the presence and absence of a bony modiolus in the cochlea. According to his classification, a bony modiolus is present in IP-II, CH-III, LVAS, and a normal inner ear, while CC, IP-I, IP-III, CH-I, and CH-II have a cystic cavity without a bony modiolus.[3]

We evaluated CI outcomes by category of auditory performance (CAP) scores,[6] hearing thresholds of pure-tone sounds, infant word speech discrimination scores, and monosyllabic word speech discrimination scores at one to three years after implantation. A subject with 0-4 CAP scores could not even understand common phrases without visual language and, therefore, we defined 5-7 CAP scores as a good CI outcome and 0-4 CAP scores as a poor one.

Results

We categorized our patients based on the two criteria as described above. In this study, there was no case categorized in Group 4. Group 1, Group 2, and Group 3 consisted of 11, 7, and 6 cases, respectively. MR imaging revealed CND in all cases of Group 3.

The post-operative CAP score was equal or over five in all cases of Group 1, but did not exceed four in all of Group 3. In Group 2, the post-operative CAP score was still four in two cases even after three years of CI usage, but reached to five or six in the remaining five cases. As shown in Figure 1, using our new categorization instead of the existing classifications, we can better discriminate between a good and poor outcome.

We examined speech discrimination scores of 22 cases except for two cases of Group 3 whose response to voice was poor. The correct percentage of the closed-set infant word discrimination test was ≥ 80 in all cases of Group 1, while the score ranged from 40 to 60 in tested cases of Group 3. The correct percentage of Group 2 widely varied between cases, ranging from 55 to 100. The open-set monosyllabic word discrimination test is much more difficult than the closed-set infant word discrimination test and, therefore, only 17 of 24 patients, who were over five years old and used their CI for more than two years, underwent this examination. All tested cases of Group 1 and 3 cases of Group 2 could answer correctly in equal or over 80% of accuracy. The correct percentage of the remaining cases, including all tested cases of Group 3, was ≤ 30.

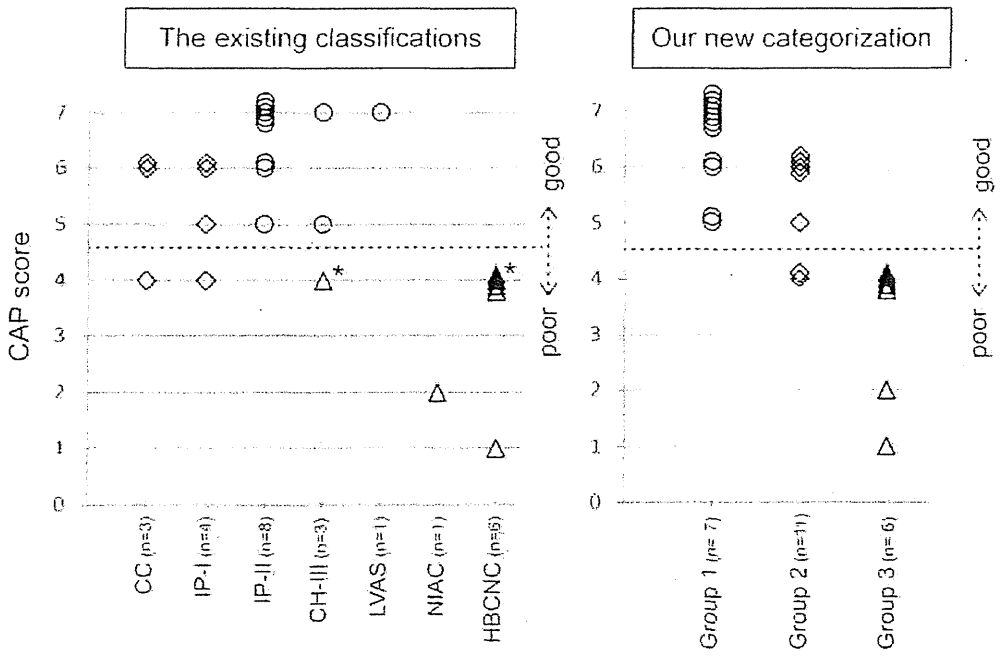

Fig. 1. A. The post-operative CAP score of each type of malformations based on the existing classifications. One case with both CH-III and HBCNC is plotted twice (*). B. The post-operative CAP score of each group of our new categorization. In both graphs, the members of Group 1, Group 2, and Group 3 are represented by a circle, diamond, and triangle, respectively.

Discussion

In this study, we established a new CT-based categorization including both the inner ear and IAC malformations. This categorization is defined by two criteria; (1) the presence or absence of a bony modiolus in the cochlea; and (2) the diameters of IAC and BCNC. We focused on these structures because the bony modiolus contains spiral ganglion cells, the major target of CI-mediated electrical stimulation, and their axons go through BCNC and IAC.

Group 1, which is defined by the presence of a bony modiolus of the cochlea with a normal IAC and BCNC, showed the best CI-aided hearing performance among three groups. The high proportion of post- or peri-lingually deaf cases might also contribute to the high CI outcomes of this group.[7] Group 2 is defined by the absence of a bony modiolus with a normal diameter of IAC. The CAP score and speech discrimination score varied widely between cases in this group, but five out of seven cases could understand common phrases without visual languages. Group 3 is defined by the presence of a bony modiolus in the cochlea with NIAC or HBCNC and their post-operative improvement of hearing performance was limited. Visual languages were necessary for them to understand common phrases even after long usage of their CI. MR imaging revealed CND in all cases of Group 3, which might be responsible for their poor outcomes.

Conclusion

Our new CT-based categorization, which was based on the presence or absence of a bony modiolus in the cochlea and the diameters of IAC and BCNC, was effective in predicting CI outcomes of children with inner ear and/or IAC malformations. The CI outcomes were the best in Group 1, followed by Group 2 and Group 3. All cases of Group 1 showed good CI outcomes and could communicate orally. On the other hand, all cases of Group 3 showed poor CI outcomes and used lip-reading or sign language to understand common phrases. The CI outcomes of Group 2 varied between cases, but many of them showed good CI-aided hearing performance.

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小さな common cavity 例の人工内耳手術

内藤 泰

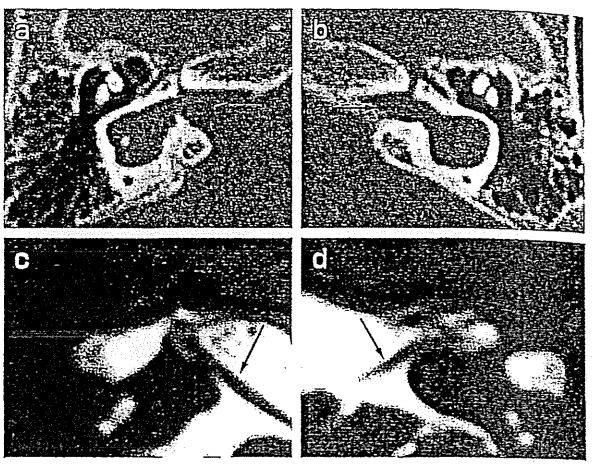
小さな common cavity 例の手術は難しい

人工内耳手術は内耳奇形例でも可能であるが，蝸牛と前庭が分離せずに1つの腔になっている common cavity 奇形では内耳形態にさまざまなバリエーションがあり，個々の症例に応じた工夫が必要である[1]．本項では，内耳奇形の人工内耳のなかでもとくに難度が高い，小さな common cavity 例の手術について述べる．

症例は女児で，言語発達の遅れにより耳鼻科を受診し両側高度難聴の診断が確定した．その後の補聴器装用で効果が得られず，当科紹介となった．2歳5か月時の所見で，聴性定常反応（ASSR）で両側無反応．乳幼児有意味聴覚統合スケール（IT-MAIS）は2点（40点満点），新版K式発達検査では，認知適応領域の発達指数（DQ）104に対して，言語社会領域の DQ が48と低い成績であった．

画像検査所見

側頭骨 CT では両側とも common cavity 奇形があり，内耳道から内耳まで軟部組織陰影が連続している（❶a, b→）．MRI では，両側で第8脳神経が明瞭に観察される（❶c, d→）が，蝸牛神経と前庭神経の分離は確認できない．内耳道と内耳腔のあいだの隔壁は MRI でも不明瞭で，内耳開窓で gusher（脳脊髄液の噴出）をきたす可能性がある．cavity は右のほうが若干大きいので，右側の手術を行う方針とした．



❶ 側頭骨の画像検査所見（a, c：右，b, d：左）

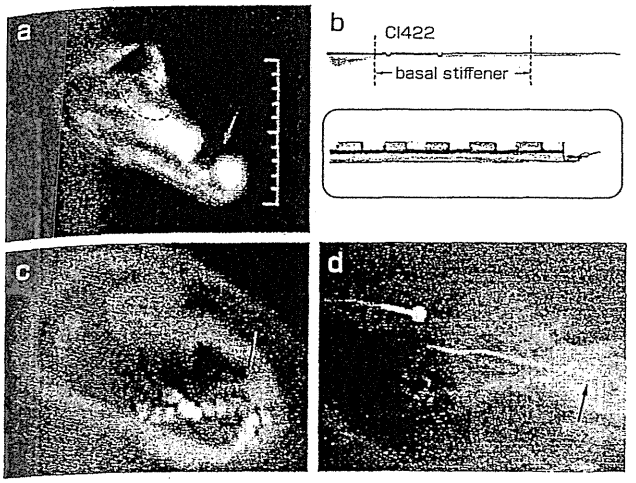
cavity の大きさを計測して電極を選択する

右内耳の三次元再構築 MR 像（❷a）をみると，cavity 前方の蝸牛相当部分の直径は3 mm 程度であり，その後方に顔面神経迷路部に該当する内腔の切れ込み（❷a→）がある．このように小さな空間に電極を敷設するには，できるだけ細い電極が有利と考え，コクレア社の CI422 電極（❷b，拡大図は電極アレイ先端部分の形状）を選択した．この電極は先端付近の直径が0.3 mm，根元が0.6 mm と細く，アレイの片側だけに電極がある half band 構造になっている．内耳奇形例で通常用いられる同社のストレート電極の先端付近の直径は0.4 mm と若干太く，また電極が全周にある full band 構造になっているので，狭い空間内では電極同士の接触によるショートの可能性もある．このため，本例では CI422 電極を選択し，通常とは逆に電極面を外にして弯曲させ，cavity 内腔壁に密着するように敷設する計画とした．

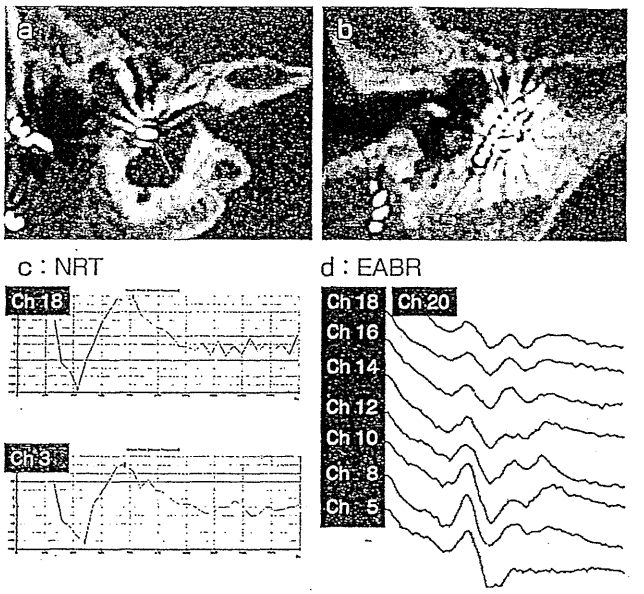
手術時の留意点

小さな common cavity では，できるだけ広い手術視野を確保し，cavity 内を明視して電極を入れないと思いどおりの位置に電極が入らない．本例では外側半規管隆起の前端付近に径3～4 mm の大きな開窓を行って内腔を観察した．gusher をきたしている所が内耳道底と考えられ，その前方がおおむね cavity の蝸牛該当部分であると推測した．

実際には cavity のどの部分に蝸牛神経が分布しているかわからないので，内腔の前端を中心にできるだけ広い範囲をカバーできるように，電極を中央で曲げて挿入し，先端の小さな空間だけでなく，その後方の cavity にも電極が触れるように工夫した．この電極の根元寄りには電極を若干固くする basal stiffener という構造がある（❷b）



❷ 術後検査所見
a：三次元再構築 MR 像，b：使用した電極，c：術後の傍冠状断平均 CT 画像，d：術後の単純 X 線像



❸ 術中・後の検査所見
a：cavity への入口部（矢印）の CT 像，b：cavity 内の電極，c：NRT 波形，d：EABR 波形

が，この適度の硬さが狭い空間内で電極を操作するのに役立った．なお，gusher は筋肉や筋膜片を cavity 内に充填することで制御できた．

手術結果

術後の CT（❷c，傍冠状断平均 CT 画像）では，計画どおり，cavity 前端付近を中心に内腔壁に密着して電極アレイを敷設できていることが確認された（❷c→）．アレイの先端と根元は前端の小さな空間から後ろにはみ出て伸びている．単純 X 線像では，アレイの固い部分の前端が狭い内腔の前端に位置しているように見える（❷d→）．軸位断 CT 像では，電極アレイが cavity の外側中央付近から挿入され（❸a→），前半部分の内腔に密着して敷設できているのが観察できる（❸b→）．

術中の電気生理学的検査（反応波形を❸c，d に示す）では，NRT で 2 番から 22 番，EABR で 5 番から 21 番電極において反応が確認された．術前に蝸牛相当部分と予想していた空間内にはおおむね 7 番から 17 番電極が収まっているが，実際にはその後方にも蝸牛神経が分布していたことがわかる．とくに cavity 内腔の下面ではほぼ電極先端まで反応があり，蝸牛神経支配がかなり尾側後方まで及ぶと推測され，今後，同様症例の手術を行ううえで参考になる．

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アドバンスドルーのポイント

- 小さな common cavity 例では術前の CT，MRI 検査で内腔の大きさを計測し，現在臨床使用できる電極のうちどれが最もフィットするか十分検討することが大切である．
- 手術では cavity をできるだけ大きく開窓し，内腔を直視しながら，あらかじめ曲げた電極を内腔に密着するように敷設する．
- 術中に単純 X 線撮影と NRT や EABR 検査を行うと，電極アレイが適切に敷設できているか否か，cavity のどこに蝸牛神経が分布しているか確認できる．

女比は1：3）．妊娠・出産で難聴が発症または悪化することも多い．難聴は一側性の場合もあるが，両側に起こることが多い（片側：両側は1：1）．一側性の難聴でも長期経過のうちに対側に難聴を生じることが多い．

鼓膜が正常で後天性の伝音難聴の場合には耳硬化症を疑う．標準純音聴力検査ではstiffness curveとよばれる，中・低音域に難聴が大きい聴力型を示すことが多い．耳小骨の固着により骨導閾値が2 kHzを中心に上昇し（Carhart notch），見かけ上混合難聴を呈する．耳小骨筋反射は，初期には逆向きやすい反応がみられ，固着が高度になると消失する．ティンパノグラムはA型またはAs型を示す．感音障害による感音難聴も出現することがある．側頭骨CTではアブミ骨は正常に描出され，前庭窓前庭に骨透亮像を認めることが多い．蝸牛周囲にわたって骨透亮像が描出されることもある．高度の病変では前庭窓が硬化病変で埋まってしまうこともある．蝸牛型耳硬化症（cochlear otosclerosis）では蝸牛迷路の病変が高度に認められる．

治療方針

有効な薬物療法はない．一般的には手術で伝音難聴の改善をはかる．40 dB以上の難聴で明らかな気骨導差を示す場合が手術のよい適応である．全身状態などから手術を行えない場合や手術を希望しない場合は補聴器を装用する．

Ⓑ 手術の分類

アブミ骨の可動をはかる方法とアブミ骨を全摘し人工骨（stapedectomy）またはアブミ骨の上部構造を切除してアブミ骨の底板に小穿孔を開け（stapedotomy），代用の人工アブミ骨を用いて再建する方法がある．アブミ骨可動術は再固着の可能性が高く，通常行われない．stapedotomyを選択する施設が多いが，日本人では底板の固着が高度でないために，アブミ骨全体が取れてしまうこともしばしばあり，その場合にはstapedectomyを行う．

Ⓒ 手術

外耳道の皮膚を深部でU字型に切開し，鼓膜まで剥離して挙上し，鼓室後方を開放する．鼓索神経を温存しつつ骨性鼓膜輪を可及的に削除してアブミ骨を明視下にする．硬化病変は前庭窓前方に観察できるが，確認できないことも多い．アブミ骨の固着を確認し，ツチ・キヌタ骨の可動性も確認する．キヌタ・アブミ関節を外し，アブミ骨底板に小穿孔を開ける（safety hole）．アブミ骨前後脚とアブミ骨底板をレーザーで焼灼または切断し，アブミ骨上部構造を摘出する．safety holeを拡大して径0.8 mmに開窓する．長さ約4 mm，径0.6 mmの人工アブミ骨のピストン部分を開窓部に挿入し，他端をキヌタ骨長脚にかけ，耳小骨連鎖を再建する．ピストンの長さはキヌタ骨長脚から開窓部までを実測して選択する．ピストン周囲にgelfoamを置き，外リンパ瘻を予防する．stapedectomyでは結合織を前庭窓のピストン周囲に置く．

Ⓒ 人工アブミ骨

人工アブミ骨にはすべてテフロンでできたテフロンピストンと，テフロンとステンレスのワイヤーでできたテフロンワイヤーピストンがある．

Ⓓ 成績と合併症

手術成績は良好で95%以上の症例で気骨導差は10 dB以内となり，長期にわたってよい聴力が維持される．術後一過性に眼振を認めることがしばしばあるが，通常1，2日で消失する．時に回転性めまいを数日間訴え，ふらつきが持続することがある．高音域の軽度の感音難聴を術直後に認めることがあるが，通常徐々に回復する．高度な感音難聴の発症はまれである．鼓索神経の一過性の障害により，舌前方の味覚障害を生じることがあるが，通常2，3週間以内に消失する．

患者説明のポイント

- 耳硬化症はアブミ骨の固着によって生じる．治療法には手術または補聴器装用がある．手術の聴力改善成績は良好である．感音難聴やめまいなどの合併症が生じる可能性があること，補聴器装用との違いを十分に説明して手術の承諾を得る．

急性感音難聴
acute sensorineural hearing loss

土井勝美　近畿大学教授・耳鼻咽喉科学

病態と診断

急激に発症する感音難聴が急性感音難聴で，急性感音難聴のうち発症原因が明らかなものは突発性難聴と称される．ウイルス感染（ムンプスウイルス・麻疹ウイルスによる聾，帯状疱疹ウイルスによるラムゼイ・ハント症候群）や細菌感染による急性内耳炎，強大音曝露による急性音響外傷（ディスコ難聴），圧外傷・内耳窓破裂を病態とする外リンパ瘻，内耳毒性を有する薬物（アミノグリコシド系抗菌薬・抗癌剤）による薬剤性難聴，聴神経腫瘍や小脳・脳梗塞による中枢性難聴，内リンパ水腫を病態とするメニエール病などがある．

一方で，内耳障害を病態とするものの発症原因が不明の急性感音難聴は突発性難聴と称され，上記の急性感音難聴と突発性難聴との鑑別診断が重要とな

る．また，低音部にのみ急性感音難聴を呈する場合は，急性低音障害型感音難聴と別に分けて診断される．

厚生労働省2001年度調査では，突発性難聴の年間の発症者数は35,000人と報告され，厚生労働省特定疾患急性高度難聴調査研究班の診断基準は，①突然の発症，②高度の感音難聴，③原因不明と定義されている．突発性難聴の病態としては内耳血流障害とウイルス感染が推察されている．

一般的に感音難聴の治療は困難とされているが，突発性難聴は早期に適切な治療を行うことで治癒も期待できる数少ない疾患の1つである．しかしながら，早期治療例でも約20%の症例は治療に無反応で，治療開始が遅れるとさらに治療成績は低下するため，より有効な治療法の開発が望まれている．前庭症状を伴う症例は約30%で，前庭症状のない症例と比較して治療成績は不良の傾向にある．

治療方針

突発性難聴では，発症後1週間以内にステロイドの大量漸減治療を開始することが，よい予後を得るための条件とされる．その他の急性感音難聴の治療も同様で，早期に適切な治療を開始することが重要となる．ウイルス感染が示唆される症例では抗ウイルス薬が併用される．ただし，ムンプス難聴の治療は不能であることが多く，ワクチン接種による難聴発症の予防が重要となる．外リンパ瘻疑い症例では，中耳試験開放により病態の有無を確認し，必要であれば内耳窓閉鎖術を施行する．メニエール病では，浸透圧利尿薬（イソバイド）の投与と併せて，高度の感音難聴に対してステロイドを追加する．急性音響外傷や急性低音障害型感音難聴についてもステロイド治療が基本になる．

ステロイド以外の薬物治療では，血流改善を目的にプロスタグランジン〔PGE_1（プロレナール）・PGI_2（ドルナー）〕，バトロキソビン（DF），ATP（アデホス），アミドトリゾ酸（ウログラフイン），蝸牛神経の賦活化を目的にビタミンB_{12}（メチコバール）が使用される．薬物治療以外では，高圧酸素治療が初期治療として有効とされる．

Ⓐ 点滴治療

Ⓡ 処方例　症状に応じて下記を適宜併用する．

1) 低分子デキストランL注（25 g/250 mL）　1回250 mL　1日1回　点滴静注
2) ソル・コーテフ注（100 mg）　1回500 mgより10日間で漸減　1日1回　点滴静注
3) アデホス-L注　1回60 mg　1日1回　点滴静注
4) メチコバール注　1回500 μg　1日1回　点滴静注

Ⓑ 内服治療

Ⓡ 処方例　病態に応じて下記を組み合わせて用いる．

1) プレドニン錠（5 mg）　6錠より開始，10日間で漸減
   メチコバール錠（500 μg）　3錠
   アデホス顆粒　300 mg（成分量として）
   カルナクリン錠（50単位）　3錠
   （分3）
2) ドルナー錠（20 μg）　3錠　分3　保外
3) プロレナール錠（5 μg）　3-6錠　分3　保外
4) イソバイドシロップ（70%）　90-120 mL　分3
5) メニレットゼリー（70%）　90 g（製剤量として）　分3

患者説明のポイント

- 早期にステロイドを中心とする適切な治療を行うことで治癒する可能性がある．
- 突発性難聴，メニエール病，外リンパ瘻の鑑別診断は，発症初期には必ずしも容易でなく，経過観察中に診断名・治療法が変更になったり，手術（鼓室試験開放）が必要になることもある．
- 心身の安静に努め，ストレスを回避するよう心掛ける．

突発性難聴

sudden deafness (idiopathic sudden sensorineural hearing loss)

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病態と診断

厚生労働省研究班の基準では，主症状として，①突然の難聴，②高度な感音難聴（ただし，明確な聴力の基準はない），③原因不明であること，が必要とされ，副症状には①耳鳴り，②めまいが挙げられる．すべての主・副症状があれば確実例，主症状のみなら疑い例になる．聴覚補充現象の有無は一定せず，聴力の改善・悪化の反復はなく，一側性が多いが両側例もあり，第8脳神経以外の神経症状はない．

わが国では年間3万-4万人が罹患し，50歳代後半から60歳代前半に発症のピークがある．病因は解明されていないが，内耳の血行障害，ウイルス感染などが想定されている．内耳血行障害説は有力ではあるが，本症が反復しないことが説明しにくい．ウイルス感染では，内耳炎のほかに感染による麻痺

STAPES SURGERY AND COCHLEAR IMPLANT SURGERY FOR SEVERE ORTOSCLEROSIS

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Introduction

Profound deafness has received increasing attention, because of the availability of cochlear implants (CI). Consequently, it is especially important to remember that a 'blank' audiogram does not necessarily mean absence of hearing. Severe otosclerosis (far-advanced otosclerosis; FAO) generally involves air conduction (AC) levels worse than 85 dB, and bone conduction (BC) levels beyond the limits of the audiometer.[1-4] If AC levels exceed 85 dB but BC levels are measurable at some frequencies but worse than 30 dB, the condition is called advanced otosclerosis (AO). Failure to recognize FAO or AO may result in unnecessary CI surgery.

Materials and methods

A retrospective analysis was conducted of the clinical charts of all patients who received stapes surgery (n = 306) and CI surgery (n = 536) at Osaka and Kinki University Hospitals from 1992 to 2012. Stapes surgery involved 210 ears in females and 96 ears in males. Otosclerosis accounted for 80% of the the stapes surgery. Objective improvement was noted in pure-tone audiogram (PTA), and subjective patients' satisfaction with amplification was the real measure of success because the stapes surgery was performed to restore a serviceable hearing with Hearing aid (HA) for these FAO and AO patients.

Results

Among 306 stapes surgery cases, one patient (NS, 45 years old, male) with FAO received stapedotomy on the right ear, and another patient (MS, 56 years old, male) with AO received bilateral stapedotomy. Both patients had a positive family history of progressive hearing loss. MS's daughter (KM, 28 years old) received partial stapedectomy on the left ear, and the result was excellent. AC levels were worse than 85 dB bilaterally in both patient, and BC levels were not measurable at most (not all) frequencies. The past audiograms and the family history help us to diagnose FAO and AO. Pre-operatively, both patients (NS and MA) were not successful hearing aid (HA) users, although both continued to use a HA anyway. Post-operatively, MS does not need HA any longer, while NS is still wearing HA unsuccessfully and considering CI surgery the left ear.

Among 536 CI surgery cases, just one patient (UH, 52 years old, male) had been found to have the history of otosclerosis preoperatively, and has been a good CI user postoperatively (Fig. 1A). HRCT demonstrated a massive sclerotic lesion bilaterally, indicating the presence of cochlear otosclerosis (Fig. 2A). Past audiograms

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clearly suggest the presence of an air-bone gap and a progressive nature of HL (Fig. 2B). After cochleostomy onto the promontory, the scala tympani was found to be filled with soft connective tissues. A full insertion of CI24RCS electrodes into the scala vestibuli was successfully completed. Among 2558 CI surgery cases, bilateral otosclerosis accounted for just 1% of the causes of deafness in Japan (Fig. 1B), according to a survey by the Cochlear Corporation in 2006.

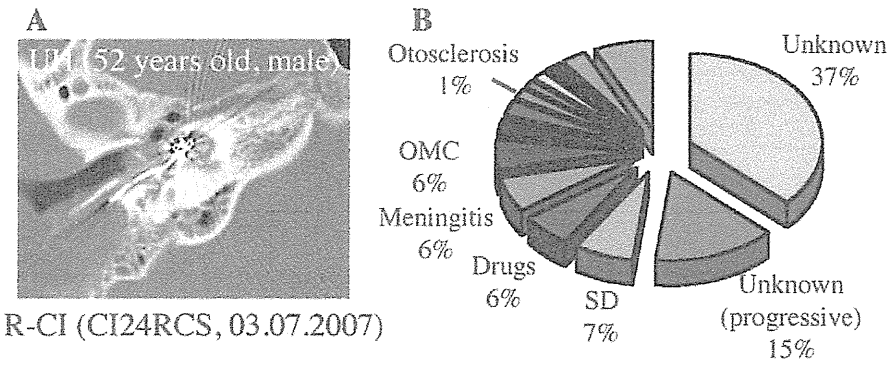

Fig. 1. Profound hearing loss caused by otosclerosis. A: a case of the CI surgery with FAO; B: the causes of deafness in Japanese CI cases (2006).

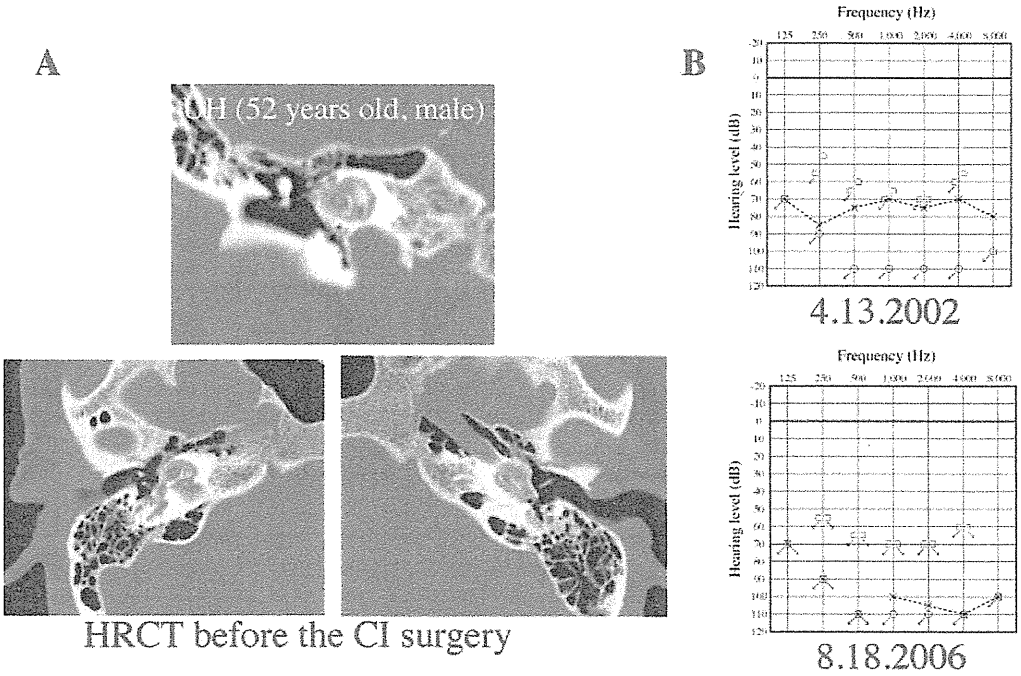

Fig. 2. HRCT and PTA of a patient with FAO who received CI surgery. A: massive sclerotic lesions within bilateral cochlea; B: past audiograms suggesting a progressive hearing loss.

Discussion

A convincing histological explanation for increased bone-conduction threshold in FAO remains an issue for continued investigation. There are two types of otosclerosis described: a conductive disturbance limited to specific areas of the oval and round windows, and a more aggressive form called 'cochlear otosclerosis' with

multiple foci developed relatively early in life. No correlation between BC thresholds and size of the lesion, activity of the lesion, involvement of endosteum or presence of a round window lesion in otosclerosis was found, while moderate diffuse loss of hair cells and cochlear neurons in the basal turn, and strial atrophy near the foci of otosclerosis were reported in FAO patients.

Sheehy[2] published specific diagnostic clues for FAO: 1) positive family history for otosclerosis; 2) progressive hearing loss beginning in early adult life; 3) paracusis during the early stage of the disease; 4) past use of bone-conduction hearing aid; 5) previous audiograms showing an air-bone gap. In addition, the following criteria can be obtained from the physical examination: 1) normal voice; 2) positive Schwarze's sign; 3) evidence of otosclerosis on HRCT; 4) a Weber test lateralizing to the poor ear or a negative Rinne test by a 512-Hz tuning fork; 5) no other apparent cause for hearing impairment. The diagnosis is just presumptive and can be confirmed only at surgery. All of our cases showed a positive family history of hearing loss, a progressive hearing loss on the past audiograms, and sclerotic findings of cochlea on HRCT.

Patients with FAO may appear to be suffering from profound sensorineural hearing loss and are frequently directed to CI programs. Specific clues shown above can lead the clinician to suspect FAO, and some FAO patients who had been unable to use a hearing aid (HA) preoperatively obtained serviceable hearing with a HA after the surgery.[1-4]

The most gratifying aspect of the stapes surgery for severe otosclerosis (FAO and AO) should be converting the patients' hearing from non-serviceable to serviceable with HA. The patients must be aware not only of the risks of the procedure, but also of the relatively limited goals. On the basis of the conventional criteria for stapedectomy surgery, objective results would be sometimes disappointing in FAO. However, some FAO patients clearly do benefit from the surgery and show marked improvement in HA performance. The success rate was reported to range within 70-100%.[1-4] If a successful outcome is not achieved, the patient might be suitable for the CI surgery.

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・あらゆる可能性を考え，薬物療法，補聴器（希望により音響療法）を試み，患者サイドに立った治療の提案を行うことが重要である．

耳閉感

病態と診断

Ⓐ 病態

耳が塞がったような感じが耳閉感である．外気圧の変化により外気圧と中耳腔の圧が不均衡になった際に感ずる症状で，高い山に登った際，高層ビルのエレベーターに乗った際，トンネルに入った際などに感ずる．外気圧の変化が誘因ではなくこのような耳閉感を感ずる場合，中耳，内耳疾患の存在を疑う．中耳疾患では滲出性中耳炎など種々の中耳炎，耳管狭窄症，耳管開放症などが原因となる．またメニエール病，突発性難聴などの内耳疾患でも耳閉感を生じる．

Ⓑ 診断

耳閉感は自覚的症状であり，他覚的検査がないのが客観的な診断を困難にしている．鼓膜所見，純音聴力検査のほか，ティンパノメトリー，自記オージオメトリー，SISI テストなどの聴覚検査，耳管機能検査，および画像検査（CT，MRI）を組み合わせ原因となる障害部位診断を行う．

治療方針

原因となる中耳疾患（耳管狭窄症，耳管開放症など），内耳疾患（メニエール病，突発性難聴など）の治療をすることにより症状は軽減する．詳細はそれぞれの疾患の項を参照されたい．

高度難聴（補聴器，人工内耳）

severe to profound hearing loss (cochlear implant, hearing aid)

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病態と診断

一般に平均聴力 70 dB 以上を高度難聴とよぶことが多い．高度難聴がある場合，聴力検査で難聴の程度を測定するだけでなく，必要に応じて他の聴覚検査，画像診断，遺伝子検査などを駆使し，できるだけ難聴の原因まで究明することが大切である．高度難聴では何らかの聴覚補償が必要だが，同程度の難聴でも伝音難聴では補聴の効果が高く，感音難聴では音の神経活動への符号化そのものが障害されるため，補聴器で入力音を増幅しても単純には語音弁別が改善しない．補聴器を装用しても日常生活に大きな支障をきたす場合，入力音の増幅という補聴戦略から蝸牛神経の直接電気刺激，つまり人工内耳という方法に移行する．

小児の高度難聴では，言語という，人として重大な生理機能の発達を扱うため，成人とは別次元の留意が必要である．最初に，補聴器や人工内耳で聴覚を活用する道を歩むのか，手話で言語を獲得するのかという根源的選択が必要であり，主治医は，両親が患児の将来を見据えた最善の判断ができるように，公正な助言ができなければならない．

治療方針

Ⓐ 補聴器

補聴器装用の適応に絶対的なものはなく，軽度難聴でも学校や職場などでの必要性が高ければ実用上のメリットも大きい．逆に中等度以上の難聴があっても日常生活で必要性を感じない人が仮に補聴器を購入したとしても非使用者になってしまうおそれがある．補聴器の適応判断や機器の選択，装用の具体的指導には，難聴の程度と性質，患者の生活状況，補聴器の性能や特徴について専門的知識を有する補聴器相談医の対応が望ましい．

言語習得前の小児ではことばの発達のために難聴の早期発見と介入が大切で，これには新生児聴覚スクリーニングが大きな役割を果たしている．スクリーニングで要精査となった場合には，各地域で日本耳鼻咽喉科学会認定の精密聴力検査機関が拠点として対応している．乳児で補聴器が必要と判断された場合には 6 か月ころから装用を開始する．音声言語の習得にはおおむね 55 dB 以下の補聴器装用閾値が得られることが必要で，これを超えると人工内耳を使用したほうが良好な言語発達が得られる例が多い．

Ⓑ 人工内耳

本邦の人工内耳適応基準は，成人，小児ともに 90 dB 以上の難聴で，補聴器の効果が乏しく，内耳が手術可能な状態であることとされ，小児ではこれに，年齢が 1 歳 6 か月以上であることと術後の療育体制が整っていることが加わる．

人工内耳手術が可能かどうかについては画像診断が大きな役割をはたす．側頭骨 CT で乳突蜂巣発育と軟部組織陰影の有無，顔面神経の位置，内耳の形態，内耳道・蝸牛神経管狭窄の有無などを観察し，MRI で内耳の線維化の有無，蝸牛神経の描出状況や太さなどを評価する．

先天性難聴小児の人工内耳手術は低年齢ほど効果が高いので，補聴器で療育を継続するか人工内耳に進むかの判断は慎重な検査・評価に基づきつつ早期に行うべきである．髄膜炎後失聴例や，遺伝子検査で有効な聴力が期待できないことが明白な症例など

では，漫然と経過を待たずに，より早期の手術も考慮する．人工内耳の装用閾値は25－35 dB程度で，低音から高音域までフラットな効果が得られる．

聴覚医学的には，聴覚補償は両耳のほうが種々の利点がある．人工内耳の使用も基本的にはこれに当てはまるが，補聴器の両耳装用と異なる点として，人工内耳には人工物を手術的に体内に埋め込むことに伴う短期的・長期的リスク，残存聴力損傷の可能性，高額の医療費などの問題もある．先天性高度難聴小児が人工内耳で高い聴覚・音声言語能力を獲得し，社会的に自立した成人になることは，患児本人だけでなく社会全体にも大きなメリットをもたらす．人工内耳の両耳装用について適切な適応基準の確立が望まれる．

また，最近は主に低音域の残存聴力がある症例で正円窓からのアプローチにより，聴力をある程度，場合によってはほぼ完全に保存できるタイプの人工内耳電極も使用可能になってきた．このような例では人工内耳をオフにしても一定の聴覚があり，さらに人工内耳を稼働させることで，騒音下での語音弁別向上など，より高度の聴覚再獲得が可能になる．将来的には，補聴器か人工内耳かという二者択一的な考え方も改めなければならないであろう．

患者説明のポイント

- 高度難聴の診療には時間がかかる．中途失聴者では筆談，小児では両親へのカウンセリングが必要である．十分な診察時間を確保するとともに，言語聴覚士や看護師などと役割を分担してチームで対応すると手厚い説明ができ，患者の疾病理解が深まる．
- 感音難聴では補聴器を使用しても大なり小なり，音が割れたり，やかましく聞こえることは避けがたく，騒音下，反響のある広い場所，多人数との会話などでの聞き取りも難しい．補聴器の限界を理解してうまく使いこなせるように丁寧に説明する．
- 補聴器や人工内耳を使用しても聴覚が正常になるわけではない．特に高度難聴小児が高い音声言語能力を習得するには長期間の専門的指導と日常生活や教育上のさまざまな支援が必要であることを両親に説明する．

看護・介護のポイント

- 難聴者，人工内耳使用者との会話では，静かな場所において1対1で正面から口の動きを大きくして，ゆっくり，はっきり話すように努め，重要事項は筆談や印刷物を併用して正確な理解を確保する．
- 小児難聴の場合，親は子どもが難聴である事実に当惑し，受け入れがたい気持ちになるのが通常である．患児の療育を円滑に推進するうえで，医学的な説明に加えて，親の心情に寄り添い，支援する姿勢が重要である．

めまい，平衡障害
vertigo and dysequilibrium

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病態と診断

めまいには，末梢前庭系の障害による末梢性めまいと，中枢前庭系の障害を原因とし，生命に対する危険性を有す中枢性めまいとがあり，両者の鑑別が重要である．

末梢性めまいには聴覚症状（難聴・耳鳴・耳閉感など）が随伴することが多く，問診の際にこれを確認する．

中枢性めまいの代表格は，Wallenberg症候群などの脳幹・小脳梗塞や小脳出血である．Wallenberg症候群におけるめまいは前庭神経核の虚血により生じるため，末梢性めまいと同様，回転性めまいが生じるので注意が必要である．前庭神経核周辺の神経核も同時に障害され，他の中枢神経症状を伴う．前庭神経核より頭側の虚血の場合，動眼系の神経核群があり複視を訴える．尾側の虚血では，三叉神経脊髄路核の障害により口囲の痛覚の低下，迷走神経背側運動核の障害により軟口蓋や声帯麻痺，交感神経下行路の障害ではHorner症候群が認められる．複視や口囲のしびれ，構音障害がなかったかを必ず問診し，他覚的にもこれらの症状の有無をチェックすることが重要である．小脳出血は初期にめまい，悪心，嘔吐，頭痛（突然ピーク形）を訴える．末梢性めまいと紛らわしい症状で発症することがあるので注意を要する．中枢性めまいが疑われる場合はCTやMRIなどを行う．発症6時間以内の脳幹・小脳梗塞超急性期の診断には，MRI（拡散強調画像）が有用である．小脳出血の診断にはCTが有用である．

治療方針

Ⓐ めまい急性期の治療

めまい急性期は悪心や嘔吐などの前庭自律神経反射による症状が強く，これらに対する対症療法が優先される．患者にとって一番楽な姿勢をとらせて，外的刺激の少ない静かな暗い部屋で体動をできる限り避けるようにして安静を保つ．病状を十分に説明して，不安感を取り除くように努める．めまい急性期は内服が困難かつ症状への速効性が要求されるこ

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Review

Current concepts in age-related hearing loss: Epidemiology and mechanistic pathways

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ABSTRACT

Age-related hearing loss (AHL), also known as presbycusis, is a universal feature of mammalian aging and is characterized by a decline of auditory function, such as increased hearing thresholds and poor frequency resolution. The primary pathology of AHL includes the hair cells, stria vascularis, and afferent spiral ganglion neurons as well as the central auditory pathways. A growing body of evidence in animal studies has suggested that cumulative effect of oxidative stress could induce damage to macromolecules such as mitochondrial DNA (mtDNA) and that the resulting accumulation of mtDNA mutations/deletions and decline of mitochondrial function play an important role in inducing apoptosis of the cochlear cells, thereby the development of AHL. Epidemiological studies have demonstrated four categories of risk factors of AHL in humans: cochlear aging, environment such as noise exposure, genetic predisposition, and health co-morbidities such as cigarette smoking and atherosclerosis. Genetic investigation has identified several putative associating genes, including those related to antioxidant defense and atherosclerosis. Exposure to noise is known to induce excess generation of reactive oxygen species (ROS) in the cochlea, and cumulative oxidative stress can be enhanced by relatively hypoxic situations resulting from the impaired homeostasis of cochlear blood supply due to atherosclerosis, which could be accelerated by genetic and co-morbidity factors. Antioxidant defense system may also be influenced by genetic backgrounds. These may explain the large variations of the onset and extent of AHL among elderly subjects.

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1. Introduction

Age-related hearing loss (AHL), or presbycusis, is a complex degenerative disease and is one of the most prevalent chronic conditions of the aged, affecting tens of millions of people worldwide. AHL is a multifactorial condition, representing the end stage sequela of multiple intrinsic (e.g. genetic predisposition) and extrinsic (e.g. noise exposure) factors acting on the inner ear over a lifetime that cumulatively lead to impairments in cochlear transduction of acoustic signals (Ohlemiller, 2009; Schuknecht, 1955).

Potential sites of pathology include the inner and outer hair cells, the stria vascularis, and afferent spiral ganglion neurons (Schuknecht et al., 1993). The stria vascularis and hair cells are particularly susceptible to injury. The stria vascularis is highly metabolically active and depends on an elaborate cellular machinery to maintain the steady-state endocochlear resting potential. Consequently, injury from multiple different pathways (e.g. age-related cell losses within the stria, oxidative stress from noise exposure, genetic polymorphisms leading to inefficient oxidative pathways or dysfunctional supporting cells, or microvascular disease in the strial vessels) could all affect strial function (Ohlemiller, 2009). The resulting loss of the endocochlear potential would impair the function of the cochlear amplifier and lead to an increase in hearing thresholds (Schmiedt et al., 2002; Schuknecht et al., 1974).

A similar multimodal pathway of injury and dysfunction is also observed in the cochlear hair cells and cochlear nerve. Post-mitotic

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hair cells are susceptible to accumulated injury over time from a combination of poor cellular repair mechanisms associated with aging, direct mechanical or mitochondrial oxidative injury from noise, and toxicity from aminoglycosides or other ototoxic medications (Liu et al., 2007; Ohlemiller, 2004; Pickles, 2008). Neuronal degeneration of spiral ganglion afferents can also be triggered by cumulative exposures to loud noise leading to glutamate excitotoxicity and loss of the afferent dendrites (Kujawa et al., 2006). Interestingly, such a mechanism of injury may allow for relative preservation of pure tone threshold sensitivity but disproportionate effects on speech perception in noise and speech understanding given the complexity of speech sounds and the need for precise temporal and frequency coding by the spiral ganglion afferents.

The complexity of factors (aging, genetic, epigenetic, environmental, health co-morbidity) and importantly the interaction of the different mechanistic pathways that can cause AHL have greatly complicate our interpretation of basic and clinical research into AHL (Van et al., 2007) and have led to some latent cynicism about the precise value of key factors contributing to AHL (Ohlemiller, 2009). In particular, the same functional consequences of *increased hearing thresholds* and *poor frequency resolution* generally occur regardless of etiology of AHL or the cochlear mechanistic pathway (Pickles, 2008). Consequently, for elderly with AHL, the main issue is often the inability to understand words rather than the inability to hear, leading to the refrains of "I can hear you but I can't understand you" or perhaps more commonly, "My hearing is fine. You're just mumbling". Most importantly, AHL gradually impairs an individual's ability to understand the meaning of everyday language (e.g. "I'll see you *Sunday*" versus "I'll see you *someday*"), in which fine auditory cues encoding semantic meaning are critical for understanding communicative meaning.

In this review, we have chosen to focus on recent works that have improved our understanding of the cellular and molecular mechanisms that could cause age-related degeneration of the cochlea. Particularly, we have emphasized the role of oxidative stress and mitochondrial dysfunction due to accumulation of mitochondrial DNA (mtDNA) mutations/deletions in the development of AHL.

2. Human studies

2.1. Prevalence of ARHL

Estimating hearing loss prevalence and identifying epidemiologic risk factors can be ascertained from large cohorts where audiometric testing was performed. A sampling of such studies include Beaver Dam (Cruickshanks et al., 2003), Framingham (Gates et al., 1990), Blue Mountains (Gopinath et al., 2009), Baltimore Longitudinal Study of Aging (BLSA) (Brant et al., 1990), and National Health and Nutrition Examination Survey (NHANES) (Agrawal et al., 2008). Reports of hearing loss prevalence across these studies vary because of different tonal frequencies utilized to obtain a pure tone average (PTA), monaural or binaural definition of hearing loss, and audiometric cutoffs used to define hearing loss. Differences in cohort characteristics (volunteer cohort or recruitment of population sample) and the age of the cohort also limit comparisons across studies.

A useful audiometric definition of hearing loss has been adopted by the World Health Organization as a speech-frequency pure tone average of thresholds at 0.5, 1, 2 and 4 kHz tones in the better-hearing ear of >25 dB (World Health Organization). The selected tonal frequency range and the use of the better-hearing ear are useful from a pragmatic perspective that emphasizes communication since 0.5–4 kHz represents the critical frequency range of speech, and the better-hearing ear would be the principal determinant of a person's communicative abilities. Using this definition of hearing loss and NHANES data (representing a cross-section of the non-institutionalized U.S. population), hearing loss prevalence approximately doubles every decade of life from the second through seventh decades (Fig. 1) (Lin et al., 2011a). Using the same definition of hearing loss, national Institute for longevity sciences-longitudinal study of aging (NILS-LSA) in Japan has reported that the prevalence rates of AHL are 29% in late sixties, 39% in early seventies, and 65% in late seventies in male, and 23%, 37%, and 59% in female, respectively (http://www.ncgg.go.jp/department/ep/monograph5th/sensory.htm).

Other reports of hearing loss prevalence have generally focused on older adults using differing definitions of hearing loss. Prevalence rates have been 29% (>26 dB in the standard PTA [0.5–2 kHz] in the better ear, subjects >60 years), 73% (>25 dB in the speech frequency [0.5–4 kHz] PTA in the worse ear, subjects >70 years), and 60% (>25 dB in the standard PTA in the worse ear, subjects 73–84 years) in the Framingham (Gates et al., 1990), Beaver Dam (Cruickshanks et al., 1998b), and Health ABC (Helzner et al., 2005) studies, respectively. Using identical definitions of hearing loss and age ranges from the latter two studies, prevalence figures calculated using the 2005–2006 NHANES dataset would be 76% and 64%, respectively (Lin et al., 2011a). However, comparing results across different studies is difficult even when applying the same definition of hearing loss given the different demographic characteristics across cohorts particularly with regard to age and race. For example, both the Framingham cohort and Beaver Dam cohorts included few African American individuals, but the Health ABC cohort included 36.3% African American. Age distributions and ranges also varied across these study cohorts. Strength of using NHANES estimates of hearing loss prevalence is that these results are generalizable to the entire civilian, non-institutionalized U.S. population.

2.2. Risk factors for AHL

Epidemiologic studies also provide insight into the modifiable and non-modifiable risk factors associated with hearing loss and provide further insight into the mechanistic pathways underlying AHL. Studied risk factors can generally be divided into four categories as discussed previously (Cooper, 1994; Cruickshanks et al., 1998a, 2003): cochlear aging (individual age), environment (occupational and leisure noise exposure, ototoxic medications, socioeconomic status), genetic predisposition (sex, race, specific genetic loci/genes), and health co-morbidities (hypertension, diabetes, stroke, cigarette smoking). Strong and consistent associations of hearing loss have generally been found with the non-modifiable

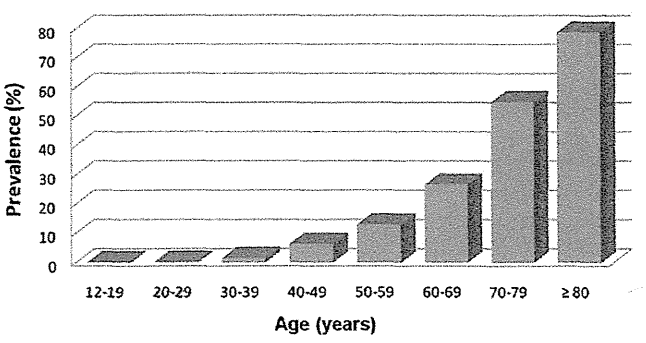

Fig. 1. Prevalence of hearing loss in the United States by age, 2001–2008. Hearing loss is defined by a PTA of 0.5–4 kHz thresholds in the better-hearing ear >25 dB.

risk factors of increasing age (increased risk), male sex (increased risk), and African American (decreased risk) (Agrawal et al., 2008; Brant et al., 1990; Gates et al., 1990; Helzner et al., 2005; Ishii et al., 1998; Jerger et al., 1986).

Genetic predisposition as shown by heritability studies among twins and longitudinal studies of family cohorts have also shown heritability indices of 0.35–0.55 (Christensen et al., 2001; Gates et al., 1999; Karlsson et al., 1997), indicating that genetic phenotype accounts for a substantial portion of hearing loss risk. Using general estimation equation analysis, Shimokata (2008) found that 28 out of 177 single nucleotide polymorphisms (SNPs) were associated with impaired hearing in the elderly subjects. Of these, 5 SNPs were significantly related to hearing impairment at low frequencies (125–500 Hz) and other 5 SNPs at high frequencies (2–8 kHz), respectively. The SNPs associated hearing loss at low frequencies were distinct from those at high frequencies, but all these SNPs are known to be associated with atherosclerosis or obesity. The odds ratio of hearing impairment between subjects with all 5 SNPs and those with none of them was 18.6 (95% confidence interval, 4.9–70.8) at low frequencies and 6.5 (95% confidence interval, 3.3–12.7) at high frequencies.

Other factors that have associations with the risk of hearing loss include hypertension and cardiovascular disease, cerebrovascular disease, smoking, diabetes, noise exposure, and alcohol consumption, with all factors being associated with increased risk of hearing loss except for alcohol consumption (Cruickshanks et al., 1998a, 1998b; Dalton et al., 1998; Gates et al., 1993; Helzner et al., 2005; Van et al., 2007; Shimokata, 2008). Cruickshanks et al. (1998a) evaluated the association between smoking and hearing loss in 3753 adults aged 48–92 years, and found that after adjusting for other factors, current smokers were 1.69 times as likely to have a hearing loss as nonsmokers (95% confidence interval, 1.31–2.17), with weak evidence of a dose–response effect. Similarly, Fransen et al. (2008) conducted a multicenter study to elucidate the environmental and medical risk factors contributing to AHL and found that in 4083 subjects between 53 and 67 years, smoking significantly increased high-frequency hearing loss with dose-dependent effect. There have been some inconsistent findings with the latter group of risk factors, which may be a consequence of how hearing loss was defined and the characteristics of the study cohort. For example, noise exposure may primarily lead to high-frequency hearing loss, whereas cardiovascular risk-factors affect both low and high-frequencies. Averaging across frequencies when defining a pure tone average could, therefore, obscure certain associations depending on which tonal frequencies are selected for the PTA. Characteristics of the study cohort may also obscure potential associations depending on the risk factors present in the risk group. For example, in a study focused on only older adults, the factors associated with older age and cochlear aging may overshadow associations with these weaker risk factors. Genetic heterogeneity within cohorts with consequent variability in gene-risk factor interactions (Liu et al., 2007; Van et al., 2007) would also likely bias any possible association toward the null hypothesis.

Previous research into hearing loss epidemiology has emphasized the study of modifiable risk factors in order to form the basis for possible hearing loss prevention strategies. However, the contribution of these modifiable risk factors (e.g. hypertension, etc.) is relatively weak in comparison to the non-modifiable risk factors of genetic predisposition and race as demonstrated by the consistency and strength of associations seen in epidemiologic studies. Further study of these non-modifiable risk factors, particularly the physiologic basis of black race being a protective factor for hearing loss and the identification of the genetic loci and genes contributing to AHL, could possibly offer the most substantial and profound insights into actual hearing loss prevention.

2.3. Impact of race on AHL

Previous observational studies investigating the role of race and hearing loss have consistently demonstrated that black race is associated with a 60–70% lower odd of noise-induced hearing loss and AHL compared to white subjects (Agrawal et al., 2008; Cooper, 1994; Helzner et al., 2005; Lin et al., 2011b). Other epidemiologic studies using a case–control approach recruiting individuals with similar occupational exposures have also demonstrated a reduced risk of hearing loss in black subjects (Ishii et al., 1998; Jerger et al., 1986). A recent epidemiologic study suggests that skin color and hence melanocytic functioning in the cochlea is the mechanism underlying the protective association of race with hearing (Lin et al., 2011b).

Melanin produced by strial melanocytes (intermediate cells) in the cochlea has been hypothesized to serve a protective role as a free radical scavenger, metal chelator, or regulator of calcium homeostasis in the stria vascularis, which is involved with generating and maintaining the endolymphatic potential necessary for normal hearing (Murillo-Cuesta et al., 2010; Riley, 1997). A recent study has also demonstrated that deficiency in strial melanin is associated with marginal cell loss and decline in the endocochlear potential (Ohlemiller et al., 2009). There have not been any further epidemiologic studies exploring the issue of race and hearing loss and little basic science research into mechanistic pathways leading to hearing preservation in individuals with darker skin. The lack of research exploring these topics is surprising, given the strength of the epidemiologic association between race and hearing loss and the fact that melanin pathways in the inner ear could potentially be pharmacologically targeted for hearing loss prevention.

2.4. Candidate genes associated with AHL

The number of genetic investigations on AHL has increased at a surprising rate recently. Association studies analyze genetic variations in unrelated individuals and try to identify those variations that are more frequent in affected individuals compared to unaffected individuals. The ultimate in association studies is a genome-wide association study (GWAS), in which hundreds of thousands of SNPs across the entire genome are analyzed in unrelated individuals. Although the use of GWAS to understand human disease is maturing, GWAS remain prohibitively expensive, and sometimes association studies are limited to a carefully selected set of candidate genes. To date, only several GWAS studies have been performed (Huyghe et al., 2008; Konings et al., 2009; Van et al., 2007, 2008, 2010; Friedman et al., 2009; Girotto et al., 2011); however, these studies have been limited in only studying a certain subset of potential genes or markers (i.e. those associated with monogenic forms of deafness) rather than examining a broad array ($>10^6$) of various polymorphisms.

Candidate-gene-based association studies also have been extensively carried out recently. This approach is based on the selection of candidate genes, which are usually implicated in a biological pathway that is plausibly related to a specific disease. A whole range of candidate genes can be proposed because perception of sound involves many complex pathways and age-related changes in any component of one such pathway could contribute to AHL. Genes causing monogenic forms of hearing loss are candidate susceptibility genes for AHL and other genes can be candidates because of a known or presumed function in the inner ear. With these considerations in mind, a number of researchers have speculated that oxidative stress, and consequently, mitochondrial DNA mutations, have important causative roles in the development of AHL. Several genes and loci have been proposed using candidate gene approaches (see review by Uchida et al., 2011), which included DFNA18 and

DFNA5 loci, chromosome 8q24, 13-kb region of KCNQ4 (Potassium channel, voltage gated, subfamily Q, member 4), N-acetyltransferase 2 grainyhead like 2, glutamate receptor metabotropic 7, glutathione S-transferase (GST), apolipoprotein E allele ε4, endothelin-1 (EDN1), mitochondrial uncoupling protein 2 (UCP2), and mitochondrial DNA mutations.

Interestingly, some of the candidate genes are well known to be associated with oxidative stress and atherosclerosis. For example, GSTs, one of glutathione-related antioxidant enzymes, catalyze conjugation of glutathione with xenobiotics and other compounds and play an important role in the antioxidant protection of the cochlea (el Barbary et al., 1993). Decreased glutathione and GST activity levels cause increased susceptibility of cells to insults and cell damage. When glutathione level is lower, cochlea becomes more vulnerable to intense noise (Yamasoba et al., 1998) and aminoglycoside-induced hearing loss (Lautermann et al., 1995). Van Eyken et al. (2007) investigated an association between AHL and genes related to oxidative stress using a large set of 2111 independent samples from two population groups, the general European and the Finnish population. Although they did not detect an association between *GSTM1* (mu, chromosome 1p13.3), or *GSTT1* (theta, chromosome 22q11.2) and AHL in the former population, there were significant associations between both genes and AHL in the latter population.

UCPs are members of the larger family of mitochondrial anion carrier proteins They facilitate the transfer of anions from the inner to the outer mitochondrial membrane and the return transfer of protons from the outer to the inner mitochondrial membrane and also reduce the mitochondrial membrane potential in mammalian cells. UCPs play a role in non-shivering thermogenesis, obesity, diabetes and atherosclerosis, but the main function of UCP2 is the control of mitochondria-derived ROS (Arsenijevic et al., 2000). Recently, Sugiura et al. (2010) reported that UCP2 Ala55Val polymorphisms, but not UCP1 A-3826G polymorphism, exhibited significant association with AHL in the Japanese population.

Endothelin is a potent vasoactive peptide that is synthesized and released by the vascular endothelium and the best-characterized endothelin, EDN1, is involved in the development of atherosclerosis. Several SNPs in *EDN1* gene have been shown to be associated with atherosclerosis, coronary disease and hypertension (for example, Yasuda et al., 2007). Further, EDN1 can induce a strong, long-lasting constriction of the spiral modiolar artery, causing an ischemic stroke of the inner ear (Scherer et al., 2005). Uchida et al. (2009) has observed significant association between the Lys198Asn (G/T) polymorphism (rs5370) in the *EDN1* gene and hearing loss in middle-aged and elderly Japanese.

2.5. Mitochondrial DNA mutations and AHL

Increases of deletions, mutations, or both in mtDNA have been reported in human archival temporal bone samples from people with AHL compared to normal hearing control tissues. Bai et al. (1997) examined mtDNA from celloidin-embedded temporal bone sections of 34 human temporal bones, 17 with normal hearing and 17 with AHL, and found that a 4977-base pair (bp) deletion, called a 'common ageing deletion,' was significantly more frequent in the cochlear tissues from patients with AHL compared to those with normal hearing. Markaryan et al. (2009) evaluated the association between the common ageing deletion level in cochlear tissue and the severity of hearing loss in elderly subjects and found that a mean level of the deletion was 32 ± 14% in subjects with AHL and 12 ± 2% in the normal-hearing age-matched controls, with statistical significance. They also observed the reduction of cytochrome *c* oxidase subunit 3 (COX3) expression in spiral ganglion cells from individuals with AHL, and in addition to the mtDNA common ageing deletion, other deletions involving the mtDNA major arc contributed to the observed deficit in COX 3 expression (Markaryan et al., 2010). Sporadic mtDNA mutations are also likely to contribute to the manifestation of AHL. Fischel-Ghodsian et al. (1997) examined the archival temporal bones from five patients with AHL for mutations within the mitochondrially-encoded cytochrome oxidase II gene and when compared to controls, the mutations occurred more commonly with AHL despite great individual variability in both quantity and location of mutation accumulation.

3. AHL studies in animals

3.1. General pathological and physiological findings

As discussed earlier, AHL is generally classified into three major types based on the relationship between cochlear pathology and hearing levels: sensory (loss of sensory hair cells), neuronal (loss of spiral ganglion neurons), and metabolic (strial atrophy) hearing loss (Schuknecht, 1955). Age-related stria atrophy or degeneration is one of the common features of AHL in both animals and humans (Gates and Mills, 2005; Ohlemiller, 2009; Fetoni et al., 2011). Aged gerbils display loss of stria capillaries (Gratton and Schulte, 1995), degeneration of marginal and intermediate cells of the stria vascularis (Gates and Mills, 2005; Spicer and Schulte, 2005), and loss of Na^+K^+ ATPase (Schulte and Schmiedt, 1992), which regulates stria function and endocochlear potential (EP) through transporting Na^+ out, while transporting K^+ into the cell (Spicer and Schulte, 2005). The loss of function of the cells in the stria vascularis and/or spiral ligament is thought to result in disruption of inner ear ion homeostasis, thereby causing a decline in EP. Consistent with this view, aged gerbils display an age-related decline in EP as well as disruption of ion homeostasis in the cochlea (Schmiedt, 1996).

There are several mouse models of aging and age-related diseases that display a variety of premature aging phenotypes, including a reduced lifespan and early onset of AHL. C57BL/6J mouse strain, one of the most widely used models for the study of aging and age-associated diseases, display loss of the hair cells and spiral ganglion neurons and increased hearing thresholds by 12 months of age (Zheng et al., 1999). Aged C57BL/6 mice display an age-related decline in the density of spiral ligament and stria vascularis (Ichimiya et al., 2000) and also an age-related decrease in the cross-sectional area of the stria vascularis as well as the survival of the Type IV fibrocytes in the spiral ligament (Hequembourg and Liberman, 2001). Interestingly, an age-related decline in EP was observed in CBA/CaJ mice and BALB/cJ mice, but not in C57BL/6 or CBA/J (Lang et al., 2002; Sha et al., 2008), which suggests that decreased EP may not be a key common feature of AHL. Since inbred mouse strains have a wide range of noise sensitivities and rates of hearing loss with age, they may not be good model for the heterogeneity of the human population. An animal population featuring a genetically heterogenous background, late onset of hearing loss and a well defined range of sensitivity to environmental factors might provide a more informative model for human AHL. Schacht et al. (2012) tested four-way cross mice from 4 parental strains, MOLF/Ei, C3H/HeJ, FVB/NJ, and 129/SvImJ, and identified several polymorphisms affecting hearing in later life (loci on chromosomes 2, 3, 7, 10, and 15 at 18 months, on chromosomes 4, 10, 12, and 14 at 22 months in noise-exposed mice, and on chromosomes 10 and 11 in those not exposed to noise). Such four-way cross mice, in which each in the progeny shares a random 50% of its genetic heritage with each other, are considered to have the advantages of providing robustness, reproducibility, and genetic tractability (Miller et al., 1999) and thus are worth for future AHL studies.

3.2. Role of ROS in AHL

It has been postulated that reactive oxygen species (ROS) play a major role in the degeneration of these cochlear cells during aging (Cheng et al., 2005; Someya et al., 2009). It is now well established that mitochondria are a major source of ROS (Balaban et al., 2005; Lin and Beal, 2006; Wallace, 2005) and that the majority of intracellular ROS are continuously generated as a by-product of mitochondrial respiration metabolism during the generation of ATP (Balaban et al., 2005; Beckman and Ames, 1998; Halliwell and Gutteridge, 2007). These ROS include superoxide ($\cdot O_2^-$) and hydroxyl radical ($\cdot OH$) which are extremely unstable, and hydrogen peroxide (H_2O_2) which is freely diffusible and relatively long-lived (Balaban et al., 2005; Beckman and Ames, 1998; Halliwell and Gutteridge, 2007). ROS generated inside mitochondria are hypothesized to damage key cell components such as nuclear DNA, mitochondrial DNA (mtDNA), membranes, and proteins. Such oxidative damage accumulates over time and leads to tissue dysfunction during aging. This by no means is in any way special to the inner ear, but has been ubiquitously found in all systems. An elaborate antioxidant system has evolved to control the damaging effects of those ROS. The system includes the antioxidant enzymatic scavengers, such as superoxide dismutase (SOD), catalase, GST, and glutathione peroxidase (Gpx) (see Halliwell and Gutteridge, 2007). SOD decomposes superoxide (O_2^-) into hydrogen peroxide (H_2O_2) and oxygen (O_2), while catalase and Gpx decomposes hydrogen peroxide into water (H_2O) and oxygen (Halliwell and Gutteridge, 2007).

It has been shown that increased Gpx activity was observed in the stria vascularis and spiral ligament in the cochlea of aged Fisher 344 rats (Coling et al., 2009). In the organ of Corti of CBA mice, glutathione-conjugated proteins, markers of H_2O_2-mediated oxidation, began to increase at 12 months of age and 4-hydroxynonenal and 3-nitrotyrosine, products of hydroxyl radical and peroxynitrite action, respectively, were elevated by 18 months, whereas antioxidant proteins AIF and enzymes SOD2 decreased by 18 months (Jiang et al., 2007). Age-related cochlear hair cell loss was enhanced in mice lacking the antioxidant enzyme *SOD1* (McFadden et al., 1999), and reduced thickness of the stria vascularis and severe degeneration of spiral ganglion neurons were observed in middle-aged *SOD1* knockout mice (Keithley et al., 2005). Similarly, mice lacking senescence marker protein 30 (SMP30)/gluconolactonase (GNL), which could not synthesize vitamin C (VC), showed reduction of VC in the inner ear, increased hearing thresholds, and loss of spiral ganglion cells, suggesting that VC depletion accelerates AHL (Kashio et al., 2009). Conversely overexpression of catalase in the mitochondria reduced oxidative DNA damage in the cochlea and slowed AHL in C57BL/6 mice (Someya et al., 2009). These findings implicate that oxidative damage in the cochlea reflects an age-related decline in the antioxidant defenses and/or an age-related increase in ROS levels and pays a crucial role in the development of AHL.

Several studies have been conducted to examine the effects of antioxidants against AHL. Seidman (2000) conducted a randomized prospective study over a 3-year period, in which Fischer 344 rats were given vitamin E, VC melatonin, or lazaroid, and observed that the antioxidant-treated animals had better auditory sensitivities and a trend for fewer mtDNA deletions compared with placebo subjects. Seidman et al. (2002) also examined the effects of lecithin, a polyunsaturated phosphatidylcholine that plays a rate-limiting role in the activation of numerous membrane-located enzymes including SOD and glutathione, on aging and AHL. When Harlan–Fischer rats aged 18–20 months were divided into controls and experimental group supplemented orally for 6 months with lecithin, lecithin-treated animals showed significantly better hearing sensitivities, higher mitochondrial membrane potentials, and less common ageing mtDNA deletion in the cochlear tissues including stria vascularis and auditory nerve compared to controls. Le and Keithley (2007) demonstrated that aged dogs fed a high antioxidant diet for the last 3 years of their life showed less degeneration of the spiral ganglion cells and stria vascularis compared to dog fed control-diet.

In C57BL/6 mice, supplementation with VC did not increase VC levels in the cochlear tissue or slow AHL (Kashio et al., 2009), but animals fed with diet comprising six antioxidant agents (L-cysteine-glutathione mixed disulfide, ribose-cysteine, NW-nitro-L-arginine methyl ester, vitamin B12, folate, and ascorbic acid) exhibited significantly better hearing sensitivity than controls (Heman-Ackah et al., 2010). When C57BL/6 mice were fed with control diet or diet containing one of 17 antioxidant compounds (acetyl-L-carnitine, α-lipoic acid, carotene, carnosine, coenzyme Q10, curcumin, tocopherol, EGCG, gallic acid, lutein, lycopene, melatonin, poanthocyanidin, quercetin, resveratrol, and tannic acid), AHL was nearly completely prevented by α-lipoic acid and coenzyme Q_{10} and partially by *N*-acetyl-L-cysteine, but not by other compounds (Someya et al., 2009). In CBA/J mice, antioxidant-enriched diet containing vitamins A, C, and E, L-carnitine, and α-lipoic acid given from 10 months through 24 months of age significantly increased the antioxidant capacity of the inner ear tissues but did not ameliorate AHL or loss of the hair cells and spiral ganglion cells (Sha et al., 2012). These findings indicate that supplementation with certain antioxidants can slow AHL in animals but that the effects depends on many factors, including the type and dosage of antioxidant compounds, timing and duration of the treatment, species, and strains. Defining these factors and those we've yet to identify is one of the goals in future research.

3.3. Effect of calorie restriction against AHL

Caloric restriction (CR) extends the lifespan of most mammalian species and is the only intervention shown to slow the rate of aging in mammals. Maximum lifespan is thought to be increased by reducing the rate of aging, while the average lifespan can be increased by improving environmental conditions. In laboratory rodents, CR delays the onset of age-related diseases such as lymphomas, prostate cancer, nephropathy, cataracts, diabetes, hypertension, and hyperlipidemia, and autoimmune diseases (see Sohal and Weindruch, 1996; Mair and Dillin, 2008). Despite such evidence, the question remains whether CR also acts to retard aging and disease in higher species such as non-human primates and humans. In monkeys, CR has been reported to result in signs of improved health including reduced body fat, higher insulin sensitivity, increase in high-density lipoprotein and reduction in very low-density lipoprotein levels (Rezzi et al., 2009). Twenty-year longitudinal adult-onset CR study in rhesus macaques maintained at the Wisconsin National Primate Research Center (WNPRC) demonstrated that moderate CR lowered the incidence of aging-related deaths and delayed the onset of age-associated pathologies, such as diabetes, cancer, cardiovascular disease, and brain atrophy (Colman et al., 2009). Very recently, a CR regimen implemented in young and older age rhesus monkeys at the National Institute on Aging (NIA) has been shown not to improve survival outcomes, contrast with an ongoing study at WNPRC, suggesting a separation between health effects, morbidity and mortality (Mattison et al., 2012).

It is difficult to determine whether CR has beneficial effects on longevity and age-related diseases in humans because there are no validated biomarkers that can serve as surrogate markers of aging and because it is impractical to conduct randomized, diet-controlled, long-term survival studies in humans. Nonetheless,

data from epidemiologic studies suggest that CR may have beneficial effects on the factors involved in the pathogenesis of primary and secondary aging and life expectancy in humans. Food shortages during World War in European countries were associated with a sharp decrease in coronary heart disease mortality, which increased again after the war ended (Hindhede, 1921; Strom and Jensen, 1951). Another study among Spanish nursing home residents undergoing long-term alternate day feeding regimen also demonstrated decreased morbidity and mortality (Vallejo, 1957). In addition, inhabitants of Okinawa island, who ate ≈30% fewer calories than the rest of Japanese residents, had ≈35% lower rates of cardiovascular disease and cancer mortality than the average Japanese population and had one of the highest numbers of centenarians in the world (Kagawa, 1978). Due to the Westernization on the nutrition, resulting in increased meat intake and fat energy ratio and decreased intake of beans and vegetables, the longest life expectancy at birth for men in Okinawa is now no higher than the national average in Japan, reflecting increased mortality ratio due to heart disease and cerebrovascular disease (Miyagi et al., 2003) .It should be noted, however, that these associations do not prove causality between decreased calorie intake and increased survival and that CR studies in humans did not always show influence on age-related changes.

The preventive effect of CR against AHL has been inconsistent across reports (see review by Someya et al., 2010a). Fischer rats that were calorie restricted to 70% of the control intake beginning at one month of age and then housed for 24–25 months showed significantly better hearing thresholds, reduced hair cell loss, and decreased mtDNA common deletion in the auditory nerve and stria vascularis of the cochlea compared to controls (Seidman, 2000). CR also delayed the onset of AHL in the AU, CBA and B6 strains of mice, but not in the DBA, WB, or BALB strains. Beneficial effects by CR have been reported in monkeys maintained at WNPRC, but not in those at NIA. Interestingly, high fat diet given for 12 month, which is opposite to CR, elevated hearing thresholds at high-frequency region and increased ROS generation, expressions of NADPH oxidase and UCP, accumulation of mtDNA common deletion, and cleaved caspase-3 and TUNEL-positive cells in the inner ear of Sprague–Dawley rats (Du et al., 2012).

The underlying mechanisms for the CR-associated benefits remain unclear. Someya et al. (2007b) observed that C57B/6 mice that received CR by 15 months of age retained normal hearing and showed no obvious cochlear degeneration and a significant reduction in the number of TUNEL-positive cells and cleaved caspase-3-positive cells in the spiral ganglion cells compared to age-matched controls; microarray analysis also revealed that CR down-regulated the expression of 24 apoptotic genes, including *Bak* (BCL2-antagonist/killer 1) and *Bim* (BCL2-like 11), suggesting that CR could prevent apoptosis of the cochlear cells. In addition, oxidative stress by paraquat induced *Bak* expression and apoptosis in primary cochlear cells, which was ameliorated in Bak-deficient cells (Someya et al., 2009). Furthermore, a mitochondrially targeted catalase transgene and oral supplementation with α-lipoic acid and coenzyme Q_{10} suppressed *Bak* expression in the cochlea, reduced cochlear cell death, and prevented AHL, suggesting that oxidative stress induces Bak-dependent apoptosis in the cochlear cells (Someya et al., 2009). It has recently been reported that CR failed to reduce oxidative DNA damage and prevent AHL in C57B/6 mice lacking the mitochondrial deacetylase Sirt3, a member of the sirtuin family (Someya et al., 2010b). In response to CR, Sirt3 directly deacetylated and activated mitochondrial isocitrate dehydrogenase 2 (Idh2), leading to increased NADPH levels and an increased ratio of reduced-to-oxidized glutathione in mitochondria. In cultured cells, overexpression of Sirt3 and/or Idh2 increased NADPH levels and protected from oxidative stress-induced cell death. These findings strongly suggest that at least a primary mechanism underlying the beneficial effects of CR is mediated by ROS-antioxidant systems and that Sirt3 is essential in enhancing the mitochondrial glutathione antioxidant defense system in the cochlea during CR.

3.4. Mitochondrial dysfunction and mitochondrial DNA mutations in AHL

Recent development of DNA microarray analysis has provided a global analysis of gene expression in the aging tissues. Someya et al. (2007a) compared gene expression profiles in the cochlea between 2-month-old and 8-month-old DBA/2J and found that AHL was associated with profound down-regulation of genes involved in the mitochondrial respiratory chain complexes in the cochlea of aged DBA/2J mice. A comparison of cochleae from middle aged C57B/6 mice under CR and normal control diet revealed that genes involved in apoptosis were down-regulated whereas those involved in mitochondrial function and DNA repair were up-regulated as a result of CR (Someya et al., 2007b).

As discussed before, mtDNA mutations and common ageing deletions have been reported to increase with aging in human temporal bones (Bai et al., 1997; Markaryan et al., 2009, 2010; Fischel-Ghodsian et al., 1997). It has been shown that accumulation of mtDNA mutations leads to premature aging in mitochondrial mutator mice (*Polg* knockin mice), indicating a causal role of mtDNA mutations in mammalian aging (Kujoth et al., 2005; Trifunovic et al., 2004). The *Polg* knockin mice were created by introducing a two base substitution, which results in a defect in mtDNA proof-reading ability. Young *Polg* mutator mice were indistinguishable from wild-type WT littermates, but 9–10 months old mutator mice displayed a variety of premature aging phenotypes, including early onset of AHL, severe loss of the spiral ganglion neurons, degeneration of the stria vascularis, and increase of TUNEL-positive spiral ganglion cells, while age-matched wild-type mice displayed only minor loss/degeneration of the cochlear cells (Someya et al., 2008). DNA microarray analysis revealed that mtDNA mutations were associated with transcriptional alterations consistent with impairment of energy metabolism, induction of apoptosis, cytoskeletal dysfunction, and hearing dysfunction in the cochlea of aged *Polg* mutator mice. Niu et al. (2007) also reported that the mtDNA mutator mice showed progressive apoptotic cell loss in the spiral ganglion, increased pathology in the stria vascularis, and accelerated progressive degeneration in the neurons in the cochlear nucleus compared to wild-type mice. These findings imply that accumulation of mtDNA mutations lead to mitochondrial dysfunction, an associated impairment of energy metabolism, and the induction of an apoptotic program in the cochlea.

4. Putative mechanisms of AHL

As discussed above by reviewing recent human and animal studies, it is now well established that oxidative stress and mtDNA mutations/deletions play a crucial role in the development of AHL. Substantial evidence has accumulated from animal studies that cumulative effect of oxidative stress could induce damage to macromolecules such as mtDNA in the cochlea and that the resulting accumulation of mtDNA mutations/deletions and decline of mitochondrial function over time progressively induce (Bak-dependent) apoptosis of the cochlear cells. Epidemiological human studies have demonstrated four categories of risk factors of AHL, i.e., cochlear aging, environment such as noise exposure, genetic predisposition, and health co-morbidities such as cigarette smoking and atherosclerosis. Genetic investigation has identified several putative associating genes, including those related to antioxidant

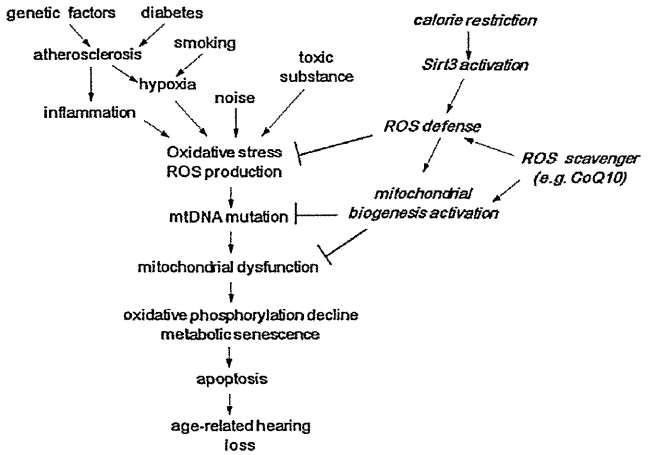

Fig. 2. Conceptual model of the development of age-related hearing loss.

defense system and atherosclerosis. Exposure to noise is known to induce excess generation of reactive oxygen species (ROS) in the cochlea, and cumulative oxidative stress can be enhanced by relatively hypoxic situations resulting from the impaired homeostasis of cochlear blood supply due to atherosclerosis, which could be accelerated by genetic and co-morbidity factors. Antioxidant defense system may also be influenced by genetic backgrounds including race. The conceptual figure of the model for the development of AHL has been shown in Fig. 2. This may explain the large variations of the onset and extent of AHL among elderly subjects. AHL has been shown to be slowed by certain interventions, such as CR and supplementation with antioxidants, in laboratory animals. Large clinical trials are needed to investigate if AHL can be delayed or prevented in humans and gain insights into the molecular mechanisms of AHL. Given the social value, quality of life and economic costs of AHL and the safety of many of the potentially effective interventions, we hope that such trials will begin in the near future.

Disclosures

Dr. Lin has served as a consultant to Pfizer, Autifony, and Cochlear Corp. Dr. Lin is on the scientific advisory board of Autifony.

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