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Population Genetical Aspects of Primary Congenital Glaucoma. I. Incidence, Prevalence, Gene Frequency, and Age of Onset

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Summary. This paper presents some characteristics of the population genetics of primary congenital glaucoma in Slovakia. The overall incidence in Slovakia is 1:10,500, while being 1:1,250 in the Gypsy subpopulation of Slovakia and 1:22,000 in the non-Gypsy population. For a special type of congenital primary glaucoma, transmitted by autosomal recessive inheritance in Gypsies the gene frequency may be estimated to reach 2.8%. Early onset of the disease enabling diagnosis soon after birth in 82% of patients may be considered another characteristic of this type of primary congenital glaucoma.

Introduction

In the last several decades, primary congenital glaucoma (PCG) has gained an adequate attention of both ophthalmologists and geneticists, due to the gravity of the prognosis of this disorder. However, basic problems of this disorder, including etiology, determination of the participation of the genetic component, pathogenesis, and therapy, are far from being considered as solved (Francois 1972; Kwitko 1973; Briard et al. 1976; d'Epinay 1980).

Participation of a genetic component in the etiology of PCG is generally accepted. In the classical ophthalmology literature, primary congenital glaucoma was considered an autosomal recessive hereditary disorder (Westerlund 1947; Kluyskens 1950; Gianferrari et al. 1954; Delmarcelle 1957; Francois 1958; Waardenburg et al. 1961). The fact that cases of congenital glaucoma mostly occurred sporadically was explained by a diminished gene penetrance (40–80%) and by a high prevalence of heterozygotes (Westerlund 1947; Delmarcelle 1957; van der Helm 1963; Francois 1972). In more recent works, multifactorial heredity of PCG has also been suggested (Fraser and Friedmann 1967; Merin and Morin 1972). Clinicogenetic analyse by a group of French investigators have suggested possible genetic heterogeneity of PCG (Briard et al. 1976; Demenais et al. 1979; Demenais et al. 1981).

One of the methods of disclosing genetic heterogeneity is genetic analysis; using this analysis, a special PCG type could be disclosed in the population of Slovakia, favoring the suggestion of genetic heterogeneity of PCG. The above-cited type may be characterized as follows: it occurs in the Gypsy ethnic only; it is transmitted by autosomal recessive inheritance with full penetrance; the eyes are bilaterally affected in all cases; progression is rapid and it has a very poor prognosis (Genčíkova et al. 1977; Gerinec and Genčíkova 1977; Genčík et al. 1980).

The present paper complements previous data on PCG in Slovakia by variables such as incidence, prevalence, estimation of gene frequencies and heterozygote frequencies, and age of onset of the disorder; these data should complement the geneticist view of this particular type of PCG.

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Material and Methods

The patient series on which the present paper is based has been characterized in detail in the genetic analysis (Genčík et al. 1980). The series included 120 families with at least one member affected, altogether 205 individuals with PCG. Of these, there were 45 Gypsy families with 118 patients. Cases with secondary congenital glaucoma as well as those with congenital glaucoma as part of an underlying disorder had been excluded. In elderly family members or those who were deceased at the time of our investigations, the disorder was considered to be primary congenital glaucoma only when medical records or other reliable documents were available. Only cases with onset of the disorder before the age of 3 years were considered as PCG.

The material was collected in cooperation with clinics of ophthalmology, departments of ophthalmology and institutes of social care in Slovakia. Since the disorder under investigation unavoidably leads all patients to consult an ophthalmologist, since its diagnosis presents no difficulties, and as the ophthalmologists have been very cooperative, our series may be expected to include all patients with diagnosed PCG in Slovakia, i.e., that the records are almost complete. This mainly applies for the non-Gypsy population. For infants born within the last 8–10 years the records can be considered as complete also in families of Gypsy provenance. Incidence calculation were therefore based on date from these latter years.

Results

Prevalence. Of the total of 118 patients with PCG, 94 patients of Gypsy provenance were alive at the time of our study. An estimation of the total number of persons of the Gypsy population is 200,000 (exact numbers are not known) and when the prevalence is calculated for the ethnic group as a whole, 1:2,120 is obtained.

PCG prevalence in the non-Gypsy group of the population can be determined much more better reliably. With 84 living patients the prevalence may be estimated to be 1:52,000.

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Incidence. Table 1 shows the number of children born with PCG in individual years (1955–1977 for the Gypsy ethnic group and 1950–1976 for the non-Gypsy population). Table 2 shows PCG incidence values in Slovakia for individual years from 1970 through 1977; based on these, the average incidence from the Gypsy and the non-Gypsy population may be determined to be 1:1,250 and 1:22,000, respectively. Average incidence of all PCG cases calculated for the entire population of Slovakia reaches 1:10,500.

Table 1. Numbers of children born with primary congenital glaucoma within 1955–1977 (the Gypsy population), and within 1950–1976 (the non-Gypsy population)

Years	Number of cases	
	Gypsy patients	Non-Gypsy patients
1977	3	0
1976	3	5
1975	4	3
1974	8	4
1973	6	5
1972	6	5
1971	5	3
1970	4	4
1969	4	4
1968	3	2
1967	4	2
1966	4	2
1965	2	1
1964	4	4
1963	2	0
1962	3	3
1961	3	0
1960	2	5
1959	2	3
1958	2	1
1957	2	1
1956	4	2
1955	2	1
1954		4
1953		0
1952		1
1951		3
1950		4

Gene Frequencies, Frequencies of Heterozygotes. Based on results of the previous analysis (Genčík et al. 1980), PCG in Gypsies may be suggested to be an autosomal recessive hereditary disorder, and gene frequencies may be reasonably calculated from the incidence values: $q = \sqrt{1/1{,}250} = 0.028 = 2.8\%$; and frequencies of heterozygotes, $2q(1-q) = 0.054 = 5.4\%$. Also, the obtained values should be considered as approximate, as this population obviously does not meet prerequisites for application of the Hardy-Weinberg law, namely; (a) there is no panmixis in this Gypsy population (since, according to recent results, this population is likely to have a high inbreeding coefficient) and (b) PCG occurs in only one subpopulation of Gypsies.

Age of Onset. One of the diagnostic criteria of PCG is that the disease is manifested before the age of 3 years (Kwitko 1973). Of our 118 patients of the Gypsy ethnic group, the age of onset (the age at which diagnosis had been established) could be found out with certainty in 78 only, while it was known in 83 of 87 patients of the non-Gypsy population. Table 3 demonstrates the numbers of patients in whom the diagnosis was established immediately after birth, within 6 months after birth, from 6 to 12 months of age, between the 1st and 2nd years of life and between the 2nd and 3rd years of life. The table shows clearly that there is a difference in age of onset between the two groups of patients. In patients of Gypsy origin, the glaucoma was obvious in as many as 82% of cases immediately after birth, while the corresponding number for the non-Gypsy population was 34%. In the non-Gypsy population PCG was diagnosed most frequently during the first 6 months of life.

Discussion

Enlargement of the globes of the eyes as a result of increased intraocular pressure has drawn the attention of physicians also to epidemiological aspects of this problem. The first data on the frequencies of congenital glaucoma began appearing in papers in the late 19th and early 20th centuries (Seefelder 1906). The high frequencies reported in these papers may be explained by: (1) a broader concept of the definition of congenital glaucoma (including the secondary glaucoma of childhood and syndromes, where glaucoma only represents one aspect of an underlying

Table 2. Primary congenital glaucoma incidence in Slovakia in 1970–1977 according to the ethnic origin

Years	Gypsy population			Non-Gypsy population		
	Number		Incidence	Number		Incidence
	Cases	Births		Cases	Births	
1970				4	81,200	1:20,300
1971				3	83,600	1:27,900
1972	6	5,813	1: 968	5	88,400	1:17,700
1973	6	6,018	1:1,003	5	93,500	1:18,700
1974	8	6,516	1: 814	4	98,300	1:24,600
1975	4	6,462	1:1,615	3	98,400	1:32,700
1976	3	6,392	1:2,130	5	100,500	1:20,000
1977	3	6,270	1:2,090			
Total	30	37,471	1:1,250	29	643,900	1:22,200

Table 3. Comparison of age at which the diagnose was established between children of the Gypsy ethnic group and non-Gypsy population

Age of diagnosis	Seefelder (1906); Dettmering, Stolting and Fleischer (1918); Anderson (1939); Van der Helm (1963)		Non-Gypsy patients		Gypsy patients	
	No. of patients	Per cent	No. of patients	Per cent	No. of patients	Per cent
At birth	203	33.2	28	33.8	64	82.0
Between birth and 6 months	262	42.9	37	44.6	9	11.5
Between 6 and 12 months	87	14.2	8	9.6	3	3.8
Between 12 and 24 months			4	4.8	1	0.8
Between 24 and 36 months	55	9.1	5	6.0	0	0
Over 36 months			1	0.8	1	0.8
Total	610		83		78	

Table 4. Comparison of primary congenital glaucoma incidence in various populations. (The two numbers represent approximate limits of incidence)

Authors	Population	Incidence
Westerlund (1947)	Region Copenhagen	1:12,500
van der Helm (1963)	Netherland	1:17,800
Briard et al. (1976)	Midi-Pyrénées	1:14,500
d'Epinay (1977)	Switzerland	1: 5,000–1:10,000
Luntz (1979)	New York	1:10,000
Travers (1979)	England	1: 5,000–1:10,000
	Slovakia	1:10,500
	Gypsy population	1: 1,250
	Non-Gypsy population	1:22,000

disease) and (2) as well as the higher frequency in consanguineous marriages these were in this time ofter. Aiming at a better comparison, Table 4 therefore presents only data concerning the incidence of congenital glaucoma from more recent years, as the diagnostic possibilities, the spread of ophthalmologic service nets, and thus the probability of diagnosing the disorder might be considered nearly the same.

The incidence of all PCG diagnosed in Gypsies and in the non-Gypsy population of Slovakia is similar to those reported in most resent works (Westerlund 1947; van der Helm 1963; Briard et al. 1976; d'Epinay 1977; Luntz 1979; Travers 1979) (Table 4), i.a., 1:10,500. This value was calculated from the 1970–1977 data for the entire Slovak population. Very similar values result when the basal period is extended to 1955–1977. When the genetic specificity of PCG in Gypsies is taken into account and such cases are excluded, the incidence of PCG in the non-Gypsy population decreases to 1:22,200. The incidence of this special PCG type in Gypsy newborns reaches a high value of 1:1,250. In addition, it should be noted that the nember of members of the Gypsy ethnic group living in Slovakia is a rough estimate, since there are no official statistical data concerning ethnic groups in the CSSR.

In the years 1974–1977 a certain propensity to limit the incidence of congenital glaucoma in Gypsies. This decrease, or the increase of this incidence in the years 1971–1974 has to be taken as above average exceptional rate. The general trend of the incidence in the past 25 years is certainly in correlation with the demographic characteristics of the Gypsy population in Slovakia (this differs from the demographic characteristics of the remaining population in Slovakia). However, this phenomenon can also be taken as frequency increase in the years 1971–1974; where above average rates were observed. It can be explained as occasional deviation from the normal values. Nevertheless, once can speculate that as a consequence of the genetics intensive work with families in which a case of congenital glaucoma was previously found the rates of PCG incidence was decreased. Technical problems should also be taken in account (belated diagnosis, restrain in the administration). Many years of continuous work will be needed to point out and clarify the question which factory influence the frequency of PCG.

Moreover, an exact estimate of the incidence is difficult to obtain because the Gypsy population of Slovakia is divided into subpopulations, which may be defined by their settlement locality, by the time of their immigration into the territory of Slovakia, and by other social characteristics. The three most numerous subpopulations can be distinguished this way. Congenital glaucoma only occurs in the subpopulation of Gypsies living within a central territorial band extending from the eastern up to the western border of Slovakia (Fig. 1). When these facts are taken into account, prevalence, incidence, and gene frequencies for PCG in Gypsies may be expected to reach even higher values in this Gypsy subpopulation.

A higher prevalence in the mainly non-Gypsy population may be expected since for patients over 25–30 years no reliable documentation concerning development of their disorder in childhood exists, and in many cases it is difficult to determine ex post facto, whether their underlying disorder had been congenital glaucoma or another condition. Thus a portion of older patients escaped the series.

The age of onset of the hereditary disorder may serve as an important sign for distinguishing genetic heterogeneity. Although the time shift of the massive PCG manifestation between Gypsies and the non-Gypsy population is not very large (several months only), it may be considered a distinguishing sign because of the manifestation of bilateral almost symmetric enlargement of the eyeballs. Table 3 shows the age of diagnosis for the Gypsy and non-Gypsy patients of our material and a summary of the results from 610 patients reported previously (Seefelder 1906; Dettmering et al. 1918; Anderson 1939; van der Helm 1963).

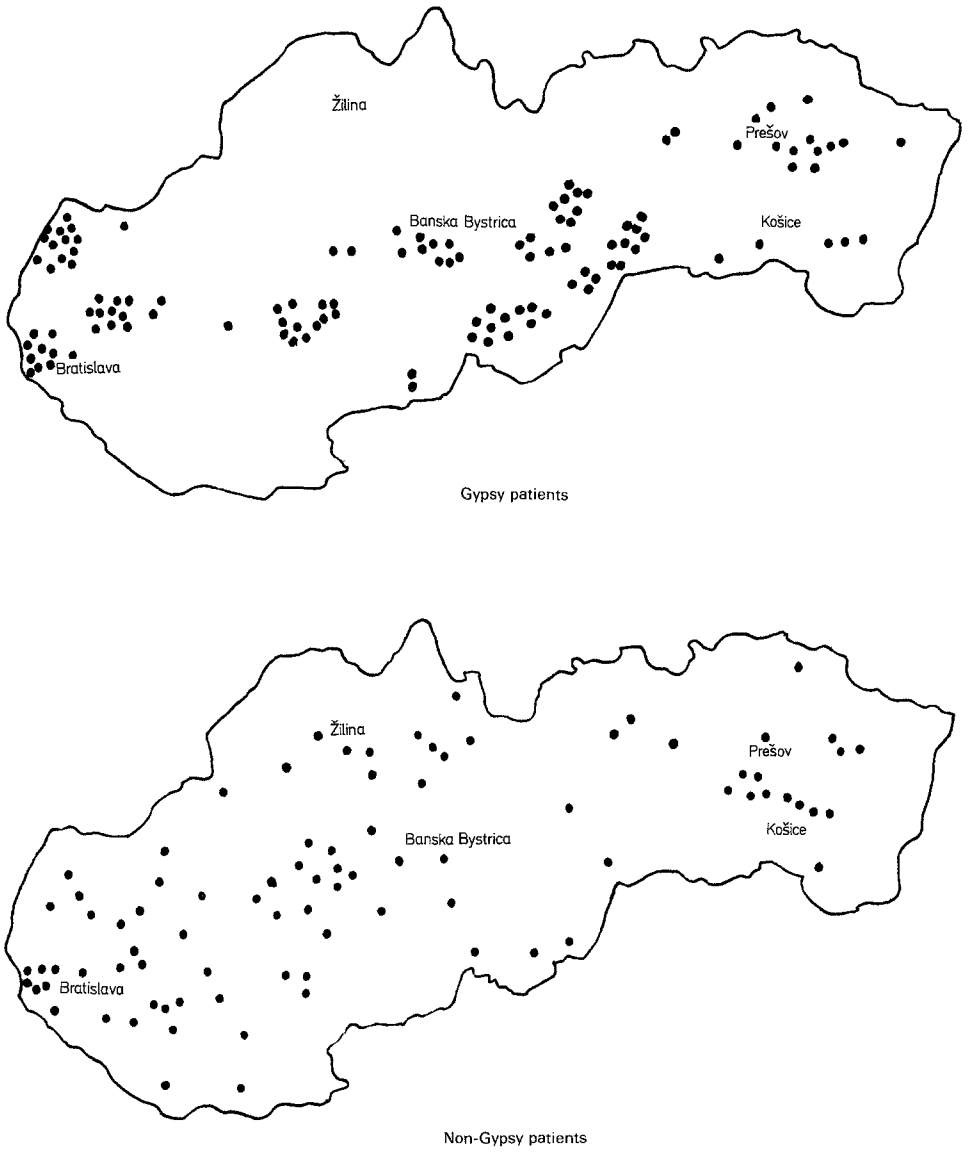

Fig. 1. Distribution of non-Gypsy and Gypsy primary congenital glaucoma patients according to their original residence in Slovakia

Their values are similar to those in our non-Gypsy patients and differ very much from values for the age of diagnosis of PCG in our Gypsy patients. Thus the age of onset may be included among the characteristics of a special type of PCG occurring in Gypsies.

In practice one should be aware of genetic heterogeneity of congenital glaucoma. Determination of the frequency of risk should be based upon the fact that in the case of congenital glaucoma in Gypsies it is an autosomal recessive inheritance. Thus in each Gypsy family where at least one child was born with PCG, the frequency of the risk is approximately 25%. Regarding genetic counselin of non-Gypsy families we are confronted with a totally different situation as we are depending on empirical data which show a 5% recurrence risk in the population of Slovakia.

The presented results from the population genetic aspect confirm the assumption of genetic heterogeneity of PCG, with a special type with autosomal recessive heredity. By chance, that this gene could apread within a more or less closed population so that its extremely high frequency enabled it to be discovered within an entire, obviously heterogeneous PCG group. Also, either the identical or another allele, or even an entirely different gene for PCG can be assumed to cause in other populations by a similar or an identical pathological mechanism a portion of PCG cases. This supported by a rich genealogical material showing autosomal recessive transmission of the gene. Now it is up to ophthalmologists to distinguish other typical features of PCG due to an autosomal recessive gene by means of clinical and pathomorphological signs or by means of performance or other tests, and to contribute further to the differentiation of congenital glaucoma.

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