A Study of Effect of Consanguinity on Cochlear Morphology in Patients with Congenital Bilateral Profound Sensorineural Hearing Loss

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Abstract Consanguinity has been considered as one of the risk factors predisposing to the development of congenital hearing loss. Effect of consanguinity on cochlear morphology has been subject of speculation, though many studies have provided insight into functional aspect of cochlea. This study was conducted to know the effect of consanguinity on cochlear morphology, if any. A prospective, observational study, including prelingually deaf children with bilateral profound sensorineural hearing loss who are registered as candidates for cochlear implantation at a tertiary care centre, was conducted. Seven children born out of consanguineous marriages and having bilateral congenital sensorineural hearing loss were imaged for their inner ears by MRI and various cochlear measurements were compared with that of seven control children born out of non-consanguineous marriages and who had congenital bilateral sensorineural hearing deafness. No statistically significant differences were noticed in the measurements of mean cochlear length, cross sectional diameter of cochlea at apex, middle turn and at basal turns; between children born of consanguineous and non-consanguineous marriages. Study revealed normal cochlear morphology in all the children born out of consanguineous

marriages. Consanguinity, as a risk factor for development of sensorineural hearing loss, may not result in gross structural anomaly of cochlea. The genetic testing of these patients need not be extensive and can be limited to selective screening of genes responsible for functioning of cochlea rather than its anatomical development.

Keywords Consanguinity · Bilateral profound sensorineural hearing loss · Cochlear morphology

Introduction

Hearing loss is a common human sensory defect. The incidence of congenital hearing impairment is at least 1 child in every 1000 born. Consanguinity has been considered as one of the risk factors predisposing to the development of congenital hearing loss. There are various studies attributing the cause for hearing loss to defect at the molecular level leading to cochlear dysfunction. However there is lack of literature which studied impact of consanguinity on the gross structural morphology of cochlea attributable to hearing loss in these group of patients. Hence a study was conducted with the aim to detect any association between consanguinity and cochlear dysmorphogenesis.

Aim of Study

To study effect of consanguinity on cochlear morphology in patients with bilateral profound hearing loss by measuring of membranous cochlear length, cross sectional diameter of cochlea at apex, mid segment and at the base, by MRI of cochlea using T2 SPACE-3D sequence.

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Materials and Methods

A prospective, observational study is conducted in a tertiary care hospital. Prelingually deaf children with bilateral profound sensorineural hearing loss who are registered as candidates for cochlear implantation at this centre were included in study.

Children presented with hearing loss were evaluated before planning for cochlear implantation, which included a detailed history, well-performed physical examination, audiological evaluation and imaging of the temporal bone and brain. Specific details of the family history including a pedigree with attention to consanguinity and hearing status of first-degree relatives were obtained. Consanguinity was classified into various degrees ranging from 1 to 3. After complete evaluation children were grouped into 2 categories. Group A (cases) included children with bilateral profound sensorineural hearing loss born of consanguineous marriage and Group B (controls) included children with profound sensorineural hearing loss born of non-consanguineous marriage. Cases were studied with respect to their cochlear morphology in terms of total length of membranous cochlea, cross sectional diameter measured at three different location i.e. at the base, mid segment and at the apex, using MRI brain with CP angle, T2 SPACE-3D sequence. Observations were made with respect to these parameters between the Group A and Group B. The study aimed to detect any association of consanguinity with the cochlear morphology as well as to know impact of known genetic mutations responsible for hearing loss having any demonstrable impact on cochlear dysmorphogenesis.

Cochlea was imaged by T2-weighted sequences, from which 3D reconstructed images were taken for cochlear measurements. A Siemens Magnetom Avanto (1.5 Tesla) MR Systems was used to image the inner ear. Coronal and axial images of the inner ear were obtained by 3D reconstruction technique. The coronal view was chosen as it has increased visibility of the turns of the cochlea. Curved MPR method was used to perform virtual uncoiling of cochlear turns so as to measure the length of the membranous cochlea accurately. The length of the uncoiled cochlea was measured using digitized ruler in millimetres, from its apex to its junction to the vestibule (Figs. 1, 2, 3). In addition the maximum diameter of each of the turns of cochlea were measured.

Both the groups were compared with respect to cochlear length and cross sectional diameter of its turns using analysis of variance (Anova test).

Imaging Protocol

MRI Sequence—T2 Weighted High Resolution 3D SPACE sequence

Aquisition—Axial plane
RF coil—head coil
TR—1100 ms
TE—264 ms
Slice thickness—1 mm
Base resolution—320
Phase resolution—101%
Phase encoding direction R $\gg$ L
Voxel size— $0.6 \times 0.6 \times 1$ mm

Results

Study had 7 children in both the groups. Age range was between 2 and 9 years in Group A and 3–8 years in Group B. Mean cochlear length in Group A was 22.56 mm and that of Group B was 22.47 mm with the *p* value of 0.90 which is statistically not significant. Mean apical diameter in Group A was 1.14 mm and in Group B it was 1.13 mm with *p* value of 0.8 which is also not significant statistically. Mean midsegment diameter in Group A was 1.39 mm and in Group B it was 1.37 mm with *p* value of 0.83 which is statistically not significant. Mean basal diameter in Group A was 1.87 mm and in Group B it was 1.75 mm with *p* value of 0.37 which is statistically not significant. Cochlear measurements observed in this study are depicted in Table 1 and 2.

Discussion

Consanguineous marriages are prevalent in many parts of world more so in Indian subcontinent. It has been a socially accepted practice especially amongst Southern Indian states. Various studies have proven that children born out of these consanguineous marriages are known to develop multiple physical and psychological anomalies secondary to either genetic or non-genetic causes. Profound sensorineural hearing loss is also commonly seen deficit in these children as found in a study amongst Jewish children, conducted by Feinmesser et al. [1]. With this background, the present study was planned and conducted to detect any effect of consanguinity over the morphology of the cochlea in terms of its length and cross sectional diameters at various points and compared with that of children with bilateral profound sensorineural hearing loss born to non-consanguineously married parents. The study was also intended to correlate effect of certain genes which are known to result in cochlear dysmorphogenesis and hence by ruling out these cochlear structural anomalies one can narrow down the genetic testing to those which result in profound sensorineural hearing loss with any structural anomalies of cochlea.

Fig. 1 High resolution T2 weighted space sequence of MRI of inner ear: curved MPR reconstruction image of the membranous cochlea measuring the length

Fig. 2 High resolution T2 weighted space sequence of MRI of inner ear: coronal reformat image of the membranous cochlea measuring the width of apical turn

The mammalian cochlea is a uniquely coiled structure with diverse cell types having an intricate architecture. Various studies of mammalian cochlea especially that of mutant and knockout mice in recent years has increased our understanding of cochlear development and physiology. It is ethically not possible to knock-out particular genes and study their effect in humans. Due to genomic conservation

Fig. 3 High resolution T2 weighted space sequence of MRI of inner ear: volume rendered MIP image of the membranous cochlea

between mice and humans, the mutated genes can be positioned and identified in the mouse and the homologous human genes can be identified and sequenced for possible mutations. Secondly, the mouse cochlea is structurally very similar to humans in its organization and specialization. So one can retrospectively study the genetic basis of dysmorphic cochlea in terms of detecting those specific genes which result in particular structural defect and hence narrow the list of genes to be screened.

Several genes expressed in the otic epithelium are important for the normal development of the cochlea. For example, the absence of Pax2, a paired-box transcription factor, leads to agenesis of the cochlea [2]. The development of inner ears of Eya1 knockout mice arrest at the otic vesicle stage [3]. In these mice, the endolymphatic duct is either absent or malformed, and the VIIIth ganglion fails to form. Both Otx1 and Otx2 are expressed in the otocyst and are important for cochlear and vestibular development. In Otx1-knockout mice, the lateral canal and ampulla were missing, the cochlea was misshapen, and the utricle and saccule failed to form separate chambers [4, 5]. Inner ears of Otx1-knockout mice with one disrupted allele of Otx2 mice showed more severe defects, particularly the saccule and cochlea, which normally express Otx2. The absence of the spiral ganglion may affect proper formation of the modiolus (the bony tube that forms the central axis of the cochlea), which in turn may have a secondary effect on the final shape of the cochlea. In ngn 1-knockout mice, the modiolus is also missing and the coiling of the cochlea is tighter than is observed in wild-type mice [6]. Despite the defects in the ganglion and sensory organs of ngn 1-mutant mice, the sensory hair cells appeared normal.

Table 1 Observations in Group A (cases)

S. no.	Age (year)	Gender	Degree of consanguinity	Hearing status	Side	Cochlear length (mm)	Diameter at apex (mm)	Midsegment diameter (mm)	Diameter at base (mm)
1	5	M	2	Profound Bilateral SNHL	Rt	21.6	1.1	1.1	1.7
					Lt	22.6	1.1	1.5	2.2
2	2	F	3	Profound Bilateral SNHL	Rt	23.8	1.1	1.1	1.3
					Lt	22.7	1.0	1.0	1.3
3	5	F	2	Profound Bilateral SNHL	Rt	22.4	1.1	1.1	1.6
					Lt	21.4	1.1	1.1	1.4
4	9	F	2	Profound Bilateral SNHL	Rt	20.8	1.2	1.7	2.2
					Lt	19.7	1.1	1.5	1.9
5	3	F	2	Profound Bilateral SNHL	Rt	20.9	1.2	1.6	2.2
					Lt	23.6	1.4	1.7	2.1
6	3	M	2	Profound Bilateral SNHL	Rt	23.9	1.3	1.7	2.2
					Lt	22.8	1.2	1.5	2.1
7	3	M	2	Profound Bilateral SNHL	Rt	24.1	1	1.3	2
					Lt	25.6	1.1	1.6	2

Table 2 Observations in Group B (controls)

S. no.	Age (year)	Gender	Degree of consanguinity	Hearing status	Side	Cochlear length (mm)	Diameter at apex (mm)	Midsegment diameter (mm)	Diameter at base (mm)
1	8	M	Nil	Profound Bilateral SNHL	Rt	19	0.9	1.0	1.1
					Lt	21.8	0.8	1.1	1.5
2	3	M	Nil	Profound Bilateral SNHL	Rt	18.3	0.9	1.0	1.2
					Lt	20.9	1.1	1.1	1.2
3	4	F	Nil	Profound Bilateral SNHL	Rt	22.7	1.0	1.3	1.7
					Lt	23.9	1.3	1.4	1.6
4	3	F	Nil	Profound Bilateral SNHL	Rt	20.9	1.1	1.2	2
					Lt	21.8	1.2	1.3	1.9
5	5	M	Nil	Profound Bilateral SNHL	Rt	24.8	1	1.5	2
					Lt	25.4	1.4	1.6	2.2
6	3	M	Nil	Profound Bilateral SNHL	Rt	24.3	1.2	1.8	2.1
					Lt	23	1.3	1.7	2.1
7	7	M	Nil	Profound Bilateral SNHL	Rt	23.8	1.3	1.5	1.9
					Lt	24.1	1.3	1.7	2

In the current study, no statistically significant differences were noticed in the measurements of mean cochlear length, cross sectional diameter of cochlea at apex, mid-segment and at basal turns; between children born of consanguineous and non-consanguineous marriages. The study group showed no known gross structural anomalies of cochlea. This could possibly alleviate the need for battery of tests for screening for genes responsible for gross morphological anomalies of cochlea. So, one can limit the genetic testing to detect those genes which are responsible for functional integrity of cochlea.

Conclusion

Consanguinity, as a risk factor for development of sensorineural hearing loss, may not result in gross structural anomaly of cochlea. The genetic testing of these patients need not be extensive and can be limited to selective screening of genes responsible for functioning of cochlea rather than its anatomical development. However a larger study series with bigger sample size shall be more reliable in terms of statistical significance of the cochlear measurements and yield definitive results that can be applied in clinical practice.

Compliance with Ethical Standards

Conflict of interest None of the authors involved in this study have any conflict of interest.

Informed Consent Informed consent has been taken from the parents/guardians of all children enrolled in this study.

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