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Genetic Epidemiological Studies of Hearing Loss in Faisalabad City, Pakistan

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Keywords: epidemiology, deafness, inheritance, pedigree.

I. Introduction

Deafness, a sensory defect, affecting 1 / 500-650 newborn children and 250 million people worldwide (Olusanya et al., 2007), of whom two thirds are in developing countries. It is considered to be second major cause of disability. Frequency of hearing loss in Southeast Asia varies from 4.6% to 8.8% (Garg et al., 2009). There are approximately 63 million (India) 28 million (USA) and 9 million (UK) hearing impaired people according to WHO survey. Deafness can be categorized as genetic or non-genetic, prelingual or postlingual, and syndromic or non-syndromic.

Approximately 60% cases of deafness have genetic basis (Mehl and Thomson, 2002). Environmental factors are responsible for upto 40% cases and few are due to unknown causes (Willems, 2000; Reddy et al., 2006). In genetic cases, 85% of the hearing impairment is described as non-syndromic (Kenneson et al., 2002).

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Comparatively to advanced countries, people from developing countries are three to four times more susceptible to deafness largely because of unfavourable environmental factors. Asian, African and Latin American population practice consanguineous marriages frequently, so siblings of these marriages are at high risk of autosomal recessive disorder. Consanguinity basically disturbs the normal genetic pathway and paves the way for the development of hearing loss (Reddy et al., 2006). Autosomal recessive non-syndromic hearing impairment (ARNSHI) can be traced easily in Pakistani population due to the availability of large extended and highly consanguineous pedigrees (Santos et al., 2005). The prevalence of bilateral deafness in Pakistani population is as high as 1.6 per 1000, 60% higher than the world average (Elahi et al., 1998). In Pakistani population 80% marriages are first-cousin and 60% are consanguineous (Hussain, 1998). Neonatal, infant and childhood periods face the highest death rates because of this consanguinity (Bittles, 2001).

For present epidemiological study deaf population was selected at district level to collect data for determination of prevalence rates. Effect of consanguinity on congenital deafness, social and economic status impacts and mode of inheritance of genetic cases were studied.

II. Materials and Methods

The families for genetic epidemiological studies were collected from different schools for special education of district Faisalabad, Total twenty-two families were scored by collecting data of about 436 deaf patients from special schools and different areas of Faisalabad city. These families provided necessary relevant information for genetic epidemiological studies. Family consisted of 4 or 5 generations was considered in which at least 4 or 5 individuals were afflicted with congenital deafness, to get better results.

The details of the family were traced back through the proband. The information was collected from subjects with the help of a data sheet including their surname, parental marriage age, parental relationship of marriage, their family history including information about number of offsprings (sex, birth order), similar and other disease in family, number of normal and diseased individuals in family and the age of onset of disease.

a) Data analysis

The data was analyzed in three ways. Firstly, the sample was analyzed as a whole to get information of population and second in relation of consanguinity. Third pedigrees were draw in order to evaluate the mode of inheritance of disease. Genetic relationships in marriages were classified into first cousins (1C), first cousin once removed (11/2C), second cousins (2C), distant relatives (DR), bradari (B) and unrelated (U) (Shami and Iqbal, 1983).

b) Statistical analysis

The statistical analysis carried out for this study included percentage (%), mean (M), standard error (S.E) and chi-square test (χ^2). Mean coefficient of inbreeding (F-value) was calculated by following the method of Wright (1992).

III. Results

a) General population study

Out of 436 deaf patients, 347 belonged to urban areas and 89 belonged to rural. Male patients were 65.165% in rural and 52.44% in urban areas whereas females were 34.83% and 47.55%, respectively.

b) Parental marriage age

In case of female patients mean maternal marriage age was 20.61±0.262 years whereas mean paternal marriage age was 25.010±0.335 years. Similarly in case of male deaf patients mean maternal and paternal marriage age was 20.654±0.207 and 24.971±0.284, respectively. It was seen that second age group (18-22 years) of maternal marriage was more commonly distributed in deaf male and females than any other age group (Table-1).Children of couples with age difference ranged from 0-4 years had high percentage (59.63 %) of disease. Difference of 2, 3, 4 and 5 years at marriage have high percentages 20.87%, 13.76%, 10.55% and 11.46% of deaf patients, respectively.

Table 1 : Distribution of mean maternal marriage age (MA) of deaf patients in different age groups

Age groups at marriage (Years)	Maternal age of male patients (X ± S.E)	Maternal age of female patients (X ± S.E)	Sexes Combined (X ± S.E)
13-17	16.20 ± 0.208 (25)	16.136 ± 0.136 (22)	16.170 ± 0.127 (47)
18-22	19.940 ± 0.123 (166)	19.609 ± 0.127 (133)	19.793 ± 0.089 (299)
23-27	24.341 ± 0.155 (41)	24.645 ± 0.189 (31)	24.472 ± 0.120 (72)
28-32	29.571 ± 0.481 (7)	29.571 ± 0.297 (7)	29.571 ± 0.272 (14)
33-37	37.0 ± 0.00 (1)	35.333 ± 0.333 (3)	35.750 ± 0.479 (4)

$\chi^2 = 223.96$; d.f=9, $P<0.001$

The number mentioned within parenthesis ( ) is the number of deaf patients.

c) Birth order

Different birth orders of 436 deaf patients were recorded up to 12th birth order. Percentage distribution of combined sex in different birth orders shows that 1st (24.54%), 2nd (22.24%) and 3rd (17.20%) birth order had the highest representation while 9th (0.45%), 10th (0.68%) and 12th (0.229%) birth order had the lowest representation. In male deaf patients 1st (29.16%) and 2nd (22.08%) birth order and in female deaf patients 2nd (22.44%) and 4th (21.42%) birth order showed maximum percentages. Tenth and 12th birth order (0.416%) in males and 8th birth order (0.51%) in females were least suffered (Table-2).

Table 2 : Percentage distribution of deaf males and females in different birth orders

Sex		1st order	2nd order	3rd order	4th order	5th order	6th order	7th order	8th order	9th order	10th order	11th order	12th order
Males	No	70	53	36	31	20	14	6	6	2	1	-	1
	%	29.16	22.08	15.0	12.91	8.34	5.83	2.5	2.5	0.834	0.416	-	0.416
Females	No	37	44	39	42	18	8	5	1	-	2	-	-
	%	18.87	22.44	19.89	21.42	9.18	4.08	2.55	0.51	-	1.02	-	-
Combined Sex	No	107	97	75	73	38	22	11	7	2	3	-	1
	%	24.54	22.24	17.20	16.74	8.715	5.04	2.52	1.60	0.45	0.68	-	0.229

d) Socio- economic status, life style and education

Highest percentage representation of deaf patients was seen in skilled manual occupation (43.34%), followed by professional-managerial (19.03%) and unskilled categories (14.90%), respectively. Distribution of deaf patients according to their educational level was in primary (49.77%), Middle (14.90%), Matric (13.30%) and college education (2.52%), respectively. Ratio of uneducated smokers (53.45%) and non-smokers (34.29%) were highest in representation as compared to educated non-smokers (4.33%) and smokers (0.628%), respectively.

e) Consanguinity and deafness

Deaf patients were explored on the parental consanguinity basis, showed first cousin (67.66%), first cousin once removed (0.458%), second cousin (0.68%), distant relations (11.23%), bradari (5.27%) and unrelated spouses (14.67%), respectively. First cousin marriage couples had maximum number of affected children as compared to unrelated. Table-3 shows analysis of goodness of fit for father's occupation and different genetic relationships of deaf patients, which indicated that father's occupation and genetic relationships had highly significant effect on the development of deafness (χ^2 = 68.774; d.f = 25; p< 0.01). Educational contributions and different genetic relationships of parents were also compared in deaf patients that indicated a highly significant effect of education and genetic relationships on deafness (Table-4) (χ^2 = 349.41; d.f = 40; p< 0.01).

Table 3 : Test of goodness of fit between father's occupation and different genetic relationships of deaf patients

Genetic relationships	Father's occupation						Total
	I	II	IV	V	VI	VII	
1C	57	39	125	2	42	30	295
	(56.16)	(32.48)	(127.88)	(2.71)	(43.98)	(31.80)	(295.0)
$1^{1/2}$C	-	-	-	1	1	-	2
	(0.38)	(0.22)	(0.87)	(0.02)	(0.30)	(0.22)	(2.00)
2C	1	-	2	-	-	-	3
	(0.57)	(0.33)	(1.30)	(0.03)	(0.45)	(0.32)	(3.00)
B	4	2	11	1	3	2	23
	(4.38)	(2.53)	(9.97)	(0.21)	(3.43)	(2.48)	(23.00)
DR	9	2	24	-	9	5	49
	(9.33)	(5.39)	(21.24)	(0.45)	(7.31)	(5.28)	(49.00)
U	12	5	27	-	10	10	64
	(12.18)	(7.05)	(27.74)	(0.59)	(9.54)	(6.90)	(64.00)
Total	83	48	189	4	65	47	436

χ^2 = 68.774; d.f =25 P < 0.01. The value mentioned within parenthesis ( ) is the expected value 1C= First cousin.$1^{1/2}$= First cousin once removed.2C= Second cousin.B = Bradari

Table 4 : Test of goodness of fit between parental educational combinations and genetic relationships

Genetic Relationships	FATHER / MOTHER'S EDUCATION								
	N/N	N/S	S/N	S/S	S/C	C/N	C/S	C/C	U/U
1C	106 (106.23)	10 (15.56)	61 (52.10)	85 (87.96)	- (1.35)	2 (2.30)	19 (16.92)	6 (6.09)	6 (6.77)
$1^{1/2}$C	- (0.72)	- (0.11)	- (0.35)	1 (0.60)	- (0.01)	- (0.01)	- (0.11)	0 (0.04)	1 (0.05)
2C	- (1.08)	- (0.16)	- (0.53)	1 (0.89)	2 (0.01)	- (0.02)	- (0.17)	- (0.06)	- (0.07)
DR	17 (17.64)	6 (2.58)	4 (8.65)	17 (14.61)	- (0.22)	- (0.34)	2 (2.81)	- (1.01)	3 (1.12)
B	7 (8.28)	5 (1.21)	3 (4.06)	8 (6.86)	- (0.11)	- (0.16)	- (1.32)	- (0.47)	- (0.53)
U	27 (23.05)	2 (3.38)	9 (11.30)	18 (19.08)	- (0.29)	1 (0.44)	4 (3.67)	3 (1.32)	- (1.47)
Total	157 (157.0)	23 (23.00)	77 (77.00)	130 (130.0)	2 (2.00)	3 (3.00)	25 (25.00)	9 (9.00)	10 (10.0)

$\chi^2 = 349.412$; d.f =40, $P < 0.01$

The value mentioned within parenthesis ( ) is the expected value
N = Nil
S = School
C = College/University
U = Unknown

f) Disease in family

In 436 deaf patients, 282 (64.67%) cases had this disease in their family. Out of which 148 (52.48%) males and 134 (47.51%) females were those who had the same disease in their family, whereas 92 male (59.74%) and 62 female (40.25%) cases did not have family history for the disease. Table-5 represents the distribution of deaf males and their relatives diagnosed for the same disease. One forty eight affected males had 284 (47.17%) affected relatives. Among those the close blood relatives such as father, mother, daughter, son, sister and brother were 181 (63.73%) followed by 13 paternal (4.57%) and 8 maternal relatives (2.8%). 82 affected relatives (28.87%) were kept in category of others. One thirty four affected females had higher affected relative number (318) than that of males (284) and these affected relatives consisted of 188 close blood relation (59.11%), 15 maternal (4.71%), 14 paternal relatives (4.4%) and 101 (31.76%) included all these three relations (Table-6).

Table 5 : Distribution of deaf males and their relatives diagnosed for the same disease

Type of Relation	Affected Relatives	No of Affected Relatives	No of cases
Only Close Blood Relation Relatives	Only Sister	19	18
	Only Brother	51	42
	Only Mother	1	1
	Sister + Brother	88	34
	F+ M+ S+ B+ D+ Son	22	7
Only Maternal Relatives	M.G.F+ M.G.M+ M.A+ M.U+ M.C	8	7
Only Paternal Relatives	P.G.F + P.G.M + P.A + P.U + P.C	13	11
Close blood relation Relatives & Maternal-Paternal Relatives	F+ M+ S+ B+ D+ Son+ P.G.F+ P.G.M+ P.U+ P.A+ P.C+ M.G.F+ M.G.M+ M.A+ M.C+ M.U+ M.N+W	82	8
	Total	284	148

F = Father P.G.F = Paternal-grandfather, M = Mother P.G.M = Paternal-grandmother
S = Sister P.U = Paternal uncle B = Brother P.A = Paternal Aunt
D = Daughter P.C = Paternal Cousin W = Wife P.N = Paternal nephew
H = Husband M.G.F = Maternal grandfather M.G.M = Maternal grandmother
M.A = Maternal Ant M.U = Maternal uncle M.C = Maternal cousin M.N = Maternal nephew

Table 6 : Distribution of deaf females and their relatives diagnosed for the same disease

Type of Relation	Affected Relatives	No of Affected Relatives	No of cases
Only Close Blood Relation Relatives	Only Sister	45	31
	Only Brother	23	21
	Only Son	3	1
	Sister + Brother	97	34
	F+ M+ S+ B+ D+ Son	20	5
Only Maternal Relatives	M.G.F+ M.G.M+ M.A+ M.U+ M.C	15	8
Only Paternal Relatives	P.G.F + P.G.M + P.A + P.U + P.C	14	7
Close blood relation Relatives & Maternal-Paternal Relatives	F+ M+ S+ B+ D+ Son+ P.G.F + P.G.M + P.U + P.A+P.N+P.C+M.G.F + M.G.M +M.A+ M.C+ M.U+ M.N+H	101	27
	Total	318	134

F = Father, P.G.F = Paternal-grandfather, M = Mother, P.G.M = Paternal-grandmother
S = Sister, P.U = Paternal uncle, B = Brother, P.A = Paternal Aunt
D = Daughter, P.C = Paternal Cousin, W = Wife P.N = Paternal nephew
H = Husband M.G.F = Maternal grandfather M.G.M = Maternal grandmother
M.A = Maternal Ant M. U = Maternal uncle M.C = Maternal cousin M. N = Maternal nephew

g) Pedigree analysis

After studying the genetic cases of disease, twenty-two patients with family disease history were selected in total scored cases. Among Mendelian modes of inheritance only autosomal recessive mode was observed.

IV. Pedigree

a) Epidemiology

Pedigree (Fig-1) is an illustration of a Rajput family who is settled in Ali Hassan colony of Faisalabad. Eleven members including six males and five females were affected with congenital deafness. Individual III-5

was proband through which disease was traced back in his family. In first three generations, no affected individual was found except one affected male (III-5) produced in third generation. In this generation, first consanguineous marriage produced two affected sons (IV-1 and IV-3) and two affected daughters (IV-4, IV-6). But the second first cousin marriage of an affected male and normal female (III-5 and III-4) produced one affected daughter (IV-10), two affected sons (IV-7 and IV-8) and one normal son (IV-12). In fourth generation, two marriages were practiced, first was a consanguineous marriage between two congenitally deaf persons (IV-6 and IV-7) that produced all affected offsprings including one male (V-3) and two females (V-1 and V-2). Whereas second consanguineous marriage between an affected female and normal male (IV-10 and IV-11) produced three normal daughters (V-4, V-5 and V-6).

b) Result

This pedigree also shows an autosomal recessive mode of inheritance (Fig-1).

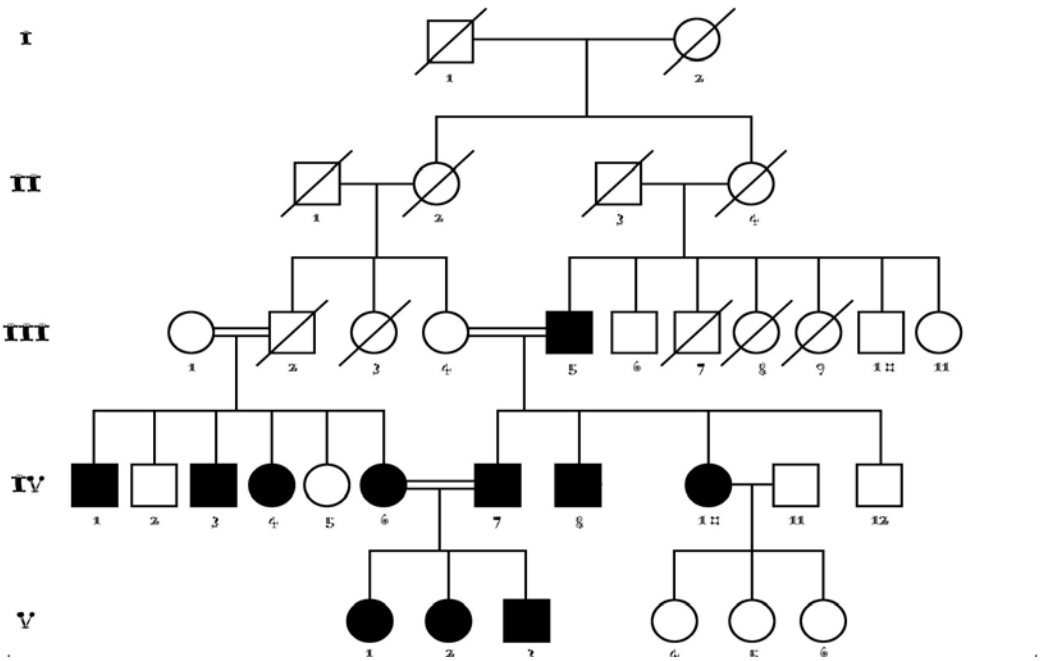

Figure 1 : pedigree reflecting an autosomal recessive mode of inheritance

V. Discussion

This study showed that males were more liable to congenital deafness as compared to females. Same results were found by Liu et al. (1999). Mean maternal marriage age and mean paternal age was 20.63 ± 0.163 and 24.989±0.217 recorded. Early age parental marriages could be a strong risky factor but it needs further investigation.

According to birth order study, 1st (24.54%), 2nd (22.24%) and 3rd (17.20%) birth orders were mostly affected with disease as compared to other birth orders irrespective of sex (Table-5). No supporting evidence is encountered on the importance of birth order because detailed literature review is silent on this aspect. Present study revealed that disease was common in lower social class (Category-IV), which was the case of skilled manual. This finding is comparable with the work of Bafaquee et al. (1994).

Highest percentage of deaf offspring was observed in uneducated people (49.77%) sector as compared to educated ones (2.52%). These investigations clearly show that lack of education increases the risk of disease that was also reported by Bafaquee et al. (1994).

In Pakistan first cousin marriages are more common and rates of inbreeding ranges from 37.8% to 48.9%. Calculated coefficient of inbreeding (F) for general population ranged from 0.0236 to 0.0286 (Shami et al., 1990).

Das (2006) examined that there was an increase in genetic disorders with an increase in inbreeding in almost all populations. Consanguineous children had more familial aggregation of disease. The consanguinity rate was too high which is in agreement with Ansari et al. (2004). In Iran, the frequency of consanguinity of parents was 59.7% in congenitally malformed population and 31.5% in normal population (Khushki and Zeyghami, 2005).

It was found that most common parental relationship was 1st cousin marriages (67.66%) than unrelated marriages (14.67%). These findings are in accordance with those of Bafaquee et al. (1994), Zakzouk (2002), Bener and Hussain (2006) and Reddy et al. (2006).

Socio economic status showed significant ($P<0.01$) influence on occurrence of congenital deafness among different marriage relationships. Education of parents also had significant effects ($P<0.01$) on the occurrence of disease in their children. (Table-4). Similar arguments are reported by Bittles (2001) and Aber et al. (2005) for Muslim populations.

Only Mendelian mode of autosomal recessive inheritance pattern was observed in this study. Marazita et al. (1993) found that 62.8% causes of early onset deafness were genetic in which 47.1% were recessive and 15.7% were with dominant cases. Same analysis was revealed by Longtiano and Brunoni (2000). Park et al. (2003) concluded that recessive mutations are common cause of deafness due to consanguineous matings in Pakistani and Indian populations. Calapoglu et al. (2005), Zolotogora and Barges (2003) also reported the same findings in Muslim Israeli population.

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