Systemic associations of uveal coloboma

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Closure of the optic cleft occurs about the sixth week of intrauterine life. Clinically, failure of complete closure results in a coloboma of the uveal tract which is variable in its position and extent, and there is sometimes also an associated coloboma of the optic nervehead; defective closure of the cleft is known to be under genetic influence. The usual mode of transmission of such a defect is dominant, but a recessive inheritance, a probable sex-linked transmission (Goldberg and McKusick, 1971), and an apparently sporadic incidence have also been described. The extensive literature on the subject is reviewed by François (1961) and Waardenburg, Franceschetti, and Klein (1961). There has been a high degree of phenotypic variability in all modes of transmission, and this variability has increased with the documentation of syndromes caused by abnormal chromosomes. Most chromosomal defects occur before zygote formation. The primary causations of colobomatous syndromes thus have their origins before fertilization and not during intrauterine development (atypical colobomata excluded).

The present paper describes the colobomatous syndromes that have presented at The Hospital for Sick Children, Great Ormond Street in the last 10 years.

Results

25 case histories were examined. Uveal coloboma was an isolated finding in five instances. The findings in the other twenty are summarized in Table I. The systemic associations are divided into five groups for simplicity of discussion, and to show their relationships to previously described associations. The grouping is not intended to display necessarily different syndromes. There is considerable overlapping of associated findings. All cases in Group A have uveal coloboma and cleft lip and/or cleft palate. All cases in Group B have uveal coloboma and oligophrenia. Group C probably represents two further cases of the oculo-anal syndrome which has received scant attention since its original description by Haab (1878). Group D represents two cases of hypersplenism with uveal coloboma, an association not recorded previously in the literature. Group E concerns two miscellaneous cases which may represent a partial expression of those represented elsewhere in the series.

One of the patients with isolated uveal coloboma had a sibling with a congenital dislocation of the hip, and another had a sibling and an aunt with bilateral anophthalmos.

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Table I  Findings in twenty cases

<table>
<thead>
<tr>
<th>Group</th>
<th>Case no.</th>
<th>Ophthalmic</th>
<th>Systemic</th>
<th>Family History</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>Left inferior iris coloboma</td>
<td>Incomplete right cleft lip Nose flattening</td>
<td>None</td>
<td>Not studied</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Bilateral iris and choroidal colobomata with microphthalmos</td>
<td>Bilateral cleft lip and palate Hypertelorism</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Bilateral choroidal colobomata</td>
<td>Bilateral cleft lip and palate Congenital dislocation right hip Calcium deformity</td>
<td>Not known</td>
<td>Not studied</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Coloboma left iris</td>
<td>Cleft palate, oligophrenia, microcephaly, micrognathia, deafness</td>
<td>Not known</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Bilateral iris and choroidal colobomata LEFT optic disc coloboma</td>
<td>Bilateral complete cleft lip, cleft palate, displaced premaxilla, nasal flattening, double aortic arch, patent ductus arteriosus, oligophrenia, deafness, low-set abnormal ears, inguinal hernia, oesophageal incompetence</td>
<td>Not known</td>
<td>Normal</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>Bilateral iris and choroidal colobomata</td>
<td>Oligophrenia</td>
<td>None</td>
<td>Not studied</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Right iris coloboma Right “leucoma adherens” (? Peters’ anomaly)</td>
<td>Oligophrenia, micrognathia, single palmar creases</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Bilateral iris colobomata Divergent squint Nystagmus</td>
<td>Oligophrenia, long upper lip, flat nose, high palate Spina bifida, dental abnormalities</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Left inferior iris coloboma Left choroidal coloboma P toes Positional nystagmus</td>
<td>Oligophrenia, defective speech, ventriculo-septal defect Pulmonary stenosis Dental abnormality</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Right iris coloboma RIGHT optic disc coloboma Left coloboma, involving iris choroid, and optic disc Left microphthalmos Left convergent squint Nystagmus</td>
<td>Oligophrenia, arrested hydrocephalus Convulsions Iron deficiency anaemia</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Left coloboma of optic disc and choroid RIGHT optic disc and partial choroidal coloboma RIGHT macular pigmentary change</td>
<td>Oligophrenia Microcephaly Malrotation of mid gut loop</td>
<td>None</td>
<td>Not studied</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>RIGHT coloboma of iris, choroid, and optic disc Divergent squint</td>
<td>Oligophrenia Microcephaly Diffuse EEG abnormality</td>
<td>Sibling had cleft palate and lip, and congenital dislocation of hip</td>
<td>Not studied</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>RIGHT coloboma involving choroid and optic disc RIGHT microphthalmos and convergent squint Bilateral nystagmus</td>
<td>Oligophrenia Single palmar creases Low set ears, hydrocele, hypospadias</td>
<td>Sibling</td>
<td>Not studied</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Bilateral choroidal colobomata RIGHT optic disc coloboma</td>
<td>Oligophrenia Ventriculo-septal defect</td>
<td>None</td>
<td>Not studied</td>
</tr>
<tr>
<td>C</td>
<td>15</td>
<td>Right iris coloboma</td>
<td>Rectal agenesis, imperforate anus Hydrospadias, horseshoe kidney, transposition of great vessels, extra right auricle Talipes equino varus Constriction of right middle finger</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>Left iris coloboma Intermittent left divergent squint</td>
<td>Imperforate anus, rectovaginal fistula</td>
<td>None</td>
<td>Not studied</td>
</tr>
<tr>
<td>D</td>
<td>17</td>
<td>Bilateral partial iris colobomata</td>
<td>Hepatosplenomegaly, leucoerythroblastic anaemia Congenital dislocation of hip Flat nose Oligophrenia</td>
<td>None</td>
<td>Not studied</td>
</tr>
</tbody>
</table>

Contin.
**Systemic associations of uveal coloboma**

D 18  Left coloboma of choroid and disc  
Right coloboma of iris, choroid, and disc  

E 19  Bilateral iris colobomata  

20  Bilateral iris colobomata  
Bilateral ptosis  
Broad epicanthus  
Bilateral epiphora  

|  | Splenomegaly  
|---|---  
|  | Myeloid hyperplasia of bone marrow  
|  | Leucoerythroblastic blood picture  
|  | Hypertelorism, low set ears  

Brother had hypertelorism, oligophrenia, "pixie-like" facies, bilateral inguinal hernia, left hydrocele  
Parents and brother normal  

|  | Hypertrophy right arm  
|---|---  
|  | Paraumbilical hernia  

None  
Not studied  

|  | Recession of upper jaw  
|---|---  

None  
Not studied  

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**Discussion**

This series of cases is highly selective. The cases that present to a hospital dealing with general paediatric disorders are more likely to have systemic abnormalities.

The commonest association finding was oligophrenia (Group B—9 cases, also Cases 4 and 5 in Group A and Case 17 in Group D). This is in accord with previous findings (Mollenbach, 1947).

Oligophrenia occurs in trisomy D and E (Valentine, 1969) and is found in all chromosomal abnormalities (except those of the sex chromosomes). The proper anatomical and functional development of the brain is dependent on many genes which are likely to be located on several chromosomes. The grouping of cases under the common presence of oligophrenia is thus artificial, but within the group distinct entities may be present.

The closure of the optic cleft itself is dependent on the action of a number of genes, as shown by the diverse modes of inheritance of colobomata. Uveal colobomata also occur in trisomy D and E (Cagianut, 1968) and in the oculo-anal syndrome—another chromosomal anomaly (Schachenmann, Schmid, Fraccaro, Manini, Tiepolo, Perona, and Sartori, 1965). The possible multiplicity and complexity of colobomatous syndromes is thus explained. This paper attempts to group the associations on clinical grounds. A more fundamental approach would be a grouping based on a detailed genetic analysis with precise information about chromosomal defects, but such a method is not at present readily available in the clinical sphere.

**GROUP A**

Cleft lip and/or palate and uveal coloboma can occur together as part of the trisomy D (Cagianut, 1968; Valentine, 1969). However, in our series of five cases, there was a normal karyotype in Cases 2, 4, and 5; chromosomal analysis was not undertaken in the other two. Despite these findings, we feel that these cases may well represent a true group, with a spectrum of clinical involvement from mild (Case 1) to severe (Case 5), dependent on the amount of chromosomal abnormality present. Patau, Therman, Inhorn, Smith, and Ruess (1961) have stated that "partial trisomy may only occasionally be detected microscopically". Other cases described in the literature of cleft lip and/or palate and uveal coloboma may belong to this group. Rocher and Pesme (1945) described ectromelia of upper limbs, Ueshiba (1952) facial clefts, Hoffmann-Egg and Velissaropoulos (1953) upper and lower lid colobomata and abnormalities of the external ear, and Tower (1953) absence of fingers and abnormalities of the upper limbs and nasolacrimal apparatus.

It is also possible that colobomata and/or cleft lip or palate, could be absent from the clinical picture and the phenotypic variability be even greater. Hence, in the syndrome of the first arch (François and Haustrate, 1954), where colobomatous microphthalmos was associated with general facial hemihypoplasia (deviation of the mouth to the left, aplasia of
the ascending branch of the mandible, malformation of the temporo-mandibular joint, and malformation of the outer ear), one brother out of four showed incomplete hare-lip. Abnormality of first arch is common in chromosomal disorders (Valentine, 1969).

In a cleft lip clinic, one in 100 cases corresponded to the oro-facial digital syndrome (Gorlin and Psaume, 1962). Here cleft palate can exist with polydactyly or syndactyly. As can be seen above, both these features are recorded with uveal colobomata. Grebe (1954) also described zygodactilia of first and second toes with inherited colobomata and oligophrenia. Gorlin and Psaume (1962) pointed out that several features of the oro-facial-digital syndrome are shared by other syndromes—Ellis-Van Crewel, Treacher Collins, Franceschetti, and Waardenburg. Likewise, several of the features are shared by colobomatous syndromes.

**GROUP C** presents two further cases of the oculo-anal syndrome. In a review of the previously recorded cases, Weber, Dooley, and Sparkes (1970) point out that Schachennann and others (1965) were the first to show that an extra chromosome was present. Associated abnormalities recorded were preauricular fistulae or skin tags, renal abnormalities, and oligophrenia. The features of Case 15 here extend this list (Table I). Conductive deafness, hypoplasia of the mandible, growth retardation, and hypoplasia of the bladder have also been observed (Gerald, Davis, Say, and Wilkins, 1972). Such phenotypic variability is thus explained in terms of a known chromosomal abnormality. We have already suggested that the phenotypic variability of Group A may likewise have a chromosomal abnormality which has not yet shown itself to be microscopically evident. Furthermore, the oculo-anal syndrome shows how an inherited colobomatous syndrome may not follow simple genetic laws. Thus, in one recorded family, the mother had the extra chromosome and was mildly retarded with bilateral uveal colobomata and renal abnormalities as shown by an intravenous pyelogram. Three phenotypically normal members showed chromosomal mosaicism with a proportion of their cells containing the extra chromosome. It would seem possible that some of the other familial colobomatous syndromes previously reported in the literature maybe explained on the basis of undetected chromosomal defects rather than in terms of one gene affecting many systems.

**GROUP D** includes two cases of the 'oculo-splenic' syndrome. This syndrome has not been reported previously. The features are listed in Table I. The familial nature of the hypersplenism and the phenotypic variability is compatible with an underlying chromosomal defect, as has been found in the oculo-anal syndrome. However, the brother and parents of Case 18 had detailed banding analysis of the chromosomes by the Giemsa technique and all had apparently normal karyotypes. A recessive mode of inheritance for this new syndrome thus appears more likely at present. Details of the blood analysis are given in Table II.

**GROUP E** probably represents partial expression of similar cases listed elsewhere in our series. Similar features have been described in previously reported cases (Waardenburg and others, 1966).

**Summary**

(i) Two cases of a previously undescribed association between uveal coloboma and hyper-splenism are reported.
Table II  Leucoerythroblastic blood picture of oculo-splenic syndrome
(Case 18) (percentages to nearest whole number)

<p>| | | | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Hb</td>
<td>14·2 g./100 ml.</td>
<td>Basophils</td>
<td>1 per cent.</td>
</tr>
<tr>
<td>W.B.C.</td>
<td>6,500 cu.mm.</td>
<td>Blast cells</td>
<td>4 per cent.</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>39 per cent.</td>
<td>Promyelocytes</td>
<td>1 per cent.</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>29 per cent.</td>
<td>Myelocytes</td>
<td>5 per cent.</td>
</tr>
<tr>
<td>Monocytes</td>
<td>4 per cent.</td>
<td>Megamyelocytes</td>
<td>9 per cent.</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>7 per cent.</td>
<td>Platelets</td>
<td>40,000 cu.mm.</td>
</tr>
</tbody>
</table>

Bone marrow result
Basophil precursors were particularly prominent. The neutrophils showed a bizarre nuclear pattern.

Splenectomy revealed a spleen weighing 200 g.

Sinusoids
There was diffuse myeloid metaplasia with granulocytes, red cell precursors, and primitive stem cells.

(ii) Two new cases of the oculo-anal syndrome are described.
(iii) Cleft lip and/or palate with uveal coloboma appear to be part of a distinct syndrome, with a wide spectrum of severity.
(iv) Oligophrenia is the commonest associated abnormality with uveal coloboma. There is a wide range of associated abnormalities which do not allow clinical classification.

We should like to thank Dr. Malcolm Ferguson Smith of the Genetics Institute, Glasgow University, for kindly undertaking the detailed banding chromosome analysis on relatives of Case 18.

We should also like to thank Dr. Peter Harper for his help and discussion of the genetic aspects of this paper.

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