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Posterior axial corneal malformation and uveoretinal angiodysgenesis – a neurocristopathy?

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Abstract. This clinicopathological report describes an unusual combination of axial corneal malformation and angiodysgenesis in the uvea, retina and optic nerve in three eyes. In each specimen there was hypocellularity in the posterior axial stroma, with corresponding loss of the corneal endothelium. The vascular malformation consisted of numerous telangiectatic endothelium-lined tubes with inconspicuous or absent media. One globe was obtained from a stillborn fetus (36 weeks) in which renal agenesis and a sireniform malformation (mermaid fetus) occurred in conjunction with a Fallot's tetralogy, pulmonary hypoplasia and atresia of the trachea and duodenum. Eyes with almost identical malformations were obtained from a 39-week female neonate who died after 5 h as a consequence of renal agenesis and pulmonary hypoplasia. This combination of ocular tissue malformations can be explained by embryological studies, which have shown that the corneal stroma and endothelium and the ocular periendothelial vascular tissues are derived from the neural crest.

Introduction

In 1984, Rotberg et al. [37] reported the ocular pathology in six cases (8 eyes) of Potter's syndrome and reviewed the pathology in ten other specimens (six of which had not previously been published). Among the 18 eyes in this group, abnormal iris vessels were observed in 10 and retinal angiomatous malformations were seen in 5, while evidence of a persistent posterior primary vitreous was noted in 2 eyes. Peripheral retinal neovascularisation was observed in four specimens. The frequency of an ocular vascular malformation (or angiodysgenesis) in association with renal agenesis was emphasised, as was the rarity with which such gross systemic malformations could be related to an identifiable chromosomal abnormality.

By contrast, in the case of Potter's syndrome described by Brownstein et al. [11], emphasis was placed on an interesting malformation of the axial cornea in which there was keratocyte loss in the posterior stroma with a corresponding loss of endothelium; axial stromal acellularity was reported in only one of the six new cases presented by Rotberg et al. [37], but was recorded in the cited, unpublished case (2 eyes) of Manschot and reported by Ginsberg et al. [15].

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The ocular abnormalities associated with renal agenesis (Potter's syndrome) are widely diverse and have not yet been adequately documented. To add further emphasis to the unusual combination of corneal malformation with uveal and posterior neuroretinal vascular malformation, we report two cases of Potter's syndrome (3 eyes) in which axial stromal and endothelial dysgenesis occurred in the cornea in combination with angiodysgenesis in the uvea, retina and optic nerve. This combination of malformations is discussed with reference to the role of the embryonic neural crest in the formation of ocular and periocular tissues. The ocular malformations, as well as those of the facial skeleton, may be a result of abnormal neural-crest cell behaviour during development.

Case reports

Case 1

A female infant was born after 36 weeks of gestation. The parents were not related, and this was their second child; the first child was normal. The pregnancy appeared uneventful until the 22nd week, when the fetus was noted to be small for the dates. Radiological examination suggested hyperflexion and dysmaturity. An assisted breech delivery was performed and the baby was stillborn.

Case 2

A female infant, first pregnancy, was born by caesarian section at 39 weeks of gestation. The Apgar score was 1/3, 5/7. In addition to growth retardation, on examination the baby had low-set ears, a small, pinched nose, congenital cataract and an anteriorly placed anus. X-ray of the chest showed an abnormal cardiac contour and poorly aerated lung fields. On abdominal examination, the kidneys could not be palpated. The baby was noted to be grunting and cyanosed and died after 5 h. Clinical pictures were not available.

Ocular histology

Autopsies were carried out on both infants. The left eye of case 1 and both eyes of case 2 were submitted for pathological examination. The eyes were fixed in 10% neutral formalin and PO blocks were embedded in paraffin. Horizontal serial sections (200) were cut at 10 μm through the

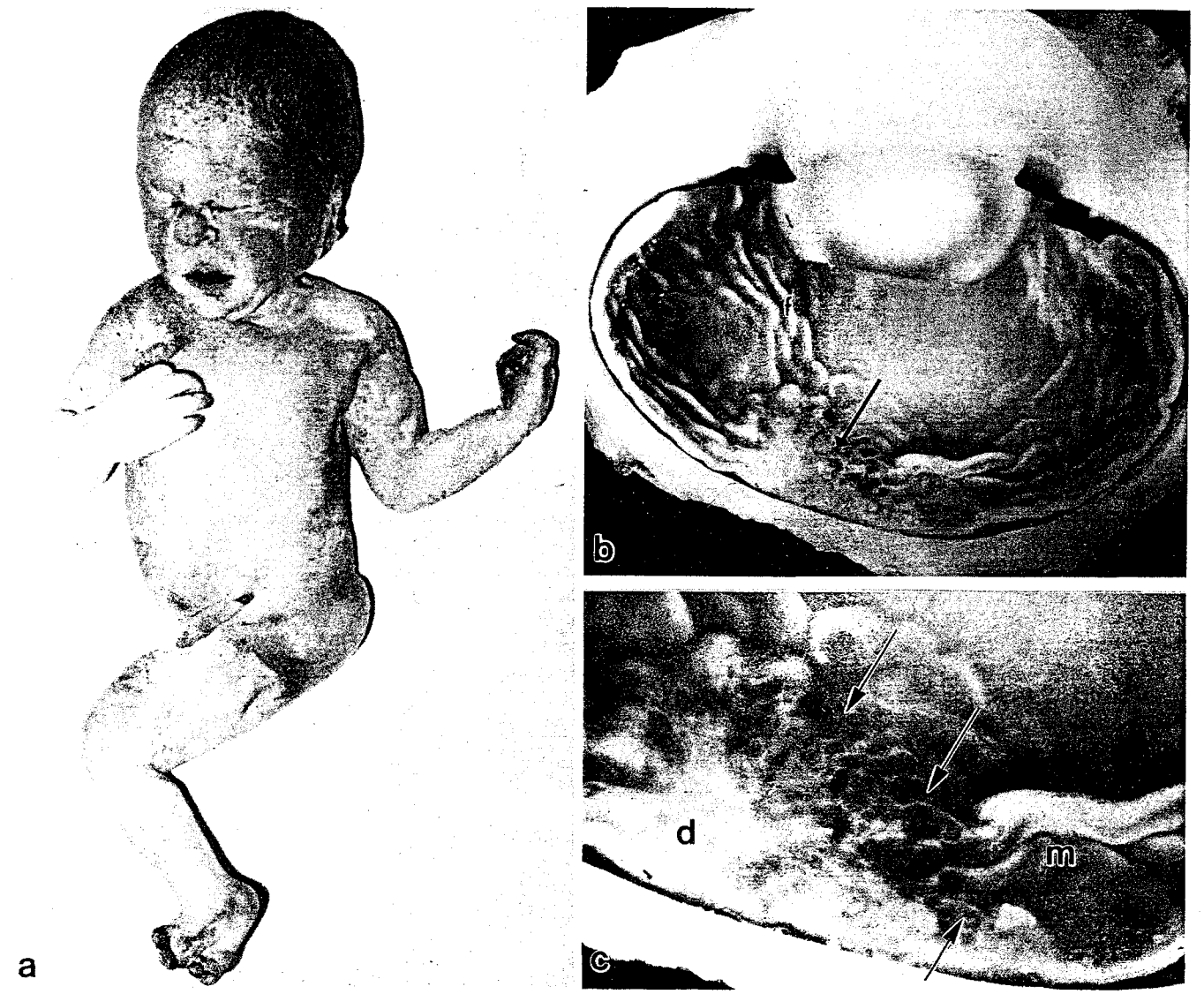


Fig. 1. a The external appearances of case 1. Note the flattened nose and the low-set ears (Potter's facies). The left leg is missing and there is an equinovarus deformity (Mermaid fetus) with an absence of genitalia. **b** A horizontal section through the globe reveals autolytic retinal folds (*f*) and grape-like vascular malformations (*arrow*) in the posterotemporal retina. ×7. **c** Detail of the posterior pole, showing the disc (*d*), folded macula (*m*) and cystic blood-filled structures (*arrows*). ×25

PO block and were stained where appropriate with the following: haematoxylin and eosin (H&E), periodic acid Schiff (PAS), reticulin, Masson, Masson-Fontana, Perl's Prussian blue, Bodian and Loyez. Sections from case 2 were studied by the peroxidase-anti-peroxidase (PAP) technique using anti-glial fibrillar acidic protein (GFAP) antibodies and anti-factor VIII antibodies.

Results

Autopsy findings

Case 1. The fetus was small for 36 weeks, gestation: the length and the head circumference were average for 31 weeks, development. On external examination the fetus was a sirenomelus, i.e. mermaid fetus (Fig. 1a). The left leg was missing. The right thigh and leg had a normal bony complement; however, the right foot showed equinovarus deformity, hypodactyly and comptodactyly. The digits of the hand were contracted. The external genitalia were aplastic and the anus was atretic. The eyes had an upward position and there was some hypoplasia of the midface, with the typical Potter facies [41]. The ears were low-set and the eyes appeared to be small.

Internal examination revealed hypoplastic lungs (total weight, 10 g), renal agenesis and the absence of both ureters; the bladder was hypoplastic. Ovaries were present (confirmed histologically). A pelvic cavity as such could not be identified due to marked dysgenesis of the bony pelvis. A small, rounded mass of cartilage presumed to represent the developing head of the femur was found free in the left gluteal region. There was a Fallot's tetralogy in addition to laryngeal stenosis, tracheal atresia, duodenal atresia and a blind-ending sigmoid colon. Fibroblasts from the fascia lata were used for chromosome analysis, which revealed a normal karyotype.

Case 2. The female infant weighed 1,663 g and measured 44 cm crown-heel (CH) and 30.5 cm crown-rump (CR). The head circumference (HC) measured 32 cm and the foot, 6.5 cm. The features were squashed and bilateral cataracts were noted. There were prominent epicanthic folds and large, low-set and slightly rotated, floppy ears. Redundant skin was present on the back of the hands, which showed a single, right-transverse palmar crease. Contractures of both hips were detected.

On internal examination, the brain appeared to have a polymicrogyric pattern. The lungs were congested and hypoplastic. Neither renal tissue nor the ureters could be identified, but the bladder was normal, as were the gastrointestinal tract, ovaries and genital tract. On radiological examination, no skeletal or other abnormalities were noted. The maturity was consistent with 35 weeks, gestation. A normal karyotype was demonstrated in fibroblasts from the fascia lata.

Ocular pathology

Case 1

Macroscopic examination. The left eye measured $11 \times 15 \times 13$ mm: the optic nerve was cut flush. The cornea (9×8 mm) contained a central opacity on transillumination and appeared to be globular. The anterior chamber was shallow, the angles were narrow and the iris appeared to be a thin rim of tissue. The lens was opaque due to fixation, whereas a clear vitreous enabled a good view of the posterior fundus. There was autolytic folding of the peripheral retina, but at the posterior pole the disc was hidden by a fibrous membrane that was surrounded by a small, intraretinal grape-like malformation, which extended beyond the macula (Fig. 1b). The ciliary body, the choroid and the sclera appeared normal.

Microscopic examination. The cornea was abnormally thick (2 mm) and in the axial part the posterior third of the stroma was hypocellular (Fig. 2a, b). The anterior third of the stroma contained thick, birefringent collagen bundles in which large keratocytes were numerous. The corneal epithelium was attenuated throughout and in some parts was only three cells deep. Bowman's layer was intact and Descemet's membrane was uninterrupted and of normal thickness. At the periphery the membrane was lined by plump endothelial cells, but centrally the cells diminished in number and in the axial part the membrane was devoid of a lining layer (Fig. 2a, b).

The angles were partially closed by iridotrabecular contact (Fig. 2c, d). The outflow system appeared to contain fewer trabeculae than is normal at this stage of development, and an interesting feature in some levels was the presence of vascular channels replacing the trabecular tissue (Fig. 2d). In the majority of sections the iris stroma was replaced by dilated vascular channels that had a distinct endothelium but lacked an adventitia (Figs. 2c, e). The anterior surface of the iris was lined by spindle cells and there was some displacement of a normal, two-layered pigment epithelium around the pupil. An inconspicuous sphincter pupillae was identified, but the presence of a dilator muscle was difficult to determine with certainty (Fig. 2e).

The ciliary processes were stunted and fused in some levels, and the muscle contained dilated vessels that were continuous with those in the iris; the endothelium of these vessels was lined by a PAS-positive basement membrane, but smooth muscle and adventitia were not identified with special stains. The lens appeared normal.

The retinal abnormalities of greatest interest were found in the peripapillary region (Figs. 1b and 3a, b), where the inner part of the retina contained large, multiloculated vascular channels that were surrounded by a basement membrane but not by smooth-muscle cells or an adventitia. Capillaries projected through the inner limiting membrane at some points, and occasional mononuclear cells were present in the vitreous. In the region of abnormal vascularity, the ganglion-cell layer and the nerve-fibre layer were absent, and at the periphery there was some gliosis in the inner retina. The outer nuclear layer was of normal density; the photoreceptors were autolysed. The retinal pigment and Bruch's membrane were normal. The choroid contained dilated vessels that had little, if any, organised periendothelial tissue, and melanocytes were not identified in the stroma. The anterior part of the optic disc contained abnormal vessels that were limited anteriorly by collagenous tissue. Remnants of a hyaloid artery were found in serial sections that also enabled the demonstration of abnormally large vessels in the centre of the optic nerve (Fig. 4). The axonal content of the optic nerve was low (Fig. 4). The posterior ciliary arteries were of normal histology but were dilated and tortuous.

Case 2

The left ($16 \times 15 \times 15$ mm) and right ($17 \times 15 \times 15$ mm) eyes with attached optic nerves contained identical abnormalities and these were considered as one.

Macroscopic examination. Horizontal sections revealed a thickened and opaque cornea (Fig. 5A) and a shallow anterior chamber with closed angles. The periphery of the iris contained prominent, dilated vessels. The lens was spherical due to cortical liquefaction, and an opaque nucleus was present. The ciliary body, vitreous and peripheral retina were unremarkable, but the peripapillary retina contained blood vessels that had an abnormal tortuosity (Fig. 6a). A prepapillary vascularised mass was identified, from which a persistent hyaloid artery extended into the vitreous. The choroid and sclera were normal.

Microscopic examination. The corneal pathology was very similar to that described in case 1. Bowman's layer and Descemet's membrane were normal, and the endothelium was absent in the axial part but present at the periphery (Fig. 5b). Axial acellularity was demonstrable in the posterior two-thirds of the stroma and hypercellularity, in the anterior third (Fig. 5c).

The angle was closed by complete iridotrabecular contact (Fig. 5b), and red cells were present in the spaces within the trabecular meshwork. Especially at the pupil and the periphery, the iritic stroma contained multiple, dilated and congested vascular channels of varying size, which were lined by endothelial cells (Fig. 5b, d, e) that reacted positively with factor VIII antibody. In parts, the anterior surface of the iris was formed by vascular channels. A normal adventitia was not identified around these abnormal vessels, which were also found in the ciliary body, albeit to a lesser extent than in case 1.

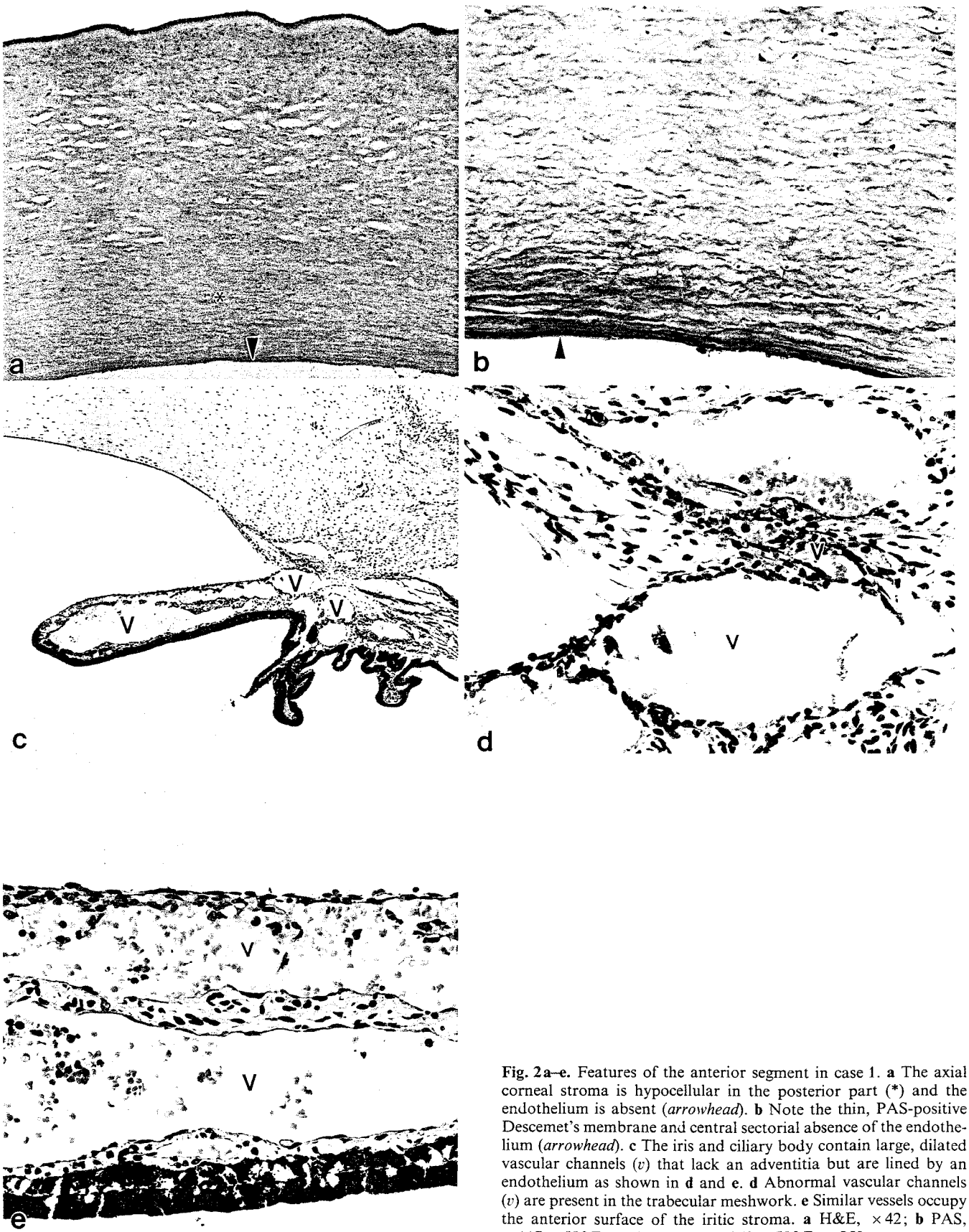


Fig. 2a–e. Features of the anterior segment in case 1. **a** The axial corneal stroma is hypocellular in the posterior part (*) and the endothelium is absent (*arrowhead*). **b** Note the thin, PAS-positive Descemet's membrane and central sectorial absence of the endothelium (*arrowhead*). **c** The iris and ciliary body contain large, dilated vascular channels (*v*) that lack an adventitia but are lined by an endothelium as shown in **d** and **e**. **d** Abnormal vascular channels (*v*) are present in the trabecular meshwork. **e** Similar vessels occupy the anterior surface of the iritic stroma. **a** H&E, ×42; **b** PAS, ×117; **c** H&E, ×42; **d** H&E, ×250; **e** H&E, ×250

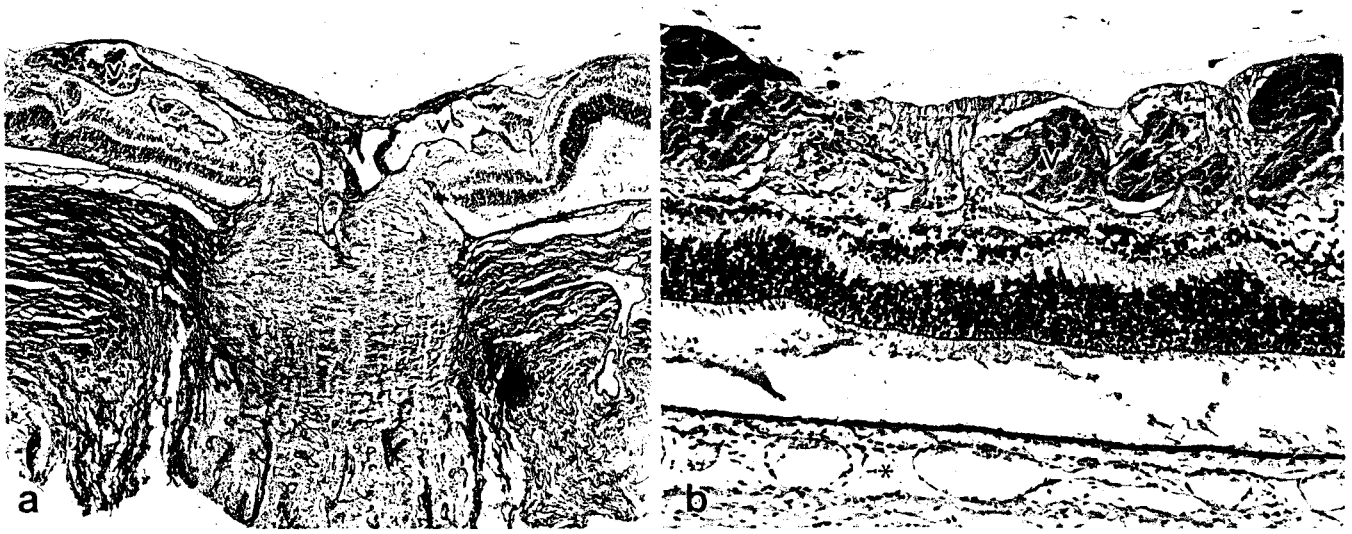


Fig. 3a, b. Abnormal vascular channels (*v*) in the disc, retina and choroid (*) are lined by endothelium but do not have adventitial cells. **a** PAS, ×35; **b** H&E, ×86

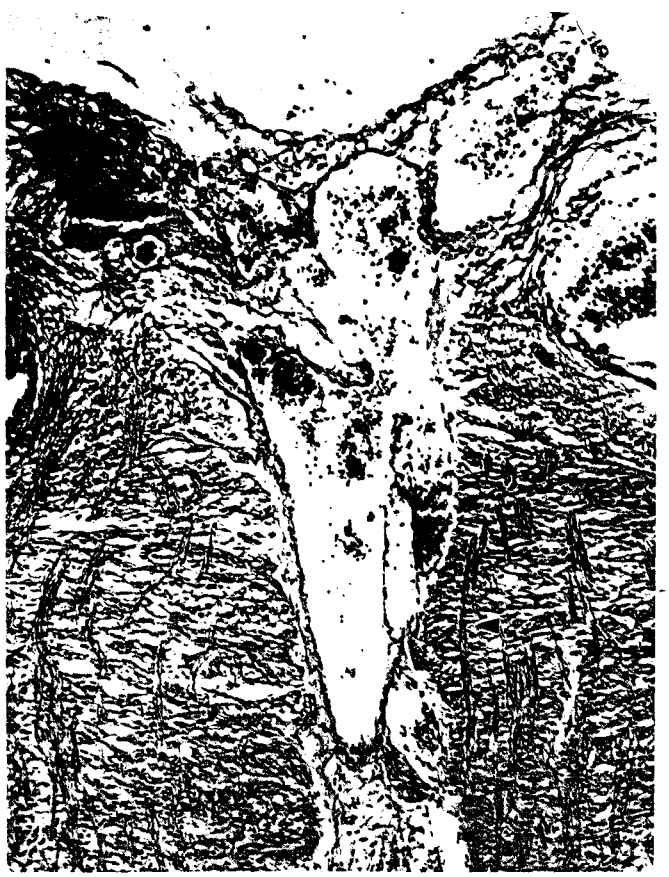


Fig. 4. The optic nerve contains small bundles of axons (*arrowhead*) and the central vessels are replaced by abnormal vascular channels. Bodian, ×117

The ciliary muscle was poorly developed; the processes were irregular and occasionally arose from the iris root. In the lens, the epithelium was swollen and posterior migration was a feature. An equatorial nuclear bow was not identified and the lens-fibre outlines were lost in the liquefied cortex (Fig. 5a, b); the nucleus was acellular.

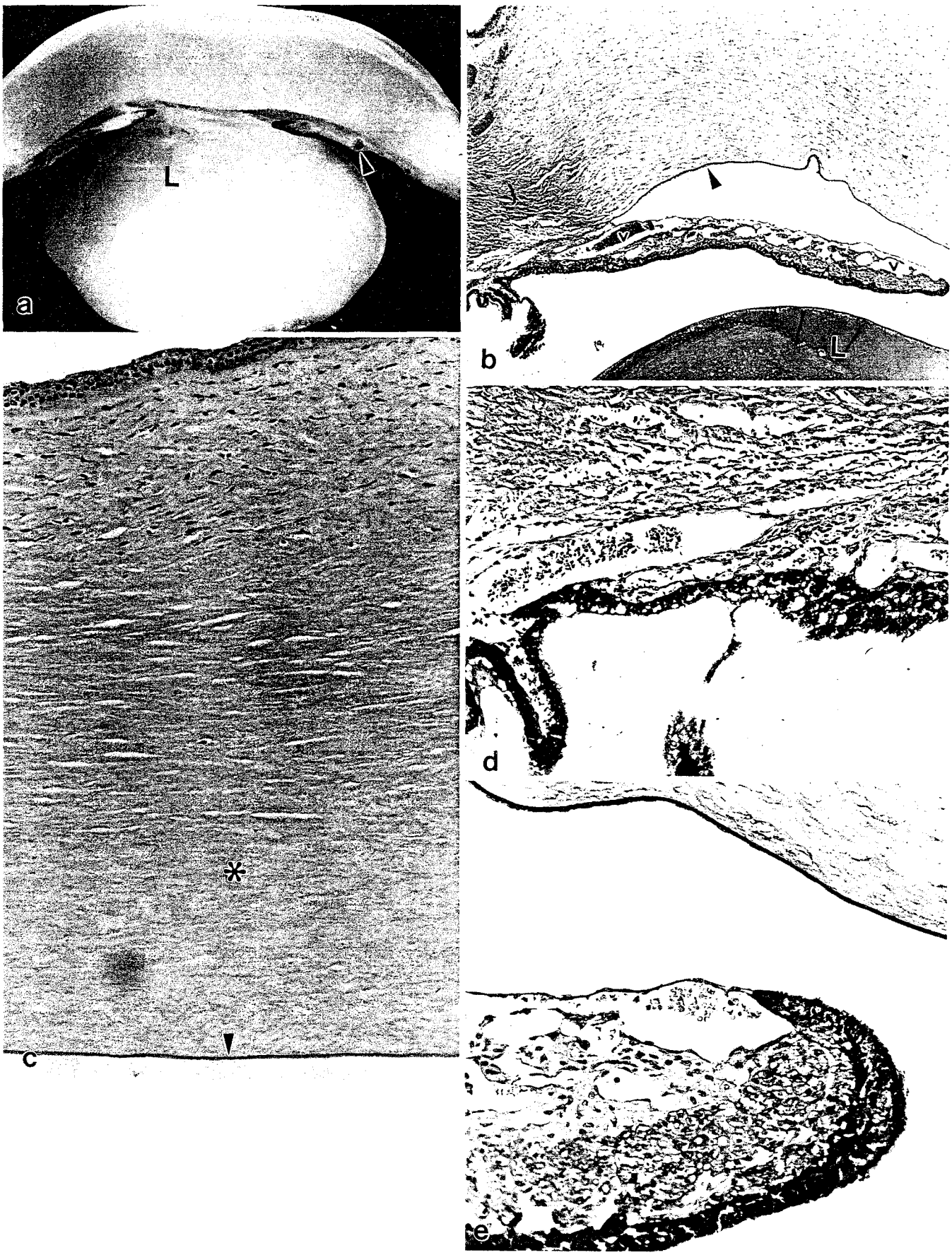
At the periphery and mid-periphery, the architecture of the outer retina, pigment epithelium and choriocapillaris was preserved. Ganglion cells and axons were sparse in the inner retina, but an interesting feature was the presence of small tufts of spindle cells projecting through the inner limiting membrane in association with small vitreous condensations. The choroidal vessels were dilated and lined by a normal endothelium, but adventitial cells were sparse; melanocytes were not present in significant numbers in the stroma.

The disc and peripapillary retina were distorted by traction via a prepapillary band of vascular tissue; this resulted in folding in the outer retina (Fig. 6a, b). The prepapillary and intraretinal vascular channels were lined by endothelial cells that stained positively for factor VIII and formed intraluminal proliferations (Fig. 6c, d). Smooth-muscle cells and pericytes were not found around these channels, which ramified within the gliotic inner retina. The optic nerve also contained an excess of glial cells (GFAP-positive), and the axonal content was low. The central retinal vessels and the posterior ciliary vessels were tortuous, but the adventitia appeared normal.

Discussion

Few reports concerning ocular pathology in Potter's syndrome have been published to date [11, 15, 37]. In these, a range of defects occurring in various permutations has been described. The most constant finding has been angiodysgenesis in uveal tissues, with or without similar vascular anomalies in the retina and optic nerve. The abnormalities have included abnormal, dilated vessels in the iris, choroid and retina (especially the prepapillary area) [15, 37] such as those observed in our cases.

Corneal pathology has been reported less frequently in cases of renal agenesis. Acellularity in the posterior axial cornea, almost identical to our findings, has previously been described in only three reports [11, 15, 37]. However, in only one of six cases described by Rotberg et al. [37] was corneal acellularity present, and this differed slightly from that in the other cases [11, 15] cited. Although an infre-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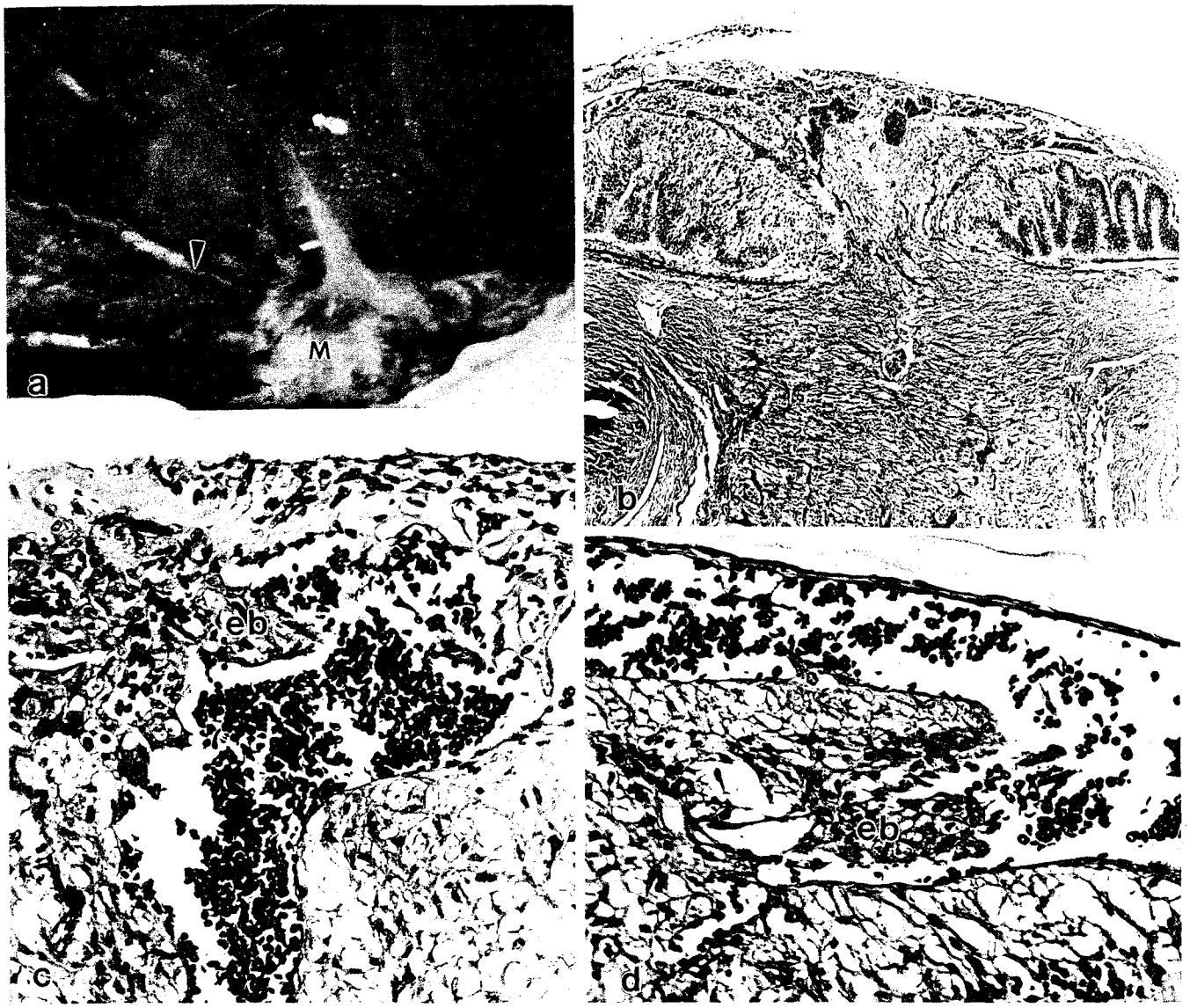

Fig. 6a–d. Features of the posterior globes in case 2. **a** Macroscopic examination reveals radially orientated folds in the retina (*arrowhead*) and a prepapillary vascularised mass (*M*), from which a hyaloid remnant extends into the vitreous. **b** The optic disc is distorted and the outer retina is folded by a broad band of abnormal vascular channels. **c, d** Endothelial cells bud (*eb*) into the ramifying channels, which are lined by endothelial cells but lack an adventitia. **a** ×15; **b** H&E, ×40; **c** ×250; **d** ×250

quently reported combination, the co-existence of corneal defects and angiodysgenesis may aid our understanding of the pathogenesis of these defects.

Because of the rarity of sirenomelia, there is very little information in the literature concerning ocular malformation associated with this extreme skeletal malformation. Rotberg et al. [37] described one case of sirenomelia (case 2) with vascular malformations similar to those in our first case, but without the corneal abnormality.

The corneal abnormalities observed in our cases and by others [11, 15] are particularly interesting. Although autolysis should always be suspected in autopsy material, it is difficult to accept this as an explanation for a well-demarcated axial loss of endothelium when the peripheral monolayer is well preserved and the corneal epithelium is not vacuolated. We are confident that the absence of stromal keratocytes in the posterior axial cornea could not be artefactual because the surrounding cells appeared normal. Initially, the possibility of a *forme fruste* of Peter's anomaly or keratoconus posticus [44] seemed to be an appropriate classification for this unusual disturbance. However, in Peter' anomaly there is a defect in Descemet's membrane

Fig. 5a–e. Features of the anterior segment in case 2. **a** Abnormal vessels (*arrowhead*) are present in the iris, which lines a shallow anterior chamber; the lens cortex (*L*) is degenerate. **b** The iris and ciliary body contain abnormal vessels (*v*) and the lens cortex (*L*) is liquefied; the corneal endothelium is well preserved at the periphery (*arrowhead*). **c** In the axial part, the endothelium is absent (*arrowhead*) and the posterior stroma is acellular (*). **d** The outflow system contains plentiful trabeculae, but vascular channels are prominent in the iritic stroma. **e** The iris is lined by a thin-walled vascular channel that lacks an adventitia. **a** H&E, ×10; **b** H&E, ×34; **c** PAS, ×140; **d** H&E, ×250; **e** H&E, ×250

and the posterior stroma and, in addition, iridocorneal contact is an essential part of the syndrome [5, 42, 43]. In posterior keratoconus there is a defect in the posterior corneal stroma [44].

It is difficult to explain the abnormalities we observed if our understanding of ocular development is based on descriptive works alone [18, 26, 32]. However, the use of cell markers to trace morphogenetic events in embryos of non-primate species is beginning to reveal the true nature of the processes involved in ocular development, and it is of interest to apply such recently acquired information to the malformations under discussion.

In avian embryos, the neural-crest-derived mesectoderm of the head is the source of most ocular tissues. The following originate entirely from the neural crest: the corneal endothelium and keratocytes; the connective tissues of the trabecular meshwork, iris, ciliary body and choroid; the ciliary muscle, the walls of blood vessels, with the exception of the endothelium (which is of mesodermal origin). The sclera is almost entirely of neural-crest origin, having only a minor component derived from mesoderm, and the vitreous has an unquantified derivation from the neural crest [21]. For comprehensive reviews, see the works of Hay [18], Noden [30] and Le Douarin [25].

Clearly, if these findings are extrapolated to the human eye, the defective tissues in our cases could be assumed to be of neural-crest origin. Thus, these malformations may be a manifestation of a limited form of "neurocristopathy" [8]. Indeed, attempts have been made to explain Peter's anomaly and other malformations of the anterior chamber by invoking a disturbance in the migration of neural crest cells [2, 6, 12, 23, 24, 36]. Unfortunately, the experimental evidence necessary for a clear definition of the origin of ocular tissues in mammals is not yet available. Although the extent to which avian data can be applied to human embryogenesis must be questioned [31], comparative studies indicate that neural-crest development is fundamentally similar in all vertebrate embryos [20]. Furthermore, recent experimental work has provided direct evidence that the neural crest contributes to craniofacial development in mammals [40]. Therefore, it would seem reasonable to invoke a comparable role for the neural crest in the development of the human eye.

During corneal development, the corneal endothelium arises from a primary stream of migrating cells that move through the primary stroma between the epithelium and the lens capsule. This precedes a second wave of cell migration from which the corneal keratocytes are derived [3, 13, 18, 29], and it is noteworthy that the cellularity of the embryonic cornea varies in density between the anterior and posterior parts [32]. Initially, we considered the possibility that the corneal abnormalities we observed are a result of abnormal crest-cell migration. Some of the features found in our cases may not be compatible with this "migration theory" because the corneal stroma was of normal thickness and Descemet's membrane was intact. Since the corneal endothelium is known to produce Descemet's membrane [13, 18] and the mesectodermal keratocytes produce the secondary stroma [18], the acellularity that we and others have described must be attributed to an event that occurred after the cells of the cornea had migrated and formed stromal collagen.

The corneal endothelial cells at the edge of the "bare" area in our cases were thin and attenuated. This morphology matches that of cells found at the front of the wave of migrating endothelial cells during normal morphogenesis [3, 13, 29]. This finding would suggest that these cells were moving towards the "bare" area at fixation. Since it seems unlikely that these cells were arrested in their primary migration, it is more feasible that they were attempting migration across a secondarily denuded area. This central corneal endothelial deficiency may be the result of an abiotrophy that caused the degeneration of this specific population of neural-crest-derived cells. Programmed cell death is a widespread phenomenon during normal morphogenesis [16, 17, 33] and has been described as being a common event during the remodelling of the chamber-angle recess in the rat [35]. It is possible that this process could have become aberrant, producing the defects we described.

It has been suggested that the severe absence of caudal tissues in sirenomelia may result from a disruption of critical nutrient supplies following a local vascular accident [4, 19]. This severe ischaemic type of mechanism would be unlikely to produce subtle and specific ocular anomalies such as those under discussion. More generalised ocular anomalies would be expected following such an event, and only then if the impaired vascular supply also affected the developing ocular area. Ischaemia, or any other nutrient deficiency, could only produce specific cellular deficiencies if the absent cells had been preferentially susceptible to a partial but generalised nutrient insufficiency. Naturally, this does not exclude the possibility that a catastrophic vascular accident was involved in the pathogenesis of any of the numerous associated malformations remote from the eye in our cases.

A defect in the migration or subsequent differentiation of neural-crest cells, or even abnormal cell death (as discussed above), could explain the absence of smooth-muscle cells in the retinal vessels and many of the larger uveal vessels. In normal development, the structure of venules and arterioles in the human choroid becomes established between weeks 15 and 22 of gestation [39]; thus, this cellular component should have been present in the specimens under investigation. The absence of a degree of restraint normally provided by supporting tissues could easily account for the telangiectasia and endothelial budding illustrated in our material (Figs. 2e and 6c, d) and demonstrated in figures published in previous studies [15, 37]. This possibility is also discussed by Naidoff et al. [28], who described a case of ocular angodysgenesis in association with diffuse congenital haemangiomatosis. A distinctive absence of periendothelial cells was noted in their case, which may well share a similar pathogenesis with out cases.

Interestingly, treatment of early chick embryos with *Streptomyces* hyaluronidase results in large, dilated plexiform blood vessels, consisting of only an endothelial lining, around the neural tube [38, unpublished observation BJC]. These bear a remarkable resemblance to the abnormal, dilated vessels described in the present study. It is thus possible that a disturbance of the extracellular matrix environment around the primordial blood vessels was responsible for the dilated, abnormal vessels. Although a hyaluronate-rich matrix is considered to be important for the migration of neural-crest cells [34], it is interesting that hyaluronidase treatment had no effect on crest-cell migration [1, 27].

Endothelial cell proliferation into the adjacent retina and into the lumen of the abnormal vascular channels could be a manifestation of the absence of the interaction with

surrounding tissues, but it could also be explained by the hypoxic milieu of the infants. The absence of vessels towards the periphery of the retina and the accumulation of spindle cells in the inner retina are reminiscent of the retinopathy of prematurity; this has previously been illustrated by Rotberg et al. [37] and Ginsberg et al. [15] in this form of angiodysgenesis. The most acceptable explanation is that normal ingrowth of vessels into the retina requires that the endothelial cells be accompanied by cohort pericytes and smooth-muscle cells.

Convincing support for the unifying hypothesis explaining these ocular malformations as a form of "neurocristopathy" is that melanocytes were not observed in the uveal tissues in case 1. As elsewhere in the body, uveal melanocytes are exclusively of neural-crest origin [21, 25, 30] and are usually present by 7 months' gestation [32]. Furthermore, when one considers that the facial skeleton is wholly derived from neural crest in chicks [21, 25, 31] and that abnormalities in crest development are thought to result in facial deformity [14, 20, 25], it seems possible that the co-called Potter facies found in our cases may represent another manifestation of abnormal neural-crest development.

Although Potter facies is commonly considered to be a deformation resulting from facial compression due to the oligohydramnios that accompanies renal agenesis [41], this may not be the case. It has been suggested that these facial abnormalities represent the cranial extension of a primary mesenchymal disruption, which also leads to the many other associated malformations of Potter's syndrome [22]. Therefore, Potter facies and renal agenesis may not have a causal relationship but may be parallel phenomena produced by the same teratogenic insult. It is worth speculating that the proposed mesenchymal disruption involved the "ectomesenchyme" of neural-crest origin at the cranial level to produce the ocular and facial defects we described.

Several abnormal morphogenetic cell-behaviour patterns [7] may be invoked to explain the apparent neural-crest abnormalities in our specimens:

1. Deficiencies in the number of crest cells [20] is unlikely to have played a great role, since most crest derivatives albeit hypoplastic, were present to some extent.

2. Abnormal migration of crest cells may be due to disturbances of the complex interaction with the extracellular matrix [9, 10, 31]. The role of this mechanism is unclear, since almost all crest derivatives except the investing layers of the vasculature would seem to have reached their final positions.

3. Abnormal differentiation of crest cells may also be attributable to disturbances of the extracellular matrix [21, 25, 31], which may have resulted in the production of abnormal corneal stroma or in the failure of crest cells to differentiate into the periendothelial tissues of the vasculature.

4. Abnormal death of crest cells may have produced the acellularity of the posterior corneal stroma and the overlying area that was denuded of endothelium, or even result in the loss of vascular periendothelial tissues.

In summary, we presented the pathology of a rare form of ocular malformation and would suggest that the best explanation for this spectrum of malformations involves a limited defect of the neural-crest-derived cells of the cornea and the periendothelial connective tissues of the uvea and retina. This defect may be the result of abnormalities in the neural-crest cells at virtually any stage between their initial appearance and their final differentiation.

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