CONGENITAL OPACITIES OF THE CORNEA*

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CONGENITAL corneal opacities vary greatly in extent and location and are usually associated with other anomalies of the anterior segment. Although a variety of clinical terms, such as cornea plana, sclerocornea, Rieger's anomaly, Axenfeld's syndrome, has been used to describe these anomalies, recent evidence (Goldstein and Cogan, 1962) suggests that they are all closely related entities. Theodore (1944) believed that the anomalies were the result of an abnormal mesodermal development and supported the earlier views of Collins (1907) and Seefelder (1920), who attributed the corneal opacities to a defect in Descemet's membrane. Forsius (1961) has drawn attention to the familial occurrence of cornea plana which emphasizes the importance of genetic factors when considering the aetiology of these anomalies. However, many sporadic cases have been reported (Goldstein and Cogan, 1962), frequently in association with other systemic and neurological defects, and the possibility that some of the anomalies may be due to teratogenic agents should not be overlooked. A group of 7 patients has been examined in whom the principal clinical finding was dense congenital opacification of the cornea. The problems associated with their aetiology, diagnosis, and management will be illustrated by reference to the clinical histories and the pathological examination of three eyes.

Case Reports

Case 1.—A first-born female child who weighed 6 lb. at birth after the mother's uneventful pregnancy and labour. The mother had ulcerative colitis which required intermittent treatment with adrenal steroids and Neurotrasentin. There was no history of maternal infection or other drug ingestion apart from vitamin supplements. After birth it was seen that the child's corneas were opaque but not enlarged (Fig. 1). A provisional diagnosis of congenital glaucoma was made but

FIG. 1.—Case 1. Corneal opacities at age of 10 days.

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intra-ocular pressure readings were not determined. General physical examination revealed a loud systolic murmur and the child's legs were maintained in a foetal position. Death from gastro-enteritis and pneumonia occurred twelve days after birth and both eyes were obtained for pathological study. The first eye was embedded in celloidin and routine sections (Fig. 2a-d) revealed a marked thickening of the cornea, an open angle with large quantities of uveal pigment deposited in the ciliary sulcus, and a nuclear cataract. Many cells in the pigment epithelium of the iris were vacuolated and were the most likely source of the pigment seen in the anterior chamber. Although Descemet's membrane was intact, it was thinner centrally and in many sections was detached from the posterior surface of the cornea. An intact pupil membrane was noted in serial sections which occluded the pupil opening. The posterior segment appeared normal. The second eye was examined under a dissecting microscope and the corneal diameters were noted to be 8.0×8.5 mm. The eye was bisected at the equator and the lens was removed. The anterior segment was then divided along the horizontal meridian and the anterior chamber was studied carefully. A pupil membrane was again noted which extended from the minor collarette of the iris to the posterior surface of the cornea where it was firmly attached. Traction on the iris produced a detachment of Descemet's membrane. A small amount of pigment was lying free in the anterior chamber, but the chamber angles themselves were open and normally developed. Openings were present in the pupil membrane close to its attachment to the iris and further sectioning of the

FIG. 2.—Case 1. Sections to illustrate (a) Diffuse corneal thickening, persistent pupil membrane (dots), open angle. The separation of Descemet's membrane is an artefact. (b) Attachment of pupil membrane to minor collarette. (c) Pigment (arrow) trapped in root of iris. (d) Transition from normal nuclei of peripheral cortical fibres to pyknotic nuclei in lens nucleus.

membrane showed frequent open vessels. Flat preparations (Fig. 3) were made at the site of attachment of the pupil membrane to the posterior surface of the cornea and these showed a sharp line of demarcation between normal corneal endothelium and a central plaque of primitive mesenchymal cells. There were no signs of inflammation. The general post-mortem examination revealed numerous cysts in the white matter of the brain (Fig. 4) but the remaining organs had developed normally. Microscopic examination of the brain showed loss of substance in the white matter, occasional foci of lymphocytes, and areas of calcification in the walls of some intracerebral vessels. Genetic studies revealed a normal complement and pattern of chromosomes.

FIG. 3.—Case 1. Flat preparation from posterior surface of left cornea showing abrupt transition from normal endothelium to a central plaque of primitive mesenchymal cells.

FIG. 4.—Case 1. Sections of brain illustrating extensive cyst formation in cerebral white matter (arrows).

Comment.—The corneal opacities in this infant can be attributed to the presence of a plaque of mesenchymal cells which replaced the normal endothelium lining the central portion of the cornea. The size of the plaque which corresponds to the pupil opening, the nuclear cataract surrounded by healthy cortex, and the uveal pigment trapped in the root of the iris, indicate a disturbance in development occurring after completion of the ingrowth of the iris and just before the atrophy of the pupil membrane at the beginning of the fifth month of gestation. The cysts in the white matter indicate that the ocular anomalies are only part of a more generalized disturbance of development.

Case 2.—The second of dizygotic twins born as a double footling breech after 8 months' gestation, this male infant weighed 4 lb. 13 oz. at birth. The first female twin was normal and weighed 5 lb. 10 oz. One placenta weighed 325 g. and was normal, whereas the second weighed 348 g. and showed an extensive calcified infarct. In the second (present) twin ocular anomalies and hypospadias were noted immediately after birth, and it was subsequently established by a buccal smear and laparotomy that the child was a male with undescended testicles. Ocular examinations showed bilateral dense corneal opacities and the corneal diameters measured 11.0 × 9.5 mm. in the right eye and 10.0 × 8.5 mm. in the left eye (Fig. 5). Each lens had a dense nuclear cataract and was attached to the posterior surface of the cornea resulting in very shallow anterior chambers. The peripheral cornea was also hazy in the right eye and in both eyes only a narrow rim of iris was present. A red reflex was present in the left eye but no fundus details could be seen. Intra-ocular pressure readings were 40 in each eye and a trephine operation was performed on the right eye at three months of age. Re-examination at six months indicated a persistent elevation in intra-ocular pressure in each eye although at nine months of age the pressure appeared to be normal in the left eye. Throughout the period of observation there was no appreciable change in the corneal and lenticular opacities and when the child was last examined at eighteen months of age there was evidence of light perception in the left eye. The child is retarded but it is too early to establish whether or not true mental deficiency is present. Five siblings are reported to be normal.

Comment.—The nuclear cataract, partial aniridia, obliteration of the anterior chambers, and hypospadias indicate a disturbance of development occurring before the fourth month of gestation. The birth of a normal twin sister and the finding at delivery of a calcified placental infarct suggest that the disturbance to development may have been an interruption in the foetal blood supply.

FIG. 5.—Case 2. Corneal opacities at age of 2 years.

FIG. 6.—Case 3. Corneal opacities at age of 3 months.

Case 3.—A first-born female child weighing 4 lb. 9 oz. at birth after the mother's normal pregnancy which lasted nine months. Immediately after birth bilateral corneal oedema was noted which was a little more marked in the left eye than the right. The corneal opacities were most marked centrally and obscured all details of the iris and pupil opening (Fig. 6). A peripheral band of clear cornea was present in the limbal area of each eye and no vascularization had occurred. Transillumination showed clear lenses and a normal pupil opening which in the left eye appeared to be displaced a little nasally. This technique also revealed in the left eye several small V-shaped clefts in the iris which formed a ring near the limbus. In the right eye two small radial slit defects were

present just peripheral to the sphincter at 9.00 and 7.00 o'clock. When the child was first examined under anaesthesia in December, 1963, the intra-ocular pressures were apparently elevated and bilateral goniotomies were performed, the provisional diagnosis being congenital glaucoma. The opacities did not clear and when she was re-examined under anaesthesia one month later the corneal diameters measured 9.5×9.0 mm. in the right eye and 10.0×9.0 mm. in the left eye. At this time the intra-ocular pressures were 25 in the right eye and 18 in the left eye. A detailed clinical examination has not revealed any associated anomalies and the child has gained weight and developed normally. Nystagmus has developed at nine months and there is evidence of some reduction in the extent of the central corneal opacities.

Comment.—Although not established definitely by clinical examination, it seems most likely that a central defect in the corneal endothelium was responsible for these congenital opacities.

Case 4.—A female infant, the eighth in a family of healthy children. Delivery was normal after full-term pregnancy and the child weighed 6 lb. The mother stated that she had had German measles during the second month of her pregnancy. At birth bilateral dense central corneal opacities and bilateral clubbed feet were noted. The corneal opacities were most dense centrally and prevented a detailed examination of the anterior segments (Fig. 7). Near the limbus the corneas were more transparent and in the left eye the iris was visible. On examination under general anaesthesia it was found

FIG. 7.—Case 4. Corneal opacities at age of 10 months.

that the corneal diameters measured 12 mm. in each eye and the intra-ocular pressures measured 49 in the right eye and 42 in the left eye. A thermal sclerectomy was performed on the right eye and trephining on the left eye. It was noted at the time of surgery that the anterior chambers seemed shallow and vitreous presented after the trephine operation was performed. There was no immediate change in the ocular findings post-operatively. At eleven months of age the child was re-examined under general anaesthesia and the corneal diameters were again 12 mm. There was evidence of slight reduction in the extent of the corneal opacities but no further details could be seen of the anterior segments. At this time, when nearly one year old, the infant weighed only 11 lb. and the parents stated that she was difficult to feed and could not sit up. Shortly afterwards, death occurred from pneumonia and a post-mortem was not performed.

Comment.—The ocular findings in this child are very similar to those in Case 3, although the failure to gain weight and feed properly indicates a more general disturbance in development.

Case 5.—A full-term male infant who weighed $8\frac{1}{2}$ lb. at birth after a normal delivery. The mother had had no significant illness or unusual drug intake during pregnancy and two siblings are healthy. The mother's first child was stillborn close to term for no apparent reason. At birth in the child here reported bilateral dense corneal opacities were seen in each eye but no other anomalies were found on general examination. At 3 months of age a detailed examination was made under general anaesthesia. The right cornea was almond-shaped and measured 10.0×7.5 mm. and the left measured 10.5×8.2 mm. Dense central corneal opacities extended to the limbus superiorly in each eye and covered the pupil opening in the right eye, while in the left eye the lower border of the

pupil was exposed (Fig. 8). Below the lower edge of the opacities the corneas were clear and the anterior chambers were present but shallow. Vascular loops were present on the surface of the iris in the left eye which appeared to be attached to the back of the cornea. Gonioscopy subsequently showed irido-corneal adhesions beneath the opacities. Both lenses were clear and a red reflex was present in each eye. Retinal vessels were seen in the left eye. Intra-ocular pressures were difficult to measure because of the small palpebral fissures but there seemed to be a significant elevation in the right eye.

FIG. 8.—Case 5. Corneal opacities at age of 3 months.

Comment.—In this child a more detailed clinical examination was possible which indicated that the corneal opacities were associated with extensive adhesions between the iris and cornea.

Case 6.—A 30-year-old professional writer came under observation because of secondary glaucoma in her left eye which failed to respond to medical and surgical measures. At birth this patient had weighed 7 lb. 6 oz. after her mother's full-term pregnancy and normal delivery. Three siblings have healthy eyes. Cloudy corneas were noted at birth and no systemic abnormalities were found. On examination her visual acuity was 20/200 in the right eye and light perception in the left eye. Corneal diameters measured 8.5 mm. in each eye. In the right eye a peripheral corneal opacity formed an irregular band at the limbus which was more marked on the temporal side. The pupil was elliptical and was displaced temporally towards a dense adhesion between the iris and posterior surface of the cornea which was present 2 mm. inside the limbus at 10.00 o'clock. Gonioscopy again revealed the irido-corneal adhesion stretching across the anterior chamber and in addition showed an extensive peripheral union of iris and cornea, except for two small clefts at 11.00 and 5.00 o'clock. The media and fundi appeared healthy. In the left eye bullous keratitis prevented a detailed examination. Intra-ocular pressure was normal in the right eye and elevated in the left eye. The patient continued to experience discomfort in the left eye and an enucleation was performed.

The gross specimen was bisected equatorially and examination of the posterior segment revealed a pale cupped disc. The lens was removed and no posterior synechiae were found. The anterior segment was divided in the horizontal meridian and two silicone setons, which had been introduced to induce trans-scleral filtration, were located in the anterior chamber, and a large iridectomy was present superiorly. Inferiorly, a continuous adhesion was present between the mid-peripheral portion of the iris and cornea, producing a false chamber angle. Peripheral to this adhesion, the iris separated from the cornea and a true chamber angle was present. Microscopic examination confirmed the presence of irido-corneal adhesions and showed, in addition, partial reduplication of the pupil sphincter and splitting of the anterior layers of the iris (Fig. 9a, b). A defect in Descemet's

FIG. 9.—Case 6. Sections of anterior segment illustrating (a) true and false chamber angle created by a fine irido-corneal adhesion in mid-periphery, and (b) splitting of anterior layers of iris at the site of a more extensive adhesion.

membrane was present where the adhesions were most extensive. The true chamber angle was quite well developed. A ciliary sulcus was present and the trabecular meshwork, although more pigmented than usual, was laminated and the innermost fibres were normal in length. Schlemm's canal was present and the scleral plexus was open.

Comment.—In this patient the corneal opacities were not well delineated and appeared most dense near the limbus. In each eye extensive irido-corneal adhesions produced a false angle, but microscopic examination showed that peripheral to the adhesions a true angle had developed, which indicates that the interference with development occurred sometime after the differentiation of the true angle had taken place. The clinical findings in this patient have many features in common with a mesodermal dysplasia of Rieger.

Case 7.—A 28-year-old male shipper was referred to the corneal clinic for assessment of bilateral congenital corneal opacities. The patient was unaware of any obstetrical problems prior to his birth and stated that seven siblings had healthy eyes. On examination, visual acuity was light perception in the right eye and 20/100 in the left eye. Corneal diameters measured 7.5 mm. in each eye and it was difficult to determine the position of the limbus because of central and peripheral opacities (Fig. 10). The whole of the right cornea was involved except for two clear peripheral islands at 3.00 and 7.00 o'clock. The central portion of the left cornea was clear but the periphery, especially inferiorly, was opaque and was difficult to differentiate from sclera. A single adhesion between the iris and cornea was present behind the area of scarring at 3.00 o'clock in the left eye, but no further details of the angle were visualized. The lens and posterior segments were healthy and intra-ocular pressure readings were normal.

FIG. 10.—Case 7. Corneal opacities at age of 26 years.

Comment.—In the right eye the scarring was most marked centrally and was similar to the opacities in the first four cases. In the left eye the scarring was more marked at the periphery of the cornea, which is typical of sclerocornea.

Discussion

Clinical Findings

The presenting ocular abnormality in this series of patients was a congenital opacity of the cornea (Table I). The opacity varied from total corneal involvement to small central leucomas. Although central corneal involvement was most frequently recorded, peripheral concentric bands adjacent to the limbus and wedge-shaped opacities extending from the centre of the cornea to the limbus were also observed. Uninvolved areas of cornea retained a normal transparency. There was no evidence of inflammation, and vascularization was found in only one eye. The condition was bilateral in all cases and showed no tendency to progress. The associated ocular abnormalities on clinical examination consisted of central lens opacities (4 eyes) and elevated intra-ocular pressure (definite in 5 eyes and probable

TABLE I
SUMMARY OF OCULAR FINDINGS

Case	Corneal Opacity	Corneal Diameter	Iris	Lens	Intra-ocular Pressure	Surgery
1	Bilateral total	8.0 × 8.5 mm.	Bilateral persistent pupil membrane adherent to cornea	Nuclear cataract	Unknown	None
2	Bilateral small central	Right eye: 11.0 × 9.5 mm. Left eye: 10.0 × 8.5 mm.	Bilateral partial aniridia	Bilateral nuclear cataract, lenticulo-corneal adhesions	Bilateral elevation	Right eye: Trepine
3	Bilateral large central	Right eye: 9.5 × 9.0 mm. Left eye: 10.0 × 9.0 mm.	Fine peripheral clefts on transillumination	Clear on transillumination	Apparent initial elevation	Bilateral goniotomy left eye. Iridectomy
4	Bilateral large central	Both eyes: 12 mm.	Not visualized	Not visualized	Apparent initial elevation	Thermal sclerectomy and trephine
5	Bilateral wedge-shaped from limbus to pupil	Right eye: 10.0 × 7.5 mm. Left eye: 10.5 × 8.2 mm.	Irido-corneal adhesions both eyes	Clear on transillumination	Elevated in right eye	None
6	Right eye: Extensive peripheral Left eye: Diffuse	Both eyes: 8.5 mm.	Both eyes: Irido-corneal adhesions	Clear	Elevated in left eye	Left eye: Several filtering procedures Enucleation
7	Right eye: Almost total Left eye: Extensive peripheral	Both eyes: 7.5 mm.	Right eye: Not visualized Left eye: Iridocorneal adhesion	Clear	Normal	None

TABLE II
SUMMARY OF GENERAL FINDINGS

Case	Birth-weight	Sex	Siblings	Associated Abnormalities
1	6 lb.	F	0	Died 12 days after birth; extensive cyst formation in cerebral white matter
2	4 lb. 13 oz.	M	5	One of dissimilar twins, calcified placental infarct, hypospadias, undescended testicles; retarded mentally at 18 months
3	4 lb. 9 oz.	F	0	Apparently healthy
4	6 lb.	F	7	Bilateral clubbed feet, failed to gain, and died at eleven months
5	8 lb. 8 oz.	M	2 normal 1 stillborn	Apparently healthy
6	7 lb. 6 oz.	F	3	Healthy
7	Unknown	M	7	Healthy

in 4). Measurement of intra-ocular pressures was difficult because of the small palpebral openings, and small corneal diameters. Iris anomalies consisted of irido-corneal adhesions (seen clinically in 4 eyes) corectopia (1 eye), and partial aniridia (2 eyes), and pathological study revealed irido-corneal adhesions in another eye and a persistent pupil membrane in two additional eyes.

The associated general abnormalities (Table II) in this series consisted of hypospadias and undescended testicles (1 infant) and bilateral clubbed foot (1 infant).

Another infant who died at twelve days showed pathological evidence of widespread cyst formation in the cerebral white matter, and a second who died at eleven months after failure to develop may also have had cerebral involvement. One of the three surviving infants shows mental retardation and may be defective, while the remaining two infants are too young to assess, although they are developing normally. The two adults earn their living and appear to have average and superior intelligence.

Differential Diagnosis

The common diagnosis made in the infants was congenital glaucoma, and glaucoma surgery was performed on six eyes. Features which differentiate the cases from primary glaucoma are small corneal diameters, the generally sharp discontinuity between clear and opaque areas of cornea, failure of the corneal opacity to clear when intra-ocular pressure is reduced, and shallow anterior chambers. A congenital dystrophy is characterized by uniform corneal haze and the corneal diameters are normal. The anterior chambers are well formed and there is no evidence of iris involvement. In contrast, the corneal opacities in these patients were unevenly distributed, the anterior chambers were shallow, and irido-corneal adhesions were frequently found. If the corneal opacities are extensive they may obscure the underlying pathology in the anterior chamber making a correct diagnosis difficult.

Pathogenesis

The immediate cause of the corneal oedema and scarring in the first case was a plaque of primitive mesenchymal cells which replaced the normal corneal endothelium, and formed part of a persistent pupil membrane. In the second case the cornea and lens were bound together centrally, but in the third and fourth cases, which resembled the first, the corneal opacities were so extensive that the underlying pathology was obscured. In the last three cases there was further evidence of irido-corneal adhesions. Thus in five of the seven cases there was definite evidence of an abnormal attachment between the iris-lens diaphragm and the posterior surface of the cornea. The opacities therefore appear to be the result of an interruption in the normal corneal endothelium.

Adhesions similar to those found in these patients are acquired in adult life as a surgical complication of flat anterior chambers, and it would appear that the iris and cornea are very liable to form a permanent union after prolonged contact. In the middle trimester of foetal life a comparable situation exists and it is surprising that anomalous irido-corneal adhesions are so rare. During this period the cornea is in intimate contact with the developing iris and pupil membrane, and these separate when perforations in the pupil membrane permit formation of the anterior chamber in the early part of the last trimester. The anomalies in these patients can best be explained by assuming an interference with foetal development during this period. For example, in the first case the adhesion must have formed quite late in foetal life, as Descemet's membrane, although thin centrally, was intact, and the anterior chamber and iris were normal. The position and extent of the abnormal mesenchymal cells on the posterior surface of the cornea indicates a developmental disturbance just before the normal atrophy of the pupil membrane. In contrast, the partial

aniridia in the second case and the associated hypospadias indicate an earlier developmental disturbance which resulted in a permanent lenticulo-corneal adhesion and prevented the normal ingrowth of iris. The evidence does not support an earlier view that the central corneal scarring is related to a disturbance in the development of the primary lens vesicle from surface ectoderm (Mans, 1927).

Irido-corneal adhesions and scarring may be the result of an inherited mesodermal defect or may be associated with detectable chromosome anomalies (Cogan and Kuwabara, 1963). In this series familial involvement was not recognized and in two patients the chromosome pattern was normal. This evidence does not rule out a genetic defect; nevertheless, consideration should be given to the possibility that some of the sporadic cases described in this series and in the literature are acquired as a result of a teratogenic agent influencing foetal development. It is important to remember that acquired and inherited anomalies may resemble each other closely.

Ballantyne (1905) and Von Hippel (1908) considered the possibility of infection *in utero*, but pathological studies have frequently failed to show evidence of inflammation. A review of the maternal and obstetrical histories has failed to suggest a common teratogenic agent. However, the occurrence of congenital corneal scarring in one of dissimilar twins in association with a calcified placental infarct is of considerable interest. This observation suggests that the disturbance to development, if acquired, is probably intrinsic to the foetus, and may be a metabolic disorder related to a failure in blood supply. Further support for the concept that a failure in blood supply leading to foetal hypoxia might be responsible is provided by the finding of widespread cystic changes in cerebral white matter recorded in Case 1. The degeneration in white matter is characteristic of infants who have experienced hypoxia in the pre-natal period (Benda, 1952; Cammermeyer, 1958). Hypoxia might also explain the absence of inflammatory signs and the release of uveal pigment in this infant. Neurological defects were suspected in the second and third cases in this series, and have been associated with several of the mesodermal anomalies reported in the literature. Most of the reported cases of cystic degeneration of white matter have occurred in infants subjected to hypoxia close to term, which may explain why ocular anomalies have not been found. In order for corneal opacities to occur it seems likely that the disturbance to development must take place before the formation of the anterior chamber. Although in several instances the cause of foetal anoxia has been obvious, Cammermeyer notes that "a large number of reports contain no information about antenatal disturbances of the mother". It is not surprising, therefore, that the maternal obstetrical histories have been normal.

Treatment

The two adults in this series have sufficient clear cornea in one eye to achieve a visual acuity of 20/200 and in one of the infants this level of vision can be anticipated. However, one of the five survivors has extensive bilateral central corneal opacities, and nystagmus has developed. An optical iridectomy has been performed and a penetrating keratoplasty appears to be the only additional means of improving vision. Glaucoma has fortunately affected only the more severely involved eyes and treatment consisting of trephining, sclerectomy, and goniotomy has had no effect on the corneal

opacities and a questionable effect on the glaucoma. In planning treatment and advising parents, the neonatal mortality and the possibility of mental deficiency should be considered.

Summary

Extensive bilateral congenital corneal opacities have been found in 7 patients in frequent association with a persistent contact between corneal endothelium, iris, and pupil membrane. The adhesions appear to be the result of an interference with foetal development in the middle trimester. A common teratogenic agent has not been identified, and it is possible that an inherited primary mesodermal defect is responsible for some of the anomalies, although familial involvement was not recorded. The presence of widespread cystic degeneration of cerebral white matter in one child, and the finding at the birth of another of a calcified placental infarct, suggests that foetal hypoxia may be another important aetiological factor.

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