Different mutation of the XLRS1 gene causes juvenile retinoschisis with retinal white flecks

EDITOR—Juvenile retinoschisis is an X linked inherited vitreoretinal degeneration that results in splitting of the superficial layers of the retina.1 Retinal white flecks are rarely present in retinoschisis.2 Because we have three families with retinoschisis with retinal white flecks, the clinical features and genetic analysis of both XLRS1 and RDHS genes were investigated in these families to characterise this unusual fundus finding.

CASE REPORT

Case 1
A 17 year old young man was diagnosed as having retinoschisis at 11 months of age. We have reported some of his clinical findings at the age of 10 years.3 His maternal grandfather and his younger brother (case 2) are also known to have this condition (Fig 1a). Both fundi showed the typical star-shaped configuration in the macula and peripheral retinoschisis inferiorly with multiple small white flecks scattered in the temporal posterior pole (Fig 2a). Full field ERG recordings showed markedly reduced scotopic response and even greater reduction in the photopic responses and a negative-type ERG with a single bright flash stimulus. Corrected visual acuity at the age of 17 years was right eye 20/200 with S+4=C−2×160°, and left eye 20/100 with S+4=C−2.5×20°.

Case 2
A 14 year old boy, a brother of case 1, was found to have poor visual acuity at the age of 5 years. He was diagnosed by us as having retinoschisis at the age of 13 years. Both fundi showed the typical star-shaped configuration in the macula and peripheral retinoschisis inferiorly without the multiple small white flecks (Fig 2b). The full field ERG showed a similar pattern as in case 1. During the 6 year follow up, the white flecks did not appear. Corrected visual acuity at the age of 14 years was: right eye 10/20 with S+4=C−1×160°, and left eye 20/100 with S+4=C−1×160°.

Case 3
A 9 year old boy was found to have poor visual acuity, and was referred to us. He was diagnosed as having retinoschisis at the age of 5 years. Both fundi showed the typical star-shaped configuration in the macula. Multiple small, white flecks were scattered in the posterior pole of the left eye (Fig 2c). The white flecks were not present in the right eye. The full field ERG showed a similar pattern as in case 1. Visual fields showed a large scotoma in the left eye. Corrected visual acuity at the age of 9 years was: right eye 10/20 with S+2.25=C−1×75°, and left eye 10/1000.

Case 4
A 22 year old man was found to have hypermetropia and was corrected by glasses at the age of 1 year. He was diagnosed as having retinoschisis and esotropia and consulted us at the age of 13 years. Pedigrees of case 4 showed an X linked inheritance pattern (Fig 1b). Although the left fundus showed the typical star-shaped configuration in the macula, the right macula showed degenerative changes. Multiple small, white flecks were scattered in his left temporal posterior pole (Fig 2d). The full field ERG showed a similar pattern to case 1. Corrected visual acuity at the age of 22 years was: right eye 30/500 with S+7, and left eye 40/200 with S+5.25=C−1.75×90°.

Informed consent was obtained from the patients after an explanation of the study. Genomic DNAs were extracted from leukocytes of peripheral blood. Exons 1–6 of the XLRS1 gene and exons 2–5 of the RDHS gene were amplified by polymerase chain reaction (PCR) using primers and condition described before.3,4 The PCR products were purified and directly sequenced using an automated DNA sequencer, Model 373 (Applied Biosystems, USA). The hemizygous XLRS1 gene mutations were recognised in all four patients as shown in Figure 1. No mutation of the RDHS gene was detected in exons 2–5 as well as flanking intron sequences.

COMMENT

Retinal flecks are sometimes observed in different types of retinal dystrophies.5 6 We have already reported that the retinal white flecks rarely accompany retinoschisis.7 Recently, a report indicated that mutations of the RDHS gene, which is highly expressed in the retinal pigment epithelium, causes fundus albipunctatus.8 To assess them at the genetic level, we investigate both the XLRS1 and RDHS genes in four cases of retinoschisis including three patients with retinal white flecks. Although we could not detect any
An Australian family with macular dystrophy linked to autosomal recessive alopcaia universalis

Editor—A strong linkage between autosomal recessive alopcaia universalis and macular dystrophy has not been described before. Recently, the gene for this form of alopcaia, the human hairless gene, has been identified at chromosome 8p12-22. There are currently no retinal or macular associated genes which have been described at this locus.

CASE REPORT

A 28 year old landscape gardener presented to the Lions Eye Institute, Perth, with visual problems and a request for assessment. On examination, it was noted that she had marked bilateral, symmetrical, atrophic maculae (Fig 1). In addition, she had marked hair thinning and loss involving the entire head. Her best corrected visual acuity was recorded as 6/36 in both eyes, with the right eye improving to 6/12 with pinhole. She wore a spectacle correction of −4.00 sphere right and −3.50 sphere left. Her past history noted hair loss but not symptomatic visual loss as a child. She was seen recurrently at the Royal Children’s Hospital, Melbourne, for alopcaia and fitting of wigs but not for vision loss. She complained of changing vision affecting reading and other activities in her teens. The visual loss had progressed through her teens and had become a significant disability to function. She did not complain of night blindness.

The patient also described her brother in Melbourne and a cousin in Berlin both of whom had the combination of vision loss and alopcaia. The relationship between affected individuals is shown in Fig 2. None of the clinical features described in the affected children were present in the parents or the grandparents. Although neither of the parents of the affected children, nor the grandparents, were symptomatic, they were from the same small town, Kostanjica, in a hilly region of Croatia. The presence of a likely small gene pool in the region where all the members of the pedigree were from would be consistent with a recessive disease.

Electrophysiological tests were carried out with a normal EOG and normal peak to trough ratios. The scotopic and photopic flash ERG results were reported as unreliable but the tests were not repeated. The pattern ERG was abnormal in the right eye and grossly abnormal in the left with no identifiable components. Flicker ERG responses were at the extreme lower limit of normal in the right and abnormal in the left eye with reduced b-waves.

Other tests showed a total error score on the Farnsworth 100 hue test of 136 right, and 176 left. Goldmann visual fields showed a central scotoma of abnormal degree to the stimulus but sparing the superonasal quadrant to the fixation point. The margin of the spared area did not respect the vertical or horizontal meridians. A central scotoma of 10 degrees to the stimulus was seen in the left with no areas spared.

COMMENT

The identification of new, macular related, and disease related genes is sometimes helped by strong linkage to a second disease or marker trait. The strong association of alopcaia and macular degeneration does not appear in the literature. Recent identification of alopcaia associated genes has allowed the identificaion of clinical disease entities to these genes.

The patient described here has the clinical diagnosis of autosomal recessive alopcaia universalis. This condition has recently been identified to be associated with mutations in the human hairless gene on chromosome 8p12-22 in some families. Expression of this gene has been shown to occur in the brain and because of the origin and nature of the retina would make this a plausible candidate. There are currently no reported macular diseases associated genes that are present at this locus. Two chromosome-8 related retinal genes have been identified. These are a gene encoding a new oxygen regulated photoreceptor protein causing autosomal dominant retinitis pigmentos, a linked to 8q11-13 and a “macular hypoplasia with ERG suggestion of gross abnormality of cone function” in a case of trisomy 8 mosaic syndrome.

The primary aim of this case study is to report a family that has a strong linkage of congenital alopcaia and macular degeneration. Given the recent identification of the gene responsible for autosomal recessive alopcaia universalis this may suggest the site of a, currently unknown, gene associated with retinal dystrophy.

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Figure 1 Clinical photograph (A) and (B) showing the patient’s alopcaia. Fundus photographs (C) and (D) of the patient, and (E) and (F) of the patient’s brother.
Cystic epithelial growth after penetrating keratoplasty: successful curative treatment by block excision

EDITOR,—Most of the reported cases of epithelial growth in the anterior chamber are related to cataract surgery and injuries.1–3 Epithelial invasion of the anterior chamber after perforating keratoplasty (PK) is a rare complication. Only a few authors report on epithelial cysts after PK,4 while the majority of the presented patients in the literature suffer from diffuse epithelial downgrowth.5–7 We present three patients with cystic epithelial growth in the anterior chamber 1–10 years after primary PK and histopathological findings after complete removal of the cyst.

CASE REPORTS
All three patients were referred to our department with cystic epithelial growth in the anterior chamber. Primary PK was carried out elsewhere. Block excision and corneoscleral grafting were performed by one of us (GOHN) in all three patients. Technical aspects of block excision have been described in detail earlier.

Patient 1
Patient 1 is a 31 year old man. He underwent PK on his right eye because of keratoconus. Thirteen months later cystic epithelial growth in the anterior chamber was noted with increase in size. At the time of operation the cyst size was below two clock hours on the limbal circumference. Block excision (6.0/6.1 mm) was performed in toto. Histological specimen showed a epithelial cyst formed by non-keratinising epithelium with goblet cells. During the follow up period of 48 months no recurrence of epithelial growth was observed. Preoperative visual acuity at the time of block excision was 20/20, visual acuity at the last check was 15 mm Hg.

Patient 2
A 29 year old woman underwent PK on her right eye because of lattice corneal dystrophy. After 47 months a epithelial cyst was seen for the first time. Block excision (6.0/6.1 mm) of the cyst, which had increased in size (below three clock hours of the limbal circumference), was performed. The histological finding was a cystic epithelial growth by non-keratinising epithelium. Goblet cells were not observed in the specimen (Fig 1). Visual acuity at the time of surgery was 8/20; the last examination during the follow up period (13 months) revealed a visual acuity of 10/20, IOP was 19 mm Hg both preoperatively and postoperatively.

Patient 3
This was a 29 year old woman. She had undergone PK on the left eye 10 years earlier after herpes simplex keratitis. Cystic epithelial growth was noted 10 years after PK. Epithelial cyst (below three clock hours of the limbal circumference) was removed by block excision (7.5/7.6 mm) in toto. Histological examination revealed cystic epithelial growth by non-keratinising epithelium with goblet cells. Cystic epithelial ingrowth was removed in toto. Visual acuity at the time of surgery was 4/20, IOP was within normal limits. The last follow up (follow up time 7 months) revealed a visual acuity of 6/20, IOP was within normal range (18 mm Hg).

COMMENT
In all three patients the cyst was adjacent to the corneal surface, the iris, and the chamber angle structures.

Several other surgical methods have been described for treatment of epithelial ingrowth. Proposed methods are aspiration of the cyst, diathermy, cryocoagulation, YAG laser treatment of the cyst wall, or excision of the cyst itself. In our experience, surgical opening of the corneal surface, the chamber angle or iridotomy with cystic epithelial growth into the anterior chamber 1–10 years after primary PK and histopathological findings after complete removal of the cyst.

Excision of the cyst itself on the other hand is not possible, because in all histological specimens obtained by block excision (up to 60 patients) the epithelial cyst covered the corneal surface, the chamber angle structure, the anterior surface of the ciliary body, and the iris surface.

The pathway for the epithelial ingrowth is uncertain; possible pathways are sutures, forceps and other surgical instruments, prolonged postoperative hypotony, and retardation of wound healing and wound dehiscence.

The interval between primary surgery and clinical appearance of epithelial ingrowth may vary from 1 week to 38 years.1–3 In our patients the symptom-free interval was 1–10 years. In cystic epithelial ingrowth increase in the cysts size seems to be limited by the corneal endothelial cell layer on the surface of the cyst (“Zagorski effect”).1

The purpose of every treatment of cystic epithelial growth should be the complete eradication of the invaded epithelium. Surgical opening of the cyst (for example, by laser application) is contraindicated, because this intervention may transform cystic epithelial ingrowth into a diffuse epithelial ingrowth, resulting in severe secondary glaucoma and eventually the loss of the eye. Reported rate of local recurrences (up to 14–100%) and following enclosures (up to 18–33%) in reported series are relatively high.

In conclusion, cystic epithelial ingrowth after PK without previous ocular surgery or trauma is very rare. In our experience block excision and corneoscleral grafting are the treatment of choice if the cyst is not above five clock hours of the limbal circumference. This procedure leads to morphological and functional rehabilitation of the eye.

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Ocular scleromalacia caused by leishmaniasis: a rare cause of scleral perforation

EDITOR,—The clinical manifestations of leishmaniasis depend on complex interactions between the virulence, characteristics of the infecting Leishmania species, and the immune response of its host.1 Leishmaniasis sometimes involves the eye as a result of contagious spread from the eyelid and conjunctiva, by the haematogenous route, or by inoculation of the conjunctiva by the patient’s own fingers, usually caused by L donovani.2

Figure 1 Histological specimen of the cyst (patient 2); periodic acid Schiff staining. Descemet’s membrane defect (black arrow); cystic epithelial invasion (white arrows) by non-keratinising epithelium without goblet cells.

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We report a case of an Afghan boy suffering from general mucocutaneous leishmaniasis caused by *L. tropica* and a bilateral intraocular manifestation of this disease.

**CASE REPORT**

An 11 year old Afghan boy with known general mucocutaneous leishmaniasis caused by *L. tropica* stayed in the “Friedendorf International”, Oberhausen, Germany, for treatment of his disease. After he had undergone a systemic eradication therapy in the summer of 1995 (Institute of Tropical Medicine, University of Tuebingen, J Knobloch and the Paul Lechler Hospital for Tropical Diseases, Tuebingen, Germany), the boy was first seen in the Department of Ophthalmology, Mülheim/Ruhr, Germany, in January 1996 with biconcular uveitis and secondary cataract. The right eye showed only slight inflammation, but the left eye severe inflammation of the anterior chamber. The cataract was more advanced in the right eye, visual acuity reduced to light perception in the right eye, to 0.2 in the left. Local anti-inflammatory therapy was started and cataract surgery was intended. The patient was seen again in spring 1996. Both eyes were painful, visual acuity in the left eye had also decreased to light perception, inflammation had severely increased with granulomatous and vascularisation on the iris and narrowing of the anterior chamber in both eyes. After eradication therapy reinfection was thought to be very unlikely at this time but the patient deteriorated rapidly. Severe scleromalacia appeared in both eyes near the superior limbus followed by scleral perforation of the right eye. Severe pain, loss of vision, the extent of perforation, and inflammation made the enucleation of the right eye inevitable (Fig 1A).

Macroscopic examination showed the perforated sclera, with prolapse of the lens, parts of the iris, and the vitreous body (Fig 1B). The histopathological examination showed many histiocytes filled with encapsulated leishmania 2–4 µmol in length (Fig 1C). The diagnosis was confirmed by transmission electron microscopy showing frequent amastigote organisms within the cytoplasm of histiocytes, with a nucleus, a kinetoplast, and an intracellular flagellum (Fig 1D). After histological examination intensive anti-infectious therapy was started again. Despite all efforts, scleral perforation also occurred in almost the entire inferior part of the sclera near the limbus of the left eye, so enucleation of the left bulbus had to be performed. Intraoperatively, both orbits were without pathological findings and the postoperative recovery was without complications.

**COMMENT**

The estimated worldwide overall prevalence of leishmaniasis is 12 million with the population at risk approaching 350 million. Visceal leishmaniasis is typically caused by *L. donovani*. Leishmania of the eye is very rare and the few reported cases were either due to *L. donovani* or the *Leishmania* subtype was not characterised. Leishmania tropica was thought to cause cutaneous infection exclusively, but in a small group of American military personnel who served in Operation Desert Storm, *L. tropica* was isolated from bone marrow specimens taken after the soldiers had developed chronic low fever, fatigue, and in some instances diarrhoea. This kind of leishmaniasis was named “viscercrotropic leishmania” (VTL) because the clinical symptoms differed in some points from the typical visceral leishmaniasis. In this boy’s case the channel of transmission could not be determined. However, as no pathogenetic findings of the eyelids could be observed the very rare haematogenous route seems to be the most likely mode of infection, possibly caused by the previously diagnosed *L. tropica* being the cause of the generalised mucocutaneous leishmaniasis. Identifying the species of *Leishmania* is especially important for the evaluation of treatment and their different sensitivities to anti-infectious drugs.

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**Clinical manifestations of protein C deficiency: a spectrum within one family**

**EDITOR,—**Homozygous protein C deficiency is rare with an estimated incidence of one in 500 000 to one in 750 000. It presents shortly after birth with life threatening thromboses involving the central nervous system, eyes, kidneys, and skin (purpura fulminans). Protein C activity, in affected individuals, is usually less than 1% (normal 70–140%). Management, in the acute phase, is with intravenous protein C concentrate (ImmunoAG, Vienna, Austria). Untreated cases usually result in death.

We present a family exhibiting a spectrum of features caused by protein C deficiency.

**FAMILY REPORT**

The pedigree is shown in Figure 1. Individuals IV:1 and IV:2 (the parents in our family) are second cousins and both heterozygous for protein C deficiency. Protein C activity is approximately 50% in both and they are healthy. The mother (IV:1) had five miscarriages and one neonatal death; the baby had undetectable protein C levels and died at the age of 4 weeks from severe purpura fulminans and cerebral involvement. Two of her children (V:3 and V:7) were healthy with normal protein C levels. One sibling (V:5) has been described previously. Briefly, she presented 6 days after birth with purpura fulminans on her left calf, bilateral central retinal vein occlusions, vitreous haemorrhages, and a right central retinal arterial occlusion. Despite treatment
with intravenous protein C concentrate she developed bilateral retinal detachments. Now, aged 7, she is bilaterally blind, has a scar corresponding to the area of purpura fulminans, but has otherwise developed normally. She receives subcutaneous protein C injections every fourth day.

The youngest child (V:10) was prenatally diagnosed as homozygous protein C deficient. She was born by emergency caesarean section at 36 weeks’ gestation because of reduced fetal movements. At birth ultrasonography diagnosed an intraventricular and right intracerebral haemorrhage. Ocular examination demonstrated right leucocoria with an underlying total retinal detachment and a left macular haemorrhage. Intravenous protein C therapy (80 IU/kg) was initiated at birth and titrated relative to serum levels. Despite early intervention she developed hydrocephalus requiring a V-P shunt at 3 weeks of age. Protein C therapy can be given and avoid the complications associated with the deficiency.

This family demonstrates a spectrum of clinical manifestations ranging from no symptoms in the homozygous state to spontaneous abortion and neonatal death in the homozygous state. Individual V:10 was delivered by emergency caesarean section and a suspected intrauterine cerebral event was confirmed. This challenges the hypothesis by Hattenbach et al that thrombotic events only occur postnatally. In utero treatment is not currently possible because maternal supplements do not cross the placenta and the biological half-life of protein C is short (<8 hours) so that direct fetal replacement is not practical.

In this family, the disease allele appears to be preferentially transmitted making accurate genetic counselling more difficult. We have shown that in utero thrombotic events can occur around 36 weeks’ pregnancy. Accurate data were not available for the distance deviation at this time owing to the young age of the children. The mean refractive error (spherical equivalent) was +6.6 dioptres for the right eye (range +4.00 to +8.75) and +6.8 dioptres for the left eye (range +4.75 to +10.75). Patients 1 and 2 had anisometropia of 2.50 DS and 2 DS respectively. The remaining patients had no significant anisometropia. At initial presentation all the children had a degree of amblyopia, which improved with appropriate occlusion therapy and spectacle wear. At subsequent visits abnormal binocular single vision was established with the Bagolini lensette, although none demonstrated stereopsis, with no response being elicited for either the Frisby or Titmus (housefly) stereotests. The presence of motor fusion was confirmed by the ability to overcome a 20 dioptre base out prism. This is a routinely used diopter base out prism. This is a routinely used test for preschool visual screening, with the mean size of the esodeviation all had visual acuities of 6/12 or better, with the mean size of the esodeviation being 33 prism dioptres for near (range 15–50) without spectacle correction. The deviation data were not available for the distance deviation at this time owing to the young age of the children. The mean refraction error was +6.6 dioptres for the right eye (range +4.00 to +8.75) and +6.8 dioptres for the left eye (range +4.75 to +10.75). Patients 1 and 2 had anisometropia of 2.50 DS and 2 DS respectively. The remaining patients had no significant anisometropia. At initial presentation all the children had a degree of amblyopia, which improved with appropriate occlusion therapy and spectacle wear. At subsequent visits abnormal binocular single vision was established with the Bagolini lensette, although none demonstrated stereopsis, with no response being elicited for either the Frisby or Titmus (housefly) stereotests. The presence of motor fusion was confirmed by the ability to overcome a 20 dioptre base out prism. This is a routinely used test for preschool visual screening, with the mean size of the esodeviation all had visual acuities of 6/12 or better, with the mean size of the esodeviation being 33 prism dioptres for near (range 0–16) and 5 prism dioptres for distance (range 0–16). The mean size of the subsequent esodeviation with spectacle correction was 8 prism dioptres for near (range 2–16).

Spontaneous consecutive exotropia in children with motor fusion

Editor,—The development of spontaneous consecutive exotropia is not uncommon in patients with esotropia. They characteristically have an early onset partially accommodative esotropia associated with poor binocular function including weak motor fusion, which is thought to prevent stable eye alignment. We report the findings in five patients with partially accommodative esotropia who developed spontaneous consecutive exotropia despite having adequate motor fusion.

CASE REPORTS

We reviewed the case records of five children with partially accommodative esotropia who attended the orthoptic clinic within the department of ophthalmology and were noted to have developed spontaneous consecutive exotropia despite having motor fusion. Each child had undergone cyclicropic or surgically corrected unilateral exotropia, with full hypermetropic correction prescribed. A full orthoptic and ophthalmic examination had also been performed. None had any significant medical history of note.

The findings are summarised in Table 1. The mean age of presentation of the exotropia was 2½ years (range 1½–3½), with the mean size of the esodeviation being 33 prism dioptres for near (range 15–50) without spectacle correction. The data were not available for the distance deviation at this time owing to the young age of the children. The mean refraction error was +6.6 dioptres for the right eye (range +4.00 to +8.75) and +6.8 dioptres for the left eye (range +4.75 to +10.75). Patients 1 and 2 had anisometropia of 2.50 DS and 2 DS respectively. The remaining patients had no significant anisometropia. At initial presentation all the children had a degree of amblyopia, which improved with appropriate occlusion therapy and spectacle wear. At subsequent visits abnormal binocular single vision was established with the Bagolini lensette, although none demonstrated stereopsis, with no response being elicited for either the Frisby or Titmus (housefly) stereotests. The presence of motor fusion was confirmed by the ability to overcome a 20 dioptre base out prism. This is a routinely used test for preschool visual screening, with the mean size of the esodeviation all had visual acuities of 6/12 or better, with the mean size of the esodeviation being 33 prism dioptres for near (range 0–16) and 5 prism dioptres for distance (range 0–16). The mean size of the subsequent esodeviation with spectacle correction was 8 prism dioptres for near (range 2–16).

Letters


Table 1

Data from five patients who spontaneously developed consecutive exotropia

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<thead>
<tr>
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<td>6/6</td>
</tr>
<tr>
<td>Left</td>
<td>6/6</td>
<td>6/6</td>
<td>6/6</td>
<td>6/6</td>
<td>6/6</td>
</tr>
<tr>
<td>Refraction: spherical equivalent (dioptres)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>7</td>
<td>8.75</td>
<td>5.75</td>
<td>4.5</td>
<td>8.5</td>
</tr>
<tr>
<td>Left</td>
<td>6.25</td>
<td>9.5</td>
<td>6</td>
<td>5.25</td>
<td>9</td>
</tr>
<tr>
<td>Deviation with glasses ( prism dioptres)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Near</td>
<td>8 EX</td>
<td>2 EX</td>
<td>16 EX</td>
<td>10 EX</td>
<td>2 EX</td>
</tr>
<tr>
<td>Distance</td>
<td>4 EX</td>
<td>18 EX</td>
<td>18 EX</td>
<td>14 EX</td>
<td>20 EX</td>
</tr>
<tr>
<td><strong>Treatment:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of reduction in lens power (dioptres)</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Outcome:</td>
<td>MicroEX</td>
<td>MicroET</td>
<td>MicroEX</td>
<td>MicroET</td>
<td>MicroEX</td>
</tr>
</tbody>
</table>

ET = esotropia; EX = exotropia; NA = no data available.

and 15 prism dioptres for distance (range 4–20). The mean interval between initial diagnosis and appearance of exotropia was 2 years (range 1/2–3) with the mean age at onset of the exodeviation being 4 1/2 years (range 3–6). Cycloplegic refraction was rechecked following the onset of the exotropia and found to be unchanged. Visual acuities were also unchanged.

The consecutive exotropia was managed in all patients by decreasing the strength of the hypermetropic prescription by a mean of 1.00 DS (range 0.50–1.50). This resulted in three children developing a microexotropia and two children developing a microesotropia during the follow up period (mean 14 months, range 3 months to 3 years).

COMMENT

This study demonstrates that spontaneous consecutive exotropia can develop in certain patients with accommodative esotropia despite the presence of motor fusion. Moore reported four patients with evidence of peripheral fusional amplitudes who developed consecutive exotropia, although the actual extent of their fusional reserve was not recorded. It has been suggested that full correction of a significant hypermetropic refractive error in children with early onset esotropia predisposes to the development of spontaneous exotropia in some cases. The degree of hypermetropia in our cases is similar to that of patients reported in earlier studies, and it may well be that full correction of this amount of hypermetropia is the cause of the exodeviation. Just before the onset of the exodeviation all of our patients had acuities of 6/12 or better in the worse eye, with one subject seeing 6/6 with each eye. This is in keeping with the findings of Beneish et al. and Moore, who concluded that amblyopia was not an important factor in the development of spontaneous consecutive exotropia. The time interval between initial diagnosis and development of exotropia in the present study is similar to that of Beneish et al. although our patients were slightly younger (4 1/2 as opposed to 5 1/2). However, the children are much younger than those described by Moore who reported an average age of onset of 9.

Why should the eyes of patients with motor fusion diverge? Although these patients had “risk factors” for developing consecutive exotropia and could be expected to show a reduction in angle of esotropia with the passage of time, the presence of satisfactory motor fusion, as judged by the 20 dioptre base out prism test, should have prevented them diverging. Ciner and Herzberg suggested that spontaneous consecutive exotropia is the result of poor accommodative function, while van Lammeren et al. proposed that it is related to anomalies of the vergence system. In addition Burian found that a low AC: A ratio was a risk factor for the development of a consecutive exotropia but unfortunately this ratio was not formally recorded in our subjects.

Our patients were managed by reducing the strength of the hypermetropic prescription, which was effective in all cases. This might suggest that they were all overcorrected to begin with. However, repeated refraction by optometrists experienced in the assessment of paediatric patients confirmed that their initial refractions were accurate. Interestingly, previous reports document a variable response to the treatment of spontaneous consecutive exotropia. For example Swan reported that it was of little benefit, with all six of his patients subsequently requiring surgery, while Beneish et al. found that eight out of 22 patients improved significantly following a reduction in their hypermetropic prescription. It is conceivable that such a response is only observed in patients with underlying motor fusion.

When motor fusion is present there may a tendency not to think about the possibility of a consecutive exodeviation developing in children with exotropia but as this study illustrates this is not necessarily the case.

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Practice patterns of pneumatic retinopexy in the United Kingdom

EDIToR,—Pneumatic retinopexy (PR) has been the subject of one multicentre randomised controlled trial1 and many uncontrolled studies with reported success rates with one procedure of 53–84%.1,2 In a retrospective review of 31 cases published in 1999, we reported a primary reattachment rate of 61% with this procedure, with a relatively high incidence of secondary breaks and proliferative vitreoretinopathy.3 Because of these variable success rates, PR is viewed as controversial by many surgeons. We conducted a postal survey to estimate the acceptability and prevalence of PR for the treatment of primary rhegmatogenous retinal detachment among vitreoretinal surgeons in the UK.

Questionnaires were posted in July 1999 to 80 members of the British and Eire Association of Vitreoretinal Surgeons (BEAVRS). We questioned the number of PR procedures they performed per month, their reasons for selecting it as a first procedure, and their estimated primary success rates. The data were collected anonymously.

RESULTS
A total of 69 questionnaires were returned (86%). Thirty (43%) of the 69 vitreoretinal surgeons indicated that they never perform PR, 28 (41%) use it occasionally (less than once a month), and only 11 (16%) surgeons use it frequently (one to four times a month).

Surgeons who don’t perform pneumatic retinopexy
A third of the surgeons who don’t perform PR said that they had tried it in the past and abandoned it. Ninety per cent of these surgeons believe that pneumatic retinopexy has a lower reattachment rate than other techniques and a third associate it with a high rate of complications.

Surgeons who perform pneumatic retinopexy occasionally
The mean success rate of the 41% surgeons who perform PR occasionally is estimated at 73% (SD 20.2). Their main indications for using this procedure are patient unfit for more invasive surgery (70%), simplicity and ease of the technique (53%), and the lack of theatre time or anaesthetic cover (32%).

Surgeons who perform pneumatic retinopexy frequently
The 16% of surgeons who said that they perform PR frequently estimated their success rate at 80% (SD 8.8). The simplicity and ease of the procedure is their main reason for using it (57%), other indications include its high success rate for primary reattachment (64%) and patients unfit for more invasive surgery (55%).

COMMENT
This study demonstrates that pneumatic retinopexy is not popular as a first procedure in the treatment of primary rhegmatogenous retinal detachment among most vitreoretinal surgeons in the UK. A survey conducted in North America and published in 1993 revealed the selective use of this technique among American vitreoretinal surgeons with geographic pockets of increased use in California and Florida. A more recent survey confirmed these regional differences and demonstrated an increase in the popularity of PR among younger retinal specialists.3

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Table 1 Results ranked in order of increasing pain score

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mean pain score</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>0.16</td>
<td>0.27</td>
</tr>
<tr>
<td>Cyclopentolate with prior proxymetacaine</td>
<td>0.36</td>
<td>0.60</td>
</tr>
<tr>
<td>Proxymetacaine</td>
<td>0.79</td>
<td>0.86</td>
</tr>
<tr>
<td>Cyclopentolate with prior saline</td>
<td>4.19</td>
<td>2.43</td>
</tr>
</tbody>
</table>

Table 2 Combined pain score

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mean pain score</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline plus cyclopentolate</td>
<td>4.29</td>
<td>2.54</td>
</tr>
<tr>
<td>Proxymetacaine plus cyclopentolate</td>
<td>1.16</td>
<td>1.10</td>
</tr>
</tbody>
</table>

Does instilling proxymetacaine before cyclopentolate significantly reduce stinging? The implications for paediatric cycloplegia

EDITOR,—Cyclopentolate 1% is the drug most commonly used to obtain paediatric pupil dilatation and cycloplegia. It is widely disliked by children and ophthalmic staff because of the severe stinging instillation may produce. As a result many children develop a negative association with the clinic, and become distressed and uncooperative before drop instillation and during subsequent examinations. To try to reduce this discomfort, previous investigators have advocated in a single study,1 which reported significant benefit. However, this was a retrospective study, with the particular limitation of using parental recall of their child’s distress a year previously, because discomfort with the use of cyclopentolate alone. We therefore considered that more data were required before the use of proxymetacaine is included in routine cycloplegia.

Because cyclopentolate is unstable at neutral pH preparations are acidified with dilute hydrochloric acid to around pH 4 so that stinging on instillation might be expected. Although, however, proxymetacaine has been shown to sting less than other local anaesthetic drops, it is also acidified with hydrochloric acid to a similar pH and can cause discomfort.

It could be that stinging is not the sole reason for children’s unhappy memories of their clinic visit. Factors not yet evaluated include lack of understanding, a dislike of eye examination, and the collection of the prolonged blurring produced by the cycloplegia in hypermetropes.

We designed a study to quantify the pain experienced by patients specifically attributable to cyclopeptolate instillation, and demonstrated that this is significantly less with and without previous instillation of proxymetacaine minims.

We enrolled only adult subjects to allow for accurate numerical pain scoring and to exclude the confounding factors mentioned above. Subjects were adult patients attending the ophthalmology clinic for the first time. Exclusions were pre-existing ocular disease, eye surgery, eye drop use, or an inability to understand the pain scoring system. Informed consent was obtained including the use of an information sheet approved by Tayside ethics committee.

Participating subjects had either proxymetacaine 0.5% or saline instilled in their first eye (either left or right was chosen randomly). Using a standard numerical pain scoring system of 0 to 10, the subjects were asked to record the pain score after all stinging pain has stopped. They were encouraged to record the score of the stinging at its peak. The score was re-recorded after instilling the second, remaining drop in the fellow eye. The process was repeated with the instillation of cyclopentolate 1%, sequentially, in each eye approximately 45 seconds later.

We used a standard numerical pain scoring system 0 to 10. The saline and proxymetacaine labels were covered so that the tests were double blind. All the tests were carried out by one investigator (MS).

In all, 29 subjects completed the study. The age range was 29–84 years, with an average age of 66 years. The mean pain score for proxymetacaine was 0.79 (SD 0.86). This compares with a mean pain score of 0.16 (SD 0.27) with saline. The difference between these is statistically significant (p <0.001).

The mean pain score for cyclopentolate instilled after proxymetacaine was 0.36 (SD 0.60). This compares with a mean pain score of 4.19 in the patients who received cyclopentolate after the placebo saline (SD 2.43). This result was highly significant (p <0.001). Taking the total pain scores for each eye and using a parametric test the difference between the total pain scores was found to be highly significant (p <0.001) (Whitney U test). These results are summarised in Tables 1 and 2.

COMMENT
In this study we found a highly statistically significant reduction in total discomfort with cyclopentolate instilled after premedication with proxymetacaine compared with the use of cyclopentolate instilled after a placebo. We also demonstrated that proxymetacaine does cause some discomfort although this is minor compared with cyclopentolate alone. Most of the pain from the combined medication came from the initial proxymetacaine drop. It has
been demonstrated elsewhere that diluting proxymetacaine 0.5% can reduce this stinging substantially without compromising efficacy. In practice, however, only the 0.5% preparation is currently commercially available.

This study provides support for the hypothesis that previous instillation of local anaesthetic should reduce discomfort in paediatric cycloplegia. However, as other factors may contribute to the discomfort experienced by children, further studies are required to determine if this benefit is realised in practice. Even if pretreatment with proxymetacaine does prove to be advantageous, it remains an unsatisfactory compromise. Ultimately the best solution to this important issue will be the development of a short acting, non-stinging solution to this important issue will be the development of a short acting, non-stinging cycloplegic which is stable at a neutral pH and iso-osmolar with tears.

The authors would like to thank Dr Ruoling Chen for his help preparing the statistics in this study.

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Delayed quinicine toxicity mimicking open angle glaucoma

Editor,—Ocular quinicine toxicity from acute overdose is much more rare than in the past. It manifests as severe peripheral vision loss associated with severe retinal arteriolar constriction. Although the optic nerve head does not develop characteristic cupping, the extensive field loss can be misinterpreted as glaucoma.

CASE REPORT

This 79 year old non-English speaking, Greek woman was referred for evaluation and management of advanced glaucoma. According to the referring physician, the patient had a history of glaucoma diagnosed approximately 2 years earlier. Intraocular pressures had been in the high teens to low 20s range on a regimen of Xalatan QHS in both eyes. Humphrey visual fields had been obtained revealing severe peripheral loss.

On presentation the patient complained of poor vision for the past few years, the right eye worse than the left and discomfort in the right eye. She had been seen by ophthalmologists in Brazil, Greece, and the United States. She had undergone laser procedures twice in the right eye and once in the left, for glaucoma. Her past medical history was only significant for falls resulting in an ankle and hip fracture approximately 3 months ago. Review of systems was non-contributory. The patient was on no systemic medications except for pain medications for a painful hip. She was also taking Xalatan 0.005% QHS in both eyes. According to the referring physician’s note, the patient had not tolerated Timoptic, Alphagan, and Trusopt.

Visual acuity was 20/60–2 right eye and 20/80–1 left eye. Manifest refraction improved visual acuity to 20/30 right eye with +4.00–1.50 × 90° and to 20/40 left eye with −3.00–1.00 × 90°. Goldmann visual fields demonstrated severe constriction in both eyes.

External examination revealed bilateral ptosis in both eyes. The pupils were equal and reactive to light without afferent pupillary defect. Ocular motility was intact.

Slit lamp examination revealed dry eyes, clear corneas, and deep and quiet anterior chambers in both eyes. Patent peripheral iridotomies were present superiorly in both eyes. Intraocular pressures by Goldmann applanation tonometry were 20 mm Hg right eye and 21 mm Hg left eye. Zeiss gonioscopy revealed grade 3 to 4 open angles in both eyes.

Dilated slit lamp examination revealed 2+ nuclear sclerotic changes in the right eye and 3+ nuclear sclerotic changes in the left. Dilated fundus examination revealed drusen in the mid-periphery. The retina appeared to be slightly hazy. Thin threadlike arteries and veins were noted in both eyes (Fig 1). Dilated stereobiomicroscopic examination of the optic nerve heads revealed pale nerves in both eyes and areas of peripapillary atrophy. Central cups with approximate dimensions of 0.4 vertically by 0.3 horizontally (c/d ratio) were present in both eyes (Fig 1).

The patient then volunteered one additional piece of information that she had withheld from her past ocular history. She revealed that 49 years earlier she had attempted suicide ingesting 120 tablets of quinine (unable to determine the actual amount of quinine that she had consumed). She was hospitalised for...
more than 10 days and she had apparently lost her vision for approximately 1 week following this attempted suicide. Vision had slowly recovered after this period of total blindness. An ERG was obtained on a separate visit (Fig 2). ERG recordings were obtained from the two eyes simultaneously. Under photopic conditions, there was an unusual scotopically absent wave with b-wave amplitudes of only 60 µV. B-wave implicit times were prolonged. Responses to photopic flicker were similarly reduced in amplitude and prolonged in latency. Following dark adaptation, scotopic wave forms showed an electrotensive wave form with a-b wave amplitudes of about 160 µV.

COMMENT
This is a case of quinine toxicity which has been extremely rare in recent years. Quinine is an alkaloid obtained from cinchona bark and has been used principally as an antimalarial agent. Although it is one of the oldest antimalarials it is now indicated in the treatment of chloroquine resistant malaria caused by Plasmodium falciparum.1 Quinine has also been used for the prophylaxis and treatment of nocturnal leg muscle cramps2 as well as in the treatment of severe babesiosis caused by Babesia microti.3 In the past quinine has been used as an abortifacient.4
    It has been known for approximately 150 years that quinine can disturb vision and hearing, especially in people who have taken an overdose.5 More than 250 articles have been published in the past 80 years concerning the toxic effect of quinine on the eyes. Mild effects include impairment of vision and hearing while more severe intoxication has led to visual loss.6

The technologies of digital image analysis and artificial neural networks (ANN) are not new in the field of macular degeneration (ARMD) screening. The ANN used was a feedforward neural network approach as described by Hopfield.7 The validating criteria for the study came from a small group of ophthalmologists carrying out masked assessment of a series of fundus images (stereo 35 mm slides and digital fundus images) which either contained ARMD at different confidence levels of judgment or which did not contain ARMD. The overall accuracy of the ANN test feature classes was 11 × 11 pixels of intensity information (the intensity information was the relative “brightness” of the feature within the range, 1–255 black to white). The feature types assessed constituted three subcategories within the grading system hierarchy: these were hard drusen (HD), large soft distinct drusen (LSD), and serogranular drusen (SGD). All other features indicative of ARMD such as haemorrhages, blood vessels, etc., were grouped into the background fundus class (FB) actively excluding them from further assessment. The choice of kernel size at 11 × 11 pixels was chosen because the main focus at this stage of the research was to differentiate the drusen subtypes using hard distinct drusen as the main discriminator and generally all sample features fit well within this window size. The ANN required approximately 10 000 iterations in order to categorise the training samples to within the accepted error margin of 0.01 and, after being analysed by both the expert assessor and the ANN model, the sample outputs were finally compared as shown in Table 1 to assess the accuracy of the computer based analysis system with the clinical standard. The ANN, compared with the reference assessment across all test feature classes, yielded an overall accuracy of 69.21%, with sensitivity to drusen classes (HD/SGD) being 95%/99% respectively and specificity 55% and 75%.

The overall accuracy of the ANN test method across the two test feature classes was

### Progression of age related macular degeneration using an artificial neural network approach

**Figure 1** Flow diagram of image analysis methodology.
found to be 66%, with 72% and 90% sensitivity (HD/SGD) and 72% and 63% specificity respectively. Current published literature on ANN pattern recognition tasks suggests that results of ~70% overall accuracy indicate a good result for first stage ANN analyses. The results obtained in this study with values of (95%+ sensitivity, 75% specificity) indicate that both types of drusen are being clearly differentiated by the ANN.

The neural network was trained to an accuracy of within 0.01 for each drusen subtype (hard, serogranular, and large soft distinct drusen) before the validation set was classified. Results indicate that the neural network performed better with more numerous feature classes available; the system sensitivity overall performed better with more numerous feature classes available; the system sensitivity overall being found to be 95% with 75% specificity.

**COMMENT**

A simple methodology for using computer based image processing and feature detection techniques to accurately quantify drusen has been presented and results are comparable with clinical trials. This approach could be applied to operational assessment of fundus diseases providing benefits both in time management and associated cost.

Thanks are due to the Gift of Thomas Pocklington and the Royal College of Surgeons for funded support towards this study.

**Table 1** Error matrix of ANN assessment against reference (clinical) assessment

<table>
<thead>
<tr>
<th>ANN classification</th>
<th>Clinical assessment</th>
<th>FB</th>
<th>HD</th>
<th>SGD</th>
<th>LSD</th>
<th>Total</th>
<th>Operation accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundus background</td>
<td></td>
<td>62.9</td>
<td>373.1</td>
<td>10.9</td>
<td>230.6</td>
<td>677.5</td>
<td>55.07%</td>
</tr>
<tr>
<td>Serogranular drusen</td>
<td></td>
<td>393.5</td>
<td>15.9</td>
<td>1279.2</td>
<td>15.5</td>
<td>1704.1</td>
<td>75.07%</td>
</tr>
<tr>
<td>Large soft distinct drusen</td>
<td></td>
<td>0.03</td>
<td>3.32</td>
<td>2.5</td>
<td>0.31</td>
<td>6.16</td>
<td>5.03%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>456.43</td>
<td>392.32</td>
<td>1292.6</td>
<td>246.41</td>
<td>=⇒</td>
<td>2387.76</td>
</tr>
</tbody>
</table>

**System accuracy**

---

**Note:** The tabular data above are raw output values of likelihood weightings produced from the ANN analysis.

**Iatrogenic keratectasia after phototherapeutic keratectomy**

Enerton. Several cases of iatrogenic keratectasia have been reported after laser in situ keratomileusis (LASIK). Until now, there has been no report of keratectasia after phototherapeutic keratectomy (PTK), presumably because PTK employs less laser ablation of the corneal stroma than LASIK. Previous studies demonstrated that thickness of the residual stromal bed is critical in the development of this complication.

We describe a case of progressive corneal ectasia following PTK for the treatment of band keratopathy. Even though the residual corneal thickness was greater than 500 µm, the patient developed steepening of the cornea, irregular astigmatism, and progressive myopia.

**CASE REPORT**

A 76 year old woman was referred to Miyata Eye Hospital for the treatment of bilateral band keratopathy. She had no apparent systemic or ocular disorders related to the development of band keratopathy, such as uveitis, long term use of miotics, hypercalcemia, chronic renal disease, tuberculosis, or connective tissue diseases. The best spectacle corrected visual acuity (BSCVA) was 6/20 in the right eye with a refraction of cyl −1.5 dioptries (D) and 8/20 in the left eye with +1.5 D cyl +1.0 D. The central corneal thickness measured with the ultrasound pachymeter (UP-2000, Nidek Co, Ltd, Aichi, Japan) was 541 µm and 540 µm in the right and left eyes, respectively. PTK was performed on the right eye with Star excimer laser system version 2.50 (Viss, Inc, Santa Clara, CA, USA). Using the transepithelial technique, 200 pulses were applied to ablate 48 µm of the cornea. The treatment zone was 6 mm in diameter with a 0.7 mm transition zone. A soft contact lens was worn for 3 days following the procedure. The re-epithelialisation was complete within the first postoperative week. One month after surgery, BSCVA was 20/20 with −3.5 D and corneal thickness was 517 µm. By the third month after surgery, BSCVA deteriorated to 10/20 with a spectacle lens of −10.0 D. At 6 months after surgery, BSCVA was 10/20 with −10.0 D and the central corneal thickness was 513 µm. The colour coded maps of the videokeratography (TMS-2, Computed Anatomic Inc, New York, NY, USA) obtained serially after surgery showed progressive keratectasia in the central area (Fig 1). The scanning slit corneal topography (Orbscan, Orbtek, Inc, Salt Lake City, UT, USA) taken 6 months after surgery revealed a marked elevation of the posterior surface in the central area,

**Figure 1** Colour coded maps taken 1, 3, and 6 months after phototherapeutic keratectomy for band keratopathy, demonstrating marked and progressive steepening of the central cornea.
indicating anterior protrusion of the central cornea (Fig 2). Since then, the anterior and posterior topographies did not show apparent progression during the observation period up to 1 year after PTK.

COMMENT

This is the first documentation of iatrogenic keratectasia after PTK. In LASIK, the minimum thickness of the residual stromal bed to avoid corneal ectasia has been claimed to be 250–300 µm, approximately corresponding to the postoperative total corneal thickness of 400–450 µm. The postoperative corneal thickness in the current patient was greater than 500 µm. Moreover, it has been postulated that the risk of keratectasia following surface excimer laser surgery might be lower than that following LASIK because of the relatively thicker effective stress bearing corneal stroma after surgery. Nevertheless, this patient demonstrated keratectasia as evidenced by steepening of the cornea, irregular astigmatism, and progressive myopia. It seems that the histopathological changes due to band keratop athy had already compromised the tensile strength of the cornea and the laser ablation further weakened the tissue to the degree that progressive ectasia ensued. The age of patient might have played a part. It was suggested that the safety limit of residual corneal thickness in normal eyes may not directly apply to diseased corneas.

None of the authors has a proprietary interest in any material or method mentioned here.

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Clinical manifestations of protein C deficiency: a spectrum within one family

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