Strabismus surgery in the management of diplopia caused by myasthenia gravis

Myasthenia gravis (MG) causes diplopia in about 90% of patients with the disease.1,2 Regardless of systemic treatments, complete remission occurs in only about 37%; and, even with prism glasses, an acceptable field of binocular single vision (BSV) is not always achieved.1,3 Minimal literature has emerged describing success with strabismus surgery in patients with diplopia caused by MG despite systemic treatments.1,3 In all cases found published to date, surgery had been performed only after the strabismus angle concerned had been stable for at least five months. We describe two patients where strabismus surgery was used to manage unstable diplopia caused by MG with long-standing success.

Case 1

A 36 year old woman presented in 1992 with fatigable right lateral rectus weakness. She later also developed fatigable dysphagia and dysphonia. Tests for MG were equivocal until 1999 when the diagnosis was supported by Tensilon testing (with eye movement recordings) and a highly suggestive single fibre EMG. Initially, she was managed satisfactorily with systemic treatments and prisms. However, in 1995, her lateral rectus weakness became increasingly worse and she began to develop fatigable right medial rectus weakness. When there was diplopia even in the primary position she was referred for surgery. At that time there was right convergent strabismus of 45 prism dioptres and limitation of full abduction, some of which was considered likely to represent permanent muscle damage. There was no vertical component. In June 2002, with her strabismus angles still unstable, she underwent surgery involving 6 mm right medial rectus recession on an adjustable suture, and 7 mm right lateral rectus resection. The result of the extent of recession was an overcorrection and was reduced on day one. Some limitation of abduction persisted as predicted. Over the last six months measured strabismus angles have been stable and the patient describes an incremental increase in her field of BSV.

Case 2

A 59 year old woman presented in 1986 with isolated fluctuating right ptosis. Ocular MG was diagnosed with positive Tensilon testing and increased anti-acetylcholine receptor and anti-nuclear antibodies. Computed tomography (CT) of the chest was unremarkable. She later also developed fatigable diplopia but was satisfactorily controlled with systemic medical treatments. After two years of relatively stable symptoms these treatments were weaned. However, after two months, she relapsed. Furthermore, the recurrent diplopia was unstable and unresponsive to retreatment. On examination there was elevation and adduction of the left eye even in the primary position. She underwent surgery in May 1989 involving 6 mm left superior rectus recession and 5 mm right inferior rectus resection. Postoperatively there was still some left hypertropia. It was thought that this might improve with time and ongoing prednisolone but, because it did not, in July 1989 she underwent left inferior oblique recession. This resulted in complete resolution of diplopia. However, in August 1989, the patient developed generalised MG and diplopia due to involvement of previously unaffected extracurcular muscles. Repeat chest CT showed an enlarged thymus which was resected with subsequent remission of all symptoms and signs. Fatigable ptosis is the only recurrent disease manifestation.

Comment

The sustained success with strabismus surgery in these two patients is related to the fact that diplopia in MG is the result of pure motor dysfunction. Central neurological mechanisms for binocular fusion remain intact. The fact that the result of the extent of surgical resection or recession varied from that anticipated in both cases is probably a consequence of the muscle pathology. Adjustable sutures allowed the necessary changes to be made relatively easily.

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References

Table 1

<table>
<thead>
<tr>
<th>Prism measurements preoperatively and 13 months postoperatively</th>
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<tbody>
<tr>
<td><strong>Prior measurements</strong></td>
</tr>
<tr>
<td><strong>Preoperative</strong></td>
</tr>
<tr>
<td><strong>13 months postoperative (July 2003)</strong></td>
</tr>
<tr>
<td><strong>180° esodeviation</strong></td>
</tr>
<tr>
<td><strong>90° esodeviation</strong></td>
</tr>
<tr>
<td><strong>45° esodeviation</strong></td>
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</table>
Orbital varices and orbital wall defects

Orbital varices are a vascular hamartoma typified by a plexus of low pressure, low flow, thin walled and distensible vessels that intermingle with the normal orbital vessels.1,2 If freely communicating with the orbital circulation, engorgement of varices can occur by increasing venous pressure through the Valsalva manoeuvre,1 bending posture,4 coughing or straining and these, in turn, lead to the clinical characteristics of variable proptosis, intermittent pain, and orbital haemorrhage.3,4 Observation is usually warranted for small lesions, but surgical intervention may be necessary in advanced cases; indications for surgical intervention include non-resolving episodes of thrombosis, severe disfiguring proptosis or displacement of the globe, and optic nerve compression.5 Surgery can be extremely difficult, as varices are very friable and intimately intermixed with normal orbital structures; there is also a significant risk of visual loss as a result of haemorrhage or optic nerve damage, the latter being generally caused by vascular compromise.5 The association of orbital venous anomalies with orbital wall defects provides a further source of surgical difficulty because of the close proximity of intracranial structures and the continuity with extraorbital or intracranial venous anomalies.

Case series

The orbital database, at Moorfields Eye Hospital, was used to identify patients with a clinical diagnosis of low pressure orbital varices and their orbital imaging (computed tomography and/or magnetic resonance image) was reviewed. Images were examined for evidence of orbital expansion, osseous defects of the orbit, nose or sinuses, and anomalies of the frontal bones. Patients who had either orbital or intracranial surgery before the date of imaging were excluded from the investigation.

The clinical diagnosis of orbital varices was identified in 310 patients, and imaging was available for 223 patients (72%). Six patients with previous orbital or intracranial surgery were excluded and nine cases (4%) had associated anomalies of the neighbouring orbital walls (table 1).

Four cases (patients 1–4) were associated with “pitting” of the orbital wall secondary to orbital varices (fig 1A). Another three cases (patients 6–8) were associated with enlarged superior orbital fissure and two cases (patients 5 and 9) with multiple orbital roof “defects” (fig 1B). Orbital varices were present up to and partially intermixed with normal orbital structures; there is also a significant risk of visual loss as a result of haemorrhage or optic nerve damage, the latter being generally caused by vascular compromise.5 The association of orbital venous anomalies with orbital wall defects provides a further source of surgical difficulty because of the close proximity of intracranial structures and the continuity with extraorbital or intracranial venous anomalies.

One patient (case 2) had thinning of the superonasal quadrant of the orbital wall, nasal orbital wall pitting, and a low ipsilateral cribriform plate, when first seen at age 21 in 1981 (fig 1E, F). On repeat imaging 20 years later (2001), this patient was noted to have developed proptosis, a defect in the superonasal wall of the orbit, and a new mid-line nasal encephalocele (fig 1I, J).

Comment

Fine cut (3 mm) orbital CT scans easily delineate varices and diagnostic phleboliths, which occur from thrombus formation,1 and provide an excellent natural contrast between brain, bone, and varix. The typical findings for varices include an ill defined multiloculated mass, with some patchy contrast enhancement, in communication with the neighbouring orbital circulation6; diffuse expansion of the orbital walls is well recognised in some cases, especially in childhood lesions.

Several factors may have biased the study population: many are symptomatic patients, having been referred from other ophthalmic units in consideration for surgical intervention. The apparent incidence of orbital variceal defects (4%) in our series may, therefore, be a slight overestimate. In a minority of patients, orbital varices may be associated with orbital wall defects, and such defects may, eventually, lead to an encephalocele formation. Clinicians should be aware of these, apparently unreported, associations before embarking on surgical intervention for orbital varices.

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Figure 1 (A) (Patient 1) Extensive left orbital varices (white arrows) causing orbital expansion, globe displacement, and “pitting” of the orbital roof and lamina papyracea (black arrows). (B) (Patient 5) Bilateral orbital varices associated with multiple defects, rather than pitting, of the orbital walls. (C) (Patient 6) Right orbital varices, with phleboliths, extending through the orbital apex into the middle cranial fossa (white arrows) and (D) associated with intracranial bone “pitting” and “defects” (black arrows). (E) Coronal and (F) axial CT scans of patient 2 with superonasal varices (white arrows) of right orbit in 1981. (G–J) Repeat coronal and axial CT scans in 2001 show significant enlargement of the bone defect with complete loss of mineralisation, and expansion of the frontal lobe meninges into the orbital wall defect (black arrow).
Table 1 Characteristics of nine patients with orbital wall defects in association with orbital varices

<table>
<thead>
<tr>
<th>No</th>
<th>Side</th>
<th>Age (years) at referral</th>
<th>Sex</th>
<th>Main location of orbital varix</th>
<th>Expansion of orbit</th>
<th>Absent walls</th>
<th>Ethmoid</th>
<th>Cribriform</th>
<th>Frontal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left</td>
<td>6</td>
<td>M</td>
<td>Medial and extensive superomedial</td>
<td>Present</td>
<td>Small roof defect</td>
<td>Pitted bone and smaller ethmoid</td>
<td>L-low R-normal</td>
<td>Dips low at cribriform</td>
</tr>
<tr>
<td>2</td>
<td>Right</td>
<td>21</td>
<td>F</td>
<td>Extraconal-medial</td>
<td>Present</td>
<td>Tiny thin area SNQ</td>
<td>Pitted bone and smaller ethmoid</td>
<td>R-low L-mild</td>
<td>Low frontal lobe over cribriform</td>
</tr>
<tr>
<td>3</td>
<td>Left</td>
<td>62</td>
<td>M</td>
<td>Superomedial</td>
<td>Present</td>
<td>Pitted roof and small defects of veins</td>
<td>Compressed Normal</td>
<td>Normal</td>
<td>Hint of varix but otherwise normal</td>
</tr>
<tr>
<td>4</td>
<td>Right</td>
<td>58</td>
<td>F</td>
<td>Panorbit intraconal and extraconal</td>
<td>Present</td>
<td>Post superior wall and pitted bone</td>
<td>Normal Normal</td>
<td>Normal</td>
<td>Varices up to frontal lobe and intraconal</td>
</tr>
<tr>
<td>5</td>
<td>Right</td>
<td>47</td>
<td>M</td>
<td>Panorbit intraconal and extraconal</td>
<td>Absent</td>
<td>Posterior orbital roof</td>
<td>Normal Normal</td>
<td>Normal</td>
<td>Varices up to dural space</td>
</tr>
<tr>
<td>6</td>
<td>Right</td>
<td>14</td>
<td>F</td>
<td>Posterior intraconal, superior extraconal</td>
<td>Present</td>
<td>Enlarged SOF</td>
<td>Normal Normal</td>
<td>Normal</td>
<td>Varices into frontal lobe and normal</td>
</tr>
<tr>
<td>7</td>
<td>Left</td>
<td>40</td>
<td>F</td>
<td>Posterior intraconal</td>
<td>Present</td>
<td>Enlarged SOF and small lateral wall</td>
<td>Slightly smaller Unknown</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>Left</td>
<td>37</td>
<td>F</td>
<td>Posterior intraconal and extraconal</td>
<td>Present</td>
<td>Very enlarged SOF, patchy SNQ defects posteriorly</td>
<td>Normal Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>Left</td>
<td>66</td>
<td>M</td>
<td>Extraconal-superior (large)</td>
<td>Present</td>
<td>Posterior orbital roof</td>
<td>Slightly smaller Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

SNQ = superonasal quadrant; SOF = superior orbital fissure.

Results

In all, 104 (62 men and 42 women) consecutive patients operated between July 1998 and July 2002 were included. The first 27 of these patients formed part of a preliminary report published previously. Median age at diagnosis was 61 years (range 21–88 years). There were no intraoperative complications in any case. Median postoperative follow up was 2.35 years (range 3 months to 4.5 years).

One patient developed pyogenic granuloma and one additional patient had large subconjunctival haematoma that resolved spontaneously. Three patients (2.9%) developed postoperative wound dehiscence. In two patients, dehiscence within 6 weeks of enucleation with exposure of the implant required replacement with high density polyethylene biomaterial implant (Medpor, USA). The remaining patient’s conjunctival wound was resutured. Three additional patients needed a lateral canthal sling operation between 6–12 months after enucleation. The overall cosmetic result was excellent in 6 weeks postoperatively and the patient was reviewed every 3–6 months.

Bovine pericardium (Ocuguard) wrap for hydroxyapatite implants

Hydroxyapatite implant becomes vascularised and integrated in the orbital tissues. In view of the rough hard external surface, wrapping materials are used to enclose the hydroxyapatite implant that facilitate attachment of extraocular muscles. Various wrapping materials have been tried including donor human sclera, acellular dermis, rectus abdominis sheath, posterior auricular musculature, polyglactin mesh, and bovine pericardium. In this report, we present our 5 year experience with the use bovine pericardium wrap. The wrap is prestretched using glutaraldehyde, ethanol, and propylene oxide to minimise the risk of transmission of bacterial and viral infections.

Figure 1 Hydroxyapatite implant and bovine pericardium wrap.

Figure 2 Hydroxyapatite implant wrapped in bovine pericardium with windows cut out for the insertion of rectus muscles.
reported. Wound dehiscence rates of 5–14% with the meticulous wound closure. Could be attributed to inclusion of cases derived tissue is proportional to the risk of encephalitis the risk of transmission of such viral and prion infections including Creutzfeldt–Jacob disease via a corneal transplant. J Neural Neurosurg Psychiatry 1997; 63:386–90. 11 Nurney WR. Risk of prion transmission with the use of xenographs and allografts in surgery. Ophthalm Plast Reconstr Surg 2001; 17:589–94.

**Cyclical esotropia following surgery for partially accommodative esotropia**

Cyclical strabismus is a rare phenomenon characterised by recurring periods of heterotropia usually on alternate days. It was first described by Bohm in 1845 and classically follows a 48 hour cycle with 24 hours of “straight” eyes followed by 24 hours of manifest strabismus. It usually appears spontaneously although has been reported in the aftermath of cataract, retinal detachment, and intracranial surgery. In addition there are two case reports of cyclical esotropia developing following strabismus surgery for intermittent esotropia and for infantile esotropia. However, there are no previous reports of this unusual condition developing after surgery for partially accommodative esotropia. We therefore present such a case.

**Case report**

A 14 year old girl was referred by her optometrist with an intermittent esotropia. Both the patient and her mother had noticed that the squint was present on some days but not on others, irrespective of spectacle wear.

Six years previously she had undergone a left medial rectus recession of 5 mm and a left inferior oblique recession for a partially accommodative left esotropia with inferior oblique overaction. Unfortunately there were no previous orthoptic measurements available. However, according to her parents her surgery was successful and she had been discharged from follow up. Subsequently, despite full time spectacle wear, there had been a gradual decrease in cosmesis to her present state. She had no other ocular or medical history of note. At the time of her most recent presentation her visual acuities were 6/6, N9 in both eyes and cycloplegic refraction was by the full prescription given by her optometrist (right+4.00/-0.50×135, left+4.00/0.25×160). Orthoptic assessment revealed a fully accommodative left esotropia with right hyperphoria. There was normal retina correspondence with sensory and motor fusion and stereo acuity was 55’ of arc (Frisby test). She was therefore advised to wear her glasses full time. On review two months later both the patient and her mother were adamant that the squint was present every second day, with that particular day being a “squinting day”, which correlated with the last clinic appointment being on a “squinting day”. She was found to have a partially accommodative left esotropia measuring with glasses 35 and 30 prism dipters (Δ) for near and distance respectively and measuring without glasses 50Δ and 40Δ for near and distance respectively. In addition she had bilateral inferior oblique overaction. Sensory fusion showed left suppression. The history and clinical findings were suggestive of a diagnosis of cyclical esotropia. She was asked to start a diary documenting the presence or absence of her squint on a daily basis until her next visit 6 weeks later, which confirmed the cyclical nature of her strabismus. Because of forthcoming school examinations surgical treatment was planned at this stage. On review a further 2 months later she felt her squint was present the majority of the time, with her eyes “straight” only every third or fourth day. Her orthoptic findings were unchanged. She was therefore listed for surgery and underwent right medial rectus resection of 3.5 mm, left medial rectus resection of 3.5mm and bilateral inferior oblique recessions. There was constant binocular single vision with a stereo acuity of 40’ of arc (Frisby test). This has remained stable during a nine month follow up period.

**Comment**

The aetiology of this unusual form of strabismus is unknown although it has been reported in association with abnormalities of the central nervous system. However, our patient was otherwise fit and well with nothing to suggest an underlying neurological problem. According to Andrew Nooden’s cyclical strabismus in childhood may last from 4 months to several years after which time it invariably becomes constant. Treatment in such patients is based upon the premise that they are basically strabismic but capable of good binocular vision. This would probably account for the reported success of surgery in these children, which is also our experience in this case. Although cyclical esotropia following strabismus surgery is a rare phenomenon, this report illustrates the importance of considering it in the differential diagnosis in those patients who have variable orthoptic findings, particularly as it is amenable to surgical management.

**References**

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Accepted 26 August 2003

1 Bohn L. Schielen und der Sehensatz in seinen Willkungen auf Stellung und sehkraft der Augen. Berlin: Kiepenheuer & Witsch, 1845:3.


3 Pillai P, Dhand UK. Cyclical esotropia with central nervous system disease: report of two cases.
Retinal progenitor cells in the posterior pars plana of rhesus monkeys

It has been generally assumed that the adult mammalian eye is devoid of retinal stem cells or progenitor cells as self-renewing and multipotential cells. In a previous study, however, identification of retinal stem cells in the mouse eye has been reported, representing a possible substrate for retinal regeneration.1 It has been paralleled by other studies on multipotent precursor cells in the ciliary margin of the frog retina,2 the role of Muller glia for neural regeneration in the postnatal chicken retina,3 progenitor cell proliferation and horizontal cell genesis in the mammalian retina,4 and differentiation of human neural stem cells into retinal cells.5 The retinal progenitor or stem cells were thought to be located in the region of the ciliary body.6 Examining rhesus monkey eyes, it was the purpose of the present histological study to look for a region in the monkey pars plana area which could serve as nidus of retinal stem cells.

Case reports
The study included 11 normal eyes of rhesus monkeys with a mean age of 18.2 (SD 2.8) years. The eyes had been enucleated, fixed in formalin, and prepared for light microscopy. An anterior-posterior segment going through the pupil and the optic nerve was cut out of the fixed globes. The segments were dehydrated in alcohol, embedded in paraffin, formalin, and prepared for light microscopy. In all eyes examined, the inner non-pigmented layer of the ciliary body in a normal human globe. Note the irregular, monolayered inner non-pigmented layer in the posterior pars plana. Red arrow: inner non-pigmented layer of the pars plana of the ciliary body.

Conclusion
In rhesus monkeys close to the ora serrata in the posterior region of the pars plana region, the inner non-pigmented pars plana epithelium is multilayered and irregularly structured showing nuclei of varying shape and location within the cell body. This heterogeneous morphology differs from the regular anatomy of the inner non-pigmented layer of the anterior region of the pars plana or the inner non-pigmented layer of the pars plicata. It is in contrast to anatomic textbooks generally describing the inner layer of the posterior pars plana as monolayered and regularly structured.7 It may correspond with the retina of fish and amphibians in which the continuous growth of the retina throughout life is accomplished by new retinal cells which are continually added at the anterior margin of the retina in a circumferential zone of cells, also known as the ciliary marginal zone.8 Correspondingly, it has recently been reported that new neurons are added to the retina of the chicken via proliferation and subsequent differentiation of neurons and glia at the retinal margin in a zone which is highly reminiscent of the ciliary marginal zone of lower vertebrates.9 Other investigations revealed that putative retinal stem cells could be isolated from the ciliary margin of the adult mouse.10 Recently, Kubota and colleagues investigated the eyes of an avian species, the quail, a marsupial species, the opossum, and a mammal species, the mouse.11 They found that the ciliary marginal zone cells gradually diminished during the vertebrate evolution. It corresponds with the present study, in which the inner non-pigmented layer in the posterior region of the pars plana region was monolayered in a normal globes showing a regular arrangement (fig 4).

Future studies may reveal whether cells originating from the irregularly structured inner non-pigmented layer of the posterior region of the pars plana close to the ora serrata may show characteristics of retinal progenitor cells, and whether they may be suitable for harvesting and cultivation to obtain autologous retinal progenitor cells for subfoveal transplantation in patients with degenerative or dystrophic diseases of the retina and retinal pigment epithelium, such as non-exudative age related macular degeneration.

Acknowledgements
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Angioid streaks in identical twins

Angioid streaks were first described in 1889 by Doyne, who described them in a patient with retinal haemorrhages secondary to trauma. Knapp first coined the term “angioid streaks” although it was Kopler, in 1917, who correctly determined that angioid streaks represented changes at the level of Bruch’s membrane. Since then, angioid streaks have been described in a diverse group of diseases including pseudoxanthoma elasticum, Paget’s disease, and the haemoglobinopathies such as sickle cell anaemia and β-thalassaemia. Although angioid streaks have been reported among siblings and family members in association with pseudoxanthoma elasticum, they have not previously been reported in identical twins without any associated systemic conditions.

Case report

A 66 year old man with no significant medical history presented to the eye clinic with reduced central vision in the left eye for 6 months. On examination, best corrected visual acuities were RE 6/12 and LE 6/36. Three months later, the identical twin of the above patient was referred by his optician with a haemorrhage at the left macula. Visual acuities were 6/6 in each eye. Funduscopy revealed a small haemorrhage along the left papillomacular bundle. Fundus fluorescein angiogram showed features similar to his brother in the form of angioid streaks associated with a subretinal neovascular membrane (fig 2).

Comment

On ophthalmoscopic examination, angioid streaks appear as single or multiple dark red/brown bands radiating form the optic
disc. They are thought to represent breaks or dehisence in a thickened, calcified, and abnormally brittle Bruch’s membrane. The most common systemic association with angioid streaks is pseudoxanthoma elasticum, although in approximately 50% of cases, no systemic association can be identified. Angioid streaks have been reported among siblings and family members in association with pseudoxanthoma elasticum. In the twins described above, there was no associated systemic condition. In pseudoxanthoma elasticum, it is likely that the defect in Bruch’s membrane may be inherited. Idiopathic angioid streaks in twins have not previously been reported. The most important complication of angioid streaks is the development of a subretinal neovascular membrane. Visual disturbance and symptoms secondary to angioid streaks are unusual unless such a membrane is present. Other complications include subretinal haemorrhage without neovascularisation that occur either spontaneously or with relatively minor ocular trauma. We believe that detailed ophthalmoscopic and fluorescein angiographic assessment in twins with angioid streaks may promote further understanding of the condition and facilitate the detection, and possible early therapeutic intervention of, secondary complications such as subretinal neovascularisation.

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References

Late recurrence of Langerhans cell histiocytosis in the orbit

We report a rare case of Langerhans cell histiocytosis (LCH) of bone in which recurrence occurred in the orbit 16 years after the initial lesion.

Figure 1 CT scan showing the osteolytic lesion in the lateral orbital wall.

Case report
An otherwise healthy 23 year old man presented to the eye casualty department complaining of severe pain around his left lateral orbital rim for 8 days. Two weeks previously he had suffered a minor blow to the left side of his face. At the age of 7 he had had a sacroiliac eosinophilic granuloma, which was treated surgically.

On examination, there was a small, tender, bony swelling immediately lateral to his left lateral canthus. There was no associated pyrexia, cellulitis, eyelid induration, or lymphadenopathy. Examination of the globe was normal. He was prescribed oral analgesics and antibiotics. One week later, the pain and swelling had increased and there was mild mechanical restriction of abduction of the left eye. His full blood count and liver function tests were normal. Computed tomography (CT) scanning revealed an osteolytic lesion of the lateral orbital rim (fig 1) with associated soft tissue swelling. A diagnosis of probable eosinophilic granuloma, disrupted by minor trauma, was made.

He underwent an open biopsy of the lesion, which was noted to be dark and friable with extensive oozing. A frozen section showed inflammation without giant cells or infection. Betamethasone was injected into the lesion (4 mg) and into the upper (2 mg) and lower (2 mg) eyelids.

Histological examination revealed pathological Langerhans cells, CD1a and S100 positivity, and the characteristic electron microscopic appearance of Birbeck granules confirming the diagnosis of Langerhans cell histiocytosis (fig 2). Review of the pelvic biopsy 16 years previously demonstrated similar histological features with positive staining of tumour cells with anti CD1a. Magnetic resonance image (MRI) scanning of his brain, chest x ray, and bone scans did not reveal any other lesions. He did not have a bone marrow biopsy.

He was referred to the haematology department and was treated with intravenous vinblastine, 6 mg/m2 bolus, weekly for 6 weeks, and oral prednisolone, 40 mg/m2 per day, for 4 weeks then tapered over 2 weeks. As this represented a recurrence of the disease, systemic treatment was chosen over local excision or radiotherapy. He suffered no adverse effects from the treatment. Within 2 months, he was asymptomatic and had recovered full eye movements.

Figure 2 (A) Photomicrograph from the orbital biopsy showing a mixed population of cells together with multinucleated cell (arrow) typical of LCH (x100). (B) Electron microscopical photograph showing Langerhans cell with several Birbeck granules (arrows) (x26 000).

A post-treatment CT scan showed no evidence of residual disease.

Comment
Langerhans cell histiocytosis encompasses three different clinical entities: (1) eosinophilic granuloma, (2) Hand-Schüller-Christian disease, and (3) Letterer-Siwe disease. They range in disease course from a benign entity with excellent prognosis in eosinophilic granuloma to the fulminant, often fatal, leukaemia-like Letterer-Siwe disease. The hallmark of LCH is the pathological Langerhans cell (PLC), which is cytologically benign and resembles the normal Langerhans cell but is not morphologically dendritic. PLCs result from monoclonal proliferation of CD1a histiocytes and co-express CD1a and S100 antigens on their surface. They also contain the characteristic Birbeck granules as seen with electron microscopy. These are striated cytoplasmic structures with a terminal or central fusiform swelling. They are believed to originate from invaginations of the cell membrane.

LCH of bone affects children more frequently than adults and occurs most commonly in the skull. Although the orbit has been implicated previously as a primary site of LCH, we could not find any cases of recurrence within an orbit in our Medline literature search. Survival of bony LCH is excellent with treatment and spontaneous remission can also occur. Recurrences after...
initial treatment are commonly found in both mono-ostotic and polyostotic cases, usually within 12–18 months of diagnosis.² A 16 year disease free interval is very rare. We have only found two other reports of recurrence after a quiescent period longer than 7 years. The first is a case of the same lesion recurring 13 years after original presentation.³ The second is that of a mastoid lesion presenting 33 years after the original mandibular lesion.⁴ To our knowledge, the case we have reported here represents the second longest disease free interval between consecutive lesions and also the first case to reveal the orbit as a site of LCH recurrence.

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Morphallaxia-like ocular histology after intravitreal triamcinolone acetonide

Morphallaxia-like ocular histology after intravitreal triamcinolone acetonide

Subretinal or retinal neovascularization, intraretinal proliferation of non-vascular cells, intraretinal or subretinal oedema, and chronic ocular hypotony have recently been found in globes enucleated because of infectious endophthalmitis, which is normally characterised by a marked destruction of all intraocular structures with dense infiltration of all ocular structures by inflammatory cells. The Morphallaxia-like morphology of infectious endophthalmitis in eyes with intravitreal triamcinolone acetonide may be parallelled by the clinical observation that patients with infectious endophthalmitis after an intravitreal injection of triamcinolone acetonide usually show almost no pain, which is uncommon for infectious endophthalmitis in eyes without intraocular steroids. The lack of inflammatory cells migrated into the eye may be the histological correlate of the clinical observation.

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References


2 Bailey W, Gass JDM. Chronic ocular hypotony have recently been found in globes enucleated because of infectious endophthalmitis, which is normally characterised by a marked destruction of all intraocular structures with dense infiltration of all ocular structures by inflammatory cells. The Morphallaxia-like morphology of infectious endophthalmitis in eyes with intravitreal triamcinolone acetonide may be parallelled by the clinical observation that patients with infectious endophthalmitis after an intravitreal injection of triamcinolone acetonide usually show almost no pain, which is uncommon for infectious endophthalmitis in eyes without intraocular steroids. The lack of inflammatory cells migrated into the eye may be the histological correlate of the clinical observation.

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References

Photodynamic therapy for corneal neovascularisation and lipid degeneration

Corneal neovascularisation, and subsequent lipid keratopathy is a potential complication of penetrating keratoplasty, corneal trauma, and corneal ulceration. Corneal neovascularisation increases the risk of corneal opacification and graft failure. Photodynamic therapy (PDT) using systemically or topically administered photosensitisers to occlude corneal vessels has successfully produced microvascular thrombosis without causing overt damage to surrounding tissues in animal models. The efficacy of PDT is achieved through the generation of reactive oxygen species from the interaction of light, oxygen, and photosensitisers such as verteporfin, commonly used to treat choroidal neovascularisation. Although animal models have demonstrated treatment parameters for corneal PDT, there have been no human studies to date. We present a case of lipid keratopathy secondary to corneal neovascularisation that was successfully treated with corneal PDT.

Case report

Our patient is a 36 year old white man who underwent penetrating keratoplasty in 1999 secondary to keratoconus complicated by acute hydrops. He presented in May 2003 with decreased vision due to lipid keratopathy secondary to corneal neovascularisation. The affected area was approximately 2.7 mm x 2.7 mm at the inferonasal margin of the corneal graft (fig 1). Best corrected visual acuity (BCVA) in the affected eye was 20/200. After reviewing treatment options at length with the patient, the decision was made to pursue PDT in an attempt to occlude the corneal vessels. Lipid formulated verteporfin was administered intravenously at a dose of 3.64 mg/m² of body surface area. Ten minutes after the infusion, light was delivered using a 689 nm non-thermal laser light for 300 seconds over a 3 mm x 3 mm spot size. A total light dose of 4.5 J/cm² was given. At the 2 week follow up, the corneal opacity was significantly reduced in size, and significant regression of corneal neovascularisation was noted (fig 2A); BCVA was 20/30. At 6 weeks after treatment continued regression was realised (fig 2B) and BCVA was 20/30.

Comment

While the cost of photosensitisers may be limiting, PDT offers a minimally invasive alternative treatment of corneal neovascularisation. Rapid elimination of photosensitisers from the body with minimal local and systemic side effects may make PDT an attractive alternative to repeat corneal grafting. The most common adverse reactions associated with verteporfin include visual disturbances, injection site reactions, and photosensitivity reactions. Because there is little or no damage to the surrounding tissues, PDT is a viable option for patients with decreased vision due to lipid keratopathy secondary to corneal neovascularisation. Additionally, because of the safety of PDT, multiple treatment sessions for recurrent or resistant neovascularisation are possible.

Retinal racemose haemangioma directly communicating with an intramuscular facial cavernous haemangioma

The triad of concomitant retinal or orbital arteriovenous malformations (AVM), intracranial AVM, and vascular facial naevoid were described in the 1940s and comprise a rare phacomatoses known as Wyburn-Mason syndrome. We present a variant of this syndrome with an association not, to our knowledge, previously reported in the literature, and discuss radiological findings, management, and therapeutic options.

Case report

An asymptomatic 14 year old girl was referred following a routine ophthalmic visit. She had been a patient at Great Ormond Street Hospital, London, with a large left cavernous facial haemangioma and had undergone several sclerotherapy injections in the past. Neurologically, there was no history of epilepsy, or evidence of midbrain or cerebellar dysfunction. Ophthalmic examination revealed visual acuities of 6/5 bilaterally with normal intraocular pressures. Colour vision was normal on Ishihara pseudo-isochromatic plates and there were no deficits detected by a Humphrey field analyser 24-2 threshold test. Fundus examination showed markedly convoluted and enlarged retinal vessels in the left eye and a normal fundus picture on the right (fig 1).

Magnetic resonance imaging (MRI) studies were performed, comprising gadolinium enhanced T1 weighted spin echo coronals with STIR sequences, T2 weighted spin axial...
and FLAIR sagittals, as well as magnetic resonance angiography (MRA). This showed a 3 × 4.5 × 6.5 cm angiomatic mass within the left sternocleidomastoid, with associated hemi-hypertrophy of the left facial tissues and hemi-mandible (fig 2). The tumour was isointense to muscle on T1 weighted images. It extended subcutaneously along the left temporalis muscle to the left temple and extends caudally to the lower border of the body of the mandible. Furthermore, the absence of signal void suggests that this is a predominantly slow flow lesion. It is particularly well seen on STIR sequences, which define its full extent, and it is notable that there is a deeper component extending into the pterygopalatine fossa, through the infra-orbital fissure, providing the likely source of abnormal tissue seen in the left orbital apex and the origin of the left retinal racemose haemangioma. There was no intracranial midbrain extension or communication with cerebral vessels.

**Comment**

Wyburn-Mason syndrome is a vascular condition synonymous with Bonnet de Chaume Blanc syndrome and is characterised by the coexistence of facial, retinal, orbital, and central nervous system (CNS) arteriovenous malformations. Theron et al reviewed 80 cases of retinal AV anastomoses and found that 30% of patients had concomitant AV malformations in the CNS, a rate much lower than the 81% association reported by Wyburn-Mason. Bech and Jensen also believe that the frequency of coexisting racemose haemangioma of the retina and brain was over-reported in the Wyburn-Mason series, suggesting that the preponderance of patients with advanced retinal lesions in the original study made associated CNS lesions more common. Isolated intramuscular haemangiomas are rare congenital benign lesions more common. Isolated intramuscular haemangiomas are rare congenital benign hamartomas, which comprise less than 1% of all haemangiomas in the body. Of those that do originate in muscle, only 15% originate in the head and neck region.

The absence of intracranial involvement in the presence of the other two characteristic features of this condition constitutes a rare clinical entity. Furthermore, the direct communication between the retinal racemose and intramuscular facial cavernous haemangiomas in our case, has not, to our knowledge been previously reported, and must be inordinately rare. This association may be consequential in our choice of therapeutic options for our patient.

Morbidly or early mortality in some Wyburn-Mason cases are secondary to the tendency of intracranial AV communications to bleed, leading to subarachnoid haemorrhage, neurological deficits and, in some cases, death. Ophthalmic manifestations may include visual loss secondary to intraretinal and macular haemorrhage, vasculitis, occlusive disease, neovascular glaucoma or vitreous haemorrhage. However, in most cases of abnormal retinal macrovessels, fluorescein angiography demonstrates stable non-leaking lesions. Management of patients with abnormal retinal macrovessels or “racemose” haemangiomas is difficult because of the heterogeneous modes of presentation. This may range from completely asymptomatic patients to those presenting with profound visual loss or neurological deficits. In the authors’ opinion, as a result of the high association with intracranial AV malformations (30–81%), imaging studies (MRI) should be carried out on all patients with retinal arteriovenous malformations. Fluorescein angiography may be carried out to demonstrate direct AV communication and to observe stability of the retinal vessels, but needs to be weighed against the risks of the procedure.

Because of the stability of most isolated retinal lesions, treatment from an ophthalmologist beyond routine periodic examination is probably unnecessary. However, failure to recognise specific neurological signs and symptoms and to make the appropriate referrals for radiological and neurological assessment, respectively, in cases of CNS involvement, may be a significant medicolegal pitfall. The important clinical correlates of Wyburn-Mason syndrome are shown in table 1. We would emphasise the need for an integrative approach, one that doesn’t consider retinal pathology in isolation, but that carries an awareness of the neurological and cutaneous manifestations of this condition.

In this particular case, owing to the direct communication of the retinal and facial vascular lesions, our options for treatment of the facial haemangioma may be limited by the risk of retinal vascular haemorrhage, occlusion, or thrombosis. The usual interventions which include injection sclerotherapy (she has had multiple treatments), embolisation of feeder vessels, laser photocoagulation, or proton beam irradiation may have implications for visual dysfunction. Direct surgical intervention may lead to massive and uncontrollable bleeding. In our asymptomatic young patient we have adopted a periodic review policy. But as adolescence and the social and cosmetic stigmata of a facial deformity make increasing assertions on our patient, we would welcome suggestions for definitive procedures that may be appropriate in the treatment of her condition.

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**Table 1 Clinical correlates in Wyburn-Mason syndrome**

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Not regarded as hereditary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Adolescence to early adulthood; usually becomes symptomatic before age 30 years</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Vascular facial naevi in up to 50% of patients, usually ipsilateral to affected eye</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td>AV communication of the midbrain may cause cerebral or subarachnoid haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Signs of midbrain lesion, hemiplegia, or hemiparesis, cerebellar dysfunction, Parinaud’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Mental changes affecting intelligence and memory</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td>Seizures in only 5% of patients</td>
</tr>
<tr>
<td><strong>Eye</strong></td>
<td>Associated AV communications of the lungs and spinal cord reported (rare)</td>
</tr>
<tr>
<td></td>
<td>Retinal AV communication (retinal AV aneurysm) unilateral, usually non-progressive</td>
</tr>
<tr>
<td></td>
<td>Pulsating exophthalmos, proptosis</td>
</tr>
<tr>
<td></td>
<td>Visual loss: secondary to retinal or vitreous haemorrhage, vascular leakage in the macular region, or nerve fibre loss secondary to mechanical compression of the optic nerve or anterior visual pathway</td>
</tr>
<tr>
<td></td>
<td>Phthisis or partial aphthalmoplegia secondary to third nerve involvement in the midbrain</td>
</tr>
</tbody>
</table>

Adapted from Albert and Jacobiec.©

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**Figure 2**

(A) Coronal T1 post-gadolinium and STIR MRI sequences. (B) Demonstrates the angiomatous lesion in left facial tissues and extending into left orbit.
Peripheral visual field loss following treatment with etanercept

Etanercept is a relatively new anti-tumour necrosis factor-α (TNF-α) therapy for inflammatory arthritides. Although there may be an association with uveitis, there have been no reports of patients experiencing visual disturbance. We present a case of a patient who developed symptomatic bilateral peripheral visual field loss shortly after initiation of treatment with etanercept.

Case report

A 59 year old woman was referred complaining of bilateral, sequential peripheral visual field disturbance, which developed during a course of etanercept therapy for rheumatoid arthritis. Initially she noticed a left upper temporal field defect occurring the day after receiving the first injection of etanercept. Following the second injection she became aware of similar visual field loss affecting the right eye. Two further injections were given (in course of five); however, treatment was stopped prematurely once the treating physicians became aware of the patient’s visual symptoms. No further subjective visual field deterioration had occurred. Paradoxically, the arthritic symptoms had significantly improved.

On examination, the visual acuities were normal at 6/6 and 6/5 in the right and left eyes respectively. The anterior segment examination and intraocular pressures were normal. Funduscopic examination revealed no abnormalities. A 120° computerised visual field assessment was performed, revealing bilateral, concentric peripheral field loss (fig 1). An urgent neurology opinion was sought. Systemic examination and further investigation including magnetic resonance imaging of the brain, visual evoked potentials, and electroretinography were all normal. A lumbar puncture was refused. An electroretinogram revealed reduced b-waves, suggesting retinal dysfunction involving the inner nuclear layer of the left eye.

Comment

Etanercept is a relatively new biological disease modifying antirheumatic drug for the treatment of active rheumatoid arthritis and is currently one of only two TNF-α blockers licensed for this use. It competitively inhibits cell surface binding of TNF and as such inhibits the pro-inflammatory effects of TNF and reduces joint inflammation.

Common side effects are injection site reactions and upper respiratory tract infections. Although neurological events have been reported, these are limited to confusion and difficulty walking and did not include visual phenomena. These effects also resolved completely or partially on cessation of etanercept. A report of a juvenile with new onset multiple sclerosis (MS) closely associated with the initiation of anti-TNF therapy has been published, and it is recommended that treatment be avoided in patients with previous MS until further long term safety data are available.

To our knowledge there have been no previous reports of visual field loss following anti-TNF treatment. Judging by the temporal proximity of the onset of the visual symptoms and the initiation of etanercept therapy, we assume a causal link. From the investigations performed this appears to be a toxic retinopathy affecting the inner nuclear layer. Interestingly, the pattern of peripheral visual field loss in this case is similar to that seen with vigabatrin toxicity.

Although we could find no evidence from the literature for TNF-α involvement in retinal physiology in healthy eyes, it is notable there has been much interest in the role it may have in neuroprotection and neurodegeneration in the retina. Perhaps TNF-α has a role in normal retinal physiology that has yet to be elucidated.

This adverse reaction has been reported to the Medicines Control Agency.

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References


Pupilsparing excision of an atypical iris melanocytoma induces remission of secondary glaucoma

Secondary glaucoma with iris melanocytoma can be successfully managed using sector iridectomy to reduce tumour burden in the anterior chamber.1 In our case of iris melanocytoma associated with glaucoma, we achieved normalisation of intraocular pressure (IOP) with pupil sparing partial iridectomy. As in previous reports,2 there was evidence of tumour necrosis, although our tumour exhibited more nuclear pleomorphism than is typical for a melanocytoma.

Case report

A 37 year old white man, with an iris pigmented mass of the left eye discovered at age 17, was followed without incident until he developed acute pain and decreased vision 4 years ago. Review of systems was not remarkable for trauma, surgery, or systemic illness.

Visual acuities were 20/20 in the right eye and hand motion in the left eye. Slit lamp biomicroscopy showed microscopic corneal oedema with 4+ suspended red blood cells in the anterior chamber of the left eye. The thick, deeply pigmented iris mass noted at the 8 to 10:30 o’clock meridian, extended from the angle to within 1 mm of the pupillary margin but did not appear different from baseline. There was slight pupillary

Figure 1 Humphrey C120 visual fields demonstrating bilateral peripheral field loss.
of cells exhibited marked nuclear pleomorphism (fig 2). There was an occasional spindle cell interspersed through the tumour but there were no mitotic spindles. Two ophthalmic pathologists rendered the diagnosis of atypical, necrotic iris melanocytoma.

Three years postoperatively, vision is 20/20 in the left eye, and IOP is 16 mm Hg without glaucoma therapy. There has been no reorganisation of a pigmented mass. On gonioscopy, there is 1+ TM pigmentation.

Comment
Several factors contribute to secondary open angle glaucoma in patients with iris melanocytoma: proximity of the tumour to the filtration apparatus; absence of tumour encapsulation with propensity to pigment dispersion; tendency for necrotic degeneration within the tumour that further enhances cellular sloughing; and secondary attraction of macrophages which engulf cellular debris and pigment. Pigment granules, viable and degenerated tumour cells and swollen macrophages obstruct the TM producing increased IOP, a condition coined melanomalytic glaucoma. Excision of the tumour via a pupil sparing partial iridectomy (when possible) accomplishes several goals: it supplies tissue for diagnostic purposes; it reduces tumour volume in the eye, allowing the TM to recover; and provides for an intact pupil.

Abrupt changes in clinical course such as exhibited by our patient raise the possibility of malignant transformation of the lesion. Malignant transformation of iris melanocytoma is rare. Nuclear pleomorphism, a cellular feature associated with malignant behaviour of pigmented tumours, was present in this tumour. Yet definite pathological characteristics of malignancy were absent in our case. There has been no reformation of the lesion or recurrence of glaucoma after 3 years of follow up.

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References
acuity was hand movements. There was minimal conjunctival injection and the cornea was clear. A 3 mm pseudohypopyon consisting of refractile crystalline particles was visible in the anterior chamber (fig 1A), associated with 3+ anterior chamber cells (or particles). Severe vitreous haze prevented visualisation of the retina.

Because an infectious endophthalmitis could not be excluded, the patient was treated with intravitreal injections of ceftazidime and vancomycin. Vitreous and aqueous taps were performed and the pseudohypopyon was completely aspired from the anterior chamber.

The following day, a 2 mm pseudohypopyon had reformed. The position of the pseudohypopyon was gravity dependent and shifted with changes in head position (fig 1B).

Vitreous and vitreous cultures were negative. Microscopy of the aspirated pseudohypopyon showed triamcinolone particles with no cells present (fig 2).

The pseudohypopyon, vitreous haze, and CMO (as demonstrated on optical coherence tomography) resolved over 6 weeks. The visual acuity recovered to 6/12.

Comment
Sutter and Gillies reported four cases of pseudoenophthalmitis characterised by painless visual loss caused by severe vitreous haze developing immediately or soon after intravitreal triamcinolone injection. The triamcinolone was dispersed throughout the vitreous rather than forming a discrete mass as is usually observed after injection. They speculated that this dispersion was due to partial “jamming” of crystalline triamcinolone in the barrel of the 30 gauge needle during injection, resulting in spraying of the drug into the vitreous at high velocity, and leading to formation of a diffuse vitreous suspension. It is possible that this tendency to dispersion may be reduced by using a 27 gauge needle.

Hyopopyon associated with non-infectious endophthalmitis following intravitreal triamcinolone injection has been described; however, the “pseudo” hypopyon is a unique feature of our case and is due to the presence of a posterior capsule defect enabling the passage of triamcinolone from the vitreous cavity into the anterior chamber. Presumably, the triamcinolone crystals are carried into the anterior chamber by currents generated by saccadic eye movements in the partially vitreoretinalised vitreous cavity.

The pseudohypopyon was distinguishable from an infective or inflammatory hypopyon by its ground glass appearance, the presence of refractile particles, and its shifting position, which was dependent upon the patient’s head position. The pseudohypopyon resolved spontaneously and was not associated with any apparent toxic effects.

The absence of ocular pain, photophobia, ciliary injection, or iris vessel dilation suggests a non-inflammatory response and perhaps it would be appropriate to monitor such patients closely rather than administering intravitreal antibiotics.

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Treatment of Erdheim-Chester disease with cladribine: a rational approach

Erdheim-Chester disease is a rare, life threatening lipid granulomatosis with fewer than 100 cases described in the world literature. The disease typically affects the long bones and symmetrical sclerosis of the diaphyseal and metaphyseal regions is pathognomonic. Extraskeletal manifestations may affect the lungs, pericardium, aorta, retroperitoneum, skin, and orbits and diabetes insipidus occurs in approximately 30% of cases. Erdheim-Chester disease is characterised microscopically by an infiltrate of lipid laden foamy macrophages (histiocytes), scattered Touton giant cells, chronic inflammatory cells, and fibrosis. The foamy macrophages can be distinguished from Langerhans cells on the basis of negative results on staining for S-100 protein and CD1a. Treatment of the disease has been on an ad hoc basis and no treatment regimen has been shown to be clearly superior.

This study documents the clinical findings in a patient with Erdheim–Chester disease, investigates the pathogenesis, and provides a rational basis for effective treatment.

Case report
This white man, aged 45, developed aching in his legs, night sweats, lethargy, and impotence in October 1988, for which no cause was found. His night sweats resolved by July 1989 and he was discharged. He presented in November 1990 with reduced vision (6/9) in the left eye, bilateral proptosis of 12 months’ duration, chemosis, ophtalmoplegia, and optic disc oedema. He still had sexual dysfunction and lethargy and now also had leg oedema and thrombocythaemia. At that time his thyroid function was normal, but erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were moderately elevated. A computed tomography (CT) scan of the orbits showed bilaterally enhancing masses lying predominantly within the muscle cone and encasing both optic nerves. An
orbital biopsy in November 1990 showed an inflammatory picture. There was no evidence of vasculitis on muscle biopsy and a clinical diagnosis of orbital pseudotumour was made. He was initially treated with prednisolone 80 mg daily then reducing, in conjunction with azathioprine 150 mg daily increasing to 250 mg daily, to which he made only a partial response. After treatment was stopped, he failed to attend in 1995 and was lost to follow up.

He presented again in January 1999 with bilateral proptosis, gross chemosis, and infiltration of the conjunctiva and ophthalmoplegia (fig 1A). At this time, the ESR was raised at 74 mm in the first hour and the CRP was elevated at 95 mg/l. A CT scan showed a marked increase in size of the orbital masses. A left anterior orbitotomy and biopsy were performed in February 1999 and histology suggested a diagnosis of fibrous histiocytoma. He was treated with intravenous methyl prednisolone and intravenous cyclophosphamide (total 11 g) but failed to respond. He was referred for consideration of radiotherapy to the orbits. A CT scan was performed which showed soft tissue shadowing around the aorta, pericardium, and kidneys and in addition small pericardial and pleural effusions. The clinical findings of proptosis and widespread soft tissue infiltration suggested Erdheim-Chester disease.

Paravertebral tissue was biopsied under CT control. A diagnosis of Erdheim-Chester disease was made on the basis of non-Langerhans histiocytosis, negative for S-100 protein and without intracytoplasmic (Birbeck) granules in this and the previous biopsy specimens (fig 2). X ray of the long bones showed the sclerosis and increased trabecular markings typical of this disease (fig 3).

He was treated with etoposide 50 mg daily and a reducing course of prednisolone, starting at 30 mg daily, without clinical improvement. Etoposide was increased to 100 mg daily with some improvement in the degree of proptosis and chemosis. However, his haemoglobin fell rapidly by 3 g to 8 g/dl and etoposide was discontinued, although a blood film suggested haemolysis or bleeding rather than etoposide induced myelosuppression. On prednisolone 30 mg daily, the haemoglobin rose and there was limited improvement in the proptosis. However, he developed back pain and long term high dose steroids were considered inappropriate.

In November 1999, his visual acuity was 6/6 in the right eye and 6/5 in the left. Colour vision and pupil reactions were normal. He had very restricted eye movements but was binocular with no diplopia. There was bilateral proptosis, right chemosis, and a soft tissue swelling at the left inner canthus. New clinical signs were increased swelling of both optic discs and the presence of choroidal folds bilaterally. Surgical debulking of the orbits was not possible as the xanthogranulomatous tissue surrounded both optic nerves and the external ocular muscles. Bony decompression was considered, but the patient was reluctant to have surgery and also he was a bad anaesthetic risk in view of his cardiac and pulmonary involvement.

In January 2000, hot spots were seen on a bone scan. Spiral CT of the chest showed pulmonary infiltration, but no fibrosis. Abdominal CT showed infiltration around the aorta; there was also enlargement of the aorta, pericardium, and kidneys and in addition small pericardial and pleural effusions. The clinical findings of proptosis and widespread soft tissue infiltration suggested Erdheim-Chester disease.

In 1999, Saven and Burian suggested monocyte activation as a significant feature of this disease. The monocytosis and highly distinctive pattern of cytokine activation detected in the peripheral blood of this patient with Erdheim-Chester disease suggested monocyte activation as a significant part of the pathogenesis of the disease. Cladribine is a purine analogue that is toxic to monocytes. Cladribine also destroys both resting and dividing lymphocytes and causes T cell depletion. In 1999, Saven and Burian described encouraging responses to cladribine in 13 patients with Langerhans cell histiocytosis. This information, together with our new evidence of **Comment**

Erdheim-Chester disease is characterised by slow progression of multiple organ system dysfunction with a high mortality. In the largest review, of 59 cases, reported by Veyssier-Belot, common causes of death included pulmonary fibrosis and cardiac failure. Treatment of patients has been on an individual basis and no randomised controlled trials have been possible as the condition is so rare. Treatments have included systemic steroids, cytotoxic agents such as vinblastine, cyclophosphamide, doxorubicin and Adriamycin, and also interferon alfa. Local radiotherapy to the orbits has been used. The results of treatment have been generally disappointing. In the review by Veyssier-Belot et al, follow up data were available on 37 patients with a mean follow up of 2.7 years. Twenty two out of 37 (59%) patients died within the follow up period, eight within 6 months of diagnosis.

Very little is known regarding the pathogenesis of this disease. The monocytosis and the highly distinctive pattern of cytokine activation detected in the peripheral blood of this patient with Erdheim-Chester disease suggested monocyte activation as a significant part of the pathogenesis of the disease. Cladribine is a purine analogue that is toxic to monocytes. Cladribine also destroys both resting and dividing lymphocytes and causes T cell depletion. In 1999, Saven and Burian described encouraging responses to cladribine in 13 patients with Langerhans cell histiocytosis. This information, together with our new evidence of **Comment**
Figure 5  Quantitative RT-PCR analysis of cytokine expression on this patient with Erdheim-Chester disease (solid bars) compared to seven normal controls (open bars). A highly distinctive pattern of cytokine activation was found in the peripheral blood. Interleukin-1α (IL-1α), IL-1β, IL-2, and IL-8 all had raised expression compared with controls, consistent with monocyte activation. Smaller rises were seen in IL-6 and tumour necrosis factor α (TNF-α).

increased monocyte activation in this patient, made cladribine, an agent toxic to monocytes, a rational choice. There has been one previous report of treatment of Erdheim-Chester disease with cladribine. That patient had orbital involvement and unfortunately developed bilateral blindness. It was postulated that cladribine might have caused toxic injury to the optic nerves which predisposed them to ischaemic injury. However, the clinical signs suggested progression of the Erdheim-Chester disease as the cause of the blindness. There has also been a case of transient blindness occurring during therapy with cladribine. If treatment with cladribine is instituted for orbital disease, careful monitoring of the degree of proptosis and optic nerve compression is mandatory.

This patient with Erdheim-Chester disease showed evidence of increased monocyte activation. He has shown a significant recovery and maintained clinical improvement following treatment with cladribine, an agent toxic to monocytes. Although the long term durability of its effect is not yet known, this patient has had a good quality of life for 2 years after stopping treatment. This is the first report to correlate the clinical findings and response to treatment with the laboratory results in peripheral blood and provides a rational basis for treatment of this life threatening condition.

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References
Partial resolution of acute ascending motor polyneuropathy after enucleation of an eye with metastatic melanoma

Malignant melanoma is an immunological tumour, and the glycoproteins on the surface of melanoma cells share immunogenic similarity with cells in the central and peripheral nervous system. Several clinical signs have been suggested to result from this similarity including vitiligo, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and chronic inflammatory demyelinating polyneuropathy. We describe a patient with metastatic melanoma in the eye, who developed uveitis associated with ascending motor neuropathy. Enucleation of her blind painful eye resulted in marked improvement in her neurological abnormalities.

Case report

A 21 year old woman with a history of stage III cutaneous melanoma presented with anterior uveitis in her left eye. Visual acuity, intraocular pressure, and posterior pole examinations were within normal limits. Right eye examination was unremarkable. A diagnostic anterior chamber tap, left eye, revealed melanoma tumour cells.

One month later she developed a profound ascending motor polyneuropathy compatible with the diagnosis of Guillain-Barré syndrome. Clinical examination showed weakness of her upper and lower extremities, and decreased reflexes with no signs of sensory neuropathy. Lumbar puncture demonstrated 3 white blood cells ×10⁶/L. Magnetic resonance imaging of her thorax, cervical and lumbar spine showed no evidence of spinal cord or leptomeningeal disease.

The neurological symptoms worsened proportionally to the disease progression in her eye, and the level of neuron specific enolase (NSE) rose from a low value of 16 to a high value of 36 ng/ml. She was treated with several courses of high dose intravenous gamma globulin (IVIG) with slight but temporary improvement.

Six weeks after initial presentation, because of severe refractory disease in the left eye (fig 1), she underwent a left eye enucleation. Histopathological examination showed malignant melanoma involving the ciliary body, iris, trabecular meshwork, and vitreous cavity (fig 2). Since the enucleation her polyneuropathy has markedly improved. NSE decreased to 12 ng/ml (normal 0–10). She has continued to receive IVIG and autologous dendritic cell vaccine and, 18 weeks after enucleation, showed partial (>50%) resolution of the polyneuropathy with substantial but as yet incomplete recovery of lower and upper extremity weakness.

Comment

The patient presented with uveitis and metastatic melanoma in her left eye. She developed a severe ascending motor polyneuropathy compatible with the diagnosis of Guillain-Barré syndrome. Enucleation of the blind, painful left eye resulted in substantial clinical and laboratory improvement in the polyneuropathy.

As ascending motor polyneuropathy in our patient may have been caused by an immune reaction directed to antigens in the tumour that cross reacted in the nervous system. Marked improvement in her overall peripheral muscle strength after the enucleation suggests a relation between the progressive dysimmune polyneuropathy and the intraocular involvement. More evidence of a tumour related immune response was shown by post-enucleation decrease in the level of NSE, a specific marker for metastatic disease in melanoma where its increase points to disease progression.

Various paraneoplastic neuropathies have been described in association with cancer, including subacute sensory neuropathy/paraneoplastic encephalomyelitis, Guillain-Barré syndrome, and axonal polyneuropathy and specifically in melanoma: chronic inflammatory demyelinating polyneuropathy, ophthalmoplegia, and subacute motor axonal neuropathy.

The relation between enucleation and improvement of the neuropathy is not clear; improvement may have been due to spontaneous remission. However, the appearance of neuropathy soon after the onset of uveitis and the partial (>50%) resolution after enucleation raise the possibility that molecular mimicry and antigenic cross reaction were the cause of the polyneuropathy. Enucleation, by reducing the cross reacting antigens, is likely to have contributed to resolution of the polyneuropathy.

References


Aspergillus keratitis following corneal foreign body

Recognition, diagnosis, and management of fungal keratitis remain difficult despite significant advances in our understanding of the disease.

We report three cases secondary to corneal foreign body which were managed at Manchester Royal Eye Hospital (MREH).

Case reports

Case 1

A 22 year old man presented to MREH with a metallic corneal foreign body that was removed; chloramphenicol eye drops were prescribed. He returned 3 days later with pain, hand movement vision, a round corneal ulcer, and a hypopyon. A corneal scrape was performed and he was treated with intensive topical antibiotics. The Gram stain showed few fungal hyphae which were thought to be contaminants. The patient was reviewed by the corneal service 6 days after his injury. As...
The patient was referred to MREH corneal service 29 days after his injury with no change in the clinical picture (fig 1B). The cornea was rescraped confirming presence of aspergillosis infection. Topical treatment was changed to amphotericin eye drops and oral itraconazole was increased to three times daily.

Finally, a penetrating keratoplasty was performed with intracameral amphotericin-B (7.5 µg). Aspergillus fumigatus was present in the corneal button with a clear edge.

Phacoemulsification and lens implantation were carried out 2 months after the graft. Thirty months after keratoplasty the graft remained clear with 6/18 vision.

Comment
Most fungal keratitis is caused by filamentous fungi with the epidemiology varying throughout the world. It is believed to be rare in Britain especially after injury with a metallic foreign body. Our cases demonstrate the difficulties in establishing a diagnosis by culture. Two patients required a therapeutic keratoplasty, which eliminates 90–100% of fungal infections. In recent reports intracameral amphotericin B has been used, as part of the medical treatment which may prove useful if aspergillosis keratitis becomes more common in the Britain.

The clinical evolution of a kissing naevoid after incomplete excision

We present an interesting case of a kissing naevoid which was not completely excised during the patient’s childhood, 29 years before presentation.

Case report
A 33 year old white man complained of progressive thickening of the eyelids which caused significant inferior visual field defect with downgaze (fig 1). A large, circumorbital pigmented naevoid in the right eye had been present since birth. There was minimal growth through early childhood. This mass did not cause ptosis nor was it amblyogenic. At 4½ years of age he had excision of the naevoid of the right lower eyelid with reconstruction with a split thickness skin graft (fig 2). Of significance, he had incomplete excision of a kissing naevoid from his eyelids at age 6. A similar procedure was performed to address the upper eyelid and brow. The margin of the upper eyelid also had residual pigmentation.

When he was aged 33, we performed a biopsy to rule out malignant changes; the biopsy confirmed a diagnosis of benign naevoid. Subsequently, a complete excision of the mass from the right lower eyelid and reconstruction with a full thickness skin graft was performed.

Comment
A kissing naevoid is a type of congenital compound naevoid that affects equal portions of the upper and lower eyelid. Owing to its extension to the lid margins, the edges of the tumour touch or “kiss” during closure of the lids. The kissing naevoid origin dates to melanocyte migration during the embryological fusion of the lids at the ninth week of gestation, producing the “kissing” or split naevus.

Congenital naevoid occur in approximately 1% of all newborns, with the vast majority being less than 1.5 cm in size. Compound naevoid possess features of junctional (arising from...
from the deeper layers of the epidermis or “junctional region”) and intradermal naevi. The lifetime risk of malignant degeneration in small congenital naevi is not clearly established. Large cutaneous melanocytic naevi (more than 4 cm), however, do give rise to melanoma. The risk of malignant transformation is 4.6% during a 30 year period.

Kissing naevi of the eyelids may be cosmetically objectionable and cause functional problems including ptosis and visual field defects. Management usually requires surgical excision and reconstruction with split or full thickness skin grafts. Initial, complete excision is important because residual tumour can grow, often with a more verrucous or thickened appearance making subsequent determination of malignant transformation and reconstruction challenging.

**References**


**Authors’ reply**

We thank Dr Fan and coworkers for their letter and interest in our article. The conclusion drawn by us was that confocal microscopy was a rapid and sensitive diagnostic tool for both early diagnosis and non-invasive follow up of fungal keratitis. This in order to justify the statement, two issues of concern on the early diagnosis have to be addressed.

The first is about the sensitivity in having positive diagnosis in the untreated eyes in the first experiment. On day 2, all 14 samples were smear and culture positive for Aspergillus fumigatus, therefore confocal microscopy could not demonstrate any superiority in early diagnosis in terms of sensitivity. On days 14 and 22 their conclusion that “confocal microscopy was more sensitive than culture technique” could also not be drawn unless the authors could enlighten us with supplementary data on the percentages of positive culture in those periods together with their p values.

Another issue is about computation of statistical values in the second experiment. The authors implied that topical and orally treated eyes had significantly lower positive culture growth than the control group receiving no treatment on days 14 and 22 by listing p values of 0.002 and 0.003. However, in performing the $\chi^2$ analysis again with the data provided, we can only achieve p = 0.391 and p = 0.280 on day 14 and p = 0.308 and p = 0.237 on day 22. We would suggest that statistical differences cannot be demonstrated in these parts of study, at least, with such a sample size.
reported that about one fourth of fungal cultures became positive only after 2 weeks. Confocal microscopy is also rapid compared to biopsy staining, since to perform toluidine staining some time had to elapse. As stated in our article “Although in our model Sabouraud’s agar and corneal biopsy techniques showed similar sensitivity (100%) in the early stage, confocal microscopy appears to have a definite advantage in the later stages of infection, since not all cases of fungal keratitis could be cultured.” In the abstract we wrote that “on days 14 and 22 confocal microscopy was more sensitive than culture technique in both treated and untreated animals, since not all cases of fungal keratitis could be cultured.” We think the conclusion drawn is valid in light of the data provided in the study. In the second experiment, six rabbits were treated with topical fluconazole, seven were treated with oral fluconazole, and seven were left untreated. On day 14, we observed hyphal fragments (broken in treated corneas and full size in untreated ones) in each of 20 corneas by confocal microscopy. However, only eight of 20 scrapings grew Aspergillus fumigatus on Sabouraud’s agar culture. The difference between groups was statistically significant as is given in the text by utilizing $\chi^2$ test. Similarly, on day 22 confocal microscopy revealed hyphal fragments in 14 corneas out of 20 (three in the topically treated, four in the orally treated, and seven in the untreated groups). At this stage only five corneal scrapings grew fungus on culture. The difference was statistically significant again as given in the article by utilising $\chi^2$ test. Thus, superiority of confocal microscopy over culture technique on days 14 and 22 in treated and untreated rabbits was supported well by the data presented in the article.

In the result section, we were attempting to determine the efficacies of topical and oral fluconazole treatment by culture. However, $p$ values were not correct as a result of an error. The errors escaped both our and the reviewer’s attention. However, this part of the results section does not contain any information that could affect any conclusion drawn as a result of study data. Actually, this part was not directly linked to the main aim of the study. The authors wish to thank Dr Fan and coworkers for their careful attention.

The correct $p$ values are given here: on day 14 ($p = 0.383$ and $p = 0.296$); on day 22 ($p = 0.342$ and $p = 0.279$).

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References

Macular infarction after intravitreal amikacin
We write in reference to the letter by Galloway et al.

The authors report a single case of macular infarction in a patient who had been given intravitreal amikacin for endophthalmitis. They cite that single case plus some previous literature as a reason to support a change in the choice of antibiotic for intravitreal injection from the treatment guidelines based on the results of the Endophthalmitis Vitrectomy Study (EVS).

While aminoglycoside induced retinal toxicity certainly can occur, we disagree with their statement that there is good evidence that aminoglycosides should not be primary drugs of choice in cases of endophthalmitis. There are several theoretical and practical advantages of aminoglycosides over ceftazidime. Amikacin provides concentration dependent killing (so that the higher concentration of drug the better the outcome) which is not true for ceftazidime. This is an important issue since high concentrations of drug are administered by intravitreal injection, thus possibly allowing for more rapid kill with amikacin.

Amikacin is considered to be synergistic with vancomycin for certain Gram positive species, so its use provides benefit against Gram positive organisms, not just for Gram negative organisms. Gram positive organisms make up the overwhelming majority of cases of endophthalmitis. In addition, there has been a recent report that ceftazidime may precipitate in the vitreous at normal body temperature, possibly making it less available than one might wish in the vitreous cavity.

Finally, and very importantly, is the fact that amikacin has been found to be effective in a clinical trial but there is no such evidence yet available on ceftazidime. The only apparent advantage of ceftazidime is that it may be a somewhat safer drug in the sense that macular toxicity has not been reported. Even so, the incidence of macular toxicity is extremely rare (only once in 420 eyes in the EVS suffered macular toxicity possibly from the drug). In a very severe disease such as endophthalmitis a risk this low is worth tolerating when there may be substantial potential advantages.

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References
There are comprehensive sections on eyelid and nasolacrimal conditions, with the largest section dealing with orbital disorders. There is wide ranging coverage from simple, common conditions such as dermoids to complex craniofacial disorders. The systematic approach to the craniofacial disorders is particularly helpful, providing a useful tool in the management of this difficult area. It makes no claim to be a detailed surgical atlas, but rather is comprehensive in its account of the diagnosis, assessment, and management of each condition, with good illustrations and descriptions of the more common surgical procedures. The text is laid out logically, and is generally well written and easy to read. The authors have managed to combine an explanation of the principles of management, providing a general understanding, with detailed descriptions of the more common surgical procedures. The text is laid out logically, and is generally well written and easy to read.

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NOTICES

Cataract surgery
The latest issue of Community Eye Health (No 48) discusses a solution to reduce worldwide cataract blindness, including sutureless non-phaco cataract surgery. For further information please contact: Journal of Community Eye Health, International Resource Centre, International Centre for Eye Health, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (tel: +44 (0)20 7612 7964; email: Anita.Shab@lshtm.ac.uk; website: www.jche.co.uk). Annual subscription (4 issues) UK£28/US$45. Free to developing country applicants.

Elimination of avoidable blindness
The 56th World Health Assembly (WHA) considered the report on the elimination of avoidable blindness (doc A56/26) and urged Member States to: (1) Commit themselves to supporting the Global Initiative for the Elimination of Avoidable Blindness by setting up a national Vision 2020 plan by 2005; (2) Establish a national coordinating committee for Vision 2020, or a national blindness prevention committee to help implement the plan; (3) Implement the plan by 2007; (4) Include effective monitoring and evaluation of the plan with the aim of showing a reduction in the magnitude of avoidable blindness by 2010; (5) To support the mobilisation of resources for eliminating avoidable blindness. The WHA also urged the Director-General to maintain and strengthen WHO’s collaboration with Member States and the partners of the Global Initiative for the Elimination of Avoidable Blindness as well as aid in the coordination and support of national capability.

XVth Meeting of the International Neuro-Ophthalmology Society

4th International Congress on Autoimmunity
The 4th International Congress on Autoimmunity will take place 3–7 November 2004 in Budapest, Hungary. The deadline for the receipt of abstracts is 20 June 2004. Further details: Kones International Global Congress Organisers and Association Management Services, 17 Rue du Cendrier, PO Box 1726, CH-1211 Geneva 1, Switzerland (tel: +41 22 908 0488; fax: +41 22 732 2850; email: autoim04@kones.com; website: www.kones.com/autoim2004).

XVI International Congress for Eye Research
The XVI International Congress for Eye Research will be held on 29 August – 3 September 2004 in Sydney, Australia. For further information, please contact: icr2004@tourhosts.com.au (website: www.tourhosts.com.au/icr2004).

Tübingen University Eye Clinic holds teaching courses
The Tübingen University Eye Clinic will be holding teaching courses throughout the year and into 2005. In all cases, the scientific program has been organised by Professor Ingrid Kreissig (Department of Ophthalmology, Klinikum Mannheim, Theodor-Kutzer-Ufer 1-3, 69167 Mannheim, Germany; fax: +49 (0)621 383 3803; e-mail: ingrid.kreissig@augen.ma.uni-heidelberg.de). The programme of courses will include the following:

- Local Organization: Anne-Catherine Gribomont, MD, gribomont@ofa.ac.be
- Location: Brussels, Belgium.
- Congress language: English.

- Detachment Course with International Faculty on ’Retinal and Vitreous Surgery with Case Presentations’ will be held in Xian, PR China, on 13–14 November 2004.
- Local Organization: Professor Yan-Nian HUI, Xijing Hospital, 15 Chang-le Xi-lu Rd, Xian City, PR China.
- Location: Xian, PR China (tel: +86 29 8337 5371; fax: +86 29 8329 2763; e-mail: fmmuhyin@fmmu.edu.cn).
- Congress language: English with simultaneous translation into Chinese.

- Detachment Course with International Faculty on ’Retinal and Vitreous Surgery with Case Presentations’ will be held in Surat Gujarat, India, on 9–10 December 2004, preceding the Ophthalmological Meeting of Western India, 10–12 December 2004.
- Local Organization: Dr PN Nagpal, Dr. Yogesh Desai, Dr Nitin Trivedi, Eye Laser Clinic, Maher Park-B, Opp Fly Over Bridge, Athiba Gate, Ring Road, Surat – 395001 (fax: +91 261 22776021; tel : +91 261 2247188, -22460100 ; e-mail: eye_laserclinic@yahoo.com).
- Congress language: English.

- Detachment Course with International Faculty on ’Retinal and Vitreous Surgery with Case Presentations’ will be held in Odessa, Ukraine, on 14–15 May 2005.
- Local Organization: Professor VV Vit, SS Rodin, The Filatov Institute of Eye Diseases & Tissue Therapy, Blvd. Francois 49/51, 65061 Odessa, Ukraine (fax: +38 048(42)684851, e-mail: logay@farlep.net).
- Congress language: English with simultaneous translation into Russian.

- Detachment Course with International Faculty on ’Retinal and Vitreous Surgery with Case Presentations’ in Prague, Czech Republic, on 3–4 September 2005.
- Local Organization: Professor MU Drz. Pavol Rozsival, Dept. of Ophthalmology, Charles University, Sokolska 581, 500 05 Hradec Králové, Czech Republic (tel. and fax: +420 49 55 14 582, e-mail: rozsival@ltk.cuni.cz).
- Congress language: English.