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Consanguineous marriages increase risk of congenital anomalies-studies in four generation of an afghan family.

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Abstract

Consanguineous marriage is a common and preferable custom of marriage among Afghans. Consanguineous marriage may cause transfer of two recessive defective alleles, one from the mother and the other from the father, to offsprings; which may cause appearance of congenital anomalies. Four generation of an Afghan family, residing in Afghanistan, and in which consanguineous and non-consanguineous marriages are practiced, were studied in this article. Out of 14 marriages, 7 were consanguineous and 7 non-consanguineous. Out of the offsprings of consanguineous marriages 52.3% presented congenital anomalies while among the generations of non-consanguineous parent no considerable congenital anomaly was observed.

Keywords: Consanguineous marriages, Non-consanguineous marriage, Congenital anomalies, Pedigree.

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Introduction

Consanguineous marriage is referred to a marital union among close biological kin. In clinical genetics, it is called the relationship by marriage between first and second cousins [1]. Consanguineous marriage is most common in the Middle East, West Asia and North Africa [2,3]. Rate of consanguineous marriage in different countries are dependent on different factors like education level, religion, local tradition, and socio-economic status [4,5]. Studies over several decades have shown that there is a high correlation between consanguineous marriage and inherited congenital malformation [6].

Some of inherited genetic disorders are transferred as autosomal recessive in carrier individuals and consanguinity facilitates homozygosity mapping of these genetic disease; which appears in their offspring as congenital anomalies (disease, disorder or defect) [6].

Congenital anomalies (CA) are the structural or functional anomalies (including metabolic disorders); which are present during birth of the child. These abnormalities can be isolated or seen as part of a syndrome; which results morbidity and mortality of neonates and infants [7,8]. Based on the WHO (world Health Organization) report, 3% of newborns are associated with CA equals to approximately 3 million fetuses and infants per year [9]. CAs vary from country to country; with lowest rate in Japan (1.07%) and highest rate in Taiwan (4.3%) [10]. Social, racial, ecological, and economical issues may have a role in the rate variation [10, 11].

Congenital anomalies can lead to infant mortality and it has been seen that more than 70% of such infants die in the first month of birth [12-15]. Etiology shows that 30-40% of congenital malformation is genetic [16]. One of the major factors contributing to the increased risk of congenital malformation and infant mortality is consanguineous marriage [17-19].

The offsprings of consanguineous parents are at a risk of a host of disease like cancer, mental disorders, hypertension, hearing deficit, diabetes mellitus, epilepsy, asthma, leukemia [6], beta thalassemia [20], congenital and non-congenital heart diseases [21].

In Afghanistan, like many other countries, parents usually find spouses for their children. Due to socio-economic conditions selection of spouse is sometimes very difficult. Hence, someone well known and having the qualities of joining their families is preferred. Therefore, consanguineous marriages are preferred and the first cousin is the first choice. Over several generations consanguineous relationships become closer and complicated.

Materials and Methods

This study includes the pedigree of 4 generation of an Afghan family to observe the effect of consanguineous and non-consanguineous marriages on their offspring. Data collection was done through questionnaires and interviews. Questionnaires were made in Dari language and included relationship between couples (consanguineous or non-consanguineous), age of marriage, addiction to any drug,

and use of alcohol during pregnancy (Table 1). Same questions are asked in the case of interviews.

Subjects

Four generations of an Afghan family are studied here. As showed in Figure 1, Pedigree Chart, first generation (G1); is a male and female married as consanguineous marriage (father's side cousins). Generation 2, the offsprings of the G1, consisted of 8 individuals (5 M and 3 F). G3: the offsprings of the G2; with 40 individuals (27 M and 13 F), and G4: the offsrpings of G3; including 22 individuals (11 M and 11 F). The 4th generation members are still single, some of them are not in the age of marriage and some of them will marry in the close future.

Consanguinity rate

Out of 14 marriages, 7 (50%) are consanguineous marriages and 7 (50%) are non-consanguineous marriage (Table 2).

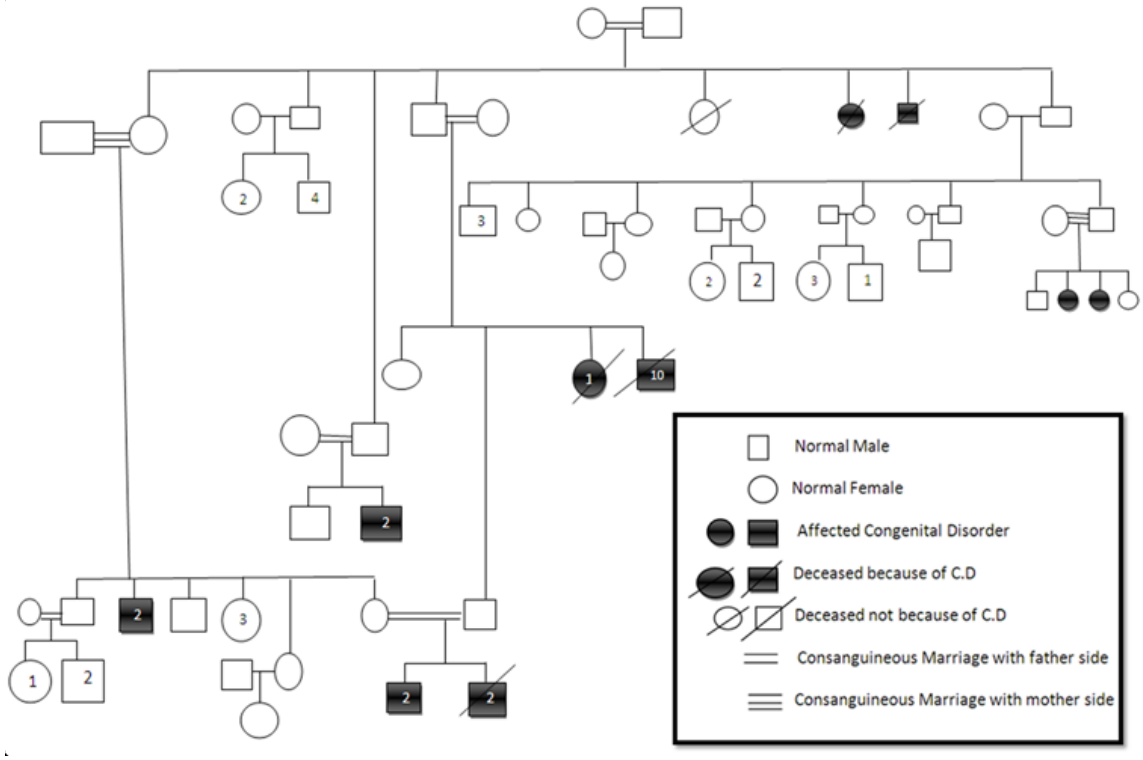

Figure 1: *Pedigree chart of the subject family.*

Table 2. *Population size and consanguinity.*

Generation	Population			Marriage type	
	Total	**male**	**female**	**CM**	**Non-CM**
G1	2	1	1	1	0
G2 (offspring)	8	5	3	3	2
G3 (offspring)	40	27	13	3	5
G4 (offspring)	22	11	11	0	0
Total (offspring)	**72**	**44**	**28**	**7**	**7**

In this table spouses are not included (except first generation).

Table 1. *Socio-demographic information from subjects.*

Parameters		**Generation 1**	**Generation 2**	**Generation 3**	**Generation 4**
Consanguinity	Yes	1	3	3	0
	No	0	2	5	0
Age of marriage	<20	1	0	0	0
	20-25	1	10	6	0
	26-30	0	0	7	0
	>30	0	0	3	0
Addiction to narcotics	Yes	0	1	1	0
	No	2	12	46	21
Use of alcohol during pregnancy	Yes	0	0	0	0
	No	all	all	all	0

Table 3. *Number of congenital anomaly evident in offsprings from consanguineous and non-consanguineous marriages.*

Condition	Types of CA	CM offspring			Non-CM offspring		
		Male	Female	Total	Male	Female	Total
Congenital anomalies	**Died within first month of birth**	13	2	15	0	0	0
	Hearing deficit	2	0	2	0	0	0
	Low IQ	2	0	2	0	0	0
	Kyphotic spine	2	0	2	0	0	0
	Cerebral palsy	0	2	2	0	0	0
	Others	0	0	0	0	0	0
Total Congenital anomalies		19	4	**23 (52.3%)**	0	0	0
Healthy		11	10	**21 (47.7%)**	13	13	**26 (100%)**

Results

Fourteen marriages tool place among member this family, out of which 7 are consanguineous. At least 2 children from each consanguineous marriage have congenital anomalies. Offspring of one consanguineous parent didn't show any considerable congenital anomalies yet, as these children are still very young. School performance, height and other non-congenital diseases; which demonstrate the effect of consanguineous marriage, are not yet evident. Out of 44 offspring from consanguineous parents, 23 individuals (19 males & 4 females) equal to 52.3%, have considerable congenital anomalies or died within first month of birth as result of congenital anomalies. Among 26 individuals (13 M and 13 F) from non-consanguineous parents, no considerable congenital anomaly has been seen (Figure 1). Out of 23 individuals with congenital anomalies, 2 have hearing deficit, 2 show low school performance or very low IQ, 15 died within the first month of birth, 2 have Cerebral Palsy (CP) and 2 have kyphosis (Table 3).

Discussion

This study is conducted to show effects of consanguineous marriages versus non-consanguineous marriages on their offspring, in those people who are very close and have high similarities in heredity, life style, socio-economic status, environment, nutrition, and history of disease. As other factors like hereditary, age of parents [22], addiction to narcotics, other drug abuse, etc., may also have a role in the development of congenital anomalies and hence may interfere on consanguinity study we preferred to study consanguineous marriage effects in a different generation of family in which consanguineous and non-consanguineous marriages are equally practiced. The main impact of consanguineous marriage is an elevation in the rate for homozygotes in recessive disorders [23-25]. If a new mutation is inserted in such a population, it will spread rapidly and lead to an elevation in carries' prevalence and an increased number of affected homozygous individuals [26]. It is believed, but has not been proved yet, that high inbreeding rates through several generations may removes deleterious recessive genes from the gene pool [24]. Studies from India (South India), where for more than 2,000 years inbreeding is practiced, show no appreciable elimination of recessive lethal and sublethal genes from the gene pool [27]. The highest rate of congenital malformation and genetic disorders with more than 65 affected children per 1,000 live births is reported in the Eastern Mediterranean region as compared to Europe, Australia and North America with 52/1,000 live births [28]. Consanguinity rate can be defined in to four major areas: 1) Regions with <1% consanguineous marriages (consanguineous marriage beyond the second cousins may exist f<0.0156), e.g., North America, Australasia and most of Europe, 2) Regions with 1-10% of consanguineous marriage e.g., Japan, South America and the Iberian Peninsula, 3) Regions with 20-50% of consanguineous marriages e.g., North Africa, much of west, Central, and South Asia, and 4) The highest rate of consanguineous marriages e.g., Pondicherry, South India [29], where 54.9% consanguineous marriages have been recorded which is equivalent to mean coefficient of inbreeding of α=0.044, and among army families in Pakistan where the percentage of consanguineous marriage percentage is 77.1% (α=0.0414) [30]. Consanguineous marriage percentage in 6 north provinces of Afghanistan including Kabul shows 46.2%. [31], and in Afghan refugees in Pakistan shows 55.4% [32]. Till date there are no confirmed studies to shows consanguinity rate and related congenital anomalies in Afghanistan. Our next study will include a larger population with congenital anomalies to show its relationship with consanguinity.

The prevalence of consanguineous marriages is above 50% in Muslim countries of the Middle East, Pakistan and Afghanistan, but there is no specific guidance in the Holy Qur'an that could be interpreted as encouraging consanguineous marriages [33]. Indeed, according to one of the hadiths, recorded pronouncements of the Prophet Mohammad (PBUH), cousin marriages were best discouraged. So, it is traditional and socially practice taken up by Muslim countries.

In a multi-national study, that was performed recently, to estimate the mortality rate, pre- puberty deaths of

first cousin offspring show 4.4% higher value than non-consanguineous unions, in over 600,000 pregnancies and live births [34]. The high mortality rate in developing countries, associated with consanguinity, largely occurs within the first year of birth [35-38]. In most of the cases the exact cause of death is not cleared because of the unavailability of proper diagnostic facilities, and lack of initiative of parents to sanction prenatal diagnosis or autopsy examinations. An obvious correlation between consanguinity and autosomal recessive disease was evident where the diagnosis was possible [27, 39-42]. Several deaths have also been reported in a proportion of consanguineous families in developing countries [43]. More than 20 loci identified which may cause inherited autosomal non-syndromal hearing loss [44], with higher rate of incidence in consanguineous families [45]. Studies on UK Pakistanis show high rate of cerebral palsy cerebral palsy in consanguineous matrimony [46] with the autosomal recessive gene located on chromosome 2q [24-25]. This gen has been identified in several consanguineous families with affected progenies [47]. The adult offspring of consanguineous families are more represented in institutions for caring mental retardation patients [48] but association between consanguineous marriage and adult-onset behavioral and psychiatric disorders (like schizophrenia) have not yet been clearly described [49-51]. Although a preliminary report from Pakistan suggests that the prevalence of certain cancers and cardio-vascular disease are higher in consanguineous progenies [52].

Considering results of this study, it is highly recommended that consanguineous marriages be prevented especially if previous consanguinity is present in the family. For those couples who are first or second cousins, pedigree chart of their four generation should be provided (including offspring, siblings, parents, grandparents, aunts, uncles, nieces, nephews, and first cousins) and studied for any congenital anomalies or early death. Also, the presence of some disease like birth defects or congenital anomalies, early hearing impairment, early vision impairment, mental retardation or learning disability, developmental delay or failure to thrive, inherited blood disorder, unexplained neonatal or infant death in offspring, epilepsy and undiagnosed severe condition, should be queried. For families with known autosomal recessive disorders, clinical and molecular diagnosis should be established if possible. Predictive premarital genetic testing should be carried out on prospective consanguineous couples; if diagnosis fails then risk estimation should be taken into account. For consanguineous couples with affected children prenatal diagnosis can be done if possible.

Conclusion

Congenital anomalies in this family are: death within first month of birth mostly because of malformation of gastro-intestinal system while some were unrecognized, hearing deficit, mental retardation, cerebral palsy, and kyphosis. Several studies have also shown the existence of a relationship of above conditions and defects with consanguineous parents. Regarding kyphosis, however, there is no specific study to show its relationship to consanguinity.

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