Acetazolamide, alternate carbonic anhydrase inhibitors and hypoglycaemic agents: comparing enzymatic with diuresis induced metabolic acidosis following intraocular surgery in diabetes

We describe a case of acetazolamide induced acidosis associated with the precipitation of a hyperosmolar state in a diabetic patient 6 weeks after routine phacoemulsification. While renal tubular acidosis is well reported with acetazolamide, this case suggests that a direct diuresis induced acidosis can also have significant effects, producing serious complications when acetazolamide is prescribed to a diabetic patient, and those with renal impairment, with important implications for prescribing.

Case report

A 47 year old female patient underwent technically uncomplicated left phacoemulsification with intraocular lens implant in 2002. Medical history included insulin dependent diabetes since 1971. She had treated, stable proliferative diabetic retinopathy, relatively mild diabetic nephropathy (proteinaemia with a stable creatinine in the region of 140 μmol/l for several months), and mild diabetic autonomic neuropathy. Serum urea had been slightly raised in the past, though had normalised. Serum electrolytes were also within normal limits. The patient was compliant with instructions and blood glucose had been well controlled over many years with regular subcutaneous insulin, no episodes of ketoacidosis or a non-ketotic hyperosmolar state.

Six weeks after cataract surgery she developed left cystoid macular oedema. Confirmed by fundus fluorescein angiography, treatment was started with topical ketorolac and frequency of postoperative topical steroid increased. Treatment was later started with acetazolamide 250 mg orally twice a day, with instructions to drink lots of sugar free fluids to compensate for the diuretic effect. Arrangements were made for regular monitoring of her electrolyte status.

The patient started to progressively deteriorate over the next few days, reporting a massive diuresis. She required emergency admission 6 days after starting treatment. Biochemical results are shown in table 1. Subcutaneous insulin was administered and acetazolamide discontinued. A sliding scale of insulin and intravenous saline drip were commenced on admission. Full blood count was normal, with no evidence of neutrophilia. Arterial blood gas analysis is shown in table 2. This shows that she had a metabolic acidosis. Arterial blood pH 7.3 after initial resuscitation implies that she was even more acidic before fluid resuscitation. The hyperglycaemia, absence of ketones, and raised osmolality led to the diagnosis of hyperglycaemic hyperosmolar non-ketotic syndrome (HONK).

The patient stabilised rapidly overnight, with normal blood gases, blood glucose, and an improving serum creatinine of 141 μmol/l by the next day. A sliding scale was discontinued 2 days following admission, when she was recommenced on a subcutaneous insulin regimen and discharged as an inpatient.

Comment

This case suggests that the diuretic induced mechanism for acetazolamide acidosis can be a cause of severe metabolic acidosis in susceptible patients, and that the diuresis can be severe enough to precipitate a life threatening diabetic crisis. Carbonic anhydrase inhibitors such as acetazolamide affect the metabolism of carbonic acid, bicarbonate, and carbon dioxide within the proximal tubule cell, inducing a slight diuresis. It is rare for severe metabolic acidosis to develop outside advanced renal failure, chronic dialysis, in the elderly and those on nephrotoxic drugs. While the patient’s renal impairment was only moderate with serum creatinine of 140 μmol/l, when acutely unwell it approached 150 μmol/l, a level which would have necessitated referral to a renal specialist to plan end stage renal replacement therapy. This is because patients with diabetic nephropathy tend to do less well than those with other causes of renal impairment and, in fact, renal dialysis may in any case be required at relatively low levels of creatinine such as less than 200 μmol/l.

Most reports in the literature do not specify the underlying pathophysiological mechanism causing metabolic acidosis with acetazolamide. Some cases have been suspected to be the result of a biochemical effect operating at an enzymatic level to increase urinary loss of bicarbonate producing a metabolic acidosis— for example, renal tubular acidosis, and potentially also lactic acidosis, damage to the tricarboxylic acid cycle, ketosis and inhibition of pyruvate carboxylase. However, the biochemical results in this patient, together with the rapidity of acidosis, do not suggest a tubular origin for the acidosis. Instead the patient displayed an alternative mechanism that accounts for the metabolic acidosis. This was causing the physiological effect of diuresis causing loss of excess body water in a diabetic patient. Further, there was no history of biguanide use; metformin is an oral hypoglycaemic agent that can cause lactic acidosis to the extent that it is contraindicated with a creatinine level of 150 μmol/l or more. Basic physiological work suggests that a diuresis induced acidosis can be a significant factor with acetazolamide.

Biochemical results in this patient directly correspond to those obtained when healthy subjects have been given three 250 mg doses of acetazolamide. Acute clinical doses of the drug cause a change in body fluid compartments leading to a moderate isosmotic hypoosmolarity of the postulate that acetazolamide was the culprit. Theoretically, a diabetic ketoacidosis is also possible, though we are unaware of specific reports to date in this context. HONK is arbitrarily defined as serum osmolality >320 mOsm/kg and a blood glucose level >33 mmol/l, without excessive ketones, and

<table>
<thead>
<tr>
<th>Table 1 Biochemistry on admission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum glucose</strong></td>
</tr>
<tr>
<td>Patient Normal range</td>
</tr>
</tbody>
</table>

*Normally no ketones are detected on stick testing of urine.*
Table 2  Arterial blood gases on admission

<table>
<thead>
<tr>
<th>Patient</th>
<th>pH</th>
<th>pCO₂</th>
<th>pO₂</th>
<th>Base deficit (excess)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>7.3</td>
<td>3.4 kPa</td>
<td>15 kPa</td>
<td>-10.3 mmol/l</td>
</tr>
<tr>
<td>range</td>
<td>7.3–7.45*</td>
<td>4.5–6.0 kPa</td>
<td>12–15 kPa</td>
<td></td>
</tr>
</tbody>
</table>

*Life threatening at and beyond 7.2 and 7.6.

†Normal >23 mmol/l: -<3 mmol/l = metabolic acidosis, >3 mmol/l = metabolic alkalosis, -3 mmol/l to +3 mmol/l = mild metabolic acidosis, severe metabolic alkalosis, or mixed metabolic disturbance.

was clearly induced by the stress of diuresis in this patient, with which it is associated. It would also have compounded the patient’s existing dehydration. Mortality from HONK can be as high as 40% despite hospital admission.1

It is possible that the precise mechanism of metabolic acidosis seems not to have been considered in most case reports as treatment was, in many ways, unaffected. Alternately, it may be that the effect reported in this case is extremely rare. However, the clinical findings in this case are supported directly by correlation with the findings of basic physiological work on the pharmacodynamics of acetazolamide, together with work on the pathophysiology of HONK.2,3 This suggests that the observations made on this case are certainly of much broader significance and raise an issue of concern about the drug prescription in both diabetes and renal failure. While manufacturer’s recommendations for acetazolamide in Britain include contraindications to its use in suprapenal dysfunction, they do not issue cautions for its use in diabetes. Thus this case’s principal value lies in evaluating current prescribing practice, particularly as diabetics are a very common group of patients in ophthalmic practice, and acetazolamide is not uncommonly prescribed in many different areas of clinical ophthalmology, as well as by other clinicians. Until further data are forthcoming, including data on newer slow-release formulations, good practice should be to prescribe the drug with especial caution in diabetics, particularly for those conditions, including this case, where its prescription is not routine. In the context of its use in diabetes it is also certainly worth comparing acetazolamide with other carbonic anhydrase inhibitors. One of the other carbonic anhydrase inhibitors that have been used in diabetes it is also certainly worth comparing acetazolamide with other carbonic anhydrase inhibitors. One of the other carbonic anhydrase inhibitors that have been used in diabetes, particularly for those conditions, including this case, where its prescription is not routine. In the context of its use in diabetes it is also certainly worth comparing acetazolamide with other carbonic anhydrase inhibitors. One of the other carbonic anhydrase inhibitors that have been used in diabetes, particularly for those conditions, including this case, where its prescription is not routine.

This case should also serve as a reminder that patients with any level of renal impairment are a group that are vulnerable to acetazolamide toxicity. The data sheet and toxicsheet of acetazolamide, together with work on the pathophysiology of HONK,2,3 This suggests that the observations made on this case are certainly of much broader significance and raise an issue of concern about the drug prescription in both diabetes and renal failure. While manufacturer’s recommendations for acetazolamide in Britain include contraindications to its use in suprapenal dysfunction, they do not issue cautions for its use in diabetes. Thus this case’s principal value lies in evaluating current prescribing practice, particularly as diabetics are a very common group of patients in ophthalmic practice, and acetazolamide is not uncommonly prescribed in many different areas of clinical ophthalmology, as well as by other clinicians. Until further data are forthcoming, including data on newer slow-release formulations, good practice should be to prescribe the drug with especial caution in diabetics, particularly for those conditions, including this case, where its prescription is not routine. In the context of its use in diabetes it is also certainly worth comparing acetazolamide with other carbonic anhydrase inhibitors. One of the other carbonic anhydrase inhibitors that have been used in diabetes, particularly for those conditions, including this case, where its prescription is not routine.

The art of retinal detachment surgery: a photoessay

Subjective visual experience has been described previously in patients undergoing intraocular surgery, and may occur following either topical anaesthesia or regional anaesthesia (peribulbar, retrobulbar, subtenons).1,2 Published reports suggest most or all patients undergoing cataract extraction under local anaesthesia will report some visual symptoms when questioned immediately after their procedures. These symptoms are common therefore and range from perception of light, photopsia, colours, and movement, through to more formed visual sensations such as patterns, instruments, and surgeon’s fingers/hands/detail. It is not surprising that patients undergoing vitreoretinal surgery under local anaesthesia might also experience visual symptoms.

We present illustrations and comments (figs 1–4) made by an artist who underwent retinal detachment surgery. He presented with macula-on retinal detachment successfully repaired by vitrectomy, cryotherapy, and 20% SF6 gas performed by peribulbar anaesthesia. They provide an interesting insight into previously unreported visual experience during vitreoretinal surgery. As visual symptoms are both common, and may be perceived to be frightening in a small percentage of patients,1,2 we reinforce the view that informed patient consent procedures should include the possibility of visual experience during vitreoretinal surgery under local anaesthesia.

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References

Figure 1 (A) “Now we are going to shine a very bright light light into your eye…” … and indeed it was bright. The light pulsed gently and sparkled at the edges where the heavenly blue began. (B) It was outshone by an even brighter light … more pulsations and shimmerings of an intense whiteness followed and two glowing red circles appeared, the lower one seeming to be a secondary image or reflection of the upper one.

under local anaesthesia might also experience visual symptoms.

We present illustrations and comments (figs 1–4) made by an artist who underwent retinal detachment surgery. He presented with macula-on retinal detachment successfully repaired by vitrectomy, cryotherapy, and 20% SF6 gas performed by peribulbar anaesthesia. They provide an interesting insight into previously unreported visual experience during vitreoretinal surgery. As visual symptoms are both common, and may be perceived to be frightening in a small percentage of patients, we reinforce the view that informed patient consent procedures should include the possibility of visual experience during vitreoretinal surgery under local anaesthesia.

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Figure 2 (A) From time to time liquid was splashed on to the eye, producing quite remarkable starbursts of bubbles and comet trails of light. (B) The brilliant light faded and was replaced by deliquescent magenta coloured shapes, glowing like neon, constantly forming and reforming and with sparks coruscating round the edges … a real fireworks display. (C) Quite suddenly the fireworks gave way to this darker mood … the shapes still forming and reforming but more slowly, no longer glowing, but in a complementary colour to that of the previous image … a muted lime yellow. (D) Next came perhaps the most extraordinary and delightful of all the images … this near perfect facsimile of a Chinese silk painting of bamboos gently swaying, as if in a slight breeze, in front of a full moon. (E) Alas, the “Chinese painting” gave way to the appearance of “long whiskers”—rather like huge stray eyelashes—moving slowly but sometimes jerkily, at the top right of the field of vision. (F) Darker than this, richly beautiful and gently blurred, this next image somehow resembled a shallow stream. Clear water rippled over sunlit pebbles and water plants, long streamers of which gently swayed in the movement of the water. Sunlight flickered gently over everything—in many ways, a surprisingly realistic image. (G) This very powerful yet momentary image occurred towards the end of the operation. The incandescent green cross burned powerfully like an electric filament … an inspection light perhaps?

Apolipoprotein E polymorphism in patients with cataract

Based on similarities in epidemiology and biochemistry, it has been suggested that cataract and Alzheimer’s disease (AD) share the same aetiological mechanisms. Comorbidity of cataract and AD in trisomy 21 (Down’s syndrome) is well known1 and both diseases are characterised by aggregated proteins exhibiting excessive glycation and racemisation of aspartyl residues.2 Several AD
related proteins—amyloid precursor protein (APP), β amyloid (Aβ), and presenilin (PS)—are expressed in the lens and Aβ is accumulated in the cytosol of lens fibres in cataractous lenses of people with AD.

Human apolipoprotein E (apoE) exists in three major isoforms encoded by distinct alleles (APOE ε2, ε3, and ε4). The different APOE alleles have been studied in relation to several human age related diseases: inheritance of the ε4 allele is a strong risk factor for AD and influences Aβ metabolism. The purpose of this study was to investigate the APOE ε2/ε3/ε4 polymorphism in patients with cataract.

After informed consent, patients with senile cataract and control individuals were recruited from two ophthalmic clinics in Tartu and the south Estonian area. The study was approved by the ethics committee at the University of Tartu, Estonia. Before surgery, the type of cataract was determined using biomicroscopy and ophthalmoscopy. Secondary cataracts were excluded. The case group included 502 patients; 77 with nuclear, 155 with cortical, 119 with posterior subcapsular, and 151 with mixed opacities. Mean age was 72.0 (SD 8.7) years (range 47–93 years) and 348 (69.3%) were women. The control group consisted of 187 individuals without cataract, uveitis, or glaucoma. Mean age was 72.0 (SD 8.7) years (range 43–90 years) and 136 (72.7%) were women. The power of the study was >99% as calculated according to Altman on the basis of APOE ε4 allele frequencies in a recent study on AD.

The APOE alleles and genotypes were determined as previously described. The allele and genotype frequencies of cataract cases and controls were compared using a two tailed Fisher exact test, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using STATA as software (SPPS Inc, Chicago, IL, USA). Statistical significance was defined as p<0.05.

APOE allele and genotype frequencies found in this study are well in accordance with those reported in other Northern European populations. No significant differences were seen between the control and cataract groups for any of the APOE alleles (table 1) or APOE genotypes (table 2). Neither were there any differences between the control group and the specific cataract subgroups. In order to prevent the data from being influenced by age differences between the groups studied, age matched control individuals were selected and compared with the cataract group and vice versa, without resulting in any significant changes in APOE allele or genotype frequencies.

Alzheimer’s disease and cataract both exhibit large aggregates of aberrant proteins, senile plaques composed of Aβ and neurofibrillary tangles containing the cytoskeletal protein tau in the former case, and light scattering high molecular weight aggregates of crystallins in the latter. Together with several other diseases characterised by protein aggregates, such as amyloidosis and prion diseases, the term “conformational disease” has been created, suggesting a common aetiology.

The APOE ε4 allele is a strong risk factor for AD, and it is believed that in neuronal tissue, apoE is important for mobilisation and redistribution of lipids, and for maintenance and repair of neuronal cell membranes. However, in age related macular degeneration (AMD)—a condition characterised by accumulation of extracellular deposits termed drusen, containing among other things neutral lipids, cholesterol, and apoE—the ε4 allele appears to confer protection, whereas the ε2 allele is associated with a moderately increased risk of AMD. The APOE ε4 allele also seems to play a protective role during embryogenesis, suggesting different effects of the gene early and late in life.

To our knowledge, this is the first study to investigate the APOE polymorphism in cataract patients. No differences in the distribution of APOE alleles and genotypes could be seen between controls and cataract patients in spite of a large number of participants and a very high power. This indicates that if there is a common pathogenic mechanism for cataract and AD, it does not involve the

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**Table 1** APOE allele frequencies for control and cataract groups

<table>
<thead>
<tr>
<th>APOE allele*</th>
<th>Controls (n = 374)</th>
<th>Nuclear (n = 154)</th>
<th>Cortical (n = 310)</th>
<th>Posterior subcapsular (n = 238)</th>
<th>Mixed (n = 302)</th>
<th>All cases (n = 1004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε2</td>
<td>0.112</td>
<td>0.110</td>
<td>0.113</td>
<td>0.071</td>
<td>0.126</td>
<td>0.107</td>
</tr>
<tr>
<td>ε3</td>
<td>0.773</td>
<td>0.792</td>
<td>0.774</td>
<td>0.832</td>
<td>0.768</td>
<td>0.789</td>
</tr>
<tr>
<td>ε4</td>
<td>0.115</td>
<td>0.097</td>
<td>0.113</td>
<td>0.097</td>
<td>0.106</td>
<td>0.105</td>
</tr>
</tbody>
</table>

n, number of alleles. *p<0.05 for all alleles when comparing controls and cataracts (all cases) or cataract subgroups. 95% confidence intervals of all odds ratios included 1.0 (no difference).

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**Table 2** APOE genotype distributions for control and cataract groups

<table>
<thead>
<tr>
<th>APOE genotype</th>
<th>Controls (n = 187)</th>
<th>Nuclear (n = 77)</th>
<th>Cortical (n = 155)</th>
<th>Posterior subcapsular (n = 119)</th>
<th>Mixed (n = 151)</th>
<th>All Cases (n = 502)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε2/ε2</td>
<td>0.011</td>
<td>0.013</td>
<td>0.013</td>
<td>0.017</td>
<td>0.020</td>
<td>0.016</td>
</tr>
<tr>
<td>ε2/ε3</td>
<td>0.182</td>
<td>0.156</td>
<td>0.181</td>
<td>0.101</td>
<td>0.179</td>
<td>0.157</td>
</tr>
<tr>
<td>ε2/ε4</td>
<td>0.021</td>
<td>0.039</td>
<td>0.018</td>
<td>0.008</td>
<td>0.015</td>
<td>0.015</td>
</tr>
<tr>
<td>ε3/ε3</td>
<td>0.588</td>
<td>0.636</td>
<td>0.587</td>
<td>0.697</td>
<td>0.596</td>
<td>0.624</td>
</tr>
<tr>
<td>ε3/ε4</td>
<td>0.187</td>
<td>0.156</td>
<td>0.194</td>
<td>0.168</td>
<td>0.166</td>
<td>0.173</td>
</tr>
<tr>
<td>ε4/ε4</td>
<td>0.011</td>
<td>NO</td>
<td>0.006</td>
<td>0.008</td>
<td>0.007</td>
<td>0.006</td>
</tr>
</tbody>
</table>

p<0.05 for all genotypes when comparing controls and cataracts (all cases) or cataract subgroups. 95% confidence intervals of all odds ratios included 1.0 (no difference). NO, not observed.
APOE polymorphism. Of course the results need to be confirmed by other groups before the APOE polymorphism can be regarded as significant in cataractogenesis. Bearing in mind the similarities between cataract and AD is very important, however, as progress in aetiological research of one disease may contribute to elucidating the pathogenesis of the other.

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Mitomycin C in sebaceous gland carcinoma with pagetoid spread

Sebaceous gland carcinoma is a rare eyelid tumour comprising less than 1% of all eyelid malignancies. It commonly arises from the meibomian glands of the tarsus, but may also arise from the glands of Zeis or from the sebaceous glands of caruncle. It can present in a nodular or diffuse infiltrative form. The latter form with intraepithelial (pagetoid) invasion has poor prognosis as a result of delay in diagnosis as well as more extensive involvement of ocular tissues. Topical application of mitomycin C, a non-cell cycle specific alkylating agent, has been advocated for pagetoid spread of sebaceous gland carcinoma. We report the use of mitomycin C as adjuvant therapy in a patient with completely excised sebaceous gland carcinom and pagetoid spread.

Case report

A 78 year old man was referred to the ocuoplastic clinic with epiphora and irritation of right eye for 2 years. There was no previous ocular or medical history. Clinically he had a unilateral right upper lid entropion with tarsal-conjunctival epithelialisation (fig 1) and bilateral dermatochalasis. The patient underwent bilateral blepharoplasty and biopsy of right upper lid tarsal plate and conjunctiva. The biopsy confirmed sebaceous gland carcinoma with pagetoid invasion of the conjunctival epithelium (fig 2).

He had a full thickness wedge excision of the right upper lid with tarsocconjunctival biopsies. These showed sebaceous gland carcinoma to the margin of the excision with pagetoid invasion of the conjunctiva and epidermis of the lid margin. A wider excision of the lid and further conjunctival biopsies were performed with frozen section revealing complete excision of the tumour. Reconstruction of the posterior lamellae was achieved using a hard palate graft and the anterior lamellae was repaired by a myocutaneous flap with post auricular skin graft and a bilobed flap medially.

Conjunctival map biopsies were clear of tumour 1 and 6 months post excision. In view of pagetoid spread, the patient was commenced on three cycles of topical mitomycin C 0.02% four times a day. Each cycle consisted of 2 weeks of mitomycin C and 2 weeks off therapy. Corneal epithelial toxicity and ulceration was noted with mitomycin C therapy, requiring preservative free lubricants and lateral tarsorrhaphy. Two years after excision of tumour, the patient remains disease free.
treatment of sebaceous gland carcinoma. In the pilot study by Shields et al11 there was complete resolution of tumour with no recurrences over 12 month follow up. Mitomycin C as adjuvant treatment in pagetoid spread of sebaceous gland carcinoma may reduce the need for more invasive treatment options.

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A questionnaire survey of patient acceptability of optic disc imaging by HRT II and GDx

Glaucoma is an insidious condition which remains asymptomatic until very advanced with nerve damage occurring before detectable visual field loss.1 Early detection and treatment result in a better prognosis with retardation of progression.2

The Heidelberg retinal tomograph (HRT II) (Heidelberg Engineering, Germany) and the GDx Nerve fibre analyser (Laser Diagnostic Technologies Inc, San Diego, CA, USA) are instruments which use scanning laser technology to diagnose and monitor the progression of glaucoma. We conducted a questionnaire survey of subjects undergoing imaging by these methods in a primary care setting to compare patient acceptability of the two tests.

Methods

Seventy new patients referred with a possible diagnosis of glaucoma were asked to complete a questionnaire about their experience of optic disc imaging. Informed consent was obtained and the study had approval from the Moorfields Eye Hospital research and ethics committee. None of the subjects who had undergone disc imaging previously. Subjects underwent sequential disc imaging by experienced technicians using HRT II then GDx or vice versa in approximately equal numbers. Only subjects who had vision of at least 6/12 and who had successful imaging by both methods were included.

The questionnaires consisted of two identical sets of six direct questions using a size 14 font (Appendix 1). Questionnaires were completed immediately after imaging to reduce the potential for recall bias. Statistical significance was determined using Binomial and McNemar’s tests.

Results

Sixty seven questionnaires were completed. Demographic and diagnostic data are shown in table 1 and patient responses in table 2. The majority of patients found both tests agreeable with regards to each characteristic under study other than chin rest comfort. Sixteen patients found the HRT II comfortable but not the GDx, compared with just one patient finding the GDx comfortable but not the HRT II (p = 0.0003). Despite this, there were slightly more patients reporting that the HRT II chin rest only was uncomfortable (p = 0.052). Nine patients found that imaging with GDx but not HRT II took too long compared with no patients finding the HRT II but not GDx too long (p = 0.0039). Similar numbers of patients reported that only one of the imaging techniques was too bright. Nineteen patients had trouble fixating with the GDx but not the HRT II compared with just three patients having trouble fixating with HRT II but not GDx (p = 0.009).

Despite these differences, 28 subjects (42%) stated no preference for either imaging technique. Of the 39 subjects who did state a preference, 31 (79%) preferred HRT II compared with eight (21%) who preferred GDx (p = 0.0003, Binomial test). Twenty of the 31 subjects (65%) who chose HRT II did so because it was of a shorter duration, five of the 31 (16%) said that it was more comfortable, and six of the 31 (19%) said that it was easier to perform the test. Four of the eight subjects (50%) who chose GDx did so because it was easier, two (25%) said that it was more comfortable and two (25%) did not give a reason.

Comment

Diagnostic and screening tests should be safe, specific, sensitive, and acceptable to patients. The HRT and GDx have cited sensitivities of 0.42–0.88 and 0.64–0.96 and specificities of 0.84–0.90 and 0.74–0.96 respectively.3,4 Most patients found both tests to be fairly acceptable. Twenty eight (42%) subjects stated no preference but of those who did, a significant proportion of patients preferred HRT II over GDx. The most common reason given was a shorter test duration implying that acquisition time may have an impact on acceptability. Examination with the GDx may be longer because of the external fixation target, which a greater proportion of subjects found difficult to focus on. In contrast the HRT II has an internal fixation target.

Table 1

<table>
<thead>
<tr>
<th>Question</th>
<th>GDx</th>
<th>HRT</th>
<th>p Value (McNemar’s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the test comfortable? (n = 65)</td>
<td>46 16 2</td>
<td>46 14 2</td>
<td>0.0033</td>
</tr>
<tr>
<td>2. Was the light too bright? (n = 38)</td>
<td>2 4 0</td>
<td>2 4 0</td>
<td>0.3877</td>
</tr>
<tr>
<td>3. Was the chin rest uncomfortable? (n = 65)</td>
<td>26 8 19</td>
<td>26 8 19</td>
<td>0.0522</td>
</tr>
<tr>
<td>4. Was the test too long? (n = 65)</td>
<td>1 9 0</td>
<td>1 9 0</td>
<td>0.0039</td>
</tr>
<tr>
<td>5. Did you have trouble keeping your eye still? (n = 65)</td>
<td>14 19 3</td>
<td>14 19 3</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Table 2 Patient responses

References


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Although the HRT II was found to be a more comfortable test, a higher proportion found the HRT II chin rest to be uncomfortable possibly because of the forward sloping angulation.

We did not correlate patient preference with image acquisition time. More open questions may have helped to find the reasons for certain preferences. We were unable to determine the strength of preference from the collected data. Our study was also not randomised but roughly equal numbers had either HRT II or GDx first. We do not feel that there was a significant order effect. As our patients were new referrals, their responses were not biased by familiarity with previous tests. Patients underwent both tests sequentially on the same day by trained technicians reducing the likelihood of prolonged acquisition time due to inexperienced operators. All patients had good vision so locating the target was not an issue. Additional work examining the factors which affect acquisition time (for example, refractive error, presence of media opacity, pupil size) is needed to further understand patient preference.

It is uncertain if the differences in preference between the two tests will have a significant impact on patient satisfaction and compliance with clinic visits as a whole. Other factors, such as waiting time and comfort of waiting room, will have to be examined as well.

In conclusion, our study highlights the importance of both test characteristics and comfort of waiting room, will have to be examined as well. Other factors, such as waiting time and comfort of waiting room, will have to be examined as well.

Appendix 1
The questions were:
1. Was the test comfortable? Yes or No?
2. Was the light too bright? Yes or No?
3. Was the chin rest uncomfortable? Yes or No?
4. Was the test too long? Yes or No?
5. Did you have trouble keeping your eye still? Yes or No?
6. (a) Which test did you prefer? HRT or GDx? (b) Why?

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References

A novel mutation in the alternative splice region of the PAX6 gene in a patient with Peters’ anomaly

The PAX6 gene is involved in ocular embryogenesis. This gene seems to be the master control gene for morphogenesis of the eye. Mutations in the PAX6 gene have been detected in various ocular anomalies suspected to have bilateral genetic backgrounds during development, including aniridia, Peters’ anomaly, and foveal hypoplasia.

In 1994, a sporadic case of Peters’ anomaly and a small family with a range of anterior segment malformations, including Peters’ anomaly, were shown to have a mutation of the PAX6 gene. More recently, Azuma et al reported a subject with Peters’ anomaly having a missense mutation in the alternative splice region of the PAX6 gene in 1999.

Here we report a novel PAX6 gene mutation in a patient with Peters’ anomaly.

Case report
The present study had the approval of Kyoto Prefectural University of Medicine ethics committee and was conducted in accordance with the World Medical Association Declaration of Helsinki. Genomic DNA samples were isolated from the whole blood of patients and their relatives after informed consent. Each exon of the PAX6 gene and its immediate flanking sequence were amplified by polymerase chain reaction (PCR). Purified amplified fragments were sequenced using an ABI Prism 3100 genetic analyser (Applied Biosystems, Foster City, CA, USA). To confirm the sequence of mutations, the SNaPshot method was performed.

Of the four patients studied, we detected a novel missense mutation in one patient. The patient, a 20 year old girl, had bilateral Peters’ anomaly showing corneal opacity with iridocorneal adhesion and nyctagmus (fig 1). The fundus of both eyes could not be seen because of corneal opacity. No systemic associations with Peters’ anomaly were identified. Sequence analyses revealed a heterozygous mutation as A/G at the 38th position which resulted in Q13R substitution in the PAX6 gene. No mutation was found in her parents and elder brother, which is consistent with the fact that they show no abnormal findings on clinical examination (fig 2).

Comment
We have identified one missense mutation in the alternative splice region (exon5a) of the PAX6 gene in a subject with Peters’ anomaly. This missense mutation was the substitution from glutamine to arginine at the 13th codon, which is the second reported position in the exon5a.

The Pax family of developmentally regulated transcription factors share an amino terminal DNA binding motif known as the paired domain. The paired domain has a bipartite structure with a highly conserved N-terminal subdomain (NTS) and C-terminal subdomain, which bind distinctive consensus sequences, and the insertion of exon5a into

Figure 1 Photographs show the anterior segment region. (A) The anterior segment of the patient. She had bilateral Peters’ anomaly and showed corneal opacity with iridocorneal adhesion and nyctagmus. The best corrected visual acuity was 20/100 (right) and 20/200 (left). The fundus of both eyes could not be seen because of corneal opacity. (B) The anterior segment of patient’s father. (C) The anterior segment of patient’s mother. (D) The anterior segment of patient’s elder brother. No congenital ocular abnormalities of anterior segment region were found in her parents or elder brother.
the N-terminal subdomain abolishes the DNA binding activity of the NTS.5

Interestingly, in 1999, Azuma et al proved that the mutation in the NTS of the paired domain partially restored the DNA binding activity of the NTS, using functional analyses.6 In addition, because the amino acids glutamine and arginine belong to hydrophilic and basic amino acid respectively, they have different electronic charges. Therefore, this amino acid substitution may affect the structure of the PAX6 protein and then change DNA binding activity of the paired domain. In other words, such a single amino acid substitution is an important motif as the paired domain such as we have found may severely damage the normal protein function. In fact, except for aniridia, other missense mutations that result in a serious congenital eye disease such as Peters’ anomaly or foveal hypoplasia, also exist in the paired domain. The typical clinical presentation with a missense mutation in a highly conserved and functionally important region suggests there is a reasonable likelihood that this sequence variant is caused by the patient’s phenotype. Our report adds a novel and potentially structurally significant mutation in the PAX6 gene to the present spectrum of mutations.

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Figure 2 (A) Pedigree of the patient (arrow). All of the members represented here were examined. Solid symbol indicates Peters’ anomaly and open symbols indicate normal phenotype. Sequence analysis revealed a heterozygous mutation in the alternative splicing region in the patient. However, no mutation was found in her parents or elder brother. (B) Direct sequencing of PAX6 PCR product from the patient with Peters’ anomaly showed an A/G heterozygosity at the 28th position which resulted in Q13R in exon 5a (arrow). (B-1) Electropherogram of forward sequence of PAX6 exon 5a. (B-2) Electropherogram of reverse sequence of PAX6 exon 5a. (C) The result of sequencing of PAX6 PCR product from the patient with Peters’ anomaly and open symbols indicate normal phenotype. Sequence analysis revealed a heterozygous mutation at the base position of 38 which is consistent with sequencing results. (C-2) Normal subjects represent a single peak corresponding to A indicating no mutation at the position. (D) Direct sequencing of PAX6 PCR product from the patient’s relatives indicates that they do not have the same mutation.

References

Tuberculous intraocular infection presenting with pigmented hypopyon: a clinicopathological case report

Tuberculosis still remains a major cause of morbidity and mortality today. Globally the incidence of this disease is increasing by eight million new cases annually and is a cause of death for two to three million patients every year.1 The ocular manifestations of tuberculosis are diverse, and depend on the immunological, bacteriological, and epidemiological variables.2 Individuals with compromised immune status usually present with atypical presentations.3 This clinicopathological report of a patient treated with immunosuppressive agents shows intraocular tuberculosis presenting with pigmented hypopyon.

A 38 year old female patient with a history of polyarthralgia, anaemia, hypertension, and an impaired renal function with a possible clinical diagnosis of systemic lupus nephropathy underwent renal biopsy, which disclosed membranous glomerulonephropathy with peripheral granular deposits of IgG, C3, and IgM on immunofluorescence. Her erythrocyte sedimentation rate was elevated (74 mm in the first hour) and she had positive antinuclear antibody; negative rheumatoid factor, VDRL, HIV, and tuberculin skin test (PPD). She was treated with intravenous cyclophosphamide 1 g per day once every month for 3 months and corticosteroids 30 mg/day. At the time of the third intravenous injection of cyclophosphamide, she noticed deterioration of vision in the right eye. On examination, right eye visual acuity was hand movements close to face. The conjunctiva was congested and the cornea was oedematous. The anterior chamber was shallow, and a 3 mm pigmented hypopyon was noted (fig 1). The left eye was unremarkable and the vision was 6/6. Blood and urine cultures showed no growth, and smears of anterior chamber fluid were negative for bacteria and fungi. Oral ciprofloxacin (500 mg twice per day) was started in addition to topical corticosteroids and mydriatics. A week later, the pigmented hypopyon had increased to 5 mm; it was aspirated and submitted for cultures and staining. Ziehl-Nielsen’s stain revealed several acid fast bacilli (AFB). The culture was positive for AFB and the Tuberculosis Research Centre in Chennai, India, identified the organisms as Mycobacterium tuberculosis based on pigment production, positive niacin, and catalase test. The patient was re-examined for evidence of systemic tuberculosis. Her PPD was negative and there were no radiological or clinical evidence of extraocular tuberculosis. Despite treatment with four antituberculosis drugs (rifampicin 450 mg, isoniazid 300 mg, ethambutol 800 mg, and pyrazinamide 1500 mg), and oral steroids (20 mg) for her polyarthralgia, the patient developed multiple scleral abscesses and lost the remaining vision. She underwent enucleation of the right eye and was continued on antituberculosis agents for 6 months. She was continued on tapering dose of systemic corticosteroids for 3 months following a fourth intravenous cyclophosphamide injection. She was followed for two more years and there were no signs of disseminated tuberculosis during that time.

Figure 1 The right eye shows oedematous cornea with presence of pigmented hypopyon.
Histopathological examination of the enucleated eye showed infiltration of acute inflammatory cells and macrophages in the posterior half of the corneal stroma (fig 2). The anterior chamber was filled with pigment containing necrotic cells, macrophages, and proteinaceous exudate. The iris and ciliary body were necrotic and were infiltrated by pigment laden histiocytes. The sclera revealed necrosis with infiltration of acute inflammatory cells. The vitreous cavity contained proteinaceous exudate without significant inflammatory cell infiltration. Acid fast stains disclosed an abundance of AFB deep in the corneal stroma, in the anterior chamber exudates, and in the necrotic iris (fig 2). Histopathological diagnosis was tuberculous necrotising keratouveitis.

Comment

In this case, the pigmented hypopyon was made up of melanophages. Darkly pigmented hypopyon may appear in eyes harbouring necrotic uveal melanomas in endogenous endophthalmitis caused by Listeria monocytogenes and Serratia marcescens. The cause of dark hypopyon in the endophthalmitis cases was assumed to be a dispersion of melanin from the necrotic iris. This hypothesis also showed necrotic iris and dispersed melanin granules in the anterior chamber, suggesting a common underlying pathology for the formation of pigmented hypopyon. To the best of our knowledge this is the first known case of pigmented hypopyon in a biopsy and culture proved intraocular tuberculosis, and highlights the need for anterior chamber fluid analysis in arriving at the diagnosis.

The clinical spectrum of ocular tuberculosis infection includes chronic uveitis, interstitial keratitis, scleritis, sclerouveitis, optic neuritis, choroiditis, retinitis, chorioretinitis, and panophthalmitis. Hypopyon is rarely noted in tuberculosis. Ni et al presented cases of intraocular tuberculous with turbid, haemorrhagic, greyish yellow exudate in the anterior chamber in one case, and fibrinous hypopyon in three other cases. Hypopyon may appear in rifabutin treated patients who had Mycobacterium avium complex infection. In all instances, the hypopyon was not darkly pigmented. The clinical and histopathological features suggest that the ocular infection could be endogenous; however, systemic evaluation did not disclose extracocular focus. The presence of large numbers of acid fast organisms in the histological sections suggests that the organisms could be atypical mycobacteria. However, the cultures showed that the organisms were Mycobacterium tuberculosis. Presence of such large numbers of the organisms in the ocular tissue could be from treatment induced immunosuppression.

Acknowledgements

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References


Spontaneous stabilisation of symptomatic schisis detachments

Acquired retinoschisis affects 7% of people aged 70–40 years and is bilateral in 85%.1,3 Although retinoschisis is generally asymptomatic and stable, retinal detachment can supervene in one of three ways. Two of these are rare, are associated with posterior vitreous detachment (PVD), and justify surgical correction; thus, a retinal tear and detachment may originate within non-scleritic retina or open breaks in the inner leaf of a schisis may allow fluid vitreous to be recruited into the cyst and thence to pass through breaks in the outer leaf, causing it to separate from the retinal pigment epithelium (RPE) over a wide area. The third mechanism—‘schisis detachment’—is quite common (for example, 9% had a PVD) and results in his recommending that surgery for schisis detachments be limited to eyes with symptomatic progression.1,4 We present a patient with sequential bilateral schisis detachments, each of which was symptomatic at onset but which settled spontaneously.

Case report

In March 2000 a 46 year old man was referred with a 2 day history of photopsia and a disturbance in the upper part of the visual field in his right eye. Visual acuity was 6/5 unaided in each eye, and neither eye had a PVD. Funduscopy revealed a schisis detachment inferiorly in the right eye with a curvilinear outer leaf break at the posterior limit of the cyst (fig 1A). The detachment extended midway between the inner and outer retinal layers and the inner leaf break was not involved, the left fovea. Given the patient’s history, surgery was assumed to be a dispersion of melanin from the necrotic iris. This hypothesis also showed necrotic iris and dispersed melanin granules in the anterior chamber, suggesting a common underlying pathology for the formation of pigmented hypopyon. To the best of our knowledge this is the first known case of pigmented hypopyon in a biopsy and culture proved intraocular tuberculosis, and highlights the need for anterior chamber fluid analysis in arriving at the diagnosis.
Trypan blue: authors’ reply

We would like to thank Dr Rodrigues and colleagues for bringing up this interesting point of what exactly trypan blue stains.1

In our study, immunohistochemistry was performed to determine the nature of cells involved in the epiretinal membranes (ERM) —not to determine the presence or absence of the ERM. Presence or absence of ERM was determined by examining routinely stained sections (haematoxylin and cosin, periodic acid Schiff) for cytoplasm/nuclei of epiretinal cell elements. All four of the macular hole internal limiting membrane (ILM) specimens were examined in this way.2 Furthermore, trypan blue (in low concentrations) stains the anterior lens capsule.3 Since this capsule lacks glia, we do not believe that the evidence supports the contention of the correspondents that the staining of our ILM specimens is due to undetected “glial cell elements of the highly cellular ERM” rather than ILM. 

Clinically two features are observed with the use of trypan blue. Firstly, the whole posterior pole that comes into contact with trypan blue is stained a faint blue in all cases. The staining pattern is diffuse and not patchy, suggesting trypan blue staining is indiscriminate of ERM or ILM. Secondly, in cases of macular pucker, the trypan blue stained ERM can be removed separately, leaving intact ILM behind, which can be further stained and removed. In cases of macular hole where a clinical ERM is not present, it appears that only the ILM is stained and peeled. We have harvested these membranes and confirmed that the membranes only consist of ILM and without a secondary ERM.

There is no doubt that trypan blue stains both ERM and ILM. We, however, have no knowledge as to what the structural elements of these membrane that the dye is attached to. We concede that staining of ILM with trypan blue can be variable and sometimes rather faint. Since our publication, Perrier and Sebag have also reported their experience with trypan blue in staining ILM and ERM.4 Although histological findings were not given in these studies, clinically the authors found the dye to be useful in both types of membranes. Given the many concerns regarding the use of indocyanine green,5 we believe it is a positive development that an alternative clinically useful dye is available.

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References
Indeed, bilateral advanced visual field defects are important in the diagnosis of CBS. Impairment may have been due to visual field Snellen acuity of all four patients was the criterion for diagnosis. Further, although the population is possibly attributable to the children following profound visual loss. This documented in cases of acquired deafness.


Charles Bonnet syndrome and brimonidine: comments We read, with interest the article published in the BJO by Tomskä et al. Interest in the Charles-Bonnet syndrome (CBS) has escalated late, highlighting the probable 15% incidence of the condition in patients with significant visual impairment coupled with a clear sensorium. The authors implied that CBS was induced in four patients by brimonidine tartrate on the basis of patient age and the instigation of brimonidine therapy, with discontinuation resulting in eventual resolution of the hallucinations. Firstly, the diagnostic criteria proposed by Gold and Rabins and Podell et al. quite rightly made no reference to age being indicated in CBS, although incidence certainly increases with age. Schwartz and Vahigel found that CBS also occurred in children following profound visual loss. This suggests that the high incidence in the elderly population is possibly attributable to the increased incidence of acquired visual loss occurring with age; therefore, age is not a criterion for diagnosis. Further, although the Snellen acuity of all four patients was reasonably good in at least one eye of each patient, it may be surmised that severe visual impairment may have been due to visual field loss secondary to glaucomatous damage. Although this is not clear from the article, the cause of visual impairment and bilateral sensory deprivation is important in the diagnosis of CBS. Indeed, bilateral advanced visual field defects induced by glaucoma and homonymous hemianopia have resulted in CBS. A prevailing theory suggests sensory visual deprivation as an integral causative factor in CBS. Interestingly, and supportive of this theory, musical pseudohallucinations have been documented in cases of acquired deafness. Sensory deprivation in the presence of a clear sensorium will be necessary bilaterally to induce CBS, although no lower limit of Snellen visual acuity has been defined as a level for which CBS symptoms are stimulated. In the article case 4 seems to have sufficiently adequate visual function in the right eye to justify a definite misdiagnosis of CBS.

Secondly, as mentioned by the authors, brimonidine-agonists have been shown to cause systemic and neuropsychiatric phenomena. As with the discontinuation of any medication, the procedure is simpler than the resultant shortened duration of action. The authors have to be commented for the excellent description of this novel technique.

The efficacy of various methods of corticosteroid injection has always been a matter of debate with different studies giving different results. McCarty et al. showed that the major route of penetration of steroids after subconjunctival injection was directly through the sclera, choroid and retina. In addition, the authors described methods to inject steroids in the sub-Tenon’s space, a similar route of injection of steroids has not become popular in diabetic macular oedema in contrast with the increased popularity of intravitreal steroid injections. Interestingly, Freeman et al. have postulated that the loss of therapeutic response to sub-Tenon’s corticosteroids may be because of placement at a site relatively far from the target zone. They determined the location of repository corticosteroid after sub-Tenon’s injection by echography and showed that the steroid was deposited within the sub-Tenon’s space over the macula in only 11 of 24 cases. They hence concluded that the therapeutic response manifested by improvement in macular function may be related to the proximity of the corticosteroid to the macular area. The impressive efficacy reported in the study by Okada et al. could probably be the result of reliable drug placement thanks to the visual confirmation of paraxial mode into the sub-Tenon’s space, as the authors speculate. However, it is important to note that most of the patients in the study continued to receive topical steroid drops. Whether these drops had an additive effect is unclear. It would probably be worthwhile to consider a planned, primary intravitreal injection of corticosteroids under trephine control that has the distinct advantage of getting distributed into a much larger volume for selected conditions. There would be no cases of “therapeutic failures” that are seen after injection of steroids into the sub-Tenon’s space, and the resultant confusion as to whether the unsatisfactory response is secondary to the disease process or failure to inject the steroid into the sub-Tenon’s space or the debated lower efficacy of this route of injection. The procedure is simpler than the described trans-Tenon’s retrobulbar injection (no special cannula is required), but the risk of endophthalmitis is daunting.

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www.bjophthalmol.com

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Transcaruncular approach for the management of frontoethmoidal mucoceles: a comment

We read the article by Lai et al with interest. The authors report a modification of the non-oblitrative external procedure that was first described by Lynch in 1921.1 The Lynch-Howarth procedure2 involved transnasal stenting to prevent medial-ward collapse of the orbit obstructing drainage from the frontal sinus into the nose. Although the transcaruncular procedure uses a different external approach, it nevertheless often involves removal of part of the lamina papyracea for access to the sinuses. Hence, as with the Lynch approach, prolapse of orbital contents into the defect may occur, increasing the risk of re-stenosis. In addition, the cells in the frontal recess are not formally cleared and thus drainage into the nasal cavity is not assured. Stenting of sinus openings results in a significant fibrotic reaction in a proportion of patients, and closure of such a previously stented opening is likely. Furthermore, the follow up period in this study is too short to confirm the success or failure of this technique as recurrence often takes years to manifest.3

Endoscopic management of mucoceles protruding into the other sinuses or nasal cavity has been an accepted treatment for years.4 Frontoethmoidal mucoceles are typical of such mucoceles where the bony wall surrounding the mucocele is thin and therefore easily accessible transnasally. The endoscopic procedure creates a large area clear of cells which allows the greatest possible marsupialisation of the mucocele. No stenting is required. Har-El4 reported the largest series of 108 mucoceles with a median follow up of 4.7 years with a recurrence rate of only 0.9%. Therefore, we would recommend an endoscopic approach for frontoethmoidal mucoceles as the integrity of the lamina papyracea is maintained and the largest possible opening is created into the mucocele, which in turn minimises the chances of recurrence.

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2 Lynch RC. The technique of a radical frontal sinus operation which has given me the best results. Laryngoscope 1921;31:1–5.

Cataract surgery

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

Elimination of avoidable blindness

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

XVth Meeting of the International Neuro-Ophthalmology Society

The XVth Meeting of the International Neuro-Ophthalmology Society will take place 18–22 July 2004, in Geneva, Switzerland. Further details: Prof. A Safran, University Hospital Geneva, c/o SYMPORG SA, Geneva (fax: +4122 839 8484; email: info@symorg.ch; website: www.symorg.ch).

4th International Congress on Autoimmunity

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

XVI International Congress for Eye Research