Persistent Fifth Aortic Arch Associated with 22q11.2 Deletion Syndrome

Meng-Luen Lee,* Hsiao-Neng Chen,1 Ming Chen,2,3 Lon-Yen Tsao,1 Bao-Tyan Wang,2 Mei-Hui Lee,2 Ing-Sh Chiu4

Background: Chromosome 22q11.2 deletion is frequently associated with conotruncal malformations and aortic arch anomalies. This study investigated the association of chromosome 22q11.2 deletion with clinical manifestations in four pediatric patients with persistent fifth aortic arch.

Methods: Four patients with persistent fifth aortic arch treated between July 1997 and June 2004 were included in this retrospective study. There were two girls and two boys, aged 2 days to 11.3 years, with persistent fifth aortic arch and cardiac conotruncal malformations. Chart recordings, plain chest films, two-dimensional and Doppler echocardiograms, cardiac catheterization with angiograms, surgical findings, and cytogenetic study were analyzed.

Results: Clinically, all four patients had the cardinal phenotypic features of 22q11.2 deletion syndrome, including cardiovascular malformations (conotruncal malformations and aortic arch anomalies), abnormal facies, thymic hypoplasia, canopy anomaly of the palate (high-arched palate, rather than cleft palate), and hypocalcemia (or hypoparathyroidism). All four patients were confirmed to have chromosome 22q11.2 deletion.

Conclusion: Congenital conotruncal malformations, including tetralogy of Fallot with pulmonary atresia or stenosis, and aortic arch anomalies including a persistent fifth aortic arch or a right aortic arch, should lead to suspicion of chromosome 22q11.2 deletion when manifested together with any one of the other four cardinal phenotypic features. [J Formos Med Assoc 2006;105(4):284–289]

Key Words: aortic arch syndrome, conotruncal cardiac malformation, human, UFDIL protein

Chromosome 22q11.2 deletion is frequently associated with cardiac conotruncal malformations and aortic arch anomalies.1,2 However, among these cardiovascular malformations, there are limited data on persistent fifth aortic arch as a cardiovascular phenotype in patients with CATCH 22 (cardiovascular malformations, abnormal facies, thymic hypoplasia, canopy anomaly of the palate in terms of high-arched palate or cleft palate, hypocalcemia or hypoparathyroidism, and chromosome 22q11 deletion). This study investigated the clinical features of CATCH 22 in four pediatric patients with persistent fifth aortic arch.

Methods

Four patients with aortic arch anomaly of persistent fifth aortic arch and conotruncal cardiac
malformations, treated between July 1997 and June 2004, were included in this retrospective study. Data collected from medical records included physical manifestations, plain chest films, two-dimensional echocardiograms with color Doppler, cardiac catheterization with cineangiograms, surgical findings, and chromosome analysis with fluorescence in situ hybridization (FISH) study. FISH analysis was performed using a TUPLE 1 gene (22q11.2) specific probe (SpectrumOrange™ Probe; Vysis Inc, Des Plaines, IL, USA) in order to identify any deletion in this region. The ARSA probe for the arylsulfatase A gene (SpectrumGreen™; Vysis Inc) was also used as an internal control.

Illustrative case
A 2-day-old male neonate (Case 4) was transferred from a local obstetric clinic to the intensive care unit under the impression of cyanotic congenital heart disease due to clinical manifestations of appreciable acrocyanosis with oxygen saturation < 60% on the peripheral pulse oximeter, tachypnea, subcostal retraction, tachycardia, and a faint heart murmur. He was born uneventfully at 41 weeks of gestation by spontaneous delivery, with a birth weight of 2.25 kg (< 10th percentile), which is considered to be small for gestational age.

On the first day in the intensive care unit, his respiratory rate was 62 breaths/min, heart rate was 160 bpm, and blood pressure was within normal limits. Oxygen saturation was 81% on the peripheral pulse oximeter under inhalation of 30% oxygen. Physical examination showed a small baby for gestational age with hypertelorism, tented mouth, low-set ears, high-arched palate, and bilateral clubfeet. On chest auscultation, there was a single second heart sound over the left upper sternal border and a faint systolic murmur over the left second intercostal space. Hemoglobin was 13 g/dL. Profiles of coagulation study and intact parathyroid hormone were within normal limits on the first day of hospitalization. Ionized calcium was 0.63 mmol/L (normal range, 0.9–1.25 mmol/L). Plain chest film showed decreased pulmonary vascular markings. Scanty pulmonary blood flow from the patent ductus arteriosus, which was documented by Doppler echocardiography on the background of tetralogy of Fallot with pulmonary atresia, prompted intravenous infusion of prostaglandin E, in order to increase pulmonary arterial blood flow, which was reduced due to the ductal-dependent obstructive right heart lesion. The oxygen saturation exceeded 90% after intravenous infusion of prostaglandin E, at a dosage of 30 ng/kg/min.

Emergency cardiac catheterization and angiography identified non-confluent pulmonary atresia with severe stenosis of both branch pulmonary arteries (3.0 mm in diameter in each), and limited ductal flow of the patent ductus arteriosus (3.0 mm in diameter) from a relatively small persistent fifth aortic arch (3.2 mm in diameter). The persistent fifth aortic arch had a peculiar course, with takeoff very early as the first branch from the ascending aorta, connecting proximally to the non-confluent pulmonary artery via the patent ductus arteriosus, and continuing distally as the left common carotid artery (Figure A). The left subclavian artery arose aberrantly as the last branch from a right aortic arch (Figure B). Creatine kinase (3409 U/L) and its myocardial fraction (97 U/L) were highly elevated. The patient died while pending surgical construction of a Blalock-Taussig shunt. The abnormal pattern of the aortic arch was further sketched by hand to illustrate the branching anomalies simultaneously (Figure C).

Cytogenetic analysis and FISH study (Figure D) of the proband’s blood confirmed chromosome 22q11.2 deletion, with a karyotype of 46,XY,del(22)(q11.2 q11.2)(TUPLE-1). The embryogenesis of the aortic arch anomalies in this case can be summarized as follows: (1) persistence of the right-side fourth dorsal aortic artery as a right aortic arch; (2) persistence of the retroesophageal aortic artery in a right aortic arch as an aberrant left subclavian artery from a right aortic arch; (3) persistence of the left-side fifth dorsal aortic artery as a persistent left fifth aortic arch; (4) persistence of the left-side sixth distal aortic artery as a patent ductus arteriosus; (5) persistence of the left third dorsal aortic artery as a left common carotid artery;
and (6) regression of the left fourth dorsal aortic artery (absence of a left aortic arch).

Results

The clinical features of the four patients with persistent fifth aortic arch and chromosome 22q11 deletion are summarized in the Table. The cardiovascular phenotypes included the following: tetralogy of Fallot in four; right aortic arch in four; persistent fifth aortic arch in four; pulmonary atresia in two; pulmonary stenosis in two; aberrant left subclavian artery in two; non-confluent pulmonary artery in two; abnormal origin of the left common carotid artery from the persistent fifth aortic arch in one; isolated infundibuloarterial inversion in one; vascular ring composed of a right aortic

Figure. Illustration of abnormalities in Case 4 with persistent fifth aortic arch. (A) The ascending aortography shows early and immediate opacification of a persistent fifth aortic arch that takes off very early as the first branch from the ascending aorta of a right aortic arch, connects proximally as the non-confluent pulmonary artery via the patent ductus arteriosus, and continues distally as the left common carotid artery. (B) The left subclavian artery is visualized only after the descending aorta, i.e. showing aberrant takeoff as the last branch of a right aortic arch in the ascending aortography. (C) The branching pattern of the aortic arch is summarized: 1 = left common carotid artery; 2 = right common carotid artery; 3 = right subclavian artery; 4 = aberrant left subclavian artery; 5 = persistent fifth aortic arch; 6 = patent ductus arteriosus. (D) Fluorescence in situ hybridization (FISH) in the proband, using a probe from the DiGeorge syndrome deletion region, shows a karyotype of 46,XY.del(22)(q11.2 q11.2)(TUPLE-1). FISH analysis was performed using the TUPLE 1 gene (22q11.2) specific probe (SpectrumOrange™) in order to identify any deletion in this region. The ARSA probe for the arylsulfatase A gene (SpectrumGreen™) was also used as an internal control. A total of 10 metaphase cells were scored and all cells had only a single green signal for the TUPLE 1 gene, i.e. loss of the red signal, indicating a deletion at 22q11.2.
Table. Clinical profiles of four patients with persistent fifth aortic arch and 22q11.2 deletion (CATCH 22 or 22q11.2 deletion syndrome)

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11 mo</td>
<td>5 d</td>
<td>11 yr 4 mo</td>
<td>2 d</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>CATCH 22 acronym</td>
<td>PFAA, TOF with PS, IIAI, RAA, and a vascular ring made of a RAA, an aberrant LSCA, and a LLA</td>
<td>PFAA, TOF with PA, RAA, PFAA with distal continuation as LSCA, and a MAPCA from LSCA to non-confluent pulmonary artery</td>
<td>PFAA, TOF with PS, RAA, PFAA with distal continuation as LCCA</td>
<td>PFAA, TOF with PA, RAA, an aberrant LSCA, and PFAA with distal continuation as LCCA and proximal connection via PDA to non-confluent pulmonary artery</td>
</tr>
<tr>
<td>Cardiac defects or malformations</td>
<td>Hypertelorism, narrow nasal alae, long philtrum, prominent nasal bridge</td>
<td>Hypertelorism, small tented mouth</td>
<td>Hypertelorism, narrow nasal alae, long philtrum, prominent nasal bridge</td>
<td>Hypertelorism, small tented mouth, low-set ears</td>
</tr>
<tr>
<td>Abnormal facies</td>
<td>Narrow cardiac waist</td>
<td>Narrow cardiac waist</td>
<td>Narrow cardiac waist</td>
<td>Narrow cardiac waist</td>
</tr>
<tr>
<td>Thymic hypoplasia</td>
<td>High-arched palate without a cleft</td>
<td>High-arched palate without a cleft</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Canopy or ceiling anomaly of the palate*</td>
<td>De novo</td>
<td>Maternally inherited unbalanced (2;22) translocation</td>
<td>De novo</td>
<td>De novo</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>22q11 deletion</td>
<td>Yes</td>
<td>Maternally inherited unbalanced (2;22) translocation</td>
<td>VPI with nasal voice, speech/language delay, hearing impairment, mental retardation</td>
<td>Small for gestational age, clubfeet, died</td>
</tr>
<tr>
<td>Annotations</td>
<td>Congenital chylothorax, stridor, bacteremia, VPI with nasal voice, speech/language delay, hearing impairment, mental retardation</td>
<td>Cat-like crying, hoarseness, sudden cardiac death</td>
<td>VPI with nasal voice, speech/language delay, hearing impairment, mental retardation</td>
<td>Small for gestational age, clubfeet, died</td>
</tr>
</tbody>
</table>

*Canopy or ceiling anomaly of the palate may be a more appropriate description than cleft palate to represent the features comprising the acronym CATCH 22. IIAI = isolated infundibuloarterial inversion; LCCA = left common carotid artery; LLA = left ligamentum arteriosum; LSCA = left subclavian artery; MAPCA = major aortopulmonary collateral artery; PA = pulmonary atresia; PDA = patent ductus arteriosus; PFAA = persistent fifth aortic arch; PS = pulmonary stenosis; RAA = right aortic arch; TOF = tetralogy of Fallot; VPI = velopharyngeal insufficiency.

The abnormal facies included hypertelorism in four patients, prominent nasal bridge with narrow nasal alae in two, short philtrum in two, small and tented mouth in two, and low-set ears in one. All four patients had thymic hypoplasia silhouetted as a narrow cardiac waist on plain chest film. None of the four patients had cleft palate. Each patient, however, had a high-arched palate forming a canopy or ceiling over the oral cavity. All four patients had hypocalcemia, and only one of them had seizure attack. *De novo* chromosome 22q11 deletions were found in three patients and partial monosomy 22q due to an unbalanced (2;22) translocation inherited from the mother, with a karyotype of 45,XX,der(2)(2;22)(q37;q12.1)mat., was found in one patient.

Congenital chylothorax and stridor, which was related to a vascular ring, was noted in one patient. Bacteremia developed in one patient, cat-like crying with hoarseness in one, and small for gestational age with clubfeet in one. Two neonates died while waiting for surgical construction of Blalock-
Taussig shunts. Two patients survived total correction of their cardiac malformations. Both of these patients had velopharyngeal insufficiency with nasal voice or hypernasality, speech and language delay, hearing impairment, and mental retardation during 5 years’ follow-up.

Discussion

The 22q11.2 deletion syndrome is frequently associated with conotruncal malformation and aortic arch anomaly.1–13 However, there are few reports of the clinical linkage of persistent fifth aortic arch with chromosome 22q11.2 deletion.11,12 The 22q11.2 deletion syndrome has been reported to encompass the three major syndromes of DiGeorge syndrome (DGS), velocardiofacial syndrome (VCFS) and conotruncal anomaly face syndrome (CTAFS),9,13 which affect the development of the third and fourth branchial pouches and manifest variable phenotypes due to migration disorder of neural crest cells.

Some complex cardiovascular defects with 22q11.2 deletion have been considered to be isolated from extracardiac phenotypic expression and assumed to represent a different subgroup, in addition to their syndromic combination with the extracardiac features identified in patients with tetralogy of Fallot.3 This does not, however, account for the high variability in the phenotypes of the above three syndromes,3,14 and the subtle expression of extracardiac features can be overlooked or unrecognized without scrupulous identification.14 The variable phenotypic expression may be due to migration disorder of neural crest cells in different degrees and amounts.3,4,15,16 Identification of the six characteristic phenotypes of CATCH 22 in cases of DGS, VCFS and CTAFS is not difficult, but recognition of less characteristic phenotypes and of the seemingly isolated complex cardiovascular malformations which manifest in CATCH 22 may be delayed. Cardiac defects (conotruncal malformations and aortic arch anomalies; 100%) and abnormal facies (or facial dysmorphism; 92%) reminiscent of DGS, VCFS and CTAFS, which likely manifest early in life, may be considered to be the cardinal and consistent features of CATCH 22.13,14 Hypocalcemia, thymic hypoplasia and cleft palate were observed in 62%, 41% and 0%, respectively, in one report of 13 patients with CATCH 22.13 All four (100%) of our patients had cardiac defects, abnormal facies, thymic hypoplasia and hypocalcemia. None of our four patients had cleft palate, while each had a high-arched palate. Cleft palate was often observed in VCFS,1,14 while high-arched palate is the characteristic palatal anomaly in DGS16 and CTAFS.3 With the collaboration of pediatric cardiologists, neonatologists, and dysmorphologists, 22q11.2 deletion syndrome can be differentially diagnosed easily by recognition of the characteristic cardiac malformations and facial dysmorphism. However, the four cases in this study suggest that canopy (or ceiling) anomaly of the palate should be substituted for cleft palate as one of the terms forming the CATCH 22 acronym, since cleft palate is not a pertinent finding.

Kirby et al reported that many cardiovascular malformations, including inflow, outflow, and aortic arch artery anomalies, developed after removal of neural crest cells in chicks.1,2 Patterning anomaly of the aortic arch has an established clinical and etiologic basis.1–8,10–13 We documented persistent fifth aortic arch associated with 22q11.2 deletion in four patients, which was due to de novo deletion in three of four patients, and to partial monosomy caused by an unbalanced (2;22) translocation inherited from the mother in one patient.12 Maternal transmission of unbalanced translocation of chromosome 22, in addition to de novo deletion,11 may play a role in the inherited 22q11.2 deletion syndrome.12 In general, besides maternal transmission of unbalanced translocation, other inheritance patterns should be considered, such as parental origin of deletion, since parental inherited 22q11.2 deletion was reported to be responsible for 6–10% of cases of 22q11.2 deletion.17 Parental karyotyping as well as FISH are, thus, recommended.

Persistent fifth aortic arch is an often ignored and underestimated disease, and may be roughly
Persistent fifth aortic arch in 22q11.2 deletion included in the broad spectrum of cardiovascular defects associated with 22q11.2 deletion syndrome.\textsuperscript{18,19} Recent studies have searched for possible candidate genes of DGS. The \textit{TBX1} gene, harbored in a 3 Mb critical region within 22q11.2, was thought to be a strong candidate because of the five cardinal phenotypes of 22q11.2 deletion syndrome.\textsuperscript{17,20} Aortic arch defects were also noted in haploinsufficiency for \textit{Tbx1} in a mouse model of DGS.\textsuperscript{21} Screening of the mutations in the \textit{TBX1} gene awaits further study. A cascade of molecular biology may occur initially by gene deletion, resulting in defective or abnormal migration of the neural crest cells to the target areas, and subsequent development of cardiovascular malformations.\textsuperscript{11,12} Thus, persistent fifth aortic arch may represent cardiovascular phenotypes related to patterning anomaly of the aortic arch.

In conclusion, it is important to perform FISH study for 22q11.2 deletion in patients with the cardiac phenotype of persistent fifth aortic arch, especially when any one of the extracardiac stigmata of 22q11.2 deletion syndrome is identified, in that persistent fifth aortic arch could be a harbinger of 22q11.2 deletion.

References