Congenital Cardiovascular Disease and Anomalies of the Third and Fourth Pharyngeal Pouch

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SUMMARY

Patients with the third and fourth pharyngeal pouch syndrome, thymic and parathyroid aplasia or hypoplasia, have a very high incidence of aortic arch anomalies and congenital heart disease. These patients present with a unique syndrome characterized by profound hypocalcemia, defective thymic-mediated cellular immune function, and cardiovascular anomalies. The cardiac abnormalities most frequently are conotruncal malformations of the tetralogy of Fallot or truncus arteriosus types and are often the cause of death. Patients with profound neonatal hypocalcemia should be screened for evidence of normal thymic function and congenital heart disease.

Additional Indexing Words:
Aortic arch anomalies  Congenital heart disease  Conotruncal anomalies
DiGeorge syndrome  Parathyroid glands  Pharyngeal pouch syndrome
Thymus

Anomalies of the aortic arch and congenital cardiac disease have been noted in patients with defective development of the third and fourth pharyngeal pouches. Complete failure of the development of the derivatives of these pouches results in combined thymic and parathyroid deficiency as the thymus derives its origin entirely from the third pharyngeal pouch and the parathyroid glands from the endoderm of the third and fourth pouches. This developmental failure, first noted in the English literature by Lobdell, in 1959, produces a unique clinical syndrome characterized by profound neonatal hypocalcemia, defective cellular immunity (thymic-dependent), and frequently a typical facial appearance. The thymic-dependent immune deficit was first suggested in these patients by DiGeorge in 1965, and the designation DiGeorge syndrome is now commonly used in describing patients with congenital aplasia or hypoplasia of both thymus and parathyroid glands.

A wide spectrum of anomalies can result from either complete or partial failure of development of the third and fourth pharyngeal pouches. Complete aplasia of both thymus and the parathyroid glands is perhaps the most severe form of the syndrome, but patients with partial defects of the thymus and parathyroid glands (incomplete third and fourth pharyngeal pouch syndrome) have also been described. Cases of isolated thymic agenesis or hypoplasia (suggesting isolated third pharyngeal pouch maldevelopment) have also been reported.

Although congenital cardiovascular malformations have been briefly mentioned in reports of isolated cases of the third and
fourth pharyngeal pouches or DiGeorge syndrome, a systematic study of this association has not been undertaken. The purpose of this communication is to document the association of congenital cardiovascular malformations in the 10 patients with the DiGeorge syndrome studied at The Children's Hospital Medical Center (C.H.M.C.) over the past decade and to review the literature to ascertain the nature of the cardiovascular anomalies and overall incidence of this association.

Clinical and Laboratory Diagnosis of the Third and Fourth Pharyngeal Pouch (DiGeorge) Syndrome

It is not within the scope of this paper to describe in detail the differentiation of thymic-dependent cellular immunity from humoral immunity for several comprehensive reviews are available. Suffice it to say, however, patients with defective cellular immunity have normal polymorphonuclear leukocyte function, immunoglobulins, and form antibodies, but have defects consisting of delayed hypersensitivity, allograft rejection, and in vitro lymphocyte response to phytohemagglutinin or other antigenic stimulation. Thus, if patients had (1) clinical evidence of severe, persistent hypocalcemia, almost invariably dating from the neonatal period, and (2) a normal humoral immune system, but evidence of a deficit in thymic-mediated cellular immunity, they were considered to have an anomaly of the third and fourth pharyngeal pouches.

The family histories have generally been unremarkable and we have been unable to document genetic transmission. Gestational histories have been normal in the majority of cases, but preeclampsia, maternal tuberculosis, and genitourinary infections have been noted. No seasonal incidence could be found in our small series. The birth weights have usually been in the normal range. The sex predilection (based on cases encountered in this hospital and on review of the literature) has been predominantly male, approximately in the ratio of 2:1 (15 males to eight females).

In our experience, the majority of our patients have facies (fig. 1A, B, and C) characterized by mild hypertelorism, slight antimongoloid slanting of the eyes, asymmetric low-set, malformed ears, short philtrum.

Figure 1

(A) Patient 1 at 18 months; (B) patient 8 at 18 months; (C) patient 7 at 7 months. Note varying degrees of hypertelorism, shortened philtrum, most marked in patient 1, slight antimongoloid slanting of the eyes, and ear malformations. (Figure 1A reproduced from R. Kretschmer et al. courtesy of the New England Journal of Medicine.)
CONGENITAL ANOMALIES

with the appearance of a fish-mouth, and an anomaly of the palate. A degree of psychomotor retardation seems a rather consistent feature in patients who survived infancy. The finding of an abnormally lucent retrosternal space has not been particularly useful in the diagnosis of thymic aplasia, although this has been helpful in the experience of Kirkpatrick and DiGeorge.11

Results

Table 1 presents the clinical and anatomic features of the 10 patients (cases 1 to 10) with defective development of the third and fourth pharyngeal pouches studied at C.H.M.C. and 13 patients reported on in the literature (cases 11 to 23), a total of 23 patients in the present review.

Cardiovascular Abnormalities (Table 1)

Nineteen patients (82.6%) had an anomaly of the aortic arch or congenital cardiac disease. Four patients (17.4%) did not have significant cardiovascular anomalies.

Aortic Arch Anomalies (Nine Patients, 39%)

Six patients (cases 1, 5, 6, 9, 19, 22; table 1) had a right aortic arch with or without an aberrant subclavian artery. One of these (case 5) had an associated left ligamentum arteriosum producing a vascular ring necessitating surgical intervention. The seventh patient (case 11) had a double aortic arch with a dominant right aortic arch and a patent ductus arteriosus. Another patient (case 14) was found at postmortem examination to have an interruption of the aortic arch distal to the left common carotid artery, a bicuspid aortic valve, a membranous ventricular septal defect, and a patent foramen ovale. An isolated anomalous right subclavian artery was found in one patient (case 20).

Conotruncal Anomalies (Nine Patients, 39%)

Eight patients had tetralogy of Fallot (five patients) or persistent truncus arteriosus (three), and one patient (case 17) was found at postmortem examination to have transposition of the great arteries, pulmonary valve atresia, a large ventricular septal defect, and a right patent ductus arteriosus. Tetralogy of Fallot was found in four patients at postmortem examination (cases 3, 10, 16, 18; table 1), and in one patient (case 7), who is still alive, the diagnosis was based on typical clinical features and was confirmed by selective right ventricular biplane cineangiograms. The diagnosis of persistent truncus arteriosus was made at autopsy in two patients (cases 12 and 13). In one patient (case 4), who is currently alive, the clinical diagnosis was substantiated by selective left ventricular and aortic root biplane angiograms.

Other Congenital Heart Disease
(One Patient, 4%)

A single patient (case 8), who is still alive, has typical clinical findings of mild pulmonic stenosis.

Status of Thymus and Parathyroid Glands at Postmortem Examination (Table 1)

Complete aplasia of the thymus and parathyroid glands was found in 12 of the 14 deceased patients; in one patient, both derivatives of the third and fourth pouches were markedly hypoplastic and ectopic, and in another the thymus was absent, and the parathyroid glands were very hypoplastic. No correlation could be made between the degree of thymic and parathyroid hypoplasia and type of cardiovascular malformation.

Extraocular Findings

Esophageal atresia was found in two patients (cases 17 and 20); one of these patients (case 17) had choanal atresia and a tracheoesophageal fistula. Another patient (case 3) had agenesis of the gallbladder. This patient also had a mild degree of pulmonary hypoplasia. Bilateral hydronephrosis (case 7), hyposmia (case 9), and cataracts (case 19) were each found in a single patient. One patient (case 11) was also found to have agenesis of the thyroid isthmus. Two patients (cases 15 and 18) had microscopic evidence of nephrocalcinosis. No patient had significant splenic abnormalities or abdominal heterotaxy. Significant central nervous system anomalies were not documented. No patient exhibited pathologic evidence of adrenal insufficiency.
### Table 1

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Source</th>
<th>Present status</th>
<th>Typical facies</th>
<th>Cellular immune deficit</th>
<th>Neonatal tetany</th>
<th>Postmortem</th>
<th>Cardiovascular anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>C.H.M.C.(^2)</td>
<td>3 yr, L</td>
<td>+</td>
<td>S</td>
<td>+</td>
<td>–</td>
<td>Right aortic arch; aberrant left subclavian artery</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>C.H.M.C.(^2)</td>
<td>5 yr, L</td>
<td>+</td>
<td>S</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>C.H.M.C.(^2,7)</td>
<td>12 days, D</td>
<td>+</td>
<td>NE</td>
<td>+</td>
<td>H</td>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>C.H.M.C.</td>
<td>17 yr, L</td>
<td>+</td>
<td>P</td>
<td>+</td>
<td>–</td>
<td>Truncus arteriosus (type 1(^7))</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>C.H.M.C.</td>
<td>9 yr, L</td>
<td>+</td>
<td>P</td>
<td>+</td>
<td>–</td>
<td>Right aortic arch; left ligamentum arteriosum</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>C.H.M.C.</td>
<td>27 yr, L</td>
<td>+</td>
<td>P</td>
<td>+</td>
<td>–</td>
<td>Right aortic arch</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>C.H.M.C.</td>
<td>3 mo, L</td>
<td>+</td>
<td>N(^*)</td>
<td>+</td>
<td>–</td>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>C.H.M.C.</td>
<td>3 yr, L</td>
<td>+</td>
<td>P</td>
<td>+</td>
<td>–</td>
<td>Pulmonic stenosis</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>C.H.M.C.</td>
<td>18 yr, L</td>
<td>0</td>
<td>P</td>
<td>+</td>
<td>–</td>
<td>Right aortic arch</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>C.H.M.C.</td>
<td>9 yr, D</td>
<td>+</td>
<td>N</td>
<td>+</td>
<td>A</td>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>Lodell(^8)</td>
<td>55 days, D</td>
<td>0</td>
<td>NE</td>
<td>+</td>
<td>A</td>
<td>Double aortic arch; patent ductus arteriosus</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>Harvey et al.(^4)</td>
<td>24 days, D</td>
<td>0</td>
<td>NE</td>
<td>+</td>
<td>A</td>
<td>Truncus arteriosus (type 1(^4))</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>Harvey et al.(^4)</td>
<td>27 days, D</td>
<td>0</td>
<td>NE</td>
<td>+</td>
<td>A</td>
<td>Truncus arteriosus (type 4(^4))</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>Takeuchi et al.(^13)</td>
<td>11 days, D</td>
<td>0</td>
<td>NE</td>
<td>0</td>
<td>A</td>
<td>Interruption of aortic arch; bicuspid aortic valve; ventricular septal defect; patent foramen ovale</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>Taitz et al.(^16)</td>
<td>65 days, D</td>
<td>0</td>
<td>P(^+)</td>
<td>+</td>
<td>A</td>
<td>–</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>Hart et al.(^15)</td>
<td>58 days, D</td>
<td>0</td>
<td>NE</td>
<td>+</td>
<td>A</td>
<td>Pulmonary valvular atresia; ventricular septal defect; patent ductus arteriosus</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>Dische(^16)</td>
<td>4 days, D</td>
<td>+</td>
<td>NE</td>
<td>+</td>
<td>A</td>
<td>Transposition of the great arteries; pulmonary valve atresia; ventricular septal defect; right patent ductus arteriosus</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>Huber et al.(^17)</td>
<td>6 mo, D</td>
<td>0</td>
<td>NE</td>
<td>+</td>
<td>A</td>
<td>Tetralogy of Fallot; patent foramen ovale</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>Cleveland et al.(^18)</td>
<td>18 mo, L</td>
<td>0</td>
<td>S</td>
<td>+</td>
<td>–</td>
<td>Right aortic arch; anomalous subclavian artery</td>
</tr>
</tbody>
</table>
Among 23 patients in the present series, nine are living and 14 are dead. In seven (50%), the cause of death can be directly attributed to congenital heart disease, and a further patient died with acute hepatic necrosis 4½ months following complete repair of his tetralogy of Fallot. One patient's death was attributed to laryngeal spasm, presumably secondary to hypocalcemia. Another patient succumbed to postoperative complication (peritonitis and sepsis) following surgical intervention for esophageal atresia. Primary infection may be blamed for the early demise of only four patients (all with complete agenesis of both thymus and parathyroids).

### Discussion

The majority of patients with defective development of the third and fourth pharyngeal pouches have anomalies of the aortic arch or conotruncus. This striking association has not been found in patients with hypoplastic, X-linked intalite agammaglobulinemia, Wiskott-Aldrich syndrome, transient hypogammaglobulinemia, Wiskott-Aldrich syndrome, immunodeficiency with thymoma, short-limbed dwarfism, or combined immunodeficiency. The finding of profound, persistent hypocalcemia in the neonate should alert the clinician to the possibility of defective thyrocalcitonin production and congenital cardiovascular disease. This is especially important in the neonate when cyanosis might easily be attributed to recurrent seizures rather than to congenital heart disease or to a vascular ring.

The frequency of a right-sided aortic arch in the general population (based on consecutive necropsies) is reported from 0.04% to 0.10%. The finding of six patients (26%) in the present series with right aortic arch is noteworthy. In the developing human fetus, the two pairs of parathyroid glands are derived from the endoderm of the third and fourth pharyngeal pouches, and the thymus has a bilateral origin from part of each third endodermal pharyngeal pouch. The intimate endodermal pharyngeal pouch has a bilateral origin from part of each third endodermal pharyngeal pouch.
proximity of these structures to the developing aortic arch system and truncus arteriosus has been pointed out by Boyd and associates. These latter authors conclude that the concurrence of lesions of the parathyroid glands, thymus, and fourth aortic arch derivatives must be attributed to local damage to the third and fourth pharyngeal pouch area at approximately 4 weeks' gestation.

Nine patients (39%) had anomalies of the conotruncus. Tetralogy of Fallot and truncus arteriosus are morphologically similar, sharing a deficiency in conal development. Transposition of the great arteries with a ventricular septal defect and pulmonary atresia results in part from abnormal conal growth, specifically a bilateral conus with a well-expanded subaortic conus. Furtherore, aortic arch interruptions have been attributed to a highly characteristic leftward shift of the crista supraventricularis, but unfortunately Takeuchi and associates did not characterize the crista in their case report. It is difficult to relate thymic and parathyroid anomalies to abnormalities of conal growth and expansion merely on the basis of proximity.

The high frequency of cardiovascular anomalies with the third and fourth pharyngeal pouch syndrome in the present review of 23 cases is consistent with the experience of St. Christopher's Hospital for Children, Philadelphia, Pennsylvania. Of 20 patients in whom absence, hypoplasia, or malsecton of the thymus was confirmed anatomically or highly suspected on clinical grounds at that institution, 12 had anomalies of the aortic arch or trunk, and eight had conotruncal abnormalities. Death resulted from the cardiovascular lesions in eight patients. No significant cardiovascular anomalies were detected at autopsy in four cases. (Lischner HW, Huff DS, Arey JB, DiGeorge AM: Personal communication, September 1971). Discrepancy between totals is due to the presence of more than one lesion in some patients.

Congenital absence or deficiency of the parathyroid glands does not appear essential to the morphogenesis of aortic arch anomalies and congenital cardiac disease. In 1965, Cameron reported in a brief abstract the association of thymic aplasia or hypoplasia and congenital heart disease, stating specifically that there was no indication of hypoparathyroidism in these patients. He mentioned eight patients with either absence or marked hypoplasia of the thymus who had "major anomalies of the cardiovascular system including defects of the ventricular septum, common truncus, Fallot's tetralogy, atresia and coarctation of the aortic arch, right aortic arch, and anomalies of the subclavian arteries." He also mentioned two infants with hypoplasia and anomalous location of the thymus, both of whom had absence of the pulmonary valve, small ventricular septal defect, absent ductus arteriosus, and aneurysmal dilation of the pulmonary arteries with bronchial compression characteristic of the absent pulmonary valve syndrome.

The observation that some patients with an obvious anomaly of the third and fourth pharyngeal pouches and congenital cardiovascular disease have normal or nearly normal mechanisms of cellular immunity suggests either that a significantly defective thymus is not a prerequisite of the cardiovascular anomalies or that the mechanisms of cellular immunity may not be wholly derived from the thymus. This latter suggestion gains some support from the observation that one patient (case 10; tables 1 and 2) survived to 9 years of age without serious infection, had tolerated cardiopulmonary bypass (and blood products) without a demonstrable thymus being found at surgery or on an en bloc dissection at necropsy.

What, then, is the relationship between anomalies of the third and fourth pharyngeal pouches and congenital cardiovascular disease? We doubt there is any causal relationship, but until suitable biologic models become available this will have to remain speculative. It is most interesting that first the spleen and now the thymus, both lymphoreticular structures, have been associated with congenital heart disease. It is likely, however, that just as abnormalities of the spleen (asplenia, hyposplenia, or polysplenia) are not
truly basic to cardiovascular anomalies or to heterotaxy but are rather just the biologic expression of incomplete organogenesis, so too, parathyroid and thymic aplasia or hypoplasia are probably merely the expression of a teratogenic factor that exerts its influence on the developing third and fourth pharyngeal pouches, aortic arch system, and possibly on the conotruncus itself.

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