Ocular signs associated with a rhodopsin mutation (Cys-167→Arg) in a family with autosomal dominant retinitis pigmentosa

Editor—Retinitis pigmentosa (RP) comprises a group of hereditary progressive retinal degenerative conditions characterised by typical fundus alterations, loss in visual field, and severely reduced or uncorrectable electroretinograms (ERG). The first reported disease related mutations in the human rhodopsin gene, described in 1990 by Dryja et al,1 was a heterozygous C→A transversion in the second nucleotide of codon 23. Since then many further mutations have been identified to a current total of about 90.2

Here we describe, for the first time in the literature, the clinical phenotype associated with a Cys-167→Arg mutation (TGC→CGC in exon 2) in an Italian family affected by autosomal dominant retinitis pigmentosa (ADRP). The same mutation was noted by Dryja et al,1 but there has been no report of correlated clinical data.

CASE REPORT
Four patients (see Fig 1) of a family from the Campania region of southern Italy, have been studied.

Patient II-1
The patient, a 45 year old woman, had central visual acuity 20/25 in both eyes with +1.00 −3.00 180° in right eye and −4.50 −2.50 180° in left. Nascent posterior subcapsular cataract and vitreous corpuscles were present. Fundus examination revealed waxy optic disc pallor, attenuated retinal vessels, atrophic retinal pigment epithelium (RPE), and bone spicules in the middle periphery on 360° (Fig 2). Goldmann kinetic visual field examination showed a concentric isoptere shrinkage up to 10° in the centre in each eye (I,4 and II,4). No peripheral vision island was observed. Goldmann–Weekers adaptoperimetry examination are similar to the patient III-1. ERG showed a microvoltage photopic graph with implicit time of the a wave equal to 32 ms and implicit time of the b wave equal to 52.20 ms, with a differential width of 10.75 μV. The scotopic graph was extinguished.

Patient III-1
This patient, a 11 year old male had central visual acuity 20/25 in both eyes with +1.00 −3.00 180° in the right and left eye. Fundus examination showed a corrected visus 20/25 in both eyes with +1.50 +0.50 100° in the right and left eye. The fundus, Goldmann visual field and the Goldmann–Weekers adaptoperimetry examination are similar to the patient II-1. ERG showed a microvoltage photopic graph with implicit time of the a wave equal to 32 ms and implicit time of the b wave equal to 52.20 ms, with a differential width of 10.75 μV. The scotopic graph was extinguished.

COMMENT
This study has correlated a mutation Cys-167→Arg of the rhodopsin gene with phenotypic type I in an Italian family. The mutation segregated with the clinical disease, and all affected patients showed a similar phenotype. The disease has a very early onset: in the youngest subject the diagnosis was made at 16 months of age. The first symptoms in all subjects were night blindness and visual field shrinkage (restricted side vision). Examination of the fundus of the eye identified a typical RP form, with vessel narrowing and osteoblast-like pigmentation in the middle retinal peripheral area in four sectors.

Atrophic changes of the RPE in the macular region and in the middle periphery were identified only in the patient II-1. Electroretinography showed an early alteration of the photoreceptor cell function, whereas cone function was not completely compromised until almost age 18.

Clinical examination repeated yearly for up to 7 years in three subjects indicated that the disease progresses very slowly.

Furthermore, the exact mechanism involved in affecting the visual cycle is difficult to imagine. Cysteine at position 167 of the rhodopsin gene is highly conserved during the evolution of mammals, but there has been no report of correlated clinical data.

The authors would like to thank the family for its contribution to these studies. The authors were also grateful to Professor G Imbucci, of ORAO association; A Terracciano for technical assistance, and to Servizio di Tecnologie Biomolecolari, AREA di Ricerca CNR Naples, where the sequences were performed. This work was supported by Telethon-Italy, grant no E546 to AC and CNR grant no CTB.94.2863 to ER; MGM is a Telethon-Italy fellow.

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Haemangiosarcoma of the breast, metastatic to the ciliary body and iris

Editor—Angiomatous tumours of the ciliary body and iris are very rare. Even metastatic foci of angiosarcomas are not seen often in this location. This is why we are publishing our case of disseminated haemangiosarcoma...
with metastatic involvement of the ciliary body and the iris. The eye maintained useful function until the patient’s death 1 year after the appearance of the focus in the eye.

CASE REPORT
Clinical observation
A 53 years old woman was admitted to our eye clinic for deterioration of vision in her left eye and headaches. A tumorous focus involving the ciliary body and the radical part of the iris was revealed both clinically by ultrasound and with magnetic resonance imaging (MRI). The tumour had grown laterally at the 3 o’clock position (see Fig 1A and appeared to have a solid structure. The diameter of its base was about 6 mm. The vision was 6/12 when the patient was first examined but quickly deteriorated to light perception only, because of the blood in the anterior chamber. After removal of the blood from the anterior chamber, the vision improved again to 6/12. The intraocular pressure was normal (18–20 mm Hg) at all times.

Haemangiosarcoma of the right breast treated by ablation and actinotherapy was noticed in the patient’s medical history. The original tumour had grown within the breast stroma. Its diameter was about 3–4 cm. The histological pattern varied from relatively well formed vascular channels surrounded by multilayering endothelium to poorly differentiated solid areas formed by poorly differentiated cells with frequent mitoses. Epithelioid differentiation was not noticed. Some areas were haemorrhagic. There were no risk factors for angiosarcoma such as previous radiotherapy in the patient’s history. The patient was HIV negative. Because of tumorous dissemination in the skin and brain, ocular surgery was abandoned. Removal of blood from the anterior chamber was necessary once more before the patient’s death, 1 year later; otherwise, chemotherapy remained the only suitable treatment. However, the intraocular focus stopped its macroscopical growth and even partly regressed after chemotherapy by cyclophosphamide and vincristine (compare Fig 1A and B). The eye maintained useful function with measurable vision for 1 year until the patient’s death due to haemorrhage from metastasis in the brain at the end of July 1993. Postmortem examination of the left eye confirmed histologically the haemangiosarcomatous origin of the intraocular focus.

Histopathology
Gross examination of the eyeball
The enucleated left eyeball measured 23 × 23 × 22 mm with 4 mm of optic nerve. The pupil was slightly oval owing to lateral pressure on the nasal side. Transillumination and opening of the globe revealed approximately half rounded infiltrate which involved the lateral part of the ciliary body (see Figs 1B and 2A). The centre of this infiltrate was at the 3 o’clock position, its vertical diameter was 5 mm and horizontal diameter was 3.5 mm. The aqueous and vitreous were clear. The

Figure 1  (A) Patient’s left eye at the time of diagnosis of the intraocular tumorous focus. (B) The same eye removed after the patient’s death before postmortem histological processing. The arrows indicate half rounded tumorous focus within the ciliary body. Note the difference in the size of tumorous focus.

Figure 2   (A) Histological section from the same eye in the low power magnification. Note the haemorrhage and the artificial cavity after another haemorrhage within the tumour. Anterior synechiae closing the chamber angle in the region around the tumorous focus are also visible. Haematoxylin and eosin staining, magnification ×12.5. (B) The same specimen as in (A), tumorous infiltrate under high power magnification. Note the tendency to form blood vessel spaces and cellular atypias. Haematoxylin and eosin staining, magnification ×500.
Persistent pupillary membranes

EDITOR,—Persistent pupillary membranes (PPMs) which are large enough to interrupt the visual axis are uncommon. If left untreated they may cause stimulus deprivation amblyopia.

We report a case of bilateral persistent pupillary membranes which were successfully treated surgically before the patient was 6 weeks old.

CASE REPORT
A healthy baby induced at 41 weeks was born by normal vaginal delivery following a normal pregnancy. He weighed 8 lb 8 oz (3.8 kg) and was noted to have an abnormal red reflex from both eyes on routine ophthalmic check by a paediatrician before discharge from hospital after birth. He appeared to fix briefly on a light but did not really look at toys. The red reflexes were significantly reduced centrally and there were peripheral spoke-like opacities. Even with dilatation only a poor fundal view was obtained. The view was particularly poor on the right eye. An ultrasound scan of the posterior pole was normal for each eye. Further examination under anaesthetic showed that the child had bilateral persistent pupillary membranes in both eyes (Fig 1).

Blood could be seen flowing through the blood vessels within the membranes under the operating microscope. There were no other abnormal examination findings. Screening tests for toxoplasmosis, cytomegalovirus, rubella, and treponemal antibodies were all negative. There was no known history of substance abuse by the mother. The visual axis especially on the right side was significantly obstructed and even when the pupils were dilated and consequently we thought that the risk of stimulus deprivation amblyopia was high if they were left in place. The membranes were removed from the right eye when the child was 4 weeks old and from the left eye when he was 5 weeks old.

The same operative technique was used for each eye. A small superior corneal section was made and a further side incision was made. A Simco irrigation/aspiration canula was inserted into the corneal wounds each eye. The membranes were removed with a Simco irrigation/aspiration canula. The corneal wounds each eye had a single 10/0 nylon suture which were removed under anaesthetic 3 months postoperatively.

COMMENT
Persistent pupillary membranes are very common occurring in 95% of normal newborns. Early development of the crystalline lens at about the sixth week coincides with the growth of the tunica vasculosa lentis which nourishes it. The anterior portion of this is continuous with the pupillary membrane which draws its blood supply from the capillaries which arise from the branches of the long posterior ciliary arteries and the major arterial circle. The pupillary membrane is fully developed by 9 weeks' gestation. These blood vessels begin to undergo remodeling and regression in a process involving phagocytosis by macrophages at around 5 months' gestation. Dysfunction of macrophage invasion and phagocytosis is thought to play a role in the pathogenesis of PPMs.

PPMs are thought to be derived from the tunica vasculosa lentis (TVL) and have normally disappeared by the 34th week of gestation. These membranes are often observed by neonatologists as they are frequently seen in premature babies. They can be used to identify the gestational age of a newborn infant (between 27 and 34 weeks) and they failed to have any effect. The membrane strands were cut with vitreous scissors and the freed membrane was removed with macroscopic forceps. There was a small amount of bleeding from one of the more vascularised strands of membrane but the other smaller vessels retracted without bleeding. The proviso was removed with a Simco irrigation/aspiration canula. The corneal wounds each eye were left in place. The membranes were removed under anaesthetic 3 months postoperatively.

The visual axis was clear following surgery and there was no evidence of cataract. Histology showed a thin membrane of spindle-shaped cells some of which were pigmented. A fine network of blood vessels extended through the membrane.

Follow up of the child 5 months after the operation revealed no evidence of cataract formation in either eye. The eyes were straight and visual assessment showed that he objected to occlusion of each eye equally with a binocular acuity of 6/19 using Cardiff cards.
continue to regress at the same rate as if the child had not been born prematurely. There is some more recent evidence that intrauterine stress, particularly from chronic maternal hypertension, may accelerate the disappearance of these membranes.

Although not commonly associated with any other pathology there has been a previous report of positive toxoplasma serology occurring in a 30 week premature baby with PPMs. There has also been a report of PPMs occurring in an infant with congenital rubella virus. We believe that any child with a congenital abnormality of the anterior chamber should be screened for possible intrauterine infections. A series of five cases of persistent membranes associated with congenital dystrophy myotonica have been described. There have also been reports of PPMs occurring with a variety of other abnormalities of the anterior chamber which in some cases seem to be familial with autosomal dominant inheritance but in our case there was no family history. There have been case reports of spontaneous haemorrhage occurring form PPMs but these are unusual.

When Persistent PPMs are usually so small as to not need treatment since they shrink significantly over the first year of life. There is some evidence that not all PPMs behave in this way. Some membranes appear to become more hyperplastic after birth rather than remodel. Some authors believe that hyperplastic membranes should be considered as a distinct type of PPM and that they may be less likely to regress than thinner membranes that appear similar to be persistent rather than hyperplastic although no formal study has looked at this.

Smaller membranes than the ones we report have been successfully treated with mydriatic therapy until spontaneous involu- tion occurred. However, the smallest useful pinhole size (and presumably pupil aperture) is thought to be 1.5 mm without which normal visual development is unlikely to take place. In our patient the visual axis, especially the right side, was significantly obstructed even when the pupils were dilated and consequently we thought that the risk of amblyopia using this treatment strategy was high. Early surgical treatment was therefore considered in this condition at 5 days of age with good fixation and a clear visual axis a year later. If there is clear evidence that the membranes are shrinking over the first few weeks of life then it may be reasonable to wait for spontaneous resolution. In our case there was no evidence of regression over a period of 3 weeks and this contributed towards the decision to operate.

There have been recent reports of neondymium:YAG laser treatment to remove similar membranes from teenage children for cosmetic reasons. The long term risk of cataracts from this technique is likely to be high particularly if it were to be used on an infant. There are no published studies of long term follow up of these patients. We believe that a conventional surgical technique is more appropriate than laser treatment in an infant although the operator must be aware of the risk of inducing cataract from unnecessary contact with the lens.

There is growing evidence that the severity of deprivation amblyopia is minimised by earlier treatment to remove any obstruction to the visual axis particularly in the case of unilateral congenital cataracts. It is likely that a similar critical period applies to bilateral visual obstruction. Some authors feel that there is no visual advantage to be gained by removing these membranes after the sensitive period for visual development is over although modest improvements have been reported in teenagers.

If bilateral membranes are large enough to put a child at significant risk of amblyopia then it is our view that a surgical approach to this condition should be taken within the first 6 weeks of life as after this time the amount of irreversible visual dysfunction from amblyopia may well increase. Patients treated surgically for this condition should be followed up carefully because of the long term risk of developing amblyopia, membranes requiring patching, and glaucoma which may accompany congenital abnormalities of the anterior segment.

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Accepted for publication 21 January 1998


Candida glabrata endophthalmitis following penetrating keratoplasty

EDITOR,—Transmission of infection by donor tissue is a well known, albeit rare, complication of corneal transplantation. We have found two reports of C. glabrata endophthalmitis, one with an organ cultured cornea when systemic antifungal treatment contributed to the patient’s death.

CASE REPORT
A 43 year old man with keratoconus had two previous right corneal grafts. The first, in 1974, became vascularised and oedematous after several months; the second, in 1990, failed after two rejection episodes. In February 1995 he underwent further keratoplasty using tissue type material, stored in organ culture for 20 days and transport medium (5% dextran) for 2 days. On the first postoperative day UK Transplant Support Service Authority reported culture of a yeast from the transport medium, subsequently identified as C. glabrata. Clinically the graft was satisfactory but topical econazole 1% (in arachis oil) was given prophylactically six times daily.

Increasing anterior uveitis was treated by increasing topical prednisolone acetate 1% from 2 hourly to hourly at postoperative day 4 and adding oral prednisolone 80 mg daily at day 11. At this stage a tiny white endothelial deposit developed at the graft interface. Over 4 days this became a white plaque of 2 mm diameter (Fig 1) but remained asymptomatic. The lesion was aspirated by paracentesis; microscopy showed a yeast and subsequently C. glabrata was cultured. Amphotericin B 5 μg in 0.1 ml was injected into the anterior chamber immediately and 3 days later, and topical amphotericin B 0.15% commenced 1 hourly. The graft remained clear and the uveitis settled. Oral steroid was withdrawn completely over 7 weeks.

Further threatened rejection with anterior uveitis associated with loose corneal sutures occurred 5 months postoperatively. This was treated with hourly drops of prednisolone acetate 1%. Three weeks later an enlarging...
white mass, initially 0.75 mm in diameter, appeared elsewhere on the host endothelium.

Amphotericin B 10 µg in 0.1 ml was injected into the anterior chamber, with subconjunctival injection of amphotericin B 300 µg in 0.5 ml. Topical amphotericin B 0.15% hourly and prednisolone 1% hourly were given. Both injections were repeated at 3 and 20 days. The uveitis settled, topical amphotericin was discontinued, and the graft remains clear 2.5 years later on prednisolone drops once daily.

No toxic effects have been noted from intracameral or topical amphotericin B.

**COMMENT**

Endophthalmitis flared up twice associated with intensive topical and/or oral steroid. *Candida glabrata* was cultured from the transport medium and the recipient anterior chamber, implicating the donor cornea as the source of infection. *Candida glabrata* is a relatively resistant organism and treatment was guided by antifungal susceptibility testing of the isolate. This suggested that the isolate was resistant to fluconazole (minimum inhibitory concentration, MIC >128 mg/l) and itraconazole (MIC 16 mg/l), but was of intermediate sensitivity to econazole (MIC 1 mg/l and 4 mg/l variously on different tests) (Table 1). The latter may explain econazole’s failure to prevent infection becoming established. Although the isolate was sensitive to amphotericin (MIC <0.25 mg/l), this was avoided as prophylaxis because of potential toxicity; however, no toxic effects occurred when it was subsequently used.

Failure of amphotericin B in the organ culture medium to eradicate *Candida glabrata*, despite its apparent sensitivity, has been described. A recent report showed 1.1% bacterial or fungal contamination of organ cultured corneas accepted for transplantation despite use of antimicrobial agents in the medium. Over 2.5 years Bristol Eye Bank records showed four occasions, including the present incident, when corneas were grafted and the transport medium was subsequently found to be infected. Two cases developed endophthalmitis (*Candida* spp and *glabrata*), while two remained clear of infection (*Pseudomonas* sp and *Penicillium* sp). Over 4500 corneas from the Bristol Eye Bank were grafted during this time, thus the incidence of known graft transmitted endophthalmitis is 0.04%. While accepting that some cases may go unreported, this can be compared with an overall incidence of postoperative endophthalmitis in the literature of 0.1–0.8%. After corneal grafting with *glabrata* cultured from corneas at 4°C, and of 0.09% following extracapsular extraction.

This patient remained asymptomatic throughout, which cutis laxa is associated with corneal clouding, mental retardation, and athetosis. Possible pathogenic mechanisms are increased tropoelastin degradation and reduced elastin content. The association of this with cutis laxa has been described only recently.

**Table 1. Antifungal susceptibility testing of initial *Candida glabrata* isolate**

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>MIC (mg/l)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>0.25</td>
<td>sensitive</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>&gt;128</td>
<td>resistant</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>16</td>
<td>resistant</td>
</tr>
<tr>
<td>Econazole</td>
<td>1 and 4 (variously on different tests)</td>
<td>intermediate</td>
</tr>
</tbody>
</table>

No aetiological role of dermatophytes in endophthalmitis has been established.

**Figure 2** Almost 6 months postoperatively: white mass at different site on host endothelium.

**Figure 1** Characteristic facets of cutis laxa in a 37 year old woman showing a prematurely aged appearance, lax redundant skin, downward slanting palpebral fissures, and a broad flat nose. Bilateral orbital fat is visible beneath temporal subconjunctiva of the right eye.

**COMMENT**

Cutis laxa (generalised elastolysis) is characterised clinically by generalised lax pendulous skin which hangs in redundant folds and recollies only slowly after stretching. Histologically, there is sparsity, fragmentation, and aggregation of elastic fibres in the dermis. Possible pathogenic mechanisms are increased tropoelastin degradation and reduced elastin production—skin fibroblasts have diminished mRNA for elastin in some patients. Cutis laxa may be inherited (autosomal dominant or recessive) or acquired. In the commoner, recessive form, characteristic facies have downward slanting palpebral fissures, a broad flat nose, sagging cheeks, and large ears producing a bloodhound or premu-

**Figure 2** Prolapsed orbital fat beneath temporal bulbar conjunctiva of the right eye. The anterior edge is indicated by arrows.
turely aged appearance. Herniae, diverticula, pulmonary emphysema, cor pulmonale, and aortic aneurysm are important complications resulting from abnormal elastic fibres. Acquired forms of cutis laxa may follow inflammatory skin disease or may be associated with hypersensitivity reactions, multiple myeloma, systemic lupus erythematosus, amyloidosis, or maternal penicillamine therapy.

Tenon’s capsule normally separates intracanal and extracanal orbital fat from sclera. Surgical or traumatic dehiscence of the capsule more than 10 mm from the limbus may allow forward prolapse of intracanal fat beneath Tenon’s capsule.1 In the elderly, fat prolapse may occur without such an antecedent event and is more frequently located superotemporally.2 3 Orbital fat prolapse is usually diagnosed clinically,4 but may be mistaken for a dermolipoma, dermoid cyst, lacrimal gland tumour, infiltration or granuloma, extraocular muscle enlargement, or an orbital lymphoid proliferation.5 6

The largest case series of orbital fat prolapse reports 15 patients aged between 49 and 94 years (average 65 years) of whom 33% were affected bilaterally.7 The case we report is significantly younger. Although the occurrence bilaterally of this finding at a young age may be coincidental, it suggests that abnormal elastin in Tenon’s capsule allowed it to dehisce, creating a route between intracanal fat and the sub-Tenon’s space. This report suggests an association between cutis laxa and orbital fat prolapse.

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Accepted for publication 21 January 1998

Ocular signs associated with a rhodopsin mutation (Cys-167 → Arg) in a family with autosomal dominant retinitis pigmentosa

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doi: 10.1136/bjo.82.6.709

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