

Frequency of Consanguinity and Its Effect on Congenital Malformation - A Hospital Based Study

Pages with reference to book, From 75 To 78

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Abstract

A consecutive sample of 5000 families of Armed Forces personnel was analysed to study the prevalence of consanguineous marriage and its effect on the prevalence of hereditary gross (physical) malformations. The overall frequency of inbreeding was 76% with a coefficient of 0.04151 which is probably the highest figure reported in literature. The overall prevalence of congenital malformations in children of related parents was 40% (1530 out of 3820) and in non-related parents 26% (305 out of 1180) ($p < 0.01$). Considering the prevalence of malformations with the types of relationship of parents, the inter-marriage with first cousins alone, was highly significant ($p < 0.01$) (JPMA 47:75,1997).

Introduction

More than 20% of the world population favours consanguineous marriages because of its social benefits¹ - It certainly is supportive to the women in patrilineal descent of families in the developing countries. In the Middle East, it has been invogue for thousands of years² and approximately 6,5%. of couples actually make such a marriage world-wide¹. Despite the religious and legal sanctions imposed by certain societies, consanguineous marriages still prevail in certain social groups which have varied attitudes toward them withall their associated prejudices and problems. The prevalence of such marriages is dictated, to a large extent, by culture, religion, tradition and civil laws³. They are prohibited in certain parts of the world (e.g., North America) because of religious sanctions. The effects of consanguinity on such parameters as fertility, infant and child development, mortality and morbidity are well known and havebeen studied in American⁴, Japanese⁵ and Indian populations⁶. Perinatal malformation related mortality has recently been studied in Europeans and Pakistanis settled abroad⁷⁻⁹ (Table).

Table I. Perinatal mortality due to congenital malformations per 1000 births.

Author	European population	Pakistanis
Chitty and Winter ⁶	3	6.9
Balrajan ⁷	1.9	5.7
Bunday et al ⁸	0	7.3

One evident factor was the different inbreeding coefficient of the two populations which probably was responsible for such significantly different results. A Birmingham study proved that the relationship of parents significantly and adversely affected the child, the total prevalence of congenital malformations and handicap of 9% in the consanguineous group (mainly Pakistanis settled in the UK) as compared to 3% in the general population. This study reports the prevalence of consanguineous marriage and its

effect on the prevalence of congenital gross malformations in Northern Pakistan, a region which has, probably, the highest coefficient of inbreeding in the world.

Patients and Methods

A consecutive sample hospital based prospective survey of 5000 Armed Forces families was carried out in the Department of Paediatric Surgery at Military Hospital, Rawalpindi from April, 1992 to April, 1993. The parents of children visiting out-patients department were asked to answer a questionnaire which included, among other variables, parents relationship to each other (whether first cousins (n=3125), first cousins once removed (n=200), second cousins (n=330), second cousins once removed (n=50) and the couples who were related but the exact relationship could not be established distant relatives (n=115)). A note was also made whether the couples were married in their father's family (n=1895, 50%), mother's family (n=1820, 47%), or whether they were related to both (n=105, 3%). Any gross, physical malformations in the presenting child and the sibling were noted in detail. This study was only confined to visible or easily detectable malformations. Inherited metabolic, haematological, enzymatic and chromosomal defects were not included. An enquiry into history of exposure to any factor known to cause congenital malformations was also made and families with such a history were excluded from the study. The sample plan was designed to have an adequate representation of all the socioeconomical and demographic groups. The data of the families was divided into groups in two ways i.e., whether the parents were related or unrelated and whether their children had any congenital malformation or not. The number of malformed children in related and unrelated parents were noted and subjected to various comparative methods of analysis. The group of parents with malformed children was defined as "malformation group", whereas, the parents with no abnormalities in their children acted as "comparison group" for the purpose of statistical analysis.

To measure the effect of relationship on breeding, the term "coefficient of inbreeding" is used. This measures the likelihood that any two persons with common ancestors have received the same genes from them and if mated, pass these to their offsprings. The coefficient itself is calculated taking into account the total number of married couples, number of related couples, the number of various types of relationships and coefficients of relationships, using a complex formula¹⁰ These relationships were used to calculate coefficient of inbreeding in the families under study, but for the sake of statistical analysis, first cousins once removed were grouped with second cousins and second cousins once removed were considered together with distant relatives, The data was subjected to detailed statistical analysis. Chi square and p-values were calculated along with contingency coefficients.

Results

The overall frequency inbreeding in this study was 76% and the coefficient of inbreeding was 0.04151 (Table II).

Table II. Coefficients of inbreeding in various parts of the world.

Country	Value X 10 ⁴
USA ¹¹	1.15
Japan ¹¹	34.90
India ¹¹	209.30
Iraq ²⁰	241.10
Pakistan	415.10
(Present series)	

The coefficient of inbreeding of families with malformed children was 0.043425 as compared to 0.039352 in controls. This fact alone was a good enough indication that the parents of malformed children were more closely related. Regarding the association of types of relationship to malformations, of the total related parents (n=3820), 50% of second cousins had malformations in their children. The figures for first cousins and distant related parents were 39% and 36% respectively (Figure 1).

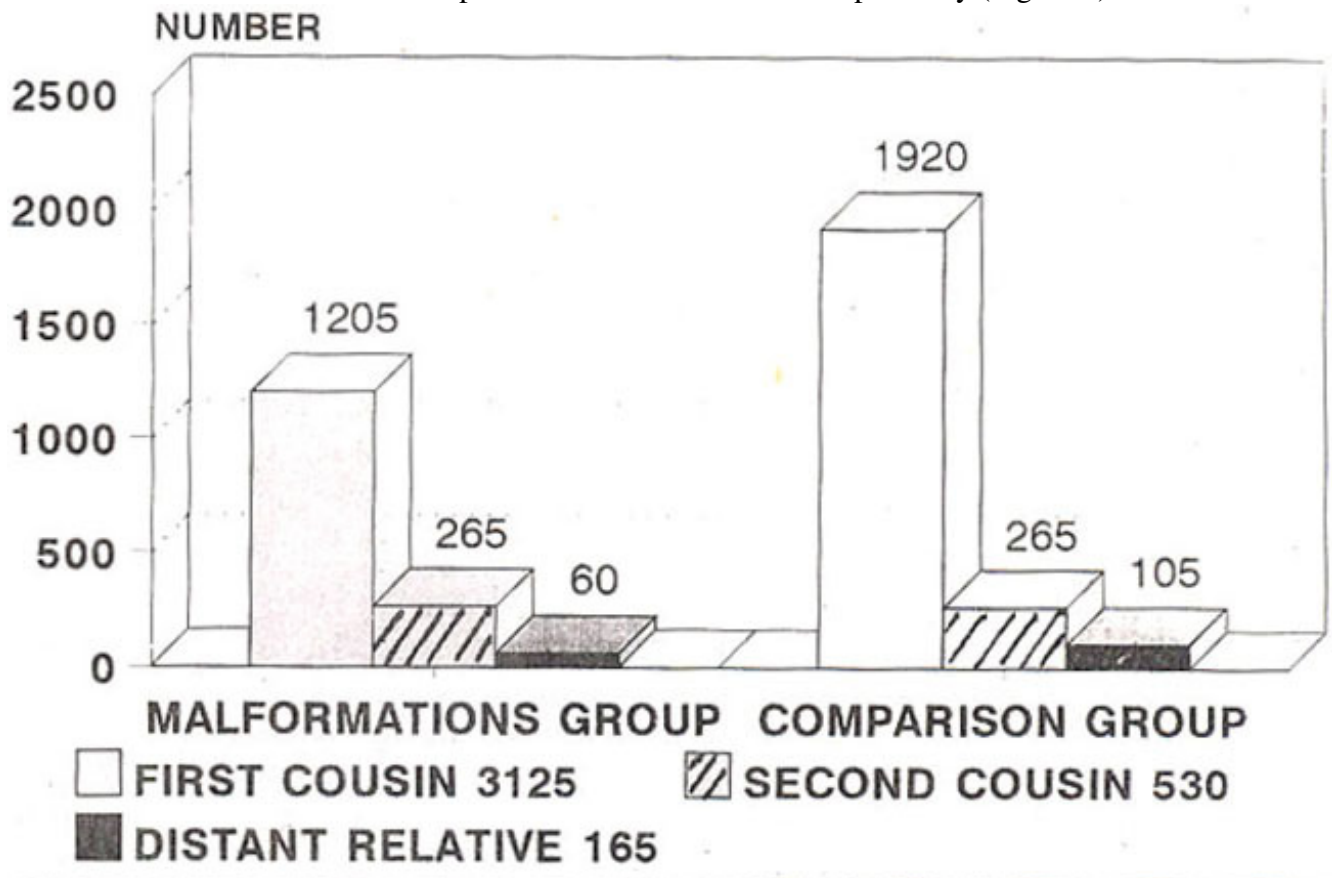


Figure 1. Relationship and malformations.

There was no significant preference for marriage towards paternal side, maternal side or both, as the percentage ratio of first cousins, second cousins and distant related couples was nearly the same in all the groups (Table III).

Table III. Parental preference for marriage.

Relationship	Paternal side	Maternal side	Both sided
	No (%)	No (%)	No (%)
First cousins (n=3125)	1530 (49)	1515 (48)	80 (3)
Second cousins (n=530)	275 (52)	235 (44)	20 (4)
Distant related (n=165)	90 (54)	70 (43)	5 (3)
Total (n=3820)	1895 (50)	1820 (47)	105 (3)

Forty percent (1530 out of 3820) of related parents had congenital malformations in their children (Figure 2)

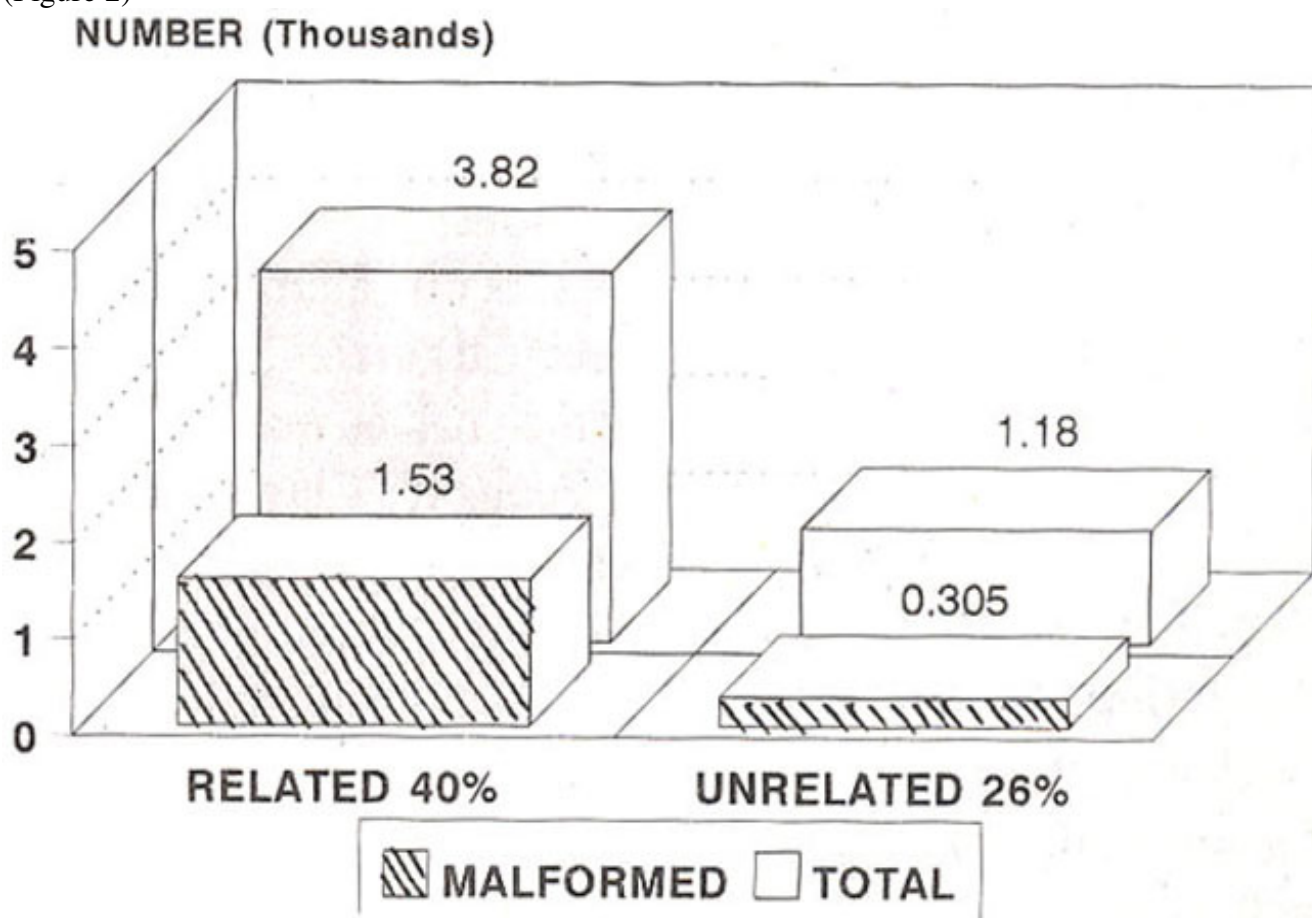


Figure 2. Consanguinity and malformations.

as compared to 26% (305 out of, 1 180) in unrelated ($p=0.00008$). Of all the children with malformations, 83% (1530 out of 1835) were the product of consanguineous marriages with a ratio of 5:1 between related and unrelated parents as compared to 2.6:1 in the comparison group which had no malformations in their children with a $p=0.00008$, Pearson's Chi square value of 15.66 and a contingency coefficient of 0.12417, making this association highly significant. The association of types

of relationship to production of malformations in children was calculated to have a Chi square value of 5.135 with a $p=0,0767$, but when considered individually for various types of relationship, was highly significant for first cousins with a $p<0.01$ (Figure 3).

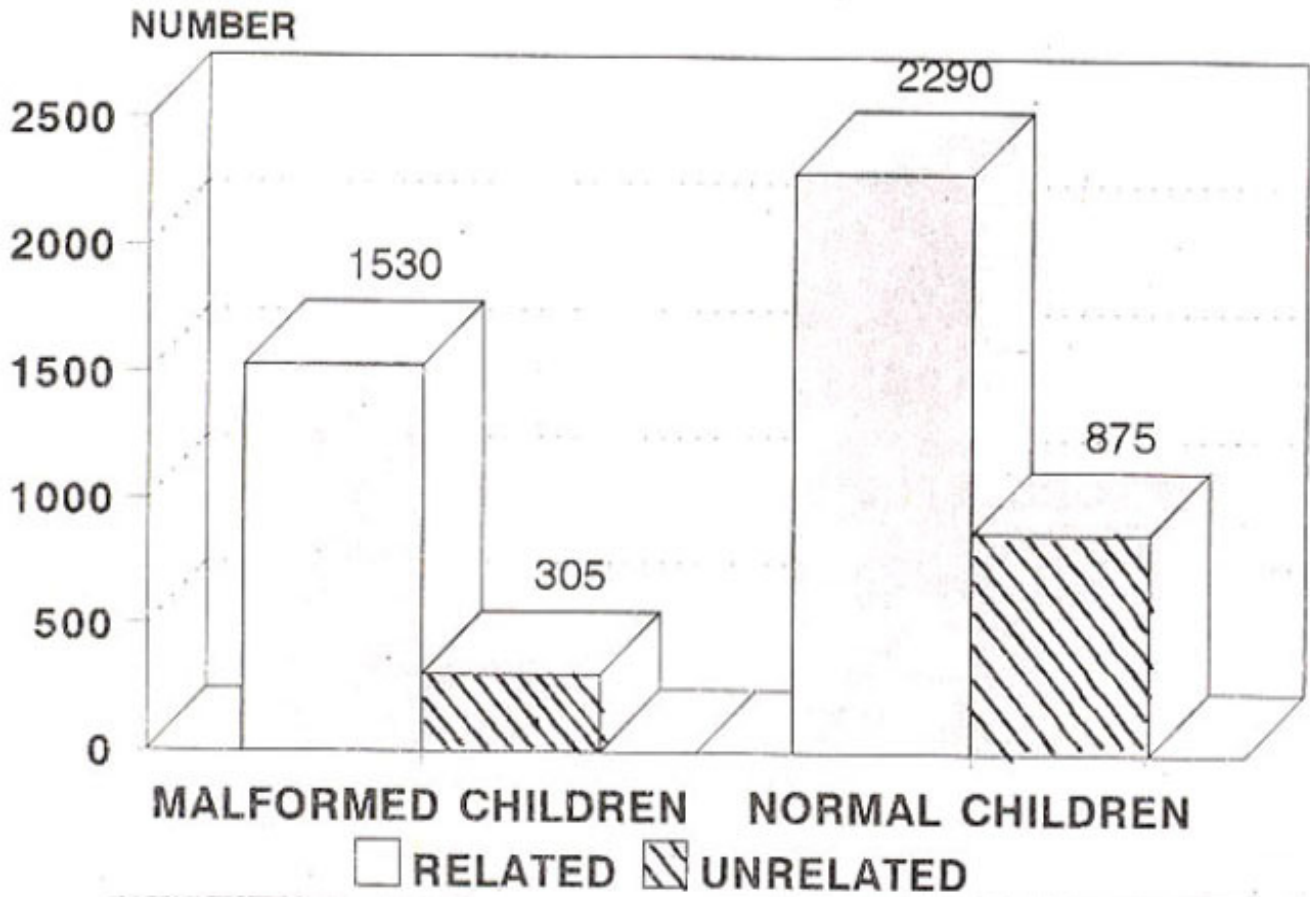


Figure 3. Malformations and consanguinity.

Complete analysis of malformed children (Figure 4)

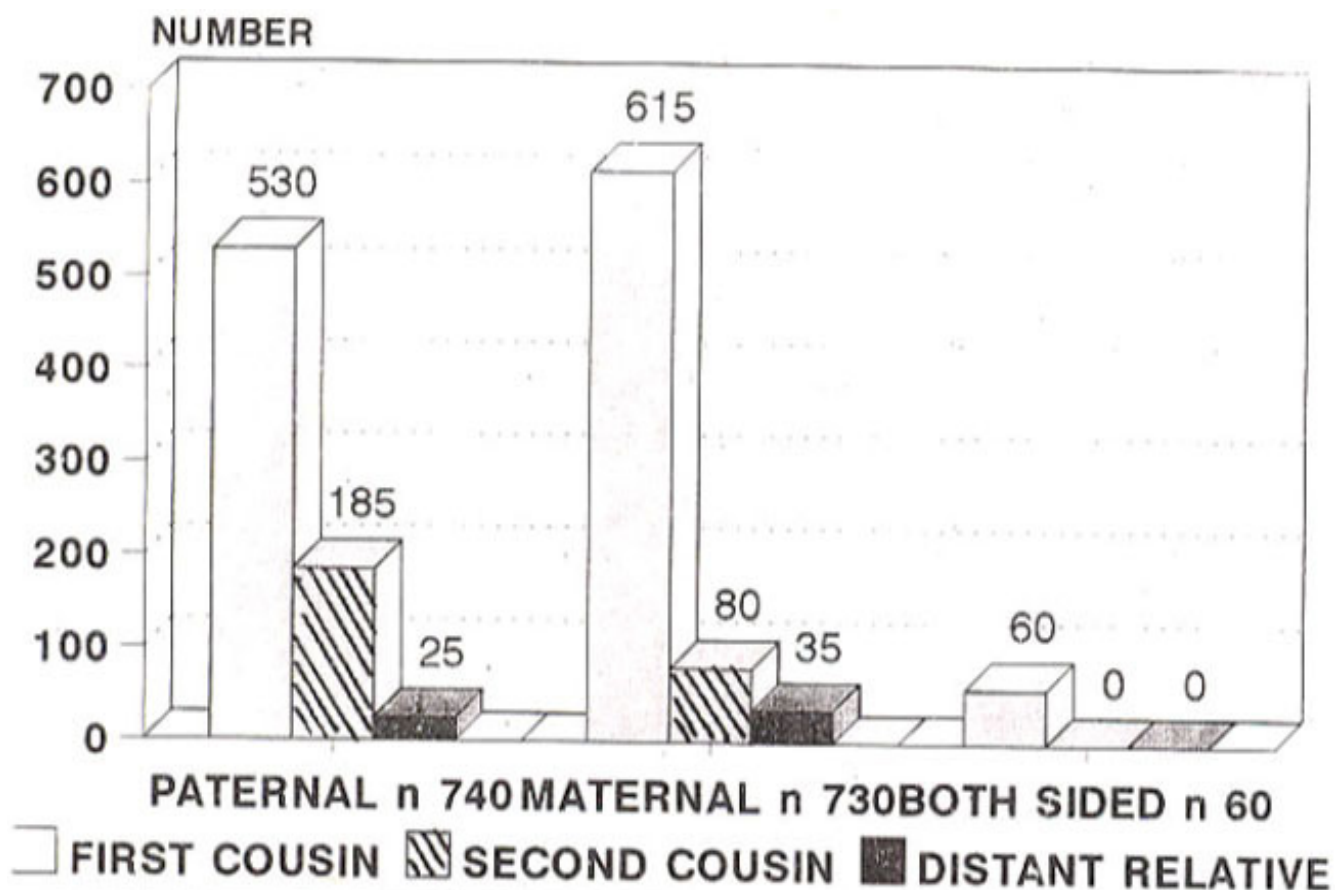


Figure 4. Relationship amongst group with malformed children.

clearly shows that 70% (185 out of 265) second cousin marriages resulted in malformations from father's side, 51% (615 out of 1205) first cousin marriages caused malformations from mother's side, whereas, 100% (60 out of 60) of children had malformations if the parents were first cousins both from paternal and maternal sides. One hundred and fifty-five siblings were also found malformed in 145 families. One hundred and thirty-five of these families had one additional child malformed, whereas, 10 had two malformed children in addition to the index child with whom they reported. Almost all of the above mentioned families (except 5) belonged to the group which presented with a malformed child. It shows that once a malformation is noted in a family, the risk of its recurrence is high. Four percent of these malformed siblings were found in related families (125 in 3820) as compared to 2% (20 in 1180) in unrelated couples.

Discussion

The genetic significance of consanguinity was reported as early as 1902 by Garrad who, along with Gallon are considered to be founders of medical genetics¹¹. Because of deleterious effects of such marriages on perinatal and infant mortality and occurrence of congenital malformations¹², Japan¹⁰ has shown a remarkable decrease in the incidence of consanguinity over the past 40 years. Such a decline has not been seen anywhere else due to the positive social benefits which such marriages provide, especially to women. Recently, China has imposed new laws forbidding marriages between first and second cousins. In certain Indian communities, uncle-niece relationship is the commonest¹³, whereas, preference is given to first cousin marriages in Pakistan (82% in our series) and Saudi Arabia¹⁴. Most societies share an incest taboo against marriages between first degree relatives. Some societies use

religious or legal sanctions to discourage such marriages. Increased risk of abnormalities in the offspring is often advanced to explain such restrictions, but the underlying reasons could only be social and anthropological¹⁵, because, a custom so popular must have significant social advantage. A study done on various isonymic groups in Pakistan¹⁶ showed the highest coefficient of inbreeding in Khokhars (0.05 120) and the lowest in Mughals (0.0 175). The inbreeding of 76% in this study corresponds with that of Darr and Model¹⁷ who found 75% consanguinity in Pakistanis settled in U.K. The coefficient of inbreeding is highest in this series and lowest in U.S.A.” (Table II). In Turkey, consanguinity has been shown to be directly related to the education of women¹⁸ whereas in our series, no such effects were noted and consanguinity was as common in uneducated population as in the educated. The reason could be the parent’s influence dominating the choice of the marriage partners. Kulkarni¹⁴ in his study found malformations of major body systems to be significantly more common amongst consanguineous couples, whereas malformations of eye, ear and skin did not show any gross effects of consanguinity. In our series, this fact could not be proved. The high incidence of consanguinity in our series was due to social custom, the practice of arranged marriages within the families and unawareness of the public about the adverse genetic effects of such practice. It is clear from this study that the consanguineous couples are a population at high genetic risk. It is, therefore, imperative that future health care programmes be directed towards prenatal diagnosis of congenital malformations, screening of population for carriers and genetic counselling centres especially when we have the highest coefficient of inbreeding in the world.

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