Major and Minor Anomalies in Japanese Children with Down's Syndrome

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SUMMARY

Fifty-five percent of 106 Japanese patients between 2 days and 5 years of age with Down's syndrome were found to have major congenital cardiac defects. Autopsy was performed on 18 cases. Of these, 11 had major congenital heart defects. In addition, all 18 autopsied cases revealed many minor cardiac abnormalities, such as nodular or diffuse hypertrophic valves, parachute formation of atrioventricular valves, hypoplastic papillary muscles, and abnormal attachment of chorda tendineae. It is postulated that minor cardiac abnormalities are secondary to abnormal endocardial and bulbar cushion formation.

Additional Indexing Words:
Down's syndrome Major cardiac anomalies Minor cardiac anomalies

CONGENITAL heart disease has long been known to be commonly associated with Down's syndrome.1), 4), 5), 7), 8), 11) - 14) The average age of death in children with Down's syndrome has been reported to be between 9 and 14 years.7) During the neonatal period, the major causes of death are severe anomalies of the gastrointestinal tract, respiratory distress syndrome, or infection. Deaths due directly or indirectly to congenital cardiac anomalies become more frequent after the newborn period.11) 7), 8) Due to modern improvements in diagnosis and therapy, the average life span is increasing. Nevertheless, it is certain that mortality of children with Down's syndrome still is higher than the normal population.

The present study is an analysis of the occurrence of cardiovascular disease in 106 Japanese patients with Down's syndrome who were 2 days to 5 years old.

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MATERIAL AND METHODS

All 106 infants and children studied were referred to the National Children's Hospital of Tokyo between January 1966 and March 1968. The ages of the children ranged from 2 days to 5 years. A definite diagnosis of Down's syndrome was made by karyotype analysis in all 106 patients. Each patient was examined by a pediatric cardiologist. A standard 14-lead electrocardiogram and a roentgenogram of the chest were obtained. Cardiac catheterization and cineangiocardiography were performed in 8 cases. Autopsy was performed in 18 cases.

The term, "major cardiac anomaly" is used to include typical cardiac morphological defects, such as ventricular septal defect or endocardial cushion defect. "Minor cardiac anomaly" is used to describe unusual abnormalities found at autopsy, such as abnormal chorda tendineae or papillary muscles.

RESULTS

1. Frequency of the association of Down's syndrome with major cardiac abnormalities in different age groups (Table I). Fifty-eight of the 106 subjects were found to have major congenital cardiac malformations. Of these 58, 70%

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of cases</th>
<th>No. of major cardiac defects</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 6 months</td>
<td>54</td>
<td>38 (70%)</td>
<td>14 (26%)</td>
</tr>
<tr>
<td>6-12 mos.</td>
<td>19</td>
<td>7 (37%)</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>1–2 years</td>
<td>15</td>
<td>7 (47%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>2–3 years</td>
<td>7</td>
<td>3 (43%)</td>
<td>0</td>
</tr>
<tr>
<td>3–5 years</td>
<td>11</td>
<td>3 (27%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>58 (55%)</td>
<td>20 (19%)</td>
</tr>
</tbody>
</table>

were initially seen during the first 6 months of life, 37% between 6 and 12 months, 47% between 1 and 2 years, 43% between 2 and 3 years, and 27% between 3 and 5 years of age.

2. Frequency of death in different age groups (Table I). The greatest number and total percentage of deaths (26%) occurred during the first 6 months of life followed by a 21% death rate during the next 6 months. The total mortality was 20 of the 106 subjects (19%). Almost all cardiac deaths occurred within the first year of life, 12 secondary to congestive heart failure. The oldest child who died was 3 years of age; death occurred in the home and was caused by a severe anoxic spell secondary to tetralogy of Fallot.

3. Nature and frequency of the major cardiovascular abnormalities found in 59
Table II. Major Cardiovascular Anomalies in Different Age Groups

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of total cardiac defects</th>
<th>VSD</th>
<th>AVC</th>
<th>ASD (2)</th>
<th>TF</th>
<th>PDA</th>
<th>All others</th>
<th>PPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 6 month</td>
<td>39</td>
<td>14 (6)</td>
<td>10 (10)</td>
<td>7 (1)</td>
<td>3</td>
<td>2 (2)</td>
<td>2</td>
<td>1 (1)</td>
</tr>
<tr>
<td>6-12 mos.</td>
<td>7</td>
<td>4 (3)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1-2 years</td>
<td>7</td>
<td>4 (3)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2-3 years</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>3-5 years</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>24(12)</td>
<td>11(11)</td>
<td>11(1)</td>
<td>5</td>
<td>2 (2)</td>
<td>5 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

All others: VSD+PS, AVC+PS, PDA+MI, ASD (primum)+MI, and complicated anomalies. Parenthesis: number of marked accentuated second sound in the pulmonary area. VSD: ventricular septal defect, AVC: persistent common atrioventricular canal, ASD (2): secundum atrial septal defect, TF: tetralogy of Fallot, PDA: patent ductus arteriosus, PPH: primary pulmonary hypertension.

of the 106 subjects (Table II). There were 11 types of major cardiovascular abnormalities in the 59 patients with major cardiovascular disease. Twenty-seven or 46% of the 59 subjects had an accentuated second sound in the pulmonary area. This physical finding was most common among the patients with ventricular septal defect. Common atrioventricular canal was the most common defect in the 0-6 months age group.

4. Minor cardiac anomalies associated with major cardiac malformation (Tables III and IV, and Fig. 1). In 11 autopsied subjects, common atrioventricular canal occurred in 6 cases, ventricular septal defect in 2 cases, tetralogy of Fallot in 2 cases, and a complicated cardiac malformation in one (single ventricle with small outlet chamber, complete transposition of the great vessels with pulmonary atresia, total anomalous pulmonary venous return, common atrioventricular orifices, and common atrium).

Abnormal formation of the chordae tendineae and papillary muscles, especially in the right ventricle, occurred in 10 of these 11 cases. Abnormalities of the atrioventricular valves occurred in all. Two cases (Cases 2 and 11) had absence of the muscular component of the lower atrial septum adjoining the posterior atrioventricular ring.

5. Isolated minor cardiac anomalies (Tables V and VI, and Figs. 2, 3, and 4). An additional 7 patients without major cardiac anomalies were autopsied. Five died after non-cardiac operations. Death of the sixth patient was caused by pneumonia, and the seventh patient's cause of death was lymphocytic leukemia. Similar to findings in the Down's syndrome patients with associated major cardiac malformations, many abnormalities of valves and abnormal formation of chordae tendineae and papillary muscles were found.
Table III. Minor Cardiac Anomalies Found at Autopsy in Down’s Syndrome Patients with Major Cardiac Anomalies

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>No. of major cardiac anomalies</th>
<th>Septum</th>
<th>RA</th>
<th>TV</th>
<th>RV</th>
<th>PV</th>
<th>MV</th>
<th>LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 mos.</td>
<td>M</td>
<td>AVC  ASD (2)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 mos.</td>
<td>M</td>
<td>TF, ASD (2) PDA (small)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 mos.</td>
<td>M</td>
<td>AVC  +</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12 mos.</td>
<td>M</td>
<td>VSD</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>9 mos.</td>
<td>M</td>
<td>AVC, ASD (2) PS, PDA (large)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2 mos.</td>
<td>F</td>
<td>AVC, ASD (2) PDA (small)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>9 days</td>
<td>M</td>
<td>complicated anomalies</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>12 mos.</td>
<td>M</td>
<td>VSD</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2 days</td>
<td>M</td>
<td>AVC, ASD (2) PDA (small)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1 mos.</td>
<td>M</td>
<td>AVC, ASD (2)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>2 days</td>
<td>F</td>
<td>TF, ASD (2)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


DISCUSSION

Previously reported incidences of congenital heart disease associated with Down’s syndrome vary between 7% and 70%. The present study reports an overall incidence of 55%. Similar to the present study, the higher incidences occur in studies of younger age groups of patients. Rowe and Uchida (1961) reported a 40% association of congenital heart disease with Down’s syndrome. This was a long-term, prospective study with complete evaluation from birth. The present study reports a somewhat higher occurrence, perhaps because our hospital is a referral center and admits only acutely ill patients.

Recent studies have shown that the incidence of isolated ventricular septal defect is essentially the same as that of persistent common atrioventricular canal in patients with Down’s syndrome. Rowe (1961) estimated that the combined incidence of both entities constitutes approximately 70% of congenital heart disease in Down’s syndrome. In the present series the frequency of persistent common atrioventricular canal was higher in the younger age group suggesting that the occurrence of various types of congenital cardiac defects in Down’s syndrome should be estimated by age group.
Table IV. Minor Cardiac Anomalies Found at Autopsy in Down's Syndrome Patients with Major Cardiac Anomalies

1. Right atrium
   a. Nonlimitation of limbus fossa ovalis
   b. Herniation of septum primum into right atrium

2. Tricuspid valve
   a. Absence of muscular part of posterior atrioventricular ring
   b. Nodular hypertrophy
   c. Web-formation
   d. Fenestration
   e. Formation of double commissural leaflet
   f. Double tricuspid orifice
   g. Mitralization
   h. Parachute formation

3. Right ventricle
   a. Hypoplasia of anteroiateral papillary muscle group
   b. Absence of inferior papillary muscle
   c. Connection between posterior chorda tendinea and anterior papillary muscle
   d. Origin of chordae tendineae from the side of papillary muscle
   e. Absence of chordae tendineae

4. Pulmonary valve
   a. Diffuse hypertrophy
   b. Fenestration

5. Mitral valve
   Parachute formation

6. Left ventricle
   a. Absence of anterior chorda tendinea
   b. Absence of inferior papillary muscle
   c. Absence of both anterior and posterior chordae tendineae from a papillary muscle

Dumars has noted primary pulmonary hypertension in young patients with Down's syndrome (22 months and 11 months of age). We reported that some infants with Down's syndrome without major congenital cardiac defects may show an accentuated second sound in the pulmonary area. Most of these patients also have persistently positive T-waves in electrocardiographic leads V4R, V3R, and V1 for longer periods of time than in the normal population. In our series, one patient had primary pulmonary hypertension which was proved by cardiac catheterization at 4 months of age. It is, therefore, postulated that patients with Down's syndrome may undergo a slower decrease of pulmonary vascular resistance during early life than normal infants.

Berg, Crome, and France (1960) reported idiopathic cardiac hypertrophy to occur with equal frequency among Down's syndrome patients with or
without major congenital heart disease. In our series we found no cases of idiopathic cardiac hypertrophy in Down’s syndrome without major cardiac defect. There were many morphological abnormalities such as nodular or diffuse hypertrophic cardiac valves, parachute formation of atroventricular valves, and herniation of the atrial septum with, as well as without, major cardiac malformations. These abnormalities usually but not invariably occurred secondarily to hemodynamic changes.\textsuperscript{3, 6} Some cases of common atroventricular canal which showed combined pressure and volume hypertrophy, had hypoplastic anterolateral papillary muscle in the right ventricle. Two cases of tetralogy of Fallot showed pressure-type hypertrophy of the right ventricle but also had hypoplastic anterolateral papillary muscle in the right ventricle. Therefore, we postulate that some of these minor cardiac abnormalities were present embryologically. It is suggested that these minor cardiac abnormalities may increase the risk of infection and surgical mortality and that all hearts of autopsied patients with Down’s syndrome be carefully inspected for them.
### Table V. Isolated Minor Cardiac Anomalies in Down's Syndrome Patients (autopsy cases)

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Direct cause of death</th>
<th>Septum</th>
<th>Minor cardiac abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RA</td>
</tr>
<tr>
<td>12</td>
<td>3 days</td>
<td>M</td>
<td>postoperative (anal atresia)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>4 days</td>
<td>M</td>
<td>postoperative (anal atresia)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>20 days</td>
<td>F</td>
<td>postoperative (Hirschsprung's disease)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>19 days</td>
<td>M</td>
<td>postoperative (duodenal atresia)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>4 mos.</td>
<td>F</td>
<td>pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>1 year</td>
<td>F</td>
<td>postoperative (duodenal atresia)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>2 years</td>
<td>M</td>
<td>leukemia</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>


### Table VI. Isolated Minor Cardiac Anomalies in Down's Syndrome Patients (autopsy cases)

1. Right atrium
   a. Nonlimitation of limbus fossa ovalis
   b. Fusion between the Eustachian and Thebesian valves

2. Tricuspid valve
   a. Downplacement of septal leaflet
   b. Nodular hypertrophy
   c. Mitralization
   d. Formation of double commissural leaflet
   e. Parachute formation

3. Right ventricle
   a. Unidentified muscle of Lancisi
   b. Hypoplasia of anterolateral papillary muscle

4. Pulmonary valve
   Diffuse hypertrophy

5. Mitral valve
   Nodular hypertrophy

6. Left ventricle
   Hypoplasia of inferior papillary muscle

7. Aortic valve
   a. Multiple fenestration
   b. Formation of accessory coronary ostium
Fig. 2. Isolated minor cardiac anomalies of Case 13. Note the nodular, hypertrophic tricuspid valve and absence of the inferior papillary muscle. Anterolateral papillary muscle groups are also hypoplastic. Chordae tendineae of the anterior leaflet (AL) is inserted into the free wall of the right ventricle (RV). ML: medial leaflet of the tricuspid valve.

Fig. 3. Isolated minor cardiac anomalies of Case 15. Note downward displacement of the medial leaflet of the tricuspid valve (arrow), the nodular hypertrophic tricuspid valve, hypoplastic papillary muscles in the right ventricle (RV), and herniation of the fossa ovalis (FO) into the right atrium.
Fig. 4. Isolated minor cardiac anomalies of Case 17. Note mitralization of the diffusely hypertrophied tricuspid valve (TV) and underdevelopment of the papillary muscles in the right ventricle (RV). Delineation of the limbus fossa ovalis is not clear (arrow).

It is possible that the nature of the endocardial and bulbar cushions are unusual in Down’s syndrome. This may cause abnormal septal development and also abnormal formation of the atrioventricular valves or orifices and hypoplastic papillary muscles. For example, 2 cases of tetralogy of Fallot in our series had absence of the muscular component in the lower atrial septum adjoining the posterior atrioventricular ring. If this region was not occupied by a membranous structure, it could develop into a common atrioventricular orifice.

ACKNOWLEDGMENT

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