LETTERS TO THE JOURNAL

Sir,

Aniridia in Only One Identical Twin

Aniridia is a very rare bilateral disorder with a congenital absence of the iris, and is usually associated with nystagmus and foveal hypoplasia. This may be accompanied by cataracts, corneal opacification and glaucoma.[1] The resultant vision is poor. We present the case of identical twin girls where aniridia was only present in one sister.

Case History

A healthy 28-year-old English woman gave birth to identical twin girls during a full-term spontaneous vaginal delivery. It was noticed that the twins shared a placenta. One week after birth, it was noted that one of the twins had aniridia, after which the twins were referred for an ophthalmic opinion. The affected sister appeared normal, apart from her aniridia. The unaffected sister was entirely normal. There was no family history of aniridia, but 3 years previously a male fetus had died during birth due to anoxia secondary to abruptio placentae (Fig. 1).

When seen in the ophthalmic clinic, the finding of aniridia in only one of the twins was confirmed. The affected twin was seen to have fast nystagmus, and intraocular pressures (IOPs) as measured with a Pulsair tonometer were 9 mmHg. The corneae, optic discs and maculae appeared normal, and there was no significant refractive error. The affected sister was placed on the blind register at a subsequent visit. The twins were referred to both a paediatric oncologist (because of the risk of Wilms' tumour) and a clinical geneticist for further investigations. An abdominal ultrasound scan showed both kidneys to be normal with no evidence of a renal mass. Blood was taken from the family for genetic testing. This showed that the affected twin had a normal female karyotype.

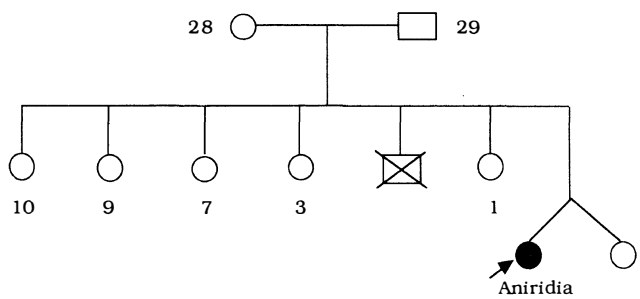

Fig. 1. *The family tree.*

Fluorescent in situ hybridisation (FISH) analysis with the probes surrounding the aniridia locus PAX6 found no abnormalities on either chromosome 11 (i.e. no increased risk of Wilms' tumour) (Fig. 2). Preparation of cell lines to test for monozygosity showed the girls not to be genetically identical. The result of the last investigation only became available once the twins were one and a half years of age.

Discussion

Aniridia occurs at a frequency of approximately 1 in 80 000. About two-thirds of children with aniridia have affected parents, with the disorder being inherited as an autosomal dominant trait with variable expressivity. About a third of individuals with the sporadic form of aniridia also develop Wilms' tumour. Those with aniridia and Wilms' tumour are usually mentally retarded and often suffer from genitourinary symptoms (i.e. WAGR syndrome).[2] Such patients are usually heterozygous for constitutional deletions of chromosomal band 11p13. The aniridia gene is located about 700 kilobases telomeric to the Wilms' tumour predisposing gene (WT1) (Fig. 2). The aniridia gene is homologous to the mouse PAX6 gene. Mutations in the PAX6 gene have been identified in familial and sporadic forms of aniridia.[3–5]

The observation of discordance in supposed identical twins could be explained by four genetic mechanisms:

(1) *Non-penetrance.* Both the twins have the mutation, which either inactivates the expression of the PAX6 gene or disrupts the PAX6 gene product –

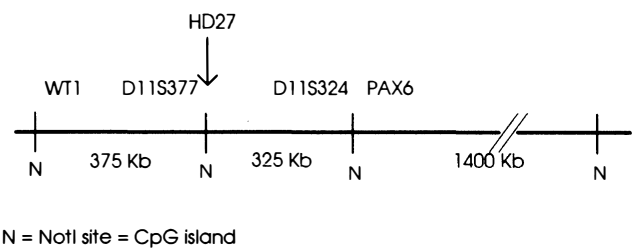

Fig. 2. *Long-range NotI restriction map of the WAGR region. WT1 is the Wilms' tumour predisposition gene and PAX6 is the aniridia gene. Cosmids for WT1, D11S324 and PAX are used to look for aniridia-associated deletions to ensure that any possible case with even partial deletion of WT1 is found.*

a regulatory protein. The phenotype presumably results from heterozygous insufficiency such that if only one copy of the gene is active, insufficient protein is produced to effect development of the iris. The threshold amount of this protein below which aniridia would occur in the developing eye may be dependent on something else – for example, an environmental factor may allow one twin to escape the disease despite having the gene. As with all congenital eye diseases, careful examination of both parents is important to try to detect a mild form of the abnormality which has not presented as disease. In this case both parents' anterior segments were absolutely normal.

(2) *Post-zygotic.* The mutation may have occurred in the embryo after twinning such that only one of the twins has the mutation. Mutation may also have occurred before twinning in which case the twins differ in the degree of mosaicism for the mutation.

(3) *Genomic imprinting.* In a number of human genetic conditions, the nature of the disease depends upon whether it has been inherited from the mother or the father. The cell appears to recognise from which parent the gene has been inherited. This so-called imprinting of the gene has been recognised in several inherited diseases, but in particular Beckwith–Weideman syndrome. The gene for this condition has been localised to the short arm of chromosome 11. At least nine cases of monozygotic twins, all females discordant for the Beckwith–Weideman syndrome phenotype, have been described.[6,7] The possibility that all would be the same sex by chance is small. In all females, one X chromosome is inactivated in every cell, and this process, X-inactivation, appears to occur at about the same time as the division of the blastocyst that results in monozygotic twins. Since X-inactivation and monozygous twinning seem to occur at about the same time in embryological development, interference or interaction of one with the other is possible. Little is known of the mechanism of imprinting. Genomic imprinting, monozygous twinning and X-inactivation may be mechanically as well as temporally related, and their interactions may provide important clues to the nature of the early development process.[8] The WT1 (Wilms' tumour predisposing) gene, only 700 kilobases telomeric to PAX6, has been shown to be imprinted. In fetal brains only the maternal copy of WT1 is expressed, whereas in the kidney both the maternal and paternal copies are expressed.[9]

(4) *Non-homozygosity.* Despite good physical evidence for homozygosity, only molecular evidence for monozygosity is proof. Preparation of cell lines to test for identity, followed by aniridia mutation analysis, are essential. In our case, after a lengthy wait, tests of genetic identity showed the phenotypically identical twins to be genotypically non-identical, i.e. non-homozygosity was the cause of aniridia seen in only one female twin.

If the twins had been monozygous, then genomic imprinting would have been the most likely mechanism to account for aniridia in only one homozygous twin, with methylation of the DNA being generally regarded as the most likely mechanism underlying imprinting. Methylation studies could have been carried out to see whether a region close to or within the PAX6 gene was differentially methylated in such hypothetically identical twins. Any such evidence would strongly indicate imprinting of the aniridia gene as the underlying cause for such discordance. Since, by analogy to the mouse and from some evidence from humans, the PAX6 gene is expressed mostly in the developing central nervous system, the nose and developing eye, direct expression studies would not be possible. In such a case where discordance is observed only in female monozygous twins, and considering the closeness of PAX6 to WT1 (and by analogy with Beckwith–Weideman syndrome), it may be plausible that PAX6 may be imprinted such that one of the twins has a silenced copy of the PAX6 gene.

S. A. Sadiq, DO, MRCOphth, FRCS
Ophthalmology Department
Queen's Medical Centre
Nottingham, UK

A. L. Sharif, BSc, PhD, MPhil
Centre for Medical Genetics
City Hospital
Nottingham, UK

R. M. Gregson, DPhil, FRCS, FRCOphth
Queen's Medical Centre
Nottingham, UK

Correspondence to:
Mr R. M. C. Gregson
Consultant Paediatric Ophthalmologist
Queen's Medical Centre
University Hospital
Nottingham NG7 2UH
UK

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Sir,

Cystoid Macular Oedema in Chronic Myeloid Leukaemia: Treatment with Acetazolamide and Response to Bone Marrow Transplantation

We report the first described case of cystoid macular oedema (CMO) occurring in a patient with chronic leukaemia. An initial resolution followed treatment with acetazolamide, previously thought useful only in ocular disease with blood–retinal barrier disruption and breaches in the retinal pigment epithelium. Complete resolution of CMO followed bone marrow transplantation, the unique relevance of which is discussed.

Case Report

A 50-year-old Caucasian man presented to his general practitioner with a 6 month history of malaise, weight loss and splenomegaly. More lately he had noticed deteriorating visual acuity in his left eye, although vision in the other eye seemed unaffected. Investigation revealed chronic myeloid leukaemia (CML) with confirmation of the BCR-ABL gene rearrangement. Treatment was commenced with hydroxyurea and immediate haematological improvement was noted at 11 days. After a further 2 weeks he was in remission and the dose of hydroxyurea was reduced. At no time did the patient show features of diabetes.

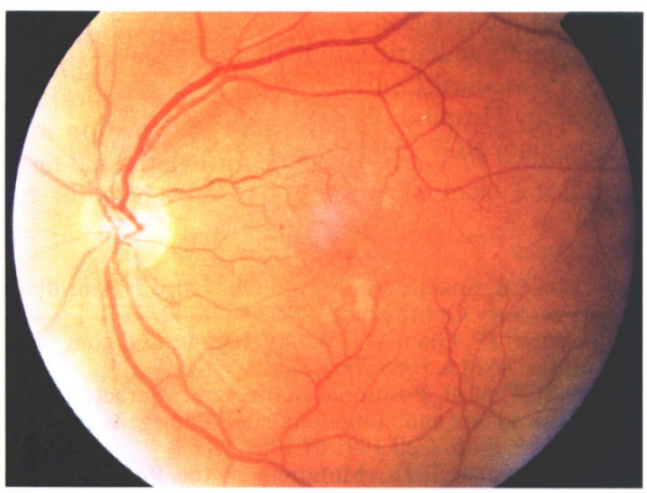

Fig. 1. *Appearance of left macula at presentation. Note the cystic changes at the fovea and scattered microaneurysms. There is an area of retinal thickening just below the fovea.*

Three months after diagnosis he presented to us with visual acuities of 6/5 right 6/60 left and no refractive improvement. Pupillary reflexes and anterior segment appearances were normal, and each retina contained a few small blot haemorrhages in its periphery. The right macula was normal but the left showed cystic changes at the fovea and several microaneurysms (Fig. 1). There were no cotton wool spots or signs of vascular occlusion. Fundus fluorescein angiography confirmed CMO in the left eye (Fig. 2), and several hyperfluorescent points corresponding to the microaneurysms seen on ophthalmoscopy.

We treated the CMO with acetazolamide slow release 250 mg twice daily. There was rapid visual improvement and after 4 weeks acuity had improved to 6/5 right OS left. The CMO appeared less marked on fluorescein angiography, as were the other points of hyperfluorescence (Fig. 3). Treatment was stopped after 7 weeks and within 5 days acuity had fallen to 6/36, with no pinhole improvement. Acetazolamide was restarted with rapid improvement to 6/5 right 6/6 left, and visual symptoms were subsequently controlled with acetazolamide 250 mg daily.

Eight months after presentation the patient underwent sibling allogeneic bone marrow transplant (BMT) from his HLA identical sister and achieved neutrophil engraftment after 27 days.

His vision was remained stable and acetazolamide was withdrawn 4 months after BMT. After a further 6 months visual acuity still measured 6/5 in each eye, with normal colour vision and retinal appearances. Fluorescein angiography at this time showed a marked decrease in hyperfluorescence both at the fovea and at the other macular locations previously exhibiting leakage (Fig. 4).

Discussion

Fundal abnormalities are well-recognised signs of leukaemia at its presentation,[1] and prior to the

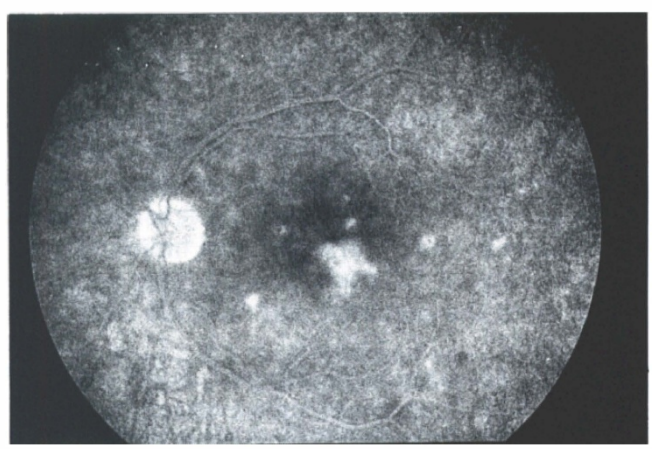

Fig. 2. *Fluorescein angiogram at presentation, showing hyperfluorescence corresponding to macular oedema and scattered microaneurysms.*