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Original Article (Pages: 10323-10334)

Hereditary Hearing Loss and Consanguinity in Turkmen Population of Iran: A Retrospective Study

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Abstract

Background: Our research focuses on different dimensions of families of Turkmen population of Iran with two or more than two affected members. A complete clinical ear test was conducted on them. It was aimed to find families with the highest chance of hereditary hearing impairment among siblings and also existence of consanguinity among their parents.

Materials and Methods

All Turkmen families with at least two hearing impaired members were screened based on prenatal and postnatal histories, family medical history, socioeconomic status as well as physical examination. For confirmation of hereditary hearing loss, a comprehensive evaluation including prenatal, perinatal and postnatal history, family medical history, pattern of inheritance, consanguinity, and three generation pedigree, the physical examination, and genetic screening by a genetic expert were used. They were referred for complete hearing evaluation including pure tone audiometry, speech recognition threshold, otoacoustic emission and auditory brainstem response.

Results

A total of 82 families with 198 hearing impaired patients were diagnosed with about 60% having two and the rest with more than two affected members. Nearly 89% (n=175) of the patients had the inherited type of hearing loss among which 95% (n=167) demonstrated non-syndromic symptoms. The rate of consanguinity among parents of the patients was about 65%.

Conclusion

This research revealed a high incidence of hereditary hearing impairment and consanguinity among Turkmen population which is in agreement with other reports from Iranian population with deaf children. In general, the rate of consanguinity in Iranian population is 38%. Therefore, it seems that consanguinity is higher in families with hearing-impaired children.

Key Words: Deafness, Consanguinity, Hereditary hearing impairment**,** Iran, Turkmen population.

*Please cite this article as: Hajilari M, Oladnabi M, Kianmehr A, Taziki MH, Zamiri Abdollahi F. Hereditary Hearing Loss and Consanguinity in Turkmen Population of Iran: A Retrospective Study. Int J Pediatr 2019; 7(11): 10323-334. DOI: **10.22038/ijp.2019.41740.3519**

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Received date: Apr.23, 2019; Accepted date: Sept. 22, 2019

1- INTRODUCTION

Hearing impairment includes a varied scope of defects which can be classified based on type (sensorineural, conductive or mixed); etiology (acquired or genetic, including syndromic or non-syndromic); age of onset (prelingual or postlingual); severity (mild, moderate, severe, and profound); audiometric profile (sloping, low frequency, mid frequency, etc); and bilateral or unilateral (1). The global prevalence of hearing impairment was estimated to be nearly 466 million worldwide, of which thirty-four million (7%) were children, including 7.5 million younger than 5 years old (2). Without timely support and intervention, hearing impairment may leave its sufferers with lifelong difficulties, ranging from language and social communication problems to complications in education and lifework.

In sensorineural hearing loss (SNHL), the main cause lies in the inner ear or its neural innervations. It is a common birth defect affecting 1-3 in every 1,000 newborns in developed communities. The prevalence was higher in developing countries such as Iran and it is estimated to be about 6 cases per 1,000 newborns (3, 4). Indeed, inheritance mostly secondary to consanguinity accounts for the majority of genetic and hereditary disorders such as hereditary hearing loss (5).

Consanguineous marriages mainly happen in the developing countries. These countries can be found in the Middle East. It has been shown that the incidence consanguineous marriage is about 20 to 70 percent (6). Accordingly, some studies have demonstrated a strong relationship between hereditary hearing loss and sharing common ancestors among siblings, cousins, or family members (7-10). It seems that consanguinity makes coupling of hearing impairment genes more likely. The purpose of this study was to investigate the clinical manifestations of hearing-impaired subjects in families with at least 2 occurrences of hearing loss among the Turkmen population of Iran. To the best of our knowledge there has not been any study conducted on this population. Occurrence of 2 cases of hearing loss in a family strengthens the likelihood of hereditary hearing loss. Hearing loss prevalence is different among different populations based on WHO report. This study can shed light on the prevalence of hereditary hearing loss in Turkmen population.

2- MATERIALS AND METHODS

2-1. Study design and population

The research is an analytical and retrospective study to gather information about hearing impaired patients based on ethnicity, number of affected members in a family, and consanguinity. Turkmen of Iran mainly live in Northeast Iran and have the population of around two million. This population is mainly located in rural and urban areas of two provinces: Golestan and North Khorasan. A total of 82 families (198 individuals) were finally identified to have at least two hearing-impaired subjects with Turkmen ethnicity. These patients were referred from auditory rehabilitation centers of Golestan and North Khorasan. The referred subjects had the age range of 6 months and older.

2-2. Methods and measuring tools

Clinical and demographic features of all the subjects were collected. For confirmation of hereditary hearing loss, a comprehensive evaluation including prenatal, perinatal and postnatal history, family medical history, pattern of inheritance, consanguinity, and three generation pedigree, the physical examination, and genetic screening by a genetic expert were used. Participants with hearing problems were referred for comprehensive hearing assessment for determining the type and degree of hearing loss. Hearing evaluation for all children

included auditory brainstem response (ABR), otoacoustic emission (OAE), tympanometry and pure tone audiometry (PTA). OAE was conducted for checking for inner ear integrity (by Madsen Capella, Otometrics). Transient evoked otoacoustic emissions (TEOAEs) was used in the screening mode with click stimuli. ABR with click stimuli was performed in addition to TEOAEs to evaluate hearing threshold and determining any possibility for auditory neuropathy (by ICS Chartr) (11). The tympanograms were classified to types A, B, and C (by Madsen Zodiac). Typanogram types are defined as follows: type A has a peak within +50 to -100 dapa pressure with static compliance of 0.3 to 1.6. Type C has a peak in -100 dapa or lower pressure. Type B is a flat graph without any peak. Only type A was considered as normal tympanic membrane, middle ear and Eustachian tube function (12). PTA was performed at 250 to 8000 HZ octave frequencies with different approaches based on children's age (by Inventis Piano audiometer).

Children under 6 months-old were assessed by behavior observation audiometry (BOA), children aged from 6 to 24 months-old were evaluated by visual reinforcement audiometry (VRA), and conditioned play audiometry (CPA) tests were used for children from 2 to 5 year-old. PTA for children above 6 years-old was performed in the same manner as adults based on ASHA guideline (2005) (11, 13). All the patients whose air conduction hearing thresholds were 20 dB or greater at any of these frequencies were classified as having a hearing loss (12, 13). Hearing loss classification was as follows: mild (26-40dB), moderate (41-55dB), moderately severe (56-70dB), severe (71-90dB), and profound deafness (91dB and above) (12). Although PTA is a gold standard for determining hearing level (13), in subjects who did not have any cooperation in PTA test, ABR was used for determining hearing threshold (applied to 17 cases who were under 3 year-old). Speech audiometry consisted of speech awareness threshold, speech recognition threshold (SRT) and Speech Discrimination Score (SDS) (by Inventis Piano). For children below one year-old and children with poor speech intelligibility and cognitive function who were unable to repeat speech materials of SRT, only SAT was performed (13). SRT was conducted with spondee materials and SDS was performed by monosyllabic materials. The procedure was according to ASHA recommendations (11). All hearing evaluations were conducted in the sound treated room. The agreement of auditory test batteries was checked for each individual subject. All cases with hearing loss regardless of type and degree were referred to an ENT physician for further evaluation and reaching final diagnosis and recommending any possible management if necessary.

2-3. Ethical consideration

An informed consent was obtained from participants and/or their guardians before entering the study. This study was approved by the Ethics Committee of Golestan University of Medical Sciences under the ethical practice code of IR.goums.REC.1395. This study was conducted from January 2016 to August 2018.

2-4. Inclusion and exclusion criteria

All families with Turkmen ethnicity who had at least two hearing impaired subjects who lived in Golestan and North Khorasan were selected (n=90). Families who were volunteers were entered the study (n=82).

2-5. Data Analyses

SPSS software version 19.0 (SPSS Inc, Chicago, IL) was used for data analysis. Association measures were extracted by Chi-squared test for all of the statistical analyses, a $P \leq 0.05$ was considered to be

statistically significant. Graph Pad Prism software (version 5.04) was also applied to draw the graphs.

3- RESULTS

3-1. Baseline Characteristics

A total of 82 families with total of 198 hearing impaired subjects were detected which were sorted based on the number of their affected members (**Figure.1**). In general, 79 (39.9%) were females and 119 (59.1%) were males **(Table.1)**. The mean age of the patients was about 19.9± 11.84 years old. Based on their residence, 125 (63.1%) patients were rural and 73 (36.9%) subjects were living in urban areas. **Figure.2** shows the type of marriage among parents of the patients who were divided into two types: consanguineous (128 [64.6%]), and non-consanguineous (70 [35.4%]). Of 128 patients who had the parents with common ancestor the degree of relatedness was also classified as first cousin (n=106), second cousin (n=16), and third cousin (n=6). Details of parental educational level and its distribution (**Figure.3**) as well as residence, number of the affected subjects in the family, and marriage type are shown in **Table.2**. Based on the etiology, as **Figure.4** shows, hearing-impaired individuals fell into two main classes of hereditary, 88.4% (175 of 198), and acquired, 11.6% (23 of 198). Here, non-syndromic hearing-impaired patients constitute the majority of hereditary cases, 95.4% (167 of 175). Considering their mode of inheritance, 153 (91.6%), and 14 (8.4%) patients had the autosomal recessive (AR), and autosomal dominant (AD) inheritance, respectively. Non-hereditary or acquired cases of deafness (11.6%) mainly had middle ear infection as their root cause.

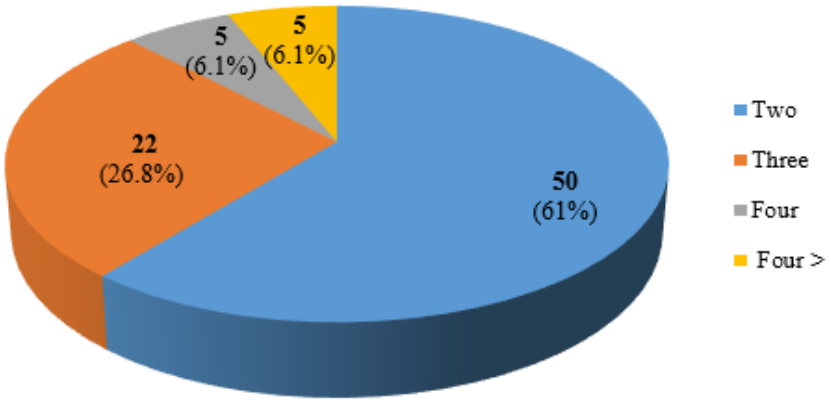

Fig.1: Number of affected cases in families.

Table-1: Baseline characteristics of participants (n=198).

Variables	Gender		Total
	Male, number	Female, number	
Age (year)			
≤ 6	11	5	16
6-12	4	12	16
12-18	19	17	36
≥18	85	45	130
Mean (SD)	19.57 (12.03)	20.23 (11.12)	19.9 (11.84)

SD: standard deviation.

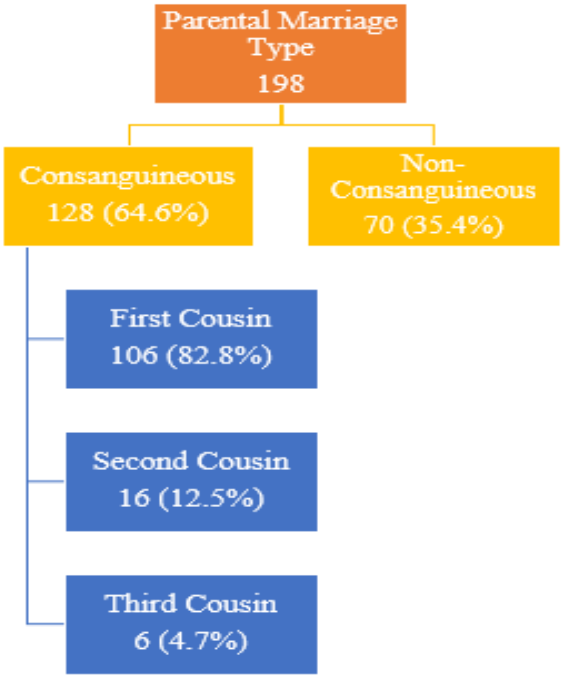

Fig.2: Marriage type and relatedness among parents. Number of people and their percentage are presented in each box.

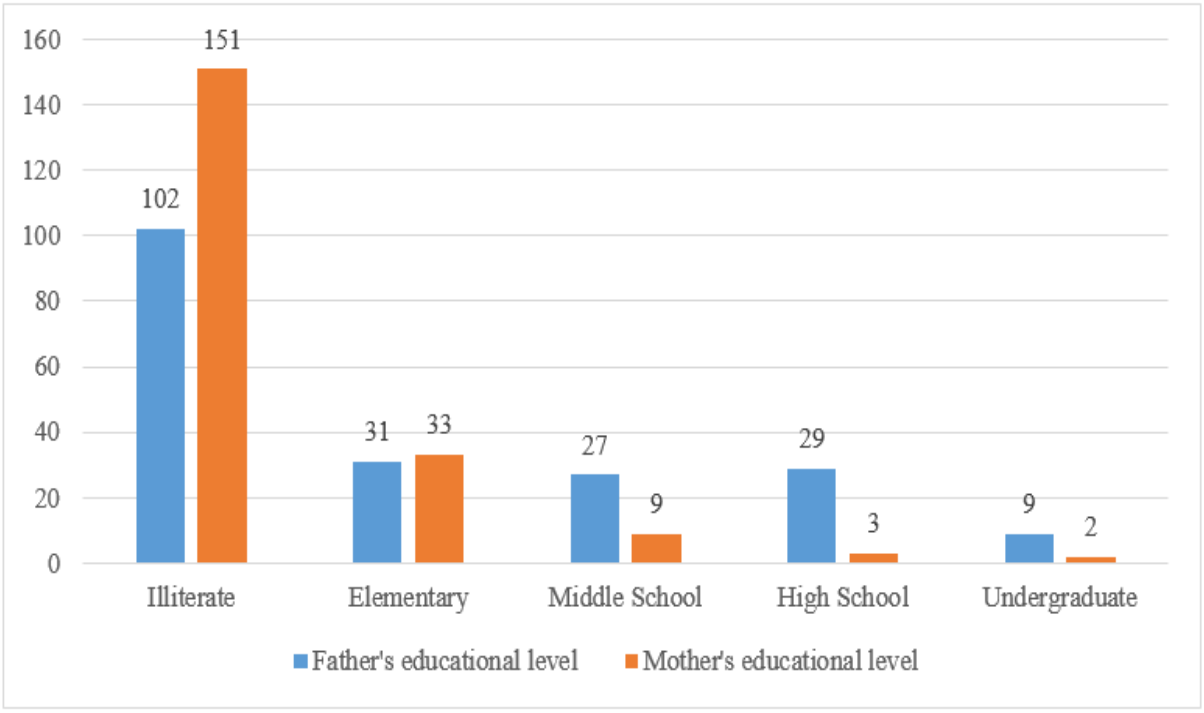

Fig.3: Parental educational levels and their distribution. Number of fathers and mothers for each item is written above each bar.

Table-2. The relationship between parental educational level and their residence, number of affected individuals in family, and marriage type. P value and phi value are presented for each item.

Parental education	Urban/Rural	Number of affected individuals in family	Marriage Type (CM/Non-CM)
Father's education (p value) (phi value)	0.001 (0.311)	0.000 (0.338)*	0.791 (0.093)
Mother's education (p value) (phi value)	0.010 (0.260)	0.000 (0.260)*	0.814 (0.089)

*Spearman's coefficient of correlation. CM: Consanguineous marriage; Non-CM: Non consanguineous marriage.

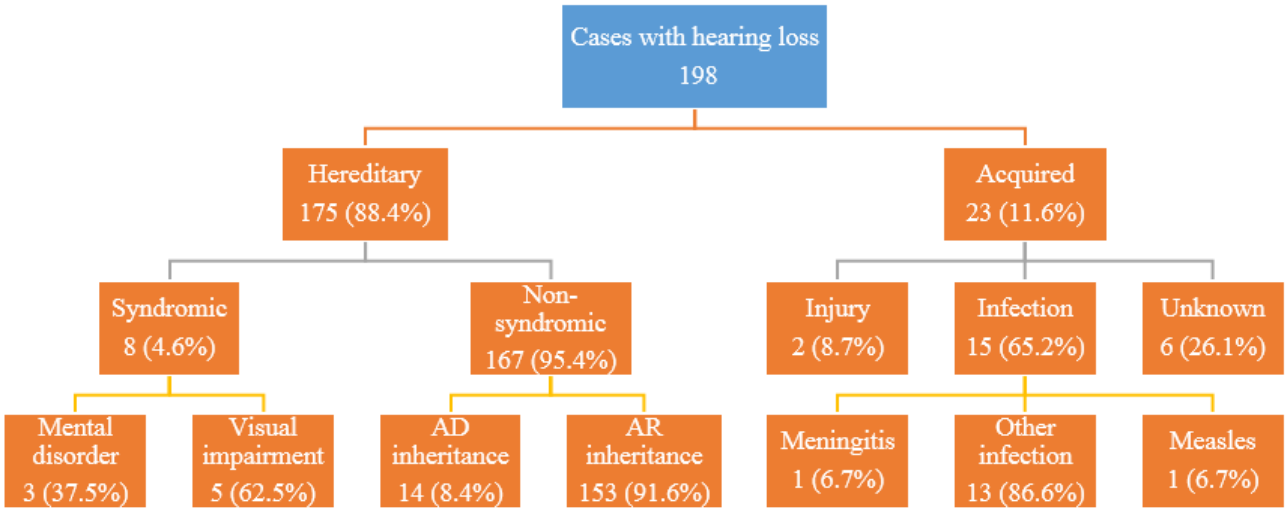

Fig.4: Overall classification of patients according to their etiology.

3-2. Clinical characteristics

According to our data, 169 (85.4%) of 198 patients were screened as prelingual hearing loss, and 29 (14.6%) of 198 patients were diagnosed as postlingual. Almost all of the patients (196 [99%] out of 198 patients) had bilateral hearing loss. While 182 (91.9%) patients suffered a stable hearing loss, the remaining 16 (8.1%) cases were diagnosed as having a progressive hearing loss. **Table.3** indicates the distribution of the type of hearing loss and its severity for each ear separately. Of the total of 396 ears, 329 (83.3%) suffered from SNHL. Conductive and mixed hearing loss affected 36 (9.2%), and 29 (7.5%) ears out of 396 ears respectively. Nearly two-thirds (66.5%) of all 396 ears had profound hearing loss or deafness. Severe and moderate to severe hearing loss affected 62 (15.6%), and 44 (11.1%) ears out of 396 ears, respectively. As shown in **Figure.5**, distribution of PTA results was written for each ear separately. Results of tympanometry were presented in **Table.4** showing nearly 84% of patients had a type A tympanogram. From the total of 198 patients who were included in the study, 17 cases who were under the age of 3 did not cooperate for PTA testing and only ABR was used for determining their hearing threshold. In general, 37 cases (36 right and 37 left ears) had the total deafness which was defined as having no measurable threshold in any frequency at PTA test. Remaining cases were tested with PTA and the results can be found in **Table.5**. Speech audiometry assessment results can be found in (**Figure.6**). Also, detailed calculations of speech audiometry tests were presented in **Table.6**.

Table-3: Severity and type of hearing loss in right and left ear. Number of ears and the percentage for each type are presented.

Characteristics, n (%)	Right Ear (n=198)	Left Ear (n=198)
Type of hearing loss		
Conductive	17 (8.7)	19 (9.6)
Sensorineural	166 (84.7)	163 (82.3)
Mixed	13 (6.6)	16 (8.1)
Severity		
Mild	5 (2.6)	4 (2)
Moderate	9 (4.6)	7 (3.5)
Moderate to severe	22 (11.2)	22 (11.1)
Severe	30 (15.3)	32 (16.2)
Profound	130 (66.3)	133 (67.2)

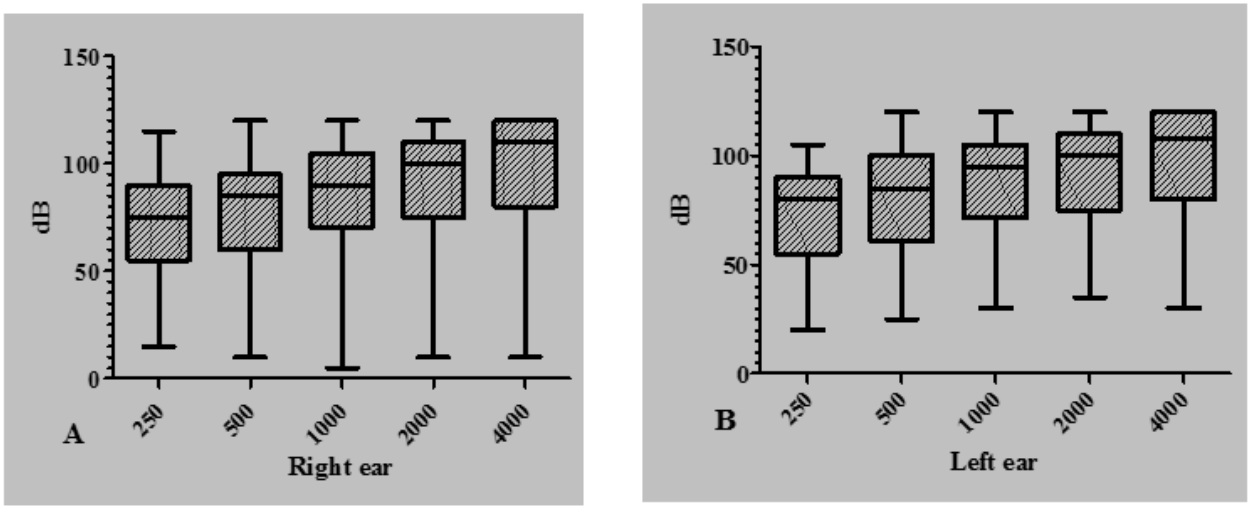

Fig.5: Box-plot comparing PTA values at frequencies of 250-4000 Hz. (A) Right ear. (B) Left ear. (Details of mean, standard deviation, and confidence intervals are presented in Table.4).

Table-4: Tympanometry evaluation. Number of ears and the percentage for each type are presented.

Type of tympanogram	Right ear (n = 198)	Left ear (n = 198)
Type A	166 (84.7)	165 (83.3)
Type B	18 (9.2)	21 (10.6)
Type C	12 (6.1)	12 (6.1)

Type of tympanograms A (normal), B (abnormal) and C (negative middle ear pressure) (11).

Table-5: Summary of observed PTA values in decibels at each frequency for right and left ear of hearing impaired subjects

Frequency Hz		Mean	Std. Deviation	Median	Mode	Minimum	Maximum	95% CI
250	Right	71.52	22.39	75	85	15	115	(67.84, 75.19)
	Left	73.93	20.56	80	85	20	105	(70.54, 77.32)
500	Right	78.40	23.59	85	90	10	120	(74.53, 82.27)
	Left	80.69	22.41	85	90	25	120	(77, 84.38)
1000	Right	85.66	24.63	90	100	5	120	(81.62, 89.70)
	Left	88.92	22.50	95	100	30	120	(85.22, 92.63)
2000	Right	92.10	24.29	100	110	10	120	(88.12, 96.09)
	Left	94.16	21.04	100	110	35	120	(90.69, 97.62)
4000	Right	97.97	23.44	110	120	10	120	(94.12, 101.8)
	Left	99.03	20.70	107.5	120	30	120	(95.62, 102.4)

PTA: Pure tone audiometry; Hz: Hertz; CI: Confidence interval. Hearing is considered normal if an individual's thresholds are within 15 dB of normal thresholds (11).

Table-6: Summary of detailed measurements of different speech tests in right and left ear in decibels.

Speech tests		Mean	Std. Deviation	Median	Mode	Minimum	Maximum	95% CI
SAT	Right	86.36	12.38	90	90	45	110	(83.13, 89.58)
	Left	89.57	11.10	90	90	50	110	(86.73, 92.42)
SRT	Right	66.14	20.05	65	60	15	110	(61.21, 71.07)
	Left	69.57	17.35	70	55*	30	105	(65.09, 74.05)
MCL	Right	86.46	16.02	90	90	45	110	(81.41, 91.52)
	Left	90.50	12.70	90	85*	60	115	(86.44, 94.56)
UCL	Right	109.2	2.774	110	110	100	110	(107.6, 110.9)
	Left	108.2	4.045	110	110	100	110	(105.5, 110.9)
SDS**	Right	81.52	21.64	89	92	20	100	(74.78, 88.27)
	Left	80.33	21.42	88	92	20	100	(73.09, 87.58)

*Multiple scores exist. The smallest value is shown. **Values in %. CI: Confidence interval; SRT: speech recognition threshold; SDS: Speech Discrimination Score; MCL: Most comfortable loudness level; UCL: uncomfortable loudness level SAT, Speech Awareness Threshold. Individuals with Normal hearing SAT & SRT ≤ 15dB, MCL (30-35 dB), UCL (90-120 dB), SDS 80-90% (11, 13).

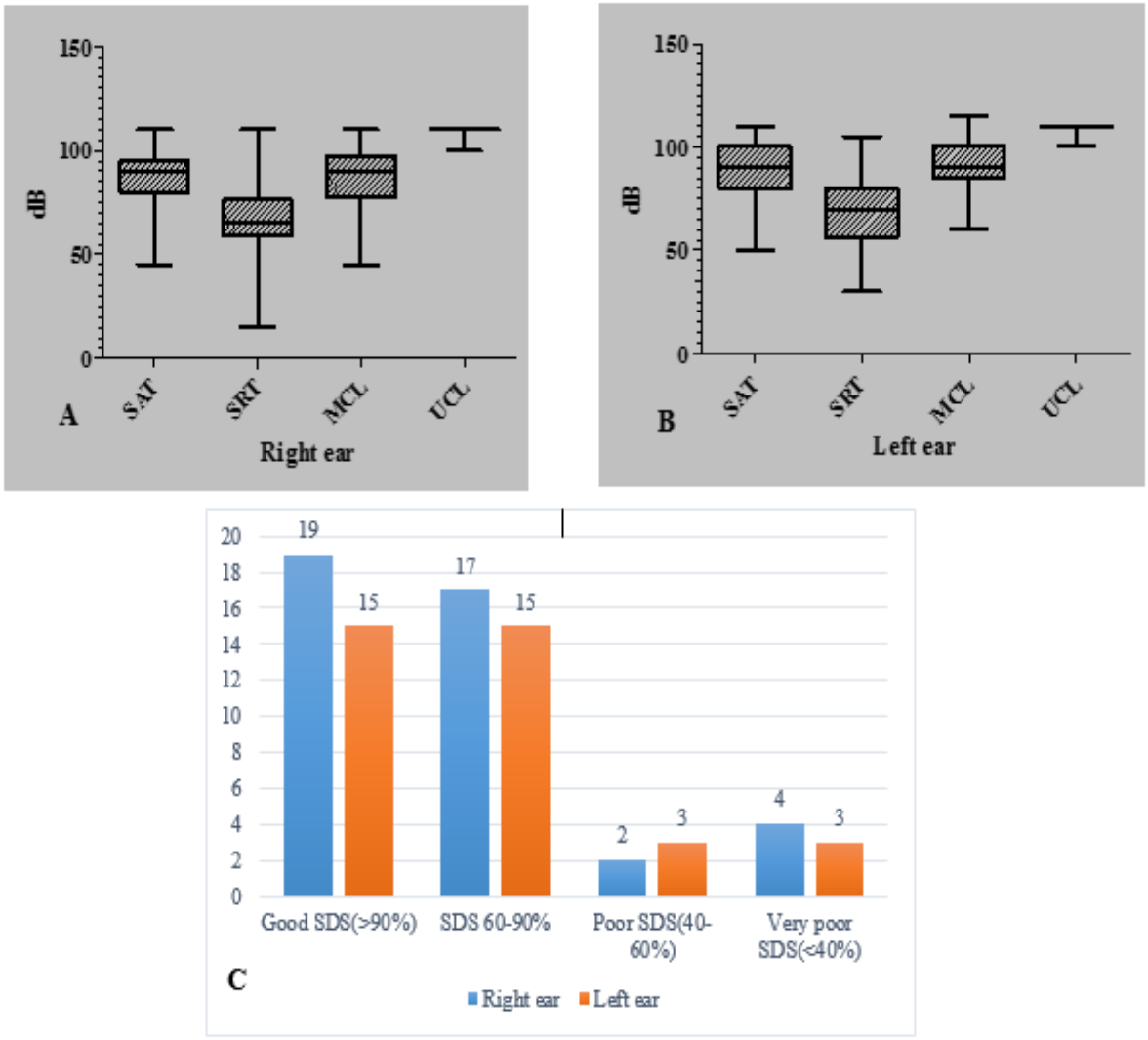

Fig.6: Types of speech audiometry tests and their measured ranges in patients with defective speech (in decibels). (A) Right ear. (B) Left ear. (Details of mean, standard deviation, and confidence intervals are presented in Table.5) (C) Speech discrimination scores and their distribution.

4- DISCUSSION

The purpose of this study was to investigate the clinical manifestations of hearing-impaired subjects in families with at least 2 occurrences of hearing loss among the Turkmen population of Iran. Nearly 89% of the patients had the inherited type of hearing loss among which 95% demonstrated non-syndromic symptoms. The rate of consanguinity among parents of the patients was about 65%. For hundreds of years, consanguineous marriage has been the preferred form of marriage in some traditional cultures like those of North Africa, West, Central and South Asia as well as Latin America. Its rate shows a variation among different populations according to their religion, ethnicity, culture, and geography. Its even more preferred among Muslim societies (14, 15). Based on the type of diseases, it seems consanguineous marriage is a predisposing factor which brings about a noticeable difference in prevalence of adulthood diseases compared to non-consanguineous marriage. Bener and Mohammad

conducted their study in a defined period and showed that the incidence of different diseases such as cancer, diabetes, hypertension, coronary heart diseases, etc. which may appear later in life, is higher among siblings of families whose parents are close relatives (16). In general, about 38% of population in Iran prefers consanguineous marriage of their close relatives. This study showed that Turkmen population has about 65% consanguineous marriage (Figure.2). The present study showed that the rate of first-cousin marriages was about 83% which is significantly higher compared to other studies conducted on Iranian population (17-19). We found that, as expected, around 92% of our patients had the autosomal recessive mode of inheritance for hearing impairment.

Another significant result of this study is the high prevalence of hereditary hearing loss (88%) which is mainly attributable to widespread consanguinity among Turkmen ethnicity in the Iranian population (Figure.4). This is in line with several similar studies on other populations with Middle East origin (15, 20-23). Bergstrom et al., reported that the risk of hearing impairment among the children of deaf parents without consanguinity is low because its hardly likely that both parents be affected by the same genetic deafness. On the other hand, deaf parents with consanguinity had the significant risk of having hearing-impaired children since the parents are more likely to be homozygous and capable of passing the trait to their offspring (24, 25).

Furthermore, the impact of consanguinity on the development of hearing impairment is highly dependent on the closeness of the consanguineous parents. A marriage between first cousins poses a greater risk, whereas a distant consanguinity has comparatively lower risk of producing defective offspring, which is also supported by our findings. Furthermore, there was a relationship between illiteracy and low educational level of parents and the prevalence of hearing impairment (Figure.3). Several epidemiological studies have also shown that consanguinity poses a significant health burden in society, especially in developing countries in which religious and socioeconomic status favor these kinds of marriages (26).

4-1. Study Limitations

There are some limitations and drawbacks in our study which confined our sample population. First, we had to exclude Turkmen families with just one member who had impaired hearing; the reason behind this exclusion was to eradicate any kind of probable environmental factor which may have caused hearing problem in our sample population. Second, genetic testing for detecting common mutations such as gap junction protein beta 2 (GJB2), which is our next project, can be the next step for other researches based on our present study. Also, we should add families that we missed due to their unwillingness to participate or the ones who refused to refer to health care centers for their hearing problems.

5- CONCLUSION

The present study illustrates the high prevalence of hereditary hearing impairment (89%), and consanguineous marriage (65%) among the population studied. Thus, it is of considerable importance to reconsider this issue in policy-making and take preventive steps such as public health education, genetic counseling, and training indigenous medical staff or health care providers, especially for remote and deprived areas of the country. Future works should attempt to study other hereditary diseases focusing on ethnic background and degree of consanguinity which might offer further insight give into the findings and significantly assist in prevention of hereditary conditions.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

We would like to acknowledge the Congenital Malformations Research Center, Research and Technology Department of Golestan University of Medical Sciences, Gorgan, Iran for funding this research project under the approval code of 950616118.

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