中2耳（34%）で不変、4耳（66%）で悪化、またHuangら(15)は、17耳中9耳（53%）に10dB以上の聴力改善を認め、8耳（47%）で変化がなかったと報告している。Shojakuら(16)は、29耳中3耳(11%)に10dB以上の改善を認め、21耳（71%）で不変、5耳（18%）で悪化を認めたと報告した。

以上をまとめると、改善15耳（22%）、不変45耳（65%）、悪化9耳（13%）であり、聴力の長期成績においてはMeniett®の明らかな効果は認められなかった。

日本めまい平衡医学会の治療効果判定基準案(1993)(19)で評価した研究では、將積ら(20)は、めまいは8例中1例（13%）が著明改善、6例（78%）が改善、1例が不変で、聴力が改善した例はなく、7例（87%）が不変、1例（13%）で悪化したと報告した。青木ら(21)は、めまいは7例中6例（86%）が改善、聴力は2例（29%）が改善、3例（43%）が不変とした。五島ら(22)は、めまいは4例中2例（50%）が改善、2例（50%）が軽度改善と報告した。

以上をまとめると、めまい発作に関しては、著明改善1例（5%）、改善14例（74%）、軽度改善3例(16%)、聴力に関しては不変が多かった。めまい発作にはMeniett®の効果が認められたが、聴力改善の明らかな効果はなく、AAO-HNSの判定基準による報告と同様の結果であった。

5） 鼓膜マッサージ器について

Meniett®は本邦では医療機器として未承認のため、Watanabeら(23)は滲出性中耳炎治療装置である鼓膜マッサージ器をMeniett®の代替として使用した。Meniett®を使用した16耳と鼓膜マッサージ器を使用した12耳の検討で、12か月後に両群ともめまい発作回数が有意に減少し、めまい症状の経時的変化も両群間に違いはなかったとしている。鼓膜マッサージ器はMeniett®と同等の治療効果が期待でき、さらに入手が容易で安価、鼓膜換気チューブ挿入が不要という利点がある。

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3．内リンパ嚢開放術

内リンパ嚢開放術 (endolymphatic sac decompression: ELSD) は、保存的治療や中耳加圧治療に抵抗する難治性メニエール病の外科的治療法の中では第一選択の位置を占める。ELSD は内リンパ水腫を軽減させる直接的な治療であるとともに、ゲンタマイシン鼓室内注入、前庭神経切断術、迷路破壊術などの外科的治療に比べて機能が温存できることがその理由である。

ELSD 術後 1～2 年目のめまい制御率は 92～94%の高率と報告されている (1, 2)。しかし 4 年以上の長期成績では 64.5～79%に低下する (3－5)。肉芽や瘢痕による内リンパ管の再狭窄から再閉鎖に至る報告もある (6, 7)。そこで再狭窄を来さない工夫がされてきた。内リンパ嚢外壁のＬ字切開, 翻転

(8) に加え、ゼルフィルムを開放部から内リンパ腔内に挿入して狭窄を予防したり (9)、側頭筋膜で翻転した内リンパ嚢外壁を挙上固定する (10) などの試みがある。癒痕防止のため開放部にマイトマイシンを塗布する報告もある (11)。また、内リンパ腔へ高濃度ステロイドを局所投与することで、めまい制御のみでなく聴力の改善や悪化防止も期待できるという (4)。

ELSD に懐疑的な意見もある。ELSD と sham surgery である乳突削開術(12)、さらに鼓膜換気チューブ挿入とを比較したランダム化比較試験 (RCT) (13) では、ELSD のめまいに対する効果は否定的であった。しかし、Pullens らは systematic review で、両論文とも研究手法や統計処理などに問題点があり、さらなる検討が必要とした (14)。また、Thomsen らの論文 (12) は再解析されており、ELSD は乳突削開以上にめまい制御の効果があるとされている (15)。同論文のデータ解釈の問題点をまとめた報告もされており、めまい, 耳鳴などに対する効果も示された (16)。ELSD は内耳機能温存手術ではあるが感音難聴のリスクはあり、短期成績では 21%、長期成績では 29%に合併するという報告がある (17)。

メニエール病の病態は初期には可逆性である。よって保存的治療が第一選択であるが、それに抵抗する難治例が存在することは疑いのないところである。難治例に対してむやみに保存的治療を継続することは避けるべきであるが、機能回復の可能性はあるため機能廃絶を目的とした外科手術は避けたい。またメニエール病の側頭骨病理の検討で約 30%で両側性に内リンパ水腫があるといわれ (18)、長い経過をたどると両側性に移行する可能性がある (19) ことからも、外科的治療にはまず機能温存を考慮した手術を選択すべきである。

両側化についてはメニエール病の初期に手術を行えば対側発症を予防できるとする報告もある (20)。北原らも本研究班の成果として、ELSD は対側に内リンパ水腫のあるメニエール病の両側化を抑制する傾向があると述べており注目される (21)。

ELSD による QOL の改善率は 80～87%と高い (5, 22)。しかし、機能温存手術であるがゆえに再発のリスクも伴う。内リンパ嚢高濃度ステロイド挿入術後の再手術所見では、乳突洞粘膜の増生による内リンパ腔の閉塞がみられたとの報告もある (23)。手術法の改善などによる内リンパ腔の確実な開存が治療成績の向上に重要であろう。

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4．選択的前庭機能破壊術

難治性のめまいに対して、前庭機能を低下させる目的の前庭機能破壊は古くから行われてきた。手術的に内耳を摘出する方法や前庭神経切断などがある。薬物の全身投与で前庭機能を破壊する方法は Fowler により試みられた(1)。Schuknecht はより局所的な作用を目的として鼓室内投与を始めた(2)。ストレプトマイシンが使用されることもあった (3) が、近年ではより前庭系への作用が大きいゲンタマイシン (GM) が使われている。ここでは GM 鼓室内注入法について述べる。

これまで GM 鼓室内注入のメニエール病への応用には多くの報告がある。しかしながら、ランダム化比較試験 (RCT) は少なく、系統的な systemic review も少数である。これには難治例自体が少ないこと、薬剤投与量・濃度が一定しないこと、内耳への吸収量に個体差が大きいこと、投与方法が多様なことなどの要因があげられる。

1） 適応

保存的治療、鼓膜換気チューブ挿入、中耳加圧治療、さらに内リンパ嚢開放術に反応しない難治性の一側性メニエール病である。原則として聴力低下例とする。少なくとも6か月間、他の治療で経過をみることが必要とされる。年齢も適応決定の要素であるが、詳しく検討した報告はない。80 歳代に施行した報告 (4) もあるが、75歳以上は少ない。高齢者ではふらつきが長引きやすいため注意が必要とされる (5)。70 歳以前を一応の適応とするのが安全と思われる。遅発性内リンパ水腫の適応条件も基本的に同じである。

2） 方法

1回注入、少量注入、titration、持続注入法などがある。GMの1回注入濃度は10－40mg/ml、titration法では20-40mg/ml が多い。一回注入量は0.4～1.0ml である。GMの内耳への吸収は、内耳窓の透過性、蝸牛小管のサイズ、感覚細胞の薬剤感受性、遺伝子異常など種々の要素で左右されるので、一回注入量や回数を一律に規定できないのが実情である。東京医科大学では一層の安全を確保するため1回10 mg/ml の低濃度としている。

3）効果

RCTは2編 (6,7) 知られており、Pullens らによるreviewもある (8)。それによると両者ともプラセボに比して有意にめまいを抑制し、聴力の変化はわずかであった。Postema ら (6) は毎週1回計4回、GM とプラセボを 28 例に投与し、前者でめまいは有意に抑制され、聴力低下は前者で平均 8dB、後者は0dB とした。また、Stokroos ら (7) はtitration法でGMとプラセボを22例に投与し、やはりGM でめまいが有意に抑制され、有意の聴力低下はなかったとした。なお、平均注入回数は 1.5 回であった。

Cohen-Kerem ら (9) は 1985 年から 2003 年までの systemic review を行った。15 の文献から 16 の患者群の研究結果について解析し、AAO-HNS のガイドラインにそった診断と治療効果を判定した。このうち前向き研究と後ろ向き研究がそれぞれ8研究ずつであった。全体のめまい発作の抑制効果はclass A で74.7%、class A とBとをあわせて92.7%であった。また、1回注入法とtitration法で効果を比較したところ、注入法にかかわらず約90%以上が効果ありと判定された。聴力の変化は1回注入法で平均5.4dB、titration法で0.02dBで、他の報告と同様、後者の方が聴力への影響が少ないとした。ただ、これらの研究はRCTでないうえ、メニエール病のめまいや聴力が変化しうることから、解釈は慎重であるべきとした。また、GMの内耳組織中の半減期が30日という実験データがあることから (10)、短期間に反復投与するよりも少量を充分な間隔で投与するかtitrationで投与する方が耳毒性を回避しやすいと考察している。

Chia ら (11) もmeta-analysisによって5つの注入経路と効果を27の研究群で比較した。Class Aのめまいのコントロールは全体で73.6%、AとBで90.2%であった。有意の聴力悪化は全体で25.1%あり、複数回の連日注入で悪化する傾向があった。また、1週1回の注入や少量注入法では聴力への影響が最小であったが、めまい抑制効果も小さかったという。Titration 法ではめまいの効果は他よりも有意に高かったが、聴力への影響は他と変わりなかった。GMに対する前庭器の感受性や薬剤浸透性の個人差を考慮すると、titration法が安全かつ有効な投与法と考えられる。工田らも27編の論文のレビューから、めまいの改善率は平均86.5%であるが、難聴の発生率の低さからtitration法を推奨している (12)。ただ、Chia ら (11) も述べるように、患者の症状、眼振所見、前庭機能などを詳細かつ経時的に追う必要があるため、医療者側への負担は比較的大きい。

勝部らは2004年から2011年の難治性メニエール病と遅発性内リンパ水腫の9例に対し、GM鼓室内注入を施行した (13)。GM10mg/ml（1回）を 8 例に titration 法、1例に1回注入法で施行した。titration法の注入回数は3回から10回で、3回が多く4例あった。日本めまい平衡医学会のめまい

係数を指標にした効果は、著明改善10例、改善1例で、100%の有効性であった。聴力は1例で悪化、1例で改善、他は不変であった。

どの時点で注入を中止するかは重要な問題である。GM の内耳への吸収は、前述の種々の要素で左右されるので、GM の濃度と投与回数は一律に規定できない。投与中は慎重に自覚症状、聴力、前庭機能をモニターし、総合的に判定して中止の時期を決定する。温度眼振反応とめまいの効果には直接の関係はない(14)。温度刺激検査が半規管感覚細胞機能のすべてを反映しないことも要因であろう。感覚細胞障害のほか暗細胞の機能低下も GM の作用メカニズムとして知られている (9)。前庭機能が廃絶しなくても反応閾値が上昇するか、暗細胞の機能が低下すればめまいはコントロールできると考えられる。勝部らの報告でも温度刺激検査でCPであったものは有効であったが、CPがなくてもC-VEMPが低下した症例は有効であった (13)。温度刺激検査でのCPを必ずしも投与中止の条件にする必要はないと考えられる。前庭機能が低下する速度が遅ければ中枢代償も作用しやすく (4,5)、Pullens らも十分な間隔をあけた少量投与法を推奨しているように(8)、少なくとも急激に前庭機能を低下させることは避けるべきと考える。なお、Stokroos ら (7) は具体的な中止の目安として、めまい症状の改善、GM 総投与量が 360mg 以上、6か月以上の治療期間、連続した2周波数域での 15dB 以上の聴力低下、反対側での発症の疑い、中耳病変の発生をあげている。工田らはさらに安全を考慮して総投与量を 50mg 未満とした (12)。

以上から、難治性メニエール病に対しては、慎重に病態を評価し、十分なインフォームド・コンセント (IC) を取得した上で、titration による投与が適当と判断したい。

なお、以下に IC のポイントをあげる。Assimakopoulos らも同様の内容を報告している (5)。

・めまい発作の改善が目的であること
・投与後の浮遊感持続の可能性
・聴力低下の可能性
・耳鳴が変化する可能性
・鼓膜穿孔残存の可能性
・平衡リハビリテーションが必要となる可能性（とくに高齢者）
・薬物の delayed toxicity

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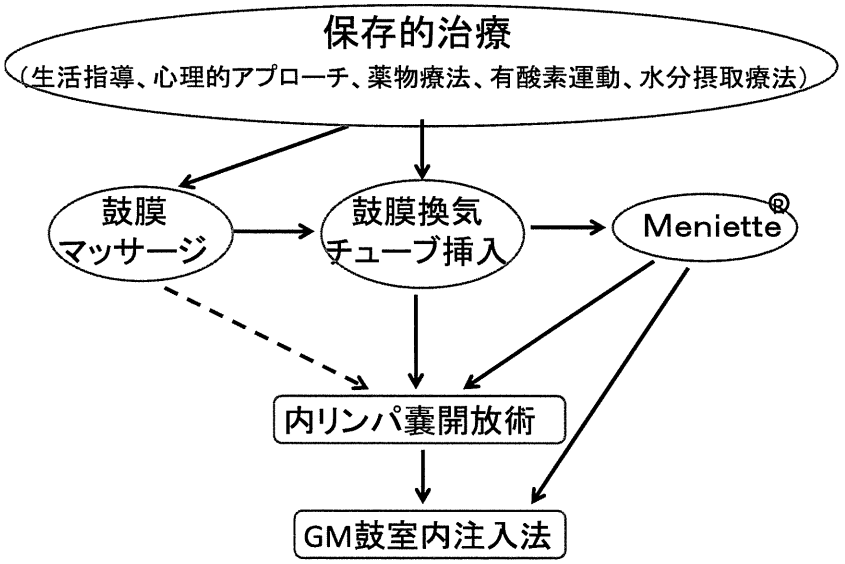
まとめ（治療のアウトライン）



Acta Oto-Laryngologica, 2011; 131: 263–268

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ORIGINAL ARTICLE

Blockage of longitudinal flow in Meniere's disease: A human temporal bone study

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Abstract

Conclusion: Blockage of the endolymphatic duct is a significant finding in Meniere's disease. The position of the utriculo-endolymphatic valve (UEV) and blockage of the ductus reuniens in the temporal bones were not found to be directly indicative of Meniere's disease. *Objective:* Comparison of blockage of the longitudinal flow of endolymph between ears affected by Meniere's disease and normal ears. *Methods:* We examined 21 temporal bones from 13 subjects who had Meniere's disease and 21 normal temporal bones from 12 controls. *Results:* The endolymphatic duct was blocked in five (23%) ears affected by Meniere's disease ($p = 0.016$). The utricular duct was blocked in 16 (76%) ears affected by Meniere's disease and 11 (52%) normal ears ($p = 0.112$). The saccular duct was blocked in 6 (28%) of ears affected by Meniere's disease and 16 (76%) normal ears ($p = 0.001$). The ductus reuniens was blocked in 10 (47%) ears affected by Meniere's disease and 10 (47%) normal ears ($p = 1.000$).

Keywords: *Histopathology, endolymphatic hydrops, endolymphatic duct, utriculo-endolymphatic valve, ductus reuniens, fistula*

Introduction

Meniere's disease is a complex condition of the inner ear, which is the most common cause of episodic vertigo combined with fluctuating hearing loss. The etiology and pathophysiology of Meniere's disease remain controversial and are not clearly understood even after a century of research. Endolymphatic hydrops was reported independently in 1938 by Hallpike and Cairns [1] and Yamakawa [2] and has been defined as a pathologic marker in Meniere's disease. Some studies describing the various congenital or developmental anomalies that involve the longitudinal endolymphatic drainage system, which could lead to Meniere's disease, exist in the literature [3,4]. It has been reported that endolymphatic flow may usually be blocked in the endolymphatic duct, ductus reuniens, and utriculo-endolymphatic valve (UEV) [4–7]. Although some reports in the literature discuss blockage in Meniere's disease, to the best of our knowledge, no study yet has compared temporal bones affected by Meniere's disease and normal temporal bones. Here, we report the histological findings of 42 temporal bones – 21 of those affected with Meniere's disease and 21 normal ears.

Material and methods

We examined 21 temporal bones from 13 patients who had Meniere's disease (mean age, 68.0 years) and 21 normal temporal bones from 12 control subjects (mean age, 61.5 years). Of the former group, five ears were affected unilaterally and eight bilaterally. Clinical diagnosis of Meniere's disease was established on the basis of the criteria of the Committee

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(Received 5 June 2010; accepted 7 October 2010)

ISSN 0001-6489 print/ISSN 1651-2251 online © 2011 Informa Healthcare
DOI: 10.3109/00016489.2010.532155

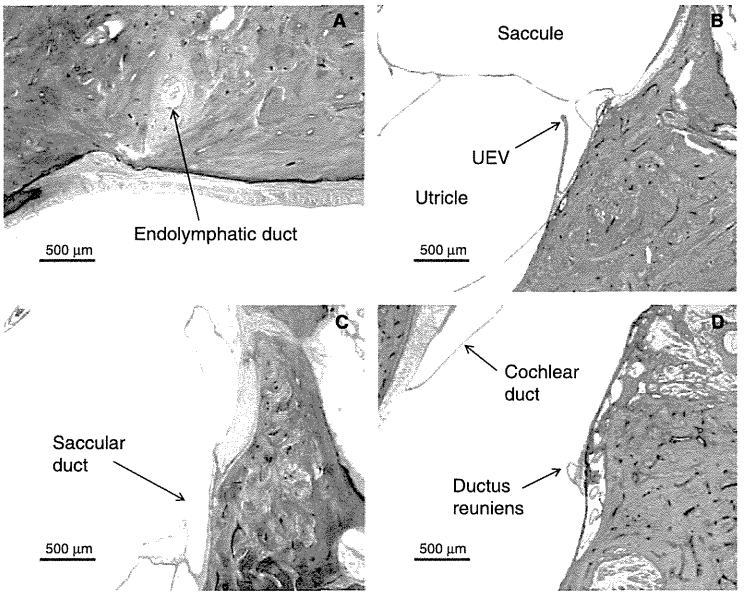

Figure 1. Patency of endolymph in ears affected by Meniere's disease. (A) Blockage of the endolymphatic duct. (B) Open utriculo-endolymphatic valve. (C) Open saccular duct. (D) Open ductus reuniens.

on Hearing and Equilibrium, American Academy of Otolaryngology-Head and Neck Surgery.

All temporal bones were removed at autopsy, fixed in formalin, decalcified, and embedded in celloidin. Each bone was cut into serial horizontal sections of 20 μm thickness. Every 10th section was stained with hematoxylin and eosin and mounted on a glass slide for light microscopic study. We checked for blockages of the endolymphatic duct, utricular duct, saccular duct, and cochlear duct and for fistulae involving the cochlear duct, saccule, and utricle. We studied the serial sections around the continuous fistulae and excluded slides that had discontinuous fistulae.

For statistical analysis, we used two-sample *t* tests to evaluate the frequency of blockages in the different groups. A difference was considered significant if $p < 0.05$.

Results

The patency of endolymph in ears affected by Meniere's disease is shown in Figure 1. The endolymphatic duct was blocked in 5 (23%) of the 21 temporal bones from patients who had Meniere's disease but in none of the 21 normal temporal bones ($p = 0.016$) (Table I). Although Meniere's disease was associated with otosclerosis in three ears, the endolymphatic duct was blocked in the temporal bone of only one of these. Other reasons for blockage of the endolymphatic duct were fibrous changes in three and mucosal proliferation in one of the above-mentioned ears. The endolymphatic sinus was blocked in only one ear affected by Meniere's disease. The utricular duct was blocked in 16 (76%) ears affected by Meniere's disease and 11 (52%) normal ears; almost all of these blockages were caused at the

Table I. Comparison of frequency of blockages or fistulae between ears affected by Meniere's disease and normal ears.

	Blockage					Fistulae				
Status	E duct	E sinus	U duct	S duct	DR	S–P	U–P	C–P	C–S	S–U
Meneiere's disease ($n = 21$)	5 (23%)	1 (4%)	16 (76%)	6 (28%)	10 (47%)	11 (52%)	9 (42%)	8 (38%)	1 (4%)	4 (19%)
Normal ($n = 21$)	0 (0%)	0 (0%)	11 (52%)	16 (76%)	10 (47%)	7 (33%)	15 (71%)	1 (4%)	0 (0%)	0 (0%)
t test	0.016	0.323	0.112	0.001	1	0.222	0.063	0.007	0.323	0.036

E, endolymphatic; U, utricle; S, saccule; DR, ductus reuniens; C, cochlear duct.

Table II. Complications of blockages and fistulae in ears affected by Meniere's disease.

	Blockage				Fistulae		
	E duct	U duct	S duct	DR	S – P	U – P	C – P
E duct (+) ($n = 5$)		4 (80%)	1 (20%)	4 (80%)	2 (40%)	0 (0%)	1 (20%)
E duct (–) ($n = 16$)		12 (75%)	5 (31%)	6 (37%)	9 (56%)	9 (56%)	7 (43%)
t test		0.829	0.647	0.106	0.549	0.026	0.364
U duct (+) ($n = 16$)	4 (25%)		5 (31%)	8 (50%)	9 (56%)	8 (50%)	6 (37%)
U duct (–) ($n = 5$)	1 (20%)		1 (20%)	2 (40%)	2 (40%)	1 (20%)	2 (40%)
t test	0.829		0.647	0.713	0.549	0.258	0.924
S duct (+) ($n = 6$)	1 (16%)	5 (83%)		4 (66%)	4 (66%)	2 (33%)	4 (66%)
S duct (–) ($n = 15$)	4 (26%)	11 (73%)		6 (40%)	7 (46%)	7 (46%)	4 (26%)
t test	0.647	0.647		0.292	0.432	0.599	0.096
DR (+) ($n = 10$)	4 (40%)	8 (80%)	4 (40%)		4 (40%)	4 (40%)	3 (30%)
DR (–) ($n = 11$)	1 (9%)	8 (72%)	2 (18%)		7 (63%)	5 (45%)	5 (45%)
t test	0.106	0.713	0.292		0.302	0.812	0.491
S – P (+) ($n = 11$)	2 (18%)	9 (81%)	4 (36%)	4 (36%)		7 (63%)	6 (54%)
S – P (-) ($n = 10$)	3 (30%)	7 (70%)	2 (20%)	6 (60%)		2 (20%)	2 (20%)
t test	0.549	0.549	0.432	0.302		0.045	0.113
U – P (+) ($n = 9$)	0 (0%)	8 (88%)	2 (22%)	4 (22%)	7 (77%)		4 (22%)
U – P (–) ($n = 12$)	5 (41%)	8 (66%)	4 (33%)	6 (50%)	4 (33%)		4 (33%)
t test	0.026	0.258	0.599	0.812	0.045		0.625
C – P (+) ($n = 8$)	1 (12%)	6 (75%)	4 (50%)	3 (37%)	6 (75%)	4 (50%)	
C – P (–) ($n = 13$)	4 (30%)	10 (76%)	2 (15%)	7 (53%)	5 (38%)	5 (38%)	
t test	0.364	0.924	0.096	0.491	0.113	0.625	

E, endolymphatic; U, utricle; S, saccule; DR, ductus reuniens; C, cochlear duct.

UEV (13/16 ears affected by Meniere's disease and 11/11 normal ears) ($p > 0.05$). The utricular duct blockages in the remaining 3 of the 16 ears were caused by compression of the distended utricle. The saccular duct was blocked in 6 (28%) ears affected by Meniere's disease and 16 (76%) normal ears. The saccular duct blockages in 4 of the 6 ears affected by Meniere's disease and in all of the 16 normal ears were caused by duct collapse; the blockages in the remaining 2 ears affected by Meniere's disease were caused by compression of the dilated saccule or cochlear duct. Saccular duct blockages were significantly more frequent in the normal ears than in the ears affected by Meniere's disease ($p = 0.001$); this blockage in the latter cases was found in only one of the five ears that also had an endolymphatic duct blockage (Table II). The ductus reuniens was not blocked in any of the normal ears with no saccular duct blockage ($p = 0.01$) (Table III) but was blocked in 10 (47%) ears affected by Meniere's disease and 10 (47%) normal ears. The blockage of the ductus reuniens was caused by the collapse of the duct in all cases. All normal ears with ductus reuniens blockage also had saccular duct blockage ($p = 0.012$). A fistula was found between the saccule and perilymphatic space in 11 (52%) ears affected by Meniere's disease and 7 (33%) normal ears ($p = 0.222$). A fistula was also found between the utricle and perilymphatic space in 9 (42%) ears affected by Meniere's disease and 15 (71%) normal ears ($p = 0.063$). Endolymphatic duct blockage was not found in any of the ears affected by Meniere's disease with fistulae involving the utricle. A fistula was found between the cochlear duct and perilymphatic space in eight (38%) ears affected by Meniere's disease and one (4%) normal ear ($p = 0.007$). In addition, fistulae between the cochlear duct and saccule, and between the saccule and utricle were found in one (4%) and four (19%)

Table III. Complications of blockages and fistulae in normal ears.

	Blockage			Fistulae	
	U duct	S duct	DR	S – P	U – P
U duct (+) ($n = 11$)		9 (81%)	5 (45%)	5 (45%)	7 (63%)
U duct (–) ($n = 10$)		7 (70%)	5 (50%)	2 (20%)	8 (80%)
t test		0.549	0.844	0.237	0.432
S duct (+) ($n = 16$)	9 (56%)		10 (62%)	6 (37%)	12 (75%)
S duct (–) ($n = 5$)	2 (40%)		0 (0%)	1 (20%)	3 (60%)
t test	0.549		0.01	0.493	0.54
DR (+) ($n = 10$)	5 (50%)	10 (100%)		3 (30%)	8 (80%)
DR (–) ($n = 11$)	6 (54%)	6 (54%)		4 (36%)	7 (63%)
t test	0.844	0.012		0.771	0.432
S – P (+) ($n = 7$)	5 (71%)	6 (85%)	3 (42%)		7 (100%)
S – P (–) ($n = 14$)	6 (42%)	10 (71%)	7 (50%)		8 (57%)
t test	0.237	0.493	0.771		0.042
U – P (+) ($n = 15$)	7 (46%)	12 (80%)	8 (53%)	7 (46%)	
U – P (–) ($n = 6$)	4 (66%)	4 (66%)	2 (33%)	0 (0%)	
t test	0.292	0.54	0.432	0.042	

U, utricle; S, saccule; DR, ductus reuniens; C, cochlear duct.

ears affected by Meniere's disease, respectively. Blockages or fistulae in normal ears are shown in Figure 2.

Discussion

The endolymphatic duct was blocked only in ears affected by Meniere's disease; this finding is consistent with the findings of the previous studies [4,8,9]. However, there was no significant difference in the frequency of utricular duct blockage between ears affected by Meniere's disease and normal ears. Schuknecht and Belal reported that the UEV is normally closed in its normal position and only became significant under pathological conditions to prevent excessive loss of endolymph from the utricle [6]. Konishi observed that the UEV opens for a few days after hydrops begins and then closes because of the compression caused by increasing hydrops [10]. In this study, the UEV was closed in 16 (76%) ears affected by Meniere's disease and 11 (52%) normal ears; the frequency of the closure was not significantly different between ears affected by Meniere's disease and normal ears. Therefore, we believe that the UEV is often closed even in normal ears under certain conditions, and the position of the UEV in the temporal bones does not directly reflect the pathological condition of Meniere's disease. The saccular duct does not have a valve like the UEV and gets blocked because it collapses on itself. The saccular duct was blocked in many normal ears but was open in ears affected by Meniere's disease and with endolymphatic duct blockage. This finding indicated that the saccular duct is usually closed to maintain the pressure within the saccule, and it opens when the pressure needs to be reduced. Blockage of the ductus reuniens is also caused by collapse. This blockage was found in 47% (10 ears) of Meniere's disease cases, which is similar to that found in 56% of cases reported by Schuknecht [4]. However, the occurrence of blockage did not differ significantly

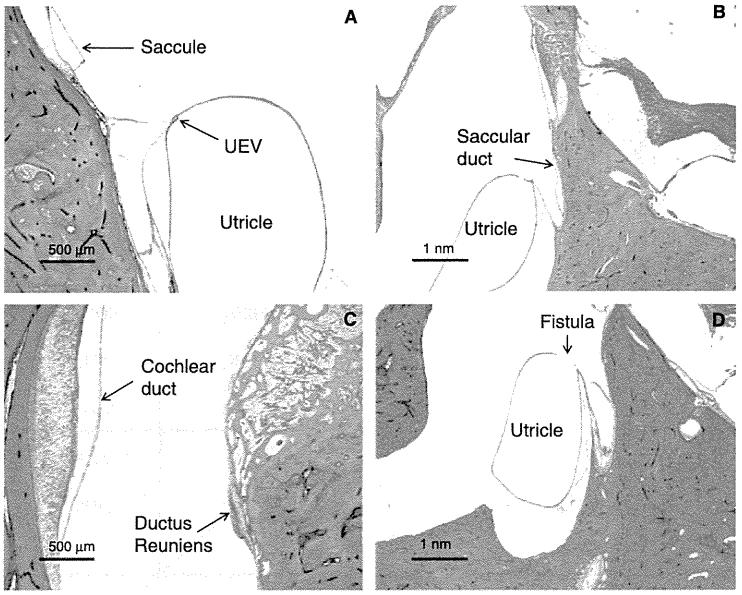

Figure 2. Blockages or fistulae in normal ears. (A) Closed utriculo-endolymphatic valve. (B) Collapsed saccular duct. (C) Collapsed ductus reuniens. (D) Fistula between the utricle and perilymphatic space.

between ears affected by Meniere's disease and normal ears. This finding indicates that ductus reuniens blockage is not of great importance in the etiology of Meniere's disease. In the normal ears with open saccular ducts, the ductus reuniens was found to be open, and in normal ears with closed ductus reuniens, the saccular duct was found to be closed. These findings probably reflect the pressure of the endolymph produced in the cochlear duct. Bachor and Karmody have postulated that the collapse of the ductus reuniens is correlated to the closure of the UEV caused by decreasing pressure in the entire endolymphatic system [5]. Kitahara et al. indicated that a negative-feedback system between plasma vasopressin and its receptor in the endolymphatic sac in normal subjects could ensure inner ear fluid homeostasis [11]. These compensatory processes may be a reason for the lack of a significant relationship between the blockage of some ducts and endolymphatic hydrops in our study. The number of fistulae between the cochlear duct and perilymphatic space has been shown to be significantly higher in ears affected by Meniere's disease, and almost all fistulae were found in the Reissner membrane. Therefore, this finding would indicate the pathological condition of Meniere's disease [12–14]. However, this finding was noted only in one normal ear in this study. Further, similar numbers of fistulae between the saccule or utricle and the perilymphatic space were found in normal ears and in ears affected by Meniere's disease. Schuknecht and Rüther reported that fistulae may theoretically act as escape routes for the accumulating endolymph and thus arrest the progression of endolymphatic hydrops [4]. In fact, many fistulae involving both the saccule and utricle were found in ears affected by Meniere's disease as well as in normal ears. This finding indicates that the elevation of endolymph pressure happens in the entire inner ear. In ears with Meniere's disease and fistulae involving the utricle, the endolymphatic duct was always found to be open. The fistula involving the utricle may have arisen as a result of endolymphatic hydrops, due to hyperproduction of endolymph in the entire inner ear [15].

Acknowledgments

This work was supported by the following institutions: the National Institute on Deafness and other Communication Disorders (NIDCD) (3U24DC008559-03S1); the International Hearing Foundation, the Lions 5M International of Minnesota; and the Starkey Foundation. We appreciate the invaluable contributions of Carolyn Sutherland and Monika Schachern.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Otology & Neurotology
33:1151–1155 © 2012, Otology & Neurotology, Inc.

Vestibular System Changes in Sudden Deafness With and Without Vertigo: A Human Temporal Bone Study

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Objective: To investigate the vestibular system changes in sudden deafness with vertigo (SDwV) and sudden deafness without vertigo (SDwoV) and the cause of persistent canal paresis (CP) in SDwV patients.
Study Design: Retrospective study.
Materials and Methods: Four temporal bones from the affected ear in 4 patients with unilateral sudden deafness (SD), 2 SDwV and 2 SDwoV, were selected. Four contralateral temporal bones with normal-hearing ears were defined as the control. Morphologic findings of the labyrinth, the number of Scarpa's ganglion cells, and the density of vestibular hair cells were investigated in all temporal bones. Clinical data and the results of vestibular tests of 11 patients with unilateral SD, as a separate group, also were investigated.
Results: Atrophic change of the organ of Corti, tectorial membrane, and stria vascularis in cochlea, and deposits and atrophic otoconial membrane in vestibular sense organs were seen on affected ears more than control ears. The density of Type I hair cells seemed to decrease on the saccular macula and the posterior semicircular canal crista on affected ears, and there was no remarkable difference between SDwV and SDwoV. In 1 patient with SDwoV who died 10 months after the onset of SD, there were large amount of deposits on the cupula, the atrophied otoconial membrane was peeling off from the saccular macula, and the saccular membrane collapsed to the saccular macula in the affected ear. In the clinical data, all SDwV who were examined within 2 years from the onset had CP, and all SDwV had profound hearing loss.
Conclusion: There is no remarkable difference between SDwV and SDwoV in the number of Scarpa's ganglion cells and the density of vestibular hair cells. The damage of the extracellular superstructure is seen in SD with or without vertigo. The damage of extracellular superstructure is potentially one of the causes of persistent CP in patients with SD. **Key Words:** Extracellular superstructure—Sudden deafness—Scarpa's ganglion cell—Temporal bone—Vertigo—Vestibular hair cell.

Otol Neurotol **33**:1151–1155, 2012.

Patients with sudden deafness (SD) often have accompanying vertigo. Kitahara et al. (1) suggested that patients with SD with vertigo (SDwV) had damage mainly in the labyrinth, which was concluded from the pattern of acceleration of central vestibular compensation. They also reported that 66.7% of SDwV with canal paresis (CP) at the onset of SD still had CP around 2 years later. Iwasaki et al. (2) reported that the lesion site of SDwV was within the labyrinth, which was concluded from the results of click– and galvanic–vestibular evoked myogenic potential, and the saccule could be involved more frequently than the semicircular canals, which was concluded from the findings of click–vestibular evoked myogenic potential and caloric test. However, it was reported that there were no remarkable histopathologic changes in the vestibular sense organs in patients with SD (3–8). Khetarpal (9) also reported that there was no significant difference in the number of Scarpa's ganglion cells or the density of vestibular hair cells among SDwV, SD without vertigo (SDwoV), and control. He suggested that SDwV was caused by ultrastructural changes in the vestibular nerves and sensory cells or alterations in their biochemical environment.

In this study, we correlated the vestibular system changes in SDwV and SDwoV and with the clinical data of patients with SD.

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This study was supported by the National Institute on Deafness and Other Communication Disorders (1U24DC011968-01), International Hearing Foundation, Starkey Foundation, and 5M Lions International

The authors disclose no conflicts of interest.

MATERIALS AND METHODS

The materials for this study were selected from the temporal bone collection of the University of Minnesota, Minneapolis. There were 4 temporal bones (TBs) from the affected ear in 4 unilateral patients with SD, 2 SDwV and 2 SDwoV, which had no history of otologic disease except SD. Four contralateral TBs with normal-hearing ears were defined as the control.

TBs were harvested at the time of autopsy, fixed in 10% formalin, decalcified with ethylenediamine tetra-acetic acid, dehydrated in graded concentrations of alcohol, and embedded in celloidin. Specimen was cut at a section thickness of 20 μm with a sliding microtome in the horizontal plane from superior to inferior. Every 10th section was stained with hematoxylin-eosin and mounted on a glass slide.

The organ of Corti, tectorial membrane, and stria vascularis in cochlea, any deposits, and integrity of membranes and cupula in the vestibular sense organs were investigated under light microscopy.

The number of Scarpa's ganglion cells was counted in all TBs. Scarpa's ganglion cells were divided into 2 cell groups, superior and inferior. Cells with nucleoli were counted separately in every 10th section under a magnification of ×200. The formula, $Ni = ni \times t/(t + d)$, was used to compensate for double counting of cells lying at the interface between sections (10). *Ni* is the estimated number of Scarpa's ganglion cells, *ni* was the counted number, *t* was the thickness of section (20 μm), and *d* was the mean value of nucleolar diameters in 100 Scarpa's ganglion cells. Finally, the number of Scarpa's ganglion cells was given by multiplying by 10 to account for unstained sections.

The density of vestibular hair cells in the cristae of the lateral semicircular canal (LSC) and the posterior semicircular canal (PSC), and utricular and saccular maculae were examined in all TBs. According to the criteria of Merchant (11), Types I and II hair cells with nucleus were counted separately under differential interference contrast (Nomarski) microscopy at a magnification of ×1,250. The results were expressed as the number of hair cells per 0.01 mm^2 of surface area, which was determined by dividing the number of counted hair cells by the surface area of the sensory epithelium. Surface area was determined by multiplying the thickness of the section (20 μm) by the length of the sensory epithelium where the count was made. The counts were performed in areas where the cut was perpendicular to the surface of the sensory epithelium. The formula, $Ni = ni \times t/(t + d)$, was again used. *Ni* is the estimated density of vestibular hair cells, *ni* was the raw density, *t* was the thickness of section (20 μm), and *d* was the mean

TABLE 1. *Histopathologic findings*

			Cochlea						Vestibular system			
				Hair cell								
Case			Turn	Inner	Outer	Supporting cell	Tectorial membrane	Stria vascularis	Portion	Deposit	Integrity of membrane	Cupula
Affected ear	1	SDwV	Apical		2+	Damage	Atrophic	Thin	Saccule	+		—
			Middle	loss	3+	Damage	Atrophic	Thin	Utricle	+		—
			Basal	loss	3+	Damage	Atrophic	Thin	LSC	+		Removed
									PSC	+		Removed
	2	SDwV	Apical		1+			Thin	Saccule			—
			Middle	loss	3+	Damage		Thin	Utricle			—
			Basal	loss	4+	Damage		Thin	LSC	+		
									PSC			
	3	SDwoV	Apical	loss	4+	Damage	Atrophic	Thin	Saccule	+	Collapse	—
			Middle	loss	4+	Damage	Atrophic	Thin	Utricle			—
			Basal	loss	4+	Damage	Atrophic	Thin	LSC	+		Deposit
									PSC	+		Deposit
	4	SDwoV	Apical		1+		Atrophic	Thin	Saccule			—
			Middle		3+		Atrophic	Thin	Utricle			—
			Basal		4+		Atrophic	Thin	LSC			Deposit
									PSC	+		Deposit
Control ear	1	SDwoV	Apical		1+			Thin	Saccule			—
			Middle		2+			Thin	Utricle			—
			Basal		3+	Damage	Atrophic	Thin	LSC			Removed
									PSC			Removed
	2		Apical		1+				Saccule			—
			Middle		2+				Utricle			—
			Basal		2+				LSC			
									PSC	+		
	3		Apical		1+			Thin	Saccule			—
			Middle		1+			Thin	Utricle		D[a]	—
			Basal		1+			Thin	LSC	+		Deposit
									PSC			
	4		Apical		2+				Saccule			—
			Middle		2+				Utricle			—
			Basal		2+				LSC			
									PSC	+		

Outer hair cell: 1+, less than 30% loss; 2+, 30% to 60% loss; 3+, 60% to 90% loss; 4+, greater than 90% loss.

LSC indicates lateral semicircular canal; PSC, posterior semicircular canal; SDwoV, sudden deafness without vertigo; SDwV, sudden deafness with vertigo.

[a]D: the processing damage.

TABLE 2. *The number of Scarpa's ganglion cells and the density of vestibular hair cells*

			Scarpa's ganglion cells			Vestibular hair cells (/0.01 mm^2)							
						Saccular macula		Utricular macula		LSC crista		PSC crista	
Case			Superior	Inferior	Total	Type I	Type II	Type I	Type II	Type I	Type II	Type I	Type II
Affected ear	1	SDwV	10814	7995	18810	21.6	19.1	25.2	20	30.5	20.7	D[a]	D[a]
	2	SDwV	8439	D[a]		8.4	11.6	18.9	17.4	17.5	17.4	14.7	18.5
	3	SDwV	9170	8404	17577	19.3	18	28.6	21.3	33.6	18.9	21.8	15.7
	4	SDwV	9013	5455	14472	10.1	17.7	26	20.4	37.1	21.1	29.4	23.5
Control ear	1	SDwV	10527	7386	17914	27.5	18	24.4	23.5	31.5	23.2	D[a]	D[a]
	2	SDwV	9413	D[a]		12.6	13.7	16.8	14.4	14.7	19.6	29.4	17.4
	3	SDwV	10344	7969	18316	26.6	18.9	24.4	23.1	37.1	20.3	35	24.6
	4	SDwV	9970	5090	15064	24.6	17.7	27.7	23.1	35	19.6	32.6	19.6

[a]D: the processing damage.

value of nuclear diameters in 100 vestibular hair cells. The density of total hair cells was calculated by summing the densities of Types I and II hair cells.

In addition, there were 11 patients with SD, 6 SDwV and 5 SDwoV, to whom pure tone audiometry and caloric test had been performed at the Paparella Ear Head and Neck Institute between July 2001 and October 2008. The criteria for SD included more than 30-dB sensorineural hearing loss occurring in at least 3 contiguous frequencies, and in addition, SDwV patients had a single attack of rotatory vertigo occurring almost simultaneously with the onset of hearing loss, and no other neurologic signs (2). Caloric weakness that was more than 25% was defined as CP. Pure tone average was calculated as the average threshold at 500, 1,000, and 2,000 Hz. Profound hearing loss was defined to be more than 60 dB in pure tone average. The recovery was defined as hearing improvement, which was more than 10 dB comparing the pure tone average with the previous one. This study was approved by the institutional review board of the University of Minnesota (0206M26181).

RESULTS

Histopathologic changes are shown in Table 1. Cochlea hair cells and supporting cells were more atrophic in affected ears than in control ears. In addition, the loss of inner hair cells was found in 3 of 4 affected ears. Stria vascularis was atrophic in all affected ears. The tectorial membrane was atrophic in all turns of the cochlea in 3 of 4 affected ears. Deposits were seen in the vestibular endolymphatic space and were more commonly attached to

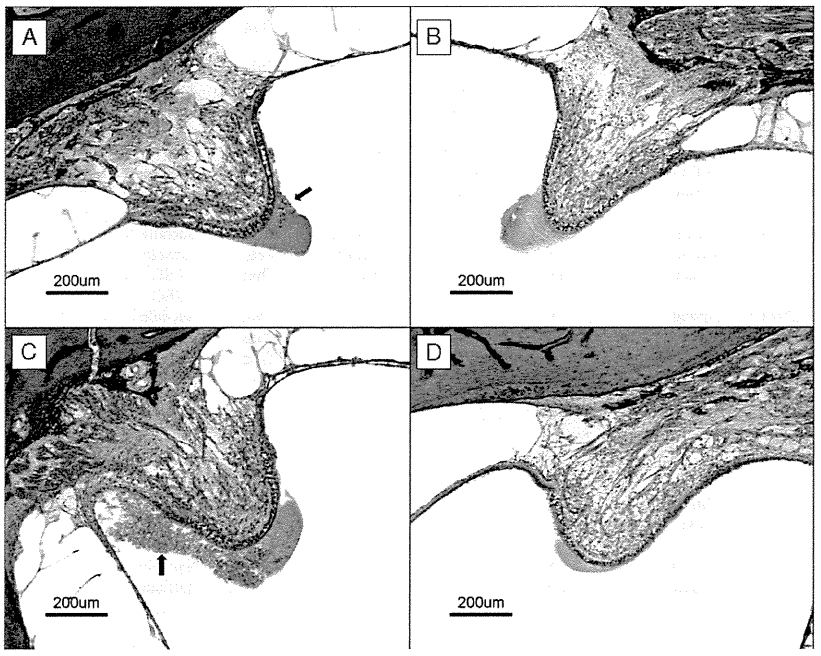

FIG. 1. Ampulae of LSC and PSC in Case 3. This figure shows the crista and cupula of LSC on the affected (right) ear (*A*) and control (left) ear (*B*), and the crista and cupula of PSC on the affected ear (*C*) and control ear (*D*). Large amount of deposits (*arrow*) are attached to cupula in the affected ear. (Nomarski microscopy; original magnification, ×1,250).

the cupula in affected ears than in control ears. The findings, which suggest previous rupture of the membranes, were not seen. There was no significant difference between SDwV and SDwoV groups regarding inner ear changes.

As for the number of Scarpa's ganglion cells and the density of vestibular hair cells in the utricular macula and the LSC crista, there was no remarkable difference between affected ears and control ears (Table 2). The density of Type I hair cells in the saccular macula and the PSC crista seemed to be lower in affected ears than control ears. There was no remarkable difference in the density of vestibular hair cells between SDwV and SDwoV.

Case 3 was a SDwoV who died 10 months after the onset of SD. In this case, there was a remarkably large amount of deposit (otolith) attached to the cupula (Fig. 1). The otoconial membrane was atrophied and peeling off from the macula in the saccule. The collapse of the saccular membrane also was seen (Fig. 2).

In the clinical data (Table 3), there were 4 patients with CP (CP+) and 2 patients without CP (CP−) in SDwV. The CP+ were examined within 2 years from the onset of SD, and the CP− were examined after 5 years and 17 years from the onset. All 6 patients had a profound hearing loss, and the recovery was seen in 2 CP+ and 1 CP−. In SDwoV, there were 3 CP+ and 2 CP−, all of which were examined within 2 years from the onset of SD. Profound hearing loss was seen in 2 CP+ and 1 CP−, and recovery was seen in 1 CP+ and 1 CP−. Mild hearing loss was seen in 1 CP+ and 1 CP−, and no recovery was noted.

DISCUSSION

In the histopathologic findings of the cochlea, the atrophic change of organ of Corti, stria vascularis, and tectorial membrane and a significant decrease in the number of the spiral ganglion cells and cochlea nerve fibers have been reported in SD (3–8,12). These changes also were seen in the current study. It was reported that there were no remarkable histopathologic changes in the vestibular sense organs in patients with SD (3–8). Also, there was no remarkable histopathologic change in TBs of patients with SD in the current study, except for deposits on the cupula.

Khetarpal (9) has found no significant difference in the number of Scarpa's ganglion cells among SDwV, SDwoV, and controls. Our findings were consistent with Khetarpal's findings in this regard. We can speculate that the Scarpa's ganglion cells are not involved in the formation of vertigo in patients with SD.

Although several literatures reported the loss of vestibular hair cells in patients with SD (3–7), which was seen mostly in saccular macula, Khetarpal (9) has found no difference in terms of vestibular sensory epithelia. In the current study, the density of vestibular hair cells seemed to decrease on the saccular macula and the PSC

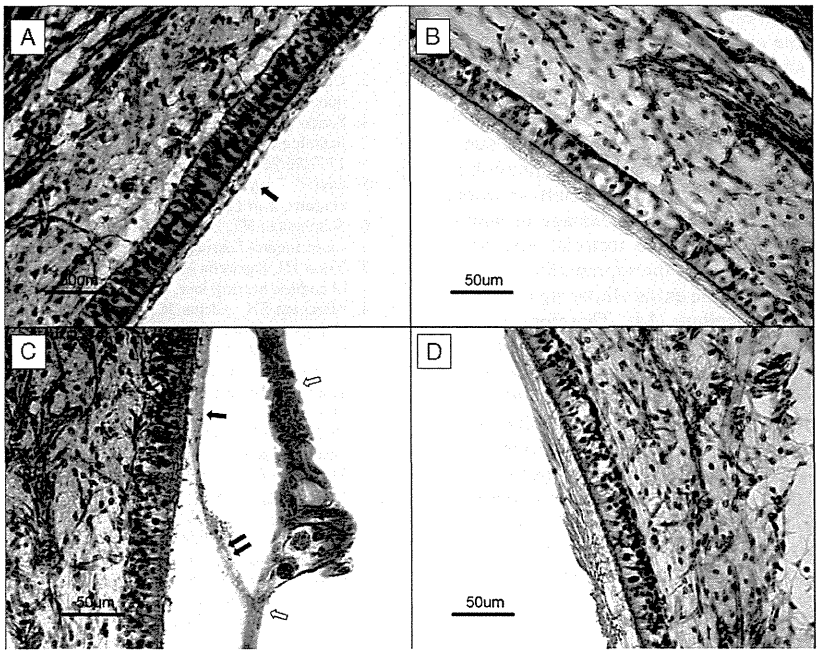

FIG. 2. Vestibular sensory epithelia in Case 3. This figure shows the utricular macula on the affected (right) ear (*A*) and control (left) ear (*B*) and the saccular macula on the affected ear (*C*) and control ear (*D*). On the affected ear, otoconial membrane is atrophied (*arrow*) and peeling off from the saccular macula (*double arrow*) and the saccular membrane collapsed to saccular macula (*white arrow*). (Nomarski microscopy; original magnification, ×1,250).

TABLE 3. *Clinical data*

			Examined date		Hearing		
			<2 Years	>2 Years	Pure tone average		R/NR
Caloric test (n = 11)	SDwV (n = 6)	CP+	4	0	Profound	4	2/2
					Mild	0	−/−
		CP+	0	2	Profound	2	1/0
					Mild	0	−/−
	SDwoV (n = 5)	CP+	3	0	Profound	2	1/1
					Mild	1	0/1
		CP+	2	0	Profound	1	1/0
					Mild	1	−/−

CP indicates canal paresis; NR, no recovery; R, recovery.

crista in patients with SD. However, it is not the main reason for the presence of vertigo in patients with SD because these findings were irrespective of vestibular symptoms.

In the clinical data, all CP+ were examined audiologically within 2 years from the onset of SD, and there was no CP+ examined more than 2 years after the onset of SD in SDwV. On the other hand, there was CP+ even in SDwoV. It is suspected that the damage might be more or less accompanied to the vestibule in patients with SD and that the damage is large enough to cause the vertigo in SDwV. In fact, all SDwV had a profound hearing loss in the current study. There was not a clear relationship between the caloric weakness, the hearing level, and the recovery.

A recoverable structure that can cause the vestibular dysfunction is thought to be the lesion site of SD. Merchant et al. (8) investigated the TB of a SDwoV who died 9 days after the onset of SD, and swelling of the organ of Corti and small spherical tectorial membrane were reported. However, they did not report the vestibular findings. In Case 3, we can see a similar change in the cochlea, the damage of otoconial membrane, and cupula deposits. Otolith is usually covered with a supraotolithic cupular zone on maculae (13). Large amounts of cupula deposits seem to be the evidence of damage of supraotolithic cupular zones. All of the tectorial membrane, otoconial membrane, including the supraotolithic cupular zone, and cupula make up the extracellular superstructure covering each neuroepithelium (14). Therefore, we suspect that the extracellular superstructure, consisting of an acellular gelatinous membrane, is one of the lesion sites of hearing loss and vertigo in patients with SD. Although it is difficult to evaluate cupula histopathologically because of its structure, Suzuki (15) reported that the shape of the cupula was changed after injecting gentamicin into the perilymphatic space in the experiment using bull frogs. The atrophic changes of extracellular superstructures also change the reactivity of the semicircular canal. It is potentially one of the mechanisms of the persistent CP in SDwV.

CONCLUSION

The density of vestibular hair cells seemed to decrease on the saccular macula and the PSC crista; however, the number of Scarpa's ganglion cells did not change in patients with SD. There is no remarkable difference between SDwV and SDwoV.

Hearing loss and vertigo in patients with SD may be due to the damage of the extracellular superstructure, and it may potentially be one of the causes of persistent CP in patients with SD.

ACKNOWLEDGMENT: The authors thank Carolyn Sutherland for the assistance in this study.

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Acta Oto-Laryngologica, 2012; 132: 228–233

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ORIGINAL ARTICLE

Changes in the cupula after disruption of the membranous labyrinth

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Abstract

Conclusion: Various changes were observed in the cupula, including shrinkage and enlarged volume, following the disruption of the membranous labyrinth. Cupular change after membranous labyrinth disruption may be a pathology of vestibular disorders. *Objectives:* To observe the morphological changes of the cupula after disruption of the membranous labyrinth and to compare the cupular changes with changes in the compound action potential (CAP) of the ampullary nerve. *Methods:* A labyrinthine injury model was created by puncturing the membranous labyrinth of bullfrogs. The cupula was observed from 3 to 17 days after the membrane puncture. The CAP in response to mechanical endolymphatic flow was recorded from the ampullary nerve. The correlation between cupular change and CAP positivity was evaluated using the authors' scale. *Results:* Various kinds of cupular changes including shrinkage were observed. Cupular change was more severe after a longer survival period. Large or elongated volume of the cupula was also observed, which was not observed in our previous study using gentamicin. The CAP could be recorded even when the cupular change was severe.

Keywords: *Semicircular canal, sensory epithelia, compound action potential, vestibular disorder*

Introduction

The cupula is a gelatinous substance that is found in the semicircular canal (SC) and ampulla, and plays an important role in the efficient transmission of rotatory acceleration to the sensory cells. However, the number of studies on the cupula still remains low because of its structural vulnerability and difficult accessibility.

Recent developments in molecular biology have enabled the identification of the major protein of the cupula and its encoding gene [1,2]. The cupula has to meet several biophysical requirements [3], such as 1) adhesiveness to the ampullary wall, 2) cohesiveness and stability against the shear force generated by the movement of the endolymph, 3) elasticity when acting as a diaphragm in the ampullary lumen, and 4) osmotic resistance against swelling and shrinking in conditions of osmotic change. We previously performed a series of experiments on the physical properties of the cupula [4,5], which confirmed all these requirements. Our most recent experiment demonstrated that the cupula undergoes significant change after gentamicin (GM) administration [6]. Change was also observed in the sensory epithelia, but the degrees of cupular and sensory epithelial damage showed no correlation. This makes the vestibular pathology of dizzy patients complex. Thus, changes of the cupula under various insults have become an important issue.

In the present study, we attempted to create a model of a different type of vestibular insult. The membranous labyrinth was punctured to simulate mechanical injury to the labyrinth, with the assumption that various changes within the inner ear would be induced, such as a mixture of endolymph and perilymph or labyrinthitis. We observed the morphological changes of the cupula and examined the associated physiological changes in the sensory epithelia.

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(Received 28 September 2011; accepted 17 October 2011)

ISSN 0001-6489 print/ISSN 1651-2251 online
DOI: 10.3109/00016489.2011.635385

Material and methods

Puncture of the membranous labyrinth

Thirty-four bullfrogs (Rana catesbeiana) were used. Under ether anesthesia, the mouth was opened to expose the palatal mucosa. The mucous membrane was incised to expose the bony labyrinth surface. A 2 mm section of the bony labyrinth was chiseled off and the saccular otoconia were visualized. A fine tungsten needle was then inserted into the labyrinth to penetrate the center part of the saccule and touch the dorsal side of the bony labyrinth (Figure 1).

Observation of the cupula

At 3–17 days after puncturing the membranous labyrinth, the animals were decapitated under deep anesthesia with ether. The labyrinth was removed to observe the cupulae of the three SCs and to record the ampullary nerve compound action potential (CAP). Indian ink was injected into the SC ampulla to stain the cupula. Subsequently, Ringer solution was gently flushed into the ampulla to exert pressure on the cupula and detach it from the crista. The morphology of the detached cupula was evaluated in accordance with the grading system of GM intoxication [6]: grade I, normal or limited change such as indentation of the apex; grade II, <50% shrinkage; grade III, 51–80% shrinkage; and grade IV, >80% shrinkage or absence. The details of this preparation technique were reported previously [4,6].

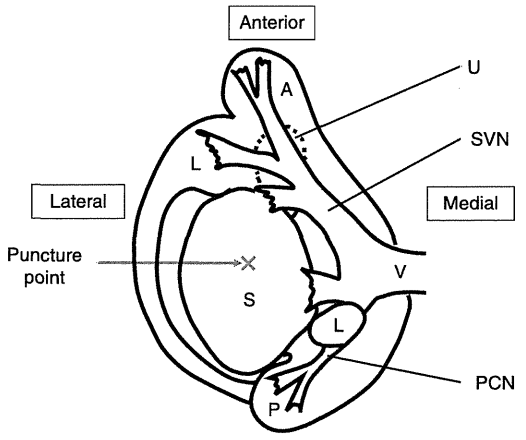

Figure 1. Diagram of the puncture point showing the right side of the labyrinth from the ventral side. A, anterior semicircular canal; L (upper), lateral semicircular canal; P, posterior semicircular canal; S, saccule; U, utricle; L (lower), lagena; V, vestibular nerve; SVN, superior vestibular nerve; PCN, posterior semicircular canal nerve.

The animals were divided into two groups, either short-term or long-term groups. In the short-term group they were sacrificed within 3–7 days, and in the long-term group they were sacrificed 10–17 days after the labyrinthine puncture. The number of examined SCs in the short-term group was 32, and the average survival period was 5.9 days. The number of examined SCs in the long-term group was 48, and the average survival period was 13.5 days. The number of examined SCs included 33 posterior SCs (PCs), 23 anterior SCs (ACs), and 24 lateral SCs (LCs). The total number of examined SCs was 80.

Physiological changes of the sensory epithelia

After evaluating cupular morphology, CAP in response to mechanical endolymphatic flow was recorded in 28 SCs in the long-term group. The mechanical endolymphatic flow was generated by manually driving a micromanipulator that was connected to a fine polyethylene tube inserted into the canal end. Since the specimen had no cupula, a large amount of endolymphatic flow (0.048 μl) of ampullopetal (A-P) or ampullofugal (A-F) direction was necessary to stimulate the sensory epithelia. The A-P stimulus was applied to the LC and the A-F stimulus was applied to either the AC or PC to induce excitatory discharge. The stimulus duration was set at 10 s with rise and fall times of 1 s.

The CAP was recorded via a glass suction electrode and was converted into spike density histograms for analysis (Figure 2). The physiological viability of the sensory epithelia was evaluated according to the presence of CAP. The maximum spike counts of 100 spikes per second or more were considered to show the presence of CAP. CAP was also recorded from normal PCs after removal of the cupula for comparison. All the above experiments followed the guidelines for animal experiments of the Ethics Committee of our institution.

Results

Findings in the inner ear after puncturing the membranous labyrinth

At 3–17 days after puncturing the membranous labyrinth, the site of needle puncture was observed under a dissection microscope. The incised palatal mucosa had healed, but granulation tissue growth, bleeding, or disarray of the saccular otoconia was observed in the operated otic capsule (Figure 3). Occasionally, bleeding was found within the ampulla.