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ARTICLE

Consanguinity, genetic disorders and malformations in the Iranian population

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ABSTRACT The present study focuses on the effect of parental consanguinity on genetic disorders in the Iranian population, which is predominantly Muslim and where consanguineous marriages are quite common. Data were collected from three genetic centers from different areas of Tehran. Out of 800 affected subjects nearly 44% were born to consanguineous parents. While 37.8% of them were born out of parallel- cousin marriages, 28.9% were from cross-cousin alliances. Frequency of occurrence of genetic disorders was twice in children born to parallel-cousin parents as compared with those occurring out of cross-cousin marriages. Psychomotor retardation (14.3%), primary amenorrhoea (11.2%), and mental retardation (6.6%) topped the list of disorders encountered in children born to consanguineous parents. Cases of phenylketonuria were encountered exclusively in children of consanguineous couples. Of the patients having positive family history of genetic disorders, 93% had consanguineous parents. Two points emerge from the present study: that related parents, whatsoever the relationship, are more likely to have children with genetic defects; consanguineous couples who already have an affected child are 13 times more likely to have another affected child.
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KEY WORDS

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Bob Edwards, the world-renowned embryologist, while speaking at the annual meeting of the European Society of Human Reproduction and Embryology in France in July 1999 said: ”Giving birth to a disabled child is a sin no parent should commit in the present era when prenatal screening for genetic diseases is increasingly available. It is the moral responsibility of the parents too not to have a child that carries the heavy burden of genetic disease. We are entering a world where we have to consider the quality of our children…”

Going by the old adage that prevention is always better than cure, present study explores once again the role of parental consanguinity often associated with a higher frequency of genetic disorders and congenital malformations in their progeny (Verma and Mathew 1983; Mukherjee 1994; Afrooz 1996). It is well supported by similar studies carried out focussing on individual malformations reported in the couples closely related (Kesavan et al. 1978; Kabiri 1995; Karimi-Nejad 1995).

In the Iranian society, which is, predominantly a muslim society where consanguineous marriages are quite common, few such studies focussing on consanguinity and genetic disorders in Iranian population are available. Jorjani (1994) selected a religious isolate group known as the Hamedanis (originally from Hamedan Province in the western part of Iran where consanguineous marriages are a norm; they migrated to India and settled down at Junnar district of Maharashtra about 400-500 years ago). It is assumed that intense level of consanguinity and inbreeding in this population must have lead to an increase in homozygosity, resulting in an increase in genetic anomalies among the Hamadanis. Another study conducted in a single village in the suburb of Hamedan reported that 60 mentally retarded children were born in the year 1995 alone there (Shariati 1996). In some other villages near Hamedan, altogether 1050 mentally retarded, deaf, blind and epileptic babies were born in the same year. Alarmed by this statistics, immediately a genetic center was opened which became functional the same year as the need was felt very strongly.

Karimi-Nejad (1995), upon comparing the frequencies of congenital malformations and multifactorial diseases in two thousands couples, studied the consanguineous couples whose inbreeding coefficient were equal or greater than 1.64. He concluded that considering the studies conducted in Shiraz and Turkey, a total of one-fourth of marriages in Iran are consanguineous and as a result congenital malformation and genetic disorders which are inherited, were higher in Iran because of high degree of consanguinity. Moreover, the frequency of malformations and diseases caused by inheritance in consanguineous marriages was twice in frequency than in non-consanguineous marriages. He commented that in cases where inherited factors were more influential, this difference was more obvious, but it was lesser in the type of

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Table 1. Consanguinity of parents of the patients

Consanguinity	Number	Frequency
parallel cousin	132	37.8
cross cousin	101	28.9
distant relative	116	33.2
sub total	349	43.6
non-consanguineous	451	56.4

diseases where the environmental factors were more effective to the causation of the disease, and vice versa. In the same year, Kabiri (1995), in his article on the frequency of phenylketonuria (PKU) in consanguineous couples in Iran, reported that the disorder was three times more frequent in children born out of consanguineous marriages than among the non-consanguineous couples. Earlier Ameli and associates (1988) reported that out of 200 cases of PKU studied by them in seven years' span (1979-1986) in a local hospital in Tehran, the frequency recorded was 1 in 4000 live births as against 1 in 10,000 live births in the US. Iran had the highest figures when compared to some other countries like North Ireland (1 in 4,500), Greece, Poland and Scotland (1 in 8,000) and Japan and Denmark (1 in 60,000), the last two countries having implemented the most advanced preventive measures to combat PKU (Ghiyasvand 1995).

In Iran the present state for diagnosis and prevention of PKU is like it was in developed countries in 1950s when they did not have advanced screening tests. The average age for diagnosis of PKU in Iran is two years, and unfortunately, by then the child is already mentally retarded and beyond cure. In another study on consanguineous marriages in different states of Iran more than 54,000 families were screened and a high rate of infant mortality was reported (Meshkani and Meshkani 1997). Afrooz (1996) based on his study concluded that " ...the rate of malformations in consanguineous marriages (in Iran) is five times more than in the non-consanguineous marriages. Out of every 100 non-consanguineous marriages two babies are born with a defect but in consanguineous marriages this rate increases to 10 defective babies."

Most of these studies in Iran have been conducted in the last decade or so and are limited to hospital birth records. The majority deals with a single gene disorder. Even though a few genetic centers have become operational in the recent past, not many systematic and well planned study has been published so far.

In the view of the limited work in this high-risk population, present research was taken up in three genetic centres in Iran focussing on the prevalence of congenital malformations and genetic diseases in the consanguineous marriages in Iranian population. An attempt was also made to examine the relationship of pattern of consanguinity of the parents of the patients, and the frequency of genetic anomalies in the offsprings.

Materials and Methods

Tehran the capital of Iran has better medical facilities as compared to other cities and rural areas of Iran. A few government hospitals have genetic clinics and diagnostic facilities for genetic diseases. There are also a few private genetic centers where karyotyping is done, which are more expensive, charging about two times of the regular fee at the government centers. Many affected individuals are brought to Tehran from neighboring towns for diagnosis, and with a hope for treatment. Data for the present study were collected from three genetic centers in Tehran. These centers, Karimi-Nejad Pathological and Genetic Center, Shahid Akbarabaadi Hospital, and Pediatric Medical Center were located in north-west, south and south-west of Tehran respectively.

Detailed information on 850 subjects was collected using an interview schedule and through daily interviews with the

Table 2. Type of consanguinity and some major disorders in the offspring

	Consanguineous parents									
Disorder	Parallel cousin		Cross cousin		Distant relative		Total consanguineous		Non-consanguineous	
	No	%	No	%	No	%	No	%	No	%
psycho. ret.	23	17.4	14	13.9	13	11.2	50	14.3	22	4.9
down synd.	15	11.4	7	6.9	20	17.2	42	12	134	29.7
prim. amen.	13	9.8	10	9.9	16	13.8	39	11.2	48	10.6
mental ret.	11	8.3	6	5.9	6	5.2	23	6.6	18	4
growth ret.	5	3.8	5	5	6	5.2	16	4.6	7	1.5
turner synd.	2	1.5	6	5.9	8	6.9	16	4.6	25	5.5
sec. amen.	6	4.5	5	5	3	2.6	14	4	14	3.1
fragile-X	5	3.8	2	2	6	5.2	13	3.7	10	2.2
microcephaly			3	3	4	3.4	7	2	3	0.7
multiple. cong. anomalies	2	1.5	1	1	2	1.7	5	1.4	3	0.7
klinefelter	2	1.5	1	1	2	1.7	5	1.4	3	0.7
P. K. U.	1	0.8	1	1	2	1.7	4	1.1		
others	85	64.4	40	39.6	28	24.1	115	33	164	36.4
total	132	16.5	101	12.6	116	14.5	349	43.6	451	56.4

Table 3. Previously affected siblings of the patients

Number of affected	Relationship of parents: Parallel cousin No.	%	Cross cousin No.	%	Distant relative No.	%	Total (CM) consanguineous No.	%	Non-(NCM) consanguineous No.	%	CM+NCM No.	%
1	13	37.4	7	20	15	42.85	35	87.5	3	6.98	38	88.37
2	2	50	1	25	1	25	4	10			4	9.3
4	1	100					1	2.5			1	2.33
Total	16	37	8	18.6	16	37	40	93	3	7	43	100

patients and accompanying persons. Their medical files and reports of their karyotyping tests were studied. Discussions with the consulting doctors were very informative. Fifty cases had to be excluded for various reasons and after the karyotyping results became known.

Results and Discussion

The majority of the patients coming to the genetic centers were from urban areas (99%) and a few were from neighboring villages. A high level of consanguinity (43.6%) was reported among the parents of the patients. While 38% of these affected children were born to parallel cousin parents, 33.2% were from marriages of distant relatives, and 29% of them were born out of cross-cousin alliances (Table 1).

Psychomotor retardation (14.3%), primary amenorrhoea (11.2%) and mental retardation (6.6%) topped the list of disorders encountered in children born to consanguineous parents. All the phenylketonuria patients were born, exclusively, to consanguineous parents (Table 2). Nearly 21% of the mentally retarded (including cases of psychomotor retardation) were born from consanguineous alliances as compared to only 8% from non-consanguineous parents. An earlier study on parental consanguinity and mental retardation reported a higher frequency of mental retardation in the consanguineous parents (Narayan and Rama Rao 1978).

It was not surprising that more than double (29.7%) the frequency of Down syndrome children were born to non-consanguineous patients as compared to only 11% of them born to related parents. The reason has been well put by Shariati (1996), the founder of first ever genetic counseling centers in Iran: "In more than 90% cases, the chromosomal disorder in the child having Down's syndrome has no relation to the chromosomal condition of the parents, and usually both the parents have a normal chromosomal arrangement as the defect mostly due to mutation…" Almost an equal frequency (10.6%) of primary amenorrhoea was observed in children born to non-consanguineous couples.

Out of the 43 subjects with at least one affected sibling already present in the family, 93% of them were born to consanguineous parents. Thus only 7% of the subjects with one earlier sibling affected were born from non-consanguineous marriages (Table 3). The frequency/chance being almost 13 times more common in the related couples to give birth to an affected child. In other words, the consanguineous parents supporting one genetically abnormal child are almost 13 times more likely to give birth to another affected child as compared to non- consanguineous couples.

In case of the patients with two siblings affected, they all had consanguineous parents, and the only case where 4 siblings in a single family were affected also had parents who were parallel-cousin (Table 3). It is important to note that out of 40 (5%) cases of the consanguineous parents where one or more affected children were already present in the same family, majority was born out of parallel-cousin marriages. In fact, the frequency of occurrence was twice in parallel-cousin when compared with those occurring out of cross-cousin marriages. Interestingly, for unknown reason an equally high frequency was observed when the parents were even distantly related (Table 3). May be these couples were not as distantly related as assumed. It seems that the exact relationship and the level of consanguinity needs to be reexamined.

Consanguinity, more specifically parallel cousin marriages, thus emerges out to be the single most important factor where the family has a history of having children with genetic disorders. This finding contradicts the earlier suggestion that inbreeding reduces the burden of deleterious genes (Rao and Inbaraj 1980).

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