients 1, 2, and 3 described in this study. Thus, surgical interventions in these patients were focused on the closure of ventricular septal defects in patients 1 and 2 and aortopulmonary window in patient 3. In patient 4, we might only speculate that the presence of left pulmonary artery stenosis, which has been surgically corrected with a pulmonary homograft patch, was related to malposition of the branch pulmonary arteries. However, it seems that malposition of the branch pulmonary arteries could cause haemodynamic repercussions in some patients. Recto et al[3] described an extremely short pulmonary artery trunk in two patients with malposition of the branch pulmonary

arteries without crossing ("lesser form"), resulting in stenosis of the right pulmonary artery and significant clinical complications after procedure of the pulmonary artery banding. In addition, Becker et al[2] stated that although the condition of cross pulmonary arteries is of no haemodynamic significance knowledge of its occurrence may add in the interpretation of certain peculiarities in the angiograms.

The multiplex ligation-dependent probe amplification testing performed in this study represents the first molecular characterisation of 22q11.2 region among patients with malposition of the branch pulmonary arteries. So far, only the presence of 22q11.2 microdeletions was demonstrated, whereas the size and extension of the deletions have not been analysed. Our results demonstrate a typical 3-megabase deletion of 22q11.2 region spanning between *CLTCL1* and *LZTR1* loci in patients 1 and 2.

In conclusion, we presume that malposition of the branch pulmonary arteries might be more common based on the fact that no more than 35 cases have been reported in the literature since Jue et al[1] provided the first description of the malformation in 1966 and finding of four cases of these anomalies within 1 year in our institution because of employment of modern technologies. We recommend that morphology of pulmonary artery ostia and branches should be carefully studied, especially in patients with ventricular septal defects, conotruncal and aortic arch anomalies. The modern imaging technologies, such as cardiac magnetic resonance angiography and computed tomography, provide precise diagnosis of this condition and might help in proper planning of cardiac repair. We stress the need for multidisciplinary assessment of patients with malposition of the branch pulmonary arteries, which should include comprehensive clinical evaluation and testing for 22q11.2 microdeletion.

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Supplementary materials

For Supplementary material referred to in this article, please visit http://dx.doi.org/doi:10.1017/S1047951112000571

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