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 melanoma presents 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 cells on a routine haematoxylin and eosin stain (fig 3). Although the lesion was pale, pigment was visible on the haematoxylin and eosin stain, 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 crano-facial-orbital resection of the tumour 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 allo- genic 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 (3% of all sinonasal malignancy).

Lacrimal sac melanoma can present with epiphora, bloody tears, and epistaxis. Sinonasal melanoma can present with nasal obstruction and epistaxis. Orbital extension causes proptosis and diplopia. Both lacrimal sac melanoma and sinonasal melanoma are insidious in onset with poor visibility leading to late presentation.

Standard 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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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 subtypes 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 #603147) may be fatal. Grunwald 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.

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 the presence of abnormalities in the serum transferrin. A decrease in transferrin and an increase in disialotransferrin are suggestive of the diagnosis.

Ophthalmic features of the most common congenital disorder of glycosylation, type la (OMIM #212065) include myopia, attenuated retinal vessels, bone spicules, esotropia, and nystagmus; this disease subtype is caused by a deficiency of phosphomannomutase (OMIM #212065) encoded by phosphomannomutase-2 (PM2; OMIM #601785) gene. In CDG type lc, much less common, a homozygous amino acid substitution, A337V substitution, in the gene encoding s1,3-glycosyltransferase 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.

Involvement of the lacrimal drainage system by malignant melanoma has a high incidence of local recurrence and distant metastases. The potential for local spread makes it imperative to ascertain the extent of the tumour. Ocular adnexal melanomas are the most aggressive of all melanomas and have a significantly worse outcome. 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.

Figure 1 Left fundus showing attenuated vessels with retinal pigment cell granularity of the macula (white arrow).

| Table 1 Reported ophthalmic manifestations in type 1 congenital disorder of glycosylation (CDG) |
|-----------------|-----------------|-----------------|
|                  | CDG la          | CDG lb          | CDG lc          |
| Strabismus       | +               | –               | +               |
| Retinopathy      | +               | –               | –               |
| Optic atrophy    | +               | –               | –               |

types I and II CDG. Many congenital disorders of glycosylation have been identified based on the presence of abnormalities in the serum transferrin. A decrease in transferrin and an increase in disialotransferrin are suggestive of the diagnosis.
had eye complaints but a maternal aun'ts daughter had bilateral keratoconus.

Ophthalmic evaluation of the elder sister revealed uncorrected visual acuity (UCVA) of 20/200 in both eyes. Her refraction was −19.0−8.0×120 in the right eye and −9.0−3.75×165 in the left eye. Spectacles improved only left eye vision slightly to 20/160. Slit lamp biomicroscopy showed bilateral central corneal protrusion and stromal thinning at the apex (fig 1A). Keratometry was 71.00/63.00 @ 68 in the right eye and 53.00/49.50 @ 135 in the left eye. Hard contact lens fitting failed and surgical intervention was not conducted.

Ophthalmic evaluation of the younger sister revealed UCVA of 20/40 in the right eye and 20/160 in the left eye, which improved to 20/80 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. Because of central corneal scarring and progressive deterioration of her left eye vision, she underwent penetrating keratoplasty (fig 1C). Fourteen months post-operatively, UCVA was 20/50, improving to 20/30 with pin hole.

Comment
Woodhouse Sakati syndrome (MIM 241080) is an extremely rare genetically determined autosomal recessive disorder. It was first described in two Saudi Arabian families, and later reported in a single Turkish family. Table 1 presents manifestations of the syndrome.

We report a new association in our two cases. Such concurrence of early keratoconus and the syndrome raises the possibility of a genetic linkage, although a chance association cannot be excluded. On one hand, either chromosomal rearrangements such as chromosome 7, 11 translocation or genetically determined syndromes such as this syndrome should be considered in cases where keratoconus is present during childhood. That may explain the early presentation of keratoconus in our cases. An additional factor is that keratoconus tends to be more prevalent and diagnosed at a younger age in Asians than in white people.

On the other hand, familial keratoconus in our cases cannot be excluded because of the presence of keratoconus in a single relative and parental consanguinity. Positive family history has been reported in 6% to 10% of keratoconus cases and is suggested to be caused by autosomal dominant inheritance with incomplete penetrance.

To the best of our knowledge, this is the first report of bilateral keratoconus in association with Woodhouse Sakati syndrome. Ophthalmologists and endocrinologists should be aware that patients with this syndrome who complain of poor vision should be suspected of having keratoconus once other more common conditions are ruled out.

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 contexts with 36 other multisystem disorders. We describe the first two cases of keratoconus in association with Woodhouse Sakati syndrome.

Case report
Two sisters (aged 14 years and 18 years) presented with history of bilateral progressive loss of vision over 8 years. Progeny of a first degree consanguineous marriage, they were the only members in the family of six siblings with a diagnosis of Woodhouse Sakati syndrome. Both sisters exhibited variable manifestations of the syndrome including hypogonadism, primary amenorrhoea, hypothyroidism, electrocardiographic abnormalities, and dysmorphic features. The elder sister also had a mild degree of mental retardation. None of their siblings or parents

References

Table 1 Variable manifestations in the nine reported patients with Woodhouse Sakati syndrome

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Delayed psychomotor development</td>
<td></td>
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<tr>
<td>Variable degree of mental retardation</td>
<td>(very frequent sign)</td>
</tr>
<tr>
<td>Alapoeia (very frequent sign)</td>
<td></td>
</tr>
<tr>
<td>Sparse/absent scalp and eyebrow hair (frequent sign)</td>
<td></td>
</tr>
<tr>
<td>Dysarthria</td>
<td></td>
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<tr>
<td>Dysmorphic features: high forehead, flat occiput, triangular face, prominent nasal root, hypertelorism, and down-slanting palpebral fissures</td>
<td></td>
</tr>
<tr>
<td>Hyper/hypothyroidism, hypogonadism and late puberty</td>
<td>(very frequent sign)</td>
</tr>
<tr>
<td>Sensorineural deafness (very frequent sign)</td>
<td></td>
</tr>
<tr>
<td>Electrocardiographic abnormalities and insulin dependent diabetes mellitus</td>
<td>(very frequent signs)</td>
</tr>
</tbody>
</table>

No ocular manifestations

Figure 1 Features of keratoconus are seen. (A) Slit lamp biomicroscopy of the right cornea in the elder patient, showing advanced cone deformation and deep Descemet’s membrane scarring. (B) Slit lamp biomicroscopy of the left cornea in the younger patient, showing dense central scarring following hydrops attack. (C) Histopathological section of left corneal button illustrating the fragmentation of Bowman’s layer (large arrow) and large break in Descemet’s membrane (small arrows) (periodic acid Schiff stain, ×200).

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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 patients whose retinal vasculopathy was diagnosed at a later sequelae stage. To our knowledge, only three cases of retinal vascular occlusion in patients with NF-1 have been previously reported. All cases were vascular occlusion in patients 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 patients whose retinal vasculopathy was diagnosed at a later sequelae stage. To our knowledge, only three cases of retinal vascular occlusion in patients with NF-1 have been previously reported. All cases were associated with NF-1 and included a male patient who presented with acute macular ischaemia combined with diffuse retinal arteriole 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, focal 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 arteriovenous filling time. It revealed occlusion of macular arterioles, retinal arteriovenous 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 arteriolar occlusions in the mid-periphery (fig 2). A panretinal photoocoagulation 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 associated with NF-1 and included a male patient who presented with acute macular ischaemia combined with diffuse retinal arteriole occlusive disease.

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 (IFMTH) include age, female, sex, and high myopia. However, we noticed the association of HFTM in our population, tended to have shorter than normal axial lengths. An age and sex matched case-control study was performed.
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 23.94 (1.96) 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 were 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 results 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–23.31 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 MSE 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 dioptric differences found may be a result of the natural process of emmetropisation of a shorter eye, or alternatively be an independent risk factor.

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.

Choroiditis and exudative macular detachments in a post transplant leukaemic 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 leukaemic 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, dyspnoea, 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
Axial lengths (mm) of patients with macular holes compared with age and sex matched controls.

References
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. Funduscopy revealed peripapillary choroidal lesions with disc swelling bilaterally (fig 2). This time the choroidal lesions were peripapillary 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. Recurrent 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


Figure 1 Multifocal, creamy-yellow choroidal lesions at both posterior poles with massive exudative retinal detachments at the macula.

Figure 2 Peripapillary choroidal lesions with disc swelling.

Prothrombotic and atherosclerotic risk factors lack significance in NAION patients harbouring mitochondrial DNA mutations

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 IIa (PIIa) 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
medical or family history of a thrombotic or vascular event.

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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.4 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 basic anterior tears was different, which made it more difficult to understand the ocular surface disorder correctly or to treat the patients suitably.5 6 Cytometric bead array (CBA) is a microparticle based flow cytometric assay5 that allows us to quantify multiple molecules from a very small sample.7 8 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 each eye by capillary flow, with no nasal stimulation or previous instillation of drugs or vital dyes. Each sample was collected at 5 pm. No anesthetic drops were instilled. The samples were collected non-traumatically from the inferior meniscus. Successively, reflex tear samples were collected by inserting application sticks into a patient’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 5 hours at room temperature, and washed to remove any unbound detector-Ab-PE reagent before data acquisition using flow cytometry. A two colour flow cytometric analysis was performed using a FACScan flow cytometer (Beckton Dickinson Immunocytometry Systems). Data were acquired and analysed using BD cytomeric 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.7 Indeed, the concentrations of tear cytokines in the present results were almost equal to the previous report using the same kit.7 Nakamura et al performed ELISA for multiple cytokines measuring pooled tears.7 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 multiple cytokines of basal and reflex tears from a single sample for the first time, which can provide concentration ranges for these cytokines in normal subjects that may prove important for studies of ocular inflammation. Of note, only the concentration of IL-8 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 defence system.6 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.7 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 a small sample 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.

References


Table 1 Ratios of cytokine concentration

<table>
<thead>
<tr>
<th></th>
<th>IL-1b</th>
<th>IL-6</th>
<th>TNF-α</th>
<th>IL-12p70</th>
<th>IL-10</th>
<th>IL-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>1</td>
<td>3.022 (0.246)</td>
<td>54.162 (6.549)</td>
<td>3.322 (0.316)</td>
<td>12.556 (0.889)</td>
<td>0.716 (0.086)</td>
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<td>TFN-α</td>
<td>0.022 (0.002)</td>
<td>0.07 (0.008)</td>
<td>1</td>
<td>0.074 (0.011)</td>
<td>0.275 (0.028)</td>
<td>0.017 (0.003)</td>
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<tr>
<td>IL-12p70</td>
<td>0.349 (0.026)</td>
<td>0.989 (0.071)</td>
<td>18.269 (2.086)</td>
<td>1</td>
<td>3.981 (0.166)</td>
<td>0.261 (0.042)</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.087 (0.050)</td>
<td>0.253 (0.02)</td>
<td>4.518 (0.47)</td>
<td>0.261 (0.012)</td>
<td>1</td>
<td>3.022 (0.246)</td>
</tr>
<tr>
<td>IL-8</td>
<td>2.14 (0.34)</td>
<td>5.576 (0.694)</td>
<td>144.913 (45.971)</td>
<td>7.447 (1.546)</td>
<td>28.257 (5.078)</td>
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<tr>
<th></th>
<th>IL-1b</th>
<th>IL-6</th>
<th>TNF-α</th>
<th>IL-12p70</th>
<th>IL-10</th>
<th>IL-8</th>
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<tr>
<td>Reflex</td>
<td>1</td>
<td>3.71 (0.252)</td>
<td>53.061 (5.46)</td>
<td>2.918 (0.331)</td>
<td>12.012 (1.123)</td>
<td>0.972 (0.094)</td>
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<td>TFN-α</td>
<td>0.304 (0.027)</td>
<td>0.078 (0.007)</td>
<td>1</td>
<td>0.062 (0.007)</td>
<td>3.381 (0.274)</td>
<td>0.276 (0.029)</td>
</tr>
<tr>
<td>IL-12p70</td>
<td>0.390 (0.023)</td>
<td>1.361 (0.082)</td>
<td>21.357 (3.427)</td>
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<td>0.254 (0.026)</td>
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<tr>
<td>IL-10</td>
<td>0.093 (0.05)</td>
<td>0.324 (0.018)</td>
<td>4.837 (0.524)</td>
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<td>0.093 (0.012)</td>
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<tr>
<td>IL-8</td>
<td>1.043 (0.231)</td>
<td>4.779 (0.665)</td>
<td>73.465 (13.897)</td>
<td>4.02 (0.727)</td>
<td>17.235 (3.251)</td>
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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 was (grade 1) ungradable (tables 2 and 3). The sensitivity was 98% and specificity 97%. The retinopathy present was 21% and the referral rate for retinopathy (STDR) was 7%; 59% did not take up the offer to be screened. Some of the reasons cited: 956 (44%) declined or did not respond, 251 (11%) are being screened elsewhere, 11 (0.5%) are not diabetic, five (0.18%) are dead, six (0.27%) are registered blind, and 21 (1%) have moved.

Comment

Our screening methods surpassed the standards set by the NICE guidelines. However 59% of patients did not take up the offer. The achievable standard to which strategic health authorities and primary care trusts are working is 90% uptake of those offered screening with the minimum standards of 70–80%, but even though quality assurance systems are in place uptake is still very poor

In the intercollegiate audit, led by the Royal College of Ophthalmologists, data were analysed from 9827 patients with diabetes from 129 general practices in 25 health authorities. The lowest level of coverage in a district was 38% and the highest 85%. In general practice the coverage ranged from 14% to 97%. The likelihood of having an eye examination was marginally higher in districts with a systematic examination rather than opportunistic or without recognised schemes at all.

In the Hounslow Primary Care Trust our hospital episode statistics (HES) are the only existing screening programme. Patients registered with a GP are referred to the HES for the screening. The reasons for the 44% who did not respond were that some did not have the time, some were elderly living on their own with nobody to take them, some did not understand the screening leaflet, and some just forgot.

Problems about coverage could be tackled if we had a central electronic database linked to all screening programmes. Although software providers have been agreed for such a data collection exercise, primary care trusts have yet to implement this. People unable to attend during the week could be accommodated in weekend or evening clinics. These clinics could also be reserved, with bilingual support workers to explain the importance of screening for the ethnic patients. Community networks like the rotary, patient groups, ethnic resource centres, and senior citizens groups can be used. The National Service Framework targets will be achieved only if the diabetic population is convinced of the importance of screening.

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doi: 10.1136/bjo.2005.076760
Accepted for publication 29 August 2005
Competing interests: none.

References


Table 1 Referred patients

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<th>Invited</th>
<th>Appointment made</th>
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<tr>
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<td>93</td>
<td>41</td>
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<tr>
<td>Diabetic patients type 2</td>
<td>Invited</td>
<td>Appointment made</td>
</tr>
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<td></td>
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<td>609</td>
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<tr>
<td>Diabetic patients type not stated</td>
<td>Invited</td>
<td>Appointment made</td>
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<td>259</td>
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Table 2 Outcome by grade

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<th>Sex</th>
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<td>363</td>
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<tr>
<td></td>
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<td>261</td>
</tr>
<tr>
<td>T</td>
<td>M</td>
<td>74</td>
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<tr>
<td></td>
<td>F</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>T</td>
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</tr>
<tr>
<td>M</td>
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<td></td>
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<tr>
<td></td>
<td>T</td>
<td>44</td>
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<tr>
<td>R2</td>
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<tr>
<td></td>
<td>T</td>
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<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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</tbody>
</table>

Table 3 Final data

<table>
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<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>4</td>
<td>644</td>
<td>8</td>
<td>98%</td>
<td>97%</td>
<td>21.78%</td>
</tr>
</tbody>
</table>
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. Most patients with this condition improve either immediately following treatment of the hydrocephalus or within a few months, 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 haematoma. He also had evidence of increased intracranial pressure and required an emergency cranial decompression procedure. 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 dioptries at distance and near, and a left hypotropia of 5 prism dioptries. An evaluation that included neuroimaging 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 quadrantic field defects. Pupils were normally reactive to light and near stimulation. In primary position, the patient 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 summary, the patient had a 4 prism dioptre intermittent left hypotropia 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 base out and 35° above the midline. He had no ptosis or lid retraction, and the results of slit lamp biomicroscopy, applanation 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. Depending on the extent of the oculomotor system damage, an affected eye 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 oculocerebellar 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. 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 improve within a few 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.

References

MAILBOX

Purification of triamcinolone acetonide suspension for intravitreal injection

In the article by García-Arumí and associates, the authors reported the results of several techniques used for purification of triamcinolone acetonide suspension for intravitreal injection (two filter devices vs. non-filtered techniques). I very much appreciate that they finally recommended our method (centrifugation for 5 minutes at 3000 rpm with extraction of 0.9 ml of the supernatant and pellet resuspension with 0.9 ml of balanced salt solution, BSS) among those compared.

This could have been an interesting report but I want to raise some important issues 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 2003 and it was first published by Hernaez-Ortega and myself in the 2004 July/August issue of this journal. 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 also 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.

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.

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

doi: 10.1136/bjo.2005.083501

Accepted for publication 26 September 2005

References


Expression of TSH-R in normal human extraocular muscles

We read with interest the paper published by Boschi et al., in which immunohistochemistry was performed on orbit biopsies from patients with thyroid associated opthalmopathy (TAO) and compared with non-diseased 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 Costagliola) 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 used in fixation is notorious for altering protein immunoreactivity, and hence masking protein expression.

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

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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Accepted for publication 11 October 2005

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 over the years to improved primary healthcare 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 complications it is important to know how many 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.

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doi: 10.1136/bjo.2005.084871

Accepted for publication 11 October 2005

Reference


doi: 10.1136/bjo.2005.66431corr1

The letter titled, Bevacizumab suppresses choroidal neovascularisation caused by pathological myopia (Br J Ophthalmol 2005;10:1368–87), was previously published online at http://bjo.bmjournals.com/cgi/content/full/89/6/e1.

doi: 10.1136/bjo.2005.68171corr1

In the letter titled, The achaetomy spectrum: congenitally reduced chiasmal decussation (Br J Ophthalmol 2005;89:1311–17), one of the authors names has been misspelt. The correct list of authors is, D A Sami, D Saunders, D A Thompson, J M Russell-Eggitt, K K Nischal, G Jeffrey, M Dattani, R A Clement, A Liasis, D S Taylor. The journal apologises for this error.

doi: 10.1136/bjo.2005.bj75184corr1

In the letter titled, Two novel mutations of connexin genes in Chinese families with autosomal dominant congenital nuclear cataract (Br J Ophthalmol 2005;89:1533–6), the authors have been listed incorrectly. The correct listing is, Z W Ma, J Q Zheng, J Li, X R Li, X Tang, X Y Yuan, X M Zhang, H M Sun.

doi: 10.1136/bjo.2005.bj82453corr1

In the mailbox item titled, TTT: local light absorption and heat convection versus heat (Br J Ophthalmol 2005;11:1544–5), the second author’s name has been misspelt. The correct spelling is D H Spliney. The journal apologises for this error.

doi: 10.1136/bjo.2005.bj74468corr1

In the letter titled, Confocal microscopy of the cornea in nephropathic cystinosis (Br J Ophthalmol 2005;89:1530–1), the order of the authors is incorrect. The correct order is A H Alshuaibani, A O Kalin, M D Wagoner. The journal apologises for this error.

doi: 10.1136/bjo.2005.bj44015corr1

NOTICES

World Ophthalmology Congress 2006 – Brazil

The World Ophthalmology Congress (which is replacing the International Congress of Ophthalmology) is meeting in February 2006 in Brazil.

For further information on the congress and committees, scientific program and coordinators of different areas are available at the congress website www.ophthalmology2006.com.br

19th International Society for Geographical & Epidemiological Ophthalmology Congress

The 19th ISGEO congress will be held in Sao Paulo, Brazil on 18–19 February 2006, just prior to the ICO. Abstract submission and registration forms can be obtained by emailing Dr Paul Courtright (pourtright@kcco.net) or by accessing the ISGEO website at www.kcco.net/sggeo.

EYE INJURIES

The latest issue of Community Eye Health (No 55) discussed the assessment and management of eye injuries in the developing world. 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; online edition: www.jceh.co.uk). Annual subscription (4 issues) UK £28/US$45. Free to developing country applicants.

8th EUNOS Meeting – 2007

The 2007 European Neuro-opthalmology Society meeting (EUNOS; www.eunos.wcbo.org) will be taking place in Istanbul, Turkey on 26–29th May 2007. For further information please visit www.eunos2007.org, email: or contact Pinar Aydin aydinp@eunos2007.org.

Teaching courses on Retinal and Vitreous Surgery

Several teaching courses on Retinal and Vitreous Surgery have been organised throughout 2006 and 2007 around the world in association with the International Faculty. For further information on each of these courses please contact Ingrid Kressig, Univ. Augenklinik Theodor-Kutzer-Ufer 1-3, 68164 Mannheim, Germany; email: Ingrid.kressig@augen.ma.uni-heidelberg.de; website: http://kressig.uni-hd.de/.
Purification of triamcinolone acetonide suspension for intravitreal injection

Enrique Soto-Pedre

doi: 10.1136/bjo.2005.083501

Updated information and services can be found at:
http://bjo.bmj.com/content/90/1/123.2

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