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Congenital Glaucoma Due to Dominant Goniodysgenesis. A New Concept of the Heredity of Glaucoma

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SUMMARY

Three typical pedigrees with hereditary glaucoma are presented, in which dominant goniodysgenesis is shown to be the actual genetic trait. Because of a marked variation in the expressivity of dysgenesis, the symptoms of the genetic malformation (elevated intraocular pressure and subsequent glaucoma) may appear early or late in life. Therefore, there is no justification in letting the patient's age at the onset of the symptoms decide the classification or the mode of inheritance of the glaucoma (infantile, juvenile, simple), when the common etiologic factor is a dominant dysgenic trait. Consequently, the term "congenital glaucoma" is inadequate and even misleading for glaucoma caused by an inborn malformation, but which may be manifested only after several years or even decades. Instead a new term "dysgenic glaucoma" is suggested as the logical term that also indicates the etiology.

INTRODUCTION

Glaucoma is defined here as a neuronal degeneration at the optic nerve head caused by an elevated intraocular pressure (IOP) (> 21 mm Hg).

Congenital glaucoma is defined as a congenital malformation of the iridocorneal angle leading to a reduced outflow of aqueous humor, elevated IOP, and glaucoma. Infantile congenital glaucoma (synonyms: congenital glaucoma, hydrophthalmos, buphthalmos, primary infantile glaucoma) was recognized very early in the ophthalmologic literature [1]. Similar conditions are found in other mammals and fish, notably goldfish.

In humans, the disorder has been subjected to numerous studies, and since a majority of cases go to blindness, it has been a continuous challenge to ophthalmologists. The dysgenic nature of the basic outflow disturbance was demonstrated early by Collins [2], Cross [3], Seefelder [4], and others. These findings have

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been clearly summarized by Anderson [5]. He stated that congenital glaucoma was probably caused by goniodysgenesis, that is, maldevelopment of the irido-corneal angle, which harbors the drainage pathways for the aqueous humor. Imperfect drainage will lead to pathologically increased IOP, which in turn will cause glaucoma with hypoxia of the optic nerve head and destruction of its nerve fibers, usually in a progressive manner.

Anderson [5] also made it clear that congenital glaucoma in infants might be either genetic or truly sporadic (e.g., due to viroses such as rubella). Usually, there is no way to tell one variety from the other, because the different kinds of fetal disturbances seem to act along a "final common path" causing an arrested development of the pertinent structures. This arrest is estimated to occur in the last trimester of fetal life [5] or perhaps in the very last month [6]. Anderson [5] also expresses the view that there is one basic etiology for both "infantile" and "juvenile" glaucomas, a view shared by Barkan [7].

The study of the genetics of congenital glaucoma in infants has attracted considerable interest, but unfortunately most investigators have concentrated on the manifestations of the genetic trait (viz., the elevated IOP and its effects, such as distension of the eyeball, clouding of the cornea, excavation of the optic disc, and, eventually, visual impairment). Additional practical and psychological difficulties have been present, such as the rarity of infants with congenital glaucoma, the frequent occurrence of truly sporadic cases (phenocopies), small sibships in the presence of glaucoma for fear of another blind child, incomplete family examinations, and reluctance of investigators to accept a genetic link between infantile and other types of glaucoma. The study of what I believe to be *the genetic trait itself*, namely, goniodysgenesis, has been largely neglected. The poor interest paid to clinical investigation of the irido-corneal angles is illustrated by the fact that gonioscopy—the only reliable clinical method to examine the pertinent angle morphology—was not reported in family studies until 1942 [8].

Thus, is it not surprising that the results of studies into the heredity of glaucoma have been vague and confusing to date. A number of large family studies with lasting impact [9–12] conclude that infantile congenital glaucoma is an autosomal recessive disorder, whereas Waardenburg et al. [13] admit to the possibility of an irregular dominant heredity. Recently, the data of Demenais et al. [14] were interpreted to indicate genetical heterogeneity of congenital glaucoma. I feel that had these investigators included gonioscopy in the examination protocol, the data obtained might have been compatible with the single-mechanism model proposed here.

In all handbooks on glaucoma, congenital glaucoma is presented as a specific class confined to infancy and characterized as a recessive or sporadic disorder. On the other hand, juvenile glaucoma has been reported to be a dominantly inherited disorder [15], while for chronic simple glaucoma of old age, opinions diverge regarding inheritance, and dominant [16], recessive [17], and multifactorial [18] models have been proposed, although for this glaucomatous disorder, no genetic factor has actually been demonstrated.

In this communication, evidence is presented that dominant goniodysgenesis is the primary genetic trait in hereditary glaucoma, not only in infants but also in youngsters and adults.

EXAMINATION ROUTINE

Pedigrees suitable for the fruitful study of any genetic trait are those with more than one member displaying the trait. In families with one member afflicted with congenital glaucoma and at least one further member afflicted with glaucoma, the aim was to examine all members with a standard examination battery, including visual acuity, slitlamp microscopy, gonioscopy, funduscopy, tonometry, and, if possible, perimetry. Here focus is on the evaluation of the basic genetic trait, goniodysgenesis, and only relevant additional details are given.

RESULTS

Pedigree 1 (fig. 1)

This large pedigree was examined by Berg [19] and has been carried up to date by Jerndal [20]. It demonstrates dominant glaucoma with infantile-juvenile onset through 9 generations. Berg [19] was convinced that dysgenesis of the anterior ocular segment was a prerequisite for subsequent glaucoma, but he did not perform gonioscopy to vindicate this idea. In figure 1, the focus is on those generations studied by me. It is clearly indicated that goniodysgenesis is distributed in an autosomal dominant mode. The age for the discovery of the associated glaucoma was quite variable, and is recorded in the figure with Arabic numerals. Goniodysgenesis was present in all members afflicted with glaucoma, but also in four children under age 7 without glaucoma. Since every adult member without glaucoma also lacked goniodysgenesis, these four children must be considered glaucoma high-risk suspects.

The actual time of onset of glaucoma in the individual members could be judged only from the time the disease was detected. Four members had a verified onset before age 1 ("infantile" type). The glaucomas of the other members were detected between ages 1 and 43.

In this context, it should be mentioned that two equally large and adequately examined pedigrees from the United Kingdom clearly demonstrate the same dom-

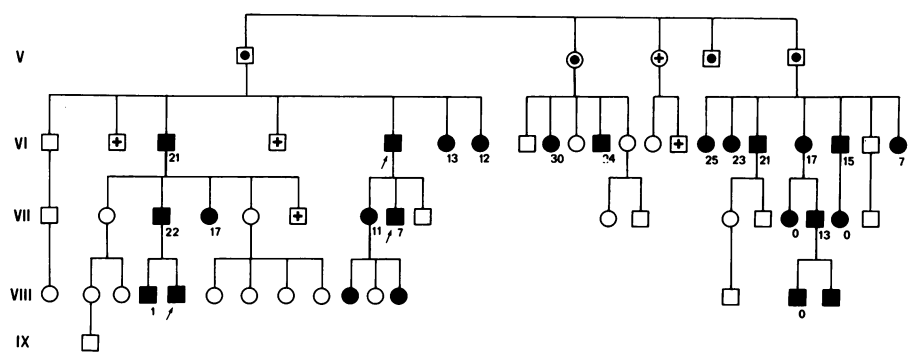

FIG. 1.—Pedigree of family originally studied by Berg [19] and updated by Jerndal [20] showing autosomal dominant inheritance of goniodysgenesis (*filled symbols*). In the diagram, only *generations V* to *IX* are shown. In generation *V*, Berg [19] verified glaucoma in four individuals (*dot within symbols*), whereas one never was examined (deceased, + *within symbol*). In generations *VI* to *IX*, all individuals have been examined by gonioscopy by the author except three (*indicated by arrows*), in whom goniodysgenesis was verified by other ophthalmologists. Age of discovery of glaucoma is indicated by *Arabic numerals next to the symbol. 0* denotes glaucoma before age 1 yr. Note that four children in generation *VIII* display goniodysgenesis but yet no symptoms of glaucoma.

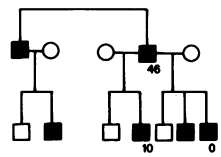

FIG. 2.—Pedigree showing autosomal dominant inheritance of goniodysgenesis. Glaucoma and goniodysgenesis were detected in two children with the same father but different mothers. When the father was examined, he displayed moderate goniodysgenesis but no glaucoma. However, he did develop glaucoma 6 yrs later. Goniodysgenesis was also detected in a third brother and in an uncle and one of his sons. These three persons are still free from glaucoma.

inant goniodysgenic trait closely associated with glaucoma of juvenile onset [21, 22].

Pedigree 2 (fig. 2)

The index patient had large eyes from birth and developed the classic picture of infantile congenital glaucoma at age 3 months. His eyes displayed severe goniodysgenesis. A number of goniosurgical interventions were carried out, but in vain, and blindness resulted. The half-brother developed glaucoma at approximately age 10 and displayed a similar goniodysgenesis but of less severe expression. Since the two afflicted boys had different mothers but the same father, the latter would be the genetic key person for a dominant trait. The father was examined at age 41. He, too, had goniodysgenesis of a moderate degree and no elevated IOP. Nevertheless, he was considered genetically afflicted and predisposed for glaucoma. This diagnosis proved to be correct 6 years later when he developed glaucoma, and he is now under treatment.

Thus, distinct genetic goniodysgenesis was present in the father and two sons with different mothers. Obvious variation in the severity of the dysgenesis led to postponement in the onset of glaucoma in the less severe cases. Two other members of this family display minor dysgenesis and are given regular checkups for signs of glaucoma.

Pedigree 3 (fig. 3)

The index patient is a girl with unilateral congenital glaucoma, diagnosed before age 1 and treated with a successful operation. Her paternal grandfather,

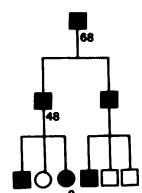

FIG. 3.—Pedigree showing autosomal dominant inheritance of goniodysgenesis through 3 generations. At the first investigation, only the one child and the grandfather were glaucomatous, but the father had typical goniodysgenesis and later developed glaucoma. Two other members of this family have goniodysgenesis but no glaucoma so far. Thus variable expressivity of goniodysgenesis causes variable penetrance of glaucoma, obscuring clear-cut dominant inheritance.

68, attended the same clinic and was diagnosed as a "late congenital glaucoma" with characteristic goniodysgenetic features of moderate severity. The girl's father and uncle were examined, and both displayed distinct goniodysgenesis with borderline IOPs. In the 7 years of follow-up, the father developed both elevated IOP and glaucomatous field defects. This pedigree demonstrates dominant dysgenesis through 3 generations, with variable expressivity leading to variable time of onset of glaucoma. Note that if only glaucoma had been studied, dominant inheritance would not have been obvious. This case also illustrates that unilateral infantile congenital glaucoma does not exclude a genetic etiology.

Six further pedigrees showing dominant inheritance of goniodysgenesis with glaucoma have been published by Jerndal and Munkby [23], and also have been discussed by Jerndal et al. [24].

DISCUSSION

Three important points regarding the heredity and clinical relevance of goniodysgenesis are clarified by the glaucoma pedigrees presented here. (1) The iridocorneal angle abnormality known as goniodysgenesis is congenital. Its pathologic anatomy in eyes with infantile congenital glaucoma is well documented by histology as well as by gonioscopy and goniosurgery. In this study, every individual with glaucoma also had typical goniodysgenesis detected by gonioscopy. (2) Goniodysgenesis displays a simple mode of inheritance—autosomal dominant, and, according to the results presented above, may constitute *the basic genetic trait* in all cases of hereditary glaucoma. (3) Normally, dominant goniodysgenesis has an intrafamilial variation of expressivity, as have many other dominant traits. Systematic gonioscopic observation and interpretation of this variable expressivity was first reported by Kluyskens [25]. He suggested the terms "early" and "late" congenital glaucoma to describe early and late onset of the disease caused by mild or severe goniodysgenesis, respectively. These useful terms, however, did not gain popularity, perhaps because of the built-in contradiction in the combination "late congenital." Kluyskens' observations were correct, however, and have been verified by others [23, 24, 26].

In contrast to the rare full-blown expression of goniodysgenesis in infantile congenital glaucoma, reduced expression may lead to a long delay of the dysfunctional signs, namely, elevated IOP and neuronal damage, as demonstrated in the pedigrees. This issue, which has a key position in the clinic, has been received with considerable incredulity. This is all the more surprising, since the biological principle of congenital malformations causing late appearing clinical manifestations is well known from other organs (e.g., cystic kidneys leading to chronic renal insufficiency, stenosis of the aqueduct producing slowly developing hydrocephalus, stenosis of the pulmonary artery causing cardiac failure, and so on). Thus, goniodysgenesis and early and late glaucoma fall into a well-established pattern of malformation and dysfunction.

A number of pedigrees in the ophthalmologic literature lend support to the pathophysiology of goniodysgenesis with variable expressivity, either indirectly—without gonioscopy [5, 19, 27–29], or directly—with gonioscopy [8, 21, 22, 30].

Thus, infantile congenital glaucoma is only the most obvious result of dysfunction caused by severe goniodysgenesis. But glaucoma induced by hereditary goniodysgenesis is by no means confined to infancy, and therefore the term "congenital glaucoma" is a misnomer, which in itself has caused much confusion. Instead, the new term "dysgenic glaucoma" is suggested as a logical alternative, which also has the advantage of indicating the basic etiology of a defined genetic malformation.

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