Charles Bonnet syndrome precipitated by brimonidine tartrate eye drops

Brimonidine tartrate (BT) (Alphagan) is an \( \alpha \)-2 adrenergic agonist marketed for treatment of primary open angle glaucoma (POAG) which may have neuroprotective effects.\(^1\) One report of acute delusional psychosis with auditory hallucinations in a 68 year old man treated with POAG has been published,\(^2\) and use of BT eye drops in an infant resulted in coma and other serious systemic abnormalities.\(^3\) Here we report four elderly patients with bilateral visual loss who developed visual hallucinations (Charles Bonnet syndrome; CBS) shortly after beginning the use of BT eye drops. The hallucinations ceased after discontinuation of BT drops in three cases, and after decreasing the dose in one case, within a time frame of days to 4 months.

Case reports

Table 1 summarises visual function and the characteristics of the visual hallucinations in all four patients.

Comment

The Charles Bonnet syndrome is characterised by persistent or repetitive formed visual hallucinations in elderly individuals in the setting of significant bilateral prechiasmal visual impairment.\(^4\) The visual hallucinations in CBS are not routinely accompanied by other psychiatric symptoms and the affected individuals retain full or partial insight into the unreality of the visions.

Brimonidine tartrate is a lipid soluble \( \alpha \)-2 adrenergic agonist that has a systemic half life of about 3 hours. It is excreted mainly by the kidneys with 87% of an oral dose eliminated after 120 hours.\(^5\) Auditory hallucinations, depression, confusion, and anxiety have been reported with BT use in an elderly adult\(^6\) and coma, hypotension, bradycardia, hypotonia, and hypothermia was caused by BT eye drops given to an infant for treatment of glaucoma.\(^7\) Clearly, BT has the capability of causing central nervous system side effects.

Oral clonidine, another \( \alpha \)-2 adrenergic agonist, is known to cause visual hallucinations. Brown and coworkers\(^8\) described the case of a 31 year old woman treated with clonidine for poorly controlled hypertension who developed visions of “hands reaching for her from a closet or an old woman following her” in the presence of an otherwise clear sensorium. Also, clonidine use has caused delusional psychoses and auditory hallucinations in other patients.\(^9\)

All of our patients were at risk for the CBS based on age and visual impairment but none had visual hallucinations before using BT. The onset of CBS ranged from 5 days to 2.5 months from starting BT. The visual hallucinations ceased in three of our patients within days of discontinuing BT (cases 1 and 3) or decreasing the dose (case 4), consistent with the washout period of the drug. In case 2, the hallucinations lasted on and off for about 4 months. Therefore the persistence of the hallucinations cannot be explained directly by persistent drug toxicity in this person. However, it is still possible that BT triggered the start of CBS in this individual. The natural history of duration of CBS is 47.4 months on average, with a range of 1–240 months.\(^10\) It should be noted that patient 2 also was taking a wide variety of drugs at the time BT was prescribed but their role, if any, in causing the visual hallucinations to persist is uncertain. For example, one study found no statistical difference in the number of drugs taken by patients seen in a geriatric psychiatry clinic who suffered from visual hallucinations when compared with a control group of elderly patients without hallucinations (4.4 (SD 3.1) drugs in the group with hallucinations).

In summary, elderly people with bilateral visual impairment should be warned of the possibility of visual hallucinations resulting from BT use.

Acknowledgement

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Conflict of interest: None of the authors has a conflict of interest involving any aspect of this publication.

Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>VA</th>
<th>Visual fields</th>
<th>Visual hallucinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>79 F</td>
<td>RE 20/20</td>
<td>Humphrey 24-2; constriction to 15 degrees; MD – 16.68 dB</td>
<td>“like dreaming while awake . . . water dripping from the ceiling”</td>
<td></td>
</tr>
<tr>
<td>82 F</td>
<td>RE 20/80</td>
<td>Humphrey 81-3 zone; 51/81 points not seen</td>
<td>“A changing visual panorama . . . halls green with diamond-like pattern . . . blue flowers covering the bathroom . . . small red and grey tiles on the carpet . . . the walls looked like they were made of brick”</td>
<td></td>
</tr>
<tr>
<td>78 M</td>
<td>RE 20/25</td>
<td>Humphrey 81-3 zone; 55/81 points not seen</td>
<td>“I saw images of my bedroom wallpaper all over my house . . .”</td>
<td></td>
</tr>
<tr>
<td>89 F</td>
<td>RE 20/40</td>
<td>Humphrey 24-2; MD – 3.14</td>
<td>People in the room that were not there . . . people or shadows standing near the elevator</td>
<td></td>
</tr>
</tbody>
</table>

VA = visual acuity; MD = mean deviation; FC = finger counting.

References

Trends in squint surgical activity

It has recently been reported that there has been a trend in the United Kingdom towards fewer children requiring strabismus surgery. Although there has been a change in the incidence of childhood strabismus, it may reflect a change in the clinical practices of ophthalmologists, optometrists, and orthoptists. One such practice is the correction of accommodative refractive errors. The correction of a hypermetropic refractive error is an important aspect in the management of esotropia. Although the full hypermetropic correction is usually prescribed for children with an esotropia, it is unclear whether this is, or has been, uniform in practice. Indeed, certain texts suggest a reduction in the hypermetropic correction following a cycloplegic refraction, to take into account so-called accommodative modus.

Because of the effect of an undercorrection of a hypermetropic refractive error on the angle of esotropia, we were interested to determine whether a change in spectacle prescribing practice had had any effect on the number of patients undergoing squint surgery.

Methods

Data were collected from the computerised hospital attendance statistics and operations at the Royal Liverpool Children’s NHS Trust Hospital, which were available from the financial year 1988–9 onwards. The annual number of ophthalmic referrals and operations, were collected within two time periods: a 4 year period from 1988–9 to 1991–2 (period 1) and a 7 year period from 1992–3 to 2000–1 (period 2). Before 1992, it had been the practice to prescribe spectacles with a 0.5–1 dioptre reduction in the spherical component of the cycloplegic refractive error. From the period 1994 onwards, it was the practice of the consultant for the full cycloplegic hypermetropic error to be prescribed. Data were not collected between 1992 and 1994 to allow for a washout period for those patients who had previously been prescribed an undercorrected hypermetropic correction and were undergoing surgery between 1992 and 1994. The total number of eye and squint operations performed per 100 patient referrals, and the ratio between the squint and non-squint operations performed were calculated. The difference between the two periods was compared using the Fisher’s exact test and confidence intervals calculated by the Miettinen approximation method.

Results

During periods 1 and 2, 4514 and 10 314 new patients were seen, of whom 23.9% and 23.6% underwent some form of ophthalmic surgery (p >0.5). There was a significant difference between the mean number of squint operations per 100 patients in period 1 compared to period 2 (14.8% and 9.3%, p <0.0001, proportion difference 0.060, 95% CI 0.047 to 0.073). There was also a significant difference in the mean number of squint operations per 100 total operations performed in period 1 compared to period 2 (61.9% and 38.2%, p <0.0001, proportion difference 0.243, 95% CI 0.203 to 0.283).

Comment

Although it was not possible to examine the population profiles in the time periods studied, there had been no known change in the population profile or referring practices. The hospital data retrieval system, unfortunately, did not permit us to differentiate between a new patient seen with a squint and another seen with a non-squint problem. While the proportion of children who required surgery had remained constant, there had been, similar to a recent report, a reduction in the number of squint operations being performed, with a corresponding increase in the proportion of non-squint operations. We agree that there were likely to have been a variety of other factors contributing to the reduction in strabismus surgery; however, this trend may reflect in part, a change in practice whereby children with strabismus who had a hypermetropic refractive error were, during the latter period, prescribed their full hypermetropic correction.

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References


Botulin toxin treatment of “one and a half syndrome”

Complex forms of nystagmus and conjugate eye movement deficits are generated if the pontine paramedian structures are damaged. These can cause troublesome and occasionally disabling symptoms. The combination of one sided horizontal gaze palsy and ipsilateral internuclear ophthalmoplegia (INO), known as “one and a half syndrome,” is most commonly caused by demyelination, vascular disease or tumours. Ophthalmological symptoms include diplopia, oscillopsia or blurred vision and are often remarkably challenging to manage. Since the introduction of botulinum toxin A (BTA) for ocular motility disorders and nystagmus there have been a number of reports that establish the use of BTA as a treatment option in the management of complex ocular motility disorders.

We report the use of BTA in a patient with one and a half syndrome.

Case report

A 52 year old white male patient was admitted to our institution with dysarthria and right arm weakness of sudden onset. Three years before he had suffered a post-coital subarachnoid haemorrhage from a right middle cerebral artery aneurysm. He had had his aneurysm clipped and had managed an almost complete recovery. He was overweight and hypertensive.

When he was admitted it was noted that he had right facial weakness and his right eye was abducted. Cranial imaging showed considerable volume loss and gliosis in the right frontoparietal region and a possible small infarct in the right side of pons. A few days after the incident and when the patient regained consciousness he complained of oscillopsia from his right eye and an ophthalmological opinion was requested.

Examination of this patient was hampered by his poor mobility and severe dysarthria. He was found to have a complete left gaze palsy and a left INO. He was divergent in the primary position with an angle of approximately 45 prism dioptries (Krimsky). Vertical eye movements were preserved, although he was reluctant to elevate or depress his eyes and the examination of convergence was inconclusive (Fig 1). His main symptom was oscillopsia due to the abducting nystagmus of his non-paretic right eye, which was only relieved with occlusion of the eye with a patch.

A clinical diagnosis of one and a half syndrome secondary to a cerebrovascular event was made. His concurrent exotropia was well described, even if uncommon feature of
structures have been shown to fluctuate with oscillopsia. Right eye. He did not report diplopia or slightly divergent in the primary position. His abducting nystagmus (Fig 2).

Three weeks after the injection the patient's deficit in the right eye, presumably as a result of the BTA injection with elimination of the nystagmus. We have not been able to explain the absence of diplopia after treatment, in spite of a small residual divergence.

There has been a previous report of a patient with one and a half syndrome treated with BTA injection in a selected extraocular muscle. In conclusion, injection of botulinum toxin to selected extraocular muscles can provide a useful alternative to occlusion, drug, or surgical therapies for patients with complex ataxic nystagmus resulting from pontine lesions. Patients suffering from oscillopsia due to ataxic disconjugate nystagmus may benefit from this approach as most other treatments are unsuitable for such cases. There does not seem to be any particular benefit in waiting for stabilisation of symptoms and signs. Selected toxin injection may improve the quality of life during the rehabilitation period.

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References

Retinal and subdural haemorrhages: Aoki revisited

In the United States and much of the English speaking world, the combination of retinal and subdural haemorrhages in a very young child is highly suggestive of non-accidental injury and felt to be incompatible with a history of a minor fall. Thus, when Aoki et al published 26 cases of infants, age 3–14 months, with this combination following minimal falls, even though they stated in their article “in this series, none of the patients had a significant medical history or were victims of child abuse before the trauma”, there was immediate concern that these may have been un-diagnosed cases of shaken baby syndrome (SBS). Aoki responded to this by saying “we do not believe the injuries were caused by battering or shaking” although noting their “series might include some injuries caused by abuse.” In 1987, Ikeda et al added cases to the Japanese experience noting these were “usually caused by a simple domestic head injury” and indicating they were aware of the battered child syndrome.

A comparison of the age distributions of the Aoki and Ikeda series shows them to be very similar (a simple t test not being able to rule they are different with even a 20% probability). However, if either Japanese series or a combination of the two are compared to Kivilu’s SBS series in the United States, it is apparent these are not the same (the probability by a simple t test shows there to be between less than one chance in 400 and a chance in a million that these age distributions are the same (Tables 1 and 2). Recent articles have again brought into question the assumption that a history of a minimal fall is incompatible with the finding of subdural haematoma and retinal haemorrhage in an infant. However, even if some of the Japanese cases are from abuse, some of the American cases may be from minimal falls. The United States assumption would require all the Japanese cases to be misdiagnosed and all 26–40 independent stories in Japan (which are similar to many of the United States stories) to be similar predictions. Instead of discarding the Japanese experience, an inquiry as to why the age distributions are so different seems appropriate.
Treatment of vascular tufts at the pupillary margin before cataract surgery

Iris vascular tufts or microhaemangiomas are an infrequent finding on ophthalmic evaluation. Previous reports have attributed vascular tufts at the pupillary margin of the iris to diabetes, myotonic dystrophy,1 in association with Sturge-Weber syndrome,2 or in association with haemangioma of the orbit or eyelid. We describe a patient with multiple cutaneous and iris margin haemangiomas who had a history of recurrent hyphaema and underwent successful argon laser treatment of pupillary margin haemangiomas before extracapsular cataract extraction with intraocular lens implantation.

Case report

The patient is a 75 year old man first seen 2 years earlier by the retinovascular service at the Wilmer Eye Institute, Baltimore, MD, USA, for recurrent hyphaema in the left eye. He was noted to have multiple haemangiomas on the pupillary border of both eyes as well as numerous cutaneous haemangiomas on his trunk. A small hyphaema was appreciated inferiorly in the left eye with no active bleeding. Gonioscopic examination was normal except for blood in the inferior angle and the intraocular pressure was 16 mm Hg in each eye. There was no corneal endothelial blood staining. He was treated with homatropine hydrobromide ophthalmic solution 5% (Ciba Vision, Duluth, GA, USA) twice a day and prednisolone acetate 1% (Falcon Pharmaceuticals, Fort Worth, TX, USA) four times a day for 1 week to decrease light sensitivity and to prevent intraocular inflammation. The hyphaema subsequently resolved without sequelae. It was suggested that if he suffered a rare occasional haemorrhage he would be treated symptomatically, but multiple repeat haemorrhages would be treated with laser coagulation or surgical excision.

He now presents to the cornea, cataract, and refractive service at the Wilmer Eye Institute for reduced visual acuity primarily in the right eye. On examination, Snellen visual acuity measured 20/400 in the right eye with afferent pupillary defect. External examination was significant for multiple 1–2 mm leaking vascular tufts at the pupillary margin. Iris angiogram showing multiple vascular loops along the pupillary margin. Figure 3

Although it was believed that cataract surgery could be done safely without addressing the management of the angiomas, the risk of lasering the angiomas was low and if closure of the vascular loops was achieved, the intraoperative risk for bleeding might be reduced. The patient was taken off aspirin before the laser treatment and an iris angiogram was performed to guide treatment in order not to miss any subclinical leaking vascular tufts (Fig 3). Argon laser was used with 200 µm spot size, power of 200 mW for 0.1 second duration. A total of 50 spots were administered to close all tufts appreciated clinically and angiographically. No bleeding was noted during the procedure. The patient subsequently underwent uncomplicated extracapsular cataract extraction through a clear corneal incision under topical anaesthesia. Upon insertion of the intraocular lens, a small amount of blood was noticed in the anterior chamber, most probably secondary to iris trauma during the manoeuvre. This was washed out with balanced salt solution. No blood was noticed in the anterior chamber on the first postoperative day nor during a 10 month postoperative follow up period.

Comment

Vascular anomalies of the pupillary margin are rarely seen but have been previously implicated as a possible cause of spontaneous hyphaema.3 More unusual are iris haemangiomas associated with cutaneous haemangiomas. Generalised cutaneous and visceral but evidence of pigment clumps on the anterior capsule in each eye. The right crystalline lens showed dense nuclear sclerosis and posterior subcapsular cataractous change. Funduscopic examination demonstrated a cup to disc ratio of 0.7 in the right eye. The disc, macula, and vessels were normal except for mild arteriolar narrowing. The examination of the left eye was significant for venous congestion with a small superficial nerve fibre layer haemorrhage on the inferior border of the disc. This possibly represented an impending vein occlusion.

Table 2 Probabilities

<table>
<thead>
<tr>
<th>t value</th>
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<tbody>
<tr>
<td>Aoki = Ikeda 0.79</td>
<td>13</td>
<td>&gt;0.200</td>
</tr>
<tr>
<td>Aoki = Kivlin 3.43</td>
<td>13</td>
<td>&lt;0.0025</td>
</tr>
<tr>
<td>Ikeda = Kivlin 4.66</td>
<td>25</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>A + I = Kivlin 6.09</td>
<td>39</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

References


Table 1 Age distributions

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
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</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>Kivlin 9</td>
<td>13</td>
<td>18</td>
<td>16</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
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<td></td>
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<tr>
<td></td>
<td>Aoki 0</td>
<td>0</td>
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<td>1</td>
<td>1</td>
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</tbody>
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haemangiomas have been described as diffuse congenital haemangiomatisos in neonates, but iris and cutaneous haemangiomas in adults are infrequently described. Vascular tufts at the pupillary margins are usually asymptomatic and if hyphaema does occur, recurrence is unlikely. Past treatment had been reserved for patients with recurrent hyphaema or bleeds recalcitrant to medical management. Argon laser treatment of a bleeding iris vascular tuft has been described twice previously for active bleeding resulting in hyphaema with increased intraocular pressure. In both case reports, few laser applications easily stopped the haemorrhaging. Our patient suffered recurrent hyphaemias in one eye and presented with a mature cataract in the other. Surgical decompression of the globe, surgical manipulation causing trauma to the fragile vascular loops, hypotony, and frequent postoperative use of mydriatics causing pupillary "gymnastics" can all cause haemorrhage in patients with otherwise asymptomatic vascular tufts. Although no previous study demonstrated bleeding of the fragile vascular tufts with surgical decompression, it was theorised that closure of the haemangiomas would reduce the intraoperative risk of bleeding during cataract surgery. The major risk of the laser was bleeding during the procedure, but this was considered low compared to a possible bleeding process during surgery because a closed eye procedure would allow for a more rapid recovery of the postoperative process. Another risk was the possible damage to the lens that would be extracted in any case. Other laser risks were intraocular inflammation due to iris or lens damage and glaucoma, which could be caused by an inflammatory process or the result of hyphaema.

We observed only minimal bleeding from the iris during cataract surgery and no further hyphaemias in the postoperative period and therefore recommend considering argon laser treatment to pupillary margin vascular tufts before surgery to decrease the possibility of intraoperative and as postoperative complications of uncontrolled haemorrhaging.

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References

Treatment of retinal folds using a modified macula relocation technique with perfluorohexyloctane tamponade

Retinal folds are a relatively uncommon complication of retinal surgery. Macula involve-ment can produce poor acuity and disturbing metamorphopsia. We report a novel treatment for macula fold using the surgical techniques of foveal translocation and perfluorohexyloctane (F6H8), a new heavier than water agent licensed for long term internal tamponade.1 2

Case report
A 51 year old man with Terson’s syndrome was found to have retinal detachment on B-scan ultrasonography. He underwent vitrec-tomy and lensectomy with C2F6 gas tampon-ade for a superior, macula off retinal detac-hement. He was postured face down overnight. A retinal fold crossing the macula was noted on the first postoperative day (Fig 1A). At 3 months the best corrected acuity was 6/24. The patient described the image in the affected eye as being split diagonally, with the two half images separated. He was referred to our unit for further management.

We used a 41 gauge needle to detach approximately one quarter of the retina by saline infusion into the subretinal space. F6H8 was injected displacing subretinal fluid (SRF) anteriorly, opening out the retinal fold and reapposing the photoreceptors to the pigment epithelium. No direct retinal manipulation was required. The SRF was left in situ and the patient postured on his back to allow the retina to “iron out” slowly as the SRF resorbed. The F6H8 was removed after 5 days. The retina remained flat, without folds (Fig 1B). Seven weeks after surgery his metamorphopsia had resolved with a best corrected acuity of 6/18+2.

Electroretinography was performed before and 10 weeks after surgery using ISCEV standard protocol. The ERG responses showed no evidence of diminution following redeployment and subsequent removal of F6H8 tamponade. (Standard flash in dark adapted state gave a-wave amplitudes of 195 mV before surgery and 219 µV after; b-wave amplitudes of 367 mV before and 453 µV after.)

Comment
Retinal folds through the macula have been reported following both vitrectomy and conventional surgery for retinal detachment.3 4 Van Meurs et al report the incidence as 2.8% with conventional surgery.5 Risk factors for retinal folds include superior bullous detachment, gas tamponade (bubble large in relation to detachment), circumferential buckles, and incomplete drainage of SRF. When gas tamaponade is used in the presence of residual SRF starting the posturing with the break dependent and slowly rolling the patient to the desired posture may reduce the risk of macula folds. Larrison et al6 reported that out of 15 cases with folds involving the macula one third had postoperative acuity of 6/60 or worse and only one third managed 6/18 or better (mean follow up 25 months). Recent data from a dog model of macula relocation7 suggest that macula folds may be associated with progressive visual deterioration. Hayashi et al demonstrated progressive loss of photoreceptors and thinning of the outer nuclear layer within retinal folds. TUNEL assay showed apoptotic cells in the outer and inner nuclear layers of the folds.

Perfluorohexyloctane is a semi-fluorinated alkane with a specific gravity of 1.35, and a high interfacial tension to water (49 mN/m). It is used in complicated retinal detachment surgery and the histology of associated epiretinal membranes have been reported.8 9 We have previously demonstrated that the retina can be stretched by brushing, a phenomenon we referred to as redistribution of neurosensory retina. Macular translocation can be achieved without sclera imbrication to generate redundancy, by introducing a gas bubble in the presence of a bullous retinal detachment. The bubble occupies the top half of the vitreous cavity. The SRF is displaced inferiorly and, confined by the anterior attachment of retina, puts the macula on stretch. Similarly, in our patient, we induced a bullous retinal detachment, used a bubble of...
heavy liquid and postured the patient supine. The F6H8 occupied the dependent part of the vitreous cavity and displaced the SRF peripherally and anteriorly. The SRF is confined by the attachment of the retina at the ora serrata. This effectively put the retina on stretch and “ironed out” the macular fold (Fig 2).

Kertes and Peyman reported treatment of retinal folds in two patients having surgery for tractional retinal detachment (one diabetic, one toxocara granuloma). They used per-operative perfluoro-perhydrophenanthrene tamponade and direct retinal manipulation with a silicone tipped cannula. No significant visual improvement was noted as the folds were outside the macula. Our technique involves no direct instrumental manipulation of the central retina. We have been able to effectively treat the macula fold by exploiting the specific gravity of the tamponade agent. Avoidance of macula folds by addressing causative factors is obviously preferable to treatment. We have been impressed with the complete disappearance of the fold in this case. In selected cases surgery may be appropriate to alleviate troublesome metamorphopsia and possibly reduce the risk of permanent and progressive reduction in vision resulting from the macular fold.

Is hyaline degeneration of the cornea a precursor of Salzmann’s corneal degeneration?

Hyaline degeneration of the cornea has been described by Smolin and Thoft as a specific and rare pathological entity. Other authors have used the term hyaline degeneration of the cornea synonymous with climatic droplet keratopathy, or spheroidal degeneration of the cornea. A literature search failed to reveal any cases of initially diagnosed hyaline degeneration of the cornea as a precursor of Salzmann’s corneal degeneration. We present the first case known to us of initially diagnosed hyaline degeneration of the cornea, assumed to be a precursor of Salzmann’s corneal degeneration.

Case report

A 34 year old woman was referred to our department in April 1998 with increasing opacity of the left cornea. Her medical and ophthalmological history was uneventful. The opacity of the left cornea. Her medical and ophthalmological history was uneventful. The left cornea showed a slightly elevated, yellowish, subepithelial opacity, sharply demarcated and separated from the limbus by a marked interspace (Fig 1A). The right eye was without pathological findings. The corneal opacity was removed by a scarifier both because of persistent foreign body sensation and for diagnostic purposes.

The histological examination of the removed corneal tissue revealed marked, diffuse hyalineosis of the stroma (Fig 1B), and focal degenerations of the overlying corneal epithelium. The presence of amyloid substance was excluded by Congo red staining. Electron microscopy demonstrated the described hyaline areas to represent collagenous tissue (Fig 1C). The assessment of the clinical and histological appearance of the corneal changes led to the diagnosis of hyaline degeneration of the cornea, according to the classification of Smolin and Thoft.

After a period of 2 years the patient presented with recurrent corneal opacity extending beyond the initial pathological area. The clinical appearance of the opacity was markedly different, consisting of several, peripheral, subepithelial, white, slightly prominent lesions. The corresponding juxtapenal cornea was characterised by cloudy opacification and the start of vascularisation (Fig 1D). The cornea of the right eye, which was without pathological findings 2 years earlier, now exhibited a circumscribed injection of limbal vessels as well as a punchiform, superficial opacity at a paracentral location (Fig 1E). The described findings were unchanged at the time of the most recent examination of the patient in August 2002. The clinical aspect of the left eye and the bilateral occurrence of corneal disease enabled the diagnosis of Salzmann’s corneal degeneration.

Comment

The diagnosis of Salzmann’s corneal degeneration is made clinically, with subepithelial, prominent corneal lesions representing the most important sign of this disease. We believe that the initial corneal alteration, clinically diagnosed as hyaline degeneration of the cornea, represents a precursor of Salzmann’s corneal degeneration. This assumption is based on the fact that the respective histological findings already indicated the presence of this pathology. To the region of nodular thickening the superficial stromal tissue consists of collagen fibrils which are hyaliniised and arranged in an irregular fashion in the absence of inflammatory changes or vascularisation. The corneal epithelium shows focal degenerations, while Bowman’s membrane is not identified at its usual subepithelial location.

This case gives rise to the question as to whether hyaline degeneration may exist as a
been reported following laser in situ keratitis may be seen following trauma that rarely causes ocular pathology. Aspergillus is a ubiquitous mould. Hospital acquired aspergillus keratoconjunctivitis is suggested by the onset of clinical signs of corneal pathologies, and a primary one. Further work is required to determine whether the aetiology of the primary variant might be related to limbal insufficiency, which eventually causes both eyes to be affected, as is suggested by the onset of clinical signs of corneal conjunctivalisation in our patient.10

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References

Hospital acquired aspergillus keratitis

Aspergillus fumigatus is a ubiquitous mould that rarely causes ocular pathology. Aspergillus keratitis may be seen following surgery to the eye and has recently been reported following laser in situ keratomileusis.12 Endophthalmitis is also a rare event after trauma or surgery. Endogenous aspergillus endophthalmitis is seen in patients who are immunocompromised, have endocarditis, or a history of injecting drug use. An outbreak of ocular aspergillus following cataract surgery has been reported in association with building a new hospital in the Middle East.13 We report a case of aspergillus keratitis associated with hospital construction in the United Kingdom.

Case report
A 43 year old man presented with a right sided corneal ulcer and a vision of hand movements (Fig 1). He had a past history of bilateral herpes simplex keratitis, rosacea related keratopathy, bilateral corneal grafts, and cataract surgery. The right corneal ulcer was treated with intensive topical ofloxacin and prednisolone acetate 1%. Alpha haemolytic streptococci and coagulase negative staphylococci were cultured from the corneal scrape. The central cornea thinned and a hypopyon became visible. The cornea then perforated and a bandage contact lens and glue was placed on the cornea while graft material was being obtained. A penetrating keratoplasty was performed with a 9 mm donor placed into an 8.5 mm recipient bed (Fig 2). Soon after surgery the microbiology laboratory grew Aspergillus fumigatus from two plates from the corneal scrape. The patient was taken back to theatre for intravitreal amphotericin B injection and topical amphotericin was commenced. The patient made an excellent recovery and has maintained a vision of 6/9 in the right eye with a refraction of −3.25/+3.00×105.

Comment
This patient has unfortunately had infection of the cornea with virus, bacteria, and fungus. The previous herpetic and rosacea related keratopathy resulted in his original corneal grafts and were a risk factor for the development of bacterial keratitis. Considerable demollition and construction work was taking place at the time the patient was admitted to the Royal Devon and Exeter Hospital. The old hospital tower block was being pulled down and the aspergillus infection was probably due to contamination from fungal spores released during the demolition work. Penetrating keratoplasty is a recognised treatment for fungal keratitis, although the graft was performed for the corneal perforation and the fungal infection was only noted after the graft. We believe this is the first documented combined bacterial and fungal keratitis in the United Kingdom that may be attributed to contamination by fungal spores released by hospital demolition work.

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References

Thyroid eye disease: an unusual presentation

Viagra (Sildenafil) is an oral preparation for the treatment of male erectile dysfunction. Although the drug is marketed solely for its therapeutic purposes, it has high potential for abuse owing to its ability to intensify and prolong erectile response. We describe here an ocular side effect following its use as a recreational drug, which led to the diagnosis of thyroid eye disease.

Case report
A 30 year old white man was referred to the eye clinic, with a history of waking up one morning with a left proptosis, having had no ocular signs or symptoms the previous day. The patient did not have any subjective symptoms of pain, redness, change in visual acuity, double vision, or of hearing any sounds. There was no history of direct or indirect trauma. He gave a history of having acquired a tablet of Viagra from a friend at a Christmas party. He ingested half and gave half to his partner. The exact dosage strength was unknown. His partner noticed increased visibility of the white of the eye under the left upper lid. He was otherwise healthy and was taking no medication.
Visual acuity was 6/5 unaided in each eye. Ocular examination showed a 3 mm axial non-pulsatile left proptosis. He was orthophoric and ocular movements were unrestricted. Anterior segment examination showed generalised conjunctival engorgement on both sides, more on the left than the right. Pupils were normally reacting and fundus examination was unremarkable. Intraocular pressure was normal with no significant difference between straight gaze and up gaze. Auscultation over the globe revealed no bruit.

The clinical findings along with the acute onset history led us to suspect superior ophthalmic vein thrombosis as a possible cause. An magnetic resonance imaging (MRI) scan was ordered with a specific request to comment on the calibre of the superior ophthalmic veins. The MRI scans showed normal superior ophthalmic veins bilaterally but thickening of all extraocular muscles, particularly the inferior recti on both sides. The inferior rectus was intensely white on T2 weighted scans. Biochemical tests for thyroid function showed him to have high T3 and T4 levels and very low TSH levels.

Comment

Sildenafil citrate has been in use since early 1998 for the treatment of male erectile dysfunction. It is a selective cyclic guanosine monophosphate dependent phosphodiesterase type 5 (PDE5) inhibitor. It potentiates the smooth muscle relaxant effect of nitric oxide and leads to engorgement of the sinusoids of the corpus cavernosa with a resultant penile erection. At the time of orgasm, emission, and ejaculation sympathomimetic substances—adrenaline (epinephrine) and noradrenaline (norepinephrine)—are released with consequent sinusoidal smooth muscle contraction and rapid loss of penile rigidity. As with any new drug, clinical information and known side effects with regard to sildenafil are limited. Ocular side effects are few. Although sildenafil was developed as a selective PDE5 inhibitor, it has about 10% selectivity for PDE6—an enzyme localised in retinal photoreceptors. This results in various visual symptoms like a blue tinge to vision, impaired colour vision, increased light sensitivity, and blurred vision. Symptoms are transient and occur between 2–4 hours after ingestion in the absence of ocular electrophysiological tests have been variable. A recent study showed no effect of sildenafil on mean blood pressure, intraocular pressure, perfusion pressure, or choroidal and optic nerve head blood flow, but there have been isolated reports of anterior ischaemic optic neuropathy, vascular third nerve palsy, and retinal vascular occlusions.

Lid retraction following ingestion of Viagra has not been reported before. We believe that the release of sympathomimetic substances may have produced a supranormal response in the form of noticeable lid retraction in a sensitised individual with thyroid dysfunction. We speculate, based on the close temporal relation between ingestion of this recreational drug and the presentation to our department, that Viagra therapy was responsible for the unmasking of latent thyroid eye disease in a sensitised individual.

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References


Mooren’s ulcer resolved with campath-1H

Mooren’s ulcer is a rare idiopathic peripheral ulcerative keratitis. The diagnosis is usually based on characteristic clinical features and absence of other causes of peripheral keratitis. The clinical course can be unremitting, particularly in bilateral disease, occasionally leading to total loss of stroma.

An autoimmune process is recognised as being central to the pathogenesis. Calgranulin-C (CaGC), produced by granulocytes and also expressed by keratocytes, appears to be the target protein for the autoimmune response that leads to Mooren’s ulcer. Previous corneal trauma and a higher prevalence of HLA class II subtypes have been associated with Mooren’s ulcer.

The disease responds to immunosuppression with variable success. Surgical treatments such as conjunctival recession have been proposed. Campath-1H is a humanised lymphocytotoxic monoclonal antibody (mAb) that targets the CD52 antigen on T lymphocytes. Successful mAb therapy using campath-1H has been reported in serious ophthalmic inflammatory conditions that were unresponsive to maximum conventional immunosuppression.

Case report

A 36 year old man presented to the eye department with a severe alkaline burn in both eyes. The right eye had severe stromal opacity and 360 degree limbal ischaemia, and was enucleated 2.5 years later after multiple surgical treatments. The left eye had partial epithelial loss and inferior limbal ischaemia (four clock hours), healing completely. Visual acuity was 20/20 a year after injury, when the patient developed an inferior-nasal gutter of 160 degrees with deep and superficial vascularisation, with progressive discomfort and photophobia, characteristic of Mooren’s ulcer. Autoanitibodies, hepatitis titres, and tests for anti-filarial serology were negative. The patient’s HLA (DR) profile was DR15(2), DR17(3), DQ6(1), DQ 2. Serum anti-calgranulin-C detection by western blot was not elevated.

Initial systemic and topical prednisolone with cyclosporin A failed to control the process. In spite of conjunctival recession, maximum dose triple oral immunosuppression with prednisolone, cyclosporin A and mycophenolate motetil, topical prednisolone and cyclosporin A, and oral doxycycline, the inflammation and corneal melting continued to advance. Corneal microperforations were treated with two consecutive applications of histoacryl glue (see Fig 1).

A 5 day course of campath intravenously was then administered. After the first week, there was marked decrease of the corneal inflammation, with epithelial healing and improvement of pain and photophobia. Immunosuppression was reduced to a low dose of oral and topical prednisolone. Two months later, a minor recurrence was treated with oral mycophenolate motetil and topical cyclosporin A. The cornea healed within a week with no further corneal inflammation and low loss of stroma.

The patient had a transient anaemia, reduction in both T and B cell counts and reversal of CD4/CD8 ratio. A posterior subcapsular cataract developed, operated on 10 months after campath-1H treatment. Fourteen months later, the eye remained quiet with a stable ocular surface and corneal stroma, and visual acuity of 20/25. His immunosuppression was being tapered gradually.

Comment

In this patient with severe Mooren’s ulcer standard treatments including conjunctival recession and aggressive triple immunosuppression did not control the disease. Treatment with campath-1H was successful. Although medium term tolerance appears to be excellent, long term risks of infection and malignancy are still to be determined. Campath-1H may be considered a last resort for use in those patients with Mooren’s ulcer in whom other treatments have failed.

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References

Does etanercept induce uveitis?

Etanercept (Enbrel) is a fusion protein of the extracellular ligand binding portion of the tumour necrosis factor (TNF) receptor p75 and the FC portion of human IgG1. This agent inhibits the action of both TNFα and TNFβ (important pro-inflammatory cytokines). It is being increasingly used in the management of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis with a good outcome in both open label and randomised controlled trials. Potentially serious but uncommon adverse effects are serositis, reactivation of tuberculosis, worsening of congestive cardiac failure, exacerbation of multiple sclerosis, and reports of less serious skin reactions, lymphoma, autoantibodies have been reported.1 Isolated case reports of the development of rheumatoid nodules and leucocytoclastic vasculitis with etanercept also exist.2 We report a case of uveitis following etanercept treatment for ankylosing spondylitis.

Case report

A 44 year old HLA B27+ve woman taking methotrexate (15 mg weekly) and prednisolone was started on Enbrel for the management of her ankylosing spondylitis. She had a history of ischaemic heart disease, hypertension, and hypercholesterolaemia. At the time of presentation, she had a visual acuity of 6/18 in the right eye and 6/12 in the left eye with a vision of 6/18 in the right eye. The logMAR acuity in the left eye was 0.46 (38 letters misread). The anterior segments and intraocular pressures were normal. Both fundi showed characteristic multiple pigmented atrophic scars in the posterior pole and mid-periphery in the absence of vitreous cells. There was a macular scar in the right eye (Fig 1). In the left eye there was an elevated grey lesion with subretinal fluid and intraretinal haemorrhages (Fig 2A). Fluorescein angiography confirmed a predominantly classic subfoveal choroidal neovascular membrane (Fig 2B and C). Argon laser photocoagulation was contraindicated because of the subfoveal location. Despite a 4 week course of oral prednisolone (40 mg a day for 1 week then reduced by 10 mg every week) the vision in the patient’s only useful eye continued to worsen. The patient refused submacular surgery because of the poor postoperative result in her right eye. Photodynamic therapy was offered as a treatment option.

After obtaining informed consent we performed five sessions of photodynamic therapy at 3 monthly intervals according to a standard protocol. Baseline and 3 monthly post-treatments logMAR visual acuities were recorded and clinical and angiographic assessment was performed. After 15 months the Snellen acuity in her left eye has stabilised at 6/18 and her logMAR acuity is 0.2 (25 letters misread). She has gained eight letters on the logMAR chart and subjectively there is less distortion. Clinically, there is resolution of the subretinal fluid and intraretinal haemorrhages and formation of a flat scar-like lesion (Fig 3A). Angiographically, despite pigment epithelial leakage, the findings are consistent with reduced activity and fibrosis of the choroidal neovascularisation (Fig 3B and C). An Indocyanine green angiography confirmed the choroidal neovascularisation secondary to punctate inner choroidopathy that failed to respond to oral corticosteroids and had poor results with submacular surgery in the contralateral eye.

Photodynamic therapy: a treatment option in choroidal neovascularisation secondary to punctate inner choroidopathy

Punctate inner choroidopathy is an idiopathic inflammatory ocular disorder characterised by yellowish, 1–3 mm sized, subfoveal lesions known as punched-out choroidal neovascularisation. Smaller circumscribed telangiectatic atrophic scars characteristic of punctate inner choroidopathy are seen in the mid-periphery of the macula.
findings of the fluorescein angiography and excluded the presence of choroidal feeder vessels that could lead to a recurrence of the neovascularisation (Fig 4).

Comment

Punctate inner choroidopathy is an idiopathic inflammatory disorder that usually occurs in young, myopic women. Both eyes are commonly affected. Symptoms include blurred or distorted vision, light flashes, or paracentral scotomas. The acute, multiple, yellow-white lesions of the inner choroid and retinal of the posterior pole evolve into atrophic pigmented scars. Vitritis and anterior uveitis are absent. Visual prognosis is good in most patients and significant visual loss is usually due to formation of choroidal neovascularisation. Choroidal neovascularisation if smaller than 100 µm in diameter may resolve spontaneously. However, subfoveal choroidal neovascularisation occurs in 40% of the patients. Argon laser photocoagulation is contraindicated for subfoveal lesions. Although good results have been reported with 1 mg/kg per day of oral prednisolone, the response to oral steroids is variable if more than 200 µm in diameter. Submacular surgery has shown promising results but recurrence is common. Photodynamic therapy using verteporfin is safe and effective for subfoveal choroidal neovascularisation in age related macular degeneration and high myopia. The verteporfin guidelines suggested photodynamic therapy for other aetiologies if outcome without treatment was likely to be poor. Preliminary success in ocular histoplasmosis syndrome, angioid streaks, idiopathic and other conditions has been reported. The recommended protocol for treatment included clinical and
angiographic review every 3 months. Retreatment was indicated if there was any fluorescein leakage from the choroidal neovascularisation. Retreatment was deferred if the visual acuity remained stable or improved and the lesion fulfilled all the following criteria: (1) minimal or no subretinal fluid on biomicroscopic examination; (2) flat scar-like appearance; (3) minimal fluorescein leakage without progression beyond the boundaries of the previous treatment or involvement of the fovea.

Photodynamic therapy in this case of subfoveal choroidal neovascularisation secondary to punctate inner choroidopathy was indicated at a post-surgical result in the fovea and the deterioration of vision in the fellow eye despite oral corticosteroid treatment. Five treatment sessions over 15 months produced subjective and visual (logMAR) improvement. Clinically there was resolution of intraretinal haemorrhages and subretinal fluid with formation of a flat scar-like lesion. The angiogram confirmed a stable lesion with minimal fluorescein leakage, no progression beyond the treatment boundaries and staining of the scar tissue. This case demonstrates that verteporfin photodynamic therapy may be a useful treatment option in choroidal neovascularisation due to punctate inner choroidopathy. Further studies are needed to confirm and support this observation.

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Non-invasive volumetric blood flow measurement in the orbit

We read with great interest the article of Orge and co-workers1 who claim a first ever solution to the problem of non-invasive volumetric blood flow measurement in the orbital circulation. There is a further problem in determination of the diameter of the ophthalmic artery. They assume the boundaries of the vessel to be where detected movement starts and ends along the m-mode line; or in other words the vessel boundaries are taken to be the positions where the grey pixels and colour pixels touch on this Doppler image. However, we are doubtful whether this is relevant for the required quantitative measurement. The first point is that for small vessels the width of the colour area (indicating blood motion) is unfortunately relatively independent of the true vessel diameter. The width of the superimposed colour area is greatly influenced by the actual technical parameters used in colour Doppler imaging (pulse repetition frequency, lateral dimension of the ultrasound beam, colour priority, motion discriminator setting, colour saturation, brightness, contrast, etc). Our second doubt is that, even on the grey scale part of the image shown by Orge et al in their Figure 1, no vessel wall is outlined with a diameter of 1 mm or above. Thus, we would expect a 2 mm diameter artery to be clearly visible, but in this case the figure is significantly larger than is suggested by other evidence. During conventional 10 MHz B-scan diagnostic examination, the ophthalmic artery diameter is never visible. However for the dilated ophthalmic vein, in exceptional cases such as in a patient with carotid–cavernous sinus fistula, or in a small baby in a bout of strenuous crying, the vein is then well outlined with a diameter of 1 mm or above. Thus, we would expect a 2 mm diameter artery to be clearly visible. This case has been described some years ago.2 Patients with a pathologically dilated ophthalmic vein are good candidates for non-invasive volumetric blood flow measurement. We were able to measure volumetric blood flow in the orbit of patients with a high flow fistula (vein diameter around 3–4 mm) using the CVI-Q technique (Fig 1). Possibly future improvements in spatial resolution may resolve this difficulty. In a vessel like the ophthalmic artery there is a further problem in determination of the average velocity, because the laminar flow in such small vessels causes a very wide velocity variation within the lumen, as can be seen from our Figure 1. In contrast, we note that the colour spectrum in the figure presented by the authors is almost completely uniform and does not show higher speed in the centre of the lumen compared to that close to the vessel wall. This might imply a relative insensitivity of velocity discrimination with respect to the vessel lumen, which in addition may be of irregular cross sectional shape (that is, not circular) but is only measured in one longitudinal plane. We agree with the authors that the analysis software is of great importance and may be a key factor in dealing with this complex situation. In spite of our reservations we, and many other workers concerned with orbital circulation, are in urgent need of a reliable solution for volumetric blood flow determination in the orbit. The results of Orge and co-workers show that we are probably not far from a definitive solution.

Acknowledgement

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We discussed the article by Cobb et al with great interest in our journal club meeting. We would like to highlight some of the issues we discussed.

Evidence in the literature suggests anisometropia is a difference of 1 DS between both eyes but the authors use a difference of 2 DS. Also the minimum criteria for diagnosing amblyopia on a test of visual acuity are accepted to be two lines difference between the eyes on linear tests. However, the authors use these criteria for the single optotype test and do not take into account the crowding effect. A two line difference on Sheridan Gardiner may actually equate to a three line difference on a linear test. The Royal College of Ophthalmologists also state that on repeated testing a difference of one line can also be included—that is, 6/9 6/6. Therefore a one line difference on Sheridan Gardiner may actually fulfil the linear criteria.

The authors stated that part time occlusion was the method of treatment. Part time occlusion can vary from as much as 6 hours to 10 minutes yet the authors did not state the amount of occlusion to the level of vision. Methods of occlusion have varied greatly between 1972 and 1995, so were the guidelines for occlusion treatment the same throughout the study period?

Furthermore ‘compliance’ with treatment is recognised as an important factor affecting the final visual outcome in amblyopia and that compliance varies with age. The authors have not analysed if compliance varied significantly with age of presentation. It has been shown that anisometropic amblyopes may have improvement in vision after a period of spectacle correction and refractive adaptation is considered an important component of amblyopia treatment. The authors did not state if occlusion was started at the first, second, or third visit after spectacle correction. We do not know if treatment had been initiated prematurely and resulted in falsely increased occlusion dose, thereby giving poorer compliance. This could have skewed the figures. So, we recommend exercising caution in interpreting the results and in concluding that time at which screening is critical in this group.

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Authors’ reply
We thank Sankari and colleagues for their helpful and interesting comments regarding our paper. We accept that the literature suggests a difference of 1 D as a definition of anisometropia but felt the stringent definition we applied would more accurately represent a degree of anisometropia that could potentially lead to amblyopia, and therefore makes the findings more robust. The average age of the cohort was 5½ years and as such the majority of tests were linear. Pure anisometropic amblyopia does not tend to cause as significant crowding as strabismic. We therefore felt that it was not necessary to equate one line of difference with Sheridan Gardiner to a two or three line difference on a linear test. Occlusion regimes and compliance are always problematic especially in retrospective studies. All parents of children were given the same advice and support regarding therapy and the outcomes, therefore the findings of our study reflect a real clinical situation. Compliance does vary with age as shown by Nucci et al, but this was significant only in the 1–2 year old age group. There were no children of this age in our study. More importantly, the effect of occlusion is inversely related to age, so the younger the child the more rapid the response. Most children were commenced on occlusion at their first visit after refractive correction, which was within 2 months of receiving glasses. We agree that anisometropic amblyopes may have a continuing improvement in their vision with just spectacle correction for some months. Depending on the response to spectacle correction, this department will now delay occlusion for up to 1 month. To suggest that initiating occlusion on earlier than may have been necessary would result in a worse outcome because of poor compliance must be considered speculative. In any case, failure to comply with occlusion would result in the now recommended treatment—that of spectacle correction alone. While there may be some debate as to the efficacy of occlusion therapy, there is currently no evidence that it is detrimental to the final visual acuity achieved in anisometropes.

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References
Can a cilio-retinal artery influence diabetic retinopathy?

Knudsen and Lervang published an interesting article in the *BJO* recently. The authors concluded that a cilio-retinal artery tends to worsen diabetic maculopathy but I believe there is an alternative interpretation of the data provided. The authors mentioned that 26/29 patients had a cilio-retinal artery in the eye with worse maculopathy, which was a statistically significant result. In the results section the authors did not report whether a unilateral cilio-retinal artery was present in the 75 subjects with identical maculopathy in the right and left eyes but they stated that this was true in all 75 subjects in the first sentence of the discussion. Therefore, in 75 patients the cilio-retinal artery had not caused worsening of the maculopathy compared to the contralateral eye. Taken together with the 29 subjects with asymmetrical maculopathy, the proportion of subjects in whom the unilateral cilio-retinal artery did not worsen maculopathy would be (75 + 3)/144 or 0.52 (95% CI 0.46 to 0.58). The proportion of cases in whom maculopathy was not worsened by a cilio-retinal artery was therefore significantly more than 50%.

The authors also reported that 51 eyes had clinically significant macular oedema (CSMO), in the group of 94 subjects with maculopathy. However, the $\chi^2$ analysis should not have been performed using each eye as a case (n=962), as it is well known that the right and left eyes of each patient are not independent (that is, if the right eye has maculopathy, the left eye has a greater chance of having maculopathy than the contralateral eye of a non-affected eye in another patient). One possible approach would be to look at all the right eyes only or to randomly look at one of the two eyes of each subject and reduce n to 481. The reader of this article will not know the outcome of this analysis without more information from the authors; however, assuming all the 51 eyes with CSMO were from different subjects, the $2 \times 2$ table may look like Table 1. This table assumes that all the 104 eyes with unilateral cilio-retinal artery and the 15 eyes from bilateral cilio-retinal cases are included, making a total of 119 subjects with cilio-retinal arteries for analysis. In the above case clearly the result is not statistically significant ($\chi^2 = 0.017; p>0.9$).

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**Reference**

<table>
<thead>
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<th>Table 1</th>
<th>The relation between the presence of a cilio-retinal artery and clinically significant macular oedema (CSMO)</th>
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<td>106</td>
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<tr>
<td>Total</td>
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Non-invasive volumetric blood flow measurement in the orbit

J Németh, Z Harkányi and F Humml

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