Morphology Studies of the Human Fetal Cochlea in Turner Syndrome

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Objectives: Turner syndrome (TS) is the most frequent sex chromosome abnormality, and sensorineural hearing loss is common. We aimed to determine whether there are consistent morphologic cochlear abnormalities during gestational development that could be associated with TS.

Design: The histology of nine fetal temporal bones of TS autopsied after spontaneous abortion was studied.

Results: Gross morphologic examination of the TS cochleae failed to reveal a pattern of structural abnormalities that would explain the development of sensorineural hearing loss. Mondini-like cochlear dysplasia was observed in one 13-wk-old TS fetus.

Conclusion: We could not demonstrate a consistent pattern of cochlear malformations.

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INTRODUCTION

Turner syndrome (TS) has a classic karyotype of 45,X0 and is defined as the loss of all or part of an X-chromosome. It occurs at a frequency that varies from 1:2000 to 1:5000 in live-born phenotypic females. Only one in 1000 embryos with a 45,X0 karyotype survives to term, however, accounting for approximately 15% of all spontaneous abortions (Sybert & McCauley, 2004). Females that survive with TS syndrome have a short stature, fail to enter puberty, and are infertile because of ovarian streaks and estrogen deficiency. Stenberg et al. (2001, 2002) demonstrated that estrogens are important for normal hearing, but the development of presbyacusis because of estrogen deficiency in the normal population has not been studied. Girls with TS, in which a lack of estrogens is one of the main characteristics, commonly develop early presbyacusis. They often suffer from recurrent otitis media and/or chronic otitis media, possibly related to poor middle ear ventilation and drainage because of Eustachian tube dysfunction. During childhood, TS girls frequently complain about the onset of social hearing problems resulting from conductive hearing loss secondary to otitis media (Stenberg, et al., 1998). A progressive sensorineural hearing loss (SNHL) often develops in the mid-range frequencies with a distinct dip in the 1.5- to 2-kHz frequency range at around the age of 20 (Hultcrantz, et al., 1994; Hultcrantz, 2003). Studies indicate that 58 to 66% of females with TS are affected by SNHL, with documented cases starting as early as 6 yr of age (Sculerati, et al., 1996). With advancing age, the SNHL can develop into a high-frequency hearing loss and become even more severe. It is believed that premature aging of the inner ear may be the result of an unknown genetic defect (Hultcrantz, et al., 1994). Investigation of possible morphologic abnormalities of the cochlea in patients with TS, therefore, may help to clarify the pathogenesis of SNHL in these patients. Based on morphologic evidence so far reported in the literature, SNHL is thought to be related to a defect in the outer hair cells (OHC) of the lower middle coil of the cochlea. This SNHL is more common in women with a 45,X0, or 45X/46i (Xq) karyotype and hearing deteriorates with age (Barrenas, et al., 1999). Inner ear anomalies of the Mondini type are documented in one case of TS, in which the cochlea was moderately to severely affected, exhibiting only a single basal turn (Windle-Taylor, et al., 1982).

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MATERIALS AND METHODS

Nine fetal cases of TS were routinely autopsied after spontaneous abortion and the temporal bones were removed for diagnostic reasons. The gestational ages of the fetuses ranged from 13 to 23 wk postconception. Temporal bones from four additional fetuses without genetic alterations ranging in age from 14 to 18 wk postconception were studied for comparison. The initial dissections were performed at the Department of Pathology, karyotyping was routinely performed at the Department of Genetics at the Medical University of Innsbruck. All research was performed on fetuses during routine clinical autopsies with permission from the Tyrolean government (permission number EK1:06.10.06). The cochleae were processed by the block-surface method (Fish, et al., 2001).

RESULTS

Morphologic Findings

Gross morphologic examination of a 13-wk-old TS fetus revealed bilaterally shortened, two-turn cochleae with an apical "tag" located distally and containing no organ of Corti (Fig. 1A). In the 16-wk-old TS fetus, only the left cochlea appeared slightly shortened (2.25 turns). Other gross anatomic abnormal findings observed in this 16-wk specimen included large oval windows that were rounded-out superiorly and unusually large internal acoustic canals with a facial nerve canal visible through the internal meatus. The inner ears of the 14-wk-old TS fetus appeared normal on gross examination, exhibiting cochleae with the typical 2.5 turns. On a surface view, the distribution of OHCs and inner hair cells was normal in the basal, middle, and apical turns in all seven TS preparations

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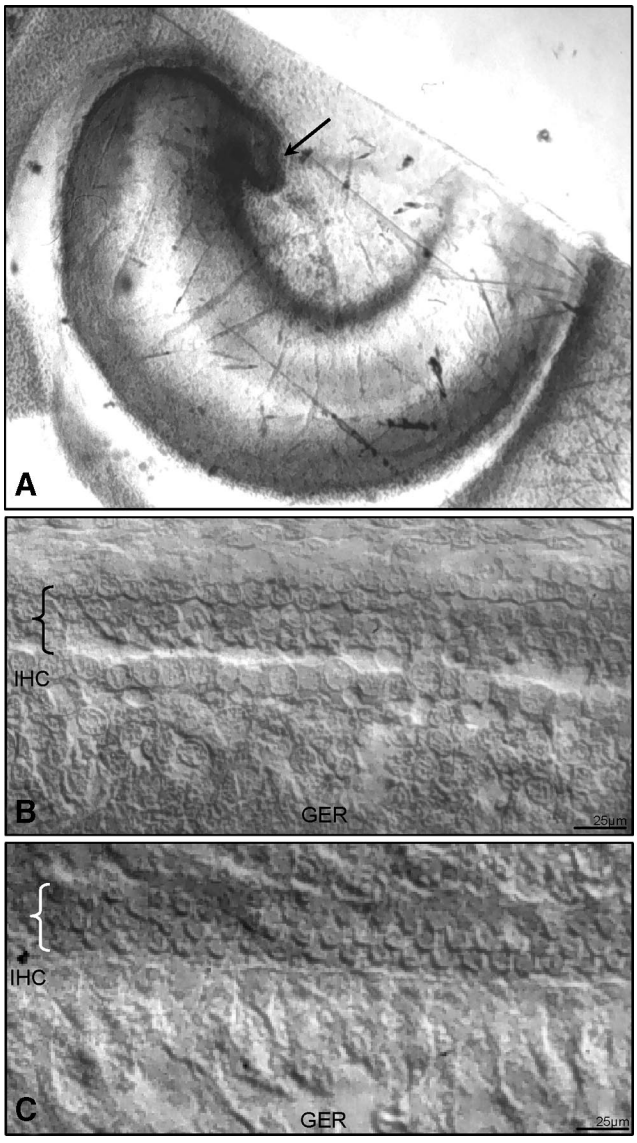

Fig. 1. A, A 63× magnified view of an apical half-turn of a 13-wk-old TS fetus with a dysplastic "tag" (arrow) at the end of a shortened cochlea with only 2 turns. B, Surface view of the middle turn of the organ of Corti in a 14-wk-old normal fetus. C, 14-wk-old TS fetus with interference contrast optics. Brackets indicate outer hair cells (OHC) in both 1B and C. IHC, inner hair cells.

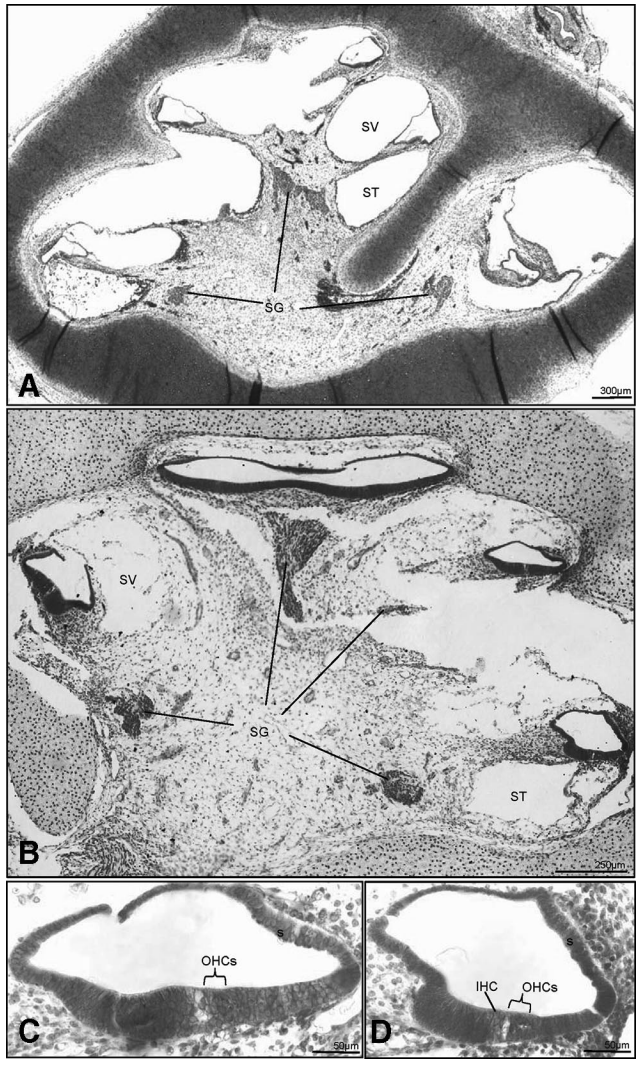

Fig. 2. A, Overview of paraffin-embedded cochleae (hematoxylin-eosin staining) from a normal 13-wk-old control fetus, (B) and a 13-wk-old TS fetus, (C) higher magnified views of the middle, (D) and basal turns. IHC, inner hair cell; OHC, outer hair cells; SG, spiral ganglion; S, stria vascularis; ST, scala tympani; SV, scala vestibuli.

(Fig. 1B). The greater epithelial ridge region appeared frayed in some TS cases, which made recognition of the inner hair cells difficult (Fig. 1C).

Paraffin-embedded sections from a normal control specimen (Fig. 2A, 14 wk old) compared with a TS specimen (Fig. 2B–D, 13 wk old) showed normal cochlear development. Light microscopic investigation of radial semi-thin sections in all cases generally revealed no signs of pathology. A 13-wk-old TS fetus showed slightly accelerated maturation with the tunnel of Corti already visible (Fig. 3D). The basal turn in two of the TS cases is shown adjacent to that of a normal 14-wk-old fetus in Figure 3. These micrographs depict nearly the same developmental stage and were evaluated according to the following criteria based on the basal turn of a normal 14-wk-old fetal cochlea: (1) the development and release of the distal part of the tectorial membrane from the greater epithelial ridge; (2) the opening of the tunnel of Corti; (3) the presence of one row of inner hair cells and at least three rows of OHCs; (4) signs of hyperplasia and membrane thickening along the greater and lesser epithelial ridges; (5) the formation of a triangular scala media as a result of cellular atrophy at its borders, forming perilymphatic spaces; and (6) formation of the outer sulcus and spiral prominence.

DISCUSSION

Several studies have investigated hearing problems among individuals with TS. Middle ear pathology leading to conductive hearing loss, SNHL of unknown etiology (Hultcrantz, et al., 1994), and associations between middle ear problems and SNHL have been described in patients with TS (Anderson, et al., 1969). Conductive hearing impairment in childhood in TS is considered to be a consequence of recurrent episodes of

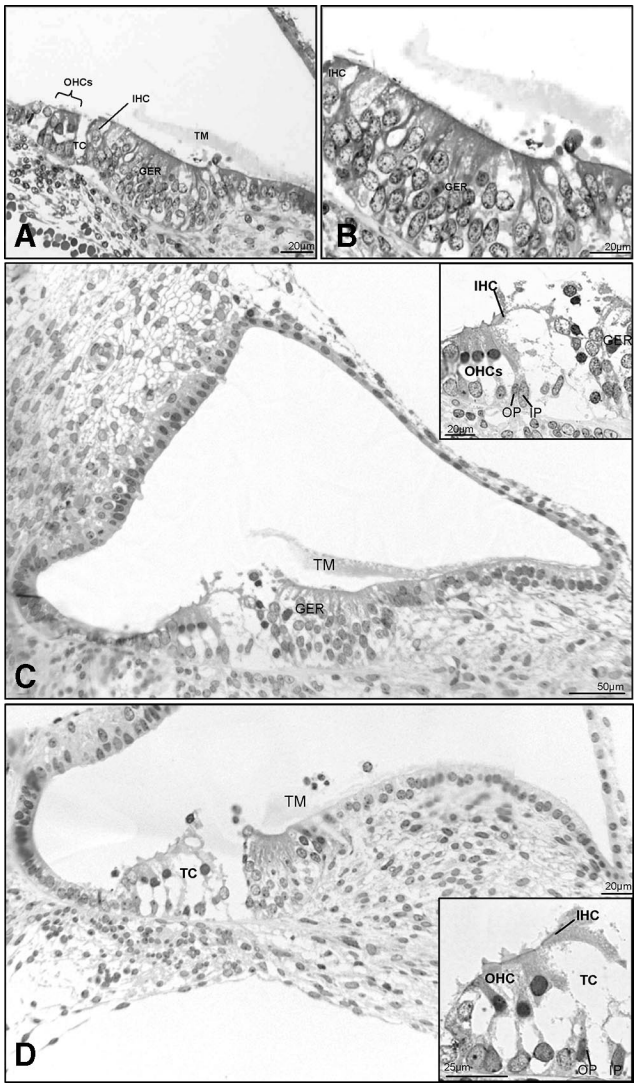

Fig. 3. A and B, The basal organ of Corti (OC) from a normal 14-wk-old fetus, (C) a 14-wk-old Turner syndrome (TS) fetus, and (D) a 13-wk-old TS fetus. Insets in C and D show a higher magnified view of the sensory epithelium of the same specimen. Sections of the OC from the normal 14-wk-old fetus are very representative of this developmental stage except for a slightly underdeveloped tunnel of Corti (TC). Inner- (IP) and outer pillar cells (OP) are still adjoined with no space between. The inner and outer hair cells (IHC/OHCs), developing tectorial membrane (TM), and normal cell proliferation can be seen in the forming greater epithelial ridge (GER). The OC of the 13-wk-old TS fetus showed advanced development of the TC and GER: the TC has opened and exhibits clear inner (IP) and outer pillar cells (OP).

acute otitis media, resulting from variations in the ear anatomy (Stenberg, et al., 1998).

SNHL in TS is correlated with both age and chromosomal deletion type, such that SNHL occurs earlier in cases with complete deletion of an entire X-chromosome (45,X0) rather than a partial deletion or mosaicism. The precise clinical features of the SNHL in TS remain unclear (Hultcrantz, et al., 1994). Audiograms recorded from patients with TS indicate that the loss occurs mainly in the 1.5- to 2-kHz region (Hultcrantz, 2003). SNHL within a higher frequency range is more common in patients with TS (Gungor, et al., 2000). In a large study including 200 female patients with TS, King et al. (2007) demonstrated a correlation between auditory phenotype and karyotype. Hearing loss was detected in approximately 100 of the females with TS.

Light microscopic evaluation of the organ of Corti from five of the TS fetuses during the 14th and 16th gestational weeks showed no significant deviations from normal development, based on reviews of the cochlear embryology by Pujol et al. (1991) and no loss of OHCs in the lower middle coil of the cochlea. Although the findings of the present study do not demonstrate a consistent pattern of unusual morphologic features of the Turner cochlea, a moderate bilateral dysplasia of the apical cochlea was observed in one case with the final half-turn existing only as a shrivelled tag (13-wk-old TS fetus). This resembled documented inner ear anomalies of the Mondini type in TS reported by Windle-Taylor et al. (1982). The abnormal findings in one 13-wk-old TS case, however, may be related with the early-onset progressive SNHL often seen in TS. Perhaps morphologic abnormalities of the cochlea in only certain subsets of TS patients cause SNHL. Long-term periodic follow-up is necessary, even after the resolution of middle ear diseases, to detect SNHL (Dhooge, et al., 2005). Histologic data from adult TS cochleae may also offer clues to a possible morphologic basis of SNHL and possible related developmental influences. In conclusion, in the present study, we did not find a consistent pattern of cochlear malformations to explain the early occurrence of SNHL in this population. A Mondini-like anomaly was observed in one 13-wk-old TS fetus. Further morphologic studies of the organ of Corti and the vestibulocochlear nerve in both fetal and adult TS are necessary to more thoroughly investigate the etiology of SNHL.

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