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Probably Norrie's disease due to mutation

Two sporadic sibships of two males each, a necropsy of one case, and, given Norrie's disease, a calculation of the gene mutation frequency

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SUMMARY Two sibships, each with two affected males but no other affected family members, are described. All four patients at birth had small eyes with white masses visible behind clear lenses. Support for a diagnosis of Norrie's disease lies in the probable mental retardation and sudden death of one child and mental retardation in the other in one of the families, and strong support in the sensorineural deafness in one child in the other family. A necropsy was performed on the dead child. Both eyes showed the retinae to be totally non-attached. The optic nerves were thin. If the diagnosis is Norrie's disease (highly probable), the birth of the second affected child in each family supports the postulate of a mutation in the *X* chromosome of a germ cell of a maternal grandparent or an earlier maternal ancestor, no previous member of the family having been affected. That implies a 50% risk of the disease in future male siblings and a 50% risk of the carrier state in female sibs. When only one child is affected, the explanation could also be a mutation in that individual. Given Norrie's disease, we have calculated a mutation rate of 3·9 per million chromosomes in the Scottish population—remarkably similar to the mutation rates calculated for many dominant diseases. A diagnosis of autosomal recessive non-attachment of retina implies a 25% risk to later siblings.

Norrie's disease (congenital oculo-acoustic-cerebral dysplasia)[1-14] is an unusual cause of blindness at birth or within the first few weeks of life, first described as an entity by Norrie in 1927.[2] In 1925 Heine[1] recorded a similar condition which he called fetal iritis. White masses of primary vitreous with some blood vessels, which are within completely detached retinae, can be seen behind clear lenses. About 55% of affected patients become mentally retarded or have infantile psychosis[15] and 30% are deaf.[6] The disease is now well established to be due to an *X*-linked recessive gene, occurring without any manifestation in the carrier females. These characteristics make the diagnosis reasonably obvious. The differential diagnosis is considered in the discussion.

The present series of two separate sporadic sibships of two males each, with a necropsy in one ('sudden infant death syndrome'), is reported to draw attention to the probable diagnosis of Norrie's disease in spite of the absence of any other affected male family members (a mutation being suspected in a germ cell of a maternal grandparent or other maternal ancestor) and to give an account of necropsy in one case. The main differential diagnosis is autosomal recessive non-attachment of retina. Given Norrie's disease, a mutation rate has been calculated.

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Case reports

In family A the history was compiled by personal interview with the parents and the maternal grandmother, while in family B it was obtained from the parents. All were able to give a clear and unequivocal account of the relatives shown in the pedigrees.

FAMILY A

Case A1

The first born was a normal female with occipitofrontal head circumferance of 35·5 cm and birth weight 2·91 kg (Fig. 1).

The second child was a male who was noted to have white pupils at birth. The birth weight was 3·29 kg and occipitofrontal circumference 33 cm. Examination under anaesthesia was reported to have revealed white fibrous-like masses behind clear lenses in both eyes, but in the right eye a red reflex was visible in one area—significantly without detectable retinal vessels. Apparently at that time no warning was given to the parents of a risk of recurrence. Since the age of about 3 years he has been reported to be severely mentally and physically retarded. No hearing tests have been done. Inversion of chromosome 8 was found as a result of an independent survey of this family. (Several others in the family have the same abnormality but are entirely healthy.)

Case A2

The third pregnancy produced another male, also tragically blind, with a birth weight of 2·63 kg and occipitofrontal circumference 33·4 cm. Under anaesthesia both eyes were seen to be small, with white retrolental masses. At about six months of age he was investigated because of fits (total of five), each lasting about 30 seconds. He was thought to be developmentally retarded and had an abnormal EEG. He died at the age of 9 months because of 'sudden infant death syndrome', with no suspicion of injury, non-accidental or otherwise. The eyes and brain were obtained for pathological examination, which is reported below. A normal karyotype was found.

The parents were informed that there was a 50% risk of congenital blindness in any future male child and that the daughter, the eldest in the family, had (like any future daughter) a 50% chance of being a carrier, in which case any male child she would have in the future would have a 50% chance of having this disease. The possibility was also mentioned of an autosomal recessive congenital non-attachment of retina, with a 25% risk of recurrence in future siblings of either sex. The parents decided against taking these high risks and the mother has been sterilised.

This family had been the subject of an independent study because of an inversion of chromosome 8 in the mother of the two boys and in her father. We judge this chromosome abnormality irrelevant to Norrie's disease though it was present in the older boy. There are several families in the records of the Medical

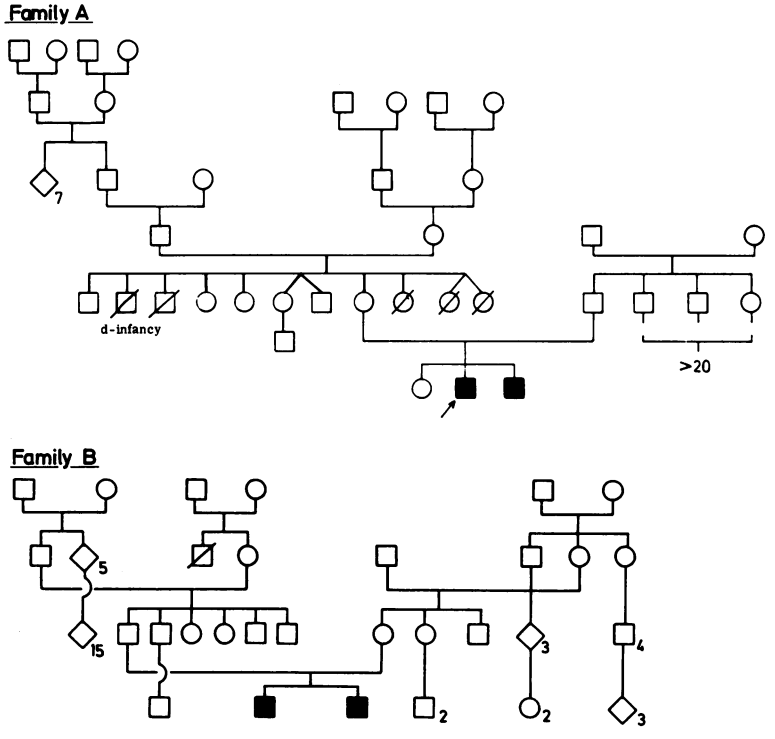

Fig. 1 *Family trees of families A and B. In both families there is a sibship of two males with the ocular manifestations of Norrie's disease but no previously affected generation within the memory of accessible relatives. The first affected child in A was mentally and physically retarded while the second child was probably mentally retarded and died aged 9 months of 'sudden infant death syndrome'. Support for the diagnosis of Norrie's disease in the first child in B is his sensorineural deafness. □=Male. ○=Female. ◇=persons of either sex to the total shown by the adjacent number. ■=Patients reported on here. Oblique stroke=person dead. d-infancy=died in infancy. Arrow=propositus. >20 Means that the total number of children from these three individuals included in the bracket numbered more than 20.*

Research Council's Clinical and Population Cytogenetics Unit with this chromosome abnormality but no abnormal clinical symptoms or signs.

FAMILY B

Case B1

The first born was a male. (Fig. 1) Bilateral white masses behind clear lenses in small eyes were seen at examination under anaesthesia elsewhere. No further details are available, except that no indication of a possible hereditary cause seems to have been given to the parents. His birth weight was 4·90 kg and occipitofrontal circumference 37·5 cm. An audiogram at the age of 6 years showed early signs of sensorineural deafness (as well as the coexistence of one perforated ear drum). The boy, now aged 8 years, has a hearing aid. These findings support a diagnosis of Norrie's disease. His mental development is normal.

Case B2

The second pregnancy tragically resulted in another male with exactly the same disease. This was a full-term pregnancy, his birth weight being 4·3 kg. His occipitofrontal circumference was 36·4 cm.

The second boy has not had an audiogram done. At age 6 years he is mentally normal. The children were judged too young for venepuncture to allow chromosome studies to be done.

The parents, who were not consanguineous, were counselled after the birth of the second blind boy that the mother was presumptively a carrier of an abnormal *X*-linked recessive gene causing Norrie's disease, though autosomal recessive non-attachment of retina was definitely possible. They decided against any further pregnancies, and the mother has been sterilised.

Mutation rate for Norrie's disease

Although we favour the diagnosis of Norrie's disease in these two sibships of two males each, there are reservations. The main one is that in neither pedigree is there an affected male on the mother's side of the family. It is theoretically possible, but unlikely, that a forgotten affected male exists far back in both families. The very unlikely possibility exists in all cases of an autosomal recessive congenital non-attachment of the retina syndrome, chance dictating that only males, not females, are affected. However, we much prefer the diagnosis of Norrie's disease, especially because of the mental retardation in both cases in one family (A) and the sensorineural deafness in one of the other sibship (B). We postulate a mutation in the germ cells of one of the maternal grandparents such that the mother is a carrier of the mutant gene which will be present in half her ova. This mutation will affect all her somatic cells also, but there is no evidence in published families of the existence of a mild form of Norrie's disease in carrier females, as might be expected from the Lyon principle. Alternatively a new mutation could have occurred in one of the ancestors of the maternal grandmother which by chance had not been manifested by the birth of an affected male in a previous generation. It is also a remote possibility that a germline mutation has occurred in the mothers of the boys. (At the stage of a singleton affected boy, a mutation in him could be the explanation.)

We have previously reported another sporadic sibship of two males as having 'congenital hereditary non-attachment or retina'[16] and before that a sporadic brother and sister with the same disease.[17] We remain confident of the autosomal recessive diagnosis in the latter sibship because of the different sexes of the two affected children. However, the two sibships described in the present paper have altered our personal prior probabilities such that we are more doubtful of the diagnosis in the former sibship.[16] Actually in that report[16] we calculated that an *X*-linked recessive disease was seven times more likely than an autosomal recessive disease: however, we placed considerable weight at the time on the absence of mental retardation and deafness as contraindicating Norrie's disease.

We now think it likely that a mutation has occurred in the gene for Norrie's disease (if it is a single-gene disease) in the germ cells of one of the maternal grandparents in both the families reported here, and so we can calculate a maximum estimate of the mutation rate. Inquiries from the Blind Welfare Services and the ophthalmologist to the School Health Service and Blind School in Glasgow (the only other Blind School in Scotland) have not revealed any other cases of Norrie's disease in Scotland. However, undiagnosed cases may exist, especially in institutions for the mentally retarded. In any case our postulated two new mutations in females will be an underestimate of the true number of new mutant females because (*a*) some new mutants will be too young to have had any children; (*b*) some new mutants may by chance have had no children, or only females, or only normal male children.

We propose to restrict the calculation to concern only women between 18 and 45 years of age in Scotland. From the 1981 *Annual Report* of the Registrar General for Scotland[18] we estimate that 25·9% of women of this age in Scotland are unmarried and 74·1% are, or have been, married.

Family size is important. Given that there is a 25% (1 in 4) risk of an affected child in the case of a woman 'carrying' an abnormal gene on one *X* chromosome,

for a woman with a family of size s the probability that she would have at least one affected child is $1-(0{\cdot}75)$.[s] The proportion of all carrier women who will have an affected child is therefore $\Sigma P_s\,(1-(0{\cdot}75)^s)$.

[s] Where P_s is the proportion of women with family size s. Estimates of P_s for married women in Britain aged 18–45 years were obtained from the 1981 census. Substituting in the above formula, we estimated the overall proportion of married mutant carriers who would be ascertained by the birth of an affected child to be 0·3515.

If we assume that single women have had no children, the proportion of new mutant carriers ascertained among all women age 18 to 45 is:

$$(0{\cdot}259)(0{\cdot}0)+(0{\cdot}741)(0{\cdot}3515)=0{\cdot}2605$$

Therefore the actual number of new mutant carriers is

$$\frac{\text{observed}}{0{\cdot}2605}=\frac{2{\cdot}0}{0{\cdot}2605}=7{\cdot}6775.$$

Now the total number of women aged 18 to 45 resident in Scotland is 978 740.

Therefore the number of mutant genes carried by these women as a proportion of the total is

$$\frac{7{\cdot}6775}{2\times 978\,740}=3{\cdot}9\times 10^{-6}.$$

Therefore the mutation rate per chromosome is $3{\cdot}9\times 10^{-6}$.

Pathological report (case A2)

The eyes and brain had been removed and fixed in formol saline within 24 hours of death.

OCULAR PATHOLOGY

Macroscopic examination

The right eye measured 18×18×10 mm, the right cornea 10×9 mm with 3 mm of optic nerve attached; the left eye 18×17×17mm, and the left cornea 9×8 mm with 5 mm of optic nerve.

The findings in both eyes were very similar and will be considered together (but where differences occurred they will be mentioned).

The cornea was clear and the anterior chamber very shallow. The pupil was small, eccentrically placed and with marked ectropion uveae. There was leucocoria. The eyes were opened horizontally, revealing total funnel-shaped retinal detachment with subretinal coagulum. The retina was yellowish and incorporated a scattering of blood and pigment.

Microscopic examination

Both eyes were serially sectioned and were stained with haematoxylin and eosin, periodic acid Schiff, Perl's, Masson's, Bodian, and Loyez stains.

The corneal epithelium was uniformly thick, with numerous mitotic figures within it. Bowman's membrane was prominent and intact, while the stroma was of normal thickness and unvascularised. Descemet's membrane was uniformly present except in one very small area axially in each eye, where there was also no endothelium; this may represent a mild degree of Peter's anomaly. The remainder of the axial endothelium was greatly attenuated, with only a rim of normal endothelial cells at the periphery. The axial endothelial cells contained pigment granules. There was an area in the axial region of the right eye where the endothelium formed two layers of spindle-shaped cells with reduplication of Descemet's membrane (Fig. 2).

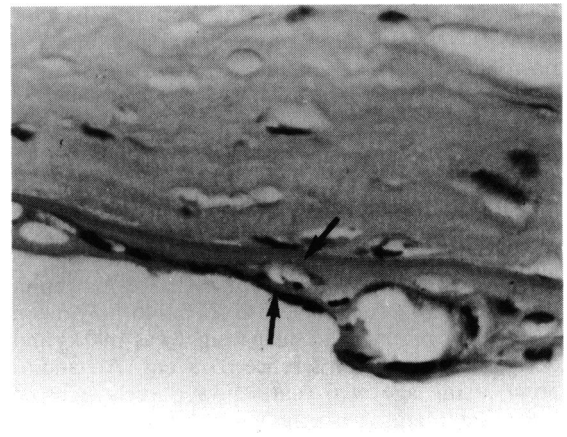

Fig. 2 *Corneal endothelium showing irregular heaping up of cells with reduplication of Descemet's membrane (arrows). (H and E, ×320).*

Extensive anterior synechiae occupied the area from the mid-zone of the iris to the pupillary margin (Fig. 3), with total posterior synechiae covering the

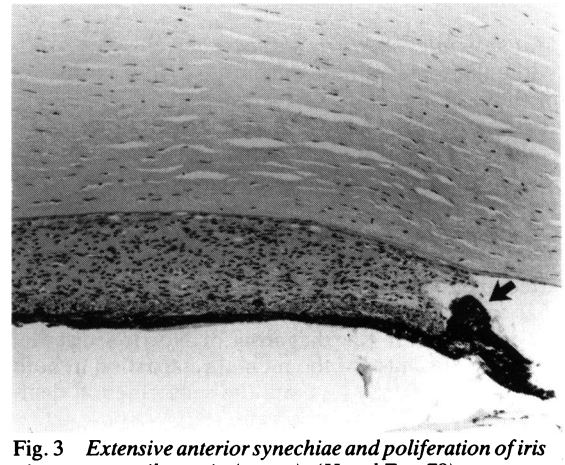

Fig. 3 *Extensive anterior synechiae and poliferation of iris pigment at pupil margin (arrow). (H and E, ×78).*

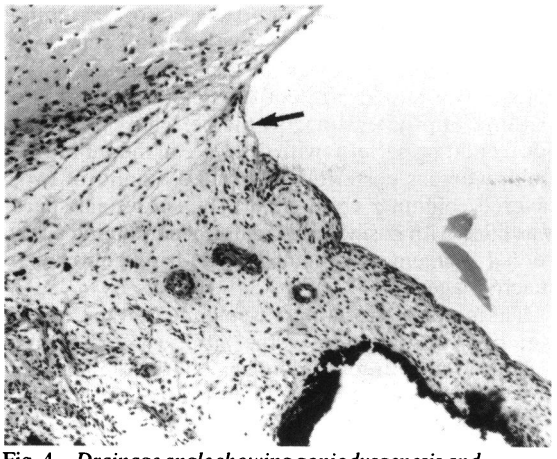

Fig. 4 *Drainage angle showing goniodysgenesis and strands of material bridging angle (arrow). (H and E, ×78).*

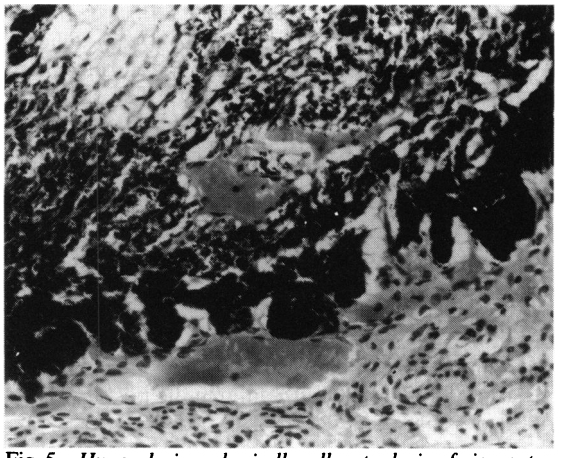

Fig. 5 *Hyperplasia and spindle cell metaplasia of pigment epithelium of ciliary processes. (H and E, ×200).*

entire lens surface. The drainage angles were open in some areas but closed in others by iris strands bridging the angle. Descemet's membrane ended in the region of the iris strands, further anteriorly than normal. There was an increased density of tissue in the region of the trabecular meshwork with the scleral roll extending

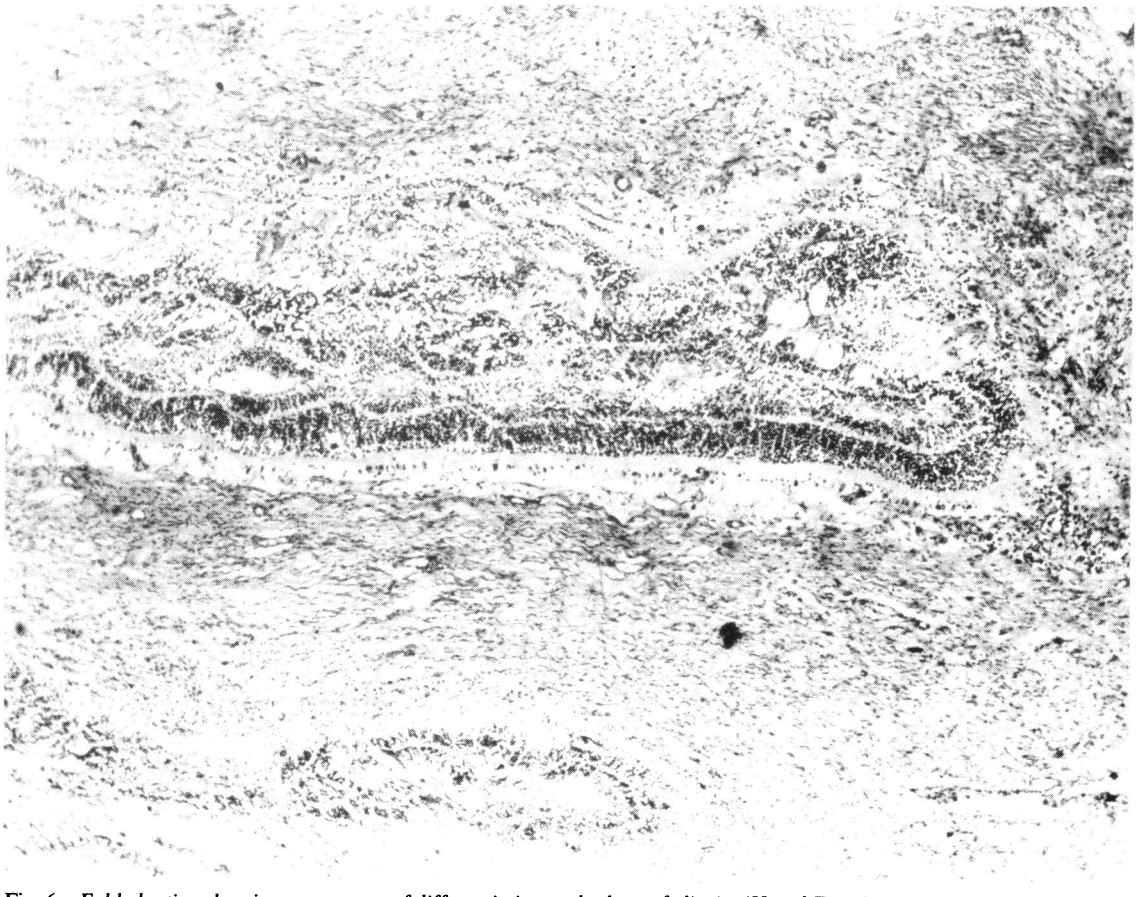

Fig. 6 *Folded retina showing some areas of differentiation and others of gliosis. (H and E, ×64).*

further anteriorly than normal, indicating a degree of goniodysgenesis (Fig. 4). There was a very delicate neovascular membrane over the iris surface with a persistent pupillary membrane. The pigment epithelium of the iris showed ectropion, with considerable proliferation of pigment over the anterior surface of the iris. The thickness of the iris was variable, with some parts being abnormally thin. The cellularity of the stroma was unremarkable.

The ciliary processes were drawn forward and elongated, but not to the degree found in persistent hyperplastic vitreous. There was very dense pigmentation of the epithelium, and both eyes showed nodular areas of spindle cell metaplasia and hyperplasia of the pigment epithelium in the posterior part of the pars plicata (Fig. 5).

The lens was displaced anteriorly. The capsule and epithelium were intact, and there was no evidence of cataract formation.

The retina was lying in a tightly folded mass behind the lens (Fig. 6) and was attached only at the optic nerve head. Moderately well differentiated photoreceptor nuclei, bipolar cell nuclei, and ganglion cells were identifiable, being arranged in recognisable layers.

Some areas were more dysplastic with rosette formation, and in particular the peripheral retina was less well differentiated, with the extreme periphery being represented by a simple columnar epithelium. The pars plana was totally detached. There had been recent as well as old haemorrhage into the retina, which contained blood haemosiderin and clumps of melanin. There was a marked glial component in the retina. The retinal pigment epithelium showed two patterns of proliferation. At the periphery it formed focal budding patterns with cells free in the subretinal fluid, whereas posteriorly it formed a uniform two-layered columnar epithelium. The subretinal space was filled with eosinophilic material containing a few retinal pigment epithelial cells and pigment laden macrophages.

There were a preretinal vascular membrane and an anterior condensation of the vitreous. Some large vessels in the vitreous in the cone of the detachment may represent remnants of a persistent hyaloid system, though all were thin-walled.

The vessels in all the layers of the choroid were patent. There was marked thickening of the sclera, but no specific abnormality.

The optic nerve was thin, with posterior bowing of the lamina cribrosa, which was the anterior extent of myelination. There was a very marked reduction in the number of nerve axons, with a more marked loss at the outer rim of the nerve and at the superior and inferior extremes (Fig. 7).

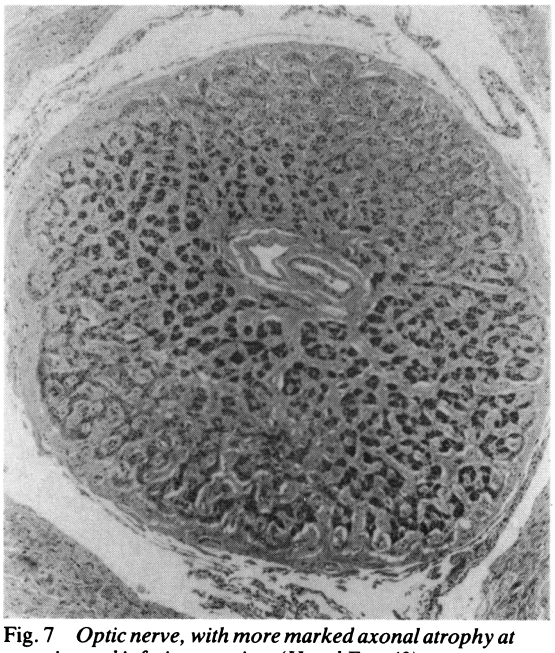

Fig. 7 *Optic nerve, with more marked axonal atrophy at superior and inferior margins. (H and E, ×40).*

EXTRA-OCULAR TISSUES

These were unremarkable. Examination of the brain showed no abnormality other than thinning of the optic nerves.

Discussion

CLINICAL AND GENETICAL

We consider it unlikely that these sibships are both examples of the autosomal recessive disease 'congenital non-attachment of retina'[16 17 19-21] rather than Norrie's disease. We postulate a reasonable chance that a mutation has occurred in the *X* chromosomes of a germ cell of a maternal grandparent in our two sibships of two males each. The hypothesised mutation might even have occurred further up the female line with diminishing likelihood, since affected males would be expected to be remembered for several generations.

The possibility that the main alternative diagnosis is congenital non-attachment of retina would imply that chance has dictated the coincidence that all four cases in the present report merely happen to be in males, that is, that affected females might have been born instead (which would effectively exclude Norrie's disease). Non-ophthalmological points in favour of Norrie's disease exist in both families: the development retardation and sudden death[22] in case A2 and mental and physical retardation in A1, and a much stronger support in case B1, namely deafness.[23]

However, these additional handicaps are by no means always present in Norrie's disease, which may in turn suggest that Norrie's disease contains several different variants—as would be expected from the variability of the biochemical lesion of the DNA in any hereditary disease. Even if linkage of a specific allele with the Norrie's disease gene were found consistently in the two families,[24] that would not constitute support for the diagnosis of Norrie's disease; conversely the absence of linkage would not contraindicate Norrie's disease.

An autosomal recessive total detachment of retina ('retinal dysplasia') with microphthalmos and nystagmus occurs in Bedlington and Sealyham terriers and Labrador retrievers.[25-28]

In the differential diagnosis we would consider but exclude persistent hyperplastic primary vitreous because it has never been recorded in sibships so far as we know, and there are claims for bilateral involvement in only three cases.[29 30] Retinopathy of prematurity can be confidently ruled out. The absence of systemic abnormalities is evidence against 'retinal dysplasia'.[31 32] That name was introduced by Reese and Straatsma in 1958[32] in their description of 44 cases of which 27 had only ocular disease. The absence of abnormalities of skin colour excludes incontinentia pigmenti, and the absence of skeletal abnormalities excludes dysplasia spondyloepiphysaria congenita[33 34] and Saraux's syndrome.[35]

It seems likely that, in the pathological evolution of Norrie's disease in intrauterine life, the retina has never been 'attached' (that is, the inner layer of the optic cup has not achieved contact with the outer

Table 1 *Summary of literature on histopathology of Norrie's disease*

	No. of cases	*Age at enucleation*	*Anterior segment*	*Posterior segment*	*Neuro-pathology*	*Comment*
Heine 1925[1]	2	4 years *4 months	Anterior synechiae Ectropion uveae	Ossification of choroid	—	Early phthisis
Whitnall, Norman 1940[36]	1	17 years	Anterior synechiae, ectropion uveae	Undifferentiated retina, ossification	Yes	Phthisis bulbi
Wilson 1949[5]	3	*1 month	Iridocorneal adhesion, hypertrophic ciliary processes	Undifferentiated retina		
		*3 months	Anterior synechiae, ectropion uveae	Moderate differentiation		Phthisis bulbi
		5 years	Anterior synechiae	Moderate differentiation of retina with retrolental haemorrhage and subretinal haemorrhage		Glaucoma
Reichel 1960[22]	2	4–5 months R:1 month L:6 months	No details	Retinal detachment with haemorrhage	Yes	Phthisis bulbi, glaucoma
Warburg 1961[4]	1	*8 months	Goniodysgenesis, ciliary epithelial hyperplasia		Yes	Early phthisis
Blodi, Hunter 1969[9]	6	14 years	Synechiae	Calcified choroid		Phthisis bulbi
		*3½ months	Shallow anterior chamber	Retinal haemorrhage		
		*1½ months	Synechiae	Retinal haemorrhage		
		5 years	Synechiae	Calcified choroid		Phthisis bulbi
		3 months	Synechiae	Retinal haemorrhage		
		2½ months	Total anterior synechiae	Retinal haemorrhage		
Brini, Sachez, Levy 1972[37]	1	*1 month	Gonidysgenesis, ectropion uveae, long ciliary processes	Moderate dysplasia		
Townes, Roca 1973[12]	1	3½ years	Advanced disorganisation			Phthisis
		11 years	Anterior synechiae	Gliotic retina		Phthisis
Apple, Fishman, Goldberg 1974[38]	1	3 months		Dysplasia		Vitrectomy specimen
Warburg 1975[15]	3	18 years	Long ciliary process	Retinal haemorrhage		?Acquired retinal detachment
		*5 months	Synechiae, ciliary epithelial hyperplasia	Dysplasia		
		15 years	Ciliary epithelial hyperplasia, long ciliary process, ectropion uveae, synechiae	Persistent hyaloid artery, calcified choroid		Phthisis

* Adequate histology possible.

layer). A study of fetuses at different stages of development in the Sealyham terrier and other dogs[25-28] would be instructive and might well cast some light on the (biochemical) cause of the disease–possibly a defect in the pumping mechanism of the retinal pigment epithelium or a defect in the hyaluronic acid between the pigment epithelium and the layer of rods and cones.

One biopsy report[13] showed normal retinal and connective tissue. This was taken during an attempt at surgical correction which failed, but the author suggests that an operation in the earlier stages might be successful.

PATHOLOGY

Although 21 cases have had histological findings reported, most had phthisis bulbi. They are summarised in Table 1, but the eight with distinguishable features have been indicated by asterisks.

Non-attachment of the retina is the major pathological as well as clinical finding. That description is used in preference to 'detachment' because of our suspicion that the inner layer of the optic cup never achieved contact with the outer layer in intrauterine life. The dysplasia of the retina may be due to lack of stimulation by the pigment epithelium to differentiate, and conversely a similar explanation may apply to the abnormal stratification of the pigment epithelium.[39] The absence of secondary vitreous suggests that the inner layer never achieved attachment because its formation is induced by the fusion of neuroretina to pigment epithelium.[7] Significant in this context is the association between defects in the formation of the optic cup and microphthalmos, which is also part of Norrie's disease. However, non-attachment of retina might be expected to produce more severe microphthalmos than is usually present at birth in Norrie's disease; these eyes shrink subsequently.[6]

The association between microphthalmos and non-attachment of retina suggests a similar explanation for malformations of the anterior segment which have been found in the few cases in which organised structures remained: see Table 1, where it will be seen that our observations correspond with those of others–goniodysgenesis, iridocorneal adhesion with ectropion uveae, a disturbance of corneal endothelium, and persistence of the pupillary membrane.

There are only three cases in which neuropathological examination was recorded. Two[4,36] showed thinning of the optic tracts and a reduction in cellularity of the lateral geniculate bodies. A third previously reported case[22] showed no morphological abnormality of the brain at necropsy. Neuropathological examination of the case reported here showed only attenuated optic nerves.

Note added in proof. Clarke's may be the first briefly recorded family,[14] followed by that of Ash in 1922,[40] extended by Fraser Roberts in 1937[41] (see Waardenburg *et al.*[42] for other early references).

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