

Ophthalmological synopses

Inheritance of retinoblastoma

Retinoblastoma, the most common intra-ocular tumour in childhood, is a malignant tumour of multifocal origin arising in the neural layers of the retina, usually appearing between birth and 4 years of age. It occurs bilaterally in 20 to 35 per cent. of cases, the age at onset being earlier in bilateral than in unilateral cases. It presents most commonly (60 per cent. of cases) as a white reflex in the pupillary area, less frequently (20 per cent. of cases) as a squint. If left untreated it spreads to fill the globe, then breaks out into the orbit and extends along the optic nerve to the brain, or spreads to distant organs *via* blood vessels and lymphatics, causing a distressing death within a year or two.

The disease usually occurs sporadically but may show an autosomal dominant inheritance with incomplete penetrance.

Sporadic cases are of two types:

(1) **SOMATIC MUTANTS** The genetic abnormality is in the retina so that the disease is not transmitted. These cases are usually unilateral.

(2) **GERMINAL MUTANTS** These represent about 10 to 20 per cent. of sporadic cases. The genetic abnormality lies in the germinal epithelial cells of the gonads of one parent (who is normal) so that the condition may be transmitted to offspring. These germinal mutants are usually more severely affected than the somatic mutants, having bilateral disease of earlier onset.

Familial cases satisfy the criteria for autosomal dominant inheritance (Blach and Jay, 1968) but because penetrance is incomplete (approximately 80 per cent.) the following features occur:

(1) There is usually direct transmission through several generations; occasionally a generation is skipped.

(2) Most affected individuals have an affected parent, unless the result of a new mutation or the offspring of a symptomless carrier.

(3) An affected individual has, on the average, 40 per cent. affected children, 10 per cent. symptomless carriers, and 50 per cent. normal children.

(4) Unaffected members of an affected family, unless they are symptomless carriers, have normal children. It is, at present, impossible to distinguish a symptomless carrier from a normal member unless an affected child is produced.

(5) Autosomal dominant traits occur with equal frequency in males and females.

Incidence This is increasing mainly because of a rising mutation rate, but also because of a fall in mortality with improved treatment (and perhaps because better case records are now available for study); 30 years ago it was 1 : 30,000 live births, whereas now it is nearer 1 : 15,000.

Genetic counselling As retinoblastoma is familial in some instances, the decision to limit procreation in any particular case may be taken by the parents after seeking genetic advice. The following general points should be noted:

- (1) Unilateral sporadic cases are usually the result of somatic mutations and do not transmit the disease to their offspring.
- (2) Bilateral cases, even if sporadic, are usually the result of germinal mutations and therefore transmit the disease to 40 per cent. of their offspring, an additional 10 per cent. being symptomless carriers.
- (3) Treatment for retinoblastoma is available and is particularly successful in early cases.
- (4) Sterilization of all affected individuals will not eliminate the disease because:
 - (a) Symptomless carriers occur.
 - (b) New mutations are constantly arising.

The risks in the more commonly occurring situations are quoted below:

A FAMILY HISTORY OF RETINOBLASTOMA IS PRESENT

- (1) The proband and one or more near relative (parent, sibling, offspring, aunt or uncle, grandparent) are affected. The abnormal gene is present in the proband and 40 per cent. of his children will be affected.
- (2) The inquirer is normal but *more than one* near relative is affected. The chance of the inquirer being a symptomless carrier is about 16 per cent. and the chance that he will produce an affected child is therefore about 6 per cent.
- (3) The inquirer is normal but one sibling is affected. The risk here is not definitely known, but the chance of the inquirer producing an affected child is small (very small if the sibling is unilaterally affected).
- (4) The inquirer is normal but has produced one affected child. The chance of producing a second affected child appears to be about 1 per cent., although probably slightly higher if the affected child has bilateral retinoblastoma.

NO FAMILY HISTORY OF RETINOBLASTOMA IS PRESENT

- (1) The proband is unilaterally affected. The chance of his being a dominant mutant is about 16 per cent. and the chance of his producing an affected child is therefore about 6 per cent. Once he has produced one affected child, the chance of his producing another affected child is 40 per cent.
- (2) The proband is bilaterally affected. Nearly all bilateral cases, even if sporadic, are the result of germinal mutations. The chance that a bilaterally affected patient may produce an affected child is, therefore, nearly 40 per cent.

It is a wise precaution to examine under an anaesthetic any baby born into a family with a history of one or more cases of retinoblastoma. The first examination should take place within the first month of life and thereafter, at gradually increasing intervals, until the child is several years old.

Reference

BLACH, R. K., and JAY, B. (1968) *Brit. J. Ophthalm.*, **52**, 718

General References

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