Ocular colobomata, cardiac defect, and other anomalies: a study of seven cases including two sibs*

C. K. HO, R. L. KAUFMAN, and S. M. PODOS

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Summary. An association of ocular colobomata and congenital heart disease was observed in seven patients. Two of these were maternal half sisters whose mother also had ocular colobomata. All the patients had normal karyotypes. There was a high incidence of other associated abnormalities involving the central nervous, skeletal, and urogenital systems. Discovery of an ocular coloboma should alert the clinician to search for other abnormalities.

Colobomatous malformations of the eye may be associated with chromosomal abnormalities (François, 1968a), maternal exposure to teratogenic substances during early pregnancy (Cullen, 1964), and Mendelian disorders (Waardenburg et al, 1961), or they may occur without apparent cause. The majority of ocular colobomata are situated inferonasally. Such colobomata are called typical. If situated elsewhere they are called atypical (Duke-Elder, 1940). Ocular colobomata may occur alone or in combination with a number of abnormalities of other organs (François, 1968b). In 1961, Angelman pointed out the association of ocular colobomata with congenital heart disease (Angelman, 1961). Such a combination of malformations may be seen in certain well-defined chromosomal syndromes, for example, 13 trisomy (Conen et al, 1966; Lee et al, 1966; Warkany et al, 1966), 13q-(Allderdice et al, 1969; Orbeli et al, 1971), 13 ring (Allderdice et al, 1969; Orbeli et al, 1971; Bilchick et al, 1972), 18 trisomy (Weber et al, 1964; Warkany et al, 1966), and cat eye syndrome (Schachenmann et al, 1965; Freedom and Gerald, 1973). There remain cases who have normal karyotypes. These are usually sporadic (Edwards et al, 1961; Lele et al, 1965).

Clinical studies of seven patients (Table 1) with ocular colobomata and congenital heart disease who had normal karyotypes in cultured blood lymphocytes comprise this report. Two of the patients are maternal half sisters.

Case reports

Case 1. A white female was born by breech presentation at term in February 1972. The pregnancy was complicated by diabetes mellitus at 2 months of gestation. The 29-year-old mother and 37-year-old father were not consanguineous. The birth weight was 2670 g, birth length 46 cm, and head circumference 34.5 cm.

Examination revealed dolichocephaly, typical iris colobomata with normal fundi, bilateral cataracts, horizontal nystagmus, prominent bifid xyphoid process, and a heart murmur described as a grade IV/VI ejection murmur loudest at the base and transmitted to the back. Findings from radiological examinations and cardiac catheterization demonstrated tetralogy of Fallot with marked infundibular and valvular pulmonary stenosis, bicuspid pulmonary valve, a large ventricular septal defect, and a right aortic arch. An intravenous pyelogram showed pelvic ectopia of the right kidney. The patient expired at 7 weeks of age due to cardiac failure. Necropsy confirmed the abnormalities described above.

Case 2, the maternal half-sister of case 1, was born at term by breech presentation 14 months after her sister's birth. Her father was a 34-year-old normal white man. He was not consanguineous with the mother and was not related to the father of case 1. Birth weight was 2870 g and birth length 47 cm. The pregnancy was complicated by diabetes mellitus discovered in the sixth month.

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of gestation, which was treated with chlorpropamide* for 1 month before delivery.

The infant had prominent frontal bossing, anteverted nostrils, typical iris coloboma with normal fundi, bilateral congenital cataracts, and a grade III/VI systolic ejection murmur located at the left sternal border. Radiographs showed mild left atrial enlargement, compatible with a small left-to-right shunt, most likely a ventricular septal defect. Cardiac catheterization has not been performed.

The mother of case 1 and case 2 had typical iris coloboma. Cataracts were found at 3 years of age and glaucoma at 24 years of age. A heart murmur was noted at 16 years of age. At age 30 cardiac evaluation including physical examination, chest radiograph, electrocardiogram, vectorcardiogram, and phonocardiogram revealed no evidence of congenital heart disease. A blood lymphocyte karyotype was normal. No other members of the family were known to have ocular coloboma or congenital heart disease.

Other cases which were sporadic are summarized in Table I.

### Discussion

The incidence of coloboma of the iris in children, according to Bolk, is approximately 4 per 10 000 (Bolk, 1904). The incidence of congenital heart disease is approximately 4 per 1000 live births (MacMahon et al, 1953). The probability of the two conditions occurring simultaneously in an individual purely by chance would be extremely small. Gardiner and Joseph (1968) reported that children with congenital heart disease had a high incidence of ocular abnormalities; among 85 patients they studied, one had coloboma of the choroid. Polani and Campbell (1955) studied 377 patients with congenital heart disease, one of whom was reported to have iris coloboma. Warkany (1971) noted several cases in which ocular coloboma and congenital heart disease occurred concurrently. In these reports karyotype results were not given, and detailed clinical descriptions are lacking. Lele et al (1965) reported five cases having coloboma of the iris; two individuals had congenital heart disease;

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### Table

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Birth date</th>
<th>Eyes</th>
<th>Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>Feb 1972 (died Apr 1972)†</td>
<td>Typical iris coloboma and cataracts, OU; nystagmus</td>
<td>Tetralogy of Fallot; bicuspid pulmonic valve; right aortic arch‡</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Apr 1973</td>
<td>Typical iris coloboma and cataracts, OU</td>
<td>Probable ventricular septal defect**</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Mar 1956</td>
<td>Typical coloboma of iris, lens, retina, choroid, OU; alternating esotropia; nystagmus; ptosis, OU</td>
<td>Atrial septal defect‡, ††</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Aug 1959</td>
<td>Coloboma of optic disc at nasal side, OS; nystagmus</td>
<td>Coarctation of aorta; bicuspid aortic valve; pulmonic valvular stenosis; coarctation of main, right and left pulmonary arteries‡, ††</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Dec 1972 (died Nov 1973)†</td>
<td>Typical coloboma of retina, choroid, OU; microphthalmos, cataract, and coloboma of optic disc, OD</td>
<td>Pulmonary atresia; right ventricular hypoplasia; patent foramen ovale; large patent ductus arteriosus‡, ††</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>Mar 1970 (died Nov 1972)†</td>
<td>Coloboma of retina, choroid at posterior pole, OU; microphthalmos, OD</td>
<td>Double outlet right ventricle; pulmonary stenosis; ventricular septal defect; right ventricular hypertrophy</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>Oct 1966</td>
<td>Typical coloboma of retina, choroid, OD; blepharophimosis, ptosis, OU; alternating exotropia, epicanthal folds, anti-mongoloid slant, hypertelorism</td>
<td>Ligamentum arteriosum connected to retro-oesophageal left subclavian artery (these and right aortic arch formed a vascular ring)‡, ††</td>
</tr>
</tbody>
</table>

* All had normal karyotypes from cultured blood lymphocytes. Patients 2 and 7 were studied with Giemsa and fluorescence banding techniques; others with Giemsa staining without banding.
† Necropsy performed.
** No cardiac catheterization performed.
‡ Cardiac catheterization performed.
†† Cardiac surgery performed.

* Trade name Diabinese ©
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AND ASSOCIATED ABNORMALITIES (PRESENT SERIES)

<table>
<thead>
<tr>
<th>Neurological</th>
<th>Skeletal</th>
<th>Urogenital</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>?</td>
<td>Bifid xyphoid process; dolichocephaly</td>
<td>Pelvic ectopia of the right kidney</td>
<td>Retarded growth and development</td>
</tr>
<tr>
<td>?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental retardation</td>
<td>Pectus carinatum; kyphosis; irregularity of vertebral bodies; short fifth fingers</td>
<td>Right kidney had double collecting system with two ureters</td>
<td></td>
</tr>
<tr>
<td>Mental retardation; convulsions</td>
<td>Short 12th ribs; four lumbar vertebrae; spina bifida occulta S1; short left 5th finger</td>
<td>Bilateral uretero-pelvic junction obstruction; bilateral extrarenal pelves; incomplete medial rotation of the left renal pelvis</td>
<td></td>
</tr>
<tr>
<td>Convulsions</td>
<td>Only 11 rib pairs; no ribs on T12</td>
<td>Undescended testes</td>
<td>Retarded growth and development; scalp defect; facial asymmetry; malformed ears with preauricular pits and skin tag</td>
</tr>
<tr>
<td>Mental retardation, microcephaly; holoprosencephaly; agenesis of corpus callosum; arhinencephaly</td>
<td>Butterfly vertebra; hemivertebra; gibbus, small sternum; shortened radii; absent thumbs; oligodactyly and syndactyly of feet; dislocated hips</td>
<td></td>
<td>Small for gestational age; retarded growth and development; micrognathia; low-set ears; simian creases; rectoperineal fistula; increased chromosomal breaks (birth control pills used in early pregnancy)</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>Asymmetrical skull; small sella turcica; pecsus excavatum; kyphosis; bilateral coxa valga; underdeveloped acetabula; flaring of iliac crests laterally; retarded bone age</td>
<td>Posterior urethral valves; hypospadias; undescended testes</td>
<td>Small for gestational age; retarded growth and development; low-set ears; short lingual frenulum; narrow trachea; cleft palate</td>
</tr>
</tbody>
</table>

one of them had pericentric inversion of chromosome number one; and the other had a normal karyotype. The seven cases reported by us represent four years of experience without specific survey. The association of ocular colobomata and congenital heart disease is thus felt to be nonrandom.

The aetiology of this association of colobomata and congenital heart disease is not known at present. Coloboma of the fundus, with or without involvement of the iris, at the typical position is due to failure of closure of the fetal fissure, which normally occurs in the sixth week of fetal life (Mann, 1964). The extent to which the cleft remains open determines which tissues of the eye manifest defects. Development of the iris normally begins in the latter part of the third month and is not completed until 8 months of fetal life (Mann, 1964). Thus, an adverse factor acting after the sixth week of fetal life may result in an isolated coloboma of the iris, without involvement of the ciliary body, retina or choroid. The critical period for the development of the heart is thought to be between 3 and 7 weeks of fetal life (Moore, 1973). It is possible that a noxious agent present in the critical period of time common to both the eye and the heart might result in malformation of these two organs. This critical time is probably before 7 weeks of fetal life.

Ocular colobomata are most frequently inherited as an autosomal dominant trait and rarely as an autosomal recessive (Waardenburg et al, 1961) or X-linked recessive trait (Goldberg and McKusick, 1971). In the family of case 1 and case 2, the recessive form of transmission seems unlikely; because the probability of both unaffected, unrelated fathers being heterozygous is extremely small. The X-linked disease mainly affects males and includes microphthalmos which was not present in our patients. Typical iris coloboma is almost always transmitted as an autosomal dominant trait. We assume that this is the situation in this family. Cataracts were also present in the mother and both children. There was no evidence of intrauterine
infections or galactosaemia. The cataracts appear to be a dominantly transmitted trait. It is uncertain whether or not the congenital heart disease, colobomata, and cataracts are inherited together as a single entity. The mother has a history of a heart murmur, but shows no evidence of congenital heart disease at present. However, 25% of ventricular septal defects present in infancy may undergo spontaneous closure in later life (Bloomfield, 1964). Thus there is a possibility that the mother may have had a form of congenital heart disease which is not now clinically evident. The fact that both sisters of different, unrelated, normal fathers have congenital heart disease suggests that the predisposition to the congenital heart disease also came from the mother.

The patients reported here and those in the literature (Rolando and Jemma, 1959; Angelman, 1961; Edwards et al, 1961; Richards, 1961; Lele et al, 1965) have a number of clinical features in common with patients having the cat eye syndrome. That condition, however, appears related to the presence of an extra acrocentric chromosome and involved individuals also have anal atresia (Schachenmann et al, 1965; Freedom and Gerald, 1973). Franklin and Parslow (1972) described two sisters with 'cat eye syndrome', who had normal karyotypes. Both had anal atresia and tetralogy of Fallot. One had a unilateral iris coloboma and the other had microphthalmos without an ocular coloboma. The parents of their patients were normal, in contrast to our patients, whose mother also had iris colobomata.

Ocular colobomata and congenital heart disease are frequently associated with abnormalities in other organ systems (Table I). The association of congenital heart disease with vertebral, anal, tracheal, oesophageal, renal, and limb anomalies has previously been reported (Quan and Smith, 1973). Of our seven cases, five had neurological problems, six had skeletal defects, and five had urogenital anomalies. These findings are in agreement with the cases reported in the literature, which are summarized in Table II. Therefore, the discovery of an ocular coloboma should alert the clinician to search for other abnormalities.

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### REFERENCES


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II
AND ASSOCIATED ABNORMALITIES (PREVIOUSLY REPORTED)

<table>
<thead>
<tr>
<th>Associated Abnormalities</th>
<th>Neurological</th>
<th>Skeletal</th>
<th>Urogenital</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocephalus; spasticity;</td>
<td>Right kidney</td>
<td></td>
<td></td>
<td>Mother had viral hepatitis during 1st–2nd months of pregnancy</td>
</tr>
<tr>
<td>psychomotor retardation</td>
<td>Talipes equinovarus, left foot;</td>
<td>hemivertebra</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal EEG; right facial</td>
<td></td>
<td></td>
<td>Agenesis, right kidney and</td>
<td>Retarded development; high-arched palate; low-set, anteriorly rotated ears</td>
</tr>
<tr>
<td>paralysis</td>
<td></td>
<td></td>
<td>ureter</td>
<td></td>
</tr>
<tr>
<td>Mental retardation</td>
<td>Abnormal left fifth finger</td>
<td></td>
<td></td>
<td>Suggestive webbing of neck; small size</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cleft palate</td>
</tr>
</tbody>
</table>


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