Truncus Arteriosus Communis Associated With Chromosome 22q11 Deletion

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Objectives. The purpose of this study was to clarify characteristics of truncus arteriosus communis associated with chromosome 22q11 deletion (del 22q11).

Background. DiGeorge syndrome and conotruncal anomaly face syndrome are associated with del 22q11 (hemizygosity). In 30% of cases, truncus arteriosus communis is associated with the deletion.

Methods. Fifteen consecutive patients with truncus arteriosus communis were checked for 22q11 with fluorescent in situ hybridization using an N25 probe (Oncor). Cardiovascular anomalies were studied with cardiac catheterization, cineangiography and echocardiography.

Results. Five patients had del 22q11. Two had a rare type of truncus arteriosus: type A3 of Van Praagh and Van Praagh with major aortopulmonary collateral arteries and pulmonary ostial stenosis. The other three had type A1 truncus arteriosus and pulmonary artery stenosis. One of them had major aortopulmonary collateral arteries. Ten patients with truncus arteriosus had no del 22q11. The types of truncus arteriosus in these 10 patients were type A1 in 7, type A2 in 2 and type A3 with closed ductus in 1. None of nine patients with type 1 or type 2 truncus arteriosus had pulmonary stenosis.

Conclusions. In truncus arteriosus communis, the rare type A3 with major aortopulmonary collateral arteries and pulmonary ostial stenosis and type A1 with pulmonary artery stenosis are associated with del 22q11.

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Truncus arteriosus communis is frequently associated with DiGeorge syndrome (1) and deletion of chromosome 22q11 (del 22q11) (2,3). Although not definitely proved, several lines of evidence suggest abnormal developmental function of neural crest tissue as a possible cause of anomalies associated with del 22q11 (4,5). Experimental ablation of the neural crest of chick embryos has suggested insufficient function of the neural crest as a possible cause of truncus arteriosus communis (6,7).

Recent studies of congenital heart diseases associated with del 22q11 (8) have confirmed the association of del 22q11 and tetralogy of Fallot with absent pulmonary valve. We (9,10) have found right aortic arch, aberrant subclavian artery, isolation of subclavian artery or a pulmonary artery, absent ductus arteriosus and major aortopulmonary collateral arteries associated with del 22q11 in tetralogy of Fallot. Characteristics of truncus arteriosus communis associated with del 22q11 are analyzed in this report.

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Methods

During the period 1993 to 1995, 15 consecutive Japanese patients (5 male, 10 female) with truncus arteriosus communis were studied in this institute for del 22q11. Five patients, aged 1 or 2 months, were studied before surgical intervention; the other 10 were aged 1 to 20 years, and 8 of these were evaluated after a Rastelli-type operation. Echocardiography and angiography were performed in all 15. Truncus arteriosus was diagnosed and classified according to the criteria of Van Praagh and Van Praagh (11). Briefly, in type A1, a short pulmonary trunk originates from the truncus arteriosus. In type A2, the right and left pulmonary arteries originate separately from the truncus. In type A3, one pulmonary artery originates from the truncus, and a ductus arteriosus or major aortopulmonary collateral arteries supply blood to the other lung. In type A4, the aortic arch is interrupted, and the pulmonary trunk continues to the ductus arteriosus and the descending aorta. Of the 15 patients, 10 had type A1 truncus arteriosus, 2 had type A2 and 3 had type A3; no patient had type A4. The clinical profiles of the 15 patients are listed in Table 1. Del 22q11 of peripheral lymphocytes was studied with fluorescent in situ hybridization (FISH) using deoxyribonucleic acid (DNA) probe Oncor N25 with written informed consent of the patient’s parent or parents.

Conotruncal anomaly facies (12) has been recognized for >20 years in this department. It includes small eyelids, hypertelorism, flat nose, small mouth, small chin and deformed ears.
Statistics. For statistical analysis, frequencies of each cardiovascular anomaly associated with del 22q11 and those associated without this deletion were analyzed with the Fisher exact test.

Results

Del 22q11 was identified in five patients (Table 1, Cases 1 to 5). Conotruncal anomaly facies was recognized in these five patients with deletion and in no patient without deletion. Truncus arteriosus communis in Cases 1 and 2 was of the rare A3 type. All five patients had pulmonary stenosis.

Case 1. This 4-year old boy had mild cyanosis and a cardiac murmur, delayed physical and mental development, conotruncal anomaly face (Fig. 1) and nasal voice. He was admitted three times, at ages 0.1, 2 and 4 years, for cardiac study including angiocardiography. Peripheral pulses were well palpable. A continuous murmur, grade 3/6, was widely audible over the anterior and posterior areas of the chest. Echocardiography revealed absent infundibular septum and a large subarterial ventricular septal defect, mild truncal valve regurgitation and solitary arterial trunk overriding the ventricular septum. Angiocardiography revealed truncus arteriosus communis type A3. The right pulmonary artery originated from the left posterior aspect of the truncus close to the sinus of Valsalva; it was small and stenotic at the junction with the truncus (Fig. 2A). Three major aortopulmonary collateral arteries arose from the descending aorta and connected to the left lung (Fig. 2B).

Case 2. This 2-week old girl had mild cyanosis, a heart murmur and feeding difficulty. Conotruncal anomaly face, hypocalcemia and mild cyanosis were noticed. Peripheral pulses were bounding. A continuous murmur, grade 2/6, was audible in the right and left sides of the chest, anteriorly and posteriorly. Echocardiography revealed subarterial ventricular septal defect, solitary arterial trunk overriding the ventricular septum, small left ventricle and parachute mitral valve. Cineangiography revealed truncus arteriosus communis type A3, right aortic arch and aberrant left subclavian artery (Fig. 2B).

Table 1. Profiles of 15 Patients With Truncus Arteriosus Communis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)/Gender</th>
<th>del 22q11</th>
<th>TA Type</th>
<th>Additional Anomaly</th>
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<tr>
<td>1</td>
<td>4/M</td>
<td>Yes</td>
<td>A3</td>
<td>MAPCA, PS, CAF, MR</td>
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<tr>
<td>2</td>
<td>0.05/F</td>
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<td>RAA, MAPCA, CCWR, PS, CAF, MR</td>
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<tr>
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<td>A1</td>
<td>PS, PL SVC, hypocalcemia, DGS, CAF, MR</td>
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<td>RAA, LDA (closed), LPA isolation</td>
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<td>4/F</td>
<td>No</td>
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A1, A2, A3 = classification by Van Praagh and Van Praagh (11). ALSA = aberrant left subclavian artery; ASD = atrial septal defect; CAF = conotruncal anomaly facies; CCWR = counterclockwise rotation; del 22q11 = deletion of chromosome 22q11; DGS = DiGeorge syndrome; F = female; LDA = left ductus arteriosus; LPA = left pulmonary artery; LV = left ventricle; M = male; MAPCA = major aortopulmonary collateral artery; MR = mental retardation; MV = mitral valve; PDA = patent ductus arteriosus; PL SVC = persistent left superior vena cava; PS = pulmonary stenosis; RAA = right aortic arch; TA = truncus arteriosus communis.
The left pulmonary artery originated immediately above the sinus of Valsalva from the left posterior wall of the truncus arteriosus (A). Three major aortopulmonary collateral arteries originate from the descending aorta (B). AoA = aortic arch; DAo = descending aorta; LCA = left coronary artery; LCCA = left common carotid artery; LSA = left subclavian artery; MAPCA = major aortopulmonary collateral artery; RPA = right pulmonary artery; TA = truncus arteriosus.

Case 3. This 6-year old boy had mild cyanosis, mental retardation and conotruncal anomaly face. Peripheral pulses were bounding. Auscultation of the chest revealed a continuous murmur, grade 3/6, at the right and left upper sternal border. Cardiac catheterization and angiography at age 6 years revealed a large ventricular septal defect, counterclockwise rotation around the cardiac long axis, solitary arterial trunk overriding the ventricular septum, and a right aortic arch (Fig. 4A). The pulmonary trunk was narrow and originated from the anterior wall of the truncus arteriosus and bifurcated to the right and left pulmonary arteries (Fig. 4B). The left pulmonary artery originated on the right and coursed leftward; the right pulmonary artery originated on the left and coursed rightward (Fig. 4B). The left pulmonary artery distributed to all segments of the left lung. The right pulmonary artery distributed only to segments 7 and 8. The mean pressure in the pulmonary trunk and the left pulmonary artery was 25 mm Hg; the aortic mean pressure was 62 mm Hg. There were three additional collateral arteries to the right lung: one from the aortic arch and two from the descending aorta (Fig. 4C). This type of truncus arteriosus communis is not described in the classification of Van Praagh and Van Praagh (11), but it might be classified as a subtype of A1.

Case 4. This 4-year old girl had truncus arteriosus communis type A1, hypocalcemia, thymic aplasia (DiGeorge syndrome), persistent left superior vena cava, conotruncal anomaly face and mental retardation. The pulmonary trunk originated from the posterior wall of the truncus arteriosus and was mildly stenotic. At age 3 weeks, the systolic pressure was 62 mm Hg in the truncus arteriosus and 32 mm Hg in the pulmonary trunk. A Rastelli-type operation was successfully performed at age 1 month.

Case 5. This 15-year old male youth had truncus arteriosus communis type A1, short pulmonary trunk and moderate stenosis (diameter 4 mm) at the origin of the right pulmonary artery.
artery causing a systolic pressure gradient of 80 mm Hg. A Rastelli repair was performed at age 2 months and a stenotic conduit was replaced at age 15 years. He has conotruncal anomaly face and mental retardation.

**Case 6.** This 2-month old girl had truncus arteriosus communis type A3, right pulmonary artery originating from the left posterior wall of the truncus, right aortic arch, closed left ductus arteriosus giving rise to a left innominate artery, isolated left pulmonary artery, minor collateral vessels to the left lung, and cleft palate. FISH study showed no del 22q11. Hypoplastic left pulmonary artery was identified by wedge angiography from the left pulmonary vein. Left pulmonary artery angioplasty with subclavian flap and left subclavian to main pulmonary artery anastomosis were performed at age 2 months.

**Statistical analysis.** The Fisher exact test revealed significant association of major aortopulmonary collateral arteries and pulmonary artery stenosis with del 22q11. Major aortopulmonary collateral arteries were found in 60% (3 of 5) of patients with del 22q11 but in 0% (0 of 10) of patients with no deletion (p = 0.022). Pulmonary artery stenosis was present in all patients with del 22q11 (5 of 5) but in no patient (0 of 10) without del 22q11 (p = 0.0003).

**Discussion**

**Truncus arteriosus type A3 and del 22q11.** Striking features of truncus arteriosus communis associated with del 22q11 were seen in two patients with type A3: absent ductus arteriosus, multiple major aortopulmonary collateral arteries and pulmonary ostial stenosis. Truncus arteriosus communis type A3 is rare. Van Praagh and Van Praagh (11) initially included only one case of type A3 with a ductus arteriosus in 57 autopsy cases. Later Calder et al. (13) found 8 cases of type A3 among 100 cases of truncus arteriosus communis. In these eight cases, an open or closed ductus arteriosus was present in four, and major aortopulmonary collateral arteries were present in the remaining four. The present study shows that truncus arteriosus type A3 with major aortopulmonary collateral arteries and pulmonary ostial stenosis is associated with del 22q11.

**Major collateral vessels and del 22q11.** This is the first report on the association of del 22q11 with truncus arteriosus communis and major aortopulmonary collateral arteries. Major aortopulmonary collateral arteries are another feature of tetralogy of Fallot associated with del 22q11. These collateral vessels may occur in tetralogy of Fallot without pulmonary atresia in patients with del 22q11, but not in patients without del 22q11 (9). In tetralogy of Fallot with pulmonary atresia, the incidence of major aortopulmonary collateral arteries is 91% in patients with del 22q11 but only 50% in patients without del 22q11 (10).

**Absence of ductus arteriosus and del 22q11.** Absence of ductus arteriosus is a feature of tetralogy of Fallot associated with del 22q11. Johnson et al. (8) reported a very high incidence (six [75%] of eight patients) of del 22q11 in patients with tetralogy of Fallot and absent pulmonary valve. This complex is usually associated with absent ductus arteriosus (14). Experimental evidence (15) supports the theory that the absent ductus is related to the absent pulmonary valve. Absence of the ductus is significantly associated with del 22q11 in tetralogy of Fallot with pulmonary atresia; the ductus is absent in 83% of patients with and in 46% of patients without del 22q11 (10).

**Pulmonary artery stenosis and del 22q11.** Pulmonary artery stenosis was present in all five patients with truncus arteriosus and del 22q11. One patient without del 22q11 had type A3 with closed ductus and isolated pulmonary artery, and pulmonary stenosis was not present in any of the other nine patients without the deletion. The etiology of pulmonary artery stenosis in these patients is not clear.

**Neural crest and anomalies of central pulmonary arteries.** The gene or genes responsible for these cardiovascular anomalies in del 22q11 are not known. However, insufficient function of neural crest cells in early embryonic development is generally assumed to be the cause of the anomalies (4–6). In the early developing embryo, neural crest cells distribute to the sixth branchial arches including the future pulmonary trunk and the junction of the right and left pulmonary arteries (6). Studies on tetralogy of Fallot with del 22q11 have suggested more widespread disturbance of the neural crest cells in the
early development in patients with than in patients without the deletion (9,10).

Potential bias of this study. These 15 patients were observed in a referral cardiac center that had a significant bias toward unusual variants of cardiac anatomy. Many of these patients were well past infancy, and there might be a bias toward survival of patients with del 22q11 because all five patients with the deletion had pulmonary artery stenosis and it is possible that patients with del 22q11 are protected from heart failure and pulmonary vascular disease. Therefore, incidence data cannot be determined from this study, and larger random population studies are needed.

Clinical implications. About 30% of patients with truncus arteriosus communis have associated DiGeorge syndrome and del 22q11 (1). DiGeorge syndrome and del 22q11 are always associated with abnormal facies (9,10,16). Association of del 22q11 in truncus arteriosus is suggested by the presence of hypocalcemia, peculiar face, cleft palate and thymic hypoplasia, and it is confirmed by FISH study using Oncor N25 (D22S75) probe. The present study suggests association of del 22q11 in patients with truncus arteriosus communis who have pulmonary artery stenosis and major aortopulmonary collateral arteries.

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References