Indian J Otolaryngol Head Neck Surg
(Jan–Mar 2014) 66(1):1–3; DOI 10.1007/s12070-014-0711-9

EDITORIAL

Preimplantation Genetic Diagnosis: Its Role in Prevention of Deafness

M. K. Taneja

Received: 8 February 2014 / Accepted: 10 February 2014 / Published online: 20 February 2014

Abstract Deafness is a global problem. In India deafness ranges from 4 % in urban to 11 % in rural and slum areas, out of which 50 % is conductive hearing loss hence curable. Genetic transmission accounts for 50 % of the cases of congenital deafness, and of these, around 30 % are syndromic and 70 % are non-syndromic. Genetic counseling is going to make aware the parents of all appropriate treatments. Preimplantation genetic diagnosis can help to have a baby free from genetic deafness. Procedure is almost safe, harmless, non-invasive and ethically acceptable. While Amniocentesis is a non-invasive method, prenatal genetic testing through Chorionic villous sampling is invasive. The connexin 26 (CX26W 24X) mutations are the most common cause of non-syndromic hearing loss and easy to identify by polymerase chain reaction. There is always co-morbidity after cochlear implantation and the person remains handicapped while baby after PGD shall be having healthy normal life and person prone to environmental factors may be counseled and guided to prevent deafness in next generation. Public must be made aware of noise pollution, tobacco toxicity and consanguinity. The Obstetrician and Pediatrician apart from ENT surgeon should be involved to prevent antenatal or neonatal deafness.

Keywords Sensorineural deafness · Preimplantation · Genetic diagnosis · National deafness programme

Hearing loss is the most common sensory impairment known to man. On an average 6.3 % of the Indian population suffers from hearing loss which ranges from 4 % in urban to 11 % in rural and slum areas. For screening, preventing, counseling and curing deafness, it can be divided into two groups—conductive and sensorineural deafness. Conductive hearing loss is a mechanical defect in sound conduction from pinna through the external auditory canal, tympanic membrane, middle ear up to the annular ligament at stapedeal foot plate (Otosclerosis) [1].

Sensorineural hearing loss is most commonly due to the involvement of sensory hair cells of the cochlea or sometimes of the auditory nerve or processing centre in the brain. About 50 % of the patients with sensorineural deafness are congenitally deaf. Genetic transmission accounts for 50 % of the cases of congenital (hereditary) deafness–most due to single gene mutations—and at least 90 % are inherited as Autosomal recessive traits. Of these, around 30 % are syndromic and 70 % are non-syndromic. The syndromic or non-syndromic hereditary deafness are due to faulty genes or faulty interaction of genes. There are over 400 syndromes that have been associated with hearing loss e.g. Alport, Usher, Pendred, Waardenburg, Treacher Collins etc. [2].

To understand the basics, one has to recapitulate that every cell of the body contains a complete set of genes (genome). There are about 30,000 genes and having two copies of each contained inside the chromosome. There are 23 pairs of chromosomes out of which 22 pairs are same in male and female known as autosomes while 23rd pair i.e. sex chromosomes (X or Y) is different in male and female.

The alteration of genes is known as mutation resulting into genetic disease. There are four ways by which gene can affect:

Autosomal recessive In majority of cases there is a second normal copy of altered gene which can come up and the altered gene remains as recessive but if the person gets

M. K. Taneja (✉)
E-982 C.R. Park, New Delhi, India
e-mail: ijo_editor@rediffmail.com

second altered gene, the end result will be deafness. If there is only one altered copy, person will be a carrier. If both parents have altered recessive gene, there is one in four chances that their offspring will have the deafness; two in four chances that their offspring will be a carrier and in 25 % cases child will be normal.

Autosomal dominant If altered copy of gene is dominant, it can lead to deafness in spite of the other copy of gene is functioning normally and out of such genes some may be resulting in late onset deafness and in these cases it is essential to take all precautions viz avoiding smoking, tobacco chewing and noise trauma. If one of the parents carries a dominant altered gene, there is a 50 % chance of the children will inherit the disease.

X linked inheritance When altered gene is located on X chromosome in a women and if the second copy gene is normal she will be a carrier but in man because of having only one X chromosome child will be suffering from deafness hence X linked recessive condition affects more often to male and usually result in more profound deafness but if the faulty gene on X chromosome is dominant then disease may prevail in both male and female children. In about 1 % non-syndromic cases, genetic deafness is due to faulty genes on X chromosome.

Mitochondrial inheritance Mitochondria are like power-house. Mitochondria are ubiquitous in the cells of the inner ear. Mitochondrial genes are transferred to offspring from the mother and not the father. These genes include various ribosomal, transporter, and messenger RNAs of the mitochondria. If there is an A-to-G mutation at position 1,555 in the 12s r-RNA gene called MTRNR1, patients develop with susceptibility to Ototoxicity when exposed to therapeutic levels of aminoglycosides [3]. Deletions in mitochondrial genes have been implicated in Presbycusis [4].

The genetic deafness depends on the location of the faulty gene that is located on a chromosome, in the nucleus of the cell or on the mitochondrial DNA and also on whether one or both the copies of the gene are faulty (mutation).

The genetic counseling is going to help the family by clarifying whether the origin of deafness is due to genetic factor or environmental factor. On average, if a couple with normal audition has had a deaf child due to any cause, they have close to a 16 % chance of having another child with a similar condition. The genetic counselor should inform the parents of all appropriate treatments. In United States now one percent of the babies are born with IVF and all over the world IVF centers are providing facility of pre-implantation genetic diagnosis.

Gene mapping began to be applied to familial deafness in the late 1980s, resulting in the first definitive information regarding the physical site and nature of the mutations affecting the inner ear.

Pre-implantation genetic diagnosis (PGD) was first reported in 1990 [5]. Pre-implantation genetic diagnosis is the genetic testing of the embryos procured through invitro fertilization by cell biopsy genetic analysis. The test may also include chromosomal analysis or DNA analysis to detect specific gene mutation [6]. PGD was initially developed to have a baby free of genetic disease. In this procedure only one cell is removed. Procedure is almost safe, harmless, non invasive and ethically acceptable. Though data are incomplete on long term health effect of IVF babies [7, 8] but 5,000 PGD cycles have been performed and the incidence of abnormalities is equivalent to the general population [9, 10].

More than one hundred genes are available which are associated with genetic deafness. Powerful genetic testing tools known as Microarrays permit multiple gene tests to be performed at one time [11]. The gold standard for molecular PGD analysis is the use of linked polymorphic markers in combination with mutation specific analysis [12]. Myosin VIIa was the first protein implicated in genetic deafness as it was first seen in shaker mice (sh1). Afterwards, its human ortholog MYO7A was found implicated in Usher syndrome type 1B. One must know the longer the gene as MYO15, the more it is difficult and expensive to develop and perform the genetic test.

Connexin is by far the most studied genetic mutations in otologic research. This protein was only recently discovered (1997) and appears to contribute to intercellular gap junctions [13]. Connexin 26 gene also known as CX26, DFNA3, DFNB1 or GJB2, is a protein that forms channels to regulate the passage of potassium ions in and out of the cells of the cochlea. This is the gene accounting for more than 50 % non-syndromic recessive deafness [14]. CJB2 is the only gene routinely tested for in the initial work-up of hearing impairment. A study conducted by Nayyar et al. [15] established the role of PCR RFLP as a cheap and reproducible method for the analysis of CX26W 24X gene mutation, which has been observed as most common (95 %) [16].

For quite some time genetic centers were performing genetic testing through prenatal genetic testing, amniocentesis and chorionic villous sampling but the final outcome is not very certain. One may predict about the deafness but termination of pregnancy (MTP) is a difficult, social and ethical issue while discarding a non-implanted embryo is not that problematic, and as per federal regulations embryos are not considered human subject [17].

Fluorescent in situ hybridization (FISH), polymerase chain reaction and haplotyping are the most commonly used technologies. FISH is used for the detection of chromosomal abnormalities and PGD for monogenic disorders. Pre-implantation haplotyping is the latest (developed in

2006) technology and uses DNA fingerprinting rather than actual genetic signature (such as point mutations) [18].

There is always co-morbidity after cochlear implantation and the child/person remains handicapped. The cost of each cochlear implant is from 5 to 10 lakh rupees plus lifelong rehabilitation. The success rate of majority of IVF centre is around 25–35 % [19]. Even after PGD and implantation the average cost of each IVF cycle is around half of a lakh rupee which can be further reduced by 50 % if the drugs are purchased in bulk on advance payment by Government directly from Pharma companies. Thus we shall be having a normal healthy hearing child. Hence in time to come we have to screen the families of the genetically affected deaf person, mainly autosomal dominant for IVF and those prone to environmental factors must be counseled to prevent deafness in next generation.

There are still many genes for which genetic testing is not available hence test result will be negative. With increase in health infrastructure deafness of infective and/or environmental origin is decreasing while that due to hereditary causes will persist. Over viewing benefits of PGD, I conclude that the National Deafness Programme should be divided into screening, preventing and curing conductive hearing loss along with identification of genetic deafness and counseling of parents to achieve reduced number of sensorineural deafness. At last Public must be made aware of side effects of noise pollution, tobacco chewing and consanguinity. As in India consanguineous marriages are still common which lead to further increased chances of expression of autosomal recessive causes, leading to congenital deafness. Orientation courses for Obstetrician and Pediatrician are a must to screen, prevent and treat antenatal and neonatal deafness and sooner or later gene therapy Behavioral enforcement eudiometry should be a regular part of OPD examination in all infants and BERA, ASSR all sophisticated tests should be reserved for selected or doubtful cases, a future hope, may come to treat the deafness itself [20].

References

1. Taneja MK, Taneja Vivek (2012) Role of ENT Surgeon in National Deafness Program for Prevention and control of Deafness. Ind J Otol 18(3):119–121
2. del Castillo FJ, Rodriguez-Ballesteros M, Martin Y, Arellano B, Gallo-Teran J, Morales-Angulo C et al (2003) Heteroplasmy for the 1555A → G mutation in the mitochondrial 12s rRNA gene in six Spanish families with non-syndromic hearing loss. J Med Genet 40:632–636
3. Cryns K, Van Camp G (2004) Deafness genes and their diagnostic applications. Audiol Neurootol 9:2–22
4. Taneja MK (2012) Preimplantation genetic diagnosis and deafness. Indian J Otolaryngol Head Neck Surg 64(2):103–105
5. Baruch S (2005) Genetic testing of embryos: a critical need for data. Reprod Biomed Online 11:667
6. Kakourou G, Dhanjal S, Daphnis D, Doshi A, Nuttall S, Gotts S (2007) Preimplantation genetic diagnosis for myotonic dystrophy type 1: detection of crossover between the gene and the linked marker APOC2. Prenat Diagn 27:111–116
7. Nayot D (2009) Severe ovarian hyperstimulation syndrome. In: The textbook of assisted reproductive techniques, supra note 23, pp 645–54; Orvieto R, Ben-Rafael Z (2009) Bleeding, severe pelvic infection, and ectopic pregnancy. In: The textbook of assisted reproductive techniques, supra note 23, pp 655–62
8. President's Council on Bioethics, Reproduction and responsibility (2004) The regulation of new biotechnologies, pp 94–5. http://www.bioethics.gov/reports/reproductionandresponsibility/chapter3.html
9. Patki A (2010) Preimplantation genetic diagnosis. Advanced infertility management. FOGSI Focus, pp 146–55
10. International Working Group on Preimplantation Genetics, International Congress of Human Genetics (2001) Preimplantation genetic diagnosis: experience of three thousand cycles. Report of the 11th annual meeting of International Working Group on Preimplantation Genetics, in association with 10th International Congress of Human Genetics, Vienna, May 2001
11. Baruch S (2008) Preimplantation genetic diagnosis and parental preferences: beyond deadly disease. Houst J Health Law Policy 245–68. ISSN 2/17/2009
12. Verlinsky Y, Cohen J, Munne S, Gainaroi L, Simpson JL, Ferraretti AP et al (2004) Over a decade of experience with preimplantation genetic diagnosis. Fertil Steril 82:302–303
13. Naz S, Giguere CM, Kohrman DC, Mitchem KL, Riazuddin S, Morell RJ et al (2002) Mutations in a novel gene, TMIE, are associated with hearing loss linked to the DFNB6 locus. Am J Hum Genet 71:632–636
14. Rabionet R, Gasparini P, Estivill X (2000) Molecular genetics of hearing impairment due to mutations in gap junction genes encoding beta connexins. Hum Mutat 16:190–202
15. Nayyar SS, Mukherjee S, Moorchung N, James E, Venkatesh MD, Sukthankar PS et al (2011) Connexin 26 mutations in congenital SNHL in Indian population. Indian J Otol 17:154–157
16. Ram Shankar M, Girirajan S, Dagan O, Ravi Shankar HM, Jalvi R, Ranghasayee R et al (2003) Contribution of connexin 26 (GJB2) mutations and founder effect to non-syndromic hearing loss in India. J Med Genet 40:e68
17. Office for Human Research Protection Guide for investors and Institutional review boards regarding research involving Human Embryonic stem cell germ and stem cell-derived test articles (19 Mar 2002)
18. Renwick PJ, Trussler J (2006) Proof of prinviple and first cases using preimplantation genetic haplotyping—a paradigm shift for embryo diagnosis. Reprod Biomed Online 13(1):110–119
19. Altarescu G, Eldar-Geva T, Brooks B, Zylber-Haran E, Varshaver I, Margalioth EJ, Levy-Lahad E, Renbaum P (2009) Preimplantation genetic diagnosis (PGD) for nonsyndromic deafness by polar body and blastomere biopsy. J Assist Reprod Genet 26(7):391–397. doi:10.1007/s10815-009-9335-5
20. Taneja MK (2012) National deafness program and behavioral enforcement of audiometery. Ind J otol 18(1):1–2