

LETTERS

Bilateral naevus of Ota with choroidal melanoma and diffuse retinal pigmentation in a dark skinned person

Naevus of Ota (naevus fuscocoeruleus ophthalmomaxillaris) was described by the Japanese dermatologist, Ota, in 1939 as a dermal melanocytic hamartoma that presents as bluish hyperpigmentation along the ophthalmic, maxillary, and mandibular branches of the trigeminal nerve. It is bilateral in less than 5% cases, occurring frequently in Orientals (0.2%–1%) and darker races and rarely in white people (0.04%). Open angle glaucomas and choroidal melanoma are the rare ocular involvements. Ota's naevus is more common in Asians than white people but uveal melanoma occurs predominantly in white populations.^{1,2} Dark skinned patients represent only 1% of all cases of orbital melanomas.³ The risk of developing uveal melanoma in a patient with naevus of Ota is one in 400 patients in their lifetime.^{1,2} We report a rare case of bilateral naevus of Ota with a right (RE) choroidal melanoma and left (LE) diffuse pigmentation of retina.

Case report

A 73 year old Anglo-Indian woman was referred with complaints of photopsia. She had black hair and light brown skin. Examination revealed a brownish-black pigmentation of the conjunctiva, episclera, and periocular skin bilaterally (fig 1). Visual acuity for distance and near was 6/6 and N5, respectively, in each eye. Heterochromia was present, the right iris being a darker brown than the left, which had a sector of light brown colour. Gonioscopy and intra-ocular pressure were normal. The right fundus revealed a pigmented, large, elevated choroidal mass 10 disc diameter (DD) in size, 4 DD superonasal to the disc. Drusen were overlying it. No subretinal fluid was seen. The left eye showed a patchy dark pigmentation 3 DD in size, at the temporal edge of the macula. A ridge-like pigmented elevation, 3 DD long, was also seen along the superonasal vessels. Both optic discs and maculas were normal. Ultrasound in the right eye showed a 10 mm tumour, 4.2 mm high. Fluorescein angiography confirmed its independent circulation. A systemic examination found no signs of metastasis. A diagnosis of a



Figure 1 Oculodermal pigmentation.



Figure 2 Choroidal melanoma.

bilateral naevus of Ota with low grade, choroidal melanoma in the right eye (fig 2) and retinal pigmentation in the left eye was made. The patient was reluctant to accept the option of enucleation in view of the right vision. A ¹²⁵I radioactive plaque was applied (COMS study). A follow up examination 3 years postoperatively showed a flatter, yellow 4 DD×1.5 DD scarred tumour with mottled pigmentation. The left melanosis remained unchanged. The vision was 6/6 in both eyes 6 years after ¹²⁵I treatment and cataract surgery.

Comment

Ota's naevus is commonly seen unilaterally (90%). Bilateral involvement is rare. It represents melanocytes that have not migrated completely from the neural crest to the epidermis during the embryonic stage. Orientals and pigmented races have a high prevalence with a predilection for women (1:4.8). Variable prevalence among different populations suggests genetic influences, although familial cases are rare. Two peak ages of onset in early infancy (50%) and in early adolescence suggest hormonal influence.¹ In addition to the skin, pigmentation may involve oral mucosa, tympanic membrane, intranasal mucosa, leptomeninges and ocular structures such as the sclera, retrobulbar fat, cornea, lens, trabeculum, disc, and retina. Associated malignant melanomas of the uvea, orbit, skin, and CNS have been described.² Choroidal melanomas are known to occur in less than 4% of cases and glaucoma has been noticed in less than 10% of cases.⁴

Our case reports a rare occurrence of bilateral naevus of Ota with choroidal malignant melanoma in the right eye and retinal pigmentation in the left eye in a pigmented person. She was born to Anglo-Indian parents but did not know how far back in time the intermarriage had occurred. Ophthalmological follow up care is necessary for patients with increased melanosis. This

case illustrates the need for regular ophthalmic review of all pigmented lesions and the recognition that patients with naevus of Ota may also have the additional complication of melanoma. There is need for close observation of all pigmented lesions of the eye. Regardless of the patient's race, there is a greater than normal chance that a patient with the naevus of Ota might have a malignant melanoma develop within one of the affected tissues.

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Treatment of neurotrophic keratopathy with nasal dilator strips

Neurotrophic keratopathy, characterised by poorly healing corneal epithelium, occurs in eyes with decreased corneal sensory innervation. Clinical findings include chronic epithelial defects and corneal ulceration. Numerous conditions predispose to neurotrophic keratopathy including diabetes mellitus, accidental and surgical trauma, herpes simplex and herpes zoster keratitis, leprosy, and topical anaesthetic abuse.

Management of neurotrophic keratopathy includes ocular lubrication, pressure patching, autologous serum eye drops,¹ fitting of a bandage contact lens,² amniotic membrane grafting,^{3,4} and surgical tarsorrhaphy. Surgical tarsorrhaphy can be very successful in resolving neurotrophic corneal ulceration,⁵ but many patients find this option cosmetically unacceptable.

We describe a novel method of non-surgical tarsorrhaphy using over the counter adhesive, non-medicated, nasal dilator strips (NDS) (Breathe Right Nasal Strips, Whippany, NJ, USA) applied vertically across the eyelids (fig 1). The adhesive strip consists of parallel bands of plastic imbedded in a pad, and is available in different sizes.

The nasal strips were originally developed to treat patients with snoring problems,⁶ or to improve nasal congestion.⁷ In rhinological applications, the strip is typically used



Figure 1 Applying a nasal dilator strip vertically over the eyelid creates an easily reversible tarsorrhaphy. It also provides an effective and, for patients, cosmetically acceptable way to treat chronic corneal neurotrophic disorders.

horizontally across the nose in order to open the nasal airway. In the current study, we applied the strip vertically over the closed eyelid as shown in figure 1. The adhesive strip creates a firm and effective eyelid closure, and patients can control the application and removal of the strip. The strips have the advantage of being relatively inexpensive, reusable, and reversible, and their use has replaced standard eye patching in our clinical practice. We have noted success with the use of these strips for the management of neurotrophic ulceration and describe two representative cases.

Case reports

A 60 year old woman developed a neurotrophic corneal ulcer following a complicated retinal detachment repair. After a year of standard medical therapies, including lubrication and frequent conventional patching, she continued to have a 4 mm×4 mm chronic non-healing epithelial defect. Treatment with reversible NDS tarsorrhaphy was initiated with instructions to apply the strips at bedtime and as much as possible during the day. Nine weeks later the corneal epithelial defect had healed completely. Over the next year she gradually decreased the wearing time of the strips and is currently stable without their use.

A 48 year old woman with a 6 mm×2 mm neurotrophic corneal ulcer was referred for management after failing numerous medical and surgical therapies including lubrication, autologous serum eye drops, patching, and an amniotic membrane graft. The patient was instructed to use NDS tarsorrhaphy according to the schedule described in the previous case. Within 2 weeks the corneal epithelial defect healed completely. The patient continues to apply the tarsorrhaphy but with decreasing frequency.

The novel use of nasal dilator strips to perform a temporary tarsorrhaphy has aided us greatly in our management of neurotrophic corneal ulceration. We believe it is an attractive, cost effective, efficient alternative to patching for any ocular condition. In addition, nasal strip tarsorrhaphy allows for immediate reversibility that facilitates patient acceptance.

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Confocal microscopy of the cornea in nephropathic cystinosis

Cystinosis is an autosomal recessive inherited disorder of amino acid metabolism characterised by the deposition of cystine crystals in the eye, kidney, reticuloendothelial system, and various other tissues.¹ Childhood or nephropathic cystinosis can present as an infantile or a juvenile variant.¹ The infantile variant tends to have a more devastating course and is associated with growth retardation, rickets, and eventual renal failure which requires transplantation within the first decade.¹ The juvenile variant has later onset and milder nephropathy.¹

In nephropathic cystinosis, crystal deposits usually appear in the peripheral, anterior cornea within the first year of life and progress centrally and posteriorly until the entire cornea is involved.^{2–7} The diagnosis can be confirmed histopathologically by demonstration of characteristic crystals by electron microscopy in a conjunctival biopsy.^{8,9} Stromal deposition of crystal deposits has been demonstrated by confocal microscopy.⁹ We provide the first demonstration, to the best of our knowledge, of cystine crystals in the corneal epithelium using *in vivo* confocal microscopy.

Case report

A 9 year old boy presented to the King Khaled Eye Specialist Hospital in Riyadh, Saudi Arabia, with a complaint of recurrent foreign body sensation, associated with severe photophobia and blepharospasm. He had been diagnosed with infantile nephropathic cystinosis at age of 9 months and had been treated with systemic cysteamine. On examination, the visual acuity was 20/20 in the right eye and 20/25 in the left eye. The



Figure 1 Crystal deposits in the right eye predominantly involving the anterior and mid-stroma, with limbus to limbus distribution.

intraocular pressure was 12 mm Hg in both eyes. Slit lamp examination showed crystal deposits of 2.5 in Gahl density score⁷ in both corneas, predominantly involving the anterior stroma and with limbus to limbus distribution (fig 1). Dilated fundus examination was normal with no maculopathy or peripheral retinal pigment abnormalities. Topical treatment with cysteamine 0.5% drops resulted in symptomatic relief.

Confocal microscopy (Confoscan 3, Nidek Technologies, Vigonza, Italy) demonstrated crystalline deposits in the corneal epithelium (fig 2A, B) and stroma (fig 2C, D). Crystal deposits in the corneal epithelium were needle shaped and fusiform shaped and oriented parallel to the plane of the epithelial cells (fig 2A, B). In the basal cell layer, the crystals were associated with dendritic cells (fig 2B). The highest crystal density was in the mid-stroma, where fusiform shaped crystals were more predominant than needle shaped crystals (fig 2C). The lowest crystal density was in the posterior stroma, where most of the deposits were needle shaped (fig 2E). Within the stroma the crystals were oriented parallel to the plane of the stromal lamella. The needle shaped crystals were highly variable in length with some as long as 100 µm. The endothelial cell layer was normal.

Comment

The current case clearly documents that crystalline deposits may be found in the epithelium of patients with nephropathic cystinosis, unlike previous electron microscopic⁸ and confocal microscopic⁹ studies that suggest these deposits are localised to the stroma. In addition, we found maximum crystal density in the mid-stroma and minimum density in the posterior stroma, in contrast with a previous report in which maximum crystal density was just anterior to Descemet's membrane.⁹

We hypothesise the presence of these abnormal deposits in the corneal epithelium may contribute, in part, to the foreign body sensation and photophobia that is invariably associated with this disorder, as well as the predisposition to recurrent epithelial erosions. Chronic low grade inflammation of the epithelium and epithelial basement membrane zone associated with recurrent epithelial erosions is the probable explanation for the presence of dendritic cells in the basal epithelium of the central cornea.¹⁰ Successful reduction in the density of corneal crystals and symptomatic relief was obtained with the use of topical cysteamine 0.5% drops, as in previous reports.^{5–7}



Figure 2 Crystal deposits in the corneal epithelium and stroma. A mixture of needle shaped and fusiform shaped crystals are present in (A) the superficial epithelial cell layer and (B) the wing cell layer. (C) Dendritic cells are present in the basal cell layer. (D) The greatest density of crystals is in the mid-stroma, where fusiform shaped crystals are the predominant morphology. (E) The least density of crystals is in the posterior stroma, where needle shaped crystals are the predominant morphology.

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Total parenteral nutrition, vitamin E, and reversible macular dysfunction morphologically mimicking age related macular degeneration

A variety of nutrient deficiencies may predispose to the development of age related macular degeneration (AMD).¹ Patients

receiving parenteral nutrition (TPN) may be at particular risk of early onset AMD, because of inadequate or excess nutritional supplementation.¹ Studies including the Eye Disease Case-Control Study and Beaver Dam Eye Study have evaluated the relation between antioxidant and micronutrient levels, and the risk of AMD.^{2–4} A protective effect of high plasma vitamin E levels was convincingly demonstrated.⁵

We describe a patient treated with parenteral fluid support who developed visual symptoms and signs of AMD, in conjunction with longstanding vitamin E deficiency. Isolated cases of visual disturbance in patients undergoing TPN have been reported in the literature^{6,7}; however, to our knowledge, no case of visual disturbance attributed to vitamin E deficiency has been reported in this context.

Case report

A 57 year old man received parenteral fluid five times a week at home because of short bowel syndrome secondary to Crohn's disease. It was thought he had undergone bowel adaptation to meet macronutrient and micronutrient needs in the 13 years since his surgery. He presented with subacute visual disturbance. He described altered colour perception in situations analogous to macular stress testing (moving from dark adapted situations to bright lights) and enlarging central scotomata. Visual acuity was 6/6 in the right eye, 6/12 in the left. Visual fields, intraocular pressures, and neurological examination were normal. Funduscopy revealed macular soft drusen, and extensive subretinal basal laminar deposits in the macular region, more marked in the right than left eye (fig 1). Electroretinogram was normal.

The patient was receiving electrolyte support 6 days a week at time of presentation. Measured haematological parameters and

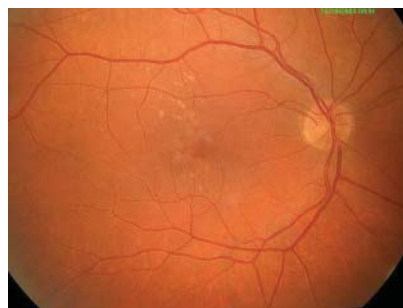


Figure 1 Macular soft drusenosis, characterised by subretinal basal laminar deposits in the macular region.

urea and electrolyte levels revealed a low haemoglobin level (11.0 g/dl), and a mild degree of macrocytosis (102.3 fl). Because hypervitaminosis and/or deficiency in trace minerals were suspected, serum values of vitamins A, E, B1, B2, B6, plasma zinc, copper, selenium, manganese, caeruloplasmin, and red cell GSH activity were measured. Results revealed vitamin E deficiency (12 µmol/l, normal range: 14–39 µmol/l). A retrospective survey of previous serum vitamin E levels suggested longstanding deficiency, with levels of 10 µmol/l, and 13 µmol/l, 6 months and 1 year respectively, before onset of symptoms. Treatment with vitamin supplementation lead to complete resolution of symptoms in 3 weeks. Vitamin E levels returned to normal; however, fundal appearances remained unchanged.

Comment

The presence of bilateral hard and soft drusen and pigmentary abnormalities in the macula are the clinical hallmarks of AMD.⁸ The early onset of morphological changes at Bruch's membrane/retinal pigment epithelium (RPE) interface may relate to vitamin or micronutrient deficiency, associated with parenteral nutrition.⁷

Cumulative oxidative damage may have an important role in the pathogenesis of AMD, since accumulation of lipofuscin pigments may arise as a consequence of antioxidant deficiency, or under pro-oxidant conditions.⁵ Evidence exists for an association between atrophic AMD and excessive lipofuscin accumulation.^{8,9} Compromised RPE in this context is believed to be due to the amphiphilic structure and photoreactivity of the di-retinal conjugate A2E, the major constituent of lipofuscin.⁹ Antioxidant vitamins have been shown to aid in the defence against AMD.⁵ Vitamins E and C suppress A2E epoxidation, suggesting one mechanism by which these vitamins may protect the ageing macula.⁹

Vitamin E deficiency was present consistently over the 12 month period preceding symptom onset, reinforcing the likelihood that the clinical presentation had been caused by vitamin E deficiency. Vitamin E deficiency results in retinal degeneration, excessive RPE lipofuscin, and decrease in the polyunsaturated fatty acid content of rod outer segments and the RPE.⁵ Furthermore, vitamin E deficiency may cause mild macrocytic anaemia and accumulation of ceroid lipofuscin in nerves, affecting function of central and peripheral nervous systems.⁶ Patients with sufficient gut length for protein calorie nutrition receiving parenteral fluids may run the risk of micronutrient deficiency despite a normal diet, and may present to the ophthalmology department. We recommend formal micronutrient screening in patients with extensive small bowel resection.

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Spontaneous involution of autologous lenses and phacoanaphylaxis reaction in Stickler syndrome

Stickler syndrome is a "hereditary progressive arthro-ophthalmopathy"¹ caused in the majority of cases by mutations of the *COL2A1* gene encoding for type II collagen.² The disease is transmitted as an autosomal dominant trait with high penetrance but variable expressivity.³ Most common ocular manifestations of the disease are myopia, vitreous veils and degeneration, early cataract, retinal peripheral breaks and retinal detachment.^{3,4}

Case report

This patient had typical ocular and extraocular clinical manifestations of Stickler syndrome. She was fitted with contact lenses (-17.00 dioptres) at the age of 1 month. Despite the relatively poor vision, hearing

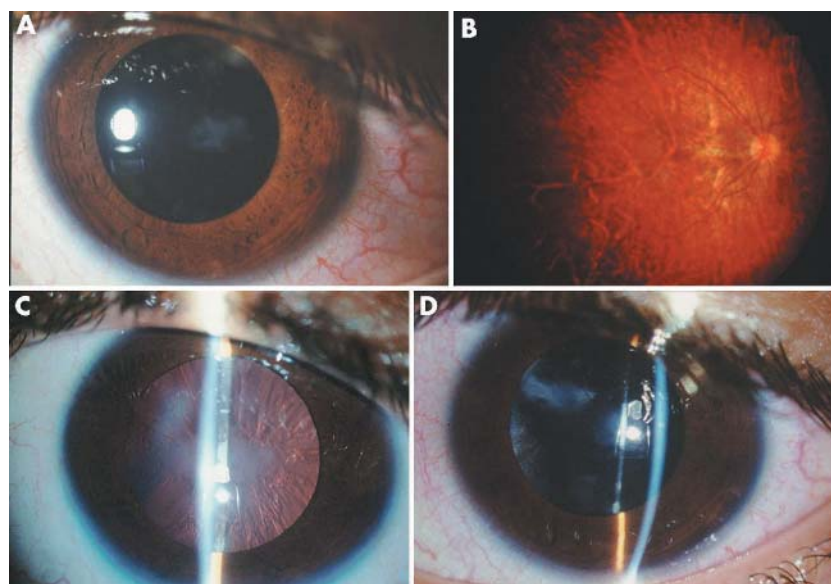


Figure 1 (A) Mild opacity of the lens posterior capsule of the right eye initially observed at the age of 7 years. (B) Appearance of the fundus demonstrating the retinal pigmentary changes in the periphery and retinal degenerative changes within the posterior pole. (C) Marked opacification and fusion of the lens capsules in the right eye observed at 9 years of age. (D) Mild capsule opacities are still observed 2 years later, at 11 years of age. The refractive error at this stage is +1.25 and the visual acuity for distance is 6/12 (20/40).

impairment and skeletal problems, she developed well mentally and attended regular school. With glasses (-15.00) the visual acuity (VA) was stable, around 6/21 (20/75) for distance and J2 for near in both eyes.

A mild central opacity of the posterior lens capsule was initially observed in both eyes

when she was 7 years old (fig 1A). The IOP was 12 mmHg, the corneas clear, anterior chambers deep and devoid of any inflammatory signs. Fundus examination disclosed no changes from previous examinations (fig 1B). Refraction and VA in both eyes remained unchanged.

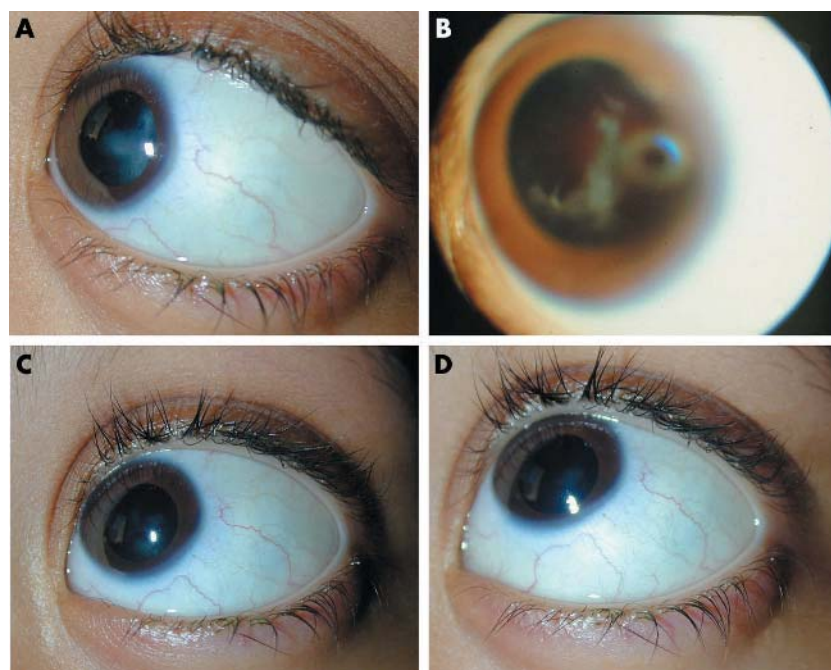


Figure 2 (A) Large cortical remnants are seen within the capsular bag remnant in the left eye with an intense flare and many inflammatory cells. The cornea is still mildly hazy 2 weeks after the phacoanaphylactic reaction. (B) The vitreous of the left eye is hazy with many cortical lens remnants observed with transillumination at the slit lamp. (C) Right eye is quiet, the refractive error is +1.25, and the uncorrected visual acuity 6/12 (20/40) despite the presence of mild lens capsule opacities. (D) Left eye is also quiet showing the same characteristics as the right eye.

On 23 June 2002, at the age of 9 years, she complained of blurred vision in the right eye. Without glasses, VA for distance was 6/60 (20/200) and for near less than J16. Involvement of the lens material with marked opacity of the fused capsules was detected (fig 1C). Accurate retinoscopy was not possible. No intraocular inflammatory signs were observed.

On 23 May 2004, the right eye lens opacities reabsorbed. Mild posterior capsule opacity remains (fig 1D). VA without correction was 6/12 (20/40) and J10. Refraction disclosed +1.25 D. The left eye VA and myopia remained unchanged.

Six weeks later sudden pain, redness, and loss of vision in the left eye occurred. A high IOP of 60 mm Hg, hazy cornea, mutton fat keratic precipitates with flare 3+ and cells 4+ were observed in the left eye anterior chamber. She was treated with corticosteroids and antiglaucoma drops. Two weeks later, a central tear of the posterior capsule with large cortical remnants within the capsular bag (fig 2A) and a multitude of floating lens remnants with a granulomatous inflammatory reaction were observed in the vitreous (fig 2B). Following complete arrest of the inflammatory processes and a return to normal of the IOP, medical treatment was discontinued 5 weeks after its initiation.

At her last visit on 21 November 2004, both eyes were quiet. Only mild scattered lens capsule opacities were detected in both eyes (figs 2C and 2D). The VA without correction was 6/12 (20/40) and J10 in both eyes. With correction (+1.25) for distance and near addition (+3.00), the VA in both eyes was 6/9 (20/30) and J1 respectively. Multifocal glasses were prescribed.

Comment

A quiet and uneventful involution of the autologous lens occurred in the right eye when the child was 9 years old. The mechanism of this phenomenon is unclear and may be associated with abnormalities of the lens collagen and/or crystallines. The lens involution in the right eye was not associated with any noticeable symptom but for a drop in vision. Progressive clearing of the lens opacity was followed by emmetropisation of the initial refractive error and visual improvement in the left eye. Two years later, spontaneous involution of the lens in the other eye was associated with a marked intraocular granulomatous inflammatory reaction ("granulomatous uveitis") reminiscent of a phacoanaphylaxis reaction. This acute reaction was, most probably, associated with the "escape" of immune tolerance towards the autologous lens antigens.

We are not aware of previous reports in the literature describing similar ocular phenomena.

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Temporal pterygium: benign or not?

A true pterygium is a degenerative and hyperplastic process in which the cornea is invaded by a triangular fold of bulbar conjunctiva. Duke-Elder states that the pterygium when single is almost invariably found on the nasal side.¹ The literature on pterygium is abundant and almost from the beginning the emphasis has been placed on its location on the nasal side.

Squamous cell neoplasia of the conjunctiva is relatively uncommon and can masquerade as common, but less significant, ocular surface conditions including pterygium or chronic blepharoconjunctivitis. We present a case of intraepithelial neoplasia, initially diagnosed as inflamed pterygium.

Case report

A 77 year old man, who had worked on the railways, presented with a 3 week history of redness on the outer aspect of the left eye. No history of associated pain, discharge, or watering was elicited.

His medical history included hypertension and hypercholesterolaemia under treatment.

Best corrected visual acuity in each eye was 6/5. On inspection of the anterior segment, the left temporal conjunctiva showed a fleshy tissue encroaching on the temporal peripheral cornea (fig 1). The peripheral cornea showed an elevated ridge with punctate staining. The overlying conjunctiva was injected. The rest of the ocular examination was within normal limits.

A provisional diagnosis of inflamed pterygium of left eye was made and the patient was commenced on prednisolone 0.5% eye drops at this stage with advice to review in 2 weeks' time.

On follow up no significant change was noticed in the lesion. On further inquiry the patient gave a history of injury to left eye with hot ashes many years earlier. In view of

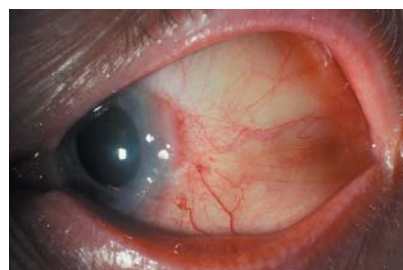


Figure 1 Left eye showing presence of a soft tissue lesion on the temporal conjunctiva encroaching on the limbus before local excision and radiotherapy.

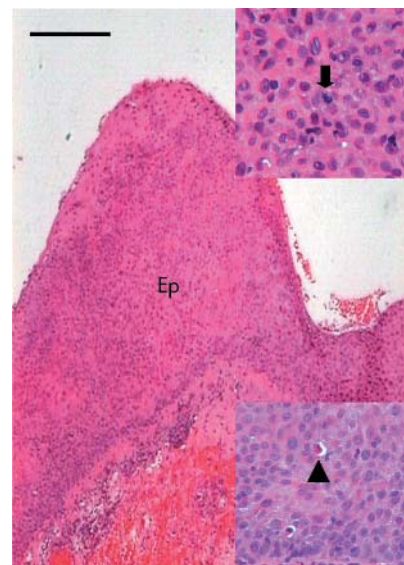


Figure 2 Section through the conjunctiva stained with haematoxylin and eosin. The main figure demonstrates grossly and irregularly thickened, dysplastic epithelium (Ep; scale bar, 100 μ m). The inserts show an atypical mitosis (above, arrow) and dyskeratosis (below, arrowhead) within the epithelium.

the atypical location and the appearance of the lesion, we did an excision biopsy of the conjunctival and corneal lesion. Histopathology revealed an irregular epithelial thickening associated with dyskeratosis and full thickness dysplasia. Numerous mitotic figures, some atypical, were present throughout the epithelium (fig 2). A diagnosis of conjunctival intraepithelial neoplasia was made. Although no unequivocal evidence of invasion was seen in the multiple sections examined, fragmentation of the tissue during processing precluded confirmation of complete excision.

The patient was referred for further treatment to an ocular oncologist and underwent ruthenium plaque therapy followed by topical 5-fluorouracil treatment.

Comment

Temporal pterygium is reported, although Dolezalova found only one case of unilateral temporal pterygium out of 1388 Arab patients with pterygia.² We would therefore consider this case to be atypical.

The role of pterygium in the development of ocular surface squamous neoplasia is unclear.³ Both conditions have a strong association with exposure to ultraviolet-B radiation. Sevel and Sealy's study of 12 squamous cell carcinoma and 17 carcinoma in situ arising in 100 pterygia found that it can be difficult to distinguish a "reactive pterygium" from carcinoma in situ and malignant change should be considered in a pterygium if there is unusual evidence of invasion, extension, or if the lesion becomes particularly vascular.⁴

To our knowledge, the last reported case of temporal pterygium was in the 1970s.^{2,5} We present this case to refresh the memory and to highlight the importance of keeping an index of suspicion for squamous cell neoplasia in any atypical presentation of the more

common conjunctival lesions such as pterygium.

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Simultaneous intraosseous and intradural capillary haemangioma of orbit

Primary intraosseous haemangioma is an uncommon tumour of bone which tends to involve the vertebrae and skull.^{1,2} Bony orbital lesions are rare with very few case reports in the literature.^{1,3,4} Simultaneous intradural involvement has never been reported in association with an orbital component. We report an unusual case of capillary haemangioma of the orbital roof with periorbital and dural involvement.

Case report

A 39 year old white male was seen with a 1 year history of painless right upper eyelid swelling and reduced superior visual field. He had marked downward (3 mm), outward (2 mm), and axial (4 mm) displacement of the right globe (fig 1A), with limitation of elevation and 5 dioptres of hypotropia in upgaze. The remaining ocular and systemic evaluation were normal.

Contrast enhanced CT and gadolinium enhanced magnetic resonance imaging (MRI) (fig 1B) demonstrated a well circumscribed faintly calcified mass centred within the bony roof of the right orbit. It was homogeneously isointense to grey matter on T1WI, slightly hyperintense on T2WI, and demonstrated marked homogeneous contrast enhancement. Transosseous extension intraorbitally was noted, with displacement of the superior rectus muscle, optic nerve, and globe inferiorly without evidence of invasion or encasement. Transosseous extension of the mass intracranially was completely extra-axial in location, with involvement of the adjacent dura. Provisional diagnosis in the absence of a known primary tumour, was intraosseous meningioma.

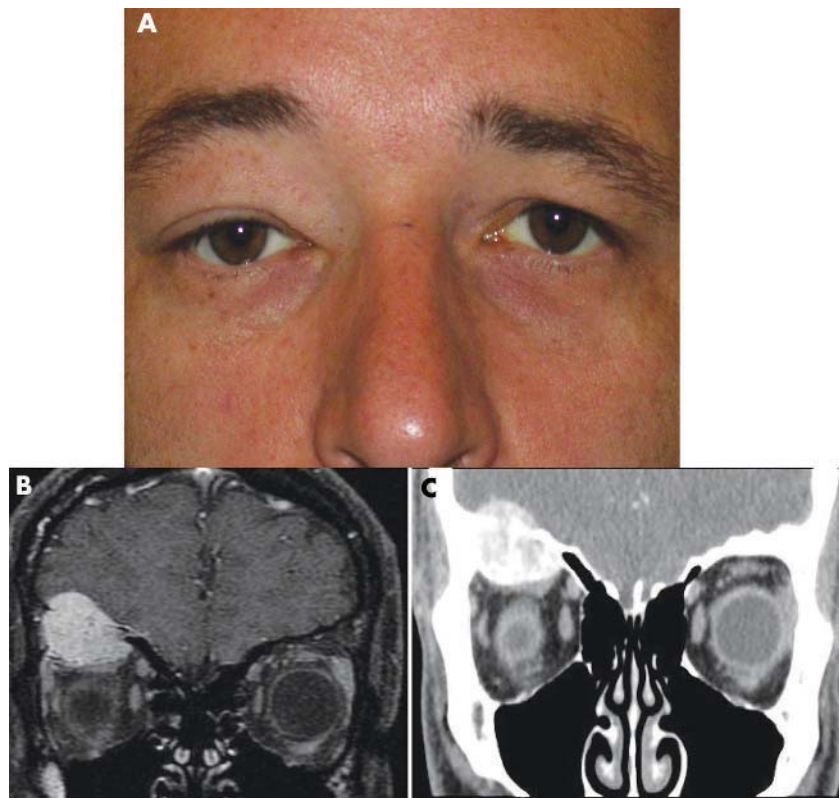


Figure 1 (A) A 39 year old patient showing proptosis and ptosis in the right eye. (B) Gadolinium enhanced coronal T1 fat saturated image through the orbits demonstrates an intraosseous mass in the right orbital roof, with intraorbital and intracranial extension. The intracranial portion was completely extra-axial, with associated dural involvement, as indicated by the thickened and enhancing dura adjacent to the dominant intracranial component. (C) Contrast enhanced coronal computed tomography (CT) image through the orbits demonstrates an intraosseous mass in the right orbital roof, with intraorbital and intracranial extension. Its heterogeneous appearance is the result, in part, of scattered calcifications throughout the mass. Mass effect upon the superior extraocular muscle group is evident.

The patient underwent right sided frontal craniotomy and orbital osteotomy with piecemeal gross total resection of the right orbital roof, the involved adjacent periorbita, dura and bone.

Grossly, pathological samples including dura (fig 2A) were soft and reddish-light tan coloured in appearance. Microscopic examination (fig 2B) revealed a cellular capillary haemangioma of bone, with periorbital and dural involvement (fig 2D), consisting of thin walled blood vessels with some osteoblastic activity and new bone formation. Tumour immunohistochemistry stains for CD34 (fig 2C), CD31, vimentin, and O13 were positive, confirming a vascular origin.

Comment

Intraosseous haemangiomas are benign tumours arising from the intrinsic blood vessels of bone and are two to three times more common in females than males.^{1,3,5} They are slow growing, accounting for only 0.7–1% of bone tumours, with the most common site being the vertebrae and skull (frontal and parietal).^{1,3,4} They are typically seen in the adult population, with a peak in the fourth decade, although any age can be affected.^{1,3–6} Haemangiomas are histopathologically classified as either cavernous (common in the skull and orbit) or capillary (found mainly in vertebrae).¹ The pathogenesis of these tumours is unknown.¹

The clinical presentation of orbital intraosseous haemangioma is usually a progressive asymptomatic mass which may lead to proptosis, diplopia, optic neuropathy, and ptosis. To date, the largest series³ contained 21 cases, of which four were of the capillary type.³ Though intracranial extension has been noted in the past, intradural lesion is reported only once with calvarial capillary haemangioma (sphenoid)⁹ but never with orbital invasion.

Plain films typically show bony erosion with scalloped bone giving a “sunburst” appearance.^{14,5} Cavernous and capillary haemangiomas usually have similar imaging findings with differentiation made on histopathological analysis.¹

The differential diagnosis for a localised lytic bone lesion with calcifications is wide, including primary bone tumours such as osteosarcoma, chondrosarcoma, meningioma, haemangioma, brown tumour, or infection. Reactive lesions, such as xanthoma of bone, aneurysmal bone cyst, and reparative granuloma are also in the differential. Careful radiological evaluation in combination with clinical history and findings usually allows for differentiation among these different lesions.

With respect to our case, the characteristic high signal intensity on T1 imaging usually seen in vertebral haemangiomas was absent, probably the result of a relatively low fat content.^{1,2}

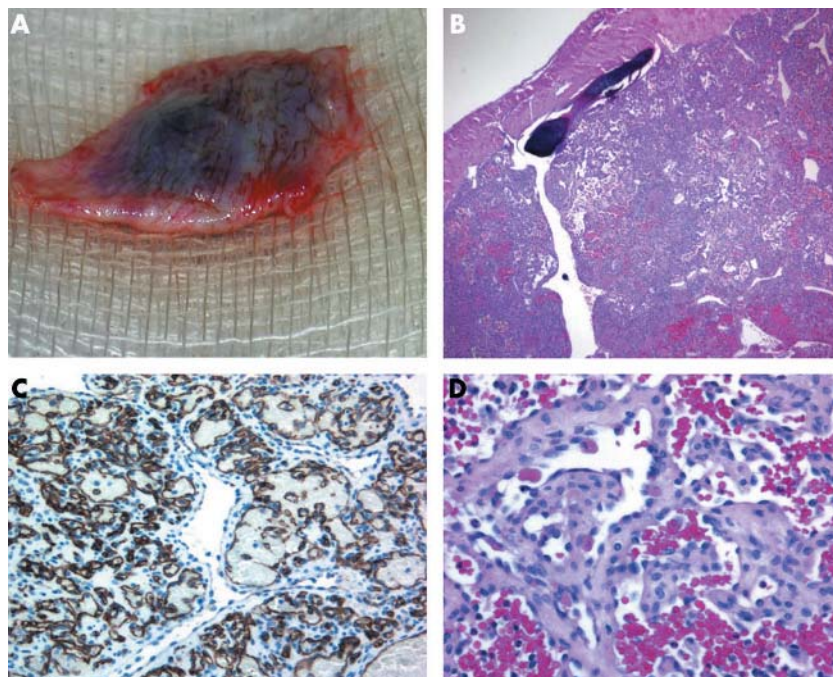


Figure 2 (A) Gross tumour mass showing involved resected dura. (B) HPE: 8x4 magnification showing thin walled blood vessels and osteoblastic activity of intraosseous cellular capillary haemangioma. (C) 6x40 magnification with CD 34 positivity confirming vascular origin. (D) 6x40 dural involvement by capillary haemangioma.

In our case, atypical dural enhancement on imaging was noted with associated erosion of overlying frontal bone.

Preferred treatment for symptomatic haemangiomas is surgical resection of the entire lesion, with preoperative embolisation.^{1-3,6} Radiation has been advocated for large and/or unresectable lesions.^{1,4,7}

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Two novel mutations of connexin genes in Chinese families with autosomal dominant congenital nuclear cataract

Congenital or childhood cataract is a clinically and genetically highly heterogeneous lens disorder, with autosomal dominant inheritance being most common. Non-syndromic congenital cataracts have an estimated frequency of 1-6 per 10000 live births,¹ with one third of cases familial. Underlying mutations have identified 14 genes involved in the pathogenesis of isolated inherited cataract, including seven genes coding for crystallins (CRYAA, CRYAB, CRYBA1/A3, CRYBB1, CRYBB2, CRYGC, CRYGD), two for gap junctional channel protein (GJA3 and GJA8), two for lens membrane protein (LIM2 and MIP), one for beaded filament structural protein 2 (BFSP2), and one for glucosaminyl (N-acetyl) transferase 2 (GCNT2), one for heat shock transcription factor (HSF4). Here we report two novel heterozygous mutations in the GJA8 and GJA3 genes, in two Chinese families affected by autosomal dominant congenital nuclear cataracts.

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Table 2 Two point LOD scores for linkage between the cataract locus and 13q markers in family B

Marker order	Map location	LOD scores at $\theta =$					
		0.0	0.1	0.2	0.3	0.4	0.5
D13S1316	0.00	-1.13	1.34	1.08	0.66	0.25	0.00
D13S1236	2.77	1.63	1.34	0.99	0.61	0.23	0.00
D13S175	6.03	1.04	0.88	0.66	0.40	0.16	0.00
D13S232	6.99	-5.25	-0.56	-0.15	0.01	0.05	0.00
D13S1243	9.79	-6.19	-0.76	-0.32	-0.12	-0.03	0.00

Pedigree and haplotype construction were undertaken using Cyrillic v.2.1 software (figs 1A and 2A).

Table 1 Two point LOD scores for linkage between the cataract locus and 1q markers in family A

Marker order	Map location	LOD scores at $\theta =$					
		0.00	0.10	0.20	0.30	0.40	0.50
D1S2651	142.24	-4.49	0.23	0.25	0.14	0.01	0.00
D1S2746	147.60	-4.39	0.53	0.60	0.46	0.22	0.00
D1S252	150.27	-3.90	0.40	0.25	0.10	0.02	0.00
D1S2344	153.59	1.44	1.29	1.03	0.70	0.32	0.00
D1S442	154.74	0.43	0.04	0.25	0.10	0.02	0.00
D1S498	155.89	2.40	1.95	1.46	0.94	0.42	0.00
D1S2346	158.75	1.20	0.93	0.65	0.36	0.11	0.00
D1S305	159.32	2.40	1.95	1.46	0.94	0.42	0.00
D1S1595	161.05	0.49	0.50	0.41	0.25	0.08	0.00
D1S2635	165.62	0.61	0.56	0.43	0.27	0.09	0.00
D1S1167	168.52	2.44	1.95	1.46	0.94	0.43	0.00
D1S2844	175.03	2.40	1.95	1.46	0.94	0.42	0.00
D1S2878	177.86	-4.75	0.09	0.23	0.22	0.14	0.00

Case report

We studied two Chinese three generation nuclear cataract families with a dominant pattern of inheritance. Clinical information and blood specimens were obtained from 16 members of family A (seven affected and nine unaffected), and 13 members of family B (nine affected and four unaffected). All participants had a full ocular assessment to document the phenotype. The phenotype of two families was characterised by bilateral nuclear cataract that was present at birth or developed during infancy. There was no evidence of other systemic or ocular defects.

After obtaining informed consent, we used a panel of 46 microsatellite markers to study 13 loci for known candidate genes of autosomal dominant congenital cataract susceptibility. The markers' order and position were obtained from the Marshfield Genetic Database (www.marshfield.org/genetics/maps). Genotyping and data collection were conducted by ABI Prism GeneMapper v 3.0 software. We carried out two point linkage analysis using the MLINK program from the Linkage v.5.10 software package. It suggested positive linkage on chromosome 1q21.1 (lod score was 2.44 for marker D1S1167) in family A and chromosome 13q11–12 (lod score was 1.63 for marker D13S1326) in family B (tables 1 and 2).

There are two strong candidate genes in these regions, GJA8 encoding connexin 50 (Cx50) and GJA3 encoding connexin 46 (Cx46). We screened the mutation of

candidate genes by bidirectional sequencing polymerase chain reaction products (300–700 bp). Sequence analysis of the entire coding region and immediate flanking regions detected a heterozygous 191 T → G (AF217524) transition in exon 2 of GJA8, resulting in a Val → Gly substitution at codon 64 (fig 1B). Sequence analysis of GJA3 detected a heterozygous 134 G → C (AF075290) transition, resulting in a Trp(TGG) → Ser(TCG) substitution at codon 45 (fig 2B). We examined all unaffected members of two families and 200 unrelated normal controls for GJA3 and GJA8 gene mutations but failed to detect these sequence variations.

Comment

Three connexins are expressed in the lens: connexin 43, connexin 46, and connexin 50. Gap junction intercellular communication is an essential part of the cell–cell communication system, which facilitates the exchange of ions, metabolites, signalling molecules, and other molecules with a molecular weight up to 1 kDa.²

Each gap junction channel is composed of two hemi-channels, or connexons, which dock in the extracellular space between adjacent cells, and each connexon comprised six integral transmembrane protein subunits known as connexins. All connexins have four transmembrane domains and two extracellular loops with cytoplasmic N and C termini.

To date, four heterozygous missense Cx50 mutations (P88S, E48K, R23T, and I247M) have been described, causing a nuclear or zonular nuclear pulverulent cataract.^{3–6} Six mutations of Cx46 have been associated with ADCC, including five missense mutations (F32L, P59L, N63S, P187L, and N188T) and one insertion mutation (1137 insC), which resulted in a frame shift at codon 380 (S380fs).^{7–12}

Currently, two mutations occurred: Cx50 (G22R and D47A) results in cataracts in the mouse,^{13,14} but no dominant spontaneous or mutagen induced cataracts have been associated with the murine gene for GJA3 (Gja3).

V64G and W45S substitutions in two Chinese families occurred within evolutionarily conserved residues across species for Cx50 and Cx46 (figs 1E and 2E). These two mutant amino acid residue locate at the phylogenetically conserved extracellular loop 1 (E1). The two extracellular loops mediate docking between connexons and the E1 loop has also been shown to be important for determinant of the transjunctional voltage required for closure of gap junction pores.¹⁵ The mutant proteins may disrupt normal interactions between the two connexons, which may reduce resistance of the intercellular channel to the leakage of small ions.

In conclusion, two novel heterozygous mutations, V64G in Cx50 and W45S in Cx46, were identified in two Chinese families. These further expand the genetic and phenotypic heterogeneity of cataract.

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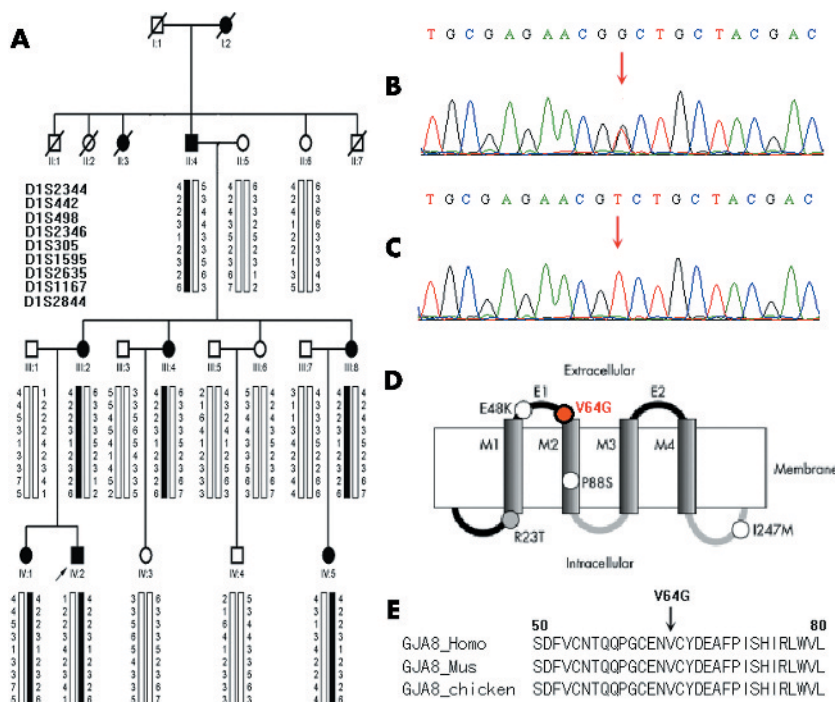


Figure 1 (A) Pedigree and haplotype analysis of family A showing segregating nine microsatellite markers on chromosome 1, listed in descending order from the centromere. Squares and circles symbolise males and females, respectively. Solid and open symbols denote affected and unaffected individuals, respectively. IV:2 is the proband. (B) Sequence chromatograms showing the heterozygous 191 T → G transition that converts a Val residue (GTC) to a Gly residue (GGC) at codon 64. (C) Sequence chromatograms of wild type allele. (D) Schematic diagram of the predicted Cx50 polypeptide and location of V64G and known mutations. M1–M4, transmembrane domains 1–4; E1 and E2, extracellular domains 1 and 2, respectively. (E) Cx50 multiple protein sequence alignment in different species. Reference sequence numbers of protein are human (NP_005258), mouse (NP_032149), and chicken (NP_990328). The arrow directed the mutant amino acid residue.

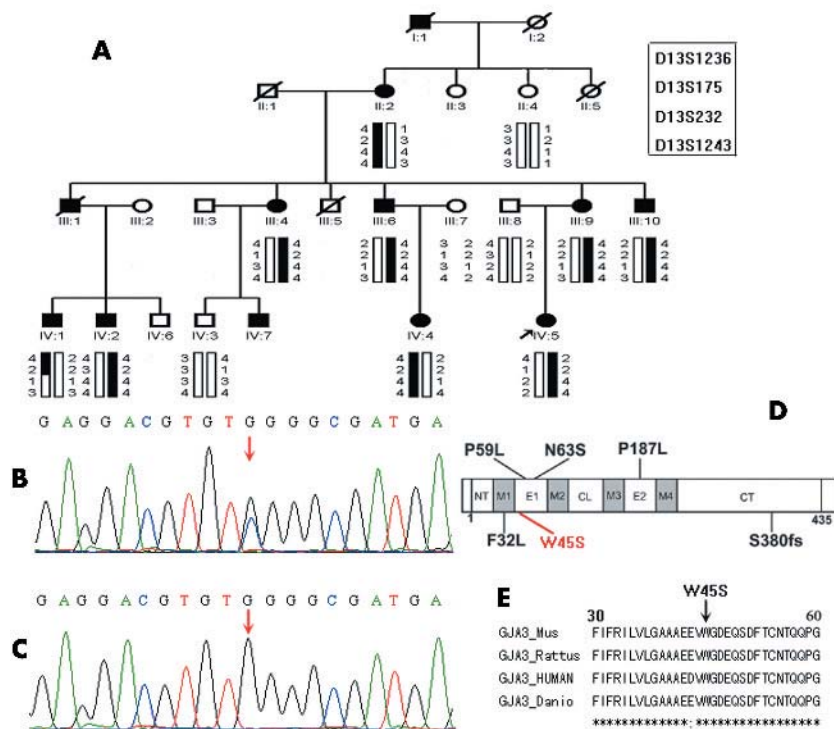


Figure 2 (A) Pedigree and haplotype analysis of family B showing segregation of four microsatellite markers on chromosome 13q. Squares and circles symbolise males and females, respectively. Solid and open symbols denote affected and unaffected individuals, respectively. IV:5 is the proband. (B) Sequence chromatograms showing the heterozygous 134 G → C transition resulting in a Trp(TGG) → Ser (TCG) substitution at codon 45. (C) Sequence chromatograms of wild type allele. (D) Exon organisation and mutation profile of GJA3. Cx46 has nine structural domains including a cytoplasmic amino-terminus (NT), four transmembrane domains (M1–M4), two extracellular loops (E1–E2), a cytoplasmic loop (CL), and a cytoplasmic carboxy-terminus (CT). The relative locations of the W45S mutation and other mutations associated with dominant cataracts in humans are indicated. (E) Cx50 multiple protein sequence alignment in different species. Reference sequence numbers of protein are human (NP_068773), mouse (NP_058671), rat (*Rattus norvegicus*) (NP_077352), and zebrafish (*Donio rerio*) (NP_997525). The arrow directed the mutant amino acid residue.

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Pneumosinus dilatans in a 13 year old female

Pneumosinus dilatans (PSD) is abnormal dilatation of paranasal sinuses that may occasionally present with visual symptoms. We present a case of PSD associated with sickle cell trait which occurred with visual deterioration.

Case report

A 13 year old female presented with gradual painless decrease of vision in both eyes for 1.5 years. Over this period her visual acuity dropped from 20/30 (RE) and 20/160 (LE) to hand motion in both eyes. Except for optic atrophy in both eyes, other ocular examinations were normal. In the visual field there was diffuse peripheral field loss and generalised depression. Past medical history was insignificant except for an appendectomy 5 years earlier.

An increased level of sickle cell haemoglobin which constituted 24.9% of her total haemoglobin was documented. Her HbA₂ and HbF were in the normal range. She had anaemia with haemoglobin level of 9 g/dl, which we could not find any reason for.

Significant expansion of paranasal sinuses including maxillary, frontal, ethmoidal, and sphenoid sinus was visible on magnetic resonance images (MRI) of the patient as shown in figure 1. Based on the MRI of the patient, the diagnosis of PSD would be appropriate.

Bilateral consecutive frontal craniotomy was performed in order to unroof the optic canal with the hope to release stretching of the optic nerve which we thought was the reason for her visual deterioration. Figure 1 (bottom) is an image of the surgical procedure. It is clear that the optic nerves have been entrapped in the bony canal and probably suffered from severe stretching and/or compressive effects. Six months after the procedure her visual acuity was 20/1200 in both eyes.

Comment

Pneumosinus dilatans is an abnormal dilatation of one or more of the paranasal sinuses. It has diverse manifestations including progressive visual loss if the sphenoid sinus is involved and/or if it is associated with optic nerve meningioma. If the ethmoidal sinus is involved it may present with proptosis.¹ Although a valve mechanism raising the pressure inside the sinus is thought to be responsible for this condition,² the exact etiology is unknown.³ In case of optic nerve damage the nerve is usually compressed in long bony tubes.⁴ Pneumosinus dilatans has been associated with meningioma of the intracranial optic nerve and anterior chiasmal angle,⁵ middle cranial fossa arachnoid cyst,⁷ cerebral hemiatrophy, and prolonged cerebrospinal fluid shunting.⁸

To our knowledge this is the first case of PSD associated with sickle cell trait. PSD has not been associated previously with haematological disorders. Considering the fact that sickle cell trait is generally an asymptomatic condition and the patient’s mother was also an asymptomatic carrier, an aetiological relation is unproved. On the other hand, both conditions are rare in our population, therefore the probability of coincidence by chance would seem to be extremely low. The question remains whether our patient had an unusual form of sickle cell trait associated with gross bony involvement and deformity.

Different treatments have been proposed for PSD. These include subtotal resection of the medial wall of the maxillary sinus by an endoscopic approach,⁹ osteotomy of the deformed fronto-orbital bossing, and obliteration of the sinus with fat.¹⁰ Because of global and massive expansion of the sinuses and severe optic nerve dysfunction in this case, we preferred to decompress the optic nerve by removing the roof of bony canal which surrounded the intracranial optic nerve. This resulted in mild visual improvement.

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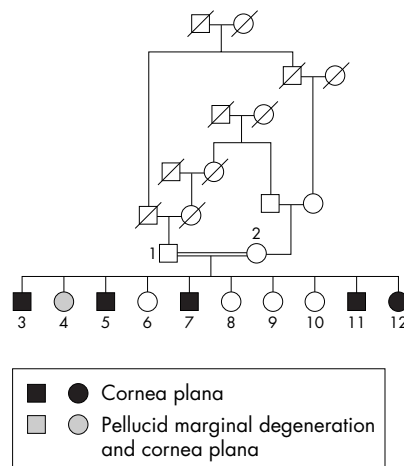
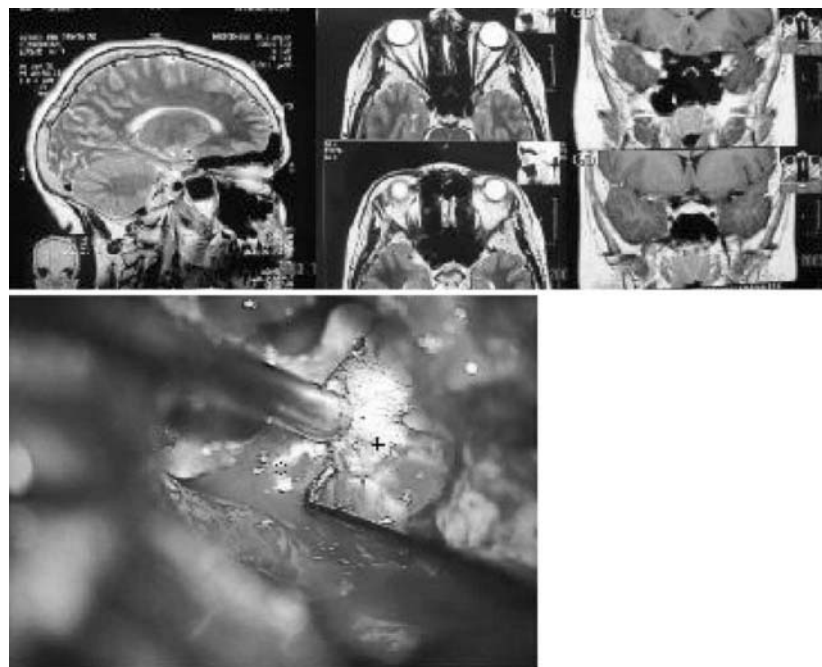


Figure 1 The family pedigree.

the rule" astigmatism, and absence of opacity.⁴ We report a case of superior PMD coexistent with cornea plana in a family exhibiting a novel *KERA* mutation and document the ophthalmic findings of the family.

Figure 1 (Top) Magnetic resonance images show significant dilatation of paranasal sinuses. (Bottom) Surgical field image. "O" is intracranial part of optic nerve, "+" is the bony canal after partial removal; the metal instrument is a suction device tip.

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Pellucid marginal degeneration coexistent with cornea plana in one member of a family exhibiting a novel *KERA* mutation

Characterised by flattening of the normally convex corneal surface, small corneas, high hyperopia, and arcus senilis, autosomal recessive cornea plana is secondary to *KERA* mutation.¹⁻³ *KERA* encodes keratocan, an

evolutionary conserved small leucine rich proteoglycan. Keratocan, highly and uniquely expressed in the cornea, is composed of core proteins consisting mostly of leucine rich repeats (LRRs).¹⁻³ All patients documented to be homozygous for one of the four previously reported *KERA* mutations have disruption of LRR architecture and demonstrate similar cornea plana phenotypes.¹⁻³ In contrast, corneal pellucid marginal degeneration (PMD) is an idiopathic progressive ectatic corneal disorder that is clinically diagnosed by characteristic thinning, resultant "against

Case series

Twelve individuals from a Saudi nuclear family were studied after institutional review board approval and family informed consent had been obtained from the family. Clinical findings and diagnoses are summarised in figures 1 and 2, and table 1. Only one family member (patient 4) had a history of progressive visual difficulty over the last several years, and this was due to an increasing astigmatic refractive error. Axial lengths and keratometry readings were recorded using the Zeiss IOL-Master (2001 model), and corneal topography was performed using the Bausch & Lomb Orbiscan 2Z (2002 model).

All family members underwent *KERA* DNA sequencing using methods previously described.³ A novel mutation was detected

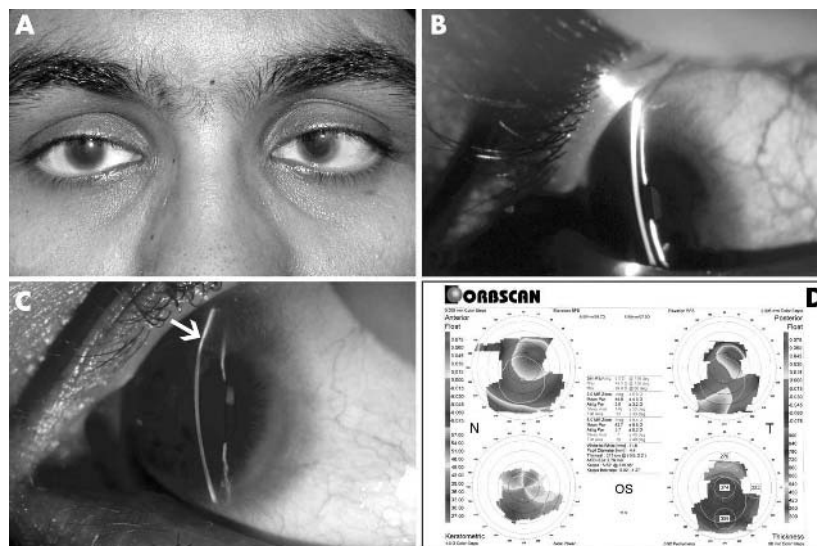


Figure 2 (A) The small flat corneas of a typical patient (No 3) are shown. (B) The slit lamp appearance of patient 3 is shown. (C) In addition to small flat corneas and early arcus senilis, patient 4 also demonstrated superior corneal thinning (arrow, LE) with associated corneal ectasia characteristic of superior pellucid marginal corneal degeneration. (D) Topography, LE of patient 4 shows the characteristic high astigmatism of superior pellucid marginal corneal degeneration.

Table 1 Pertinent biometric and clinical characteristics of the family are summarised

	1	2	3	4	5	6	7	8	9	10	11	12
Age (years)	50	43	26	24	23	19	18	17	12	10	8	6
Keratometry RE	43.32, 43.95@102	40.61, 41.06@017	26.49, 28.60@060	45.79, 52.73@085	29.74, 32.23@138	42.51, 42.78@076	28.77, 30.21@086	43.10, 43.49@077	41.01, 41.98@093	39.52, 40.37@087	23.94, 26.81@035	31.72, 33.19@180
Keratometry LE	43.44, 44.23@101	40.96, 41.98@082	26.66, 30.13@104	38.66, 47.14@149	29.76, 31.78@065	42.51, 42.94@105	29.27, 33.28@090	42.72, 43.66@093	41.11, 42.51@092	39.61, 40.27@087	24.83, 27.42@117	32.02, 33.48@158
Horizontal corneal diameter (RE, LE in mm)	10, 10	11, 11	8, 8	8, 8	8, 8	10, 10	8, 8	10, 10	11, 11	11, 11	8, 8	8, 8
Axial length (RE, LE in mm)	22.89, 22.34	23.81, 23.78	21.55, 21.62	25.17, 24.88	21.97, 22.05	23.43, 23.68	22.91, 23.65	23.19, 22.98	24.13, 24.05	24.11, 24.22	24.13, 23.88	22.18, 22.61
Cycloplegic refraction, vision with refraction RE	+0.50, 20/30	plano, 20/20	+8.50, 20/60	plano-10.00 x110, 20/60	+9.50-3.00x030, 20/30	-1.25, 20/25	+10.00-1.00x080, 20/30	-0.75, 20/20	-0.50, 20/20	-0.25, 20/20	+8.50-2.50x107, 20/40	+8.00, 2/30
Cycloplegic refraction, vision with refraction LE	+2.00, 20/60	-0.50, 20/20	+1.00-9.00x060, 20/50	plano-10.00 x070, 20/50	+11.00-2.50x140, 20/60	-1.50, 20/25	+9.00-1.00x180, 20/50	-0.50, 20/20	-0.50, 20/20	plano, 20/20	+9.00, 20/125	+8.00, 12/30
Comments	Amblyopia LE, anterior chamber shallow both eyes, peripheral stromal haze both eyes	Prominent arcus senilis both eyes, otherwise normal ophthalmic exam	Amblyopia LE, 16 prism dioptres esotropia at near with correction	Pellucid marginal degeneration both eyes, small cornea both eyes, arcus senilis both eyes	Amblyopia LE>RE, 20 prism dioptres esotropia at near with correction	Normal ophthalmic exam with deep anterior chamber both eyes	Amblyopia LE Normal ophthalmic exam with deep anterior chamber both eyes	Normal ophthalmic exam with deep anterior chamber both eyes	Normal ophthalmic exam with deep anterior chamber both eyes	Normal ophthalmic exam with deep anterior chamber both eyes	Amblyopia LE>RE, 40 prism dioptres V-pattern esotropia at near with correction, iris defect RE	Amblyopia RE>LE, poor cooperation

in exon 2, [1454 C>T, ENST00000266719], changing an arginine amino acid at position 279 to a stop codon [R279X]. The resultant truncated protein lacks the terminal 73 amino acids of normal keratocan. This mutation was homozygous in the five siblings with clinically evident cornea plana (Nos 3, 5, 7, 11, 12) and the sister with clinical findings of PMD and cornea plana (No 4). All other family members (Nos 1, 2, 6, 8, 9, 10) were heterozygous for the mutation and clinically unaffected.

Comment

All four previously reported *KERA* mutations disrupt keratocan LRR architecture and are associated with similar corneal phenotypes in documented homozygotes.¹⁻³ The current mutation [R279X] similarly disrupts LLR function, as the prematurely truncated protein lacks two LRRs of normal keratocan and is associated with the expected cornea plana phenotype. Interestingly, one homozygous individual (No 4) demonstrates corneal findings compatible with both superior PMD (corneal thinning with astigmatism) and autosomal recessive cornea plana (small corneas, arcus senilis)—the presence of arcus senilis excludes classic PMD alone by definition.^{4,5} It is unlikely that the *KERA* mutation itself is responsible for the PMD findings in this individual. The sectorial thinning and progressive high astigmatism characteristic of superior PMD have not been reported in individuals documented to be homozygous for *KERA* mutation or in other pedigrees consistent with autosomal recessive cornea plana.^{1-3,6} The PMD findings of patient 4 are most likely the result of coincidence—that is, the occurrence of both cornea plana and PMD in the same individual. However, a defect in a poorly understood mechanism other than *KERA* itself that is responsible for normal keratocan function cannot be completely excluded as an explanation for these findings.⁷

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Alteration of cyclic frequency by botulinum toxin injection in adult onset cyclic esotropia

Cyclic strabismus is an uncommon disorder in which strabismus comes and goes alternately, consistently, and repetitively over a period of time. In a 48 hour cycle, a 24 hour period of orthotropia would be followed by a 24 hour period of constant strabismus. Cycles of 24 hour¹ to 96 hour² patterns have been reported. Most cases have been described in children, and the aetiology of cyclic strabismus is still speculative.

Case report

A 57 year old woman was referred to Kaohsiung Medical University Hospital with the complaint of a periodic visual fluctuation of a “good day” and a “bad day” alternately for about 6 months. She had diplopia on bad days. She did not have diabetes or hypertension. There was no history of strabismus, amblyopia, patching therapy, ocular trauma, or oculomotor palsy. She had received trials of Mestinon treatment by two neurologists. Except for pterygium excision 4 years earlier, other ocular and medical history were unremarkable. There was no family history of strabismus.

Her visual acuity was 20/25 with +1.25 lens RE and 20/20 LE plano. Cycloplegic refraction was +1.25 RE and +0.50 LE. The anterior segments were normal except for recurrent pterygia on the nasal limbus in both eyes.



Figure 1 (A) “Good day”—orthotropia; (B) “Bad day”—esotropia.

Ophthalmoscopic examination, ocular alignment (fig 1A), and ocular motility were normal. Since the initial examination was on her “good day,” she was asked to come back the next day—that is, on the “bad day.”

The next day, there was a 25 prism dioptre, committant right esotropia (fig 1B) with full ocular motility. The visual acuity was unchanged. Brain and orbit magnetic resonance imaging studies were unremarkable except for a suspected small arachnoid cyst on the right side of the falx.

She received 2.5 U botulinum toxin (Botox) injection in her right medial rectus muscle (MR). The alignment was orthotropia 1 week after the injection. She was asymptomatic for about 2 months, but the cyclic pattern returned with a 96 hour cycle by patient history. A repeated 2.5 U Botox injection in right MR, which was given 3 months after the first, produced another asymptomatic period of 2 months. Two months after the second injection, she experienced constant strabismus without cyclic pattern, which persisted for about 1 year. She received right MR recession by 4 mm and right lateral rectus muscle resection by 5 mm for constant esotropia of 25 prism dioptres. After the surgery, the alignment was orthotropic and no recurrent of the cyclic pattern during 1 month of follow up. The stereopsis was 200 seconds of arc by Titmus test.

Comment

Adult onset cyclic strabismus is rare,^{2–8} and, to the best of our knowledge, only 10 patients have been reported. The reported cases of adult onset cyclic strabismus are summarised in table 1. The patients had various ages of onset between 21 and 67 years. Most reported cases demonstrated 48 hour cyclic patterns. The persistence of the cycles, if not interrupted by surgery, was as long as 7 years.⁸ It is interesting that adult onset cyclic strabismus occurs predominantly in females and is frequently related to ocular or orbital diseases, trauma, or surgery.^{4–8}

Botox injection has been used as treatment of cyclic strabismus.⁷ However, no change of the cyclic pattern was mentioned. We noted that the cyclic pattern in our patient changed 3 months after the first Botox injection, and the cycles were eliminated 2 months after the second injection.

The characteristics of cyclic strabismus in children are an average age of onset between 3 and 4 years, moderate hyperopia, and moderate angle.³ However, a female preponderance was not noted in childhood onset cyclic esotropia. No pertinent explanation for cyclic strabismus has been reported. Although Botox only has a temporary effect, both Botox injection⁷ and eye muscle surgery³ produce good ocular alignment results. More evidence and further investigation are required to elucidate the mystery.

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Table 1 Summary of the adult onset cyclic strabismus

Case No	Age of onset (years)	Sex	Cyclic pattern	Duration of cycles	Angle (Δ)	Related diseases or coexistent conditions	Outcome	References
1	34	Male	4 days	3 years	ET 35	Optic atrophy both eyes, alcohol abuse	No treatment	Frenkel ²
2	32	Female*	2 days	NA	ET 35	NA	No treatment, CPP?	Helveston ³
3	53	Female	2 days	NA	XT 15, RHT 30	Graves' disease	OT after muscle surgery	Knapp ⁴
4	55	Female	2 days	NA	RHT 25	Graves' disease	OT after muscle surgery	Knapp ⁴
5	67	Female	2 days	5 years	ET 25, RHT 8	RD RE, 360° encircling scleral buckling procedure RE, cyclic mydriasis and ptosis	No treatment, CPP	Troost ⁵
6	34	Female	2 days	9 weeks	LHT 20, XT 10	Craniofacial surgery for fronto-orbital fibrous dysplasia, left side	OT after muscle surgery	Metz ⁶
7	46	Female	2 days	1 year	ET 12 to 45	ECCE RE, high myopia RE	Botulinum toxin injection, ET 2 Δ with cycle eliminated after muscle surgery	Riordan-Eva ⁷
8	21	Female	5 days?	2 years	ET 25	RD RE, vitreolensotomy and silicone oil exchange RE	Botulinum toxin injection, CPP	Riordan-Eva ⁷
9	49	Female	2 days	7 years	RHT 15, ET 25	ECCE RE, RD and PVR RE, PVT and scleral buckling RE, ECCE LE, prophylactic encircling band surgery LE	OT after muscle surgery	Bagheri ⁸
10	57	Female	2 days	1 year	ET 30	Recurrent pterygia in both eyes,	Botulinum toxin injection, cyclic pattern changed, OT after muscle surgery	Present report

*Information provided by Dr Eugene Helveston (personal communication). NA, not available; CPP, cyclic pattern persisted; Δ , prism dioptre; ET, esotropia; XT, exotropia; RHT, right hypertropia; LHT, left hypertropia; OT, orthotropia; RD, retinal detachment; PVR, proliferative vitreoretinopathy; ECCE, extracapsular cataract extraction; PVT, posterior vitrectomy.

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Hand hygiene in routine glaucoma clinics

Nosocomial infection occurs via the hands of healthcare workers (HCWs).¹ Hand hygiene reduces hospital infection rates; however, HCWs seldom comply with this.²

We determined how often ophthalmologists and allied professionals cleaned their hands and whether intervention was effective.

Participants, methods, and results

We conducted the study in the daily glaucoma clinics of Moorfields Eye Hospital where policy states that all HCWs must clean their hands between patients.

For 1 week, hand hygiene practice was monitored covertly by two observers. Potential hand cleaning opportunities were before or during patient contact, before or

after manipulative procedures, and after glove removal. Manipulative procedures were defined as 5-fluorouracil subconjunctival injection, taking an eye swab, suture, or supramid removal, and bleb needling or massage.

Without revealing how the study was conducted, preliminary results were presented and also distributed by memo. Two weeks after this intervention, hand hygiene was re-monitored for 1 week.

Baseline hand hygiene episodes were 18% but increased significantly to 28% (p = 0.005) following intervention (table 1). Before intervention two out of seven people performing procedures cleaned their hands, but not for the single episode that 5-fluorouracil was used. However, after intervention six out of seven HCWs cleaned their hands (p = 0.04), including all three episodes in which 5-fluorouracil was handled.

Before intervention, female HCWs cleaned their hands significantly more than males (30% v 9%, p < 0.001). After intervention hand hygiene increased further for females (54%, p < 0.001) with no change for males (11%, p = 0.57).

Nurses had the highest frequency of hand cleaning but with no change after intervention (69% v 58%, p = 0.36). Increased hand hygiene was significant for doctors following intervention (11% v 20%, p = 0.01).

Comment

Recently, nosocomial infection has attracted considerable media interest. While problematic worldwide, the United Kingdom has one of the highest rates of methicillin resistant *Staphylococcus aureus* (MRSA).³ The hands of HCWs are a major route of transmission. Hand hygiene frequencies range from 3%,² increasing to more than 60% when HCWs are aware of being observed.⁴

In our study, hand hygiene was low (18%). Although significant improvement followed intervention (28%) this was far from the hospital standard. Our new level of hand cleaning is likely to be transient as all but one study has demonstrated sustained improvement.⁵

Previous studies, including our own, have shown that female HCWs clean their hands more often than males.⁶ In general, sex differences in hand washing are explained by the social role theory—that is, females are communal whereas men are agentic.⁷ Hence, women are more likely than men to participate in socially acceptable behaviour such as hand washing.⁸ In our study, intervention produced a significant improvement in hand hygiene for females with no effect on males. Behaviourally, men are less easily influenced than women,⁷ which may explain why intervention had no effect on male HCWs.

As with previous studies⁹ our nurses had the highest frequency of hand hygiene (69%). This could be because most nurses are female or because of an emphasis on hand washing in their undergraduate training. However, with our nurses hand hygiene did not increase following intervention. Possibly few nurses were present at the lecture, hence, they only received written information concerning initial study results.

As observed by others,⁵ we found hand hygiene among doctors was low (11%). However, intervention had its greatest effect on the doctors (p = 0.01). Although numbers are small, intervention had a positive effect on manipulative procedures, especially when using 5-fluorouracil.

Our study demonstrates that hospital policy is not being practised. Getting HCWs to clean their hands has been an ongoing struggle since Semmelweis. It has been suggested that patients should ask their healthcare professional to hand wash.¹⁰ Although controversial, this may help in the eradication of hospital acquired infection.

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Table 1 Effect of intervention on hand hygiene compliance

	Hand hygiene before intervention	Hand hygiene after intervention	p Value
	No (%)	No (%)	
Hand hygiene opportunities	249	291	
Hand hygiene episodes before patient contact	36 (14)	73 (25)	0.002
Hand hygiene episodes during patient contact	8 (3)	8 (3)	1.00
Total hand hygiene episodes	44 (18)	81 (28)	0.005
Hand hygiene episodes for procedures	2/7 (0/1 for 5-FU)	6/7 (3/3 for 5-FU)	0.04
Sex of healthcare worker			
Female	32/107 (30)*	62/115 (54)**	<0.001
Male	12/133 (9)*	20/182 (11)**	0.57
Profession of healthcare worker			
Doctor	21/191 (11)	44/220 (20)	0.01
Nurse	18/26 (69)	25/43 (58)	0.36
Optometrist	3/19 (16)	8/26 (31)	0.25
Other	2/8 (25)	1/7 (14)	0.62

Only three out of nine examination bays were observed for 1 hour at a time, in random order, during morning (from 09:30 to 12:30) and afternoon (from 14:00 to 17:00) clinics.

Data were analysed using χ^2 contingency tests.

5-FU = 5-fluorouracil.

*p < 0.001; **p < 0.001.

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Successful treatment of Wegener's granulomatosis associated scleritis with rituximab

Rituximab (Rituxan, Genentech, Inc, South San Francisco, CA, USA) is a new anti-CD20 B cell monoclonal antibody that has been used successfully to treat refractory cases of Wegener's granulomatosis (WG).^{1–3} There has been no published report of its effect in Wegener's associated eye disease. We describe the successful treatment of Wegener's associated scleritis with rituximab.

Case report

A 21 year old man with WG, proved on renal biopsy and by anti-neutrophil cytoplasm antibody (ANCA) positivity 6 years earlier, presented with bilateral, painful, red eyes. On examination his visual acuities were 6/4 right eye and 6/5 left eye. Anterior segment examination showed subconjunctival haemorrhage, congested scleral vessels, scleral oedema, peripheral corneal infiltrates, and mild anterior chamber inflammation in each eye. Funduscopy revealed bilateral swollen optic discs with scattered retinal haemorrhages in the right eye. A diagnosis of scleritis was made. Oral prednisolone was increased from 5–40 mg daily and maintenance oral mycophenolate mofetil 2 g daily was continued. Topical prednisolone acetate 1% hourly was commenced to both eyes.

Over the next month the scleritis had not improved and his systemic vasculitis had become more active, causing arthralgia, haemoptysis, and new vasculitic skin lesions. His white cell count (WCC) had risen to 13.9×10^9 compared to 9.6×10^9 the previous month. His ANCA had become positive by indirect immunofluorescence (titre of 1 in

25), and by proteinase 3 specific ELISA (titre 22 units, normal range <10). A new infiltrate was present in the lower lobe of his right lung on chest x ray.

Owing to concern over the total cumulative dose of cyclophosphamide he had previously received (>25 g), he was given an intravenous infusion of rituximab 1 g. Intravenous cyclophosphamide (12.5 mg/kg, adjusted for renal function) was also given with the rituximab infusion. These infusions were repeated after 2 weeks.

This led to an immediate significant systemic improvement accompanied by reduction of WCC to 9.6×10^9 and ANCA became undetectable. The pulmonary infiltrate resolved. The scleritis also resolved promptly, evident from completely white eyes, resolution of active scleral vessels, corneal infiltrates, optic disc swelling, and subjective resolution of ocular pain. At 7 months after the infusion, the patient remained in remission. His systemic treatment was slowly reduced to prednisolone 15 mg daily and mycophenolate mofetil 750 mg twice daily.

Comment

Rituximab is a humanised monoclonal antibody against the CD20 antigen that is expressed on the cell surface during early pre-B cell development and persists through all stages of B cell differentiation.⁴ It results in rapid depletion of CD20 positive B lymphocytes from the circulating blood and is well tolerated. The precise role of B cells in the pathogenesis of WG remains elusive at present, but several possibilities exist. B cells can act as antigen presenting cells to T cells or provide additional co-stimulatory signals for them. Another possibility is that self reactive B cells, derived from unusual B cell subsets,⁵ may follow an alternative maturation process, including the continued expression of CD20 during antibody production.

There has been no report on its effect on WG associated scleritis. Our patient was given rituximab primarily for his generalised vasculitis, but his refractory scleritis also responded promptly. Although he also received cyclophosphamide at the same time, the dose and course were limited to avoid toxicity. Therefore, in this case the prompt improvement was attributed to rituximab, rather than cyclophosphamide.

This is the first case reporting rituximab as an effective treatment for refractory WG associated scleritis.

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Retinopathy is not the only ocular symptom: myasthenia gravis in association with interferon therapy

Interferons (IFNs) have antiviral and anti-mitogenic effects and are often used in the treatment of viral hepatitis or some neoplasms. However, they have various side effects including fever, nausea, depression, retinopathy, and autoimmune diseases. Although myasthenia gravis (MG) is rarely associated with IFN therapy, some cases developing MG after IFN or IFN/ribavirin combined therapy for chronic active hepatitis C have been reported.^{1–5} We report such a case by reviewing the clinical data.

Case report

A 69 year old man with chronic hepatitis C for 11 years had been treated with IFN- α monotherapy (IFN 6×10^6 IU three times a week after 2 weeks of daily injections). The first treatment started in April 2002. There was no complication noted in that treatment. After the therapy hepatitis C virus activity settled for a while, but during the observation his clinical data showed a rise in hepatitis C virus RNA and aminotransferases. He underwent IFN- α therapy conjugated with ribavirin (IFN 6×10^6 IU three times a week after 2 weeks of daily injections, ribavirin 800 mg twice a day) again on 6 December 2002. During the course his condition was checked periodically, mainly in terms of retinopathy. He had finished 7 months of treatment without significant side effects.

Around December 2003 he began to notice fluctuating diplopia. Examination revealed his reduced right adduction, exotropia and left/right hypertropia. Since his condition drifted and there was no significant disorder on magnetic resonance imaging, MG was suspected and edrophonium chloride was tested. With the medication, his diplopia prominently improved and MG was diagnosed; however, there was no elevation in his anti-acetylcholine receptor antibody titre or other auto-antibodies, and thymoma was not detected.

Comment

It is well known that IFN therapy induces autoimmunity. Thyroid auto-antibodies are the most frequent findings; autoimmune hepatitis, rheumatoid symptoms, induction of insulin dependent diabetes, etc, are also seen. In relation to this autoimmune effect, several cases concerning MG associated with IFN therapy have been reported. Some cases developed myasthenia newly or others exacerbated pre-existing symptoms.^{1–5} It is reported that cases with pre-existing MG have a tendency to present more severe symptoms including myasthenic crisis.⁴ The pathogenesis is not completely understood

because of the complex immunological effects of IFNs, including enhanced lymphocyte cytotoxicity, inhibition of T suppressor cell function, increased expression of major histocompatibility complex (MHC) class I antigens, production of proinflammatory cytokines, and differentiation of antigen presenting cell activation of T helper lymphocytes by autoantigens. Some or all of them might contribute to the development of autoimmune disease.⁶

In this case the patient had no sign of MG or other autoimmune disease before the IFN treatment. His symptom is limited only to extraocular muscles: the condition is relatively mild. That is consistent with the previous report referring to the relation between the severity and the presence of a history of autoimmune disease; but the fact that anti-acetylcholine receptor antibody titre was not elevated is contradictory.⁴ We could not establish the causality.

These days many patients with chronic active hepatitis C virus receive IFN or IFN/ribavirin combined therapy. We usually examine these patients only in terms of retinopathy. Although this case could be a coincidental sporadic autoimmune disorder, we should take MG into consideration. We should recognise the risk of development or worsening of MG and be careful in managing patients undergoing therapy, especially when they already have MG or compatible symptoms. It can be a serious complication although it is very rare.

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Tobacco-alcohol amblyopia: a maculopathy?

Tobacco-alcohol amblyopia or toxic-nutritional optic neuropathy is a condition characterised by papillomacular bundle damage, central or caecocentral scotoma, and reduction of colour vision in a patient who abuses

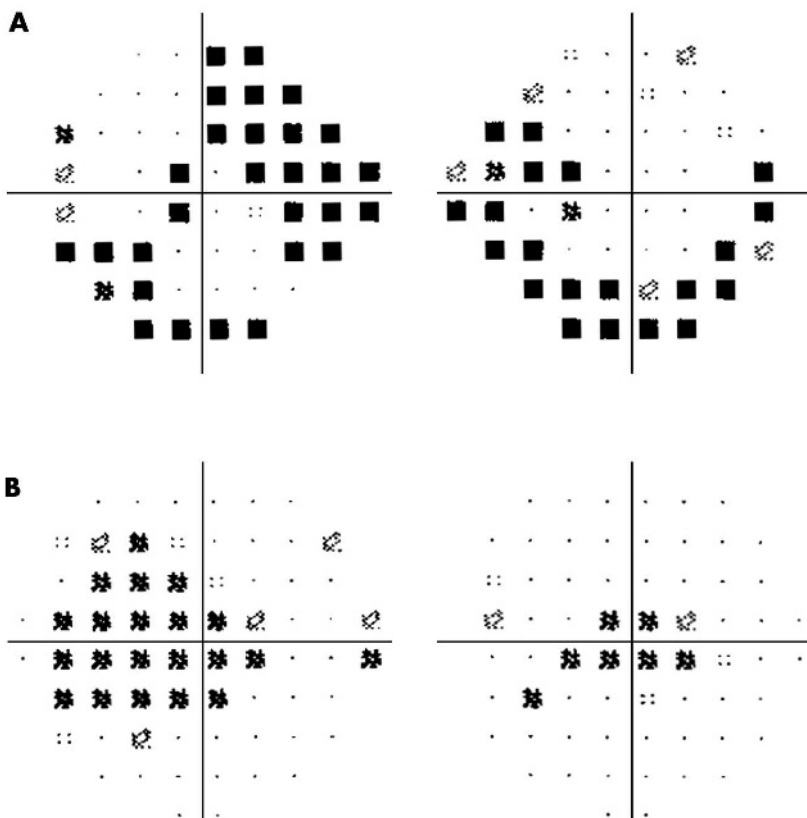


Figure 1 Static perimetry using (A) the 24-2 program shows an inferior arcuate defect in the right eye; a superonasal and an inferior defect in the left eye. (B) The 10-2 program shows bilateral central defects.

tobacco and alcohol.^{1,2} There is consensus that nutritional deficiency has an important role as well.^{3,4} The appearance of the optic nerve is usually normal, but peripapillary dilated vessels and haemorrhages have been described.^{5,6} Testing with static perimetry often reveals central scotomas. Although this syndrome has been classified as optic neuropathy, the primary lesion has not actually been localised to the optic nerve and may possibly originate in the retina, chiasm, or even the optic tracts. We report two cases of tobacco-alcohol amblyopia and their electrophysiological findings after testing with multifocal electroretinography (MERG).

Case reports

Case 1

A 47 year old woman presented with a gradual decrease in vision over 4 months. Her medical history showed that she has been in excellent health. She smoked one pack of cigarettes per week and had two to three beers daily. She denied any use of any medications in the past few months. She and her husband have been on a diet which contained fewer vegetables than their normal intake, for 4 months. Family history was unremarkable.

Visual acuity was 20/50 right eye and 20/100 left eye. Colour vision using the pseudoisochromatic plates was four of eight in right eye and two of eight in left eye. Intraocular pressure was 12 mm Hg right eye and 15 mmHg left eye. She had normal anterior segment in both eyes. Her pupils were

sluggish to direct stimulation of light with no afferent defect. Ocular motility was normal. Funduscopy showed anomalous optic nerves with no pallor, and normal maculas. Testing with 24-2 static perimetry revealed an inferior and nasal defect in the right eye; superonasal, inferior, and central defect in the left eye (fig 1A). Humphrey 10-2 static perimetry showed bilateral caecocentral scotomas (fig 1B). Magnetic resonance imaging (MRI) of the brain and orbit with and without contrast was normal. Serology tests for Lyme and antinuclear antibodies (ANA) were negative. Complete blood count, serum vitamin B12, and folate were within normal limits. MERG testing showed severe reduction in amplitude mostly centrally in both eyes (fig 2).

Case 2

A 55 year old woman presented with progressive decrease in vision of both eyes over 1 month. She had a history of multiple intracranial aneurysms that were clipped 15 years earlier. She was not using any medications. She smoked one pack of cigarette a day for 25 years and has five to eight drinks per week. Family history was positive for glaucoma in her mother. Visual acuity was counting fingers at 1 foot right eye and at 2 feet left eye. She could not identify any of the pseudoisochromatic colour plates in both eyes. She had normal anterior segment in both eyes. Pupillary reactions were sluggish to light stimulation with no afferent defect. Funduscopy showed mildly swollen optic nerves in both eyes (fig 3). Kinetic perimetry

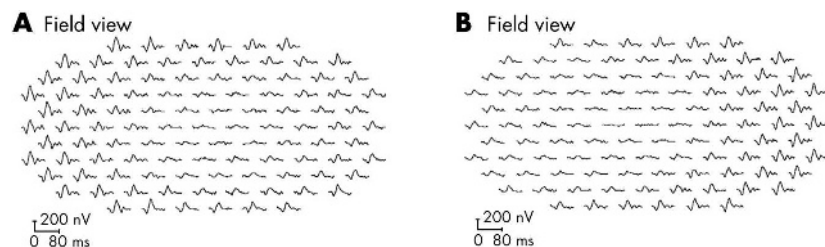


Figure 2 Trace arrays of multifocal ERG showing decreased amplitudes in both the right eye (A) and the left eye (B) with almost isoelectric responses centrally and improvement towards the periphery.

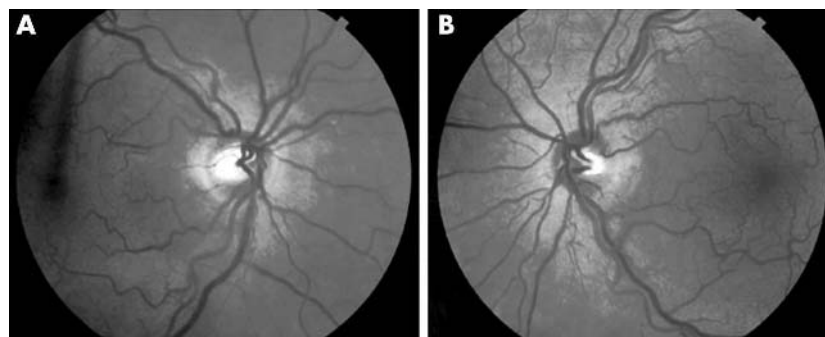


Figure 3 Fundus photographs showing swollen discs with some telangiectatic vessels in both eyes. (A) Right eye, (B) left eye.

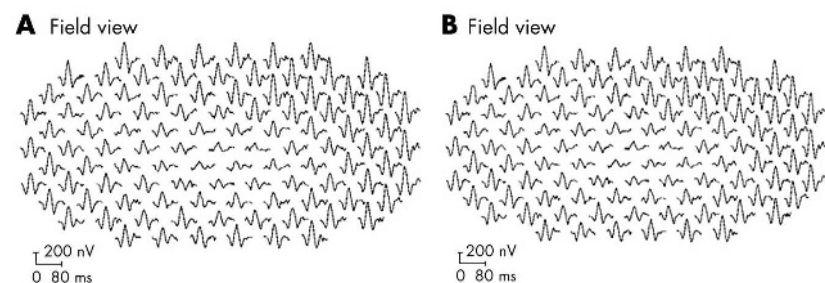


Figure 4 Trace arrays of patient 2 showing reduced amplitude in the central region of both eyes.

showed bilateral central scotomas. A CT scan (with and without contrast agent) of the brain and orbit was normal. Complete blood count, serum vitamin B12, and folate were within normal limits. Genetic testing of mitochondrial DNA for Leber's hereditary optic neuropathy showed that the patient has the LHON 3460 G mutation. Multifocal ERG was performed and showed decreased amplitudes centrally with normal latency (fig 4).

Comment

We describe two cases of "tobacco-alcohol amblyopia in patients who had a history of high alcohol intake (cases 1 and 2) and shortly after dietary alteration (case 1). In both cases, MERG testing showed decreased amplitudes in the central region, suggesting retinal dysfunction in the macula. The condition of the patient in case 2 may have been precipitated by a metabolic injury (tobacco, alcohol) to genetically "compromised" mitochondria. This shows the clinical overlap in conditions of inherited mitochondrial dysfunction and acquired ones such as tobacco-alcohol amblyopia.⁷

The clinical findings seen in tobacco-alcohol amblyopia can occur in any disease of anterior visual pathway from the retina to the optic tract and there is little evidence to suggest that the locus of pathology is restricted to the optic nerve. Histopathological studies on animal models of nutritional amblyopia showed lesions in the retina, optic nerve and tract,⁸ and the maculopapillary bundle.⁹ Electrophysiological abnormalities in animal models of tobacco-alcohol amblyopia showed reduced amplitudes with normal latencies using visual evoked potentials,^{10,11} and increased a-wave and b-wave implicit times and decreased b-wave amplitudes using full field electroretinograms.¹²

MERG signals are believed to arise from the outer retina (photoreceptor and bipolar cell layer) with only minimal contribution from the inner retina and optic nerve (ganglion cells and nerve fibre layer).¹³ Therefore, the severe reduction in amplitude in our patients suggests that the outer retina, particularly in the macula, is involved in this condition.

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The authors have no proprietary interest in any of the instruments used or any other aspect of this study.

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MAILBOX

TTT: local light absorption and heat convection versus heat conduction

Miura and co-authors have contributed valuable experimental data on transpupillary thermotherapy (TTT) for choroidal neovascularisation (CNV) in a rat model.¹ In their scholarly discussion section, they speculate that the variability in power settings they encountered in heating experimental CNV may be due to a "variation of heat conduction in experimental CNV."¹ There are more probable explanations for that variability. As reported previously in the authors' reference 7: "light absorption in pigment clumps from

prior focal photocoagulation can cause local hot spots in large TTT treatment fields.² Additionally, local choroidal blood flow² may have been altered by vascular remodelling that occurred in the 14 days between the intense focal laser photocoagulation that the authors used to produce CNV and their subsequent liposomal monitored TTT at the site.

Chorioretinal temperature rise from a lengthy 60 seconds TTT exposure is affected: (1) by pigmentation at the treatment site, which determines how effectively laser radiant energy is converted locally into thermal energy, and (2) to a lesser extent by choroidal blood flow,³ which transfers thermal energy by heat convection away from the exposure site. It is unlikely that local heat conduction is altered significantly by the initial photocoagulation or subsequent tissue remodelling because heat conduction in most normal biological tissues is essentially the same as that of water.⁴⁻⁶

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NOTICES

World Ophthalmology Congress 2006 – Brazil

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

For further information on the congress and committees, scientific program and coordinators of different areas are available at the congress website www.ophtalmology2006.com.br

Vision 2020

The latest issue of *Community Eye Health* (No 54) assesses the progress of Vision 2020 at the district level. For further information please contact: Journal of Community Eye Health, International Resource Centre, International Centre for Eye Health, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (tel: +44 (0)20 7612 7964; email: Anita.Shah@lshtm.ac.uk; online edition: www.jceh.co.uk). Annual subscription (4 issues) UK £28/US\$45. Free to developing country applicants.

19th International Society for Geographical & Epidemiological Ophthalmology Congress

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

Medical Contact Lens & Ocular surface Association Winter Symposium

The MCLOSA Winter Symposium will be held at the Western Eye Hospital, Marylebone Road, London NW1 on Friday 18 November 2005. For further information please visit the MCLOSA website at www.mcloa.org.uk/annualmtg.html.

CORRECTIONS

doi: 10.1136/bjo.2005.75895corr1

In the letter titled, Patient satisfaction with anaesthesia comparing sun-Tenon's block and topical anaesthesia (*Br J Ophthalmol* 2005;**89**:1228) the second author was omitted. The second author for this letter was R W D Bell, Sunderland Eye Infirmary, Queen Alexandra Road, Sunderland SR2 9HP, UK. The author apologises for this omission.

doi: 10.1136/bjo.2004.58941corr1

In the paper titled, En-face optical coherence tomography (OCT): A new method to analyse structural changes of the optic nerve head in rat glaucoma (*Br J Ophthalmol* 2005;**89**:1210-6) one of the author's name has been spelt incorrectly. The author Podolean AG, should be spelt Podoleanu AG. The journal apologises for this error.