Journal of Medical Genetics (1975). **12**, 289.

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

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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 I) 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

Received 8 July 1974.

* Presented in part at the annual meeting of the American Society of Human Genetics in Atlanta, Georgia, on October 27, 1973 (Kaufman *et al*, 1973).

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TABLE

PATIENTS* WITH OCULAR COLOBOMATA, CONGENITAL HEART DISEASE,

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

* 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. ‡ Cardiac catheterization performed.
** No cardiac catheterization performed. †† Cardiac surgery performed.

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

The infant had prominent frontal bossing, anteverted nostrils, typical iris colobomata 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 colobomata. 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 radiolograph, 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 colobomata or congenital heart disease.

Other cases which were sporadic are summarized in Table I.

* Trade name Diabinese ®

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 colobomata 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;

I
AND ASSOCIATED ABNORMALITIES (PRESENT SERIES)

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

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

TABLE

PATIENTS WITH OCULAR COLOBOMATA, CONGENITAL HEART DISEASE,

Reference	Sex	Eyes	Heart
Rolando and Jemma (1959)*	F	Colobomata of iris, retina, choroid, OU; microcornea, OU; exotropia; nystagmus	Ventricular septal defect
Angelman (1961; case 2)*	M	Typical colobomata, iris, retina, choroid, OU	Patent ductus arteriosis
Angelman (1961; case 3)*	F	Typical coloboma, iris and lens with thinning of choroid and retina, OS; strabismus; wide-set, prominent eyes	Pulmonary stenosis
Edwards *et al* (1961; case 1)†	M	Typical coloboma, choroid, OD	Probable ventricular septal defect
Edwards *et al* (1961; case 3)†	M	Deep excavations, optic disc; bilateral posterior staphylomata	Patent ductus arteriosus; right sided aorta
Richards (1961)*	M	Ocular coloboma, OS	Probable ventricular septal defect
Lele *et al* (1965; case 4)†	M	Typical colobomas, iris, retina, OD	Ventricular septal defect

* Karyotype not reported.
† Normal karyotype.

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.

Dr Robert L. Kaufman was supported by USPHS Postgraduate Training Grant TO1 GM0511, the Ranken-Jordan Trust Fund and the James H. Woods Foundation. Dr Steven M. Podos was supported by grant NIH-NEI 5P01 EY00336.

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II

AND ASSOCIATED ABNORMALITIES (PREVIOUSLY REPORTED)

Associated Abnormalities			
Neurological	Skeletal	Urogenital	Others
—	—	Double collecting system, left kidney; pelvic ectopia, right kidney	Mother had viral hepatitis during 1st–2nd months of pregnancy
Hydrocephalus; spasticity; psychomotor retardation	Talipes equinovarus, left foot; hemivertebra	—	Right inguinal hernia
—	—	—	Retarded growth and development; beaked nose; cleft soft palate; cyanosis; clubbing of fingers
—	—	—	Retarded growth and development; micrognathia; low-set ears
Abnormal EEG; right facial paralysis	—	Agenesis, right kidney and ureter	Retarded development; micrognathia; high-arched palate; low-set, anteriorly rotated ears
Mental retardation	Abnormal left fifth finger	—	Suggestive webbing of neck; small size
—	—	—	Cleft palate

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