Complex sporadic colobomata

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SUMMARY Sporadic colobomata may be associated with a variety of secondary changes, and these have been classified and discussed with special reference to unusual findings published during recent years. Clinically some cases may appear to be neoplastic, and pathological examination may be important in demonstrating their true nature. A malformation apparently not previously reported is described.

Bartholin (1671) appears to have been the first to understand and report the hereditary nature of colobomata in the iris. Documentation of colobomatous malformations is now enormous, and excluding those occurring as part of a more generalised syndrome they may be classified as follows: (1) Colobomata associated with intraocular tissues not normally found in the eye, e.g., lacrimal gland tissue, cartilage, bone unstriated or smooth muscle; (2) the formation of cysts in relation to coloboma oculi; (3) tumour formation along the line of closure of the embryonic fissure; (4) the coincidence of an identifiable congenital infective agent with a colobomatous defect; (5) colobomata in eyes which may have other abnormal ocular anatomical changes.

Group 1

Lesions in this group are distinguished by the presence of heterotopic intraocular tissue. Christensen and Anderson (1952) found lacrimal gland tissue in the ciliary body associated with a coloboma at the limbus as well as anterior chamber cyst formation in a 2-week full-term healthy baby. Suspected medulloepithelioma had led to enucleation. Morgan and Mushin (1972) reported an example of intraocular lacrimal gland tissue but without colobomata. Both cases presented with secondary clinical effects. The lacrimal gland does not appear embryologically until the 25-mm stage, and the fetal cleft closes at the 15-mm stage, so possible explanations for this abnormality may be (a) a defect in the sclera into which aberrant tissue grows; this requires evidence of a colobomatous defect as in the case described by Christensen and Anderson; (b) epithelial islands

developing in the aberrant tissue are carried into the mesoderm with the lens plate; or (c) the aberrant tissue develops *in situ* from lacrimal anlage cells sited in the primitive mesoderm.

Mullaney *et al.* (1971) reported a healthy baby (weight 3.3 kg) who died 48 hours after birth from bronchopneumonia with bilateral typical uveal colobomata extending to the optic disc. A focus of cartilage proceeding to ossification and encased by scleral mesoderm at all levels, approximately 3 mm from the left optic disc, lay immediately beneath the uveal coloboma and along the line of the embryonic fissure. The paraxial mesoderm which formed the scleral coat extended from the limbus to reach the posterior pole at the first month of intra-uterine life, so that the ossification could be presumed to have occurred during the last 4 fetal months. The scleral bone in this case bore some resemblance to the os opticus of avian species.

The first example of ectopic adipose tissue in an optic disc coloboma was reported by Pedler (1961). Willis *et al.* (1972) collected 26 cases of coloboma associated with heterotopic adipose and/or smooth muscle tissue including material provided by N. Ashton and W. A. Manschot.

Two groups were discussed. The average age for enucleation in the first group (16 patients) was 20 years, the reasons for surgery being either pain due to unilateral secondary glaucoma or for cosmetic reasons. In their second group of 10 cases the median age at the time of enucleation was 1.5 years, the clinical presentation suggesting an intraocular neoplasm with strabismus or leucocoria and all having optic disc colobomata. The optic disc area may be locally expanded with absence of the lamina cribrosa and expansion of the optic nerve to more than twice its normal thickness.

Microscopically, glial, osseous, and fatty tissue

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Fig. 1 Section of whole eye. Accessory ciliary body (arrow)

were present, but the most interesting finding was the existence of smooth muscle strands, often orientated concentrically within the optic nerve and frequently forming an incomplete ring about the gliosed nerve. In some instances the smooth muscle projected through the scleral defect and entered the choroid, occasionally extending for some distance along it away from the coloboma. These cases are of particular interest to the clinician because the associated changes may suggest an intraocular neoplasm. Sugar and Beckman (1969) reported movements of optic disc staphylomata coinciding with respiration, while Kral and Svarc (1971) elicited a similar reaction by shining a strong light into either the affected or the normal eye. Graether (1963); and Longfellow *et al.* (1962) had cases of episodic blindness associated with periodic dilatation of the retinal veins, due possibly to an incomplete spincter-like stricture movement by the smooth muscle over and about the optic nerve. More than one-quarter of the eyes in the study by Willis *et al.* (1972) had been clinically misdiagnosed as containing a tumour.

Mullaney *et al.* (1976) studied 100 eyes from 67 consecutive anencephalic babies, and more recently I have observed an eye of an anencephalic female baby (birth weight 2000 g) who lived for 9 days with, among other congenital ocular derangements, an accessory ciliary body (Fig. 1). The child was born to a healthy 23-year-old woman at 44 weeks of pregnancy. The right eye, apart from minor anterior segment immaturity, was within normal limits, though there was trophic superficial keratitis. The left eye was of irregular shape, with a large, thickened, white cornea measuring approximately 15 mm in diameter. A small white spot about 2 mm wide could be seen in the opened globe in the peripheral

retina beneath the cornea but remote from the optic disc. Histologically there was trophic keratitis with secondary hypopyon and an anterior chamber with usual architecture. Some distance from the ciliary body the retina contained a break which was surrounded by a well-formed pigmented ciliary process resembling a pars plicata ciliaris. Bundles of smooth muscle both of circular and of meridional arrangement were closely associated with these papillary processes (Fig. 2). The muscle of unequivocally unstriated type extended anteriorly before becoming attenuated and interrupted by collagen. It was difficult to know if the muscle fibres were continuous with those of the normal ciliary body because of the quantity of collagen present beneath the thickened corneal tissue. A small polypoid mass of mesoderm occupied the colobomatous gap in the retinal zone, and from it thin-walled vessels ramified in the nearby vitreous. Dysplastic retina led posteriorly from the ciliary-like processes into typical 'anencephalic' retina. A very small closed optic disc often seen in anencephaly was identified but was some distance from the pseudo-ciliary body. Pigmented ciliary processes are of common occurrence at the margins of colobomatous defects in the choroid (Fischer, 1934; Manschot, 1963). However, the association with smooth muscle does not appear to have been reported previously, although Andersen (1977) has seen a similar case.

Group 2

Colobomatous cysts were first categorised by Arlt (1858), who thought that they were due to incomplete closure of the embryonic cleft, and much has been written about them. Waring *et al.* (1976) describing 4 eyes with microphthalmos, large cyst formation, and multiple eye malformations, mentioned the value of orbital ultrasound in demonstrating microphthalmos where there may be a visible or palpable mass behind the lower eyelid. They also indicate that confusion with orbital meningoencephalocoeles is unusual, as the cysts often increase size with crying, and the posterior or medial orbit may be abnormal on radiological examination.

The histogenesis of a congenital iris stromal cyst was described by Mullaney and Fitzpatrick (1973). The patient, a 6-month-old girl with a sore eye, had enucleation performed because neoplasia was suspected. A coloboma in the ciliary body muscle was associated with a pouch of modified squamous epithelium of conjunctival type extending into the sclera and continuous with a large iris cyst filling the anterior chamber. The eye was otherwise normal. It appeared possible that a sequestered focus of surface ectoderm in a coloboma of the sclera and

Fig. 2 Collections of smooth muscle beneath pigmented processes. (H and E $\times 110$)

ciliary muscles had extended into the developing anterior chamber and expanded to form the cyst. The histological findings in this case explain the difficulty likely to be encountered in attempting to extirpate these lesions.

Group 3

The original cells of the optic vesicle are of neuroepithelial type and are the same as those in the embryonic cerebral wall (Mann, 1928). Choristomas and neoplasms may occur along the line of closure of the embryonic fissure. Congenital neuroepithelial tumours of the ciliary body were classified by Zimmerman (1971) as: (a) glioneuroma, (b) medulloepithelioma, (1) benign, (2) malignant, and (c) teratoid medulloepithelioma, (1) benign, (2) malignant. Glioneuromas occurring in the region of the ciliary body with colobomata consist only of brain tissue and are considered by Zimmerman to be essentially choristomatous malformations and not true neoplasms. Kühlenbeck and Haymaker (1946) described a wide coloboma of the ciliary body in a newborn girl whose eye was enucleated at the age of 2 months because of a tumour in this area. Histologically, it contained mature glial cells, mainly astrocytes, together with scattered small, fairly mature nerve cells, some of which were of pyramidal shape, with some tubular formations and rosettes, ependymal cells. This tumour emphasises the intimate genetic relationship between retina and forebrain.

Spencer and Jesberg (1973) reported 2 cases of glioneuroma arising in association with coloboma in the ciliary body region. Their first case was a white boy noted to have a coloboma of the iris in the right eye at birth. Enucleation was performed at the age of 6 months. The colobomatous defect involved the iris, ciliary body, choroid, and retina. Sections showed the tumour to be continuous with the nerve fibre layer of the retina lying along its inner surface and extending inferiorly to become episcleral in position. The majority of the cells appeared to be of glial origin, resembling fibrillar astrocytes, although neurones were also present. It appeared that portions of the iris and ciliary body failed to develop normally, producing instead a large well-differentiated mass resembling brain.

Residual rests of the medulloepithelium are the anlagen from which tumours composed of cells closely resembling medullary epithelium can arise, i.e., medulloepitheliomas, but there may also be structures similar to those derived from the secondary optic vesicle or optic cup, namely, retinal pigment epithelium, ciliary epithelium, vitreous, and neuroglia. Medulloepitheliomas of all types usually originate in the ciliary body (Andersen, 1962; Zimmerman, 1970; Reese, 1976) but may also occur anywhere between it and the optic disc (Reese, 1957; Christensen, 1973; Mullaney, 1974), and the association of these growths with complicated mesodermal tissues such as cartilage and striped muscle appears to correlate with defective closure of the embryonic fissure at any site.

Group 4

Cytomegalovirus infection (CMV) has now emerged in the USA as the commonest viral infection of the neonate with an incidence of 5 to 20 per 1000 live births. The first report of ocular involvement in a patient with a congenital infection was published 30 years ago by Kalfayan (1947). The ocular changes included chorioretinitis, perivascular exudates, retinal haemorrhages, corneal clouding, cataract, and optic atrophy. Hittner *et al.* (1976) had 4 patients with congenital cytomegalovirus infections with optic nerve abnormalities, namely, optic nerve hypoplasia, partial coloboma, and complete coloboma associated with microphthalmia, and they suggest that all congenital optic nerve malformations should be evaluated for cytomegalovirus.

Group 5

Intraocular malformations may not necessarily be directly associated with the coloboma. Foos *et al.* (1968) reported a large temporal coloboma of the lens and many other maldevelopments in a buphthalmic globe. They described a true accessory pupil and consider that their report appeared to be the first histological examination of such a case. They agree with the theory of Mann (1957) that accessory pupils are derived from partial iris colobomata wherein both mesodermal and ectodermal (sphincter muscle) bridges have played a role. Weiter *et al.* (1977) studied 13 cases with unilateral aplasia of the optic nerve and disc in otherwise healthy infants. Clinically the eyes were described as blind and usually microphthalmic. The colobomata were mainly located anterior to the equator, involving the peripheral retina and ciliary body in 11 out of the 13 cases. They were unable to account for the defective invagination of the optic vesicle which appeared to be the cause of the abnormality.

Grey and Rice (1976) described 2 well-formed clear lenses lying in the coronal plane of the eye and a typical coloboma of the iris in a 7-week-old normal baby boy. Both lenses appeared to be circular, except that the upper margin of the inferior lenses had a slightly concave outline, and each lens had an apparently separate capsule. Fundoscopy showed a typical drumstick-shaped coloboma in the choroid extending from the disc. The authors thought that a defective optic vesicle might have led to the formation of 2 lens pits and 2 separate lenses. No treatment appears to have been done.

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