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Hearing Impairment among Children and Adolescents of Consanguineous Parents: A Study with Practical Challenges Encountered in Malakand, Northern Pakistan

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AAS and MZ designed and supervised the study, was involved in data collection, statistical analysis the writing of the paper. Author AB was involved in statistical analysis, interpretation of data and writing manuscript. All authors approved the final version.

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ABSTRACT

Aim: The aim of the present study is to determine the prevalence of HI and its association with parental consanguinity in urban and rural areas of Malakand District, Khyber Pakhtunkhwa Province, Pakistan.
Methods: In this community-based study, data was collected by random sampling method.

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Families with children were recruited in the study sample. Families without children were excluded from the study sample. Information was collected by questionnaire from 1,506 families in their homes from January 2011 to February 2013 and from September 2013 to April 2014. Data collection was interrupted several times due to security concerns in the study area. In the first phase, data collection was not enough. After a while, sampling was resumed to achieve a reasonable sample size. Otoscope, Tympanometry, Tuning fork testing (Rinne Test) and Audiometry were used in this study. Audiometry was for air conduction (AC) and bone conduction (BC). Subjective testing was performed including pure tone audiometry, free field speech tests, evoked response audiometry, visual reinforcement audiometry (VRA), play audiometry (PA), speech testing and tuning fork tests. Objective testing was performed including tympanometry. Pure Tone Audiometry (PTA) was used to record the degree and types of HI in children and adolescents.

Results: A total of 7,888 out of 8,227 children born to consanguineous parents were recruited in this study. 339 children were excluded from the study sample due to incomplete data. Couples were recorded as first ($F \geq 0.125$), second ($F \geq 0.0156$), or third degree cousins ($F \geq 0.0039$), and unrelated ($F = 0.00$). The HI testing, principally by free field speech testing, otoscopy, tuning fork tests, evoke response, visual reinforcement audiometry (VRA), play audiometry (PA) were initially performed at homes with pure tone audiometry (0.5-2kHs2) and tympanometry used to confirm and record the severity of HI in the HI examination centre at Seena Medical Centre at Dargai.

Conclusion: We found a strong positive association between parental consanguinity and HI. There is a need of several efforts, including awareness and genetic counselling programs for Hearing Impairment. Prevention is becoming highly essential to reduce the risk incidence of genetic hearing loss. Meanwhile, consanguinity should be discouraged through health education of the public concerning the adverse effect of interrelated marriage. Genetic counselling, Pre-marital and antenatal screening are to be applied whenever possible, at least for those at risk of developing genetic diseases including hearing impairment

Keywords: Consanguineous marriage; hearing impairment (HI); Khyber Pakhtunkhwa; Malakand; mild HI; moderate HI; severe HI; Pakistan.

1. INTRODUCTION

Hearing impairment (HI) can result from genetic and/or environmental factors. In high-income countries, it has been estimated that approximately 60% of cases are hereditary, whereas 30% are acquired, and 10% have an undefined etiology [1-3]. However, studies on causes of Permanent Childhood Hearing Impairment (PCHI) indicated that consanguinity is a risk factor for hearing loss [4]. Non-syndromic and syndromic deafness [5,6] attributed to autosomal recessive inheritance was described by Feinmesser et al. [7]. The overall picture may be quite different in low-income countries where environmental causes, such as acoustic trauma, ototoxicity, and viral and bacterial infections account for a high proportion of cases.

Non-syndromic and syndromic disorders are responsible for an estimated 70% and 30%, respectively, of hereditary forms of hearing loss [6]. Hereditary hearing loss is highly heterogeneous and, to date, mutations associated with non-syndromic hearing loss (DFNB) have been identified in more than 70 genes with differing modes of inheritance [8]. Despite the large numbers of genes and mutations implicated, the DFNB1 locus appears to be principally involved [9-11], with the genes *GJB2* and *GJB6* present at this locus encoding the proteins connexin 26 (Cx26) and connexin 30 (Cx30). More than 100 mutations associated with non-syndromic hearing loss have been described in *GJB2*, with both autosomal recessive and autosomal dominant modes of inheritance [12].

According to WHO estimates [13], more than 360 million people are suffering from HI across the world, and the number could increase to 900 million by the year 2025. High prevalence of HI was recorded in South Asia, Asia Pacific and sub-Sahara Africa. In Pakistan, prevalence of HI is 7 to 8 per 1000 live births. The causes of HI among children are not well understood, however previous studies have reported that several risk factors including poor access to basic health facilities, post natal infections and parental consanguinity, associated to HI in Pakistan and other communities [14,15]. Elahi et al. [16] has determined that 70% hearing

losses are in consanguineous families. However, in adolescents exposure to noise such as excessive use of video games and listening music were important risk factors for HI [15,17].

At present, 21 genes are characterized for autosomal dominant (DFNA) hearing loss, 27 genes for autosomal recessive (DFNB) hearing loss and 02 genes for X-linked (DFN) hearing loss (http://www.uia.ac.be/dnalab/hhh). Studies on Pakistani populations have reported several genes loci for deafness, coined as DFN (DeafNess), DFNA for autosomal dominant deafness, DFNB for autosomal recessive genes loci and DFN for genes inherited as X-linked genes. The studies have recorded hearing loss in consanguineous families with mutations of TMC1, RDX, TRIOBP, OTOF, MYO6, MYO15A (cause less severe HI), SLC26A4 and GJB2 accounting for 3.4 to 6.1% of recessive deafness in Pakistani study population with the record of parental consanguinity. The recessive deafness in the same studies were found in genes DFNB1, DFNB3, DFNB4, DFNB9, DFNB7/11, DFNB24, DFNB37 and DFNB73 (Gene= BSND, cause less severe hearing loss in young children) [18-20]. Basit et al. [21] reported BSNB89 locus for an unknown gene causing moderate to severe hearing loss.

According to World Bank Economy report in 2016, Pakistan is a lower-middle income country. It may be expected that the majority of cases with hearing loss would be result from environmental reasons in nature. However, the population of Pakistan is also characterized by strict community endogamy, along ethnic, religious and social lines, and high rates of consanguineous marriages [22-28]. In this respect, Malakand Protected Area is typical of much of Khyber Pakhtunkhwa Province (KP), and the neighboring province of Balochistan, and 66.4% of current marriages estimated to be consanguineous with a mean inbreeding coefficient (α) of 0.0338 [26]. No previous studies have reported the detrimental health effects of consanguinity in this unrest zone such as Malakand or Northern Pakistan [26].

The aim of the present study was to assess the consanguinity profile in relation to HI in urban and rural areas of district Malakand, Khyber Pakhtunkhwa Province (KP) in Pakistan. This research is essential, as no previous studies has been conducted regarding HI and consanguinity in the selected study area, which is a problematic and declared turbulent zone due to civil unrest. Subjects in the study area are unaware regarding consanguinity and its detrimental health effects.

2. MATERIALS AND METHODS

2.1 The Study Area

The Malakand Protected Area is a Provincially Administered Tribal Area (PATA) located in the northwest of Pakistan and governed by the Government of Khyber Pakhtunkhwa (KP) Province. During the pre-independence period and until 2010, KP was known as the North-West Frontier Province (NWFP). Malakand covers an area of 952 km^2 and according to the 1998 District Census Report, it had a population of 452,000, an average household size is 9.1, and literacy rates are 55.6% and 25.5% for rural males and females, respectively. More recent estimates suggested a population of 647,000 between 2008 and 2009 [29] with substantial increase in illiteracy rates still after crossing the six decades of its independence (UNESCO, 2012). According to UNESCO (2012) report about Pakistan, there were more than 50 million illiterate people in Pakistan in 1998. Moreover, the illiteracy rate in Pakistan was 55.24% in 2010 (UNESCO, 2012).

2.1.1 Study population

Approximately 90.5% of the population in Malakand maintained their lives in rural with just a single urban municipality (Batkhela). The majority of the population are Sunni Muslim and mainly follow the Hanafi School of Jurisprudence. Ethnically, the population is Pakhtun (Pathan), and predominantly belong to the Akozai branch of the Yousafzai tribe, and their dialect is the Pashto form of the Pakhtun language [26-28]. The Pathans are descended from Saul, the first king of the Jews, and are described as the descendants of the Bani-Israel, or Israelites [29]. Various authors have considered the Pathans as originating from Indian Afghans [29], from Central Asians, and from Ghazalis (a mixed race of Persians and Turks) [29]. High consanguinity rates were reported in Pathans [22-28].

2.2 Study Design, Subjects and Practical Challenges (faced) Encountered

To optimize recruitment, most house were visited either early in the day, or in the evening, with preference given to Friday, the Muslim Holy day, or Sunday which is locally regarded as a day of rest.

A total of 8,227 pre-school and school aged children from 4 to 15 years old were initially recruited into this study. However, as 339 children were excluded (i.e. children with complicated medical history from the study, our total sample size was 7,888. The study was conducted in Malakand from January 2011 to February 2013, and part of the data collection was resumed and completed between September 2013 and April 2014. Data collection was interrupted several times due to the armed forces action (i.e. search operations and announcement of curfew) in the area, and movement in the area was almost impossible due to security concerns. Even many times our data collection process was halted due to unrest condition in the area by the non-state elements. The random sampling method was used to include children from all socioeconomic and demographic strata residing in the different localities and sub localities of the Malakand Protected Area. The hearing tests were conducted in the children's private homes. Questionnaire Part-1 was used to obtain information from the parents. Any unclear questions were fully explained to the parents in the local Pashto language. Questionnaires were printed in English and the study team collected data or filled the questionnaires in English language. However, the families were asked/ interviewed in local language.

The questionnaire part-2 used was a modified version of the WHO/PBD ear examination form (version 8. 3) (online available http://www.who.int/blindness/Ear_hearingsurveyformupdtaed.pdf?ua=1), with information on age, sex, parental consanguinity and number of children in families (Tables 1, 2).

In the rural areas of Malakand where the study was conducted, socioeconomic conditions are poor and illiteracy is high. Parents in general, and mothers in particular, were unwilling to have their young children <4 to 5 years old included in the study. Parental unwillingness to allow their child to be examined stemmed from a local belief that any form of medical examination and/or inoculation in the early years of life could lead to infertility in adulthood. According to this belief, the risk associated with medical examinations was largely dispelled in children aged 5 years and above (This was a local belief in the study area. Not reported tell now).

Each study team was comprised of five pre trained volunteer college graduate students, an ENT specialist hired from the Seena Medical Centre Dargai, a nurse, a social worker, a field supervisor, and a vehicle driver. To protect the study team, male and female security personnel were acquired with the approval of local provincial administration, working on behalf of the Deputy Commissioner of Malakand. When appropriate, the female security personnel assisted during the nurse's interview of the mothers. The children were individually examined by the technical staff and doctor.

Initial examination for HI was performed with Otoscope at the children's private homes. Initially, tuning fork tests, visual reinforcement audiometry (VRA) and play audiometry (PA) were performed at homes. Children with HI were shifted to Seena Medical Centre Dargai for further detail examination, and pure tone audiometry (PTA) and tympanometry were performed. Audiometry was performed in noise-proof booth. The average sound level of the room used for HI examination was below 20 dB. Machines used for PTA were quite new and were in use for the last two years. The machines did not need calibration setting. Computer software, i.e AUDIT was provided and recommended by the service provider to calibrate the machine automatically.

Questionnaire was pre-tested and validated. Health questionnaire including data regarding level of HI, was completed in consultation with the parents. There were two parts in questionnaire, Part-1 was about parent-children relation and Part-2 was about Hearing Impairment examination. The second part of the questionnaire also included information previously requested in Part-1 (i.e. marital relationship, and number of children per family) (Table 2).

As purdah, i.e., the seclusion of women from male strangers is strictly observed in Malakand, male family heads and the childrens' fathers were interviewed by male members of the study team whereas the childrens' mothers were interviewed by female staff. Both the husband and wife contributed to completion of the questionnaires to ensure accurate information regarding the age and health of their child.

Hearing impairment in the children was principally tested by free field speech testing along with tuning fork tests. Pure tone audiometry (0.5 - 2 kHs2) and tympanometry were employed to confirm and record the

Table 1. Screening test for hearing impairment (HI) in Malakand study cohort according to age and gender (n =7,888)

Age	Male (%)	Femle (%)	Total (%)
Age Groups:			
≥4-8 years	1494 (45.4)	1796 (54.6)	3290 (41.7)
9-12 years	1198 (45.1)	1458 (54.9)	2656 (33.7)
≤13-15 years	849 (43.7)	1093 (56.7)	1942 (24.6)
Total	3541	4347	7,888
%	(44.9)	(55.1)	(100.0)

Table 2. Number of parents, children and mean number of children per family in consanguineous marriages

Parental relationship	No. parents (%)	No of children (%)	Mean no. of children per family
First cousins	548 (36.4)	2592 (32.8)	4.7
Second cousins	332 (22.1)	1631(20.7)	4.9
Third cousins	47 (3.1)	249 (3.2)	5.3
Unrelated	579 (38.4)	3416 (43.3)	5.9
Total subjects	1,506 (100.0)	7,888 (100.0)	5.2

and record the severity of hearing loss in children. Audiometry was performed to confirm HI severity among children above six years age. Diagnostic audiometer with dimension was presented by T 35x26x8 cm, precision level was equal to sound level pressure ± 01 dB, tone was continuous pure tone, pulse tone, random error of frequency was ≤ 01%. Evoked response audiometry was initially undertaken in suspected cases of HI among children <4 years of age. Nevertheless, this form of testing was discontinued due to the very limited number of young children. For analysis of the data the severity of hearing disorder was subdivided into three groups: Mild (26 - 40 dB), moderate (41 - 60 dB), and severe (61 - 90 dB) hearing loss [5,14]. Profound hearing loss was not included in the study.

2.2.1 Sampling inclusion-exclusion criteria

Parents were un-willing to subject their 4 years below age children to the hearing impairment examination. That is why children below 4 years age were excluded from the study sample. The study also excluded the cases of profound hearing loss (≥ 90 dB), as genetic testing was the limitation of the current study.

2.2.2 Instruments and test used

Otoscope, Tympanometer, Tuning fork (Rinne Test) and Diagnostic Audiometer were used in the study. Audiometry was for air conduction (AC) and bone conduction (BC). Subjective testing was performed including pure tone audiometry (PTA), free field speech tests, evoked response audiometry, visual reinforcement audiometry (VRA), play audiometry (PA), speech testing and tuning fork tests. Objective testing was performed including tympanometry. For HI types and level of HI the authors mainly relied on PTA [14,30,31].

In the first cousin, or double first cousin unions, 1/8 of their genes are identical by descent, with coefficient of relationship (R) equal to 0.25. The coefficient of relationship denotes proportion of genes common in parents to offspring and shows proportion of genes identical by descent (IBD). In first cousin unions, the number of shared genes is 25%. Similarly, their progeny are expected to be homozygous at 1/16 (12.5%, r=0.125) of all loci, which is conventionally expressed as the coefficient of inbreeding *(F),* and equals 0.0625 for first cousin offspring. The comparable values for first cousin progeny testing are F = 0.0625, for second cousins F = 0.0156, and F = 0.0039 for third cousins [1,26-28].

The data were analysed using the Statistical Packages for Social Sciences [SPSS Version # 22]. Student-t test was used to ascertain the significance of differences between mean values of two continuous variables and confirmed by non-parametric Mann-Whitney test. Chi-square analysis was performed to test for differences in proportions of categorical variables between two or more groups. In 2X2 tables, the Fisher's exact test (two-tailed) replaced the chi-square test if

the assumptions underlying chi-square violated namely in case of small sample size and where the expected frequency is less than 5 in any of the cells. The level $p<0.05$ was considered as the cut-off value for significance.

3. RESULTS

Of the 8,227 children initially recruited into the study, 339 children were excluded from the study sample due to inadequate, or unclear information provided by their parents, or because there was only a single parent present during the study team visit. Thus our study cohort comprised 7,888 children: Males 3,541 (44.9%) and females 4,347 (55.1%) (Table 1). Majority of the time children were not at home when the study team visited, and under these circumstances a repeated household call was made. The age groups and gender distribution of the study cohort is illustrated in Table 1. There were 3,290 (41.7%) children in the age group 4 to 8 years, 2,656 (33.7%) in the age group 8 to 12 years, and 1,942 (24.6%) children between 12 to 15 years old (Table 1). Of the 7,888 children surveyed, 2,592 (32.8%) children were born to first cousins, 1,631 (20.7%) to second cousins, 249 (3.2%) to third cousins, and 3,416 (43.3%) children were born to unrelated, or non-relative category. Mean number of children per family was highest (5.9) in unrelated parents and lowest (4.7) in first cousin marriages (Table 2).

Tables 3 and 4 depict consanguinity and levels of HI in 7,888 children from 1,506 families. In our cohort 641 (8.1%) children were recorded as having HI.

Of the 641 HI children, 377 (14.6%) were offspring of first cousins and had a prevalent type of severe HI (64.2%); 192 (11.8%) were offspring of second cousins and had a more prevalent type of moderate HI (63.0 %); 22 (8.8 %) progeny of third cousins were affected with a more common type of mild HI (40.9%), and 50 (1.5%) were offspring of unrelated parents and had the most common type of mild HI (70.0%) (Table 3). Overall, hearing impairment was higher (14.6%) in closer parental relatives (F= 0.0625) compared to non-consanguineous marriages (F=0.00) (Table 3).

Regarding gender, in all parental relations, HI was more frequent in females than in males. In progeny of first cousin, second cousin and third cousin marriages, HI was higher in females, 60.2%, 52.1% and 59.1%, respectively, than in males. In the case of unrelated relationships HI was surprisingly higher in males (58.0%) (Table 4).

4. DISCUSSION

Previous studies have reported a high rate of consanguinity in the young age group due to certain social and financial benefits [22,25]. Our study sample was divided into three age groups: 1) 4 to 8 years; 2) 8 to 12 years, and 3) 12 to 15 years. In the current study sample, there were more children in the age group of 4 to 8 years. Table 1 shows that there were more females (55.1%) than males (44.9%). In the case of different parental relations, the mean number of children born was higher (5.9%) in the unrelated parental category compared to consanguineous relations thus indicating that more children are born to parents who are not blood relatives. Conversely, the mean number of children is lower (4.7%) in first cousin relations compared to other consanguinity relations. These findings regarding mean number of children born to consanguineous and non-consanguineous families are quite conflicting. Certain studies have reported high birth rates in consanguineous marriages, whereas others have reported a low birth rate in consanguineous couples (24, 25). Our data corroborates the low birth rate in consanguineous couples compared to a higher birth rate in non-consanguineous couples; this is confirmative with the previous studies [4,5,14, 16,26-27].

We obtained a high level (14.6%) of HI in close parental relations (F = 0.0625) compared to non-consanguineous relations (F=0.00). In first cousin relationships, the severe type of HI was more prevalent (64.2%). In second cousin relationships, the moderate type of HI was more prevalent (63.0%), and in third cousin relationships, the mild type of HI was more prevalent (40.9%). Our data strongly supports the close association of HI with consanguinity that is consistent with previous reported studies [4,5,14,26-27].

Our findings support results of other studies. Al-Ghazali [28] reported a high risk of HI in children born to consanguineous families. She conducted a study in the United Arab Emirates, among children from four schools for the deafness in four different Emirates. She found that 98% and 57%, respectively, of cases of non-syndromic and syndromic deafness were attributed to autosomal recessive inheritance. Similarly,

Table 3. Consanguinity and levels of hearing impairment (HI) in the Malakand study cohort (n= 7,888)

Parental relationship	F (affected children)	Affected (M1+ M2+S)* (%)			Total affected out of total study cohort (%)
		Mild HI (%)	Moderate HI (%)	Severe HI (%)	
First cousins	0.0625	36 (9.5%)	99 (26.3%)	242 (64.2%)	377/2592 = 14.6 %
Second cousins	0.0156	15 (7.8%)	121 (63.0%)	56 (29.2%)	192/1631= 11.8 %
Third cousins	0.0039	9 (40.9%)	7 (31.8%)	6 (27.3%)	22/249= 8.8 %
Unrelated	0.00	35 (70.0%)	11 (22.0%)	4 (8.0%)	50/3416 = 1.5 %
Total		95 (14.8%)	238 (37.1%)	308 (48.1%)	641/7888= 8.1 %

**M_1=Mild, M_2=Moderate, S=Severe*

Table 4. Parental relationship and level of hearing impairment (HI) by gender

Parental relationship	Total cohort (%)	Impairment (%)	Male (%)	Female (%)
First cousins	2592 (32.8)	377 (14.5)	150 (39.8)	227 (60.2)
Second cousins	1631 (20.7)	192 (11.8)	92 (47.9)	100 (52.1)
Third cousins	249 (3.2)	22 (8.8)	09 (40.9	13 (59.1)
Unrelated	3416 (43.3	50 (1.5)	29 (58.0	21 (42.0)
Total Subjects (%)	7888 (100.0%)	641(8.1%)	280 (43.7%)	61(56.3%)

Feinmesser et al. [7] reported that the prevalence of moderate-to-severe bilateral sensorineural hearing loss among 147 Jewish children born between 1968 and 1985 in the Jerusalem area declined during the years 1977-1985, in parallel with a decline in the rate of consanguinity of their parents. Ansar et al. [32] reported a novel autosomal recessive non-syndromic HI locus (DFNB38 to 6q26-q27) in consanguineous kindred from Pakistan. Our findings are strongly supported by the work of Bener et al. [1,5,31, 33]. Bener reported a cross sectional study and worked on Qatari population. The study screened out 2800 infants for hearing loss (HL) at Hamad Medical Centre in 2003. The study tested the possible relation of hearing loss (HL) with consanguinity. Hearing loss was recorded more (60.5%) in children of consanguineous relation and was less (25.3%) in children born to non-consanguineous marriages. The study revealed a strong correlation between consanguinity and hearing loss ($r= 0.217$, $p < 0.01$).

In a study of hearing-impaired children in Lagos, Nigeria, Olusanya and Okolo reported that consanguineous marriages were one of many risk factors for permanent hearing loss (34). Regarding gender, HI was more prevalent in females (56.3%) than in males (43.7%) among children born to consanguineous families. Our findings warrant further research of HI and gender correlation. Nonetheless, at this stage, we cannot generalize our findings that HI has a definite or significant relation with gender. Indeed, for such generalization, further molecular approaches are necessary to validate our findings. No previous studies have been performed to consolidate our findings regarding HI in relation to gender. This is indeed a new concept in our work. More recently a study reported in Bangladesh [17] that the odds ratio showed that the risk of profound sensorineural hearing loss in the baby of parents of consanguineous marriages 8.173 times higher than that of non consanguineous marriages.

Prevention is the only way to reduce the incidence of genetic hearing loss. This can be achieved by using genetic counselling of high-risk individuals and their related families [1,4,5, 34]. This counselling must be based on the correct diagnosis, which is the responsibility of the physicians and audiologist. Adequate understanding is necessary by the general public and medical profession. Based on the above-mentioned evidence, consanguineous marriage is an important social health problem that should be addressed by an intensive health education campaign program. In Pakistan consanguineous marriages are common practiced, there is an urgent need for public education programs and for providing the facilities for genetic counselling and reproductive risk assessment. Overall,

increase their awareness of the potential risks of consanguineous marriages, unmarried young females and males, especially those who had a genetic disorder in their families [20], should be targeted by the educational programs. Our data demonstrates that 65% of the consanguineous marriages among the parents of deaf children are statistically different than the percentage of consanguineous marriage among Iranian population (38%). This indicates an obvious relationship between sever to profound hearing loss and consanguineous marriage.

Some caution has to be applied to the results obtained in the absence of detailed information on non-genetic risk factors for HI, because of the difficult external circumstances under which the study was conducted. Detailed information was not collected on risk factors that could be associated with HI including abnormal pregnancy, abnormal labour pain, incomplete vaccination, premature birth, genetic history of the disease, home birth versus hospital birth, or environmental factors, such as acoustic trauma or ototoxicity. Instead, the study concentrated on possible associations between HI and parental consanguinity.

5. LIMITATIONS OF THE STUDY

The present study has a few limitations. Firstly, this study was based on a cross-sectional design, not case and control. Another limitation is its modality. We could not clarify cause-effect relationship because of the cross-sectional design. Moreover, profound hearing loss was not included in the study. Genetic analysis/tests along with medically important risk factors of HI were also the limitations of the current study.

6. CONCLUSION

We found a strong positive association between parental consanguinity and HI. There is a need of several efforts, including awareness and genetic counselling programs for Hearing Impairment. Prevention is becoming highly essential to reduce the risk incidence of genetic hearing loss. Meanwhile, consanguinity should be discouraged through health education of the public concerning the adverse effect of interrelated marriage. Genetic counselling, Pre-marital and antenatal screening are to be applied whenever possible, at least for those at risk of developing genetic diseases including hearing impairment.

CONSENT

Informed consent was obtained for this study due to its nature.

ETHICAL CERTIFICATES AND APPROVAL

Ethical certificates were approved and granted by:

1. The ASRB (Advance Study Research Board) Islamia College University Peshawar, KP, Pakistan, under Reg No: PH-06-2011/ICP/Z-46;
2. The study area administration, i.e. Assistant Commissioner of Malakand, working on behalf of the Deputy Commissioner of Malakand.

Ethics committee approval was received for this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bener A, Eihakeem AAM, Abdulhadi K. Is there any association between consanguinity and hearing loss. Int J Pediatr Otorhinolaryngol. 2005;69:327-333.
2. Gorlin RJ, Toriello HB, Cohen MM. Hereditary hearing loss and its syndromes. Oxford: Oxford University Press; 1995.
3. Qing J, Zhou Y, Lai RS, Hu P, Ding Y, Wu WJ, Xiao ZA, Ho PT, Liu YY, Liu J, et al. Prevalence of mutations in gjb2, slc26a4, and mt DNA in children with severe or profound sensorineural hearing loss in south western China. Genet Test Mol Biomarkers. 2015;19:52-58.
4. Ajallouyan M, Radfar S, Nouhi S, Tavallaie SA, Amirsalari S, Yousefi J, Hasanali Fard M. Consanguinity among parents of iranian deaf children. Iran Red Crescent Med J. 2016;18(11):e22038.
   DOI: 10.5812/ircmj.22038
5. Bener A, Al-Hamaq AOAA. Abdulhadi K, Salahaldin AH, Gansan L. Interaction between hearing loss and type 2 diabetes mellitus in highly endogamous population.

Diabetes Metab Syndr. 2016 Se. pii: S1871-4021(16)30203-X.
DOI: 10.1016/j.dsx.2016.09.004

6. Bitner-Glindzicz M. Hereditary deafness and phenotyping in humans. Br Med Bull. 2002;63:73-94.
7. Feinmesser M, Tell L, Levi H. Decline in the prevalence of childhood deafness in the Jewish population of Jerusalem: Ethnic and genetic aspects. J Laryngol Oto. 1990; 104:675-677.
8. Alford RL. Nonsyndromic hereditary hearing loss. Adv Otorhinolaryngol. 2011; 70:37-42.
9. Kelsell DP, Dunlop J, Stevens HP, et al. Connexin 26 mutations in hereditary non syndromic sensorineural deafness. Nature. 1997;387:80-83.
10. Estivill X, Fortina P, Surrey S, et al. Connexin-26 mutations in sporadic and inherited sensorineural deafness. Lancet. 1998;35:394-398.
11. Kenneson A, Van Naarden, Braun K, Boyle C. GJB2 (Connexin26) variants and nonsyndromic sensorineural hearing loss: A huge review. Genet Med. 2002;4:258-274.
12. Ballana E, Ventayol M, Rabionet R, Gasparini P, Estivill X. Connexins and deafness. The Connexin-deafness Homepage; 2017.
Available:http://davinci.crg.es/deafness
13. Stevens G, Flaxman S, Brunskill E, Mascarenhas M, Mathers CD, Finucane M. Global and regional hearing impairment prevalence: An analysis of 42 studies in 29 countries. Eur. J. Public Health. 2013;23: 146–152.
14. Sajjad M, Khattak AA, Bunn JEG, Mackenzie I. Causes of childhood deafness in Pukhtoonkhwa province of Pakistan and the role of consanguinity. J Laryngol Oto. 2008;122:1057-1063.
15. Sadhra S, Jackson CA, Ryder T, Brown MJ. Noise exposure and hearing loss among student employees working in university entertainment venues. Ann. Occup. Hyg. 2002;46:455.
16. Elahi MM, Elahi F, Elahi A, Elahi SB. Paediatric hearing loss in rural Pakistan. J Otolaryngol. 1998;27:348-53.
17. Sattar MA, Sultana MT. Comparison of consanguinity between parents of hearing impaired and public school children with estimation of risk mymensingh. Med J. 2015;24(4):743-9.
18. Riazuddin S, Khan SN, Ahmed ZM, Ghosh M, Caution K, Nazli S, et al. Mutations in TRIOBP, which encodes a putative cytoskeletal-organizing protein, are associated with non syndromic recessive deafness. Am J Hum Genet. 2006;78:137-43.
19. Khan SY, Ahmed ZM, Shabbir MI, Kitajiri S, Kalsoom S, Tasneem S, et al. Mutations of the RDX gene cause non syndromic hearing loss at the DFNB24 locus. Hum Mutat. 2007;28:417-23.
20. Riazuddin S, Anwar S, Fischer M, Ahmed Z M, Khan Y, Janssen AG, Zafar AU, Scholl U, Husnain T, Belyantseva IA, Friedman PL, Riazuddin S, Friedman TB, Fahlke C. Molecular basis of DFNB73: Mutations of BSND can cause non syndromic deafness or Bartter syndrome. Am J Hum Genet. 2009;85:273-80.
21. Basit S, Lee K, Habib R, Chen L, Umme K, Santos-Cortez RL, Azeem Z, Andrade P, Ansar M, Ahmad W, Leal SM. DFNB89, a novel autosomal recessive non syndromic hearing impairment locus on chromosome 16q21-q23.2. Hum Genet. 2011;129:379-85.
22. Ahmed T, Ali SM, Aliaga A, et al. Pakistan national demographic and health survey 1990/91. Islamabad and Columbia MD, National Institute of Population Studies and Macro International; 1992.
23. Bittles AH, Grant JC, Shami SA. Consanguinity as a determinant of reproductive behaviour and mortality in Pakistan. Int J Epidemiol. 1993;22:463-467.
24. Yaqoob M, Cnattingius S, Jalil F, Zaman S, Iselius L, Gustavson KH. Risk factors for mortality in young children living under various socio-economic conditions in Lahore, Pakistan: With particular reference to inbreeding. Clin Genet. 1998;54:426-434.
25. Hussain R, Bittles AH. The prevalence and demographic characteristics of consanguineous marriages In Pakistan. J Biosoc Sc. 1998;30:261-279.
26. Sthanadar AA, Bittles AH, Zahid M. Civil unrest and the current profile of consanguineous marriage in Khyber Pakhtunkhwa Province, Pakistan. J Biosoc Sc. 2014;46:698-701.
27. Sthanadar AA, Bittles AH, Zahid M. Increasing prevalence of consanguineous marriage confirmed in Khyber

Pakhtunkhwa Province, Pakistan. J Biosoc Sc; 2015a.

DOI: 10.1017/S0021932015000164

28. Al-Ghazali LI. A genetic etiological survey of severe childhood deafness in the United Arab Emirates. J Trop Pediatr. 1998;44: 157-160.
29. Wylly HC. Tribes of Central Asia from Black Mountains to Waziristan. First published in 1912, reprinted in Pakistan. Karachi: Royal Book Company Fatima Jinnah Road. 2006;03-31.
30. Landegger LD, Psaltis D, Stankovic KM. Human audiometric thresholds do not predict specific cellular damage in the inner ear. Hearing Research. 2016;335: 83-93.
31. Bittles, AH. Consanguinity in Context. Cambridge: Cambridge University Press; 2012.
32. Ansar A, Ramzan M, Pham TL, et al. Localization of a novel autosomal recessive non-syndromic hearing impairment locus (DFNB38) to 6q26—q27 in a consanguineous kindred from Pakistan. Hum Hered. 2003;55:71-74.
33. Olusanya BO, Okolo AA. Adverse perinatal conditions in hearing-impaired children in a developing country. Paediatr Perinat Epidemiol. 2006;20:366-71.
34. Al Khabori M. Causes of severe to profound deafness in Omani paediatric population. Int J Pediatr Otorhinolaryngol. 2004;68(10):1307–13.
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