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 (proteinuria 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 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 dia- lysis, in the elderly and those on nephrotoxic drugs. While the patient’s renal impairment was only moderate with serum creatinine at 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—especially, 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 hypovolaemia with an intracellular volume expansion as well as metabolic acidosis. Three 250 mg doses of acetazolamide in healthy men are associated with a significant 1.7 litres reduction in body water, compartmentalised as a significant reduction in extracellular water and increase in intracellular water. In this patient such a diuresis would have been significant enough when occurring over a few days to produce enough loss of body water to precipitate dehydration and lactic acidosis despite her drinking large volumes of fluids. Physiological stress of this nature is a well known stimulus that can precipitate a diabetic crisis in a susceptible patient, the massive rise in blood glucose largely accounting for the high osmolality in the patient. Hyperglycaemic hyperosmolar non-ketotic syndrome (HONK) does occur, although less commonly than ketoacidosis in insulin dependent diabetics. This makes plausible 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/l and a blood glucose level >33 mmol/l, without excessive ketones, and

| Table 1 Biochemistry on admission |
|----------------|----------------|----------------|----------------|----------------|----------------|
| Serum glucose | Serum Na⁺ | Serum K⁺ | Serum urea | Serum creatinine | Urine ketones* | Serum osmolality† |
| Normal range | 55 mmol/l | 3–6 mmol/l | 135 mmol/l | 3.5–5.0 mmol/l | 0 | 357 mOsm/l/kg |

*Normally no ketones are detected on stick testing of urine.
†(Na⁺+K⁺)+urea/glucose, using serum concentrations; dangerous if outside 240–330 mOsm/l/kg.
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. 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. Alternatively, 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. This suggests that the observations made on this case are certainly of much broader significance and raise an issue of concern about the drug’s prescription in both diabetes and renal failure. While manufacturer’s recommendations for acetazolamide in Britain include contraindications to its use in supraprenal 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 diabetes 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 clinical ophthalmology is methazolamide. The latter is associated with a less profound reduction in intracocular pressure, but also less acidosis. 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 electronic medicines compendia state that acetazolamide is contraindicated in marked kidney and liver dysfunction, supraprenal gland failure, and hyperchloraeic acidosis. The British National Formulary is less specific and states that it is contraindicated in renal impairment. We would suggest that diabetic patients with a creatinine level of 140 mmol/l are at quite high risk of nephrotoxic drug reactions, though caution should be exercised in even mild renal impairment.

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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 reference range | 23 mmol/l | ≤23 mmol/l | metabolic acidosis, >3 mmol/l | metabolic alkalosis, <3 mmol/l | mild metabolic acidosis, severe metabolic alkalosis, or mixed metabolic disturbance. |

| Life threatening at and beyond 7.2 and 7.6. |

The art of retinal detachment surgery: a photoessay

Subjective visual experience has been described previously in patients undergoing intraocular surgery, and may occur during either topical anaesthesia or regional anaesthesia (peribulbar, retrobulbar, subtenon). 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 and range from perception of light, photopsia, colours, and movement, 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, 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 1 (A) “Now we are going to shine a very bright 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.

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References


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 known and both diseases are characterised by aggregated proteins exhibiting excessive glycation and racemisation of aspartyl residues. Several AD...
related proteins—amyloid precursor protein (APP), β amyloid (Aβ), and presenilin (PS)—are expressed in the lens and 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 e2, e3, and e4). The different APOE alleles have been studied in relation to several human age-related diseases: inheritance of the e4 allele is a strong risk factor for AD and influences Aβ metabolism. The purpose of this study was to investigate the APOE e2/e3/e4 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 47–93 years) and 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 47–93 years) and 348 (69.3%) were women.

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>e2</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>e3</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>e4</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).

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>e2/e2</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>e2/e3</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>e2/e4</td>
<td>0.021</td>
<td>0.039</td>
<td>0.015</td>
<td>0.038</td>
<td>0.084</td>
<td>0.024</td>
</tr>
<tr>
<td>e3/e4</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>e4/e4</td>
<td>0.017</td>
<td>0.015</td>
<td>0.014</td>
<td>0.168</td>
<td>0.166</td>
<td>0.173</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.
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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 sebaceous 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 carcinoma and pagetoid spread.

Case report

A 78 year old man was referred to the oculoplastics 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 tarso-conjunctival distortion (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 tarsal conjunctival 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 lamella was achieved using a hard palate graft and the anterior lamella was repaired by a myocutaneous flap with post auricular skin graft and a bilobed flap medially.

Intraepithelial invasion in sebaceous gland carcinoma is noted to occur in 41–80% of cases. Diagnosis may be delayed as the presenting symptoms are often benign and non-specific such as blepharoconjunctivitis. Diagnosis requires biopsy of the abnormal area and conjunctival map biopsies in the presence of intraepithelial invasion. Various treatments have been used for pagetoid invasion including surgical excision with cryotherapy, external beam radiotherapy, and orbital exenteration. Eyes with pagetoid invasion are more likely to undergo exenteration.

In our case the suspicion of malignancy was raised because of the unilaterality of the clinical features. Our patient underwent extensive excision of the tumour with tumour free conjunctival biopsies. Mitomycin C as adjuvant treatment was commenced as a result of the difficulty in clinically assessing for recurrence with page-
toid invasion. Mitomycin C was associated with moderate epithelial toxicity which was self limiting.

Mitomycin C is a non-cell cycle specific alkylating agent which acts to inhibit cell proliferation, and is used successfully in the treatment of corneal intraepithelial neoplasia. This is only the second reported article where mitomycin C has been used in the

Figure 1 Upper lid tarso-conjunctival scarring.

Figure 2 Conjunctival biopsy demonstrating intraepithelial invasion of malignant cells.
treatment of sebaceous gland carcinoma. In the pilot study by Shields et al. 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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 conjunctiva by eyelid sebaceous gland
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 treatment for conjunctival–corneal intraepithelial

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. Early detection and treatment result in a better prognosis with retardation of progression. 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 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 questionnaire consisted of two identical sets of six direct questions using a 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 acceptable. Twenty eight (42%) subjects preferred HRT II to GDx, whereas five (7%) preferred GDx to HRT II (p = 0.009).

Comment

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 = 0.0039). 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).

Table 1 Demographic and diagnostic data

<table>
<thead>
<tr>
<th>Demographic features (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Age (years) Mean 57.1, SD 14.3 range 18–85</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Primary open angle glaucoma</td>
</tr>
<tr>
<td>Glaucoma suspect</td>
</tr>
<tr>
<td>Ocular hypertension</td>
</tr>
<tr>
<td>Non-glaucomatous optic neuropathy</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>No diagnosis given</td>
</tr>
</tbody>
</table>

There were eight patients (12%) who found GDx more comfortable than HRT II. The HRT II has an internal fixation target. Patients found the GDx difficult to focus on. In contrast, the HRT II target, which a greater proportion of subjects found 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.

Table 2 Patient responses

<table>
<thead>
<tr>
<th>Question</th>
<th>HRT</th>
<th>p Value (McNemar’s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the test comfortable? (n = 65)</td>
<td>HRT</td>
<td>0.0003</td>
</tr>
<tr>
<td>GDx</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2. Was the light too bright? (n = 58)</td>
<td>HRT</td>
<td>0.3877</td>
</tr>
<tr>
<td>GDx</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3. Was the chin rest uncomfortable? (n = 65)</td>
<td>HRT</td>
<td>0.0522</td>
</tr>
<tr>
<td>GDx</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4. Was the test too long? (n = 65)</td>
<td>HRT</td>
<td>0.0039</td>
</tr>
<tr>
<td>GDx</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5. Did you have trouble keeping your eye still? (n = 65)</td>
<td>HRT</td>
<td>0.0009</td>
</tr>
<tr>
<td>GDx</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

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Although the HRT II was found to be a more comfortable test, a higher proportion found the HRT II chintest 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 in instrument design. It is hoped that manufacturers take into account these factors in the design of the next generation of glaucoma imaging devices.

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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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.

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 nystagmus. 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.

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 subjected to sequenced using an ABI Prism 3100 genetic analyser (Applied Biosystems, Foster City, CA, USA). To confirm the sequence of mutations, the Snaphot 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 nystagmus (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 glutamate 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...
patients' relatives indicates that they do not have the same mutation. (D) Direct sequencing of PAX6 PCR product from the patient with Peters’ anomaly revealed a heterozygous mutation in the alternative splicing region in the patient. The typical clinical presentation with a serious congenital eye disease such as Peters’ anomaly or foveal hypoplasia. Two independent and interactive DNA-binding subdomains of the PAX6 paired domain are regulated by alternative splicing. Genes Dev 1994;8:2022–34.

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

Tuberculosis remains a major cause of morbidity and mortality 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. The ocular manifestations of tuberculosis are diverse, and depend on the immunological, bacteriological, and epidemiological variables. Individuals with compromised immune status usually present with atypical presentations. 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 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 cultures were 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 antituberculous 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 antituberculous 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.
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 posterior half of the corneal stroma (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. 3,4 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, choriorretinitis, and panophthalmitis. 5 Hypopyon may rarely noted in tuberculosis. Ni et al presented cases of intracocular tuberculous with turbid, haemorrhagic, greyish yellow exudate in the anterior chamber in one case, and fibrinous hypopyon in three other cases. 6 Hypopyon may appear in rifabutin treated patients who had Mycobacterium avium complex infection. 7 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 extraocular focus. The presence of large numbers of acid fast bacteria 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.

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Spontaneous stabilisation of symptomatic schisis detachments

Acquired retinoschisis affects 7% of people aged 70–40 years and is bilateral in 85%. 1,2 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-schitic retina or open breaks in the inner leaf of a schisis may allow fluid vitreous to be recruited into the cyst and then 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% of symptomatic cases). 3

Hypopyon is rarely associated with symptomatic retinal 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. Funduscopic 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 viscous nature of the suprachoroidal and subretinal fluids, each of which was symptomatic.

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Figure 2. (A) Haematoxylin and eosin stain reveals necrosis of iris and inflammatory exudates in the anterior chamber. (B) The anterior chamber exudate displays several melanophages and necrotic cells (haematoxylin and eosin). (C) Ziehl-Nielsen’s stain shows a myriad of acid fast bacilli in the deep corneal stroma and in the anterior chamber exudates.
November 2001, and October 2002 respectively.

Comment
Most outer leaf breaks develop well within the confines of a retinoschisis, and cyst fluid separates the RPE and outer leaf only in the immediate vicinity of the breaks. However, the giant outer leaf breaks responsible for the schisis detachments in our patient were each located at the posterior limit of a large retinal cyst. It is unsurprising, therefore, that the detachments progressed beyond the retinoschisis and were symptomatic. This is the first report of symptomatic schisis detachments that settled without surgery. We agree with Byer that the appropriate management for non-progressive schisis detachments is “to do nothing,” and believe this policy can be extended to symptomatic, inferior schisis detachments that do not involve the fovea. Surgical intervention, including retinopexy around the breaks, might well have induced sight threatening complications in our patient while offering no real prospect of a better outcome or prognosis.

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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. 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. Furthermore trypan blue (in low concentrations) stains the anterior lens capsule. 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. 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, we believe it is a positive development that an alternative clinically useful dye is available.

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References
Charles Bonnet syndrome and brimonidine: comments

We read, with interest the article published in the BJO by Tomsk et al.1 Interest in the Charles-Bonnet syndrome (CBS) has escalated of late, highlighting the probable 15% incidence of the condition in patients with significant impairment, with a clear sensorium.2

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 Rabins3 and Podell et al.4 quite rightly made no reference to age being a significant indicator of CBS, although incidence certainly increases with age. Schwartz and Vahghi1 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 bilaterality are 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.5 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 definitive misdiagnosis of CBS.

Secondly, as mentioned by the authors, norepinephrine agonists have been shown to cause systemic and neuropsychiatric phenomena.6 As with the discontinuation of any medication, the expectation would be resolution of induced symptoms and as such we believe the hallucinations may easily be explained as a side effect of the medication. Brimonidine is a known lipophilic compound able to penetrate the blood-brain barrier. Through the accompanying package insert, notable side effects such as depression and dizziness are well known. There is, therefore, little doubt that in the aged population in whom pharmacokinetics is often unpredictable, the likelihood of greater systemic absorption and pharmacokinetics is often unpredictable, the likelihood of greater systemic absorption and distribution may well lead to neuropsychiatric phenomena. Consequently, we believe that CBS was not the cause of the complex visual hallucinations experienced by these patients but may be attributed to a rarer side effect of brimonidine, which should now be included in the patient information leaflet.

References

Periorcular corticosteroid therapy: comments

I read with great interest the article by Okada et al.,4 reporting the efficacy and complications of trans-Tenon’s retrobulbar injection of triamcinolone acetonide for posterior uveitic inflammation. The authors have to be commended 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. McCartney et al.5 showed that the major route of penetration of steroids after subconjunctival injection was directly through the Tenon’s space, choroid, and retina. In addition, the authors described methods to inject steroids in the sub-Tenon’s space and concluded that the injections should be placed immediately adjacent to the site of intraocular inflammation that was under treatment. In contrast, in a study on rabbit eyes, Wilson et al.6 have elegantly demonstrated that injection of corticosteroids by the sub-Tenon’s route does not show a significant effect on the blood-retinal barrier owing to inadequate penetration. The authors analysed the severity of blood-retinal barrier breakdown following panretinal photocoagulation, using rapid sequential magnetic resonance imaging with contrast. Of note, in this study the authors have taken particular care to ensure the accurate placement of the needle in the sub-Tenon’s space. A similar result was obtained in a study Jennings et al.7 on the efficacy of posterior sub-Tenon’s injection of triamcinolone acetonide in patients with macular oedema caused by uveitis. The authors found that the injection of steroids by the sub-Tenon’s route did not consistently affect the blood-retinal barrier permeability in such patients and that there was more leakage of the steroids into the eye in therapeutically meaningful concentrations. This is of particular concern since it is the breakdown in the blood-retinal barrier that leads to influx of serum serum components leading to macular oedema, epiretinal membrane, and other sequelae.

Sub-Tenon’s injections when compared to intravitreal injections have the disadvantage of probably a decreased and difficult drug penetration through the sclera and choroid and a rapid removal of the drug by the choroidal circulation after penetration with the resultant shortened duration of action. This is probably the reason why the sub-Tenon’s 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.8 have postulated that the lack 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.4 could probably be the result of reliable drug placement thanks to the visual confirmation of cannula entry into the sub-Tenon’s space, as the authors speculate. However, it is important to note that most of the patients in this 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 microscope 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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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-oblitative external procedure that was first described by Lynch in 1921. The Lynch-Howarth procedure involved transnasal stenting to prevent medial-wall 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.

Endoscopic management of mucoceles protruding into the other sinuses or nasal cavity has been an accepted treatment for years. 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-El 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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