Correlation of Parental Consanguinity and Strabismus

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ABSTRACT

Objective: to study about the prevalence of strabismus and its types in patients with parental consanguinity

Materials and methods: A search of the literature on strabismus and its correlation to parental consanguinity using PubMed database. Articles obtained regarding strabismus, its types, the rate of strabismus and the presence of consanguinity were critically reviewed. The data of patients were collected with a positive parental consanguinity and diagnosed with strabismus. A pedigree charting was done for all the patients where the degree of relation was assessed, along with the categorization of the type of strabismus along with the degree of refractive error associated with each patient. The categorization of strabismus into infantile esotropia, accommodative esotropia, intermittent or constant exotropia, non – accommodative esotropia, accommodative esotropia. The coefficient of inbreeding was also assessed.

Results: It was seen that parental consanguinity is related with horizontal deviation along with refractive errors. In these patients, the presence of strabismus appears to be mostly in hypermetropic accommodative esotropia. A study stating that the prevalence of strabismus in the first – degree relatives is the highest in accommodative esotropia followed by partial accommodative and lastly with infantile esotropia. The coefficient of inbreeding was significantly higher in the group with strabismus than the control group. The non-accommodative acquired esotropia had the highest mean of inbreeding coefficient.

Conclusion: consanguinity is originated based on the community. Counseling in such communities is key to decrease the associated risk factors in offspring in such communities. The presence of parental consanguinity was higher in the strabismus group with the variations of degree based on the type of strabismus. this correlation needs to be assessed further with increased accuracy and precision with more detailed categorization.

Keywords: strabismus, parental consanguinity, correlation, consanguinity, hereditary, risk factor,

INTRODUCTION

There is an estimate that one billion of the current global population live in communities with a preference for consanguineous marriage (Bittles and Black 2010a; Modell and Darr 2002). In North Africa, Middle East and West Asia, consanguineous marriages are a tradition and well respected where intra – familial unions collectively account for 20 – 50+ percent of all marriages (Bittles 2011; Hamamy et al..2011; Tadmouri et al. 2009). Research states that it is important for primary healthcare providers, specifically in highly consanguineous communities, have clear evidence – based guidelines in counselling a consanguineous couple to minimize their risks for having affected offspring (Hamamy 2011). Recently, there are studies that have suggested a greater frequency of horizontal deviation amongst parental cousin marriage (Fujiwara et al..2003). A survey was conducted with 7200 patients with the history of strabismus that had shown almost 30% of the patients had a positive history of consanguinity (Hamamy 2012). A study which portrayed that inheritance plays an important role in the etiology of comitant strabismus also sheds an insight regarding the relatability of parental consanguinity and strabismus (Ziakas, Woodruff, Smith and Thompson 2002). Another study that delved into the prevalence of family history with the details related to the types of strabismus which are classified as constant or intermittent Exotropia (XT) and accommodative or partially accommodative Esotropia (ET) (Tohishiko et al.,2001). To understand the aim of assessment of the correlation between parental consanguinity to strabismus in a population that has high prevalence of parental consanguinity it is important to understand the terms as follows.

Consanguinity in clinical genetics, states that a consanguineous marriage is defined as a union between two individuals who are related as second cousins or closer, which the offspring of a consanguineous union is expected to inherit identical gene copies from both parents.

A study stated that the leading factor in birth defects where inheritance plays a role is through consanguineous marriage (Stoll et al..2005). Studies on the effect of consanguinity on incidence of strabismus are ongoing and needs to be explored. 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 (Bagheri ,Farvardin and Saadat,2015).

The objective of this paper is to present an overview and recent research regarding the effect of parental consanguinity on strabismus. To delve into the research more, the relation between hereditary and the type of strabismus associated with it. To pursue the objectives, family history and the extent to

which degree the parental consanguinity is extended is important.

METHODS

A search for the keywords "parental consanguinity" and "strabismus" on PubMed was performed. The selection of publications was thorough and recent. Other words that helped in the search were "hereditary", "squint", "relation between strabismus and consanguinity" or "relation between hereditary and strabismus" and "prevalence". The articles included in the study were those that studied the relation between different types of strabismus and the role hereditary factors in the prevalence of strabismus. An approximate of 551 articles were found at the PubMed platform. The selection process of these specific articles was based on the prevalence of strabismus and what factors influences it. The articles were based on cases that discussed about strabismus, the types of strabismus distributed among the data collected and studying the aspects of hereditary or parental consanguinity. Among the many articles read, the exclusion criteria were those that study genetic mutations, other associated factors and surgical outcomes or related to any form of intervention was excluded from the study. A total of 20 articles were studies over the span of 13 articles were finalized based on the area of the study conducted, the demographic data, the relatability to the main keywords.

RESULTS

A good insight on hereditary as a risk factor in strabismus in explained (Ziakas,2002). This article had assessed heredity as a risk factor in different types of strabismus. Many such studies have been published since. The authors in their methods had administered a questionnaire about family history. A three – generation pedigree was constructed for children under 12 years old attending the children's eye clinic for treatment of strabismus over a one-month period. Data of 100 index cases with a complete family pedigree were collected. The cases were classified into four groups: Infantile Esotropia (IE), Accommodative Esotropia (AET), Anisometropic Esotropia (ET) and Exotropia (XT). Out of which, 26 cases of infantile esotropia, 49 cases of accommodative esotropia, 15 cases of anisometropic esotropia, and six cases of exotropia. Thirty-three of the 49 cases (67.3%) with accommodative esotropia had at least one affected first degree relative, while 11 of the 26 cases (42.3%) with infantile esotropia, five of the 15 cases (33.3%) with anisometropic esotropia, and one of the six cases (16.6%) with exotropia had an affected first degree relative. The proportion of affected first degree relatives was significantly higher in the accommodative group than in any of the other three diagnostic groups. There were no significant differences between the other three categories. Therefore, the study found a statistically significant risk for strabismus in first degree relatives of patients with hypermetropic accommodative esotropia that was not present in second- or third-degree relatives. The findings do show that there is a stronger genetic element in hypermetropic accommodative esotropic than in anisometropic esotropia, infantile esotropia or exotropia in childhood, and that the role of heredity in aetiology of accommodative esotropia deserves further investigation.

Another study of consanguineous marriage as a risk factor for developing comitant strabismus (Bagheri, Farvardin and Saadat.2015), aimed to reveal the prevalence of consanguineous marriage in parents of patients with different types of comitant strabismus and comparing it with general population. A total of 461 patients underwent primary surgery for comitant strabismus between 2003 to 2013 and were categorized into the following 4 groups as mentioned previously on the type of strabismus:

(1) intermittent or constant XT, (2) infantile ET, (3) non-accommodative acquired ET, and (4) accommodative acquired ET. A randomized sampling method was used to include a total of 421 children as a control group. A questionnaire was used as a form of interview to assess the type of marriage of the parents of the patient and control groups. The mean inbreeding coefficient (α) was calculated for each category of patients and control group. The proportion of parental first cousin marriage was 37.7 and 23.5 % among patient and control groups, respectively. Parents of patients with strabismus (case group) had higher incidence of first cousin marriage compared to control group ($\chi 2 = 28.5$, df=1, $p<0.001$). Among the four types mentioned in the case group, patients with non – accommodative acquired ET had the highest mean of inbreeding coefficient (α) (0.0288). 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 aetiology of comitant strabismus. The study had some significant shortcomings, firstly the data that were collected from the 461 patients who underwent primary surgery 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, the selection process of the case group who underwent surgery was unclear. The age was not compared between the two groups. Based on the study, one of the key points is to have an earlier obligatory screening program may be needed to detect strabismus in children of consanguineous couples.

A specific study was done to see the type of horizontal deviation in consanguinity (Iqbal and Nadeem,2018). It was a cross sectional study to find out the association and types of horizontal deviation in consanguinity. A total of 93 patients were included in the study age 3 to 15 years with the diagnosis of horizontal deviation and positive history of consanguinity were included. The statistics stated were based on gender, whether the deviation is an exodeviation or an esodeviation and the refractive status of the patients which are as follows, 28 (30.1%) were males and 65 (56.9%) were females. There were 55 (59.1) patients with exotropia and 38 (40.8%) had esotropia (figure 1). There were 17 patients (18.2%) with emmetropia, 22 had (23.65%) myopia, 7 (7.5%) were hyperopes, 25 (26.8%) showed myopic astigmatism and 10 (10.7%) had hyperopic astigmatism. The remaining 12 (12.9%) had mixed astigmatic error (figure 2). The consanguinity and types of horizontal deviation is not properly identified. The mode of horizontal deviation inheritance can be dominant, recessive, or multifactorial (Oystreck and Lyons,2012). It was found that myopic astigmatism was the most common association with horizontal deviation specifically exotropia consisted of 59.1 % of the cases as opposed to esotropia that consisted of 40.8% of the cases (Figure. 1).

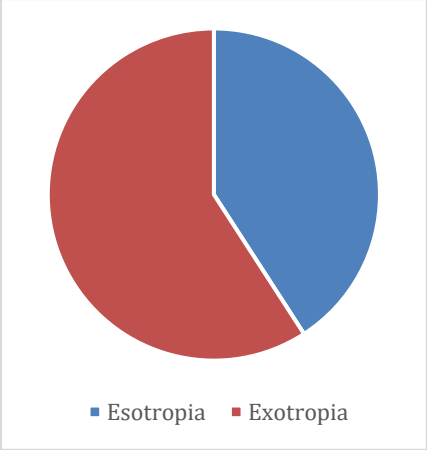

Figure 1. The distribution of horizontal deviation.

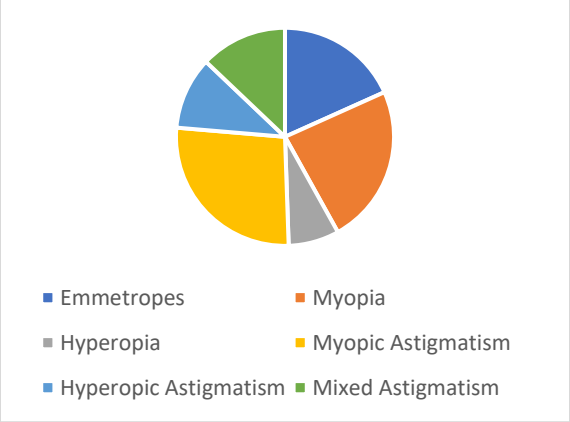

Figure 2. The distribution of refractive errors.

Lastly, a study on the role of heredity and the prevalence of strabismus in families with accommodative, partial accommodative and infantile estropia (Çorak Eroğlu, Oto, Şahin, Terzi, Özer Kaya, Tekindal,2020). The analysis of previous studies mentioned in the study explained inheritance in comitant strabismus with the help of genome – wide linkage scans while also revealing many susceptibility loci. The study focused on families where the prevalence of different types of strabismus and the root of inheritance and the role of consanguinity in the different types of strabismus was analyzed. The frequency of existing visual impairments and the presence of hypermetropia of +3.00 diopter (D) or greater within these families.

The approach was to have two different strategies to collect patient data. The first strategy was a cross – sectional review of all the patients included in the study. A total of 215 families that have passed the inclusion criteria in which 139 of the families had subjects with AET, 55 families with PAET and 21 families with IET. The exclusion criteria were taken into consideration after a detailed questioning with factors such as prematurity, organic amblyopia, presence of a neurodevelopmental disorder, residence outside the city, and failure to communicate with members of the family. An ophthalmological examination was performed on a total of 518 individuals from 168 families. It included 116 AET families, 39 PAET families, 13 IET families. The second strategy of the study was conducted prospectively at the same location between June 2010 and August 2011. The focus of data collection was based on the frequency of consanguinity of parents among the patients with strabismus, the prevalence of strabismus among the first-, second and third-degree relatives among the patients with strabismus; the number of hypermetropia which is greater than or equal to +3.00 D as well as anisometropia among the first – degree relatives. The analyses on the pedigree showed that more than half (54.0 %) a 116 probands were related to at least 1 other strabismic individual in their family. In the AET group, 59% was the positive rate of family history, in the PAET group, 45.5% was seen and in the IET group 38.1%. It was found that 1-2 affected family members in 35.1% of families, 3-4 affected members in 15.3% of families, and 5 or more affected members in 3.2% of families. When parents who underwent complete ophthalmic examinations were considered, 40.5% of probands in the AET group, 25.6% in the PAET group, and 23.1% in the IET group had an affected parent. In the study, the possibility that a subject has a strabismic sibling was 29.3% in the AET group, 23.1% in the PAET group, and 30.8% in the IET group. Regarding the refractive status of the patients, the occurrence of hypermetropia ≥+3.00 D was comparable for all strabismic subtypes. The frequency of hypermetropia ≥+3.00 D among first-degree relatives was 16.3% in the AET group, 5.2% in the PAET group, and 7.7% in the IET group. Hypermetropia ≥+3.00 D was not found in IET or PAET siblings but was observed in 11.2% of AET siblings. The rate of hypermetropia among first degree relatives with strabismus differed significantly among groups, at 36.7% for the AET group, 13.3% for the PAET group, and 25% for the IET group. A prospective study (Shah, Torner and Mehta,2008) with 81 probands of AET and their 115 siblings for the prevalence of

amblyogenic risk factors, found that 14.8% had strabismus and 23.5% had hypermetropia ≥+3.50 D.

The conclusion of this study supports the concept that a presence of positive family inheritance significantly increases the risk of strabismic deviation, which was shown to be independent of refractive error heritability; it was seen especially for AET. The study uncovered that the autosomal recessive mode of inheritance was not a frequent pattern of inheritance, even in the presence of parent consanguinity. An overview of the results section is encompassed in Table 1 (Annex 1)

DISCUSSION

The details in the literature review depicts the correlation of inheritance to strabismus also with the different types of strabismus. The increased relativity of inheritance with strabismus was noted in the Accommodative esotropia followed by partial accommodative esotropia and lastly with infantile esotropia; the rate is relatively higher with the affected first-degree relatives as well as with hypermetropic accommodative esotropia where a stronger genetic factor is noted compared to anisometropic esotropia. A possibility that the mode of inheritance with horizontal deviation may be dominant, recessive, or multifactorial. The rate of hypermetropia greater than 3.00D associated with the presence of strabismus among the first-degree relative was significantly higher compared to the other types of esotropia. The patients with non – accommodative acquired esotropia had the highest mean of inbreeding coefficient. To summarize, the literature about the correlation between strabismus and inheritance shows that there is a significant correlation between the two entities. Although more studies are required to study the role of inheritance in not just esotropia and its types but also in exotropia and its types and subtypes of strabismus. A detailed study is necessary that assesses a larger population in which all the types of strabismus are taken into consideration, along with the association to refractive errors. The distribution of the data should contain equal number of patients with and without parental consanguinity. A detailed pedigree charting is recommended which would help classify the degree of relation to the patient.

CONCLUSION

Previous literature established that the abnormality in the eyes and refractive errors are majorly caused by consanguinity. In the types of strabismus, horizontal deviation is seen in children below 15 years with a positive history of parental consanguinity. It is important to assess and review the role of parental consanguinity in strabismic population and to promote awareness about the affect it has on the offspring of the related families. The literature reviewed that the presence of family history has a significant increased prevalence and risk of strabismic deviation that's independent of the positive family history of refractive error which is true for Accommodative esotropia. In comparison to the dominant and recessive form of inheritance, the latter plays a vital role in the occurrence of comitant strabismus. There is a statistically significant higher risk of strabismus in the first-degree relatives of patients which is also associated with hypermetropic accommodative esotropia in comparison to the other groups.

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Annex 1. Table 1: An overview of the results section

Authors & years	Bagheri et al – 2015	Ziakas et al – 2002	F C Eroğlu et al - 2019	S Iqbal et al – 2018
Study type	Consanguineous marriage as a risk factor for developing comitant strabismus	Questionnaire based study	Retrospective cross – sectional review of medical records	A cross – sectional study
Data	Participants < 18 years of age	Children < 12 years of age	215 families of probands agreed to participate in the study.	Participants aged 3 to 15 years
Methods	• Patients that underwent primary surgery for comitant strabismus surgery • The data collected were divided in to 4 groups (intermittent or constant exotropia (XT), infantile esotropia (ET), non – accommodative acquired ET and accommodative acquired ET • Presence and type of consanguineous marriages were evaluated in the parents of the patient group and control group by a questionnaire. • Mean of inbreeding coefficient was calculated in each group	• Positive history of strabismus A three-generation pedigree charting done and classified in to 4 groups (infantile esotropia, accommodative esotropia, anisometropic esotropia and exotropia	Data were collected for 3 main aspects: the frequency of consanguinity among parents of probands; the frequency of strabismus among first – second – third degree relatives and the frequency of hypermetropia >= +3.00 D and anisometropia among first – degree relatives.	• Patients diagnosed with horizontal deviation and positive history of consanguinity. Data collected by a self- designed proforma after taking consent from patients.
Aim	To study the prevalence of consanguineous marriage in parents of patients with different types of comitant strabismus and comparing it with general population.	To investigate the importance of hereditary in different types of strabismus	To investigate the prevalence of strabismus in families of a proband with accommodative, partial accommodative or infantile esotropia and to evaluate the role inheritance and consanguineous marriages in the prevalence.	To find the association and types of horizontal deviation in consanguinity
Conclusion	The mean of breeding coefficient 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.	History of strabismus appears to be more common in hypermetropic accommodative esotropia than in the other groups.	In cases with cross – cousin marriages, multifactorial patterns of inheritance. Strabismus and microtropia were also significantly more prevalent among first-degree relatives and other family members compared to the general population.	A 59.1 % of patients with exotropia and 40.8 % had esotropia. Horizontal deviation is seen in the children who have had a positive history of consanguinity.