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Heredity of congenital glaucoma

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Congenital or infantile glaucoma is usually described as a hereditary condition, transmitted by a single autosomal recessive gene (Westerlund, 1944; François, 1961; van der Helm, 1963; Duke-Elder, 1964; Shaffer and Weiss, 1970; Leighton and Phillips, 1970). It has been suggested that the penetrance is as low as 40 to 80 per cent. (Westerlund, 1944; Duke-Elder, 1964; Shaffer and Weiss, 1970; Leighton and Phillips, 1970), and that the prevalence of the heterozygous state in the general population is high (2·3 to 2·8 per cent.) (François, 1961; van der Helm, 1963). These suggestions were necessary to explain the facts that the majority of cases of congenital glaucoma are sporadic and not familial and that a parent and child are frequently affected which is unusual for autosomal recessive disease.

We have studied the pedigrees of 64 families of patients with congenital glaucoma and have reached the conclusion that monomeric inheritance of congenital glaucoma is unlikely.

MATERIAL AND METHODS

The families of eighty patients with infantile glaucoma were approached by mail or in person for information on additional cases of glaucoma of any type in relatives of the propositus, and on the age and sex of siblings. Satisfactory replies were received from 64 families, who are the subject of this study. All suspected and affected relatives were examined.

Results

Nine of the 64 families had more than one member affected with congenital glaucoma (Fig. 1). Three propositi had an affected parent, four had an affected sibling and two had an affected monozygotic twin. One family (Fig. 2) had "late-developing infantile glaucoma" transmitted as an autosomal dominant trait. 55 families had only one member (the propositus) affected. Consanguinity of parents of propositi was found in two cases. The size and number of the different sibships and the number of affected sibs are shown in the Table. 64 propositi (excluding the family with the dominant disease and including the monozygotic twins as genetically one person) had 211 unaffected and four affected siblings. In all, including affected siblings and parents, 72 members of the families were affected, 47 male and 25 female.

Four out of 252 grandparents had chronic simple glaucoma, about the same ratio as is expected in the general population. Of four pairs of twins, two pairs (all boys) were monozygotic (Fig. 1). These four boys were all affected, but in one boy the glaucoma was unilateral. In each of the two pairs of dizygotic twins, only one member was affected.

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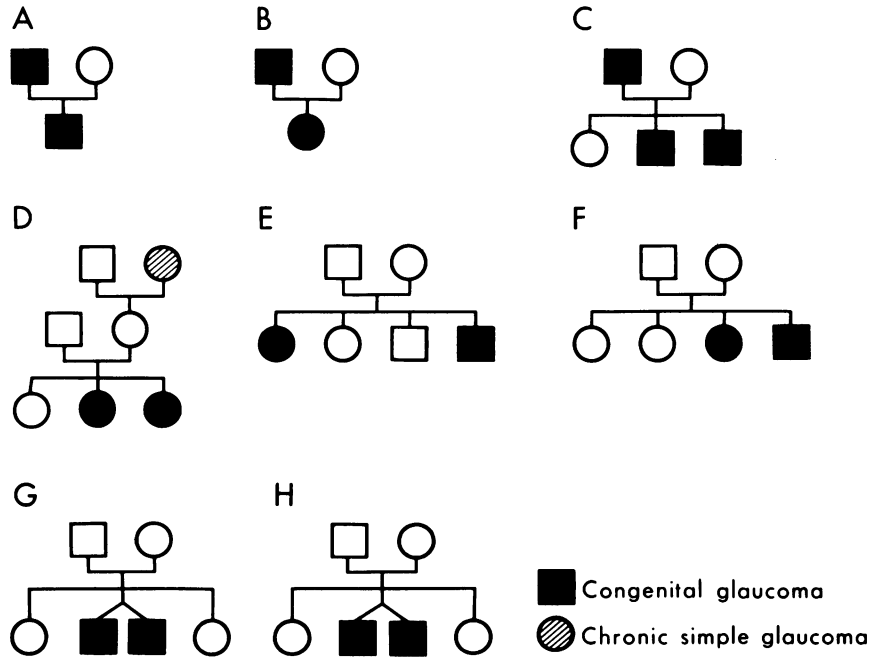

FIG. 1 *Eight families with more than one member of the family affected by congenital glaucoma. Three families (A, B, C) have a father and child affected, four families (C, D, E, F) have two siblings affected, and two families (G, H) have a pair of affected monozygotic twins, who can be regarded genetically as one person*

Table *Size and number of sibships and number of affected sibs*

Sibship size	*Number of sibships*		*Total number of sibs*	*Total number of sibs less propositi*	*Total number of affected less propositi*
	With one affected	*With two affected*			
1	7	–	7	–	–
2	13	–	26	13	–
3	14	2	48	32	2
4	8	2	40	30	2
5	6	–	30	24	–
6	6	–	36	30	–
7	3	–	21	14	–
8	1	–	8	7	–
9	1	–	9	8	–
Total	59	4	225	158	4

Discussion

One family (Fig. 2, overleaf) seemed clinically and genetically different from all the others. High intraocular pressures were discovered in all affected members after the age of 5 years, the anterior chamber angle was similar to the angle of congenital glaucoma, and the patients were successfully treated by goniotomy in contrast to those with early simple

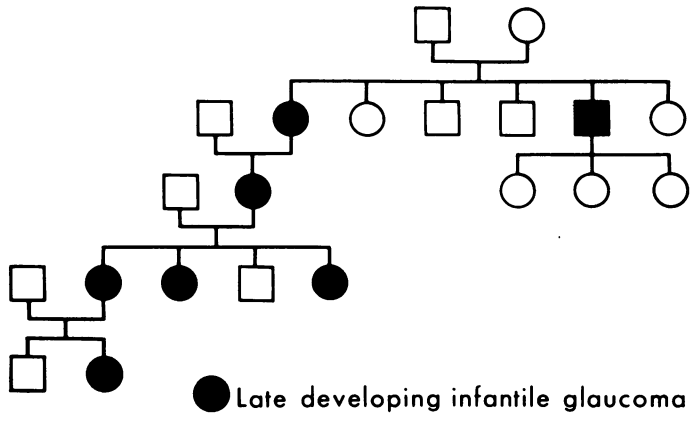

FIG. 2 *The single family with late developing infantile glaucoma. The mode of transmission of the disease is autosomal dominant*

glaucoma. Shaffer (1965) termed this type of glaucoma "late developing infantile glaucoma". Genetically, autosomal dominant transmission seems most probable for this type.

As for the other 63 families, autosomal recessive transmission of the disease is unlikely for several reasons. The number of affected siblings (four) was much lower than the expected 25 per cent. for recessive disease. The number of affected parents (three) is hard to explain by recessive heredity, as the parents of propositi are usually not affected. If we assume that this number of affected parents is a result of the high frequency of the heterozygous state in the population (François, 1961; van der Helm, 1963), we must expect that sometimes more distant relatives in the same families will also be affected. None of the families in this study, however, had a distant relative with congenital glaucoma.

Autosomal dominant transmission is also unlikely, since in none of our 63 families were more than two generations affected. Although two affected generations have frequently been reported (Delmarcelle, 1957), three or more affected generations are very rare (Heath, 1960; Jerndal, 1968). This observation is incompatible with autosomal dominant transmission of a non-lethal disease. The possibility of an autosomal dominant gene with a very low penetrance can also be excluded by the absence of grandparents affected by congenital glaucoma.

Our study indicates that the heredity of congenital glaucoma is most likely to be polygenic or multifactorial. Several facts, otherwise difficult to explain, fit well into the concept of multifactorial inheritance (Thompson and Thompson, 1966). The similarity in numbers of families with affected sibs and of families with an affected parent indicates genetic similarity between child and parents and between siblings, a basic fact in multifactorial inheritance. The unequal distribution by sex, boys being affected almost twice as frequently as girls, is consistent with multifactorial inheritance. The low number of affected sibs is similar to the expected number derived from the hypothesis of Edwards (1960) that, for multifactorial inheritance, the sib incidence is the square root of the population incidence. Since Westerlund (1947) estimated that the incidence of congenital glaucoma in the general population is 1 in 12,500, the sib incidence for this disease would be expected to be 1 in 112. This figure agrees fairly well with our obtained figure of 1 in 53.

The absence of affected distant relatives is also consistent with multifactorial inheritance, which, compared with autosomal dominant heredity, causes a lower incidence of affected distant relatives.

We suggest the hypothesis, therefore, that congenital glaucoma is inherited multifactorially like chronic simple glaucoma (Armaly, 1967) or angle-closure glaucoma (Lowe, 1970).

Is there any common genetic basis among the three types of glaucoma? The answer seems to be negative for two reasons:

(1) The incidence of chronic simple glaucoma in the grandparents of our propositi is not higher than that expected in the general population.

(2) The pair of alleles p^H and p^L (corticosteroid responsiveness), which are the most significant in relation to chronic simple glaucoma (Armaly, Monstavicius, and Sayegh, 1968), play no role in causing angle-closure glaucoma (Kitazawa, 1970) or congenital glaucoma (Leighton and Phillips, 1970).

Summary

A study of the pedigrees of 64 families has led to the hypothesis that congenital glaucoma is caused by multifactorial inheritance, as evidenced by the preponderance of affected males, the low number of affected siblings, the almost equal numbers of affected parents and siblings, and the absence of affected distant relatives.

One family had "late developing infantile glaucoma" of autosomal dominant heredity.

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