original article

Consanguinity and isolated atrial septal defect in North East of Iran

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BACKGROUND AND OBJECTIVES: The rate of consanguineous marriage is high in Middle Eastern countries such as Iran. The relationship between consanguineous marriage and congenital heart disease is discussed in some studies, but there is not much data for relationship between atrial septal defect (ASD) and consanguineous marriage. The aim of this study was to evaluate the relationship between consanguineous marriage and ASD echocardiographic characteristics.

DESIGN AND SETTINGS: This was a cross-sectional study approved by Mashhad University of Medical Sciences ethics committee and took place in Mashhad, Iran, for a period of 3 years from August 2008 till September 2011.

METHODS: In this cross-sectional study, 113 ASD patients participated and they were categorized into 3 groups on the basis of family relationship between their parents: first group—"no relationship," second group— "third-degree relationship," and third group— "far relationship."

RESULTS: Among the 54 male and 59 female ASD patients, the most prevalent type of ASD was ASD secundum (85.0%) followed by sinus venosus (8.8%). A total of 56% patients were present in the first group and 15% and 29% in the second group and the third group, respectively." The relationship between consanguinity and type of ASD ($P<.001$) and gender ($P<.001$ each) was observed. The relationship between the age of onset of disease and consanguinity($P=.003$) was also observed.

CONCLUSION: Considering the fact that there is a high prevalence of ASD and consanguineous marriage in Iran and bearing in mind the results of the present study, we recommend educating couples about the outcomes of consanguineous marriage in pre-marriage counseling.

Consanguineous marriage is defined as a union contracted between individuals related as second cousins or closer.[1] Many populations such as Northern African and Middle Eastern countries show a great rate of consanguineous marriage.[2] In most Middle Eastern countries, consanguineous marriage is a socially supported custom.[3] The inbreeding rate in Iran is about 38.6%, while the rate of consanguineous marriage is reported to be 30.5% in Mashhad, Iran.[4,5] Available data gathered from Khorasan Health Centre showed the prevalence of consanguineous marriage (third-degree relationship and far relationtionship) as 33.2% from 2001 to 2005.

Due to the proportion of shared genes, this type of marriage can have different birth outcomes compared to non-consanguineous marriages (**Table 1**).[6] In addition to consanguineous marriage, many variables such as maternal age, birth order, and socioeconomic status can affect the infant and child mortality and morbidity rate due to congenital disorders.[7]

Congenital heart defect (CHD) is linked to consanguineous marriage.[8,9] The role of consanguinity in CHD has been studied in many countries, especially in Asian countries, which have more consanguineous marriages.[10,11] Although the etiology of most types of CHDs is still unknown, a multifactorial etiology—including genetic and environmental factors—is suggested for most of these diseases.[8,9] As far as genetic causes are concerned, only a few types of CHDs are related to chromosomal abnormalities, especially trisomy of 13, 21, and 18

chromosomes as well as turner syndrome.[9] Moreover, the higher prevalence of supracristal ventricular septal defect (VSD) in Asian children or an increased recurrence risk for CHDs in children with a positive history of the disease in one of their first-degree relationships suggest the involvement of other genetic factors for some types of CHDs.[12] Previous studies reported a significant relationship between CHD and consanguineous marriage.[13-15] Becker SM et al mentioned that there could be a significant relationship between consanguinity and CHD such as atrial septal defect (ASD), VSD, atrioventricular septal defect, aortic stenosis, and pulmonary stenosis9 They also reported a significant relationship between ASD and first cousins.[9] Al-Ani also mentioned consanguinity as a significant risk factor with greater effects on ASD and VSD rather than tetralogy of fallot.[11] The study by Ramegowda and Ramachandra associated PDA in addition to ASD with consanguinity.[10]

ASD is the second common form of CHD after VSD and accounts for 7% of CHDs.[15,16] ASD is divided into the following 3 subtypes according to the atrial septum malformation:[16,17] ostium primum, ostium secondum, and sinus venosus.[18] Most of ASDs are sporadic, but autosomal dominant forms can also be seen as syndromes such as Holt-Oram syndrome, Williams syndrome (deletion of elastin gene), and alagille syndrome (micro deletion in JAG1 gene).[12,17,19,20] The aim of this study was to evaluate the effect of consanguineous marriage on ASD characteristics in a period of 3 years in Mashhad, Iran.

METHODS

Subjects

This cross-sectional study was approved by Mashhad University of Medical Sciences ethics committee and took place in Mashhad, Iran, for a period of 3 years from Aug 2008 till Sep 2011.

Data collection

All patients were referred from Imam Reza Hospital to a cardiologist clinic for further assessments. The diagnosis of ASD was confirmed by transthoracic echocardiography (Vivid 7; with 3S multifrequency probe 3-5 MHZ; GE). From a total of 2100 patients referred to pediatric cardiologists, 113 were confirmed to have ASD. Patients with other cardiac abnormalities were excluded. A patient medical record form was used to record patient's history of consanguinity, demographic data, clinical findings, and echocardiographic investigations. The parents of each patient filed a written informed consent form for participating in this study. The patients were grouped by their marriage type. Of 113 ASD patients, 64 patients (57%) had parents with no relationship (first group), 31(27%) patients had parents with the second-degree relationship (first cousins, half siblings, uncle-niece, aunt-nephew), and 18 patients (16%) had parents with far relationship (half uncle-niece, half aunt-nephew, half first cousins, second cousins relations; third group). Patients having parents with first- and second-degree relationship were not included in our study because this kind of marriage is forbidden in Iran. After initial evaluations, according to patient conditions and on the basis of the latest guidelines, patients were followed or suggested for appropriate cardiac surgery.

Data analysis

Statistical Product and Service Solutions (SPSS) software version 19.0 (SPSS Inc., Chicago, IL USA) was used to analyze the data. Continuous variables were first checked for normality using Shapiro-Wilk test. Mean and standard deviation were used for normally distributed data while median and interquartile range (IQR) were used to describe non-normally distributed data. The Kruskal–Wallis and Mann-Whitney U tests were used to compare non-parametric variables. Binary logistic regression was used to identify contributors to consanguinity with consanguinity as dependent variable and other variables as covariates. The odds ratio (OR) was used to show the relationship between study variables and consanguinity. The confidence interval was considered as 95%, and the values of *P* lesser than .05 were considered as statistically significant.

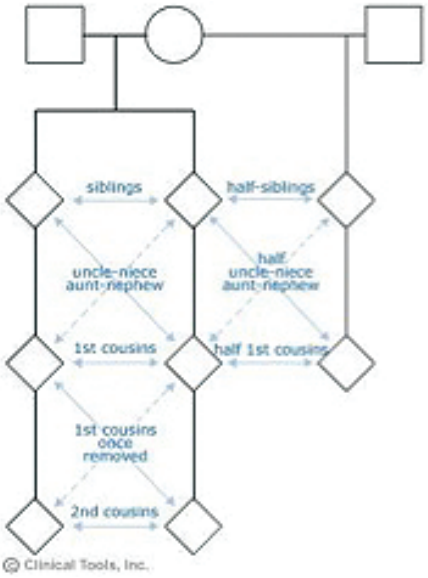
RESULTS

Of 113 cases, 54 (47.8%) were boys and 59 (52.2%) girls. The mean age of the children was 76.0 (55.5) months. The mean birth weight was 3.0 (0.6) kg. The most prevalent type of ASD was reported to be ostium secondum in 96 cases (85.0%) followed by sinus venosus in 10 cases (8.8%) and ostium primum in 7 cases (6.2%). The median and IQR for ASD defect size was 15.0 (11.0) mm (**Table 2**) (**Figure 1**).

The median and IQR for the age of diagnosis was 8 (63.5) months. The median and IQR for the number of children in family was 2.0 (2.0). A total of 64 children (56%) had parents with no family relationship, while 31 children (29%) had parents with the third-degree relationship and 18 children (15%) had parents with far family relationship. The distribution of age of referral is shown in **Figure 2**.

The ratio of ASD cases with consanguine parents to non-consanguine parents was 76.6%. A significant negative relationship was observed between the age at the onset of symptoms and the parents with the third-degree

Table 1. Proportion of shared genes and consanguineous relationships.

Relationship	Example relationships	Shared genes	Pedigree
First degree	Parent-child Siblings	1/2	
Second degree	Half siblings Uncle-niece Aunt-nephew First cousins	1/4	
Third degree	Half uncle-niece Half aunt-nephew	1/8	
Fourth degree	First cousins once removed Half first cousins	1/16	
Fifth degree	Second cousins	1/32	

(Copied from: Robin Bennett. Consanguinity Fact Sheet -- Debunking Common Myths [homepage on the Internet]. No date [cited 2013, June, 12]. Available from: http://www.larasig.com/node/2020)

relationship (P=.01), indicating that 1 month increase in age at the onset results in 0.98 reduction in the OR of having parents with the third-degree relationship. This indicates that ASD subjects with third-degree consanguine parents produced symptoms significantly earlier than those with non-consanguine parents or those with parents with far relationship (**Table 3**).

DISCUSSION

In this study, 44% of ASD subjects had parents with either the third-degree relationship or far relationship. In a study by Campbell et al, the prevalence of consanguineous marriage was reported to be 3.8% (1.9% for first cousin and 1.9% for the third-degree relationship).[21] This difference might be because of the higher prevalence of consanguineous marriage in the Middle East than in the Western countries.[3]

In our study the female-to-male ratio was found to be 1.09 (59/54). Female dominance was previously reported by Satpathy to be 3:1 (female-to-male ratio).[22] This study revealed that the size of ASD was significantly higher in males than in females. To the best of our knowledge, no study reported the difference in size of ASD between male and females. However, this study failed to identify any difference in the type of ASD and positive family history of CHD among the 3 consanguinity groups. Campbell et al could not show any re-

Table 2. Comparison of ASD size, gender, type, and family history as per consanguinity.

		First group: No relation (n=64)	Second group: Second-degree relation (n=31)	Third group: Far relation (n=18)	*P*
ASD size Median (IQR)		16.00 (10.00)[b]	14.00 (8.00)	11.00 (7.81)[b]	.04
Gender	Male	27	17c	10	<.001
	Female	37	14c	8	
ASD type	Ostium primum	4	2	1	.63[d]
	Ostium secondum	54	28	14	
	Sinus venosus	6	1	3	
Family history[a]	Positive	7	3	1	.79[d]
	Negative	57	28	17	

ASD: Atrial septal defect, IQR: interquartile range. [a]Positive family history was considered as any CHDs history in any of first- or second-degree relatives. [b]Significant difference using the Mann-Whitney test as post hoc test (*P*=.02). [c]Significant difference between gender distribution only in second group using chi-square test. [d]Non-significant using chi-square test.

Table 3. Contribution of study parameters with consanguinity.

	Third-degree relationship				Far relationship				
	Wald	OR	95% CI for OR		Wald	OR	95% CI for OR		
			Upper	Lower			Upper	Lower	
Gender	0.93	1.57	0.63	3.91	0.56	1.56	0.49	4.93	
Type of ASD	Ostium secondum	0.50	2.28	0.23	22.45	0.24	1.78	0.18	17.87
	Ostium primum	0.46	2.69	0.15	47.06	0.07	1.52	0.06	36.82
Age at onset	7.05	0.98a	0.96	0.99	0.84	0.93	0.84	1.03	
Family history of heart disease	0.36	1.59	0.35	7.23	0.10	1.45	0.15	14.06	
ASD size	0.41	1.01	0.98	1.05	2.08	0.93	0.84	1.03	

ASD: Atrial septal defect. Multinomial logistic regression was used with the group 1 (no relationship) as reference, df=1, sinus venosus, positive family history, and female gender were excluded from the model due to redundancy aSignificant at α=0.05, *P*=.01

lationship between the type of ASD and consanguinity owing to the high prevalence of ASD secundum in their population (only 3 cases out of 155 were ASD primum).[21] No other studies have assessed the relationship between the type of ASD and the degree of consanguineous marriage. The findings of this study also revealed that male dominance was only prominent in patients with parents having the third-degree relationship. No other studies have assessed the gender differences in ASD patients with different degrees of consanguineous marriage in parents.

This study revealed only a significant negative relationship between the age of onset of symptoms and the third-degree relationship (OR=0.98;CI=0.96, 0.99). This indicates that ASD patients who have parents with the third-degree relationship are more likely to have symptoms earlier than those ASD patients who have parents of far or no relationship. Moreover, the lack of significant relationship between the size of the lesion and consanguinity in the presence of a significant relationship between the age of onset of symptoms and the third-degree relationship may reflect the presence of other confounders including other congenital comorbidities in heart or other organs, such as Down syndrome.

This study could not find any significant relationship between the size of ASD and consanguinity. Almost all

available studies did not mention any relationship between consanguineous marriage in parents and ASD size. We found that the far relation group had a smaller ASD size than patients without any consanguinity status.

This study failed to identify a relationship between the family history of CHD and the presence of ASD. The study by Nora et al suggests that if ASD is the result of multifactorial inheritance, then a mother whose child has ASD and who has neither her husband nor her other close relatives had any CHDs will have approximately 2.6% risk for her unborn children in future. They also mentioned that an increased risk would be expected if they have any other affected children or siblings or parents.[23] The effect of a positive history of CHD was reported to be 13.2% in another similar study.[24]

Study limitations: We only gathered our data from 1 pediatrics unit in Mashhad. So we could not generalize our result to the entire city. This small population resulted in a low effect size (R square=0.15) in the regression analysis, which makes it difficult to infer the findings of this study to the whole population of ASD patients. However, the findings of this study provide evidence for the necessity of conducting population-wide studies to determine the ASD characteristics in consanguineous marriage.

Different aspects of consanguineous marriage in CHDs are not discussed in details in other studies. By using available data, we tried our best to conduct a study to assess the effects of consanguineous marriage on ASD. We also suggest researchers for further evaluations upon each CHD and consanguinity separately. Consanguineous marriage is not forbidden in some religions, still many people do not know the various effects of this marriage. By educating couples before marriage, we can predict and prevent possible outcomes of having an ill child in families. However, illnesses such as CHDs will require a comprehensive medical follow-up, and these expensive procedures result in an increasing economic pressure on the national health care system.

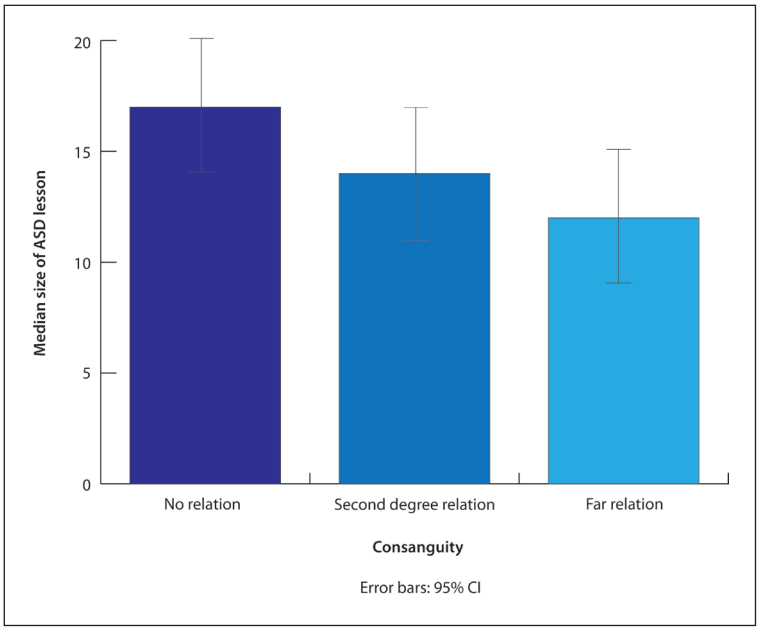


Figure 1. Median ASD lesion size as per consanguinity groups.

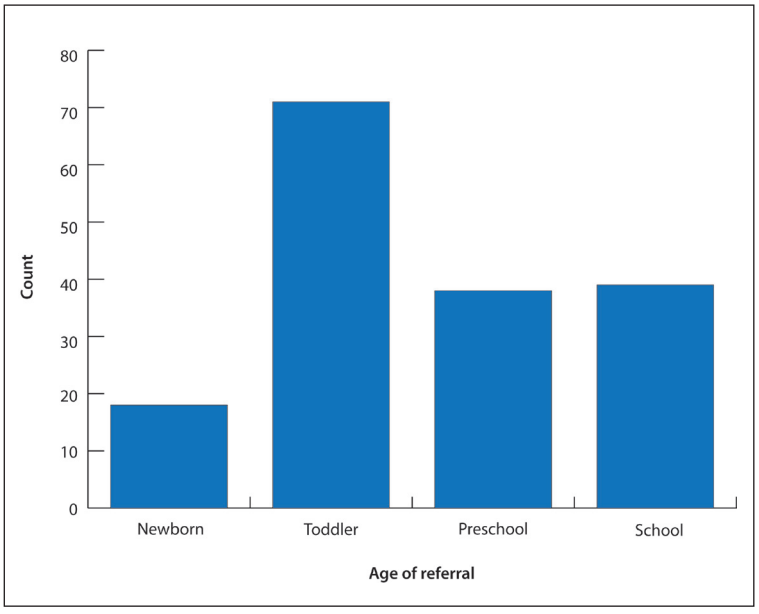


Figure 2. Distribution of age referral.

Conflict of interest

None declared.

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