Bilateral retinal detachments at birth: the osteoporosis pseudoglioma syndrome

EDITOR,—The osteoporosis pseudoglioma syndrome (OPS) is a rare autosomal recessive disorder characterised by severe juvenile onset osteoporosis and congenital or juvenile onset blindness. Over 40 cases have been documented but reports in the ophthalmic literature are exceedingly rare and we believe this is the first recorded case in the United Kingdom.

CASE REPORT

A white, male infant was noted by his parents to have roving eye movements and poor vision at 5 weeks of age. The pregnancy, delivery, and neonatal period were normal. On examination at 12 weeks of age he had very poor visual responses and variable horizontal nystagmus. Fundal examination showed a disordered retina with bilateral retrolental masses (Fig 1). This was confirmed by ultrasound scan and examination under anaesthesia.

A clinical diagnosis of retinal dysplasia associated with probable Norrie disease (ND) was made. A blood sample was taken for DNA analysis of the Norrie gene. He was seen from time to time over the next year and it was clear that he was completely blind with no response to light. He was poking both eyes but no complications, in particular glaucoma, had arisen.

At 1 year of age his elder brother fell on him in the bedroom resulting in a right fractured femur (Fig 2) which was treated with 2½ weeks of traction. One week later he sustained a left fractured femur while lying in his cot. This was treated with a hip spica. The combination of two fractures as a result of trivial trauma raised the possibility of non-accidental injury but review of the x rays revealed generalised osteoporosis with coarse trabeculae and thin cortices. A DEXA bone scan showed a moderate degree of osteoporosis.

The combination of multiple fractures and blindness suggested a clinical diagnosis of the rare osteoporosis pseudoglioma syndrome (OPS) as fractures are not a feature of Norrie disease. A diagnosis was important to differentiate these two diseases, OPS being autosomal recessive and Norrie disease X linked. It was not until he was 2½ years of age that final results of molecular genetic analysis showed no abnormality of the Norrie gene.

He is now 5 years of age and has suffered a total of five fractures. For the past 2½ years he has received 3 monthly bisphosphonate infusions and DEXA bone scans show improved bone density. He is developmentally delayed and has just commenced “bum shuffling.” There is also intellectual and speech delay, short stature, but no hearing impairment. His mother is currently 5 months pregnant and has been counselled that future children have a 25% chance of being affected with OPS.

COMMENT

This case demonstrates the blindness and skeletal handicap that characterise OPS. Other manifestations may be present but it is the eye and skeletal components which are essential for the diagnosis. Frontali et al have reviewed OPS and shown that the clinical manifestations are variable and highly variable.1 Eye features include vitreoretinal dysplasia resulting in retrolental masses. Some eyes have been mistakenly enucleated because they were thought to contain retinoblastoma.2 Other ocular features include microphthalmia, ante- rior chamber abnormalities, cataract and phthisis bulbi, although these are all highly variable. Congenital blindness is the rule but a few patients have preserved useful vision into their teenage years.3

The osteoporosis results in multiple fractures and bone deformities. The time of onset and severity of the osteoporosis is highly variable and the history of minimal trauma is typical. As the osteopoenic process seems to stabilise with age, prophylaxis and specialist care of fractures and deformities are essential to prevent incapacitating long term problems.4 Intravenous bisphosphonate therapy may prevent progressive skeletal deformity.5 Other minor features of OPS include short stature, intellectual impairment, cardiac anomalies, hypotonia, and ligament laxity.6 The pathogenesis of OPS is unknown. It is clearly a connective tissue disorder. Clinical, biochemical, and microscopic analyses suggest the defective gene may encode a matrix protein expressed in eye and bone.7 The OPS locus has recently been mapped to 11q12–13 but the precise molecular pathology has yet to be identified.

Graham Wilson
Anthony Moore
Addenbrooke’s Hospital, Cambridge, UK
Jeremy Allgrove
Nashen General Hospital, London, UK
Correspondence to: Mr G A Wilson
graham.wilson@nhs.net
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Emmetropisation after Molteno implant insertion for buphthalmos

EDITOR,—We report a series of four infant patients who underwent insertion of Molteno implants for control of buphthalmos and congenital glaucoma. In addition to long term control of their glaucoma, they each demonstrated a return to emmetropia from myopia. We are unaware of any similar case reports in the literature.

CASE REPORTS

All refractions discussed in cases were measured under cycloplegia (cyclopentolate 1% × 3) using a streak retinoscope and trial lenses.

Case 1

A male infant presented at 6 months of age with bilateral congenital glaucoma. Bilateral Molteno implants were inserted without complications and long term intraocular pressure (IOP) control was achieved. Refraction 6 months postoperatively revealed myopia of −10.5 D in both eyes. Subsequent refraction at age 2 (18 months postoperatively) revealed reduced myopia of −4.5D in both eyes. Refraction at age 6 (66 months postoperatively) revealed myopia of −4.5D in both eyes. Evolution of the intraocular pressure control was achieved. Refraction 6 months postoperatively revealed myopia of −4.5D in both eyes.

Case 2

A male patient presented at 6 months of age with bilateral congenital glaucoma. Bilateral Molteno implants were inserted without complications and long term intraocular pressure (IOP) control was achieved. Refraction 6 months postoperatively revealed myopia of −10.5 D in both eyes. Subsequent refraction at age 2 (18 months postoperatively) revealed reduced myopia of −4.5D in both eyes. Refraction at age 6 (66 months postoperatively) revealed myopia of −4.5D in both eyes.


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the parents questioned the need for glasses, and EUA revealed the patient was essentially emmetropic ( plano/+1.25DC × 045 right; plano/+1.52DC × 135 left). Other glaucoma parameters were unchanged and glasses were stopped. EUA at age 42 months (36 months postoperatively) revealed refractions of +0.5DS in both eyes which has remained stable on subsequent review to date (now 5 years postoperatively).

Case 3
A female patient presented at age 5 months with buphthalmos. EUA next day revealed horizontal corneal diameters 14 mm right and 13.5 mm left with IOPs of 33 mm Hg right and 30 mm Hg left. There was corneal oedema and normal discs. Refraction showed marked improvement with resolution of corneal oedema and normal IOP. Refraction revealed plano/+1DC × 090 in both eyes. EUA at 1 week later the left eye showed marked improvement with resolution of corneal oedema and normal IOP. Refraction at 4 months of age (1 month postoperatively) revealed plano/+1DC × 900 in both eyes. Refraction at 13.5 DC left. Subsequent refraction 9 months of age (6 months postoperatively) revealed plano/+1DC × 045 in both eyes. Refraction at 24 months of age (21 months postoperatively) revealed +0.5DS right and +0.75DS/+1.0DC × 045.

Case 4
A male patient presented aged 3 months with history of cloudy left cornea from 4 weeks of age. EUA revealed left corneal diameter of 12 mm and IOP of 50 mm Hg. The patient proceeded to a left one plate Molteno implant with Vicryl tie and slit, with a similar procedure in the left 1 week later. Subsequent EUA at 13 months (8 months postoperatively) revealed normal IOP (14 mm Hg in both eyes) with horizontal corneal diameters of 13 mm Hg right and 13.5 mm Hg left and normal discs. Refraction revealed myopia of −4.0D right and −4.5D left. EUA at 15 months (10 months postoperatively) revealed greater myopia of −7.0D right and −5.5D left and the patient was prescribed glasses (−4D right and −3D left). EUA at 21 months of age (16 months postoperatively) revealed myopia had reduced significantly to −5.5D left and the patient was prescribed glasses (−4D right and −3D left).

COMMENT
Human adults show a non-Gaussian distribution of refractive errors with a predominance of refractions around emmetropia. Other ocular parameters such as corneal power, lens power, and axial length show a Gaussian distribution. Normal ocular development is critical in the maintenance of emmetropia and component ametropia. While nanophthalmos with a steep cornea and possibly forward positioned anterior lens position—again allowing emmetropisation—probably involves the feedback of image focus centrally and EUA revealed the patient was essentially emmetropic having symmetrically large but steep corneas with very deep anterior chamber depth and posteriorly placed lens but short vitreous length, both illustrate biometric differences between these two conditions and also that emmetropisation proceeds in other conditions with altered refractive parameters (the shorter vitreous length being the principal mechanism facilitating emmetropisation).

Increased axial length and ocular distensibility fall subsequently. The comparison with X linked megalocornea where patients typically are emmetropic having symmetrically large but steep corneas with very deep anterior chamber depth and posteriorly placed lens but short vitreous length, both illustrate biometric differences between these two conditions and also that emmetropisation proceeds in other conditions with altered refractive parameters (the shorter vitreous length being the principal mechanism facilitating emmetropisation).

We report four patients (seven eyes) with congenital glaucoma and myopia. Their myopia increased initially after surgical normalisation of pressure suggesting that disturbed growth of the globe continues for a period of time (up to 12 months postoperatively in these patients). Figure 1 illustrates the refractive changes with time. After some months of normalised IOP the myopia returned to emmetropia. Thus emmetropisation must be robust enough to withstand the effects of IOP and ocular enlargement on the various parameters that determine refraction, and furthermore appropriately influence them to achieve emmetropia (or at least result in an eye that is not nearly so myopic as its abnormal axial elongation would suggest). This would provide further support for some active process as part of emmetropisation, rather than just passive proportional enlargement.
revealed a haematoma in the right P-O region. Urgent brain computed tomography (CT) abnormality. A Goldmann visual field test exhibited orthophoria with full and free counting fingers in the left eye. Both eyes neurological examinations were normal. Ophthalmoscopic examination revealed a haematoma (arrowhead, A) in the right P-O region with substantial perifocal oedema (arrowhead, B) and marked cerebral oedema in the left P-O region (arrow, A), which exhibiting hypertense signal on T2 weighted images (arrow, B).

CASE REPORT

A 54 year old woman suffered from sudden onset of severe headache and progressive visual loss in both eyes within 1 day. Her past history was unremarkable but her family history was significant for thrombophilia, pulmonary embolism (her father), and deep vein thrombosis (her son). She had just undergone hormone replacement therapy with oral conjugated oestrogen and medroxyprogesterone for 1 month.

On admission, she was conscious. Blood pressure was 156/84 mm Hg. Physical and neurological examinations were normal. Ophthalmic examinations disclosed corrected visual acuity of 1/60 in the right eye and counting fingers in the left eye. Both eyes exhibited orthophoria with full and free extraocular movement in all directions. The pupils were isocoric, 4 mm in diameter, with sluggish light reflex of both eyes, there being no relative afferent pupillary defect. Slit lamp biomicroscopy, indirect ophthalmoscopy, and fluorescein angiography did not reveal any abnormality. A Goldmann visual field test showed left homogeneous hemianopsia. An urgent brain computed tomography (CT) revealed a haematoma in the right P-O region with marked cerebral oedema and a left shifted midline. A brain magnetic resonance image (MRI) indicated hyperintensities on T1 and T2 weighted images in the corresponding area (Fig 1), although the T1 weighted image (T1WI) and hypertense signal on T2 weighted images (T2WI) indicating cerebral oedema or infarction (Fig 1). A further brain magnetic resonance venography (MRV) indicated a loss of signal in the posterior half of the superior sagittal sinus and adjacent cortical veins (Fig 2). Other laboratory investigations including blood cell counts, PT, APTT, and immunological profiles all returned normal results.

Warfarin and glycerol were administered. Her headache subsided 4 days later. A follow up brain CT 2 weeks after admission revealed the subsidence of cerebral oedema and a partial resolution of the haematoma. The patient’s vision recovered to 6/6 in both eyes 3 weeks subsequently, but the visual field defect persisted. Serial quantitative measurements of anticoagulant factors revealed an inadequate antithrombin III (AT III) level of 57% (normal range 80–120%). Her son and daughter also demonstrated a subnormal AT III level. Now she is doing well with a daily dose of warfarin (5 mg/day).

COMMENT

Acute reversible visual loss in this case was an unusual presentation for CVT. Pathogenetically, CVT may result in visual disturbance through several different mechanisms including long term ICP and complicated venous infarction involving the bilateral visual cortex. The sluggish light reflex with normal disc appearance for this patient may indicate optic nerve dysfunction secondary to acute ICP. Although acute ICP itself may result in transient visual obscurance, severe visual loss only complicates end stage ICP with optic atrophy. On the other hand, CVT associated venous infarction involving the bilateral primary visual cortex may lead to cortical blindness; however, for the present case, the rapid recovery of vision and the absence of any low density regions representing cerebral infarction over the left P-O region on the follow up brain CT excluded such a possibility.

The possible explanation for the acute, reversible visual loss in this case may be the severe left occipital lobe oedema secondary to venous congestion, concurrent with a haemorrhagic infarction in the right P-O region that resulted in the left hemianopsia. In fact, it has been reported that patients with eclampsia may demonstrate transient blindness due to occipital oedema, which may then resolve within 24 hours after delivery and the application of medication to reduce cerebral oedema. Further, when relating brain MRI of venous sinus occlusive disease to the underlying pathophysiology, Yuh et al noted a rapid resolution of the hypertense signal on T2WI after restoration of venous drainage, which indicated that the signal change on T2WI represented reversible venous congestion and pressure driven interstitial oedema. Thus, these authors concluded that early intervention might resolve the clinical symptoms and normalise the MR appearance of certain venous sinus occlusive diseases. Tissue damage for these patients was reported to be predominantly resulted from the haematomas, as was the right P-O haematoma and the persistent left homonymous hemianopsia in this case.

Of note, a combination of a hereditary AT III deficiency, which is extremely rare in orientals, and hormone replacement therapy may have been the culprits leading to an extensive CVT for this patient. In addition, in patients with superior sagittal sinus thrombosis, only one third have a thrombosis involving the posterior third of the sinus, just as in the present case. The acute reversible visual loss, a rarely reported presentation of CVT, could be attributed to the coexistence of extensive cerebral oedema and the relatively unusual site of venous thrombosis in the present case.

Department of Ophthalmology, Taipei Veterans General Hospital, and National Yang-Ming University School of Medicine, Taipei, Taiwan

Correspondence to: Po-Kang Lin, MD, Department of Ophthalmology, Taipei Veterans General Hospital, and National Yang-Ming University School of Medicine, Taipei, Taiwan

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Electrophysiological abnormalities following intravitreal vitravene (ISIS 2922) in two patients with CMV retinitis.

EDITOR—Vitravene (ISIS 2922, formerly known as fomivirsen sodium) is a phosphorothioate oligonucleotide with potent and specific anticytomegalovirus (CMV) activity.1 Vitravene binds to human CMV mRNA and inhibits the synthesis of proteins responsible for regulating virus gene expression. It is given intravitreally and its site of action differs from currently available therapies therefore reducing viral cross resistance. Minimal adverse effects have been reported1 including peripheral visual field loss and retinal pigment changes at high doses but the mechanism of this is not known.1

We report two patients in whom negative electoretinograms (ERGs) were observed following prolonged intravitreal vitravene.

CASE REPORTS

Patient 1

A 51 year old man with AIDS developed CMV retinitis (CMVR) in the left eye in zones 2–3. The right eye was normal and visual acuity was 6/5 right, 6/6 left. The patient failed to respond to standard intravenous therapies or intravitreal ganciclovir. Intravitreal vitravene (330 µg in 0.05 ml) was administered on days 1, 8, and 15 and then fortnightly for 6 months, with good effect. Although vision remained at 6/6 without active CMVR and no zone 1 involvement, the patient described mild photophobia, colour desaturation, and poor dark adaptation in the left eye. An altered macular reflex was noted and fluorescein angiography demonstrated slow choroidal filling and capillary dropout at the macula (Fig 1). Electroretinography was performed to look at retinal function (Fig 2).

Patient 2

A 52 year old man with AIDS developed CMVR in the right eye of similar extent to that in patient 1. His left eye was normal and visual acuity was 6/3 in the amblyopic right eye, 6/4 on the left. Treatment with intravenous cidofovir was successful. The left eye developed macular CMVR, which failed to respond to intravenous ganciclovir or intravitreal ganciclovir and foscarnet.

CMVR reactivated 1 year later in the right eye. Intravitreal vitravene (330 µg in 0.05 ml) was administered on days 1 and 15 and then monthly for 14 months. No further CMVR reactivation was observed in the vitravene treated eye and no new ocular symptoms developed. Retinal function was examined by electrophysiology (Fig 2).

COMMENT

Two cases of CMVR with negative ERGs following intravitreal vitravene are described. A “negative” ERG indicates post-photo-transduction dysfunction, usually post-receptorial. The normal a-wave is consistent with normal photoreceptor function; the reduced EOG light rise also observed therefore suggests additional dysfunction at the level of the RPE/photoreceptor complex. The abnormal pattern ERGs show macular involvement. RPE involvement in AIDS CMVR has been demonstrated ophthalmoscopically and confirmed by histology, immunohistochemistry and electro-oculography.1 The magnitude of EOG light rise reduction in AIDS related CMVR does not correlate with ERG a-wave amplitude, suggesting that the EOG changes are not secondary to photoreceptor dysfunction.1 There is however good correlation with the extent of RPE involvement,1 and EOG may thus be a good indicator of disease activity. Although ERG b-wave reduction may occur in AIDS related CMVR,1,4 the occurrence of a negative ERG in two eyes following intravitreal vitravene, and the normal ERG in a “control” eye with CMVR of similar magnitude which also received intravitreal medication, are in keeping with a causal relation.

H J ZAMBARAKI
S M MITCHELL
Department of Ophthalmology, Chelsea and Westminster Hospital, London, UK

S LIGHTMAN
Department of Clinical Ophthalmology, Institute of Ophthalmology and Moorfields Eye Hospital, London, UK

G E HOLDER
Department of Electrophysiology, Moorfields Eye Hospital, London, UK

Correspondence to: Dr Graham E Holder, Electrophysiology Department, Moorfields Eye Hospital, London EC1V 2PD, UK

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Affordable eye care
The latest issue of Community Eye Health (37) discusses affordable eye care. For further information please contact Community Eye Health, International Centre for Eye Health, Institute of Ophthalmology, 11–43 Bath Street, London EC1V 9EL. (Tel: (+44) (0) 20-7608 6909/6910/6923; fax: (+44) (0) 7250 3207; email: eyeresource@ucl.ac.uk) Annual subscription £25. Free to workers in developing countries.

International Centre for Eye Health
The International Centre for Eye Health has published a new edition of the Standard List of Medicines, Equipment, Instruments and Optical Supplies (2001) for eye care services in developing countries. It is compiled by the Task Force of the International Agency for the Prevention of Blindness. Further details: Sue Stevens, International Centre for Eye Health, 11–43 Bath Street, London EC1V 9EL, UK (Tel: (+44) (0) 20-7608 6910; email: eyeresource@ucl.ac.uk).

31st Cambridge Ophthalmological Symposium
The 31st Cambridge Ophthalmological Symposium will be held 3–5 September 2001 at St John's College Cambridge. The subject is Retinal Detachment. Further details: COS Secretariat, Cambridge Conferences, The Lawn, 33 Church Street, Great Shelford, Cambridge CB2 5EL, UK (tel: 01223 847464; fax: 01223 847465; email: b.ashworth@easy.net.co.uk).

1st Asia Pacific Forum on Quality Improvement in Health Care
The 1st Asia Pacific Forum on Quality Improvement in Health Care will be held from 19–21 September 2001 in Sydney, Australia. Presented by the BMJ Publishing Group (London, UK) and Institute for Healthcare Improvement (Boston, USA), with the support of the Commonwealth Department of Health and Aged Care (Australia), Safety and Quality Council (Australia), NSW Health (Australia) and Ministry of Health (New Zealand). Further details: quality@bma.org.uk; fax +44 (0) 7383 6869.

41st St Andrew’s Day Festival Symposium on Therapeutics
The 41st St Andrew’s Day Festival Symposium on Therapeutics will be held on 6–7 December 2001 at the Royal College of Physicians of Edinburgh. Further details: Ms Eileen Strawn, Symposium Co-ordinator (tel: 0131 225 7324; fax: 0131 220 4393; email: e.strawn@rcpe.ac.uk; website: www.rcpe.ac.uk).

4th International Conference on the Adjuvant Therapy of Malignant Melanoma
The 4th International Conference on the adjuvant therapy of malignant melanoma will be held at The Royal College of Physicians, London on 15–16 March 2002. Further details: Conference Secretariat, CCI Ltd, 2 Palmerston Court, Palmerston Way, London SW8 4AJ, UK (tel: + 44 (0) 20 7720 0600; fax: + 44 (0) 20 7720 7177; email: melanoma@confcomm.co.uk; website: www.confcomm.co.uk/Melanoma).