LETTERS TO THE EDITOR

Bilateral cavernous haemangiomas of the orbit

EDITOR,—The great majority of orbital tumours are unilateral. However, some conditions, such as idiopathic orbital inflammation ("pseudotumour"), granulomatous inflammation, lymphoid tumours, or metastases sometimes can be bilateral. Orbital cavernous haemangioma is almost always unilateral.^{1,2} We report a patient with bilateral orbital cavernous haemangiomas that caused unilateral proptosis and visual distortion.

CASE REPORT

A 37 year old man developed distorted vision in the inferior field of his left eye and was found to have mild left proptosis. There was mild swelling of the left optic disc and a small inferonasal visual field defect. Orbital computed tomography (CT) revealed bilateral orbital masses and the patient was referred to the oncology service for another opinion and management. His visual acuity was 6/6 in each eye and colour vision was normal in both eyes. The only positive findings were 3 mm of left proptosis, mild swelling of the left optic disc, and a subtle inferonasal field defect. The orbital CT showed a round, soft tissue mass in the left orbit temporally that displaced the ret-

robulbar portion of the optic nerve nasally. A similar but smaller mass was present in the right orbit lateral to the medial rectus muscle (Fig 1). Both masses showed slight contrast enhancement. The clinical diagnosis was bilateral cavernous haemangioma. The left orbital mass was removed intact by a superolateral extraperiosteal approach. Gross and microscopic studies revealed a benign tumour composed of large endothelial lined vascular channels separated by fibrous stroma, consistent with cavernous haemangioma (Fig 2). The patient had an unremarkable postoperative course with good visual acuity.

COMMENT

Cavernous haemangioma of the orbit is a common, benign tumour that almost always occurs unilaterally. There are rare reports of bilateral orbital cavernous haemangiomas. Fries and Char reported a case that was very similar to ours.³ They excised the tumour in one orbit and elected to follow the asymptomatic tumour in the opposite orbit. Sullivan and associates reported an unusual case of multiple bilateral orbital haemangiomas.⁴ Johnson and co-workers reported bilateral orbital haemangiomas as part of Maffucci's syndrome, a condition characterised by enchondromatosis and multiple systemic haemangiomas.⁵ Our patient was otherwise normal with no evidence of Maffucci's syndrome. There was also a recent report of bilateral orbital vascular masses, presumed orbital varices, that caused intravascular papillary endothelial hyperplasia.⁶

The widespread use of CT and magnetic resonance imaging to evaluate unrelated problems, such as headache, has led to the recognition of asymptomatic lesions compatible with orbital cavernous haemangioma. We have seen several such cases and have elected to follow without treatment these small, asymptomatic tumours, presumed to be orbital cavernous haemangiomas. Consequently, it is possible that orbital cavernous haemangioma may be more common than previously believed. If so, additional cases of bilateral orbital cavernous haemangioma will probably be recognised. In our case, the asymptomatic tumour in the right orbit most

likely is a cavernous haemangioma, but periodic observation, rather than surgical excision, would seem to be the best management. In summary, the ophthalmologist should include orbital cavernous haemangioma in the differential diagnosis of bilateral, as well as unilateral, orbital tumours.

Supported by the Eye Tumor Research Foundation, Philadelphia, PA (J Shields, C Shields), the Noel T Sara L Simmonds Endowment for Ophthalmic Pathology, Wills Eye Hospital (RC Eagle), and from Research to Prevent Blindness (RN Hogan).

JERRY A SHIELDS

Oncology Service, Wills Eye Hospital, 900 Walnut Street, Philadelphia, PA, 19107, USA

R NICK HOGAN

Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA and the Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

CAROL L SHIELDS

Oncology Service

RALPH C EAGLE, JR

Department of Pathology

ROBERT H KENNEDY

Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA and the Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

ARUN D SINGH

Oncology Service

Correspondence to: Dr Jerry A Shields

Accepted for publication 7 March 2000

- Shields JA. Vasculogenic tumors and malformations. In: Shields JA, ed. *Diagnosis and management of orbital tumors*. Philadelphia: WB Saunders, 1989:123-8.
- Shields JA, Shields CL. Vascular tumors. In: Shields JA, Shields CL, eds. *Atlas of orbital tumors*. Philadelphia: Lippincott Williams and Williams, 1999:50-5.
- Fries PD, Char DH. Bilateral orbital cavernous haemangiomas. *Br J Ophthalmol* 1988;72:871-3.
- Sullivan TJ, Aylward GW, Wright JE, et al. Bilateral multiple cavernous haemangiomas of the orbit. *Br J Ophthalmol* 1992;76:627-9.
- Johnson TE, Nasr AM, Nalbandian RM, et al. Enchondromatosis and hemangioma (Maffucci's syndrome) with orbital involvement. *Am J Ophthalmol* 1990;110:153-9.
- Shields JA, Shields CL, Eagle RC Jr, et al. Intravascular papillary endothelial hyperplasia with presumed bilateral orbital varices. *Arch Ophthalmol* 1999;117:1247-8.

Figure 1 Orbital computed tomograms with axial cut (A) and coronal cut (B), showing bilateral circumscribed orbital soft tissue masses, with a larger tumour in the left orbit and a small tumour in the right orbit.

Figure 2 Pathology. (A) Gross photograph of pseudoencapsulated reddish blue mass. (B) Photomicrograph, showing large cavernous vascular channels typical of orbital cavernous haemangioma (haematoxylin and eosin x100).

Choroidal neovascularisation at a demarcation line: an immunopathological study

EDITOR,—We describe a patient presenting with a choroidal neovascular membrane (CNVM) at the demarcation line of a longstanding rhegmatogenous retinal detachment (RRD), and characterise its immunopathological features following surgical removal.

CASE REPORT

A 46 year old myopic woman attended the vitreoretinal service with a 3 month history of a shadow in the superior half of her left visual field. Her visual acuity was 6/9 right and 6/12 left, with a refractive error of -13.0D and -9.50D effective spheres respectively.

Examination of the left fundus revealed longstanding detached and thinned retina inferiorly and a broad heavily pigmented demarcation line passing through the macula with associated retinal pigment epithelial (RPE) hypertrophy. An area of parafoveal retina adjacent to the tide mark appeared elevated and a fundus fluorescein angiogram

(FFA) revealed a juxtafoveal CNVM emerging from the edge of RPE hypertrophy. Three months later she reported decreased vision and metamorphopsia in her left eye, with a best corrected left visual acuity reduced to counting fingers. A subfoveal extension of the CNVM with bordering haemorrhage was present, confirmed by FFA (Fig 1A, B). She subsequently underwent pars plana vitrectomy, parafoveal retinotomy, and removal of subfoveal CNVM, together with external scleral buckling, argon laser retinopexy, and 20% sulphur hexafluoride gas tamponade.

Postoperatively, an area of inferior retinal detachment persisted and further surgery with silicone oil tamponade was undertaken. Subsequently, a posterior subcapsular cataract developed and she underwent left phacoemulsification with intraocular lens implantation and removal of silicone oil. Postoperatively, visual acuity improved to 6/18 and the retina remained flat with no clinically apparent CNVM (Fig 1C). Four months later, her visual acuity was reduced to 6/36. Fundal examination showed an elevated area at her fovea and FFA confirmed a recurrent CNVM. We are treating this conservatively as the patient is asymptomatic and has declined further surgery.

Figure 1 (A) Colour fundus photograph showing pigment line, pigment epithelial hypertrophy, and bordering haemorrhage from subfoveal extension of choroidal neovascular membrane. (B) Fundus fluorescein angiogram demonstrating the subfoveal neovascular membrane. (C) Postoperative colour fundus photograph showing attached retina and no clinically visible recurrence of the membrane.

PATHOLOGY

The CNVM specimen was fixed in 10% formal saline, processed through ascending concentrations of alcohol into xylene and embedded with paraffin wax. Tissue sections 5 µm thick were freshly cut for this study, dewaxed, and rehydrated before use.

The distribution of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), macrophages (PGM1), and von Willebrand factor (vWF) were investigated using a standard biotin-streptavidin-biotin, alkaline phosphatase complex method (Dako Ltd). The alkaline phosphatase label was visualised as a red final reaction product (Vector Ltd). Nuclei were weakly stained with Mayer's haematoxylin. A normal human donor eye was used as a positive control, while the negative control used was normal rabbit serum diluted to give a final protein concentration equivalent to that of the primary antibody used.

Histopathological examination revealed a CNVM consisting of numerous endothelial lined vascular channels and chronic inflammatory cells. The CNVM was lined by an incomplete layer of RPE cells on its posterior aspect, as determined by the clinical orientation of the membrane at the time of removal (Fig 2A).

A large portion of the CNVM consisted of vascular channels lined by endothelial cells displaying immunoreactivity for von Willebrand antigens (Fig 2B). There was staining for VEGF (Fig 2C) and bFGF (Fig 2D) in the extracellular matrix, with a similar distribution of immunoreactivity.

COMMENT

Choroidal neovascularisation occurs in a wide spectrum of conditions, including degenerative, inflammatory, traumatic, and hereditary disorders—all characterised by breaks in Bruch's membrane.¹ A few cases of CNVM developing at the edge of a demarcation line have been reported in both chronic rhegma-

togenous and tractional retinal detachments; however, the immunopathology does not appear to have been previously described.^{2,3}

A demarcation line ("high watermark") is characteristically found in longstanding retinal detachments that either progress very slowly or remain static.⁴ In this setting, RPE cells may detach from Bruch's membrane to proliferate and undergo metaplasia in the sub-retinal space at the junction of attached and detached retina. Clinically, a demarcation line appears as a line of increased pigmentation in this area and may form a sufficiently firm adhesion to prevent progression of a retinal detachment. The local wound healing response at the edge of the detached retina may also lead to excessive RPE proliferation. In our patient, such chorioretinal adhesion may have allowed the transmission of mechanical vitreo-retinal traction forces to Bruch's membrane.³ This could potentially have compromised the integrity of Bruch's membrane, allowing the formation of a CNVM. High myopia was a further predisposing factor for choroidal neovascularisation in this patient, making Bruch's membrane more susceptible to disruption.¹

Grossniklaus and Gass have described two fundamentally different types of choroidal neovascular growth patterns—type 1, with growth of new vessels beneath the retinal pigment epithelium, and type 2, with growth of new vessels in the subsensory retinal space.⁵

In our patient, the presence of RPE cells on the posterior surface of the CNVM indicates that it represented a type 2 membrane, as determined by its clinical orientation at the time of removal.

Experimentally detached retina in cats has been shown to possess higher angiogenic activity than normal attached retina.⁶ Indeed, peripheral retinal neovascularisation has been described in chronic rhegmatogenous retinal detachment.⁷ Retinal detachment is likely to lead to compromised metabolism and hypoxia of the outer retinal layers due to elevation of the retina from the choroid.⁶ RPE cells may

Figure 2 Histopathology of excised choroidal neovascular membrane. (A) Photomicrograph showing a fibrovascular membrane lined on its posterior aspect by an incomplete row of RPE cells (haematoxylin and eosin ×80). Inset shows numerous macrophages staining for macrophage marker PGM1 (PGM1 immunostain ×80). (B) Focal neovascularisation of membrane core is demonstrated by endothelial cells showing immunoreactivity for von Willebrand stain (von Willebrand immunostain ×100). (C) Membrane showing focal immunostaining for VEGF (arrow) (VEGF immunostain ×80). (D) A similar distribution for bFGF is shown (bFGF immunostain ×80). Inset shows appropriate negative control with no specific staining.

secrete VEGF in response to this hypoxic insult and also secondary to mechanical stress incurred at the edge of the demarcation line.^{8,9} VEGF may then stimulate the recruitment and activation of monocytes, which in turn could promote mediators of angiogenesis.¹⁰ It is therefore possible that the liberation of neo-vascular growth factors in this setting may have contributed further to the development of CNVM in our patient.

RHY Asaria is supported by the June Sutor Fellowship.

D N PARMAR
Moorfields Eye Hospital, London

R H Y ASARIA
Moorfields Eye Hospital and Institute of
Ophthalmology, London

P LUTHERT
Institute of Ophthalmology

D G CHARTERIS
Moorfields Eye Hospital and Institute of Ophthalmology

Correspondence to: Mr D G Charteris, Vitreoretinal
Unit, Moorfields Eye Hospital, City Road, London
EC1V 2PD

Accepted for publication 16 March 2000

- 1 Green WR, Wilson DJ. Choroidal neovascularisation. *Ophthalmology* 1986;93:1169-76.
- 2 Gass JDM. *Stereoscopic atlas of macular diseases*. 3rd ed. St. Louis: Mosby, 1987:716.
- 3 Lopez PF, Aaberg TM, Lambert HM, et al. Choroidal neovascularisation occurring within a demarcation line. *Am J Ophthalmol* 1992; 114:101-2.
- 4 Benson WE, Nantawan P, Morse PH. Characteristics and prognosis of retinal detachments with demarcation line. *Am J Ophthalmol* 1977;84: 641-4.
- 5 Grossniklaus HE, Gass JD. Clinicopathologic correlations of surgically excised type 1 and type 2 submacular choroidal neovascular membranes. *Am J Ophthalmol* 1998;126:59-69.
- 6 Prost M. Experimental studies on the angiogenic activity of the detached retina. *Graefes Arch Clin Exp Ophthalmol* 1990;228:83-5.
- 7 Bonnet M. Peripheral neovascularisation complicating rhegmatogenous retinal detachment of long duration. *Graefes Arch Clin Exp Ophthalmol* 1987;225:59-62.
- 8 Aiello LP, Northrup JM, Keyt BA, et al. Hypoxic regulation of vascular endothelial growth factor in retinal cells. *Arch Ophthalmol* 1995; 113: 1538-44.
- 9 Seko Y, Seko Y, Fujikura H, et al. Induction of vascular endothelial growth factor after application of mechanical stress to retinal pigment epithelium of the rat in vitro. *Invest Ophthalmol Vis Sci* 1999;40:3287-91.
- 10 Oh H, Takagi H, Takagi C, et al. The potential angiogenic role of macrophages in the formation of choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 1999;40:1891-8.

Simultaneous metastases of cutaneous malignant melanoma to conjunctiva and choroid

EDITOR,—We report an unusual case of a cutaneous malignant melanoma which metastasised to the conjunctiva in one eye and the choroid in both eyes nearly 2 years after the initial presentation.

CASE REPORT

A 42 year old white man presented with a history of a small superficial black mark in the temporal aspect of the right eye, which had increased in size for the past 2 months. There was no significant ocular history. Two years earlier he had had a large malignant melanoma, 4.5 × 3.5 cm, removed from his lower back. On histopathology, this had been diagnosed as a superficial spreading type (Clarke's level IV with Breslow thickness of 3.5 mm). The mitotic count was 5 per 10 high power field (HPF) with a sparse lymphocytic

Figure 1 Fundus photograph of the right (A) and the left (B) eye, respectively, showing extensive metastatic deposits in the choroid.

infiltrate seen at the edges. It had been excised completely with no vascular or lymphatic invasion seen in the section. He had been thoroughly screened and a computed tomograph (CT) scan of the abdomen and head had not revealed any metastases. Subsequently, he had been followed up on a 4 monthly basis over the next 2 years and no recurrences had been found. During this period he developed a severe form of asthma which was controlled by oral prednisolone 25 mg per day. He otherwise felt well and on examination seemed to be in good general health. An enlarged lymph node was found in his left axilla. Visual acuity was 6/6 in the right eye and 6/5 in the left eye. Examination of the anterior segment in the right eye revealed a small superficial blackish brown mark about 3

mm in size on the lateral aspect of the bulbar conjunctiva. Left eye anterior segment examination was normal. The intraocular pressure was 17 mm Hg in both the eyes. Fundus examination of both the eyes revealed multiple, widespread, irregular subretinal pigmented deposits (Fig 1), some flat and some slightly elevated. There was no associated cataract or retinal detachment. His creatinine levels were found to be raised at 253 µmol/l, urea at 14.5 mmol/l, and lactate dehydrogenase at 443 IU/l. Urine examination showed both blood and protein present.

A diagnosis of cutaneous malignant melanoma with simultaneous metastases to the conjunctiva and choroid and possible widespread metastases was made. The patient was counselled and referred to the oncologist

Figure 2 (A) Histopathological section of the conjunctival lesion (haematoxylin and eosin stain; original magnification 10 $\times$) showing the metastatic cells covered by the normal conjunctival epithelium. (B) Higher magnification of the same area (original magnification 40 $\times$) showing melanin pigment granule laden cells.

for possible chemotherapy. Surgery with a wide excision of the conjunctival lesion was performed the next day and the tissue was sent for histopathological examination. It was reported as consisting of a dense cellular infiltrate in the subepithelial tissue, with atypical melanocytes without any melanocytic activity in the overlying surface epithelium. The tissue showed a positive staining for S100 protein and HMB45 antibody, both of which are specific for malignant melanoma. There was no pre-existing naevus and this was compatible with a metastatic malignant melanoma (Fig 2).

CT scans of the abdomen and the head revealed no metastatic disease. Within a week he developed abdominal pain and headache with vomiting which was relieved by dexamethasone and was thought to be due to meningeal metastases. Chemotherapy was instituted with weekly intravenous vindesine 4 mg/m² and tamoxifen 160 mg orally. Four days later he developed severe nose bleeds with clots. His platelet count at that point was normal and he was thought to have metastases in the postnasal space. His condition deteriorated rapidly with development of right sided pleuritic chest pain and haemoptysis and he died 3 weeks later.

COMMENT

Secondary metastatic disease in the eye is rare compared with other sites in the body and simultaneous secondaries in both anterior and posterior segment are highly unusual.¹ The incidence of histopathologically demonstrable cutaneous malignant melanoma metastasising to these sites was seen in five of 15 cases (33%) with disseminated cutaneous malignant melanoma in an necropsy series and is thought to be more common in men.² The presentation in the eye has been variously described as ranging from distinct tumours in the fundus or small diffuse infiltrates, anterior uveitis refractory to treatment, iris heterochromia, brownish coloured hypopyon due to tumour cells, diffuse pigmentation of the iris and the lens, aqueous and vitreous seedlings, and conjunctival pigmentation.^{3,4} Patients can

present with pain and redness due to secondary glaucoma caused by infiltration of the trabecular meshwork or angle closure due to an annular haemorrhagic choroidal detachment.⁵ Retinal deposits are very rare and may cause blurred vision.⁶ Differentiation between secondary melanomas in the choroid and a primary melanoma is important in order to decide on the type of management. Bilateral diffuse uveal melanocytic proliferation is an important differential diagnosis in our patient but he had no associated cataract, retinal detachment, or severe visual impairment. The time interval between the initial presentation of the skin lesion and the occurrence of metastases may vary from months up to 10 years.^{3,7} The occurrence of ocular metastases usually indicates grave prognosis owing to widespread visceral disease, as was the case in our patient. He had undergone regular thorough screening for 2 years but no signs of metastases were found during this period. The first external sign of secondary disease was the presence of the conjunctival lesion, which led to the discovery of the intraocular lesions and the axillary node involvement. Metastases to the conjunctiva from a cutaneous malignant melanoma is again very rare (less than 1%) and is usually associated with secondaries elsewhere in the eye.⁸ These need to be differentiated from other conditions such as primary acquired melanosis, naevus, adrenochrome deposits, direct extensions from ciliary body melanomas, and foreign body granulomas. The mode of treatment of metastatic cutaneous malignant melanoma in the eye can range from local excision as in small localised iris tumours, and enucleation for a painful blind eye or palliative treatment comprising chemotherapy and radiotherapy if the disease is widespread, as is often the case.¹ Patients with a single choroidal metastasis may be considered for radioactive plaque treatment.⁷ Previous studies have reported a median survival rate of 72 days with a maximum survival of 183 days and less than 10% survive up to 8 months after the onset of ocular symptoms.² Although the survival rates are partly related to the depth of the dermal invasion⁹ ocular metastases with only superficial spreading type of melanomas have been reported and this was also true of our patient. Within days of being diagnosed as having ocular metastases, he developed signs of widespread secondaries, which led to his death within weeks.

SUSHMA DHAR-MUNSHI

Department of Ophthalmology, East Surrey Hospital, Redhill, Surrey, RH1 5RH

M AMEEN

Department of Histopathology

ROGER S WILSON

Department of Ophthalmology

Correspondence to: Ms Sushma Dhar-Munshi, Department of Ophthalmology, Room no 5.012, Level 5, Lanesborough Wing, St George's Hospital, Blackshaw Road, London SW17 0QT

Accepted for publication 16 March 2000

- Volpe NJ, Albert DM: Metastases to the uvea. In: Albert DM, Jakobiec FA. *Principles and practice of ophthalmology*. Philadelphia: WB Saunders, 1994;chapter 266:3260–70.
- Fishman ML, Tomaszewski MM, Kuwabara T. Malignant melanoma metastatic to the eye. *Arch Ophthalmol* 1976;94:1309–11.
- Char DH, Schwartz A, Miller TR, et al. Ocular metastases from systemic melanoma. *Am J Ophthalmol* 1980;90:702–7.
- Bowman CB, Guber D, Brown CH, et al. Cutaneous malignant melanoma with diffuse intraocular metastases. *Arch Ophthalmol* 1994; 112:1213–16.

- De Bustros S, Augsberger JJ, Shields JA, et al. Intraocular metastases from cutaneous malignant melanoma. *Arch Ophthalmol* 1985;103: 937–40.
- Letson A, Davidorf F. Bilateral retinal metastases from cutaneous malignant melanoma. *Arch Ophthalmol* 1982;100:605–7.
- Bell RWD, Ironside JW, Fleck BW, et al. Cutaneous malignant melanoma metastatic to the choroid: a clinicopathological case report. *Eye* 1995;9:650–3.
- Shields CL, Shields JA, Gross NE, et al. Survey of 520 eyes with uveal metastases. *Ophthalmology* 1997;104:1265–76.
- Clark WH, From L, Bernardino EA, et al. The histogenesis and biological behavior of primary human malignant melanomas of the skin. *Cancer Res* 1969;29:705–27.

Acute sixth nerve palsy in vitamin A treatment of xerophthalmia

EDITOR,—Vitamin A deficiency remains a leading cause of blindness worldwide with xerophthalmia affecting 5–10 million children, resulting in 250 000–500 000 new cases of blindness each year. In the developed world, vitamin A deficiency is rare and usually occurs in the setting of malabsorptive states (such as cystic fibrosis and small bowel disease), liver disease, or malnutrition. Xerophthalmia is a medical emergency carrying a high risk of blindness, infection and death. Immediate administration of massive doses of vitamin A is required. Such rapid restoration of vitamin status is felt to be extremely safe at recommended doses. Appropriate dosing regimens in infants have been less clear than in older children and adults.¹ Reports of side effects are limited, and therefore we report a case of acute sixth nerve palsy in an infant receiving intramuscular vitamin A for xerophthalmia secondary to cystic fibrosis.

CASE REPORT

A 5 month old male infant with a long history of feeding intolerance was admitted to our hospital for severe irritability and failure to thrive. In the course of his examination, a sweat test was performed confirming the diagnosis of cystic fibrosis. Appropriate nutritional therapy and pancreatic enzyme replacement was commenced.

The infant had also been treated by his paediatrician for “conjunctivitis” of his right eye for the preceding 2 months with topical antibiotics. On the ophthalmic examination, the infant's visual acuity was fix and follow bilaterally. Extraocular motility was full and the eyes were orthophoric. Anterior segment examination revealed conjunctival xerosis of both eyes, and an inferior corneal ulcer of the right eye measuring 2 $\times$ 4 mm. Fundus examination was normal in both eyes. A diagnosis of xerophthalmia was made.

Vitamin A therapy was promptly commenced, with 50 000 IU (water miscible retinyl palmitate) intramuscularly to be given immediately and then to be repeated on the following day. After the first 50 000 IU, prominent bulging of the fontanelle was observed, although the infant remained alert and happy, and was feeding well. The second dose of 50 000 IU was therefore postponed for 48 hours, to be administered in two divided doses over 2 consecutive days. These doses were well tolerated, with gradual improvement of the bulging fontanelle over a week. Five days after the initial vitamin A dose, a complete abduction deficit of the infant's left eye was noted, in keeping with an acute sixth nerve palsy of the left eye. The infant still remained alert and happy, and

there were no other signs of raised intracranial pressure. The corneal ulcer of the right eye was fully healed at this time. The infant was followed for 2 months over which time the sixth nerve palsy fully resolved. There were no other neurological sequelae. The infant continued to receive oral vitamin A supplementation after discharge.

COMMENT

Prompt mega-dose administration of vitamin A is essential in the management of xerophthalmia. Oral administration is preferred because of its safety, cost, and effectiveness. The recommended regimen is 200 000 IU of vitamin A on the day of diagnosis, the next day, and 4 weeks later. In the rare instances in which children are unable to swallow or absorb oral vitamin A, intramuscular injection of water miscible retinyl palmitate 55 mg (100 000 IU) should be substituted—given immediately, the next day, and 4 weeks later. Children 6–11 months of age should receive half these doses and children less than 6 months of age one quarter of these doses.² In our patient, because the child's age was approaching 6 months, we chose to administer 50 000 IU doses.

Acute vitamin A toxicity generally occurs in children when a single dose greater than 330 000 IU is ingested, although some infants can be adversely affected by single doses as low as 100 000 IU.^{3,4} Typical features include a bulging fontanelle in infants, raised cerebrospinal fluid (CSF) pressure, nausea and vomiting, vertigo, and blurred vision or diplopia. These side effects are generally transient and subside within 1–2 days. Chronic ingestion of large amounts of vitamin A can result in pseudotumour cerebri.

This case demonstrates acute toxicity occurring after a cumulative dose of 100 000 IU given over 4 days. The sixth nerve palsy occurred presumably from raised CSF pressure, a phenomenon that is not fully understood but may be due to altered CSF resorption or production.^{5,6} Acute toxicity from intramuscular vitamin A (particularly water miscible forms) may be more likely because of the higher serum levels that are achieved more rapidly compared with oral preparations.⁷ Nevertheless, this case attests to the relative safety of vitamin A administration in infants.

EUGENE W M NG
NATHAN G CONGDON
ALFRED SOMMER

Wilmer Ophthalmological Institute and the Dana Center for Preventive Ophthalmology, The Johns Hopkins Hospital, and the Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD, USA

Correspondence to: Nathan G Congdon, MD, MPH, The Wilmer Ophthalmological Institute and the Dana Center for Preventive Ophthalmology, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287, USA

Accepted for publication 15 March 2000

- 1 Agoestina T, Humphrey JH, Taylor GA, et al. Safety of one 52-μmol (50 000 IU) oral dose of vitamin A administered to neonates. *Bull World Health Org* 1994;72:859–68.
- 2 Sommer A. Treatment. In: *Vitamin A deficiency and its consequences. A field guide to detection and control*. Geneva: World Health Organisation, 1994:36–40.
- 3 Hathcock JN, Hattan DG, Jenkins MY, et al. Evaluation of vitamin A toxicity. *Am J Clin Nutr* 1990;52:183–202.
- 4 Marie J, See G. Acute hypervitaminosis A of the infant. *Am J Dis Child* 1953;87:731–6.
- 5 Maddux GW, Foltz FM, Nelson SR. Effect of vitamin A intoxication on intracranial pressure and brain water in rats. *J Nutr* 1974;104:478–82.

- 6 Becker NH, Sutton CH. Pathologic features of the choroid plexus. I. Cytochemical effects of hypervitaminosis A. *Am J Pathol* 1963;43:1017–30.
- 7 Sommer A, Muhilal, Tarwotjo I, et al. Oral versus intramuscular vitamin A in the treatment of xerophthalmia. *Lancet* 1980;1:557–9.

Successful treatment of ocular invasive mould infection (fusariosis) with the new antifungal agent voriconazole

EDITOR,—Voriconazole is a new, highly potent, triazole with broad spectrum activity against fungi, including moulds as well as fluconazole resistant *Candida* spp.¹ Like other azole antifungal agents it interferes with ergosterole biosynthesis. Its antifungal activity has been shown in several experimental as well as clinical studies.^{2–5}

CASE REPORT

In November 1998, a 16 year old girl was transferred to the university eye hospital in Duesseldorf with a severe ulcerative hypopyon keratitis in the left eye, from which she had been suffering for 3 months after swimming in a lake in Italy. Smears, scrapings, and serology gave no hint of the aetiology. Despite intensive topical antibacterial, anti-acanthamoebal, antifungal, and antihypertensive therapy, as well as cryoapplication, her clinical situation had deteriorated continuously before admission to our hospital. As an optical rehabilitation was unlikely, owing to the severely infiltrated cornea, a perforating keratoplasty was performed. Postoperatively, the patient was given systemic as well as topical antibiotics. The first 3 days postoperatively were inconspicuous, but from the sixth day on a hypopyon could again be seen. The hypopyon progressed and we could identify, by ultrasound biomicroscopy the focus at the remaining recipient cornea. We removed this focus which was highly suspected of being a fungal colony and sent it to the microbiology department (an attempt to culture bacteria or fungi failed). Antifungal therapy with systemic fluconazole (200 mg/day intravenously) and topical amphotericin B (0.3% every hour) were started, but the clinical picture still deteriorated. At that time a filamentous fungus was diagnosed histopathologically in the excised corneal button (Fig 1). Because of the morphological similarities between *Aspergillus*, *Fusarium*, and *Pseudallescheria boydii* on histology these potent causes of keratitis could not be differentiated by this technique alone. Immunohistochemical examination of mycelia containing tissue sections with a panel of specific antifungal antibodies, all Grocott methenamine silver positive hyphae were identified as *Fusarium* species because a strong and uniform reactivity was obtained only with a heterologously absorbed polyclonal antibody raised towards somatic antigens of *Fusarium solani*.⁶

As the antifungal therapy had no effect whatsoever, the regimen was changed to

Figure 1 Grocott methenamine silver positive hyphae in the excised corneal button.

Figure 2 Ultrasound biomicroscopy discloses relapse of intraocular fungal disease.

systemic itraconazole (Sempera) 200 mg twice daily (a triazole which is known to be effective against some amphotericin B resistant mould species) for 3 days again with no clinical effect.

Owing to the lack of response to conventional therapy, we obtained the new antifungal agent voriconazole, from Pfizer, on a compassionate use basis. Voriconazole was started at a dosage of 6 mg/kg intravenously twice on day 1 followed by 4 mg/kg intravenously twice daily. This well tolerated therapy produced a significant clinical improvement. However, after 10 days the disease relapsed (Fig 2). Owing to the initial positive response it was considered that the relapse might be due to suboptimal penetration to the site of infection. Voriconazole therapy was changed to 6 mg/kg by mouth twice daily. Voriconazole was also injected intracamerally, at a dosage of 10 μg/0.1 ml. Topical antifungal therapy was switched from amphotericin B 0.3% every hour to voriconazole 1% every half hour. In addition, any remaining suspicious intraocular material was again excised and the anterior chamber was irrigated with a 3 μg/ml voriconazole solution. After this procedure, healing finally took place, and the patient was released from hospital; voriconazole was discontinued after 8 weeks. The corneal graft remained clear and best corrected vision was 0.9. There were no local or systemic adverse effects during this highly potent therapeutic regimen. A transient elevation of liver enzymes (a known adverse event of azole antimycotic agents) at the end of therapy and after cessation has been attributed to the study drug. Topical administration was well tolerated.

COMMENT

This is the first time that the efficacy of voriconazole in the treatment of ocular invasive fungal infection has been demonstrated. Topical administration has been tolerated well even when injected into the anterior chamber. Its obvious antifungal activity and favourable pharmacological properties, especially the low range of side effects, will make this new drug attractive for future studies on invasive ocular infections.

ALEXANDER REIS
RAINER SUNDMÄCHER
Eye Hospital, Heinrich-Heine-University Duesseldorf

KATHRIN TINTELNOT
Robert-Koch-Institut Berlin

HANSJÜRGEN AGOSTINI
Eye Hospital, University of Freiburg

HENRIK ELVANG JENSEN
The Royal Veterinary and Agricultural University,
Department of Pharmacology and Pathobiology,
Copenhagen

CHRISTOPH ALTHAUS
Eye Hospital, Heinrich-Heine-University Duesseldorf

Correspondence to: Dr Alexander Reis, Eye Hospital, Heinrich-Heine-University, Moorenstrasse 5, 40225 Duesseldorf, Germany
reis@uni-duesseldorf.de

Accepted for publication 13 April 2000

- Sanati H, Belanger P, Fratti R, *et al.* A new triazole, voriconazole (UK-109,496), blocks sterol biosynthesis in *Candida albicans* and *Candida krusei*. *Antimicrob Agents Chemother* 1997;41:2492-6.
- Nguyen HM, Yu CY. In vitro comparative efficacy of voriconazole and itraconazole against fluconazole-susceptible and resistant *Cryptococcus neoformans* isolates. *Antimicrob Agents Chemother* 1998;42:471-2.
- Martin MV, Yates J, Hitchcock CA. Comparison of voriconazole (UK-109,496) and itraconazole in prevention and treatment of *Aspergillus fumigatus* endocarditis in guinea pigs. *Antimicrob Agents Chemother* 1997;41:13-16.
- Murphy M, Bernard EM, Ishimaru T, *et al.* Activity of voriconazole (UK-109,496) against clinical isolates of *Aspergillus* species and its effectiveness in an experimental model of invasive pulmonary aspergillosis. *Antimicrob Agents Chemother* 1997;41:696-8.
- Ruhnke M, Schmidt-Westhausen A, Trautmann M. In vitro activities of voriconazole (UK-109,496) against fluconazole-susceptible and -resistant *Candida albicans* isolates from oral cavities of patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997;41:575-7.
- Jensen HE, Salonen J, Ekfors TO. The use of immunohistochemistry to improve sensitivity and specificity in the diagnosis of systemic mycoses in patients with haematological malignancies. *J Pathol* 1997;181:100-5.

Severe intraocular inflammation after a change of HAART

EDITOR,—Patients with previous cytomegalovirus retinitis (CMVR) have been observed to get vitritis, cystoid macular oedema (CMO), and epiretinal membranes after commencing HAART (highly active antiretroviral therapy).¹⁻³ It is postulated that this is due to the improved CD4+ function that occurs with HAART.⁴

We present a patient with previously treated CMVR and immune recovery vitritis who developed further severe intraocular inflammation 6 weeks after changing HAART.

Figure 1 (A) Fluorescein angiogram of the right eye at 38 seconds demonstrating macular ischaemia. (B) Macular oedema evident in a late phase fluorescein angiogram of the left eye.

Figure 2 CD4+ lymphocyte count and viral load.

CASE REPORT

A 43 year old man, diagnosed as HIV positive in 1984, was treated in January 1996 for bilateral CMVR that responded to systemic ganciclovir.

In April 1996 he started saquinavir, stavudine, and lamivudine. A viral load was 18 000 copies × 10⁶/l and CD4+ count 40 cells × 10⁶/l. In December 1996 ritonavir was added.

In February 1997 he developed immune recovery vitritis in both eyes. Best corrected visual acuities (BCVA) were 6/6, N5 right; 6/6, N8 left. A viral load was now 7800 copies × 10⁶/l and CD4+ count 100 cells × 10⁶/l. A fluorescein angiogram showed bilateral CMO with macular ischaemia (Fig 1) and he was treated with 250 mg sustained release oral acetazolamide, twice daily. After 1 month's treatment there was a subjective improvement in vision but no objective change in VA. In September 1997 his BCVAs were 6/6, N5 right; 6/6, N6 left. In December 1997 his CMVR was inactive and ganciclovir was stopped.

In February 1998 he developed marked lipodystrophy and consequently was changed to efavirenz, hydroxyurea, didanosine, and continued on stavudine. By April 1998 his viral load had fallen to less than 500 copies

× 10⁶/l and his CD4+ count was 128 cells × 10⁶/l (Fig 2).

Six weeks after changing HAART, he complained of blurred left vision. Visual acuity was 6/6 right, 6/9 left. There was a left vitritis with a white retinal lesion along the inferotemporal vessels at the margin of inactive CMVR (Fig 3). A diagnosis of relapse of CMVR was made and he was treated with intravenous ganciclovir.

Two weeks later vision was counting fingers, the vitritis was worse, and the retinal lesion had extended with more haemorrhage. He was treated for presumed toxoplasmosis with sulphadiazine, pyrimethamine, and folinic acid but 1 week later his vision was hand movements and the lesion was larger (Fig 4). A diagnostic vitrectomy was performed. Polymerase chain reaction (PCR) was negative for CMV, toxoplasmosis, varicella zoster, and Epstein-Barr viruses. Cytology did not reveal lymphoma.

One week later the eye was painful and vision was perception of light. A retinal biopsy was performed in an area of active inflammation. Histology showed retinal necrosis and exudates. No viral inclusion bodies were found and stains for acid fast bacilli, fungi, and toxoplasma cysts were all negative. A few atypical lymphocytes were seen and PCR for

Figure 3 Inferotemporal, white retinal lesion at margin of mature CMVR with surrounding haemorrhage, sheathing of neighbouring veins but no obvious involvement of arterioles.

Figure 4 One week later the lesion has increased in size and extended to involve all retinal layers. Retinal vessels are obscured and haemorrhage persists.

B cell clonality showed oligoclonal banding. A contrast enhanced magnetic resonance imaging of the brain and orbits was normal.

Eighteen months later the BCVAs are 6/6, N5 right; perception of light, left. A chorioretinal scar persists in the macular and temporal retina of the left eye but there is no active inflammation in either eye.

COMMENT

Investigations in this patient failed to identify any cause for the intraocular inflammation; however, the cessation of the inflammatory process in the absence of any specific treatment is similar to the clinical course of immune recovery vitritis and suggests a non-infectious mechanism. The temporal association with the change in HAART, together with the PCR findings, both imply an immunological cause. It is unclear why this response was unioocular.

The presence of multiple discrete bands on PCR may indicate a premalignant lymphoproliferation but 18 months later the eye is quiet with no recurrence and the patient remains well. Our hypothesis is that the intraocular inflammation occurred because the new combination HAART produced a second, very exaggerated immune response to pre-existing antigens.

Clinicians should be aware that changing the combination of HAART may be associated with aggressive intraocular inflammation with an oligoclonal lymphocyte response. Early recognition and treatment with systemic steroids may have prevented blindness in our patient.

TIMOTHY L JACKSON
WILLIAM MEACOCK

Medical Eye Unit, St Thomas's Hospital,
London SE1 7EH

MIKE YOULE

Kobler Centre, Chelsea and Westminster Hospital,
London

ELIZABETH M GRAHAM

Medical Eye Unit, St Thomas's Hospital,
London SE1 7EH

Correspondence to: Dr E M Graham

timljackson@hotmail.com

Accepted for publication 13 April 2000

- 1 Karavellas MP, Lowder CY, MacDonald C, *et al.* Immune recovery vitritis associated with inactive cytomegalovirus retinitis: a new syndrome. *Arch Ophthalmol* 1998;116:169–75.
- 2 Silverstein BE, Smith JH, Sykes SO, *et al.* Cystoid macular edema associated with cytomegalovirus retinitis in patients with the acquired immunodeficiency syndrome. *Am J Ophthalmol* 1998;125:411–5.
- 3 Zegans ME, Walton RC, Holland GN, *et al.* Transient vitreous inflammatory reactions associated with combination antiretroviral therapy in patients with AIDS and cytomegalovirus retinitis. *Am J Ophthalmol* 1998;125:292–300.
- 4 Autran B, Carcelain G, Li TS, *et al.* Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. *Science* 1997;277:112–6.

Oriental herbal medicine induced epithelial keratopathy

EDITOR,—“Kampo” is the name given to an oriental herb medicine which has been used in China and Japan for more than 2000 years. Kampo is believed to be very mild and a safe medicine and so far there has been no report of kampo induced keratopathy.

We report a case of epithelial keratopathy, which occurred in a patient who had taken oral oriental herbal medicine for 5 years. To the best of our knowledge, this is the first

report of oriental herbal medicine (kampo) induced keratopathy.

CASE REPORT

A 30 year old Japanese woman was referred to Juntendo University Hospital with the complaint of bilateral photophobia. Visual acuity was 20/20 in both eyes. Slit lamp examination disclosed dust-like opacities in the epithelial layer in both central corneas, and brown coloured precipitates, which spread radially from the central cornea (Fig 1A). No corneal staining was observed with fluorescein. No other ocular abnormality was found. There were no remarkable findings in her past or family history.

The patient underwent therapeutic and diagnostic superficial keratectomy that provided epithelial layer for ultrastructural study. The corneal epithelial layer was processed for routine electron microscopy. Electron microscopic examination disclosed corneal epithelial cells with numerous lamellar inclusion bodies formed by series of concentrically arranged lamellae suggestive of lipid-like material (Fig 1B).

The patient was submitted to laboratory tests in order to investigate a possible metabolic disease. No abnormal data were detected except for slightly high level of total blood cholesterol. Concerning the drug history, the patient informed us that she had been taking an oral oriental herbal medicine for chronic constipation for about 5 years. The composition of the drug is shown in Table 1. Two years before the present complaint, the patient had the same symptom of photophobia which gradually disappeared several months after withdrawal of the herbal medicine. One month before the present complaint, she started taking the herbal medicine for constipation. The patient was advised to withdraw the herbal medicine. Three months after withdrawal, the corneal opacities decreased and the patient noticed relief of symptoms. One year after withdrawal, the corneal lesions had disappeared completely. No sign of recurrence

Figure 1 (A) Slit lamp examination shows numerous dust-like opacities in the epithelium at central cornea and brown coloured precipitates spreading radially from central cornea in both eyes. (B) Numerous membranous lamellar inclusion bodies in the corneal epithelial cells, suggestive of lipid-like material ($\times 16\,000$).

Table 1 Composition of the herbal medicine (7.5 g of this product contains 5.7 g of dried extract obtained from mixed raw herbs in the above ratio)

JP Scutellaria root	2.0 g
JP Glycyrrhiza root	2.0 g
JP Platycodon root	2.0 g
JP Gypsum	2.0 g
JP Atractylodes rhizome	2.0 g
JP Rhubarb rhizome	1.5 g
JP Schizonepeta spike	1.2 g
JP Gardenia fruit	1.2 g
JP Peony root	1.2 g
JP Cnidium rhizome	1.2 g
JP Japanese angelica root	1.2 g
JP Mentha herb	1.2 g
JP Saposhnikovia root	1.2 g
JP Ephedra herb	1.2 g
JP Forsythia fruit	1.2 g
JP Ginger rhizome	0.4 g
Talc	3.0 g
Anhydrous mirabilium	0.75 g

was observed until now, 4 years after the first examination.

COMMENT

Although oriental herb medicines have been beneficial to patients, scientific explanation of their pharmacological mechanisms has lagged behind the widespread use of kampo in clinical practice.¹ In this case, the clinical and morphological findings were similar to those observed in Fabry's disease² and in drug induced keratopathy.^{3–5} In drug induced lipid storage keratopathy, the corneal deposits are bilateral, dose and duration related, and gradually disappear after the drug is withdrawn.⁶ Although kampo is believed to be very safe, it seems advisable to dictate caution with respect to this possible adverse effects.

TORU AKATSU

RUTH M SANTO

KIYOO NAKAYASU

ATSUSHI KANAI

Department of Ophthalmology, Juntendo University
School of Medicine

Correspondence to: Kiyoo Nakayasu, MD, Department of Ophthalmology, Juntendo University School of Medicine, 3-1-3, Hongo, Bunkyo-ku, Tokyo, 113-8431, Japan

Accepted for publication 13 April 2000

- 1 Baker S, Thomas PS. Herbal medicine precipitating massive haemolysis. *Lancet* 1987;i:1039–40.
- 2 Frost P, Tanaka Y, Spaech GL. Fabry's disease: glycolipid lipidosis. Histochemical and electron-microscopic studies of two cases. *Am J Med* 1966;40:618–27.
- 3 Weiss JN, Weinberg RS, Regelson W. Keratopathy after oral administration of tilorone hydrochloride. *Am J Ophthalmol* 1980;89:46–53.
- 4 D'Amico DJ, Kenyon KR, Ruskin JN. Amiodarone keratopathy. *Arch Ophthalmol* 1981;99:257–61.
- 5 Holland EJ, Stein CA, Palestine AG, *et al.* Suramin keratopathy. *Am J Ophthalmol* 1988;106:216–20.
- 6 Fredro TF, Waring GO. Pathologic responses in the cornea. In: Leibowitz HM, Waring GO, eds. *Corneal disorders. Clinical diagnosis and management*. 2nd ed. Philadelphia: Saunders, 1998: 154–200.

Branch retinal artery occlusion; another complication of sildenafil

EDITOR,—Sildenafil is the oral treatment for erectile dysfunction and was licensed throughout Europe in September 1998. It is a potent, selective inhibitor of the isoenzyme phosphodiesterase type 5 (PDE 5). Inhibition of PDE5 leads to prolongation of cyclic guanosine monophosphate (cGMP) activity in erectile tissue and increases the natural

vasodilatory actions of nitric oxide on the cavernosal smooth muscle, facilitating the erectile response in men with erectile dysfunction.¹ Whereas many ocular adverse effect of sildenafil have been reported,²⁻⁵ we present, to the best of our knowledge, the first case report of branch central retinal artery occlusion following the use of sildenafil.

CASE REPORT

A 69 years old man presented with a sudden painless loss of vision in the left eye 2 days previously. The patient was fit and healthy otherwise and had no history of glaucoma, diabetes, hypertension, or other systemic vascular diseases. Visual acuity was 6/6 in the right eye and 6/24 in the left eye. Anterior segment examination was normal apart from a mild relative left afferent pupillary defect. Fundus examination of right eye was normal whereas fundus examination of the left eye revealed a superotemporal branch retinal artery occlusion. As the patient did not have any of the risk factors predisposing to arterial occlusion a more detailed history was sought and the patient informed us that he had taken a dose of Viagra (100 mg) a few hours before he experienced loss of vision in left eye. Cardiac examination revealed sinus rhythm, normal heart sounds, and there was no carotid bruit or thrill. Immediate measures taken to restore the circulation (intravenous Diamox, ocular massage, rebreathing into a bag, etc) proved futile and vision remained 6/24 over a 3 months follow up period. Full blood counts, serum electrolytes, fasting blood glucose levels, fasting total lipids and cholesterol, erythrocyte sedimentation rate, and plasma viscosity were normal. The patient has not used sildenafil since then.

COMMENT

A number of adverse effects of sildenafil have been reported and these include headache, facial flushing, dyspepsia, and nasal congestion. There have been reports of prolonged erection and priapism, myocardial infarction,⁶ sudden cardiac arrest, ventricular arrhythmias, and hypertension.² In patients taking organic nitrates, it can lead to a sudden and severe drop in blood pressure.² A cardiac examination, including exercise treadmill testing has been recommended before starting patients on sildenafil.⁷ Various ocular side effects have been described following the use of sildenafil. These fall into two major categories: (i) those secondary to the weak inhibitory effects of sildenafil on the isoenzyme PDE6 in the retina.³ These side effects include temporary loss of vision, increased intraocular pressure, green/blue tinging of vision, increased sensitivity to light, and blurred vision.² There have also been reports of retinal degeneration. A decrease in the a-wave and b-wave amplitude in the electroretinogram (ERG) of five healthy men 1 hour after oral intake of 100 mg sildenafil has also been reported and these changes completely disappeared 5 hours later.⁵ (ii) Ocular vascular events such as haemorrhages, venous occlusion, and anterior ischaemic optic neuropathy have been mentioned² but so far there has been no referenced report of retinal artery occlusion following the use of sildenafil. In addition to these ocular side effects, a pupil sparing third nerve palsy due to sildenafil has also been reported.⁴ In the case reported here, a sudden rise in intraocular pressure or an embolic phenomenon due to short lived cardiac arrhythmias may have produced branch retinal artery occlusion. This case

report clearly suggests that the earlier claim that there is no cause for alarm over retinal side effects of sildenafil⁸ must be re-examined and a potentially blinding complication like the one reported here should be seriously considered and discussed with all the patients started on sildenafil, more so because of the fact that most of the patients using this medication are already at high risk of developing vascular accidents in the body.

AJAY TRIPATHI
NIAL P O'DONNELL
Southport Eye Unit, Pilkington Road,
Southport PR8 6PH

Correspondence to: Mr Ajay Tripathi
ajay@pinkifreeserve.co.uk
Accepted for publication 18 April 2000

- 1 Umrani DN, Goyal RK. Pharmacology of sildenafil citrate. *Indian J Physiol Pharmacol* 1999;43:160-4.
- 2 Marmor MF, Kessler R. Sildenafil (Viagra) and ophthalmology. *Surv Ophthalmol* 1999;44:153-62.
- 3 Gonzalez CM, Bervig T, Huang CF, et al. Sildenafil causes a dose and time dependent downregulation of phosphodiesterase type 6 expression in the rat retina. *Int J Impot Res* 1999;11(Suppl 1):S9-14.
- 4 Donahue SP, Taylor RJ. Pupil-sparing third nerve palsy associated with sildenafil citrate (Viagra). *Am J Ophthalmol* 1998;126:476-7.
- 5 Vobig MA, Klotz T, Staak M, et al. Retinal side-effects of sildenafil. *Lancet* 1999;353:375.
- 6 Porter A, Mager A, Birnbaum Y, et al. Acute myocardial infarction following sildenafil citrate (Viagra) intake in a nitrate-free patient. *Clin Cardiol* 1999;22:762-3.
- 7 Kloner RA. Viagra: what every physician should know. *Ear Nose Throat J* 1998;77:783-6.
- 8 Zrenner E. No cause for alarm over retinal side-effects of sildenafil. *Lancet* 1999;353:340-1.