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Original Article

Consanguinity and Neural Tube Defects

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Abstract

Background: To determine the number of consanguineous unions in parents of children born with neural tube defects.

Methods: For this case-control study 190 pregnant women coming for delivery/ termination to the Obstetrics Department, Holy Family Hospital, Rawalpindi, 2005-2007 affected with a Neural Tube pregnancy and 100 control mothers were directly interviewed and a specially structured performa was filled regarding demographic, reproductive and consanguinity data .

Results: In this study 60 % of couples were consanguineous with a neural tube pregnancy as compared to 45% in controls. Of the 60%, there were 46.84 % first cousins. Neural tube defects included mostly anencephaly (18.95%), encephalocele (4.74%), meningocele (42.11%) and myelomeningocele(30%). Neural tube defects are multifactorial with genetic as well as environmental factors in its etiology. Majority (63.53%) were from rural areas. Majority of patients were illiterate or had limited education and mostly had low socioeconomic background. Neural Tube anomalies encountered were autosomal recessive with a risk of recurrence in subsequent pregnancies.

Conclusion: There were significantly more consanguineous couples with a neural tube pregnancy as compared to controls. Genetic counseling could be beneficial for consanguineous couples. There is a need to educate the public on the possible harmful effects of inbreeding, especially in developing countries with high rates of consanguinity and limited financial resources.

Key words: Consanguinity, Marriage types , Neural tube defects (NTDs),

Introduction

Consanguinity is common in Pakistan. Autosomal recessive disorders are linked with consanguinity and approximately 30% of sporadic cases of mental retardation, congenital anomalies and dysmorphisms may have an autosomal recessive etiology with risks of recurrence in future pregnancies. In Pakistan consanguineous marriages are a favoured feature, because of ethnic social, cultural and economic reasons. The offspring of consanguineous unions carry a greater risk of sharing same homozygous alleles than do unrelated individuals. A Consanguineous marriage is of genetic importance since close relatives have a greater chance of carrying the same alleles than do unrelated folks. The offspring of consanguineous unions are more likely to inherit homozygous alleles than are the offspring of unrelated parents. Consanguineous marriages have been practiced since the early existence of modern humans. The word consanguinity has its origin from the Latin words "con" meaning common and "sanguineous" meaning blood, hence the term refers to a bond between two individuals who share a common ancestor.[1, 2,3] Consanguineous marriages include unions termed first cousins, first cousins once removed and second cousins. Consanguinity is a deep rooted favoured social trend in around one-fifth of the world population customarily in Middle East, Asia and North Africa. Emigrants from these communities now residing in America, Europe and Australia show similar preponderance.[4] In consanguineous marriages the inbreeding coefficient (*F*) equals or is higher than 0.0156, where (*F*) is representative of a measure of the fraction of loci at which the offspring of a consanguineous union is expected to inherit identical gene copies from each parent[5]. There is growing public awareness on prevention of congenital disorders in highly consanguineous communities and couples are ready to seek advice on health risk for the new born[4].Consanguinity allows clustering of susceptible genes, the expression of which could possibly contribute to development of NTDs[6]. A number of researches on Middle East and Saudi Arabian population reported high rates reported high rates of consanguineous marriages (89%) in parents of spina bifida and other congenital anomalies in children.[7,8, 9] Iran has a reported high incidence of anencephaly with a high rate of consanguinity suggesting role of a major recessive gene.[10] Latin American population studies reported parental consanguinity as a risk factor for congenital anomalies including NTDs.[11] A study on congenital anomalies in Pakistani population reported

consanguineous marriages (44.74%) as a major risk factor with occurrence of NTDs. These are most common(65.8%) type of anomaly.[12]

The link between consanguinity and birth defects has been explored in several studies. A study in Palestinian Arab population, revealed 93 percent parents of children with rare autosomal disorders were found to be related, compared with a consanguinity rate of 44 percent among the general population.[13] Also found in this study were higher-than-average rates of consanguinity among parents of children with neural tube defects (NTDs), cleft lip and palate, and other congenital malformations. In studies conducted in the United Arab Emirates and in Saudi Arabia the association NTDs with consanguinity was reported. [8,14]

Consanguineous marriages continue to be commonly practiced in Pakistani population but their impact on health has not been elucidated because of paucity of epidemiological studies. To understand better the impact of inbreeding on the occurrence of some specific disorders like congenital defects may raise public awareness of the potential negative effects of intra-family marriages.

Subjects and Methods

This case-control e study was conducted at Holy Family Hospital (HFH) Rawalpindi and Quaid-i-Azam University (QAU), Islamabad. For this study women who had come to Department of Gynecology and Obstetrics with previously diagnosed pregnancy with Neural tube defect on antenatal anomaly scan or delivered a baby with Neural tube defect with no prior ante natal record were identified. Such cases were referred from nearby rural areas or small towns where health facilities are either not available or cannot cater a complicated pregnancy. Neural tube defects (NTDs) included anencephaly, encephalocele and spina bifida. Spina bifida includes meningocele and myelomeningocele. A small number of rare cases were identified in this study including lipomeningocele, spina bifida+Arnold-Chiari syndrome and syringomyelia. The diagnosis of sub types of neural tube defects was confirmed in department of Pediatrics and Department of Neurosurgery. The terminations were confirmed on Ultrasonography in Department of Radiology. For this study the woman who delivered a baby with NTD will be referred to as a case mother. After obtaining an informed consent from the mother with NTD pregnancy a direct interview was conducted with mothers after delivery and before hospital discharge. Consanguinity in case and control mothers was noted. The Study sample data were classified according to genetic relationship of parents of NTD affected babies and that of control group. Marriages were grouped as double first cousins, first cousins, second cousin, baradari, distant relations and unrelated. In distant relationship and baradari (clan), the exact genetic relationship was difficult to ascertain. These were, therefore, grouped under non consanguineous marriages. In baradari (clan)group people marry in families having the same surname disregarding whether they are genetically related or not.

Results

Frequency of consanguineous marriages among case mothers were significantly higher than in control mothers ($\Sigma\chi^2$ (1) =5.95;p=<0.015) (Table 1). In case mothers majority of marriages contracted are between first cousins (46.84%) than in control mothers (25%) (Table 2). Majority of NTDs were observed in case mothers who had contracted first cousin marriages. Prominent NTDs among first cousin marriages were anencephalic(n=16) meningoceles (n=37) and myelomeningoceles (n=28). In unrelated marriage typesanencephalic (n=10), meningoceles (n=23) and myelomeningoceles (n=15) were the prominent NTDs (Table 3).

Table 1 : Consanguinity in control and case mothers

Consanguinity	Control mothers (n=100);No(%)	Case mothers (n=190);No(%)
Consanguineous marriages	45(45)	114(6)
Non-consanguineous marriages	55(55)	76(40)
$\Sigma\chi^2_{(1)}$ =5.95; P=0.015*		

All NTDs appearing in consanguineous and non-consanguineous together showed that NTDs appeared in highly significantly greater number inconsanguineous marriages than in non-consanguineous ($\Sigma\chi^2$ (1) =7.60; p=<0.005).The calculated coefficient of inbreeding (F) in control mothers is (F= 0.0286).This is comparable to that in general population.[15] In the case mothers the coefficient of inbreeding (F) is higher (F=0.342)than control mothers which indicates that in case mothers compared to control mothers more loci show homozygosity.

Table 2 : Consanguinity and marriage types in control and Case mothers

Consanguinity	Marriage type	Control mothers (n=100); No(%)	Case mothers (n=160); No(%)
Consanguin-eous marriages	First cousins	25(18)	89(46.84)
	Second cousins	18(18)	20(10.53)
	Double first cousins	2(2)	5(2.63)
Non consanguineous marriages	Distant relation	8(8)	13(6.84)
	Baradari	12(12)	8(4.21)
	Unrelated	35(35)	55(28.95)
Coefficient of in breeding (F)		0.0208	0.342

Table 3 : Distribution of different neural tube defects among different marriage types of case mothers

Neural tube defect	No(%)	Marriage type						
		First	Second	Double	Baradari	Distant	Unrelated	Total
Anencephaly	36 (18.75)	16	4	2	1	3	10	36
Encephalocele	9 (4.74)	4	1	-	-	-	4	9
Meningocele	80 (42.11)	37	8	1	6	5	23	80
Myelomening ocele	57 (30)	28	7	2	1	4	15	57
Lipomeningoc ele	4 (2.11)	1	-	-	-	1	2	4
Dandy Walker syndrome	2 (1.05)	1	-	-	-	-	1	2
Spina bifida+ Arnold-Chiari syndrome	1 (0.53)	1	-	-	-	-	-	1
Syringomyelia	1 (0.53)	1	-	-	-	-	-	1
Total		89	20	5	8	13	55	190

Discussion

Consanguineous marriages have been in practice and preferred since the emergence of modern-day human society and more widely practiced in several global communities.[16] Consanguineous marriages continue to be extremely common in Pakistan and much of South East Asia.[17] In Pakistani society cultural, social, and family pressures compel families to arrange marriages of their children within family. In this study consanguineous marriages among case mothers were significantly higher than non-consanguineous marriages (P=<0.015). Among the consanguineous unions the most frequent type were first cousin marriages (46.84%). In control mothers consanguineous marriages were 45% and among these first cousin unions were 25 %. In consanguineous unions children are at a greater risk of inheriting genetic disorders as autosomal recessive gene mutations could be inherited from a common ancestor. There is increased probability of expression of mutated recessive genes in close biological relationship (first cousins) between parents.[16] A study on Pakistani population reported 21% consanguinity in couples with children affected with congenital anomalies. [18] Another study on congenital anomalies[12] reported 44.74% marriages were among close relations. The rates of consanguinity are dependent on socio-cultural, geographical and religious diversities.[19] South East Asia and Middle East Arab countries reveal some of the highest rates of consanguineous marriages in the world with first cousin marriages being more prevalent (25-30%) of all marriages. Among Arabs and other Middle East countries, due to consanguinity there are adverse reproductive outcomes and increase inrates of congenital malformations.[20,21] Consanguinity increases the rate of homozygosity which is one factor for such malformations.

In Pakistan consanguineous marriages are still favoured because of economic and cultural reasons particularly social security for the females. In Middle East and Saudi Arabia increased consanguinity resulted in the appearance of spina bifida, anencephaly and hydrocephalous offspring.[7,8] A similar picture was reported from Palestinian population by regarding higher incidence of malformations among children coming from consanguineous marriages. [13] The coefficient of inbreeding (F) in this study group in case mothers is F=0.0342 and in control mothers F= 0.0208 which indicates more homozygosity at certain loci but not in non-non-consanguineous marriages (F=0.021). Analysis between genetic diseases with different modes of inheritance has shown high values of inbreeding coefficients (F=0.021) as compared to controls (F=0.019) in recessive disorders reported in a study on Egyptian children with autosomal recessive disorders, a high incidence of consanguinity (60% with 48% first cousins) and the average inbreeding coefficient was higher F=0.03 compared with Egyptian population in general F=0.01.[16,22] In Indian population reported commonest types of consanguineous marriages were between first cousins (50.6%) and uncle and niece(42.4%). [23]The mean coefficient of

inbreeding was F= 0.056 which very high compared to that reported in this study. This high rate and repeated practice of consanguineous marriages are expected to increase the observed levels of deleterious homozygous alleles and escalate emergence of clinical conditions with alleged genetic etiology, particularly those with recessive inheritance.[24,25]

Conclusion

1.Consanguineous marriages are a preferred practice in most parts of Pakistan and more so in economically challenged and less educated class. There is an association of **c**onsanguineous marriages with greater risk of autosomal recessive diseases than in the general population.

2.In- breeding favours the expression of recessive lethal alleles. Frequency of consanguineous marriages was higher among parents of offspring with NTDs compared to control group, hence the need for genetic counseling to couples on risks cousin marriages and adverse reproductive outcomes.

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