

CASE REPORTS

Manifesting heterozygosity in Norrie's disease?

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It is well recognised that Norrie's disease is an X linked disorder causing blindness in early infancy, often in association with hearing loss and/or psychomotor retardation.¹ The diagnosis is established by the finding of congenital pseudoglioma in a male infant with either typical systemic features or a family history of congenital blindness in male relatives.^{1,2} We report here the ocular findings in a 2-year-old girl who appears to be a manifesting carrier of Norrie's disease, this being an observation which has important implications for genetic counselling.

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Case reports

The family pedigree is shown in Figure 1.

II-1

This deceased male lived in Mauritius and was first noted to be blind at age 2 years. At age 6 years behavioural disturbance prompted psychiatric referral. At age 20 years he was described as being severely retarded and required constant supervision.

II-2

This 30-year-old man is of normal intelligence. Assessment at age 22 years showed bilateral ptihalical eyes.

II-4

The 32-year-old mother of the proband (III-1) is of above average intelligence and has normal vision. Funduscopy and fluorescein angiography were normal.

III-1

This 8-year-old boy was found to have bilateral total retinal detachment with retrolental masses and absent electroretinogram at age 2 weeks. Horizontal corneal diameters were 10 mm (right) and 9 mm (left). Initial development appeared normal but by 3 years marked global delay was apparent. Subsequently his behaviour deteriorated and he developed corneal opacities in addition to the leukocoria. Mild hearing loss was also noted.

III-3

This 4-year-old girl, who is showing normal development, was examined shortly after delivery at term and found to have normal fundi. However at age 2 years she presented with severe visual impairment. Clinical and ultrasound examination revealed a cataract and total retinal detachment in the right eye with a vascularised

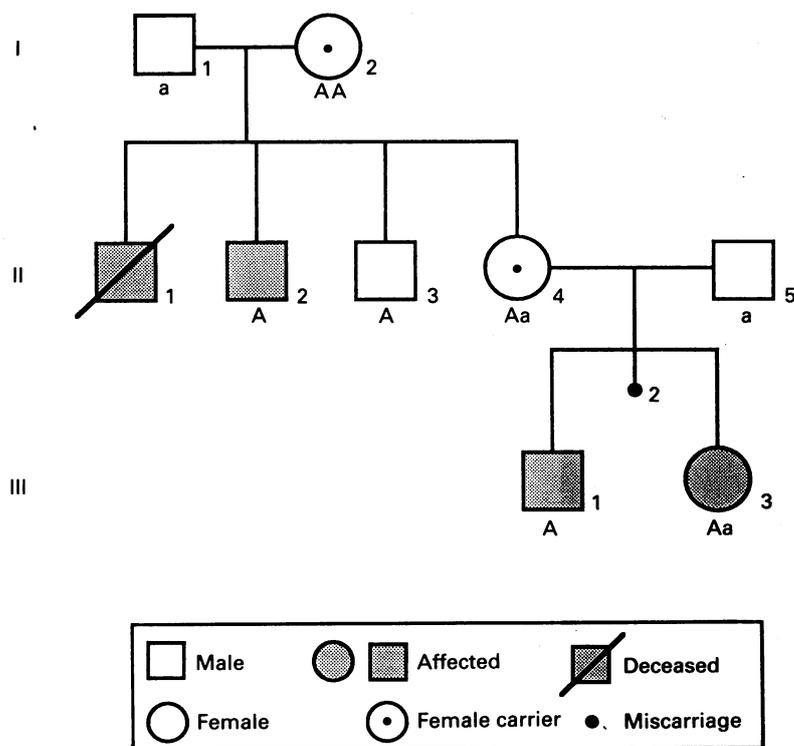


Figure 1 The family pedigree showing restriction fragment length polymorphism results obtained using L1-28/Taq I probe/enzyme combination. A=12 kb a=9 kb. Individuals III-1 and III-3 have inherited the same maternal allele.

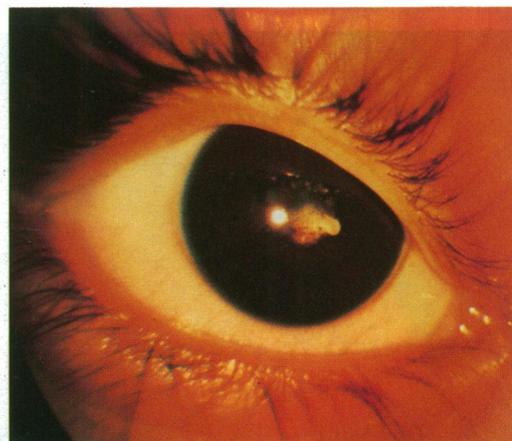


Fig 2A

Figure 2 (A) Photograph and (B) ultrasound of right eye of female sibling III-3 with cataract and a vascularised mass behind the lens.

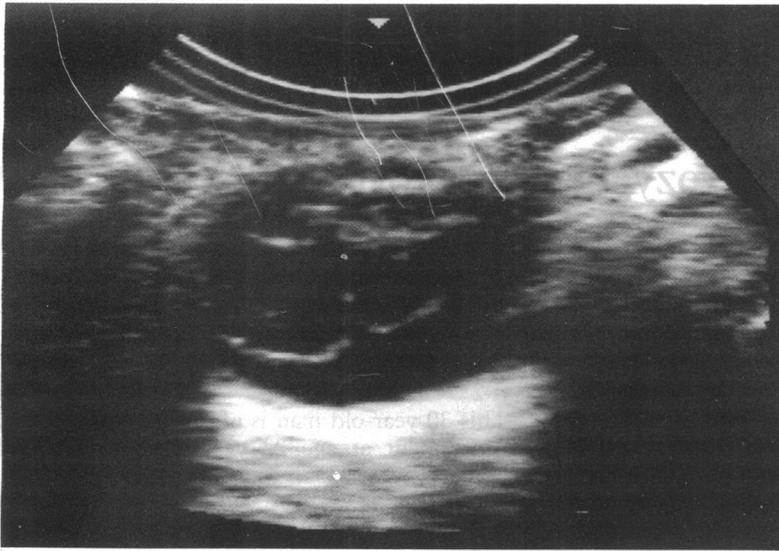


Fig 2B

mass behind the lens. In the left eye a retinal fold and traction retinal detachment in the temporal periphery were evident (Figs 2 and 3).

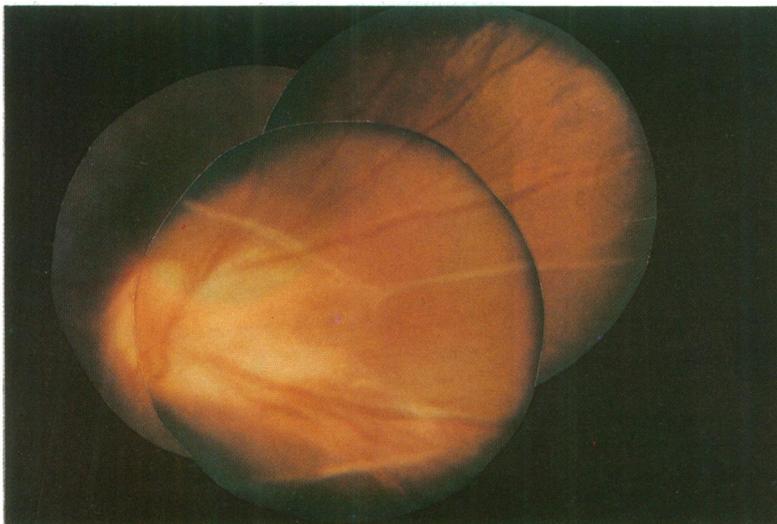
Genetic studies

Chromosome analyses in the mother (II-4) and her two children (III-1 and III-3) were normal. No deletion could be detected with probe L1-28 in the DNA of any affected family member. Restriction fragment length polymorphism (RFLP) analysis showed that the mother (II-4) had passed on her maternally derived X chromosome ('A' in Fig 1) to both of her affected children. X chromosome inactivation studies using the methylation sensitive enzyme Hpa II showed skewed peripheral leucocyte X inactivation at a ratio of 70:30 in favour of the grand-maternal X chromosome.

Comment

Differential diagnoses which have been considered and excluded in this family include autosomal dominant familial exudative vitreoretinopathy (FEVR) and the X linked primary retinal dysplasia described by Godel and

Figure 3 Left fundus photograph of female sibling III-3 showing retinal fold.



Goodman.³ In autosomal dominant FEVR mental retardation does not occur, and non-penetrance is very unusual as would be the absence of abnormalities on fluorescein angiography in II-4. In X linked retinal dysplasia, only one of nine male patients had bilateral congenital pseudoglioma and none was mentally retarded. Minor ocular abnormalities were seen in some females but none of these showed significant visual impairment.

In Warburg's original series of 35 case histories of congenital familial pseudoglioma, there was not a single affected female.⁴ However Capella *et al*⁵ reported a Norrie's disease family in which one female member had a retinal fold with dragging of the disc in one eye and a cataract in the other eye. This female was an identical (MZ) twin whose co-twin had normal eyes. Both twins went on to have affected sons. It is now recognised that there is an association between MZ twinning and non-random X chromosome inactivation⁶ so that the ocular findings in this patient almost certainly reflected expression of the Norrie's gene. Norrie's disease has been observed in a female who also had a balanced X autosome translocation,⁷ in whom it was likely that non-random X inactivation had occurred so as to maintain full activity of all autosome material.

These observations prompt us to conclude that the girl in our family probably also represents an example of manifesting heterozygosity of the Norrie's disease gene. The molecular findings are consistent with this premise although we recognise that the degree of skewed X inactivation in lymphocytes, which may not necessarily reflect the situation in eyes, does not provide conclusive evidence. Absolute confirmation of the diagnosis of Norrie's disease in this patient must await characterisation of a specific mutation in the recently identified Norrie's gene,⁸ allelic mutations which may also account for X linked exudative vitreoretinopathy.⁹ Until the situation is clear we urge caution when counselling families in which Norrie's disease is segregating.

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