CASE REPORTS

Dominantly inherited unilateral retinal dysplasia

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We present a pedigree of dominantly inherited unilateral retinal dysplasia. To our knowledge this pattern of inheritance has not been previously reported. We provide details of three cases and one strongly suspected case (now deceased) in five generations of one family.

Case report

The proband, a 4 month old male infant (V-2, Fig 1) was urgently referred to Manchester Royal

Eye Hospital. His left eye had been noted to be clinically small with an abnormal pupil and a white pupillary reflex. His general practitioner and the family were under the impression that there was a strong family history of retinoblastoma. An examination was performed under anaesthesia. The right eye was normal. The left eye was microphthalmic with a horizontal corneal diameter of 9.5 mm (right corneal diameter 11 mm). There were very prominent iris vessels and temporal posterior synechiae (Fig 2). The pupil dilated poorly. A white retrolental mass with an adherent strand to the posterior surface of the lens was present (Fig 3A). There was a large area of retinal fold (Fig 3B) and disorganised retinal vasculature. No calcification was apparent. Axial length was 14 mm (right 19.4 mm).

The child was reviewed again at 18 months of age. Examination of the right eye demonstrated good fixation and following. No fixation was apparent with the left eye which had become esotropic. There was no evidence of secondary glaucoma. His general growth and development were normal and audiometric assessment indicated normal hearing. General physical examination was unremarkable and in particular there were no dysmorphic features and no neurocutaneous stigmata.

The proband's mother (IV-3) had been noted to have a 'missing pupil' in her right eye at the age of 2 months. Following ophthalmic referral, the right eye was enucleated for suspected retinoblastoma. A pathological diagnosis of faulty retinal coaptation with secondary glaucoma and ocular enlargement was recorded in the original pathological records but, despite this, she subsequently underwent regular examinations of the other eye until adulthood. No further ocular

Figure 1 Pedigree of family affected by unilateral retinal dysplasia.

Figure 2 Normal right eye and affected left eye of proband (V-2) showing posterior synechiae and a vascularised white retrolental mass.

Figure 3 B-scan ultrasound pictures of proband (V-2) showing retrolental mass (A) and fold of (presumed) dysplastic retina (B).

Fig 3A

Fig 3B

abnormalities were found. A review of her histology revealed a globe measuring 20 mm in length, with corneal diameters 12 mm (horizontal) by 15 mm (vertical). A major retinal detachment with disorganisation and gliosis was present. The retina was totally detached and bunched up in the retrolental area, with separation from the lens by a fibrovascular layer (Fig 4). Many rosettes were present within the disorganised retina (Fig 5). There was focal proliferative activity of the retinal pigment epithelium. Anterior to the retina and separating it from the lens, was a fibrovascular layer. In the central part of this there was haemosiderin pigment, probably the remains of old haematoma. A vascularised band of granulation tissue lay internal to the distorted ciliary body. Massive subretinal haemorrhage was present, possibly from the abnormal fibrovascular area adjacent to the ciliary body. The lens was cataractous and the iris was adherent to the posterior surface of the cornea at several points (Fig 4). A delicate fibrovascular pupillary membrane was present and iris root occluded the anterior chamber angle. There were several splits in Descemet's membrane indicating secondary glaucoma. There was no evidence of retinoblastoma.

Her general growth, development, and schooling were normal. She has had no major illnesses or operations and no hearing loss. General examination at age 26 years was unremarkable. Chromosome analysis revealed a normal female karyotype, 46XX. The proband's half sister (V-1) aged 2 years had no history of visual or ocular abnormality and on clinical examination and examination under anaesthesia no ocular

abnormalities were found. Her general growth, development, and appearance were normal.

The proband's maternal grandmother (III-2) had her left eye enucleated at the age of 2 months because of leucocoria, microphthalmos, and suspected retinal mass. Histological records have unfortunately been lost. Clinical examination demonstrated a normal right eye with in particular a normal axial length and no vitreous or retinal abnormalities. The left socket was healthy.

The proband's maternal great grandmother (II-1) gave no history of ocular or visual problems beyond hypermetropia. Ophthalmic examination revealed no abnormality of either eye.

The proband's great, great grandmother (I-1) who died aged 84 ten years ago was described by the family as having a 'small abnormal right eye which was blind.' It apparently 'turned in and had a white pupil.' This is corroborated by the pathology notes of the infant's mother. She apparently had no surgery for this and no problems with her other eye. Her general health was good until her latter years.

Comment

Retinal dysplasia is a congenital abnormality in which the normal trophic influence of the retinal pigment epithelium upon the developing retina is disturbed. It appears to be a non-specific response to separation of the retina from its underlying pigment epithelium at a critical stage of differentiation.¹² This leads to abnormal retinal proliferation resulting in rosette-like configurations (see Fig 5). It may be unilateral or bilateral often with associated microphthalmos.

Figure 4 Right globe of proband's mother showing detached, disorganised mass of retina and fibrous tissue posterior to the lens. There is extensive subretinal haemorrhage. The arrow indicates the area of rosette formation shown at higher magnification in Figure 5. (Masson trichrome. $\times 2$ approx.)

Figure 5 Area of retinal detachment in Figure 4 showing disorganised, gliotic retina with rosette formation. (Haematoxylin and eosin, $\times 150$.)

Weiss *et al* found that four out of a series of 40 patients with complex microphthalmos (that is, microphthalmos associated with another ocular abnormality) had evidence of retinal dysplasia.³

Retinal dysplasia is also often associated with some degree of persistent hyperplastic primary vitreous (PHPV).¹ In Lahav *et al*'s series of four individuals with isolated retinal dysplasia, three had coexistent PHPV.⁴ Parsons *et al* postulate that in Norrie disease contraction of retrolental fibrovascular tissue, probably from a persistent primary vitreous, leads to separation of the developing retina from the underlying retinal pigment epithelium during early differentiation.⁵ They believe that this results in subsequent maldifferentiation and retinal dysplasia with rosette formation. We feel that the same mechanism explains the association of PHPV in general with retinal dysplasia. The term 'vitreo-retinal dysplasia' has been used in such cases.⁶ Glaucoma is a frequent complication and may mask an underlying microphthalmos by causing ocular enlargement.¹

Retinal dysplasia may be part of a pattern of malformations such as in Norrie disease,^{5,7} trisomy 13,⁸ incontinentia pigmentii,⁹ and Walker-Warburg syndrome.¹⁰ Environmental agents have been implicated in some cases. Animal studies have suggested that intrauterine trauma² and viral infection¹¹ can be factors. D-Lysergic diethylamide (LSD) ingestion in the first trimester of pregnancy has also been implicated.¹²

Bilateral retinal dysplasia without any other congenital abnormality was reported by Wilson in 1949¹³ and Hunter in 1965¹⁴ in a large Ojibway Indian family. The pedigree of this family is consistent with X linked recessive inheritance.

Sixteen isolated unilateral cases were reported by Hunter *et al* in 1965.¹⁴ Two had a relative with an undetermined ocular lesion suggesting a possible genetic aetiology. The pattern of affected individuals in our pedigree supports autosomal dominant inheritance and this pattern of inheritance has not to our knowledge been previously described in retinal dysplasia although vertical transmission has been described in PHPV.¹⁵ One male and two, if not three, females are affected in our pedigree with probably little variability of gene expression. The possibility does remain, however, that this could be an X linked dominant

pedigree with variable penetrance. Dominantly inherited disorders may show lack of penetrance – that is, no evidence of disease in individuals known to possess the gene (by reason of an affected parent and offspring). If individual I-1 was affected, as seems likely from the history, then II-1 with a normal ophthalmic examination shows lack of penetrance. Genetic counselling for other seemingly unaffected family members needs to take this into consideration. If this condition is autosomal dominant every known affected family member has a 50% chance of passing this type of retinal dysplasia on with each child they have.

X linked dominant inheritance would mean that an affected man would pass the trait on to all of his daughters but none of his sons, while an affected woman would have a 50% chance of having an affected son or daughter. There is no evidence so far that this condition would become bilateral in a subsequent generation, but this cannot be ruled out.

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- 1 Green WR. Retinal dysplasia. In: Spencer WH, ed. *Ophthalmic pathology*. Philadelphia: Saunders, 1985: 615–7.
- 2 Silverstein AM. Retinal dysplasia and rosettes induced by experimental intrauterine trauma. *Am J Ophthalmol* 1974; 77: 51–8.
- 3 Weiss AH, Koussef BG, Ross EA, Longbottom J. Complex microphthalmos. *Arch Ophthalmol* 1989; 107: 1619–24.
- 4 Lahav M, Albert DM, Wyand S. Clinical and histopathological classification of retinal dysplasia. *Am J Ophthalmol* 1973; 75: 648–67.
- 5 Parsons MA, Curtis D, Blank CE, Hughes HN, McCartney ACE. The ocular pathology of Norrie disease in a fetus of 11 weeks' gestational age. *Graefes Arch Clin Exp Ophthalmol* 1992; 30: 248–51.
- 6 Moore AT. Vitreous. In: Taylor D, ed. *Paediatric ophthalmology*. Oxford: Blackwell, 1990: 91–102.
- 7 Warburg M. Norrie's disease: a new hereditary bilateral pseudotumour of the retina. *Acta Ophthalmol* 1961; 39: 752–72.
- 8 Michon JJ, Borges JM, Tso MO. Heterotopic ciliary epithelial differentiation in a patient with trisomy 13. *J Pediatr Ophthalmol Strabismus* 1991; 28: 23–7.
- 9 Raab EL. Ocular lesions in incontinentia pigmentii. *J Pediatr Ophthalmol Strabismus* 1983; 20: 42–8.
- 10 Donnai D, Farndon PA. Syndrome of the month: Walker-Warburg syndrome. *J Med Genet* 1986; 23: 200–3.
- 11 Silverstein AM, Parshall CJ, Osburn BI, Prendergast RA. An experimental virus-induced retinal dysplasia in the fetal lamb. *Am J Ophthalmol* 1971; 72: 22–34.
- 12 Chan CC, Fishman M, Egbert PR. Multiple ocular anomalies associated with maternal LSD ingestion. *Arch Ophthalmol* 1978; 96: 282–4.
- 13 Wilson WMG. Congenital blindness (pseudoglioma) occurring as sex-linked developmental anomaly. *Can Med Ass J* 1949; 60: 580–5.
- 14 Hunter WS, Zimmerman LE. Unilateral retinal dysplasia. *Arch Ophthalmol* 1965; 74: 23–30.
- 15 Lin AE, Biglan AW, Garver KL. Persistent hyperplastic primary vitreous with vertical transmission. *Ophthalmic Pediatr Genet* 1990; 11: 121–2.