Primary nasolacrimal duct malignant mucosal melanoma

Primary nasolacrimal duct malignancy is rare. Only a few tumours have been reported originating from this location including lymphoma, Kaposi’s sarcoma, adenocarcinoma, angiofibroma, and squamous cell carcinoma.

Mucosal melanoma represents 1–2% of all melanomas, with 25–50% in the head and neck—that is, upper respiratory tract, oral cavity, and pharynx. Other sites include urinary, female genital, and ano-rectal tracts. These tumours are uncommon, present in the fifth to eighth decades, have slight male preponderance and are more common in darker skinned individuals. Cutaneous melanomas present two decades earlier and is more common in white people and is associated with sun exposure.

Case report

A 41 year old Asian male presented to the oculoplastic service with a 3 month history of right sided intermittent bloody tears and epistaxis. He described right simple epiphora for at least 2 years treated with a three snip procedure. Probing the right nasolacrimal system confirmed normal canaliculi and easy entry of the probe into the lacrimal sac. Irrigation demonstrated complete nasolacrimal duct block and reflux of dark bloody tears. Nasal endoscopy (rigid Hopkins nasal endoscope) revealed a greyish mass emerging from the lower end of the nasolacrimal duct into the inferior meatus (fig 1).

Magnetic resonance imaging (MRI) and computed tomography (CT) scans (fig 2) demonstrated dilation of the entire length of the nasolacrimal bony canal with a soft tissue mass occupying the lumen of the nasolacrimal duct. The mass was invading the osteomeatal complex, extending into the anterior ethmoidal sinus, causing obstruction to drainage of both maxillary and frontal sinuses.

A transnasal incisional biopsy of the inferior meatus lesion was performed under local anaesthetic. Histopathological analysis of the biopsy showed sheets of epithelioid cells with prominent nucleoli and vesicular nuclei and were suggestive of melanoma. Immunohistochemical studies were positive for immunological markers HMB45 and S-100 protein, confirming a diagnosis of melanoma.

No regional lymphadenopathy was present and PET (positron emission tomography) scan excluded the presence of metastases.

Wide local excision of malignant mucosal melanoma was performed, via a lateral rhinotomy approach (fig 4). The nasolacrimal duct, part of the lateral wall of the nose, the lacrimal sac, distal upper and lower canaliculi, and inferomedial orbital fat were excised. Tumour extended into the maxilla but not into the lacrimal sac. Peroperative frozen sections from the excision margins, including orbital fat, demonstrated clearance of tumour. This allowed preservation of the eye.

Adjunctive therapy was given to limit local recurrence and distant spread. The patient received 20 sessions of radiotherapy (30 Gy) to the right maxillary antrum, and also immunological therapy (vaccination with autologous dendritic cells pulsed with allogenic tumour lysate, and whole body hyperthermia accompanied by low dose interferon).

Three years after presentation there was no local recurrence of tumour. Unfortunately, the patient developed bone pain and CT scan revealed metastatic spread to the right acetabulum and T8, T9, and T11 vertebrae with localised spinal cord compression. He underwent radiotherapy to the right acetabulum and spine. The patient died approximately 6 months later.

Comment

Nasolacrimal duct primary mucosal melanoma is previously unreported. The closest relations are lacrimal sac melanoma (5% of lacrimal sac tumours) and sinonasal mucosal melanoma (5% of all sinonasal malignancy). Treatment of primary sinonasal melanoma is radical wide local surgical excision. Local recurrence can occur and the very vascular nature of mucosal tissue makes regional and distant metastases common, often accompanying late presentation. Post-surgical radiotherapy may prevent local recurrence, but is unlikely to prevent distant metastases. Other adjunctive treatments are not clinically proved to be beneficial. Chemotherapy has no positive effect, and newer immunological treatments are still under investigation.
Sinonasal mucosal melanoma has a high mortality rate, with 5 year survival between 10–50%. Lacrimal sac melanoma has a similar prognosis. This case demonstrates the importance of thorough clinical examination (including nasal endoscopy) and imaging in patients presenting with epiphora, bloody tears, and/or epistaxis. Delay in detection and treatment may be fatal.

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References

Glycosylation type Ic disorder: idiopathic intracranial hypertension and retinal degeneration

We report a young woman with type Ic congenital disorder of glycosylation (CDG) with new clinical features of idiopathic intracranial hypertension, retinal degeneration, and novel mutations of ALG6. Patients with known or suspected CDG should receive a full ophthalmic examination including dilated fundus examination and electroretinography.

CDG is a rare group of autosomal recessive metabolic disorders. The two major subgroups are type I, caused by dysfunction of glycosylated protein assembly, and type II, caused by abnormal processing of glycosylated protein end products after assembly. Patients with type Ic (OMIM #601347) have mental retardation, axial hypotonia, very low factor XI, and seizures; the gene defect is in z1.3-glucosyltransferase (human homologue of ALG6). Isoelectric focusing of serum transferrin is an enzyme that catalyses the transfer of the first glucose residue to the lipid linked oligosaccharide precursor for N-linked glycosylation. The reported ophthalmic manifestations of type I CDG are summarised in table I. We report a case of type Ic congenital disorder of glycosylation with new clinical features of idiopathic intracranial hypertension, retinal degeneration and novel mutations of ALG6.

Case report

Our patient, with non-consanguineous parents, was noted at birth to have incomplete digits on her hands and feet. She had episodes of apnoea early in life and the onset of seizures at age 20 months. Delayed physical and developmental milestones were evident early. Levels of follicle stimulating hormone and luteinising hormone were low and a diagnosis of polycystic ovarian disease was made. She underwent esotropia surgery at age 4 years and at 19 years developed thrombosis of the superficial femoral vein. Coagulation factor studies revealed very low factor XI levels. Isoelectric focusing of serum transferrin was suggestive of a congenital disorder of glycosylation. Sequencing of the ALG6 gene showed a novel three base substitution, in the gene encoding factor XI levels. Isoelectric focusing of serum transferrin is an enzyme that catalyses the transfer of the first glucose residue to the lipid linked oligosaccharide precursor for N-linked glycosylation. The reported ophthalmic manifestations of type I CDG are summarised in table I. We report a case of type Ic congenital disorder of glycosylation with new clinical features of idiopathic intracranial hypertension, retinal degeneration and novel mutations of ALG6.

Table 1

<table>
<thead>
<tr>
<th>CDG ic</th>
<th>CDG ib</th>
<th>CDG ic</th>
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<tbody>
<tr>
<td>Strabismus +</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Retinopathy +</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Optic atrophy +</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Comment

Isoelectric focusing of serum transferrin is the most common screening technique for types I and II CDG. Many congenital disorders of glycosylation have been identified based on mutational and enzyme analyses. Type I congenital disorders of glycosylation are caused by reduced functions of the genes for the assembly and processing pathways of N-glycosylation; a decrease in asparaginyl substitution in the ALG6 gene encoding factor XI levels. Isoelectric focusing of serum transferrin is the most common mutation. There is no known biochemical link between CDG and idiopathic intracranial hypertension; the association in our patient may be coincidental. Grumwald and colleagues found strabismus to be present in all eight patients with CDG type Ic; neither idiopathic intracranial hypertension nor retinal abnormalities were reported.

The developmental delay evident in our patient was severe. She possessed simple communication skills limiting her ability to complain of visual changes or symptoms of intracranial hypertension. No specific clinical presentation has been identified for the CDG group of diseases. Failure to thrive, unexplained seizures, hypotonia, and developmental delays are all frequently present.

In conclusion, we report an adult patient with CDG type Ic, confirmed by identification of mutations in the ALG6 gene, and describe new systemic and ocular features including idiopathic intracranial hypertension, optic
Woodhouse Sakati syndrome associated with bilateral keratoconus

Keratoconus is a non-inflammatory degenerative corneal disease characterised by a localized region of stromal thinning spatially associated with a cone-shaped deformation of the surface. It is most commonly an isolated sporadic condition. Recent reports demonstrate genetic mapping to chromosomes 16q, 21q, and 18p, as well as association of HLA-A26, B40, and DR 9. Keratoconus has been reported in clinical and molecular characterization of the first adult congenital disorder of glycosylation (CDG) type Ic patient. Am J Med Genet (accepted)

We describe the first two cases of keratoconus in our cases. An anterior keratometry of 20/40 in the right eye and 20/160 in the left eye, which improved to 20/20 with spectacles. Slit lamp biomicroscopy showed similar findings to her sister (fig 1B). Keratometry was 36.6 D/54.1 D @ 170 in the right eye and 49.2 D/56.6 D @ 46 in the left eye. She developed corneal hydrops in the left eye and contact lens fitting failed. Failure of keratoconus cases and is suggested to be associated with autosomal dominant inheritance with incomplete penetrance.

The authors have no interests or disclosures to report.

References

Woodhouse Sakati syndrome associated with bilateral keratoconus

Keratoconus is a non-inflammatory degenerative corneal disease characterised by a localised region of stromal thinning spatially associated with a cone-shaped deformation of the surface. It is most commonly an isolated sporadic condition. Recent reports demonstrate genetic mapping to chromosomes 16q, 21q, and 18p, as well as association of HLA-A26, B40, and DR 9. Keratoconus has been reported in clinical and molecular characterization of the first adult congenital disorder of glycosylation (CDG) type Ic patient. Am J Med Genet (accepted)

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References
Retinal ischaemia in type 1 neurofibromatosis

Systemic occlusive arteriopathy associated with type 1 neurofibromatosis (NF-1) has been well described in the aortic and cerebral vasculature; however, it is poorly documented in the retinal vasculature with, to our knowledge, only three reported cases of retinal non-neoplastic ischaemia associated with type 1 neurofibromatosis. Our case report describes a young woman with NF-1 who presented with acute macular ischaemia combined with diffuse retinal arterial occlusive disease.

Case report

A 26 year old woman with NF-1 presented with a sudden painless loss of vision in her left eye. Visual acuity was counting fingers left eye and 20/20 right eye. NF-1 had previously been diagnosed on the basis of multiple café au lait spots, plexiform neurofibromas, and a paternal history of NF-1. Left fundus examination revealed confluent cottonwool spots in the perifoveal area, foveal dilatations and narrowings of retinal venules, and progressive enlargement of retinal arterioles towards the periphery. The right fundus showed only peripapillary myelinated nerve fibres (fig 1).

Fluorescein angiography (FA) of the left eye showed no delayed perfusion in the choriocapillaris or central retinal artery, but a delayed retinal arteriogenous filling time. It revealed occlusion of macular arterioles, retinal arteriogenous communications in the mid-periphery, and a relatively well perfused retinal periphery (fig 2).

Cerebral and cervical magnetic resonance imaging and colour Doppler ultrasonography showed no vascular flow abnormalities. Internal medical examination and laboratory results excluded other diseases associated with retinal microvasculopathies.

One month after the initial examination, all the cottonwool spots disappeared, and sheathing appeared in a few veins. FA showed worsening of the retinal arteriovascular occlusions in the mid-periphery (fig 2). A panretinal photoacoagulation was subsequently performed. At 2 year follow up, left visual acuity remained unchanged, and the patient did not exhibit any preretinal fibrovascular proliferation.

Comment

To our knowledge, only three cases of retinal vascular occlusion in patients with NF-1 have been previously reported. All cases were diagnosed at a later sequelae stage. Modell et al. and Kadok et al., respectively, reported the cases of a child who presented with an unilateral amblyopia, and a young woman with a history of unilateral poor vision. They both presented with diffuse sheathing of retinal vessels, retinal arteriovenous communications, and avascular peripheral retina with fibroglial proliferation. Tholen et al. described a young man whose routine eye examination showed narrowing of a superotemporal retinal arteriole with irregular diameter of the corresponding vein, fibroglial proliferation, and arteriovenous communications. These authors suggested the possibility of either a primary occlusion of a retinal arterial or venous branch or alterations of vessel development.

In contrast with other reported cases, our patient presented with acute unilateral occlusion of macular arterioles, combined with diffuse retinal arterial occlusive disease, in adulthood. Panretinal photoacoagulation may have prevented fibroglial proliferation which was described in previous reported cases. Recent reports suggest that pathogenesis of NF-1 vasculopathy may result from dysfunction of neurofibromin, the NF-1 gene product, in vessel endothelial and smooth muscle cells. Our case shows that NF-1 related occlusive retinal arteriopathy may suddenly appear during adulthood and should be considered in patients with NF-1 or in young adults with retinal vascular occlusive disease and unknown NF-1.

References


Are biometric parameters a risk factor for idiopathic macular hole formation? Results of a matched case-control series

Recognised risk factors for the formation of idiopathic full thickness macular holes (IFTMH) include age, female sex, and high myopia. However, we noticed the presence of IFTMH within our population, tended to have shorter than normal axial lengths. An age and sex matched case-control study was...
therefore performed to test this hypothesis and determine whether biometric factors may be associated with formation of IFTMH.

**Methods**

Consecutive patients undergoing surgery for IFTMH had age, sex, axial length in millimetres (mm), and corneal keratometry (K) measurements in dioptres (D) recorded. For each case three age and sex matched controls were randomly identified from a cataract surgery database (Medisoft). Biometric measurements were made in all cases and controls using the IOL-Master (Zeiss, Jena). Mean corneal curvature was calculated by averaging the two K readings. Descriptive statistics and conditional logistic regression method for analysis of matched pair data were used to infer estimates.

**Results**

Thirty five consecutive cases and 105 controls were identified with a mean age of 67.3 years (35–77 years) and a female to male ratio of 24:11. The mean (SD) axial length in the cases was 22.94 (0.96) mm whereas in controls it was 23.48 (1.44) mm. The axial lengths of the cases also fell within a narrower range than those of the controls (fig 1). Mean K readings in cases was 44.04 D (range 41.87–46) and 43.44 D in controls. (range 40.56–47.92).

Evidence suggests that the longer the axial length the less the odds of being a case; odds ratio (OR) 0.67 (p = 0.036, CI 0.47 to 0.77) and the higher the dioptre power of the curvature the higher the odds of being a case as opposed to a control; OR 1.50 (p = 0.02, CI 1.07 to 2.01).

**Comment**

As in previous studies our population sample demonstrates an increased risk of IFTMH in females with most cases clustering in the 60–70 year age group. The mean axial length in controls was also found to be similar to reports in the published literature.

Mean spherical equivalence (MSE) was measured by the Eye Disease Case Control Study Group and although their findings were statistically insignificant, their regression analysis found an increased likelihood of hypermetropia in the IFTMH cases. Our cases clustered in a relatively narrow range of axial lengths (21 mm–25.31 mm in the cases compared to 20.64 mm–29.48 mm in the controls) with the maximum axial length in the cases being 25.31 mm (fig 1). In Japanese literature, high myopia is a prominent, recognised risk factor and in one study the overall mean MASE was ~0.66 D. From our study it appears myopic macular holes are encountered much less frequently in a predominantly white population.

We believe the significant corneal dioptic differences found may be a result of the natural process of emmetropisation of a shorter eye, or alternatively be an independent risk.

IFTMH are thought to arise from retinal surface traction which in turn arises from an abnormal and incomplete posterior vitreous detachment. Our results suggest that eyes with shorter than average axial lengths and therefore lower volume vitreous cavity are either at increased risk of developing such incomplete and abnormal vitreous detachments or, in the presence of such an incomplete vitreous detachment, of developing a macular hole. We are not aware that shorter axial length has previously been shown to be significantly associated with IFTMH.

**References**


**Choroiditis and exudative macular detachments in a post transplant leukaemia patient: an unusual presentation of Pneumocystis jiroveci infection**

Pneumocystis jiroveci is a commensal found in the respiratory tract of healthy individuals. It can cause infections of almost any organ in immunocompromised hosts. P. jiroveci choroiditis, featuring multifocal choroidal lesions, has been reported in immunocompromised patients despite prophylactic use of inhaled pentamidine. We report a post-transplant leukaemia patient whose posterior segment findings demonstrate an atypical picture of recurrent P. jiroveci choroiditis.

**Case report**

A 20 year old woman presented with a 1 week history of bilateral blurred vision, dyspnoca, and dry cough. Visual acuity was reduced to 6/66 bilaterally with posterior subcapsular cataracts. Funduscopy disclosed multifocal, creamy-yellow choroidal lesions at both posterior poles with exudative retinal detachments at the maculae (fig 1). Optic discs and retinal vessels were normal. Fluorescein angiography showed early patchy hypofluorescence (corresponding to the choroidal lesions) and late hyperfluorescence with pooling beneath the detachments.

Three years earlier she had undergone a successful allogeneic bone marrow transplant for chronic myeloid leukaemia. Her maintenance therapy included inhaled pentamidine as prophylaxis against P. jiroveci infection. However, she admitted to not taking her inhaled pentamidine. Molecular genetic and radiological investigations excluded leukaemic recurrence. Chest X ray showed left lung shadowing and bronchoalveolar lavage isolated P. jiroveci. P. jiroveci pneumonia with P. jiroveci choroiditis was diagnosed and high dose oral co-trimoxazole 7.2 g/day (120 mg/kg/day) and prednisolone 60 mg/day commenced. Within 2 weeks her respiratory and ocular symptoms improved. Visual acuities returned to 6/9 and the fundal appearances resolved. She was discharged on daily oral co-trimoxazole 960 mg, prednisolone 20 mg, and inhaled pentamidine.

![Figure 1](https://example.com/fig1.png)
Three weeks later she was readmitted with increasing dyspnoea and blurred vision. Chest x-ray and computed tomography findings were compatible with diffuse interstitial fibrosis in both lungs. Fundoscopy revealed peripapillary choroidal lesions with disc swelling bilaterally (fig 2). This time the choroidal lesions were papillary only rather than throughout the posterior pole, with exudative detachments inferiorly. Recurrent P jiroveci pneumonia and choroiditis was diagnosed and oral atovaquone and high dose prednisolone were commenced. Within 3 weeks her fundal appearance resolved leaving only some pigmentary changes. Her discharge medication included daily oral prednisolone 40 mg, co-trimoxazole 960 mg, and inhaled pentamidine. There have been no further intraocular recurrences.

Comment

Pneumocystis jiroveci is a commensal, found in the respiratory tract of healthy individuals. It can cause infections of almost any organ in immunocompromised hosts. P jiroveci choroiditis has been reported in immunocompromised patients despite prophylactic use of inhaled pentamidine. The diagnosis is based on the clinical findings of multifocal yellowish circular choroidal lesions at the posterior pole. P jiroveci has been found in these lesions on histological sections and the lesions resolve on systemic anti-pneumocystis treatment. However, most cases of P jiroveci choroiditis are diagnosed histologically post mortem. Thus, the acute clinical findings may be more varied than previously described. In our patient, massive exudative retinal detachments were associated with the previously described choroidal lesions. The clinical picture varied on the second presentation, but there was complete and rapid resolution of the signs with anti-pneumocystis therapy. To the best of our knowledge, this is the first report of P jiroveci choroiditis causing exudative retinal detachments. P jiroveci should be considered in the differential diagnosis of susceptible patients, even if the ophthalmological findings are “atypical.”

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References


Prothrombotic and atherosclerotic risk factors lack significance in NAION patients

We recently reported that a group of patients with non-arteritic anterior ischaemic optic neuropathy (NAION) had an increased prevalence of potentially pathological mitochondrial DNA (mtDNA) mutations, implying a link between mitochondrial disease and this optic neuropathy. We decided to investigate the association of other risk factors for NAION in these same patients.

Case reports

NAION patients were genotyped for the presence of prothrombotic polymorphisms that have been reported in association with NAION, including factor II G20210A prothrombin variant, factor V Leiden G1691A variant, MTHFR C677T and A1298C variants, platelet glycoprotein receptor IIIa (P1BB) allele, and apolipoprotein E (4) allele, as described previously. These reports included large control groups that were ethnically matched to our NAION patients and that had been queried regarding the presence of atherosclerotic risk factors. Controls older than 50 years were selected for comparison with NAION patients.

Table 1 shows that the prevalence rates for prothrombotic variants among NAION patients did not differ from controls. Reported prevalence of diabetes, hypertension, and hyperlipidaemia was relatively high in NAION patients but was also not significantly different from controls.

Comment

The lack of a significant association between NAION patients and controls in relation to thrombophilic genetics markers has been reported before, and the role of these factors remains uncertain. More surprising is the lack of a statistical association with atherosclerotic risk factors. For example, in our group of NAION patients, 68% were diabetic, but this figure did not differ significantly from the prevalence of more than 50% in well matched controls. This observation reflects the high, and rising, frequency of diabetes and other atherosclerotic risk factors in the developing world.

A few qualifications are appropriate. NAION patients were a relatively small group of Middle Eastern Arabs, and it is possible that a larger group would have yielded statistically significant results or that the observations reported here are specific to this genetically homogeneous population. Atherosclerotic risk factors were assessed by individual report from patients and controls, and the actual prevalence of these disorders may be different from that recognised. Finally, other risk factors, such as homocysteine levels, nocturnal hypotension, or environmental factors were not consistently investigated.

Nevertheless, the fact that the occurrence of NAION cannot be easily explained by the presence of prothrombotic or atherosclerotic risk factors shifts focus to the possibility that mitochondrial abnormalities may be important in the development of NAION. Based on these observations, testing for mitochondrial abnormalities may be warranted in NAION patients, especially the ones without a genetic predisposition.
medical or family history of a thrombotic or vascular event.

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References

Table 1 Comparison of risk factors in NAION patients and controls

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>NAION patients</th>
<th>Controls</th>
<th>Odds ratio</th>
<th>95% Cl</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo E4</td>
<td>0/19</td>
<td>0/593</td>
<td>3.12</td>
<td>0.60 to 16.13</td>
<td>1</td>
</tr>
<tr>
<td>Factor II G20210A</td>
<td>0/19</td>
<td>0/593</td>
<td>3.12</td>
<td>0.60 to 16.13</td>
<td>1</td>
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<tr>
<td>Factor V G1691A</td>
<td>0/19</td>
<td>0/200</td>
<td>10.5</td>
<td>0.20 to 545.6</td>
<td>1</td>
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<tr>
<td>MTHFR C677T</td>
<td>0/19</td>
<td>0/500</td>
<td>0</td>
<td>0.00 to 13.10</td>
<td>1</td>
</tr>
<tr>
<td>MTHFR A1298C</td>
<td>0/19</td>
<td>0/161</td>
<td>0.77</td>
<td>0.21 to 2.52</td>
<td>0.79</td>
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<tr>
<td>PIA2 allele</td>
<td>0/19</td>
<td>7/522</td>
<td>0.55</td>
<td>0.19 to 1.52</td>
<td>0.30</td>
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<tr>
<td>Age, mean (SD)</td>
<td>–</td>
<td>58 (8.5)</td>
<td>57 (4.2)</td>
<td>–</td>
<td>0.12–1.89</td>
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<tr>
<td>Sex (M:F)</td>
<td>–</td>
<td>14.5</td>
<td>351 (160)</td>
<td>1.28</td>
<td>0.42 to 4.13</td>
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<tr>
<td>Diabetes</td>
<td>–</td>
<td>13/256</td>
<td>2/16</td>
<td>1.61</td>
<td>0.75 to 4.67</td>
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<tr>
<td>Hypertension</td>
<td>–</td>
<td>10/209</td>
<td>2/15</td>
<td>1.61</td>
<td>0.59 to 4.38</td>
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<tr>
<td>Hyperlipidaemia</td>
<td>–</td>
<td>2/59</td>
<td>0/1</td>
<td>0.51</td>
<td>0.11 to 3.17</td>
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<tr>
<td>CAD</td>
<td>–</td>
<td>1/19</td>
<td>7/511</td>
<td>0.55</td>
<td>0.03 to 4.03</td>
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<tr>
<td>NS mtDNA changes</td>
<td>–</td>
<td>14/19</td>
<td>11/100</td>
<td>0.55</td>
<td>6.03 to 91.07</td>
</tr>
</tbody>
</table>

NAION, non-arteritic ischaemic optic neuropathy; CAD, coronary artery disease; NS mtDNA changes, non-synonymous (changing an amino acid in the resultant protein) mitochondrial DNA nucleotide change; Homo, homozygous; Hetero, heterozygous. Diabetes, hypertension, hyperlipidaemia, and CAD were assessed by patient report both from NAION patients and from controls. Controls previously reported for mtDNA changes and for atherosclerotic and prothrombotic risk factors (see text). Odds ratio and p values compare prevalence of different risk factors in NAION patients to controls.

Inflammatory cytokine of basal and reflex tears analysed by multicytokine assay

Tear cytokine has a major role in various pathophysiological conditions of the ocular surface. So far, studies on tear cytokines have shown significant progress in providing an understanding of ocular surface diseases. 18 The information that could be acquired from each subject, however, until recently has been severely hampered by limited sample volume and assay sensitivity. More importantly, it has become apparent that the relative balance between various cytokines and combinations of cytokines could be more important than absolute concentrations. Previous studies showed that the composition of basal and reflex tears was different, which made it more difficult to understand the ocular surface disorder correctly or to treat the patients suitably. 18, 19 Cytometric bead array (CBA) is a microplate based flow cytometric assay that allows us to quantify multiple molecules from a very small sample. 20 Using this method, we evaluated the inflammatory cytokines of basal and reflex tears from a single sample of individual eyes.

Methods

Twenty three normal volunteers (11 males and 12 females, 22–44 years of age, average 28 years) were recruited for this study. None of the subjects had signs of ocular diseases. The study was performed with the approval of the institutional review board. The basal tear samples of 10–15 µl were obtained from the inferior meniscus. Successively, reflex tear samples were collected by inserting application sticks into a participant’s nose. The amounts of six inflammatory molecules interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-12p70, and tumour necrosis factor α (TNF-α), were measured by CBA (BD Biosciences, San Diego, CA, USA), according to the manufacturer’s instructions. Briefly, for the tear sample and cytokine standard mixture, 10 µl of sample or standard were added to 40 µl sterile purified water, a mixture of 50 µl each of capture Ab-bead reagent and detector Ab-phycoerythrin (PE) reagent. The mixture was subsequently incubated for 3 hours at room temperature, and washed to remove unbound detector reagent before data acquisition using flow cytometry. A two colour flow cytometric analysis was performed using a FACScan flow cytometer (Beckton Dickinson Immunoassay Systems). Data were acquired and analysed using BD cytometric bead array software.

Results

The concentrations of IL-1β, IL-6, IL-10, IL-12p70, and TNF-α were not significantly different between basal and reflex tears. In contrast, the concentration of IL-8 was significantly decreased in reflex tears compared with basal tears in each eye (paired t test, p<0.01, fig 1). In order to illuminate the inter-relation of each cytokine, the ratio of two different cytokines is shown in table 1.

Comment

Previously published studies have demonstrated that CBA correlates well with enzyme linked immunosorbent assay (ELISA), but the absolute concentrations obtained from each assay were differed for kits of different manufacturers. 21 Indeed, the concentrations of tear cytokines in the present results were almost equal to the previous report using the same kit. 21 Nakamura et al performed ELISA for multiple cytokines measuring pooled tears. 21 The pooled tears enable measurement of multiple cytokines; however the results...
can be strongly influenced by samples with high concentrations. Because the absolute concentrations of tear cytokines varied widely, this can have a strong bias. In this study, to our knowledge, we measured the concentrations of tear cytokines in normal subjects that may prove important for studies of ocular inflammation. Of note, only the concentration of IL-8 in reflex tears was decreased more significantly in reflex tears than in basal tears. Maitchouk et al. showed that there is no distinctive role of major and accessory glands in secreting basal or reflex tears, thus these tears might be produced primarily by the same tissue and differences might be only the result of the secretory rate of reflex tears. It was reported that a neuropeptide released from corneal sensory nerves stimulated conjunctival epithelium to secrete IL-8. Because sensory nerves are present in the cornea so abundantly, IL-8 can be produced constantly on the ocular surface. IL-8 is a potent pro-inflammatory cytokine, and has a pivotal role in the host defense system. But excessive IL-8 might be so harmful that constant washout might be helpful for homeostasis of the ocular surface. Indeed, a large amount of IL-8 was found in the tears of dry eyes. Thus, basal tears might be composed of products of the ocular surface including IL-8 and small amounts of reflex tears that are induced by mild stimulation such as blinks.

In summary, the present study showed that pro-inflammatory and anti-inflammatory cytokines/chemokines are present in the ocular surface even in the absence of inflammation and this was detectable from samples of single eyes. Stimulating tears with the exception of IL-8, has minimal effect on cytokine concentration. We believe the CBA technique can make a valuable contribution in understanding the specific immunopathological mechanisms underlying cytokine interaction with the ocular surface.

![Graph showing cytokine concentrations](image)

**Figure 1**  Change of concentrations of cytokines in basal and reflex tears. The concentration of IL-1β, IL-6, IL-10, IL-12p70 and TNF-α are not significantly different between basal and reflex tears. In contrast, IL-8 is significantly less in reflex tears compared with basal tears in each eye (paired t-test, *p*<0.01).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Ratios of cytokine concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>IL-1β IL-6 IL-12p70 IL-10 IL-8</td>
</tr>
<tr>
<td>A</td>
<td>Basal tear</td>
</tr>
<tr>
<td>IL-1β</td>
<td>3.022 (0.246) 54.162 (6.549) 3.222 (0.316) 12.556 (0.889) 0.716 (0.084)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.386 (0.037) 23.568 (5.952) 1.238 (0.184) 4.705 (0.553) 0.246 (0.03)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.022 (0.002) 0.07 (0.008) 0.074 (0.011) 0.275 (0.028) 0.017 (0.003)</td>
</tr>
<tr>
<td>IL-12p70</td>
<td>0.349 (0.026) 1.989 (0.071) 11.532 (0.101) 3.981 (0.166) 0.261 (0.042)</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.087 (0.005) 0.253 (0.02) 0.261 (0.012) 0.953 (0.011) 0.667 (0.011)</td>
</tr>
<tr>
<td>IL-8</td>
<td>2.14 (0.34) 5.576 (0.694) 14.941 (3.971) 7.447 (1.546) 28.257 (5.078)</td>
</tr>
<tr>
<td></td>
<td>Reflex tear</td>
</tr>
<tr>
<td>IL-1β</td>
<td>3.71 (0.252) 53.061 (5.46) 2.918 (0.331) 12.012 (1.123) 0.972 (0.094)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.304 (0.027) 15.807 (1.976) 0.808 (0.061) 3.381 (0.274) 0.276 (0.029)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.021 (0.001) 0.078 (0.007) 0.062 (0.007) 0.254 (0.026) 0.02 (0.002)</td>
</tr>
<tr>
<td>IL-12p70</td>
<td>0.390 (0.023) 21.357 (3.427) 11.532 (0.101) 4.231 (0.147) 0.382 (0.046)</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.093 (0.005) 0.324 (0.018) 0.241 (0.007) 0.953 (0.011) 0.667 (0.011)</td>
</tr>
<tr>
<td>IL-8</td>
<td>1.043 (0.231) 4.779 (0.665) 73.465 (13.897) 4.02 (0.727) 17.235 (3.231)</td>
</tr>
</tbody>
</table>

Ratio of cytokine concentration was calculated as A/B. Each cell shows the mean (SEM).
Outcome of implementing the national services framework guidelines for diabetic retinopathy screening: results of an audit in a primary care trust

Systematic screening for diabetic retinopathy is the key to achieving the targets set out in the recently published national service framework (NSF) guidelines. One of the two priorities and planning framework (PPF) targets is that by March 2006 a minimum of 80% of people with diabetes are to be offered screening, rising to 100% by December 2007. Digital photography is the modality for screening. The British Diabetic Association has established standards for any diabetic retinopathy screening programme of at least 80% sensitivity and 95% specificity.

Screening programme

Our screening programme was set up to evaluate the existing nationally recommended diabetic retinopathy screening service.

In all, 2165 patients were invited over a period of 12 months; 909 participated. At the screening mydriatic drops (1% tropicamide and 2.5% phenylephrine) were instilled. The patients were photographed with a Topcon fundus camera and each photograph was screened and graded by consultant ophthalmologists (table 1). Of the total 909; there were 198 patients with retinopathy (grades R1, M, R2, and R3), 644 patients without retinopathy (grade 0), 63 patients with OL (other lesions), and one patient with ungradable disease.

Table 1

<table>
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<tr>
<th>Diabetic patients type</th>
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<tr>
<td>Diabetic patients type 1</td>
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<td>41</td>
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<td>Diabetic patients type 2</td>
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<td>609</td>
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<td>Diabetic patients type not stated</td>
<td>630</td>
<td>259</td>
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Table 2

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<td></td>
<td>F</td>
<td>261</td>
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<tr>
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<td>R1</td>
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<td>21</td>
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<tr>
<td></td>
<td>T</td>
<td>44</td>
</tr>
<tr>
<td>R2</td>
<td>M</td>
<td>17</td>
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<tr>
<td></td>
<td>F</td>
<td>9</td>
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<tr>
<td></td>
<td>T</td>
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<tr>
<td>R3</td>
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<td>F</td>
<td>0</td>
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<tr>
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<td>T</td>
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</table>

Table 3

<table>
<thead>
<tr>
<th>Total patients screened</th>
<th>Sample size</th>
<th>Ungradable</th>
<th>True positives</th>
<th>False negatives</th>
<th>True negatives</th>
<th>False positive</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Retinopathy present</th>
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<tbody>
<tr>
<td>909</td>
<td>909</td>
<td>1</td>
<td>198</td>
<td>644</td>
<td>8</td>
<td>98%</td>
<td>97%</td>
<td>21.78%</td>
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</table>

References

Late improvement in upward gaze in a patient with hydrocephalus related Parinaud dorsal midbrain syndrome

Acute hydrocephalus is a common cause of the Parinaud dorsal midbrain syndrome.1,2 Most patients with this condition improve either immediately following treatment of the hydrocephalus or within a few months,3 and it is generally assumed that those who do not do so have no potential for subsequent improvement. I recently evaluated a patient whose upward gaze spontaneously improved 4½ years after treatment of trauma related hydrocephalus.

Case report
A 23 year old Asian man was in his usual excellent general and ocular health until October 2000, when he was struck by a car while walking across the street. He was taken to a local hospital where he was found to have extensive injuries, including bilateral subdural and epidural haematomas. He also had evidence of increased intracranial pressure and required an emergency cranial decompression. Postoperatively, he was evaluated by a neuro-ophthalmologist who noted that the patient’s only ocular disturbance was a mild left trochlear nerve paresis. The paresis resolved within about 3 weeks.

About 6 months after the injury, the patient developed severe headaches and double vision. He was evaluated by the same neuro-ophthalmologist who had evaluated him previously. He noted that the patient now had a severe dorsal midbrain syndrome, characterised by lack of elevation of either eye above the midline associated with an exotropia of 25–30 prism dioptres at distance and near, and a left hypotropia of 5 prism dioptres. An examination that included neuro-imaging and measurement of intracranial pressure revealed hydrocephalus, and the patient underwent placement of a ventriculoperitoneal shunt with normalisation of intracranial pressure, resolution of neuroimaging evidence of hydrocephalus, and resolution of headaches but without any change in ocular motility or alignment. He was eventually referred to the neuro-ophthalmology unit of the Wilmer Eye Institute at the Johns Hopkins Hospital for evaluation and management.

The patient was examined by me for the first time in September 2001, 11 months after the initial injury and about 5 months after he had first been noted to have a dorsal midbrain syndrome. At that time, the examination revealed visual acuity of 20/20 in both eyes at distance and near. Automated perimetry revealed bilateral, incomplete, congruous, superior homonymous quadratic field defects. Pupils were normally reactive to both light and near stimulation. In primary position, the patient had 25 prism dioptres exotropia that increased to 35 prism dioptres on attempted right gaze and decreased to 15 prism dioptres on attempted left gaze. There was also a 5 prism dioptre left hypertropia. Examinations using Maddox sticks could elevate just barely to the midline. There was no difference in degree of elevation with pursuit versus saccades, and elevation did not improve with the oculocephalic manoeuvre. Lateral gaze and downgaze were normal bilaterally for both pursuit and saccadic eye movements. I recommended consideration of strabismus surgery and asked the patient to return in 4 months for reassessment. He did so in January 2002, at which time his ocular motility and alignment were stable. Specifically, neither eye was able to elevate above the midline, either voluntarily or by the oculocephalic manoeuvre.

In May 2002, I performed a left lateral rectus muscle recession of 7.5 mm and a left medial rectus muscle recession of 6.5 mm with superior transposition of both the lateral and medial rectus muscles one muscle width. Postoperatively, the patient had excellent horizontal alignment, although he still had a small left hypertropia of about 5 prism dioptres and was still unable to elevate either eye above the midline.

I subsequently followed the patient at regular intervals. When I examined him in April 2004, he had no change in his ocular motility or alignment, and I recommended that he consider obtaining a small vertical prism to try to eliminate his residual vertical diplopia. I also recommended that he return in 1 year for reassessment. He did so in August 2005.

When I examined the patient in August 2005, he indicated that he thought his vision had improved. He stated that although he was aware of some double vision, it was somewhat less than it had been previously. He also thought his eyes were “moving better.”

On examination, the patient’s visual acuity with correction was 20/15 in each eye at distance and J1 in each eye at near. Colour vision testing using Hardy-Rand-Rittler pseudosochromatic plates was 10/10 bilaterally. Visual fields were performed by static technique and showed stable bilateral, incomplete, congruous, superior homonymous quadratic defects, consistent with damage to both inferior occipital lobes. Pupils were isocoric and normally reactive to light and near stimulation. The patient had full abduction, adduction, and infraduction of both eyes. In addition, he now was able to elevate both eyes about 35° above the midline. He had normal velocity saccades in all directions, but he developed convergence-retraction nystagmus when looking at an optokinetic drum whose targets were being rotated downward. When the targets were moving upward, to the right, or to the left, the response was normal. In test position, the patient had a 4 prism dioptre intermittent left hypertropia at distance and near, associated with 4° of intorsion of the left eye using double Maddox rods. He was most comfortable with a 4 prism dioptre prism placed base up over the left spectacle lens, and a Fresnel prism of this strength and orientation was placed on the left lens of his glasses. He had no ptosis or lid retraction, and the results of slit lamp biomicroscopy,planation tonometry, and ophthalmoscopy were normal.

Comment
The dorsal midbrain syndrome of Parinaud usually results from damage to premotor pathways for binocular upward gaze in the dorsal mesencephalon.4 Depending on the extent of injury, the patients may have pursuit saccadic dissociation, with better upward gaze during pursuit than when attempting upward saccades, and some patients have improved upward gaze with the oculocephalic manoeuvre, indicating sparing of infranuclear pathways. The dorsal midbrain syndrome may be caused by extrinsic or intrinsic lesions, with hydrocephalus being a common aetiology in some series.1,5 Depending on the nature and extent of damage as well as the length of time the condition has been present before the underlying disorder is treated, some patients improve, often substantially, whereas others do not. In general, patients whose underlying condition is treated successfully but who do not show improvement within weeks to months are thought to have no potential to improve; however, our patient’s spontaneous improvement about 4½ years after onset and treatment of the underlying condition indicates that some patients retain the potential to improve even after several years have passed. This information may be of value in counselling patients with the dorsal midbrain syndrome who ask if there is any chance of improvement when none has occurred after months to a few years.

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References

Purification of triamcinolone acetonide suspension for intravitreal injection

In the article by García-Arumí and associates1 the authors reported the results of several techniques used for purification of triamcinolone acetonide suspension for intraocular injection (two filter techniques and two non-filter techniques). I very much appreciate that they mentioned in their paper. The source of the evaluated techniques was not clearly specified by the authors. Are they previously published techniques? Are they techniques developed entirely by García-Arumí et al? As far as I know, the centrifugation technique described by García-Arumí et al was first reported by Hernaez-Ortega in 20032 and it was first published by Hernaez-Ortega and myself in the 2004 July/August issue of Ophthalmic Surgery, Lasers & Imaging.3 In fact, the term “purification” was first applied to removal of most of the vehicle from a commercially available triamcinolone acetonide suspension by us.

Parametric tests tend to be more powerful than non-parametric tests if their distributional assumptions are met. However, non-parametric methods require fewer
assumptions, and they are generally robust against problems like outliers and non-constant variances. The authors tested statistical significance by the Kruskal-Wallis test, a non-parametric procedure that is a K-sample generalisation of the two sample rank sum test (also called the Mann-Whitney U test). It tests the null hypothesis of identical group medians, rather than means. With the data available in this report, the authors should have noticed that figures 1 and 2 show means and standard deviations; they should instead have shown group medians. Moreover, their results should have been expressed as medians. It remains unclear how many assays were performed. By looking at figures 1 and 2, it seems that three assays were done each time but somehow they were done in duplicate. This is important to show the real sample size that was used to compute the estimate.

The pellet resuspension with 0.9 ml of BSS in the centrifugation technique appeared in their final recommendation at the end of the paper. However, the authors stated in the methods section that the pellet was resuspended with 1 ml of BSS. This point needs to be explained.

1. I recommend that the authors clarify the above mentioned issues. I also suggest that they learn the golden rule of fair use of another author's protected material: take from someone else only what you wouldn't mind someone taking from you.

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The author does not have commercial interest in any product mentioned in the manuscript.

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References

PHEMA as a keratoprosthesis material

An aim to provide an optimised keratoprosthesis, with excellent biointegration, and all other properties meeting ideal requirements, is one we share with Mehta et al.1 However, their report includes some points that require clarification. PHHEMA (poly(2-hydroxyethyl methacrylate) is a non-toxic polymer of the toxic monomer HEMA, though cytotoxicity is still poor. Its biological design requires that the monomer has not been fully removed. The “polyhydroxyethyl methacrylate” the authors obtained for their study was not fully described, and may have been contact lens blanks, unlikely to have been processed for “implantable quality.” Whether the samples had been fully extracted was not stated, nor was the hydration of the samples when used for the study. Contact lens blanks are not designed for cell adhesion and the results of this study, with regard to PHHEMA, are entirely predictable and have been previously reported.

The commercially available keratoprosthesis AlphaCor is made from a form of PHHEMA, specifically modified for its intended purpose within the cornea. In particular, the AlphaCor OPTIC is made from a relatively low water content, but hydrated, microporous form, similar to the samples evaluated by the authors, specifically because it does not encourage cellular adhesion (epithelial coverage is not desired for this model, nor would adherent posterior cells and membranes be desirable).

In contradistinction, the biointegratable SKIRT region of AlphaCor is made from a macroporous form of PHHEMA with a very high water content; this material, with its interconnecting channels, has been optimised to promote viable biocolonisation, which has been extensively described in the literature. Mehta et al do concede that cells “may behave differently in colonising a 3-D porous keratoprosthesis skirt”; indeed they do. Further, very subtle modifications of the sponge structure significantly affect all aspects of biointegration.

Both early trial results, such as the preliminary cases cited by Mehta et al, and current results for over 250 AlphaCor devices, have been extensively presented and made available to all device users. Histology now available from AlphaCor devices expelled from human recipients confirms that the biointegration process in humans is similar to that previously shown in the animal model, and maintained in the long term. As expected, specific inflammatory processes can cause localised reversal of biointegration in areas of stromal melting. Certainly, porosity itself does not prevent melting processes, as is also seen in relation to hydroxyapatite keratoprotheses and orbital implants.

There is no argument that keratoprosthesis materials and devices require ongoing revision and improvement. The authors’ findings in relation to hydroxyapatite are interesting although, as they note, this rigid material has its own limitations. Novel approaches are undergoing early evaluation and may offer benefits. However, at present, in our view, AlphaCor is a device worthy of consideration for those in whom a donor graft would fail.

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References

Expression of TSH-R in normal human extracellular muscles

We read with interest the paper published by Boschi et al., in which immunohistochemistry was performed on orbital biopsies from patients with thyroid associated ophthalmopathy (TAO) and compared with non-dis eased orbital tissue.

Our laboratory recently reported positive TSH receptor staining within normal human muscle fibres, using one of the same antibodies (3G4) as Boschi et al (supplied by Costaglia) and a commercial antibody (3B12). Our findings differ from Boschi et al’s as no staining of the muscle fibres was visible in their experience.

Assessing the techniques used suggested some possibilities as to why our findings differ. Our paraffin embedded tissues were subjected to a proteolytic antigen retrieval step, as commonly used in avidin-biotin staining. The reason for this is that formalin fixed tissue is notorious for altering protein immunoreactivity, and hence masking protein expression.1–6

Moreover, the amplification immunohistochemistry kit used in our experiments is possibly more sensitive than conventional immunohistochemistry used in the experiments of Boschi et al.1

We do not dispute the finding that TSH-R expression is elevated in orbital connective tissue of diseased patients. Combined with our findings, Boschi et al’s paper also suggests that expression of TSH-R on normal muscle fibres is lower than in the connective tissue of diseased patients. Boschi et al have successfully produced more evidence that connective tissues in the orbit are active in TAO affected patients; however, the potential role of the extraocular muscle in the pathogenesis of TAO should also be considered.

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References
Trabeculotomy versus trabeculotomy-trabeculectomy for congenital glaucoma

The article by Al-Hazmi et al. states that combined trabeculotomy-trabeculectomy with mitomycin C (CTTM) gave better results than trabeculotomy alone for primary congenital glaucoma (PCG) at the King Khaled Eye Specialist Hospital (KKESH) in Riyadh, Saudi Arabia, between 1982 and 2002. For moderate PCG the success rate is stated as 40% and 80% for trabeculotomy and CTTM, respectively. For severe PCG the stated success rate is 10% and 70% for trabeculotomy and CTTM, respectively. However, without more specific information regarding when the trabeculotomies were performed at KKESH, the authors cannot advocate CTTM over trabeculotomy for moderate and severe PCG.

As the article states, over the years at KKESH, the success rate for trabeculotomy for PCG dramatically improved (29% from 1982–90; 47% from 1991–4; 82% from 1995–2002). The authors attribute these improved results to improved primary health-care facilities within the kingdom, earlier referrals, better equipment availability, and surgeons becoming more adept at surgical intervention. In contrast, CTTM for PCG was first performed at KKESH in 1994 with less of a “learning curve”; the success rate from 1994–2002 was 72%. The complication rate, however, was higher for CTTM than for trabeculotomy.

Because initial trabeculotomy success for PCG at KKESH has dramatically increased with time, it is important to know how many of the reported trabeculotomy failures for moderate and severe PCG were from the earlier periods in the hospital. This information was not in the paper. It may be that trabeculotomy as currently performed at KKESH for moderate and severe PCG has a success rate similar to that of CTTM for the same patient population with fewer surgical complications.