PostScript

LETTERS

Circumpapillary choroidal "haemorrhoid" in Klippel-Trenauney-Weber syndrome

Klippel-Trenauney-Weber syndrome is a neurocutaneous vascular disease characterised by deep venous dysplasia affecting the head and limbs.¹ Affected patients are born with bilateral facial port-wine stains, and develop progressive limb hypertrophy secondary to high tissue pressure from chronic venous and lymphatic outflow obstruction.¹ Reported ophthalmological signs include conjunctival and retinal varicosities, choroidal thickening, orbital varices and iris heterochromia.² This article describes treatment of a patient with Klippel-Trenauney-Weber syndrome and congenital glaucoma who developed circumpapillary choroidal varices in the right eye over a 15-year period of observation.

Case report

A 1-year-old girl had bilateral facial port-wine stains, lumbosacral and lower limb port-wine stains with associated limb hypertrophy, and congenital glaucoma in both eyes (fig 1A).

After surgery, intraocular pressure (IOP) was controlled by topical drugs. At age 4 years, visual acuity was 20/200 OD and 20/20 OS. Cup-to-disc ratio was 0.6 OD with no peripapillary atrophy and no associated choroidal varix (fig 1B), and 0.75 OS. By 12 years of age, incipient choroidal varices encircled the right optic disc (fig 1C). Magnetic resonance imaging with phlebography showed no abnormalities of the central nervous system.

The patient discontinued her drugs and was lost to follow-up until the age of 18 years. On re-examination, IOP was 42 mm Hg in the right eye and 32 mm Hg in the left eye. Corrected visual acuity values were 20/400 OD and 20/50 OS. Cycloplegic refraction was $-4.50+3.25 \times 92^\circ$ OD and $-2.50+0.50 \times 16^\circ$ OS. Retinal examinations showed peripapillary ectasia with circumpapillary choroidal varices bordering the staphylomatous area in the right eye (fig 1D). Fluorescein angiography showed uniform hypofluorescence of the superior varices with no leakage. Four months after Ahmed valve implantation and normalisation of IOP in the right eye, these circumpapillary varices showed no change in appearance.

Comment

Posterior choroidal outflow routes are common in highly myopic eyes.³ Using indocyanine green

videoangiography, Ohno-Matsui *et al*³ observed choroidal venous outflow through posterior routes in 61 of 255 (23.9%) highly myopic eyes versus only 1 of 42 (2.4%) control eyes. In all, 39 eyes had venous drainage into the optic nerve margin (known as chorio-vaginal veins of Coats),⁴ 24 eyes had macular vortex veins and 4 eyes had vortex veins that penetrated the sclera just within the edge of a peripapillary staphyloma, as in our patient. These posterior veins tended to be dilated and tortuous and showed delayed drainage, suggesting that they provided collateral venous outflow in the presence of choroidal circulatory stasis.³

Klippel-Trenauney-Weber syndrome is associated with orbital venous stasis and secondary glaucoma.¹ Our patient's choroidal varices demarcated an area of peripapillary ectasia, suggesting that a posterior pressure differential contributed to their development at this site. Increased vortex venous pressure or thrombosis due to a combination of orbital venous hypertension and raised IOP probably led to compensatory enlargement of pre-existing choroidal venous bypass channels. The evolution of this circumpapillary choroidal "haemorrhoid" is another ocular manifestation of the orbital venous stasis and raised IOP, which complicates the Klippel-Trenauney-Weber syndrome.

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Informed consent was obtained for publication of fig 1.

doi: 10.1136/bjo.2006.102079

Accepted 30 June 2006

Funding: This study was supported in part by an unrestricted grant from the Research to Prevent Blindness (New York) and the Pat & Willard Walker Eye Research Center, Jones Eye Institute, University of Arkansas for Medical Sciences (Little Rock, Arkansas).

Competing interests: None declared.

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The enhanced S-cone syndrome in children

The enhanced S-cone syndrome (ESCS), a retinal degenerative disease often associated with *NR2E3* mutation,¹⁻⁴ is due to increased numbers of S-cones at the expense of other photoreceptors or miswiring distal to the photoreceptors.⁵ Adults complain of hemeralopia, and are diagnosed from their unique

Figure 1 Klippel-Trenauney-Weber syndrome. (A) Facial photograph showing bilateral port-wine stain. (B) Retinal photograph at 4 years of age, showing normal peripapillary choroid in the right eye. (C) Retinal photograph at 12 years of age, showing early formation of circumpapillary choroidal varices in the right eye. (D) Retinal photograph at 18 years of age, showing prominent circumpapillary choroidal varices. Informed consent was obtained for publication of this figure.

Figure 1 (A, case 1) In both eyes, the retinal pigment epithelium (RPE) had an unhealthy appearance, with scattered subretinal deposits most prominent in the fovea. No pigmentary deposits were seen. (B, mother of case 1) The appearance was classic for enhanced S-cone syndrome, with deep clumped retinal pigmentary deposits and RPE atrophy outside the vascular arcades of both eyes. Foveal schisis was seen in the left eye (not shown). (C, case 2) A prominent subretinal lesion was seen in a similar location in the posterior pole of both eyes (arrow). In addition, scattered small subretinal deposits and spots of pigments were present (arrowheads). (D, case 3) The RPE had an unhealthy appearance, with scattered small subretinal deposits and subretinal spots of pigment (arrowheads). One larger subretinal deposit was adjacent to the disc in the right eye (arrow).

retinal and electroretinogram (ERG) findings^{1–4}—characteristic deep clumped pigmentary deposition around the vascular arcades;^{1–4} varying degrees of retinoschisis;^{1–4} a similar, simplified and delayed ERG waveform response to flashes under photopic and scotopic conditions;^{2,3} and a delayed 30-Hz flicker ERG amplitude lower than that of the photopic a-wave.^{2,3} Paediatric ESCS and its differing clinical features is the subject of this report.

Case series

Three children were evaluated because of inward eye turn and poor night vision noted since approximately 2 years of age. Retinal examination (fig 1) and cycloplegic refractions were performed 40 min after cyclopentolate 1% drops. *NR2E3* was directly sequenced¹ from venous blood samples. ERGs, performed under chloral hydrate sedation and according to the recommendations of the International Society for Clinical Electrophysiology of Vision,³ were consistent with ESCS (fig 2). Family history was significant only for case 1.

Case 1 (a 3-year-old girl)

The patient's mother had a history of poor night vision for many years. The patient had central/steady/maintained vision in either eye, 18-prism diopters oesotropia at distance and near, and a cycloplegic refraction of +5.75–1.50×180 OD (right eye), +6.00–1.50×180 OS (left eye). Both eyes had an unhealthy retinal

pigment epithelium (RPE) appearance with subfoveal lesions OU (fig 1A). Wearing her full cycloplegic refraction, the patient had no oesotropia. Examination of her mother showed no strabismus, uncorrected visual acuity of 20/60 OD and 20/200 OS, deep clumped pigmentation outside the vascular arcades OU (fig 1B), foveal schisis OS, no significant cycloplegic refraction and an ERG diagnostic for ESCS (fig 2B). Both mother and daughter were homozygous for a previously reported *NR2E3* splice mutation (IVS1-2A→C).¹ The father (the mother's cousin) was confirmed as a carrier.

Case 2 (a 5-year-old boy)

The patient had a visual acuity of 20/80 OD and 20/40 OS, 20-prism diopters oesotropia at distance, 25-prism diopters oesotropia at near, and a cycloplegic refraction of +6.00–2.00×115 OD and +6.00–2.00×75 OS. There were multiple subretinal white deposits and an unhealthy appearance to the RPE (fig 1C). Wearing his full cycloplegic refraction, the patient had no oesotropia at distance and 20/30 vision in either eye. Direct sequencing of *NR2E3* was negative. Additional mutational analyses^{6,7} were not performed.

Case 3 (a 5-year-old boy)

The patient, not cooperative for visual acuity testing, had approximately 20-prism diopters oesotropia at near. Cycloplegic refraction was +7.25 OU. Retinal examination was significant

for subretinal white lesions (fig 1D). Wearing his full cycloplegic refraction, the patient had no oesotropia at distance and 20/30 vision OU. *NR2E3* sequencing showed homozygosity for a previously reported missense mutation (R311Q, CGG→CAG).¹

Discussion

The unique retinal phenotype that typically leads to the diagnosis of ESCS in adults was not observed in the children of this case series. The fact that the affected mother of case 1 exhibited the classic pattern of clumped pigmentation unique to ESCS led us to suspect the diagnosis in her 3-year-old daughter and raised our awareness for subsequent similar paediatric patients (cases 2 and 3). Murine models suggest that typical adult retinal phenotype develops over time.⁸ In one previously reported case, the characteristic retinal clumped pigmentation pattern developed between 9 and 11 years of age.⁴ The authors of that report also believed that significant hyperopia is a recurring feature of ESCS that may be missed without a cycloplegic refraction. Our case series suggests that night blindness, refractive accommodative oesotropia and subretinal lesions are presenting features of ESCS in young children.

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Parental/guardian informed consent was obtained for publication of the person's details in this report.

doi: 10.1136/bjo.2006.097956

Accepted 3 July 2006

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Figure 2 The electroretinograms (ERGs) of (A) case 1, (B) her mother, (C) case 2 and (D) case 3 were diagnostic for enhanced S-cone syndrome (ESCS)—a similar, simplified and delayed waveform response to flash under photopic and scotopic conditions; and a delayed 30-Hz flicker amplitude lower than that of the photopic a-wave. The left tracings of each column are for the left eye and right tracings for the right eye. Stimulus intensities are described in logarithmic (log) units relative to the standard stimulus (1.5–3 Candelas/m² at the surface of the Ganzfeld bowl). For each ERG in the first column (Rod Response), top tracings are for a minimal (0.25 log units) blue (430 nm) stimulus, middle tracings are for a standard (1.0 log unit) red (644 nm) stimulus, and bottom tracings are for a maximal (1.5 log units) white flash. Repeat recordings are seen in (A). In the second column (cone response), for the tracings in (A) and (C), the top tracings are for maximal flash with low background illumination (1 foot Lamberts), the middle tracings for standard flash with high background illumination (30 foot Lamberts), the second to last tracings are for maximal intensity flicker (30 Hz) with low background illumination, and the bottom tracings are for standard intensity flicker with low background illumination. Repeat recordings are seen for these tracings in (B) and (D), the top tracings are for maximal flash with low background illumination and the bottom tracings are for maximal intensity flicker with low background illumination; no repeats were done.

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Retinal and subdural haemorrhages from minor falls?

Retinal and subdural haemorrhages with or without occult bone fractures in children aged <3 years is a characteristic presentation of the shaken baby syndrome (SBS) with or without blunt head impact.^{1–3} The signs may pose diagnostic dilemmas resulting from an inconsistent history given by the child's caretakers and the frequent absence of evidence of

external injury. Accidental blunt impact that leads to subdural haemorrhage is usually associated with significant trauma, skull fractures and only rare cases of retinal haemorrhage. There is abundant evidence that minor head trauma, in the absence of underlying medical conditions such as osteogenesis imperfecta type I,⁴ is only very rarely associated with severe intracranial injury or retinal haemorrhage, particularly the extensive multi-layered haemorrhages extending to the ora serrata, as seen in two thirds of the victims with SBS.^{1–3, 5}

A letter in the *British Journal of Ophthalmology* considers prior reports regarding Japanese children who sustained subdural and retinal haemorrhage after short falls.⁶ We believe that the statistical analysis and discussion

presented in the letter have inaccuracies that could lead to the incorrect conclusion that biological factors may explain the reported clinical findings which otherwise disagree with the findings in the world's literature on this topic.

Gardner suggests statistically significant discrepancies in age distribution between two Japanese cohorts with allegedly accidental head trauma^{7, 8} and Kivlin's American series of victims with shaken baby syndrome³ as one possible biological explanation for the unique nature of the Japanese cohorts, which he claims have statistically similar ages.⁶ One of the Japanese publications reports on 26 infants with retinal and subdural haemorrhages after fall backwards from sitting or standing on tatami mats.⁶ The other does not include the mechanism of injury or eye examinations.⁷

The degree of freedom (df) for two-sample independent t tests, assuming equality of variance, is $(n_1 - 1) + (n_2 - 1)$, where n_1 and n_2 are sample sizes of the two groups. When variances are unequal, Satterwaite adjustment is recommended.⁹ For data presented by Aoki, Ikeda and Kivlin, the sample sizes are 26, 14 and 102, respectively. When comparing Kivlin's cohort with Aoki's, df is 126 for equal variances and 65.3 for unequal variances. For t tests conducted by Gardner, df values were 13, 13, 25 and 39, which should have been 38, 114, 126 and 140 for equal variances, and 22.2, 20.2, 65.3 and 103 for unequal variances, for testing Aoki versus Ikeda, Ikeda versus Kivlin, Aoki versus Kivlin, and the combined Japanese studies versus Kivlin, respectively. As p values depend on df, the correct p values are 0.0247, <0.001, <0.001 and <0.001, respectively. Gardner's conclusion of similarity in age distribution between the two Japanese groups is therefore incorrect.

Classical p values represent the probability of making an incorrect rejection of the null hypothesis: the probability of saying that the mean ages of two groups are different when they are equivalent. p Value is not the probability of ruling in or out differences in group means or proportions (not being able to rule out a difference with a 20% probability).⁸

The two Japanese cohorts actually have significantly different ages, and both are different from Kivlin's sample. It is therefore unlikely that age is an explanatory factor for their unusual clinical findings. In addition, the mere act of falling over from a sitting or standing position is not developmentally possible in most victims of SBS, the incidence of which is highest in the first 6 months. Crying is a major factor in inciting SBS. The normal crying curve is similar to the SBS incidence curve.¹⁰

Thus, it is not surprising that Kivlin's patients are different from the Japanese samples. But why are the Japanese reports of subdural and retinal haemorrhage after minor trauma so very different from the bulk of the world's literature? Some of the Japanese patients were recruited before SBS had even been described or widely recognised in the world's literature. Gardner notes the admission in Aoki's paper that cases of abuse might have been included. At the time of Aoki's study, there were no child abuse teams or reporting laws in Japanese society.² Abuse could not have been adequately ruled out.

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