

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.

Table I Findings in twenty cases

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

Contin.

D 18	Left coloboma of choroid and disc Right coloboma of iris, choroid, and disc	Splenomegaly Myeloid hyperplasia of bone marrow Leucoerythroblastic blood picture Hypertelorism, low set ears	Brother had hyper- splenism, oligoph- renia, "pixie-like" facies, bilateral inguinal hernia, left hydrocele	Parents and brother normal
E 19	Bilateral iris colobomata	Hypertrophy right arm Paraumbilical hernia	None	Not studied
20	Bilateral iris colobomata Bilateral ptosis Broad epicanthus Bilateral epiphora	Recession of upper jaw	None	Not studied

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 zygodactylia 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 Creweld, 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 Schachenmann 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 1. 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 hypersplenism are reported.

Table II *Leucoerythroblastic blood picture of oculo-splenic syndrome*
(Case 18) (percentages to nearest whole number)

Hb	14.2 g./100 ml.	Basophils	1 per cent.
W.B.C.	6,500 cu.mm.	Blast cells	4 per cent.
Neutrophils	39 per cent.	Promyelocytes	1 per cent.
Lymphocytes	29 per cent.	Myelocytes	5 per cent.
Monocytes	4 per cent.	Megamyelocytes	9 per cent.
Eosinophils	7 per cent.	Platelets	40,000 cu.mm.

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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