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.3,4 Minimal literature has emerged describing success with strabismus surgery in patients with diplopia caused by MG despite systemic treatments.5,6 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 1998 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 1999, 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 divergent 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-anti 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 abduction 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 recession. 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 extracranial 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.

References
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Table 1   Prism measurements preoperatively and 13 months postoperatively

<table>
<thead>
<tr>
<th>Prism measurements</th>
<th>Preoperative</th>
<th>45° esodeviation</th>
<th>&gt;45° esodeviation</th>
<th>&gt;45° esodeviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>18° esodeviation</td>
<td>0</td>
<td>10° esodeviation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20° esodeviation</td>
<td>0</td>
<td>10° esodeviation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13 months postoperative</td>
<td>0</td>
<td>10° esodeviation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(July 2003)</td>
<td>0</td>
<td>10° esodeviation</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</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.1–4 If freely communicating with the orbital circulation, engorgement of varices can occur by increasing venous pressure through the Valsalva manoeuvre,5 bending posture,6 coughing or straining and these, in turn, lead to the clinical characteristics of variable proptosis, intermittent pain, and orbital haemorrhage.7,8 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.9 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.10 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 lobes. 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 the dural space in two cases (patients 4 and 5), and involved the frontal lobe parenchyma in one case (patient 6; fig 1C, D).

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,10 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 circulation;11 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 wall 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</td>
<td>Normal</td>
<td>Varices up to frontal lobe and intraconal</td>
</tr>
<tr>
<td>5</td>
<td>Right</td>
<td>57</td>
<td>M</td>
<td>Panorbit intraconal and extraconal</td>
<td>Absent</td>
<td>Posterior orbital roof</td>
<td>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</td>
<td>Normal</td>
<td>Varices into frontal lobe 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>62</td>
<td>M</td>
<td>Posterior intraconal and extraconal</td>
<td>Present</td>
<td>Very enlarged SOF, patchy SNQ defects posteriorly</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>Left</td>
<td>66</td>
<td>M</td>
<td>Extracanal–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.

References


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 enucleate the hydroxyapatite implant that facilitate attachment of extraocular muscles. Various wrapping materials have been tried including donor human sclera,1 acellular dermis,2 rectus abdominis sheet,3 posterior auricular muscle,4 polyglactin mesh,5 and bovine pericardium.6 In this report, we present our 5 year experience with the use bovine pericardium wrap. The wrap is presterilised using glutaraldehyde, ethanol, and propylene oxide to minimise the risk of transmission of bacterial and viral infections.

Patients and methods

All patients undergoing primary enucleation for large choroidal melanoma with the insertion of hydroxyapatite implant wrapped in processed bovine pericardium were included in the study. Patients with less than 3 months’ postoperative follow up or radiotherapy were excluded.

Three consultant ocular oncologists performed all the surgeries. After enucleation and haemostasis, a size 18 or 20 mm hydroxyapatite orbital implant was wrapped with bovine pericardium wrap (Ocugaurd Supple, Bio-Vascular Inc, St Paul, MI, USA) (fig 1). The posterior loose ends were anchored securely on the implant with a 6–0 Dacron suture joining opposite ends of the wrap. Windows in a square or slit configuration were cut into the wrap and all four rectus muscles were attached to the anterior lip of the apertures (fig 2). The Tenon’s capsule and the conjunctiva were closed in two layers with interrupted 6–0 Vicryl sutures. An artificial eye was inserted approximately 6 weeks postoperatively and the patient was reviewed every 3–6 months.

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.7 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 haemorrhage 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
101 patients (97%) and with ocular motility satisfactory to the patients.

Comment

It is important to have a wrapping material that is safe and easy to use. The harvesting of autologous materials leaves scars and increases the surgical time.

Sclera is the most commonly used wrapping material for hydroxyapatite implants associated with varying rates of wound dehiscence (7.5%–19.3%). Comparable wound dehiscence rates of 5–14% with bovine pericardium wraps have also been reported. 5,6 Wound dehiscence/implant exposure rate of 2.9% in our series is much lower than other published series using bovine pericardium or human donor sclera. 3,10 Low complication rate in our series could be attributed to inclusion of cases without any orbital pathology, exclusion of cases treated previously with irradiation, and the meticulous wound closure.

Concerns regarding possible association of the use of sclera with the transmission of viral and prion infections including Creutzfeldt-Jakob disease have forced the clinicians to search for alternative materials. 11,12 It is believed that the risk of transmitting prion disease by human or animal derived tissue is proportional to the risk of the donor having them. 13 With the use of bovine pericardium originating from countries not known to have bovine spongiform encephalitis the risk of transmission of such infections can be minimized.

Our study suggests that the use of bovine pericardium as a wrap for hydroxyapatite implants is a safe alternative to other wrapping materials and has a low rate of complications when performed in the setting of primary enucleation.


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References


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 Bohn 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 after a period of time has been reported in the aftermath of cataract, retinal detachment, and intracranial surgery. 14 In addition there are two case reports of cyclical esotropia developing following strabismus surgery for intermittent exotropia 15 and for infantile esotropia. 16 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 orthoptist 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 left esotropia measuring with glasses 35 and 30 prism diptres (Δ) for near and distance respectively and measuring without glasses 30Δ and 40Δ for near and distance respectively. It was confirmed that she had bilateral inferior oblique overaction. Sensory fusion showed left suppression. The history and clinical findings were suggestive of a diagnosis of cyclical esotropia and 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 her forthcoming school examinations and 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 “cyclical” only every third or fourth day. Her orthoptic findings were unchanged. She was therefore listed for surgery and underwent right medial rectus recession of 3.5 mm, left medial rectus recession of 5.5 mm and left inferior oblique recession of 4.5 mm, leaving a 8Δ left exotropia. Postoperatively there was a fully accommodative left esotropia measuring 6Δ for near and distance with glasses, and 25Δ and 20Δ for near and distance respectively without glasses. There was constant binocular single vision with a stereo acuity of 40‘ of arc (Frisby test). This had remained stable during a nine month follow up period.

References


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. It has been paralleled by other studies on multipotent precursor cells in the ciliary margin of the frog retina, progenitor cell proliferation and horizontal cell genesis in the mammalian retina, and differentiation of human neural stem cells into retinal cells. The retinal progenitor or stem cells were thought to be located in the region of the ciliary body. 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 during life, prepared cryo, and prepared for light microscopy. An anterior-posterior segment going through the pupil and the optic nerve was cut out of the eye. The segment was dehydrated in alcohol, embedded in paraffin, hydrated in alcohol, embedded in paraffin, dehydrated in alcohol, embedded in paraffin, and prepared for light microscopy. The eyes were examined for regularity, cell size, and nuclei size. The study design complied with the National Institute of Health's guidelines as well as the University of Iowa Institutional Guidelines for the Care and Use of Laboratory Animals, and the guidelines of ARVO.

Conclusion

In rhesus monkeys close to the ora serrata in the posterior region of the pars plana region, the inner non-pigmented layer was monolayered and more regularly arranged. Here, the cell shape was columnar, and the cell nuclei were located in the basal cell region (fig 2). In the pars plicata of the ciliary body, the inner non-pigmented layer was monolayered with a cuboidal cell shape and the cell nuclei located in the basal region of the cell (fig 3). In contrast to the monkey eyes, in a human globe, the inner non-pigmented layer in the posterior pars plana region was monolayered and more regularly arranged (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 pseudo-xanthoma elasticum, Paget’s disease, and the haemoglobinopathies such as sickle cell anaemia and thalassaemia. Although angioid streaks have been reported among siblings and family members in association with pseudo-xanthoma 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. Fluorescein angiography showed features similar to his brother in the form of angioid streaks associated with a subretinal neovascular membrane (fig 1). Visual acuity deteriorated to counting fingers in the left eye over 9 months and, to date, he maintains acuity of 6/12 in the right.

Comment

On ophthalmoscopic examination, angioid streaks appear as single or multiple dark red/brown bands radiating form the optic disc. Fluorescein angiography showed increased transmission of fluorescence overlying the streaks and peripapillary region. The macula also showed leakage of fluorescein suggestive of a subfoveal neovascular membrane (fig 1). Visual acuity deteriorated to counting fingers in the left eye over 9 months and, to date, he maintains acuity of 6/12 in the right.

References


Figure 1 Fundus and fluorescein angiographic pictures of twin 1.

Amsler grid testing of the central field showed a central scotoma in both eyes, more pronounced in the right. Funduscopy revealed bilateral, red/brown bands radiating from the optic disc suggestive of angioid streaks, and a lesion at the left macula suggestive of a subretinal neovascular membrane. Fluorescein angiography confirmed angioid streaks showing increased transmission of fluorescence overlying the streaks and peripapillary region. The macula also showed leakage of fluorescein suggestive of a subfoveal neovascular membrane (fig 1). Visual acuity deteriorated to counting fingers in the left eye over 9 months and, to date, he maintains acuity of 6/12 in the right.

Figure 2 Fundus and fluorescein angiographic pictures of twin 2.

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. Fluorescein angiography showed features similar to his brother in the form of angioid streaks associated with a subretinal neovascular membrane (fig 2).
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.

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References

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 saccorhoidal 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.

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 fulminating, often fatal, leukaemia-like Letterer-Siwe disease. The hallmark of LCH is the pathological Langerhans cells (PLCs), 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. 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. The second is that of a mastoid lesion presenting 33 years after the original mandibular lesion. 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**

Subretinal or retinal neovascularization, intraretinal proliferation of non-vascular cells, intraretinal or subretinal oedema, and chronic ocular hypotony have recently been treated by intravitreal injections of steroids such as triamcinolone acetonide. The diseases included long standing macular oedema due to central retinal vein occlusion, diffuse diabetic macular oedema, exudative age related macular degeneration, proliferative diabetic retinopathy, neovascular glaucoma, proliferative vitreoretinopathy, chronic pre-phthisical ocular hypotony, chronic uveitis, persistent pseudophakic ciliary macular oedema, and other clinical conditions. Systemic or local side effects reported so far include cataract, secondary ocular hypertension leading in some patients to secondary chronic open angle glaucoma, non-infectious endophthalmitis or “pseudo-endophthalmi
tis”, and post-injection infectious endophthalmitis. Safety and toxicity investiga
tions have not revealed a negative effect of intravitreal corticosteroids on intraocular structures, yet. Besides a recent report, other histological examinations of globes after intravitreal injections of triamcinolone acetonide in patients have been lacking so far. It was, therefore, the purpose of the present report to describe pathohistological findings after an intravitreal injection of triamcino
tone acetonide.

**Case report**

An 86 year old patient received an intravitreal injection of triamcinolone acetonide as treat
ment for exudative age related macular degeneration in her left eye. Visual acuity was 0.10 left eye, and hand movement right eye. After returning home, she fell hitting her head and eye against a heating apparatus 1 week after the injection. Two days later, she was found lying on the floor almost uncon
scious. A paralimbal corneal wound corre
tponding to a former cataract surgery was widely open, and clinical signs of endoph
thalmitis were present. Since the patient did not perceive any light in her left eye, the eye was enucleated and fixed in a solution of 4% formaldehyde. The globe was prepared in a routine manner for light microscopic exami
nation. An anterior-posterior segment going through the pupil and the optic nerve was cut out of the fixed globe. The segment was dehydrated in alcohol, embedded in paraffin, sectioned for light microscopy, and stained by the periodic acid Schiff (PAS) method.

Histology showed a marked destruction of the whole globe. The paralimbal sclerocorneal incision dating back to the previous cataract surgery was ruptured. Intraocular tissue such as iris, ciliary body, and retina, were marked
dly destroyed with pronounced loss of cell nuclei and melanin. The blood vessels were widely dilated, filled with erythrocytes, and showed thrombotic signs. The most striking finding was that some areas showed massive infiltration by granulocytes, while other areas were almost completely devoid of inflamma
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**Comment**

The globe presented in this report showed a Morphallaxia-like histology in which a dense infiltration of granulocytes was sharply demarcated by tissue areas in which inflam
amatory cells were almost completely missing. Such a histology, normally characteristic of demarcation and destruction of necrotic anamnic tissue like intrauterine resorption of a dead fetus, may be explained by the intraocular presence of high concentrations of triamcinolone acetonide. As a steroid, it may have inhibited the immigration of granulocytes into those areas in which the triamcinolone acetonide crystals had not been rinsed out of the eye through the trau
matically opened cataract surgery wound. Morphallaxia-like histology is not commonly found in globes enucleated because of infec
tious 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 intravi
treal triamcinolone acetonide may be paralleled by the clinical observation that patients with infectious endophthalmitis after an intravitreal injection of triamcino
tone 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

Figure 1 Histological slide showing marked granulocytic infiltration sharply demarcated from areas almost without any infiltration by inflammatory cells. Staining by the periodic acid Schiff method.

Figure 2 Histological slide showing marked granulocytic infiltration sharply demarcated from areas almost without any infiltration by inflammatory cells. Staining by the periodic acid Schiff method.
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 rejection. 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 keratocous complications 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 20/50. 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 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.

References


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 naevi 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 optometry 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 x 4.5 x 6.5 cm angiomatous 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 temporals 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 infraorbital 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 haemangiomata 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 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.

Morbidity 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 intra-retinal and macular haemorrhage, vaso-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 “race-mose” 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 stigma 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.

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

- **Aetiology**
  - Adolescence to early adulthood; usually becomes symptomatic before age 30 years
  - Vascular facial naevi in up to 50% of patients, usually ipsilateral to affected eye
  - AV communication of the midbrain may cause cerebral or subarachnoid haemorrhage
  - Signs of midbrain lesion, hemiplegia, or hemiparesis, cerebellar dysfunction, Parinaud’s syndrome
  - Mental changes affecting intelligence and memory
  - Seizures in only 5% of patients
  - Associated AV communications of the lungs and spinal cord reported (rare)
  - Retinal AV communication (retinal AV aneurysm) unilateral, usually non-progressive
  - Pulsatling exophthalmos, proptosis
  - 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
  - Phthisis or partial phthisical type secondary to third nerve involvement in the midbrain

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 a 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 electromyography 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 pre-existing 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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Pupil sparing 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. 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, 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 microscopically corneal oedema with 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 dilatation due to the iris mass, and there was no obvious structural tilt of the anterior chamber.

Figure 1 Humphrey C120 visual fields demonstrating bilateral peripheral field loss.

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Figure 1 Humphrey C120 visual fields demonstrating bilateral peripheral field loss.
distortion and intraocular pressure (IOP) was 55 mm Hg. On gonioscopy the angle was open, although heavily pigmented, except where it was physically obstructed by the mass. Ultrasound biomicroscopy showed no ciliary body involvement. Comprehensive examination of the right eye was unremarkable. IOP of the left eye normalised after starting medical therapy and the hyphaema resolved in 3 months. Glaucoma medications were discontinued without increased IOP.

Eleven months later, vision remained 20/20 but IOP increased to 39 mm Hg in the left eye. Clinically the iris mass appeared unchanged (fig 1A). Gonioscopy showed a significant increase in trabecular meshwork (TM) pigmentation. A pupil sparing excision of the mass through a limbal incision was performed. Postoperatively, pigment deposition was evident on the corneal endothelium overlying the iridectomy and in the scleral wound (fig 1B). Pathological examination revealed a heavily pigmented tissue devoid of cellular detail and acellular areas consistent with tissue necrosis. Bleached sectioning revealed few cells with typical oval shape, abundant cytoplasm and round nuclei, rather, the majority 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 pathology rendered the diagnosis of atypical, neoplastic 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


Pseudohypopyon after intravitreal triamcinolone injection for the treatment of pseudophakic cystoid macular oedema

Intravitreal triamcinolone injection is a safe and effective treatment for cystoid macular oedema (CMO) caused by uveitis,1 diabetic maculopathy,1 central retinal vein occlusion,1 and pseudophakic CMO.2 Potential risks include glaucoma, cataract, retinal detachment, and endophthalmitis.

We present a case of pseudohypopyon and sterile endophthalmitis following intravitreal triamcinolone injection for the treatment of pseudophakic CMO.

Case report

An 88 year old woman underwent phacoemulsification surgery which was complicated by posterior capsule rupture. Anterior vitrectomy with implantation of a silicone intraocular lens into the sulcus was performed. Postoperatively, CMO developed. This failed to respond to treatment with topical dexamethasone, topical ketorolac, and posterior sub-Tenon triamcinolone injection, limiting visual acuity to 6/24 at 7 months following the cataract surgery.

An intravitreal injection of triamcinolone acetonide (4 mg in 0.1 ml) (Kenalog, Bristol-Myers Squibb, Middlesex, UK) was administered through the pars plana with a 30 gauge needle using a sterile technique.

Three days later, the patient reported painless loss of vision which had developed immediately after the injection. The visual
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 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 cefazidine and vancomycin. Vitreous and aqueous taps were performed and the pseudohypopyon was completely aspirated 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). Aqueous and vitreous cultures were negative. Microscopy of the aspirated pseudohypopyon showed triamcinolone particles with no cells present (fig 2).

The pseudohypopyon, vitreous haze, and CMA (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 pseudoendophthalmitis 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” hyopopyon 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 vitrectomised vitreous cavity.

The pseudohypopyon was distinguishable from an infective or inflammatory hyopopyon 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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References

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, ophthalmoplegia, 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 5 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 decompensation was considered, but the patient was reluctant to have surgery and also he was a bad anaesthetist 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 abdomino-testicular folds bilaterally. Surgical debulking 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 decompensation was considered, but the patient was reluctant to have surgery and also he was a bad anaesthetist risk in view of his cardiac and pulmonary involvement.

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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.

Acknowledgement

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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 immunologic similarity with cells in the central and peripheral nervous system. Several clinical signs have been suggested to result from this similarity including vitiigo, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and chronic inflammatory demyelinating polyneuropathy.¹⁻³

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 x 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 enucleation 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. Further 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.¹⁻¹

Various paraneoplastic neuropathies have been described in association with cancer, including subacute sensory neuropathy/paraneoplastic encephalomyelitis,⁴ Guillain-Barré syndrome, and axonal polyneuropathy,⁵ and specifically in melanoma: chronic inflammatory demyelinating polyneuropathy,⁶ ophthalmoplegia, and subacute motor axonal polyneuropathy.⁷

The relation between enucleation and improvement of the neuropathy is not clear; improvement may have been 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.¹⁻²

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

Figure 1
Marked uveitis, left eye, with ciliary injection, corneal oedema, and 3 mm hyphaema.
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 rescoped confirming presence of aspergillus 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 has been used, as part of the medical treatment which may prove useful if aspergillus keratitis becomes more common in the Britain.

Case 2
A metallic corneal foreign body was removed from a 53 year old man; he was treated with chloramphenicol eye drops.

Two days later he developed a corneal ulcer with a hypopyon which was scraped and treated with intensive topical antibiotics. The corneal scab showed a scanty growth of Aspergillus fumigatus. He was commenced on amphotericin eye drops 0.15% hourly and antibiotics were discontinued.

He was referred to MREH 23 days after his injury with no improvement (fig 1A). A second corneal scab was scraped which showed hyphal fragments on the Gram stain. Oral itraconazole 200 mg three times daily was added to treatment.

In view of the deteriorating clinical condition a penetrating keratoplasty was performed and amphotericin (7.5 μg) was given intracameraly. Aspergillus fumigatus was present in the corneal button with a clear edge. Thirty months after surgery his best corrected vision was 6/6.

Case 3
A metallic corneal foreign body was removed in casualty from a 46 year old man; he was treated with chloramphenicol eye drops.

Two days later, he presented with increasing pain, hand movement vision, and a corneal ulcer which was scraped. The Gram stain showed a few inflammatory cells. The patient failed to respond to intensive topical antibiotics.

Aspergillus fumigatus was reported and he was treated with hourly natamycin and clotrimazole eye drops, and oral fluconazole 200 mg twice daily. On day 23 fluconazole was discontinued and itraconazole 200 mg twice daily was commenced.
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.

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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, not that it was superior to culture and corneal biopsy staining techniques in the early stage of fungal keratitis. It is rapid compared to culture and biopsy staining techniques, since we were able to detect fungal hyphae in all rabbit eyes 2 days after fungal inoculation, but at least 2–3 days had to elapse to determine any fungal growth on Sabouraud’s agar. Moreover, O’Day et al.

Comments on confocal microscopy of Aspergillus fumigatus keratitis
We read with great interest the article of Avunduk and coworkers,1 who conducted a study in using confocal microscopy to evaluate Aspergillus fumigatus keratitis in treated and untreated rabbit eyes. They concluded that “confocal microscopy is a rapid and sensitive diagnostic tool for both the early diagnosis and non-invasive follow up of fungal keratitis.” 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” also could 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 χ² 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.

Acknowledgment
We thank Dr Fan and coworkers for their reply and interest in our article.

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Reference

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, not that it was superior to culture and corneal biopsy staining techniques in the early stage of fungal keratitis. It is rapid compared to culture and biopsy staining techniques, since we were able to detect fungal hyphae in all rabbit eyes 2 days after fungal inoculation, but at least 2–3 days had to elapse to determine any fungal growth on Sabouraud’s agar. Moreover, O’Day et al.
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 stage 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 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 the $\chi^2$ test. On day 22 confocal microscopy revealed hyphal fragments in 14 corneas out of 20 (three in the treated and 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 the $\chi^2$ 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 efficiencies 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 $p = 0.279$).

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 more in-depth discussions of the details when appropriate. As the editor stresses, children are not just little adults, and this book has excelled in demonstrating the importance of managing children with ocu-loplastic and orbital diseases appropriately.

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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.Shah@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
The XVth Meeting of the International Neuro-Ophthalmology Society will take place 18-22 July 2004, in Geneva, Switzerland. Further details: Prof. A Safran, University Hospital Geneva, c/o SYMPORG SA, Geneva fax: +41 22 839 8484; email: info@ symprop.ch; website: wwwSYMprop.ch.

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: Kemes 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@kemes.com; website: www.kemes.com/autoim2004).

XIIVth International Congress for Eye Research

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.ucal.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, PR China; tel: +86 29 8337 5371; fax: +86 29 8329 2763; e-mail: fmnuhyun@fmnu.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, Mahat Park-B, Opp Fly Over Bridge, Athwa 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 (0482) 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 MUDr. Pavel 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@lfhk.cuni.cz).
- Congress language: English.