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ORIGINAL ARTICLE

A study of consanguineous marriage as a risk factor for developing comitant strabismus

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Abstract Inheritance has an important role in the etiology of comitant strabismus. Consanguineous marriage is a leading factor in birth defects in which inheritance has a role. The aim of this study is to reveal if consanguineous marriage increases the risk of developing comitant strabismus. We included 461 patients who underwent primary surgery for comitant strabismus in Shiraz University Khalili Hospital (Fars province, southern Iran) between years 2003 and 2013 in our study. All the patients were living in Shiraz, Iran. Patients were categorized into the following 4 groups: (1) intermittent or constant exotropia, (2) infantile esotropia, (3) non-accommodative acquired esotropia, and (4) accommodative acquired esotropia. A total of 421 healthy children who were born in Shiraz, at the same period of time, were also studied as a control group. Presence and type of the consanguineous marriages were evaluated in the parents of the patients and control group by a questionnaire. Mean of inbreeding coefficient (α) was calculated in each group of patients and was compared with those of control group. The proportion of parental first cousin marriage was 37.7 and 23.5 % among patient and control groups. The mean of inbreeding coefficients (α) were 0.0236, 0.0283, 0.0288, and 0.0236 in four groups of the patients, respectively. The mean of inbreeding coefficient was 0.0263 in total patients, which was significantly higher than 0.0164 of control group (T=5.27, df=880, P<0.001). Patients with non-accommodative acquired esotropia had the highest mean of inbreeding coefficient (α) (0.0288). It seems that recessive form of inheritance plays an important role in the etiology of comitant strabismus. Modified screening programs may be needed for earlier detection of strabismus in the offspring of consanguineous couples.

Keywords Consanguinity · Strabismus · Inbreeding coefficient

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Introduction

Strabismus is classified largely to comitant and non-comitant types. Comitant strabismus is a deviation that is the same magnitude at all gaze positions. Comitant strabismus includes intermittent or constant exotropia (XT), infantile esotropia (ET), and accommodative or non-accommodative acquired ET. Exotropia and esotropia are two main forms of strabismus when the eyes are deviated outward or inward, respectively. Infantile ET is a form of ET in which the deviation is recognized before 6 months of age. Accommodative ET is a convergent deviation of the eyes associated with activation of accommodative reflex due to moderate to large amount of hyperopia.

Previous studies have demonstrated that inheritance plays an important role in the etiology of comitant strabismus (Ziakas et al. 2002). Family history is significantly more prevalent in several types of strabismus such as intermittent or constant XT and accommodative or partially accommodative ET (Tohishiko et al. 2001). Furthermore, it has been noted that the risk of developing squint is approximately four times higher if either the siblings or the parents have strabismus (Aurell and Norrsell 1990).

Consanguineous marriage is a leading factor in birth defects in which inheritance has a role (Stoll et al. 2005). To the best of our knowledge, no one has studied the effect of consanguinity on incidence of strabismus. We started this

investigation on the assumption that consanguineous marriage increases the risk of developing strabismus. The aim of this study is to reveal the prevalence of consanguineous marriage in parents of patients with different types of comitant strabismus and comparing it with general population.

Materials and methods

Data were collected from 461 patients who underwent primary surgery for comitant strabismus in Shiraz University Khalili hospital (Fars province, southern Iran) between years 2003 and 2013. All the patients were living in Shiraz, Iran. Patients had exotropia or esotropia in isolation and did not have any abnormalities in eye structure. Patients who had strabismus secondary to poor vision were excluded. Type of the strabismus was collected from patients' hospital records. According to the type of strabismus, patients were categorized into the following 4 groups: (1) intermittent or constant XT, (2) infantile ET, (3) non-accommodative acquired ET, and (4) accommodative acquired ET. Simple randomized sampling method was used to include a total of 421 healthy children as a control group. All of these children were born in Shiraz at the same period of time. The type of marriage of the parents of each individual in the patient and control groups was evaluated by an interview using a questionnaire. All participants provided informed consent. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences.

The inbreeding coefficient (F) is the probability that an individual has received both alleles of a pair from an identical ancestral source or the proportion of loci at which he is homozygous. The inbreeding coefficients (F) were calculated by the degree of relationship between the couples: double first cousins (1/8), first cousins (1/16), first cousins once removed (1/32), and second cousins (1/64). The mean inbreeding coefficient (α) was calculated for each category of patients and control group.

Results

Demographic characteristics of patients with comitant strabismus are demonstrated in Table 1. The numbers of the different types of consanguineous mating and the mean of inbreeding coefficient (α) among the parents of each group of the patients, total patients, and control group are shown in Table 2. The proportion of parental first cousin marriage was 37.7 and 23.5 % among patient and control groups, respectively. Parents of patients with strabismus had higher incidence of first cousin marriage compared to control group (χ^2=28.5, df=1, p<0.001). Patients with strabismus had higher mean inbreeding coefficient (α) compared to control group (T=5.27, df=880, P<0.001). Patients with non-accommodative acquired ET had the highest mean of inbreeding coefficient (α) (0.0288).

Table 1 Demographic characteristics of the patients with comitant strabismus

Patients	Age [mean (SD), range]
Intermittent or constant exotropia	19.50 (6.06), 1–36 y
Infantile esotropia	15.46 (4.12), 1–24 m
Non-accommodative acquired esotropia	8.66 (5.14), 3–31 y
Accommodative acquired esotropia	6.71 (2.02), 5–18 y

y year, *m* month

Discussion

Comitant strabismus affects up to 4 % of the general population and has many long-term personal and public consequences (Oystreck and Lyons 2012; Khan et al. 2011a). The etiology of comitant strabismus has remained unclear and several hereditary and environmental factors are considered to have a contribution (Oystreck and Lyons 2012). Understanding the potential risk factors for developing comitant strabismus is very important, because it helps to modify the screening programs to detect the children with strabismus at early age. Such early detection may lead to early therapeutic approaches and less long-term consequences.

Several studies suggest that inheritance has an important role in the etiology of strabismus. Previous twin studies showed a concordance rate of 73 to 82 % among monozygotic twins and 35 to 47 % among dizygotic twins (Paul and Hardage 1994; Matsuo et al. 2002). A higher prevalence of strabismus among families of an affected individual have been demonstrated in several population studies (Ziakas et al. 2002). A cohort study of 7100 strabismic patients revealed that about 30 % of the patients had a close relative with strabismus (Paul and Hardage 1994). Cotter et al. reported association between positive family history of strabismus and XT, which was independent from hereditability of the refractive error (Cotter et al. 2011). In another investigation, strong genetic element in hypermetropic accommodative ET was proposed (Ziakas et al. 2002). Tohishiko et al. reported prevalent family history in intermittent or constant XT and accommodative or partially accommodative ET (Tohishiko et al. 2001). Schlossmann and Priestley demonstrated that 47.5 % of patients with strabismus, 48.9 % with ET and 36.8 % with XT, belonged to families with two or more affected members (Schlossmann and Priestley 1952). Familial incidence of strabismus has been reported to be as high as 65 % in other studies (Dufier et al. 1979).

Table 2 Number of different types of consanguineous mating and mean of inbreeding coefficient (α) among the parents of each group of patients, total patients, and control group

Type of marriage	Type of disease					
	Intermittent or constant exotropia	Infantile esotropia	Non-accommodative acquired esotropia	Accommodative acquired esotropia	Total patients	Control group
Double first cousin	1	0	0	0	1	0
First cousin	56	35	68	15	174	99
Cousins once removed	2	2	3	0	7	8
Second cousins	24	8	21	5	58	29
Unrelated marriages	89	39	70	23	221	285
Total	172	84	162	43	461	421
Mean of inbreeding coefficient (α)	0.0236	0.0283	0.0288	0.0236	0.0263	0.0164

The genetics of common forms of comitant strabismus is not well identified (Khan et al. 2011a). The mode of comitant strabismus inheritance may be dominant, recessive, or multifactorial (Ziakas et al. 2002; Paul and Hardage 1994). Several chromosomal susceptibility loci have been suggested (Fujiwara et al. 2003). It seems that both recessive and dominant linkage and also codominant inheritance model of transmission is related to infantile ET (Khan et al. 2011a). Khan et al. suggested a recessive susceptibility locus (16p13.12-p12.3) for different phenotypic forms of childhood strabismus (Khan et al. 2011a). Khan et al. suggested oligogenic inheritance for infantile ET by linkage analysis in a large consanguineous family (Khan et al. 2011b). An autosomal recessive inheritance in concomitant strabismus has been suggested in a first cousin marriage couple and their 8-year-old identical twin daughters with ET (Li and Chen 1991).

Consanguinity increases the risk of recessive forms of ocular diseases due to increase in the likelihood of presence of pathogenic mutations in a homoallelic state (Khan et al. 2011a). Consanguinity is favored among one fifth of the world population especially among residents of the Middle East, West Asia, and North Africa (Hamamy 2012). Currently, many young consanguineous couples want to know the consequences of consanguinity on their offspring. Moreover, health programmers should be aware of possible pathologies to change the screening guidelines for consanguineous couples and their offspring. On this basis, we studied the prevalence of consanguineous marriage in parents of patients with different types of comitant strabismus. Mean of inbreeding coefficient (α) was higher in all groups of patients with comitant strabismus compared to control group. Patients with non-accommodative acquired ET had the highest mean of inbreeding coefficient (α).

Regarding these data, it seems that recessive form of inheritance plays an important role in the etiology of comitant strabismus. Modification of screening programs may be needed for earlier detection of strabismus in children of consanguineous couples. Current screening strategy for early detection of amblyopia and strabismus in our country is a two-stage program: first, elective screening of refractive error and amblyopia in 4–6 year old children; second, obligatory screening of strabismus, refractive error, and amblyopia in 6 year old children prior to school entrance. According to our study results, earlier obligatory screening program may be needed to detect strabismus in children of consanguineous couples.

Our study has some significant shortcomings. First, our data were collected from 461 patients who underwent primary surgery in a referral eye hospital in Shiraz. Although most of the patients with comitant strabismus need surgery, some of the patients with accommodative-acquired ET may not need, and some other patients may not desire to have operation. Second, our control group comprised 421 healthy children, born at the same period of time in Shiraz. We have not

compared the age of parents of the two groups. Increasing trend of consanguineous marriage during the last century was reported in a study done in Tehran, Iran (Akrami et al. 2009). However in that study, percentage of consanguineous marriage was relatively similar between individuals who married in 1949–1979 and after 1979. According to the age of our patients and control group, almost all of the parents' marriage occurred after 1949. Furthermore, the inbreeding coefficient of our control group was 0. 0164, which was closely similar to inbreeding coefficient of Shiraz general population (0.0152), reported in a national research project done in 2001, with multistage sampling design and large sample size (Saadat M. [The incidence of consanguineous marriage in Iran.] Shiraz University Press 2002; Saadat et al. 2004).

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Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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