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CONGENITAL CATARACT – AUTOSOMAL RECESSIVE FORM – IN AN ETHNIC ISOLATE, INTENSELY INBRED

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Abstract

The most common lens defect in the neonate is cataract. It may occur as an isolated defect or it may be associated with other ocular or systemic abnormalities. We propose to study the congenital cataract in an isolate, in order to identify the etiology, the type of inheritance and the genetic and clinical characteristics. The study group comprises an isolate population of approx. 200 individuals, with 8 cases of congenital cataract identified so far. The pedigree, segregation study and the probability calculation using the Bayes formula have been accomplished for each family. Endogamy in this isolate is of 80%. The consanguinity coefficient of the population forming the isolate is 0.004373 and the frequency of consanguineous marriages is 20%. The frequency of heterozygous carriers is 32.: Congenital cataract, usually rare, can reach an unusually high incidence in isolates. Its study becomes more interesting today, as isolates are disappearing.

Key words: Congenital Cataract; Isolate; Consanguinity

INTRODUCTION

The most common lens defect in the neonate is cataract. Cataract may be unilateral or bilateral, anterior or posterior in the lens, and partial or total. It may occur as an isolated defect or it may be associated with other ocular or systemic abnormalities. Cataract may be inherited or sporadic. The most common inheritance pattern is autosomal dominant; autosomal recessive inheritance occurs less frequently and is sometimes found in populations with high rates of consanguinity. The prevalence of congenital cataract varies from 5% to 20% among severe blindness in childhood and the causes are heterogeneous.

As isolates are disappearing, we propose the study of congenital cataract in an isolate, in order to identify the etiology, the type of inheritance and the genetic and clinical characteristics.

Types Of Congenital Cataracts

- **Anterior polar cataracts** are well defined, located in the front part of the eye's lens and thought to be commonly associated with inherited traits. These types of cataracts often are considered too small to require surgical intervention.

- **Posterior polar cataracts** also are well defined, but appear in the back portion of the eye's lens.
- **Nuclear cataracts** appear in the central part of the lens and are a very common form of congenital cataracts.
- **Cerulean cataracts** usually are found in both eyes of infants and are distinguished by small, bluish dots in the lens. Typically, this type of cataract does not cause vision problems. Cerulean cataracts appear to be associated with inherited tendencies (Boke W 1989, Casidy L, Taylor D1999).

Cataracts, which can be defined as lens opacities, have multiple causes, but are often associated with breakdown of the lens microarchitecture (Fakhour 2015) possibly including vacuole formation and disarray of lens cells, which can cause large fluctuations in density resulting in light scattering. In addition, light scattering and opacity will occur if there is a significant amount of high molecular weight protein aggregates of approximately 1000 Å or more in size (AfsanY et al2010, Lin et al, 2014). The short-range ordered packing of the lens crystallins is important in this regard. For transparency, crystallins must exist in a homogeneous phase with significant short-range spatial ordering (Niwald et al, 1996, Sheeladevi S et al, 2016). This condition will be abrogated in the presence of aggregates of partially denatured or even native proteins. In fact, disruption of lens microarchitecture and protein denaturation is not mutually exclusive events, and both may play a part in some cataracts. The physical basis of lens transparency can be complex, and has been reviewed elsewhere (Wu X et al, 2016, Pichi F et al, 2016).

MATERIAL AND METHOD

The study group comprises an isolate population of approx. 200 individuals, with 8 cases of congenital cataract identified so far. The pedigree, segregation analysis and the probability calculation using the Bayes formula have been accomplished for each family. Description of the isolate: Vadu Crişului is a village located on the Crişul Repede river, at around 50 km far from Oradea, in Western Romania. A colony of nomad gypsies settled close to the village 54 years ago, in 1947. Their initial number is unknown. Presently, the colony is formed of approx. 200 persons; the exact number is difficult to estimate, as they are highly mobile.The whole population of the isolate is named with three last names: CIURAR, ROŞTAŞ and COVACI. These can actually be reduced to only two names, as ROŞTAŞ and CIURAR are in fact the same name, one in Hungarian, the other one in Romanian. The mix with the local population is practically absent, and the mix with other populations is sporadic. Endogamy in this isolate is 80%. The consanguinity coefficient of the population forming the

isolate is 0.004373 and the frequency of consanguineous marriages is 20%. Gypsies forming the colony don't usually marry legally (Fig1).

There were 21 families (couples) identified inside the colony. At least 18 of these are endogamous, representing an endogamous percentage of 80%. Of these unions, at least 4 (20%) are consanguineous between first degree, second degree or first degree cousins of one parent (see pedigree). The average number of offspring for a couple is 7-8 children. All these characteristics allow the definition of an ethnic isolate, with social and cultural components. Endogamy and consanguinity are relevant from a genetic point of view.

RESULTS DISCUSSIONS

Congenital cataract was noticed in 8 patients of 4 siblings, which yields a prevalence of the disease of 7.4% inside the isolate (1/14). All cases presented with total bilateral cataract since birth, with no other associated malformations. The pedigree corresponds to the autosomal recessive inheritance pattern: the parents of affected children are healthy; "horizontal" pattern of distribution in the pedigree; no gender predilection; consanguineous marriages; the average percentage of patients in the 4 siblings (30%) is close to the expected theoretical percentage of 25% for autosomal recessive disorders.

The following were excluded: toxic constitutional factors: maternal diabetes mellitus, embriopathy, drugs; viral infections: rubella, influenza, mumps, varicella, measles; parasitary factors: toxoplasmosis; local causes: mechanic, traumatic, inflammatory; hereditary syndromes that present with cataract; numeric and structural chromosomal anomalies. Bayes' formula was used for calculating probability. As each family has at least one affected child, both parents are assumed to be carriers.

Therefore, for Family I:

$p_{anterior}$ = 1/2, i.e. the consultand has 50% chances of being a heterozygous carrier;

$p_{conditional} = (1/2)^5$, as 5 healthy children were born, each having a 1/2 chance of being a heterozygous carrier;

$p_{united} = p_a \times p_c = (1/2) \cdot (1/2)^5$, as the 2 families can appear together

Therefore:

$$p_{posterior} = \frac{p_a \cdot p_c}{p_a + p_c} = \frac{every\ probability}{sum\ of\ probabilities} = \frac{(1/2)\cdot(1/2)^5}{(1/2)\cdot(1/2)^5} = 1$$

For family II, III and IV, see Table 1

Table 1

Bay's formula for family II, III, IV

For family II:	For family III:	For family IV,
$p_a = 1/2$ $p_c = (1/2)^2$ $p_u = 1/8$ $p_p = 1/5$	$p_a = 1/2$ $p_c = (1/2)^9$ $p_u = (1/2) . (1/2)^9$ $p_p = 1/513$	the situation is identical with family II (2 normal children).

Calculation of carrier frequency was done using **Hardy-Weinberg's law:**
Frequency of the disease in the population (8/200) is equal to the frequency of recessive homozygotes:

$R = q^2 = 1/25$ (0,04)

Frequency of recessive genes: $q = \sqrt{\frac{1}{25}} = 1/5$ (0,20)

Frequency of the normal, dominant gene: $p = 1–q = 4/5$ (0,80)

Frequency of dominant homozygotes: $D = p^2 = 16/25$ (0,64)

Frequency of carrier heterozygotes: $H = 2pq = 8/25$ (0,32)

Therefore: $R + D + H = 1/25 + 16/25 + 8/25 = 1$

The calculated risk for the 4 families varies between 1/513 and 1/5. The frequency of heterozygous carriers is 32%.

The recurrence risk for normal parents of an affected child, with no identifiable causes like rubella or toxoplasmosis, is 1:10. If a second child with cataract is born in the same family, the autosomal recessive inheritance pattern is accepted and the recurrence risk changes to 1:4 b (Bembea M, 2001, Covic M et al 2011).

Therefore, at a frequency of affected children (recessive homozygotes) of 1/25, the frequency of carriers (heterozygotes) in the population is 8 times higher (Freire et al, 1984, Huo LA et al, 2014) Also, the frequency of the gene in the population of 20% is very high. Given these values, it is expected that the frequency of the disease would rise in the present generation. For the next generations, a diminution of homozygocy is expected, by fitness reduction (Jaber et al, 1991, Hammami et al, 2005). The fitness reduction is already noticeable: 3 out of the 8 children with congenital cataract died during the first years of life. Other 3 children are abandoned in social care units, with reduced chances of recovery and social insertion. The other 2 children that are raised in family associate severe mental retardation; the family's preoccupations for education and social insertion are minimal (Hernandez et al, 1989, Jacquard A et al, 1970).

There are, therefore, minimal chances that recessive homozygotes would transmit the gene to the next generations, due to a fitness approaching

zero. A large number of genes are thus eliminated. In the case the isolate is maintained, the risk of perpetuation of the disease is high, given the high frequency of carriers and the consanguinity noticed. We are not able to determine heterozygotes. Theoretically, in all 4 siblings, the chance of having heterozygous children is 50%, as both parents are heterozygotes (Bardelli et al., 1989).

The role of the isolate in maintaining and transmitting the recessive gene is therefore, decisive. Only an obvious breaking of the isolate (very discrete at present time) could lead to a reduction of the frequency of the disease (Bembea M, 2015).

Genetic counseling in this situation is very important and is primarily endorsing the avoidance of consanguineous and endogamous marriages, as the disease frequency in the isolate is very high. The cultural level of the population is making these attempts very difficult, as the receptivity of the population is low. Still, many adult members of the isolate were receptive and showed interest in reducing the recurrence risk. The tradition of early, illegitimate, endogamous unions remains difficult to influence for the future (Cernea 198l, Bardelli et al., 1989).

CONCLUSION

Congenital cataract, autosomal recessive form, usually rare, can reach an unusually high incidence in isolates. Its study becomes more interesting today, as isolates are disappearing.

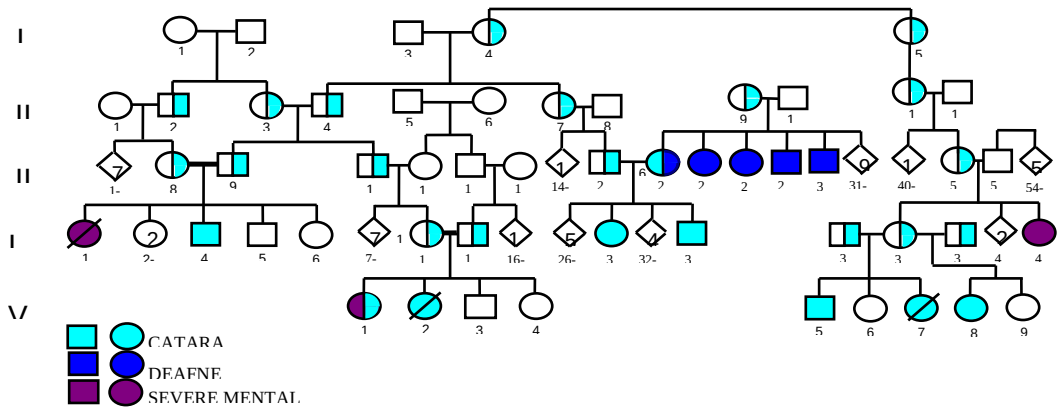

Fig. 1 Pedigree of the 4 families of the 8 affected individuals.

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