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Clinical Problems

Bilateral Retinoblastoma: A Dominantly Inherited Affection

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Summary

Ten survivors of sporadic bilateral retinoblastoma had 14 offspring, of whom eight were affected, seven of them in both eyes. Other reports from the literature raise the total of similar unselected cases to 19 survivors with a total of 39 offspring, of whom 17 were affected in both eyes and three in one eye.

The high incidence of the bilateral affection in dominantly inherited retinoblastoma—as recorded in the literature—and in the offspring of survivors from sporadic bilateral retinoblastoma, as reported in the present study, establish all cases of bilateral retinoblastoma as a dominant disorder either in transmission or as a new mutation. This disorder, though fully or almost fully penetrant, is not always fully expressed. A small proportion, probably about 5 to 10% of all cases of the much more common sporadic unilateral affection, are in fact incompletely expressed germinal mutations for bilateral retinoblastoma. There is some evidence that histological appearances may distinguish these potentially transmissible unilateral tumours from the mass of unilateral retinoblastoma which have no genetic significance.

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Introduction

The designation of retinoblastoma, which has replaced the older name of glioma of the retina, emphasizes the fact that this

infantile affection is regarded as a developmental disorder. Apart from the reputed (and rare) cases of spontaneous cure through necrosis of the tumour untreated retinoblastoma is invariably and rapidly lethal. The standard treatment evolved during the second half of the nineteenth century was excision of the globe, and this was a life-saving measure when carried out early. A perturbing sequel became apparent by the end of the century. De Gouvea, of Rio de Janeiro, reported in 1896 and more fully in 1910 the occurrence of the affection in three out of seven children born to a man who had lost an eye from retinoblastoma in infancy.[1] A substantial number of similar pedigrees and of affected sibships without an antecedent history were recorded in the subsequent years. Such cases were, however, found to be exceptional—of the order of 2% of all retinoblastomas.

Analysis of the accumulated material showed that transmission was in a dominant manner (occasionally "irregularly" so) and that affected infants showed a high incidence of bilateral involvement, possibly as high as 65%, against some 15-20% in the sporadic form of the disease.[2] The possibility that the hereditary cases with their high incidence of bilateral tumours constituted a distinct histological entity was suggested by Cumings and Sorsby,[3] who found that the unilateral cases originated exclusively from the outer nuclear layer of the retina while the bilateral cases had a more diffuse origin.

Vogel in 1954 and 1957 stressed the distinctive character of the bilateral cases on genetic grounds.[4 5] He followed up the offspring of survivors of the two varieties of sporadically occurring retinoblastoma, the unilateral and the bilateral. In sporadic unilateral retinoblastoma he found transmission to the offspring in only one instance in 34. With many similar findings in the earlier literature this excluded the possibility that the bulk of cases of unilateral retinoblastoma were dominant mutations, and he held that the equilibrium between mutation and selective elimination maintained in rare dominant traits would be determined in retinoblastoma by mutations postulated for the relatively uncommon sporadic bilateral tumour. Survivors of bilateral sporadic retinoblastoma rarely produce families, both because the affection is relatively uncommon and because of the severe social disabilities of such patients. Vogel could trace only two survivors with offspring, of whom there were three in all and none were affected.

Smith and Sorsby,[6] in a study on five survivors of the bilateral affection who had married, found only one who had a child, and he was affected. In an extensive inquiry in Holland, Schappert-Kimmijser, Hemmes, and Nijland[7] traced seven survivors with a total of 22 offspring, of whom 12 were affected; only two of the seven survivors had exclusively healthy children.

To these reports can now be added the present study based on the substantial material available in the records of the Royal National Institute for the Blind. The study concerns the offspring of 10 survivors of bilateral retinoblastoma.

Present Study

In 1920 the Sunshine Homes for Blind Babies were opened by the National Institute for the Blind, and between then and the end of 1968 a total of 2,003 infants were admitted to the homes. A classification of the types of affection seen has been recorded elsewhere.[8] Included in these admissions were 92 infants blind from bilateral retinoblastoma. Twenty-one of these were born before 1937. Apart from three who died, two inmates of institutions for the mentally subnormal, and one with a possible family history of retinoblastoma there were 15 who in 1958 were at least 21 years of age and thus potential parents. These 15 patients, of whom five had married, were the subject of a communication referred to above[6]; the one child born was affected.

The present study gives the findings 13 years later. The five marriages and one child recorded by 1958 had increased substantially (Tables I and II). Of the 37 relevant survivors aged 21 years or more 19 had not married. For the period 1921-37 (previously reviewed) there were seven marriages with offspring to three, and for the years 1938-50 there were 11 marriages with offspring to seven—a total of 18 marriages of which 10 resulted in issue. Of the seven babies born to four of the affected mothers and to three of the affected fathers, all with one child each, four were affected and three were normal. Of the four children born to two affected mothers (two children each) both sibships had one affected and one normal child. The one mother with three children had two affected and one normal. There were thus eight affected infants out of a total of 14 born. Of these eight, seven showed bilateral retinoblastoma. Of the three parents in this series of 10 who did not have affected offspring only one child had been born to each.

Varieties of Retinoblastoma

STANDARD PATTERNS

Bilateral Retinoblastoma.—When a child born of parents with clear antecedents has bilateral retinoblastoma it must be assumed that if he survives he may be the starting-point of a dominantly transmitted bilateral affection. This is shown by the accumulated data in available studies summarized in Table III.

TABLE I—*Marital and Parental Status of Survivors of Sporadic Bilateral Retinoblastoma*

Year Survivors Born	No. of Survivors	No. not Married		No. Married			
				Without Issue		With Issue	
		M.	F.	M.	F.	M.	F.
1921-37	12*	3	2	4	0	1	2
1938-50	25†	6	8	3	1	2	5
Total	37	9	10	7	1	3	7

*Only 12 of the 15 reported on in 1958[6] could be followed up further.
†Excluding one man, an inmate of an institute for mental defectives, and two women with a suspected family history of retinoblastoma.

TABLE II—*Incidence of Disorder in Offspring of Affected Parents Recorded in Table I*

Parents	Offspring		
	Total No.	No. Affected	No. Unaffected
No. of affected mothers with: 1 Child 4	4	2	2
2 Children 2	4	2	2
3 Children 1	3	2	1
No. of affected fathers with 1 Child 3	3	2	1
Total	14	8	6

TABLE III—*Available Data on Offspring of Survivors of Sporadic Bilateral Retinoblastoma*

	Parents			Offspring			
	Total No.	No. with Healthy Children	No. with Affected Children	Total No.	Healthy	Affected	
						Both Eyes	One Eye Only
Vogel[5]	2	2	0	3	3	0	0
Schappert-Kimmijser *et al.*[7]	7	2	5	22	10	10	2
Present series	10	3	7	14	6	7	1
Total	19	7	12	39	19	17	3

Altogether 19 such survivors had 39 offspring, of whom 20 were affected and 19 were not affected, conforming to the expectation of 50% for simple dominant inheritance. The high incidence of bilateral involvement, present in 17 of the 20 affected offspring, completes the picture of a well-defined disorder with relatively little deviation from the standard pattern. There is nothing in the data to suggest any sex predilection in manifestation.

Unilateral Retinoblastoma.—As already noted an almost equally clear picture emerges from the many studies on sporadic unilateral retinoblastoma. Transmission in such cases is exceptional and only exceptionally is a sib also affected. Sporadic unilateral retinoblastoma is typically an isolated event in a family.

ANOMALOUS FEATURES

There are, however, deviations from the standard pattern in both varieties of sporadic retinoblastoma, clinical in the bilateral type and genetic in the unilateral form. These deviations call for detailed consideration.

Bilateral Retinoblastoma.—The essential deviation is that bilateral retinoblastoma does not always manifest itself clinically in its full form. Suppression of manifestation may be extreme, as in the few pedigrees of "irregular dominance" in which a phenotypically normal individual of a family with dominant retinoblastoma transmits the affection. More commonly suppression is more limited in that the affection is manifest in one eye of a patient who was the starting-point of a line of dominantly transmitted bilateral retinoblastoma; this, in fact, was the case in the first report on the inheritance of retinoblastoma—that of de Gouvea, in which a man with right-sided retinoblastoma had three daughters affected in both eyes. Vogel computed that penetrance in dominantly inherited retinoblastoma is of the order of 80%. If judged by the data now available on the offspring of survivors of bilateral retinoblastoma penetrance is probably distinctly higher, though incomplete expression is not very exceptional (3 in 20 instances in this series).

Unilateral Retinoblastoma.—As noted above, affected sibs or an affected parent are exceptional in the extensive literature on unilateral retinoblastoma. In a critical analysis of the more recent investigations on the family history of patients with sporadic unilateral retinoblastoma, Vogel[9] found that 15 out of 135 such probands had affected children, the number of such children being 21 out of a total of 311. On this basis the risk of offspring being affected is 6·75%. A lower incidence—of the order of 4%—is given in the analysis of Smith and Sorsby[6] and of Nielsen and Goldschmidt.[10] An incidence of 9·0% (16 affected children in a total of 177 offspring of 68 parents with sporadic unilateral retinoblastoma) was recorded by Schappert-Kimmijser *et al.*[7] on data which are not above criticism. It is clear that the phenotypically similar cases of sporadic unilateral retinoblastoma consist of two genetically dissimilar groups—the bulk of cases, some 90-95% of the total, are not transmitted and the rest are germinal mutations for bilateral retinoblastoma incompletely expressed.

Genetic Counselling

Except for a small group discussed below it is fairly easy to distinguish the non-hereditary from the hereditary cases. As for the latter, there is no evidence for any mode of inheritance other than autosomal dominant with almost full penetrance and rather less full expression. In counselling two distinct issues arise: recognition of dominant inheritance and the problems presented by sporadic unilateral retinoblastoma.

DOMINANT INHERITANCE

Dominant inheritance can be assumed when there is a history of direct transmission over two generations and also in the exceptional event of affected sibs, the offspring of an unaffected individual. In the first instance "regular dominance" applies and in the second "irregular dominance", sometimes easily determined by a history of retinoblastoma in collaterals. Affected individuals are likely to show the bilateral form, although unilateral retinoblastoma may occur.

In sporadic cases a dominant mutation must be assumed if there is bilateral involvement. Such cases are the starting-point of a new line of the affection.

Until the degree of penetrance and the incidence of incomplete expression are adequately established the chance of transmission in dominant inheritance of retinoblastoma must be considered as not very much less than the theoretical 50%.

SPORADIC UNILATERAL RETINOBLASTOMA

These cases are important as they are much the commonest. Two questions arise—firstly, the danger of transmission. Unilateral retinoblastoma is regarded as a somatic mutation (although theoretically it could be genetically determined with an exceptionally low degree of penetrance). There is therefore no danger of transmission except for the consideration already stressed—namely, that a small proportion of these cases are incompletely expressed bilateral retinoblastoma. The existence of such cases thus precludes unqualified assurance of freedom from danger, which indeed is present in some 5 to 10% of cases. The second question is the danger of further sibs being affected. This can be dismissed in all cases of sporadic retinoblastoma, bilateral no less than unilateral.

It needs to be stressed that in sporadic unilateral retinoblastoma it is essential to probe deeply in the family history, for the rare irregular dominance with its serious implications can easily be overlooked. The one substantial difficulty that arises in counselling in sporadic unilateral retinoblastoma would be resolved if the incompletely expressed bilateral cases could be identified. The histological differences between unilateral and bilateral cases already indicated[3] may make that identification possible. Further histological studies are needed with particular attention to the crucial unilateral cases met in dominantly inherited retinoblastoma.

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the Blind for making this investigation possible, and to Mrs. J. M. Blackburn and Miss E. M. Gower for painstaking help.

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Today's Drugs

With the help of expert contributors we print in this section notes on drugs in common use

Treatment of Trigeminal Neuralgia

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Though the drugs discussed here primarily concern the treatment of idiopathic trigeminal neuralgia (tic douloureux), some of them may be helpful in relieving trigeminal pain secondary to discoverable lesions such as multiple sclerosis, tumour of the trigeminal nerve, and sinus infections (combined, of course, with treatment of the underlying condition.)

The aetiology of tic douloureux is not known and, though it may occur at any age, it is usually seen in patients over the age of 50 years. Spontaneous recovery is rare, but remission for a variable interval from months to years may take place. Unfortunately with recurrence, attacks tend to follow each other at increasingly shorter intervals and finally they may occur many times per day and be completely unpredictable. In addition to spontaneous attacks there are those triggered off by tactile or proprioceptive stimuli, occurring during the daily activities of shaving, washing, eating, or talking—and the patient may quickly be reduced to a state of complete misery. Hence it is not surprising that since Fothergill's initial report[1] of "a painful condition of the face" in 1773 medical efforts to alleviate the pain have seen a succession of almost every conceivable remedy, some of which have enjoyed an apparent, if transient, success.

Evaluation of treatment is difficult because of the remittent character of the affliction[2] and initially favourable results have not proved consistent and reproducible as further experience has accumulated.[3] Simple analgesics such as aspirin are of no avail, but a mixture which has proved helpful consists of potassium bromide 600 mg, tincture of gelsemium 0·6 ml, phenazone 450 mg, and water to 10 ml.—taken thrice daily. Another drug which may benefit this condition is mephenesin carbamate suspension, 5 ml thrice daily (1 g/5 ml), which in 1965 was reported[4] to give rapid suppression of pain. If tolerated, the dose may be increased to 3 g five times daily, taken after a meal or with milk. Side effects (especially with the larger doses), include diplopia, ataxia, and weakness but these quickly subside on reducing the dose. Relief of pain may occur in 3-14 days, but if the patient is not free of symptoms within three weeks continuation is pointless.

Phenytoin

The idea that the paroxysmal nature of tic douloureux is akin to epilepsy has been prevalent since Trousseau[5] used the expression "névralgie épileptiforme," and the analogy was sufficiently close to lead to a trial of anticonvulsants, beginning with potassium bromide in 1876. Phenytoin (Epanutin) was first shown to relieve the pain of tic douloureux in the 1940's[6] and subsequent trials confirmed this property.[7 8] It is customary to start with 100 mg twice or thrice daily and increase the dose as required, sometimes to as much as a total daily dose of 800 mg. Many patients experience benefit within 24 to 48 hours and occasionally it may be apparent after a single dose. In some cases relief is complete, but in others, though this is only partial, the frequency and severity of attacks are reduced and become bearable.

PRINCIPLES OF TREATMENT

After one week free of pain the dose is decreased and an attempt made to tail the phenytoin off altogether, but some of the patients will relapse and need a further course. If symptoms recur after an interval phenytoin is restarted and patients can be instructed to do this at the first hint of relapse. Long-term continuous administration may be associated with loss of efficacy in later episodes, and phenytoin is therefore best employed to treat acute episodes on a short-term basis. Unfortunately, with high doses side effects are frequently troublesome and may be intolerable, leading to discontinuation of the drug. Some side effects, such as drowsiness and fatigue, may merely be a nuisance, but others such as confusion and hallucinations are more serious. Diplopia, tremors, and the development of a cerebellar syndrome—with nystagmus, dysarthria, and ataxia—are relatively frequent features of acute phenytoin intoxication, but usually subside quickly when the drug is withdrawn. Continuous phenytoin medication may cause gingival hyperplasia, hirsutes, lymphadenopathy, megaloblastic anaemia, rashes, gastrointestinal upset, and occasionally jaundice, but more often these occur with chronic usage in epileptics. It is worth noting that a patient who has been on