Original Article

Consanguinity and Increased Risk of Congenital Ptosis: A Case–Control Study from Southern Iran

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Abstract

Purpose: To assess consanguinity as a probable risk factor for congenital ptosis.

Methods: In this case–control study, 97 patients with congenital ptosis and 97 participants as the control group were included. The age, sex, and residence area of the control group were matched with the cases. The inbreeding coefficient (F) was calculated for each participant, and the mean of the inbreeding coefficient (α) was calculated for each group.

Results: The prevalence of consanguineous marriage in parents of cases with congenital ptosis and those of the control group was 54.6% and 30.9%, respectively ($P < 0.002$). The mean of the inbreeding coefficient (α) in patients with ptosis was 0.026, whereas it was 0.016 in the control group ($T = 2.51$, degree of freedom = 192, $P = 0.0129$).

Conclusions: The rate of consanguineous marriage was significantly higher among the parents of patients with congenital ptosis. It implies a probable recessive pattern in the etiology of congenital ptosis.

Keywords: Congenital ptosis, Consanguinity, Genetic, Inbreeding coefficient

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Introduction

Blepharoptosis, which is commonly shortened as ptosis, is characterized by low-lying upper eyelid margins with secondary narrowing of the palpebral fissure. It is classified into congenital and acquired according to the age of onset. Congenital ptosis is defined as the presence of the disease since birth or within the 1st year of life.[1] Although it is mostly an isolated condition and does not progress over time, it can cause deprivation amblyopia as a result of visual axis occlusion.[2] It can also be associated with significant functional, cosmetic, and psychosocial problems in children.[3] The prevalence of congenital ptosis is not officially available, but one of the largest studies on more than 700,000 people in China in 1986 reported a prevalence of 0.18%. The mentioned study aimed to investigate the prevalence and mode of inheritance in some ocular diseases. Among the patients with congenital ptosis, the prevalence of sporadic cases was 67.1%. Autosomal dominant and autosomal recessive patterns were seen in 18.4%, and 14.5% of the cases, respectively.[4] Some studies have also discovered specific genes for isolated congenital ptosis with various and distinct patterns of inheritance.[5,6] These studies imply the presence of strong and complex genetic background in the pathogenesis of congenital ptosis.

Consanguineous marriage, the marriage between individuals with a common ancestor, occurs frequently in many communities. Inbreeding increases the level of homozygotes for autosomal recessive disorders; hence, consanguinity is associated with an increased incidence of congenital defects,

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particularly when an autosomal recessive pattern is present.[7] Consanguinity has been also studied as a risk factor for some congenital ophthalmic defects. Bagheri *et al*. showed that the parent's consanguinity was a significant risk factor for the development of comitant strabismus in the offspring.[8] Another study carried out by Gordon-Shaag *et al*. aimed to find out any relationship between consanguinity and keratoconus. They found a remarkable association between parental first-cousin consanguinity and keratoconus.[9]

The total prevalence of consanguineous marriage in Iran is estimated as 38.6%, and it reaches 74.6% in some regions.[10] Finding possible associations between consanguinity and congenital defects can help health authorities for future planning.

To the best of our knowledge, no previous study has investigated the association between consanguineous marriage and congenital ptosis. Accordingly, the aim of this study was to reveal any association between consanguinity and congenital ptosis.

Methods

This case–control study was conducted from February to April 2019 in Poostchi Eye Clinic affiliated with Shiraz University of Medical Sciences, Shiraz, Iran. Poostchi Ophthalmology Clinic is a referral eye center in Southern Iran. As a result, a significant proportion of patients are from other southern provinces of Iran.

Ninety-seven patients with the diagnosis of isolated congenital ptosis who had undergone reconstructive surgery between 2009 and 2018 were included in the study. Based on clinical presentation and clinical examination, other causes of ptosis such as congenital third nerve palsy, monocular elevation deficiency, congenital fibrosis of extraocular muscles, blepharophimosis, and other eyelid disorders were excluded. All the patients had a documentary file in Poostchi Eye Clinic that contained demographic data and procedure reports. Sixty-five patients were from Fars province and 32 were from other southern provinces. After evaluating the recorded files, using a phone call, a questionnaire containing some questions such as family history regarding the parents' consanguinity, family history of congenital ptosis, and congenital strabismus was filled out.

The controls were 97 participants who were matched with the cases by age, sex, and residence area. The control individuals were recruited through paper announcements in Poostchi Eye Clinic. To eliminate any confounding factors, we excluded those with any history of genetic eye disease. Matching with one of the cases was performed regarding age, sex, and residence area. People who met the inclusion criteria were asked to take part in an interview. During the interview, a questionnaire containing age, sex, residence area, and history of parents' consanguinity was filled out. The recruited participants were matched by age, sex, and residence area of the cases. It should be noted that an age difference of <5 years with the cases was considered acceptable in the inclusion criteria. Participants had no knowledge of the study purpose and effect of the parents' consanguinity until all questions were asked.

This study protocol was approved by the Ethics Committee at Shiraz University of Medical Sciences with the code of IR.SUMS.MED.REC.1398.299. The study was conducted in accordance with the tenets of the Declaration of Helsinki. The aims and objectives of the study were explained, and written informed consent was obtained from the patients or their parents. This study has been extracted from a thesis for fulfillment of the medical doctor's grade.

Statistical analysis

All items of the questionnaire were entered into the Statistical Package for the Social Sciences version 14.0 (IBM, Chicago, IL, USA) by an expert operator. Twenty percent of the entered data were randomly selected and double-checked to ensure entrance accuracy. The coefficient of inbreeding (*F*), which is the probability that a person with two identical genes receives both genes from one ancestor, was determined for each individual by the degree of the consanguinity of the parents. Thus, the inbreeding coefficient was determined as 1/8 for the double first cousin, 1/16 for the first cousin, 1/32 for the first cousin once removed, and 1/64 for the second cousin. The mean of the inbreeding coefficient (α) was then calculated for each group.

Results

Demographic characteristics of the patients and control group are demonstrated in Table 1. The mean age of patients and controls was similar (22.00 ± 12.45 and 22.23 ± 12.24,

Table 1: Demographic characteristics of the patients and control groups

Variables	Patients	Control
Mean age±SD (year)	22.00±12.45	22.23±12.24
Sex		
Male	56	56
Female	41	41
Residence		
Shiraz	29	29
Fars province except Shiraz	36	36
Kohgiluyeh and Boyer-Ahmad province	11	11
Hormozgan province	9	9
Bushehr province	6	6
Khuzestan province	5	5
Kerman province	1	1
Degree of consanguinity of parents		
Double first cousin	0	0
First cousin	34	22
First cousin once removed	9	7
Second cousin	10	1
Not relative	44	67

SD: Standard deviation

respectively). Male-to-female ratio was 1.36. The majority of patients were living in Fars province (n = 65), and others were living in some other southern provinces of Iran (n = 32).

The prevalence of consanguineous marriage in the parents of the cases with congenital ptosis and those of the control group was 54.6% and 30.9%, respectively ($P < 0.002$). The mean inbreeding coefficient (α) of the cases was 0.026, while it was 0.016 in the control group (T = 2.51, Degree of Freedom = 192, $P = 0.0129$).

Positive family history of congenital ptosis was found in 17.4% of the patients (9.2% in the first-degree and 8.2% in the second-degree relatives). A positive family history of congenital strabismus was found in 10.3% of the patients. 5.2% of the congenital ptosis cases were simultaneously affected by congenital strabismus.

Discussion

Congenital ptosis is a rare condition characterized by lower positioning of the upper eyelid that is present at birth.[11] It can negatively affect the individual not only physically but also psychologically and functionally.[3] Many theories have been proposed regarding the etiology of this disease. In the past, it was thought that congenital ptosis might be a disorder of muscle development. However, more recent studies have suggested that congenital ptosis should be classified as a variant of congenital cranial dysinnervation disorders (CCDD). The term CCDD implies that the major problem is a primary neuro-maldevelopment rather than muscle abnormality.[12] Understanding the potential risk factors for congenital ptosis is an important step in improving the screening programs and detecting the affected individuals as soon as possible. Various studies have shown that inheritance plays an important role in the etiology of congenital ptosis. Vestal *et al*. investigated the concordance of congenital ptosis in monozygotic twins. A heritability index was calculated for congenital ptosis which showed a value of 0.75, indicating that 75% of the phenotype is attributable to genetic factors. Their study supported a transmissible genetic defect as a contributing factor to the development of congenital ptosis.[13] Furthermore, Stein *et al*. found a systemic disorder in 35% of the studied children with congenital ptosis, of which the most common were genetic, chromosomal, or neurologic disorders.[2]

It has been shown that various genes play important roles in the development of this disease. The first genetic locus identified for congenital ptosis was PTOS1. Engle *et al*. studied DNA from the blood samples of 42 individuals belonging to a family, in which 20 members were affected by congenital ptosis in at least one eye. They found that the gene responsible for congenital ptosis (PTOS1) resides on the short arm of human chromosome 1 (1p32–34.1), most likely within the 3 centi-Morgan intervals defined by the polymorphic markers D1S447/D1S2733 and D1S1616. For this gene, the pattern of inheritance is autosomal dominant with incomplete penetrance.[5,12] McMullan *et al*. studied a large family affected by isolated, congenital bilateral ptosis, in which no male-to-male transmission was observed. They extracted DNA from family members for linkage analysis and suggested a new mode of inheritance, X-linked dominant, for congenital ptosis. In addition, their linkage analysis defined a critical region between Xq24 and Xq27.[6] In another study, McMullan *et al*. identified the ZFH-4 gene as a candidate gene for bilateral congenital ptosis after DNA analysis of a child affected by this disease. Chromosome analysis of their patient revealed two chromosome breakpoints and a *de novo* balanced translocation of chromosomes 10 and 8 affecting the ZFH4 gene (8q21.12). It has been shown that this gene codes for a zinc finger homeodomain protein and is a transcription factor expressed in both muscle and nerve tissues.[14]

Consanguinity, the marriage between relatives, is a common issue in many regions of the world, especially Asia and Africa due to socioeconomic, cultural, and religious factors.[15] Consanguineous marriage has been identified as a risk factor for many adverse health outcomes, as the offspring of this type of marriage may be at increased risk for autosomal recessive disorders and also for multifactorial diseases. It should be noted that the closer the degree of the biological relationship, the greater the risk of unfavorable outcomes becomes.[10]

Several studies have investigated the association between ocular disorders and consanguinity. Kumaramanickavel *et al*. reported that 28.8% of the patients who were tested for ophthalmic genetic disorders had a family history of consanguinity. In addition, among these patients, 63.9% had retinitis pigmentosa.[16] Nirmalan *et al*. obtained details regarding the consanguinity of the parents from 10,290 participants. They found microcornea to be significantly associated with both an uncle-niece and a first-cousin relationship between the parents. Furthermore, they found that retinitis pigmentosa was significantly associated with a first-cousin relationship between the parents.[17] Hornby *et al*. studied 56 children with ocular coloboma. They reported that 44.6% of the participants with nonsyndromic ocular coloboma had consanguineous parents.[18] Bagheri *et al*. also evaluated the relationship between consanguineous marriage and comitant strabismus. Their results showed that the mean of the inbreeding coefficient (α) was significantly higher in the patients compared to the controls. They suggested that the recessive form of inheritance plays an important role in the etiology of comitant strabismus.[8]

To the best of our knowledge, this is the first study that evaluated the relationship between consanguinity and congenital ptosis. Our results showed that the inbreeding coefficient was significantly higher in the patients compared to the controls. Based on these data, it seems that recessive forms of inheritance might play an important role in the etiology of congenital ptosis. The discovered genes for isolated congenital ptosis have suggested a strong genetic basis of the disease though none of them is distinctly matched with an autosomal recessive pattern of inheritance. Considering the results of our study and some other studies discussed earlier, there may be

an unknown causative gene or group of genes with a recessive mode of inheritance.

Consanguineous marriage is an important health problem that should be addressed by a health education campaign. In some countries such as Iran, where the rate of consanguineous marriages is high, there is an urgent need for public educational programs and provision of the facilities for genetic counseling.[15]

The current screening program for early detection of ocular disorders in our country includes two stages: first, elective screening of refractive error and amblyopia in 4–6-year-old children and second, obligatory screening of strabismus, refractive error, and amblyopia in 6-year-old children.[8] As previous studies have shown, the incidence of amblyopia in congenital ptosis is high.[2,19] Therefore, a modified screening program may be needed at an earlier age to detect amblyopia in children with congenital ptosis.

One limitation of our study is that we did not compare the age of the parents of the patients and controls. However, Akrami *et al*. have shown that the prevalence of consanguineous marriage is relatively similar between individuals who married in 1949–1979 and after 1979. According to the age of our patients and control group, we can assume that almost all the parents' marriage occurred after 1949.[20]

We enrolled in the study the patients who were candidates of reconstructive surgery. This group might have had more severe ptosis. Therefore, the results may not be necessarily applicable to all congenital ptosis patients.

Further large-scale studies with details regarding the age of parents are encouraged to shed more light on this issue. More investigations are required to discover probable causative genes and patterns of inheritance in congenital ptosis.

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Conflicts of interest
There are no conflicts of interest.

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