殖因子を徐放するかは重要な課題であった。われわれが開発したゼラチンハイドロゲルによる内耳への神経栄養因子や細胞増殖因子の徐放システムは，この問題に対する1つの回答といえる。現在の臨床試験では1回投与での有効性を調べているが，複数回投与を行うことによりかなり長期の徐放も可能となり，更なる有効性が期待できる。また，複数の神経栄養因子や細胞増殖因子を同時に徐放することも技術的には可能であり，今後複数の神経栄養因子や細胞増殖因子の投与による相乗効果も調べていく必要がある。神経栄養因子や細胞増殖因子は，他の神経疾患にも応用することが可能であり，今後さらに多くの神経栄養因子や細胞増殖因子が臨床的に使用可能となることが期待される。特に耳鼻咽喉科や眼科領域では局所投与が有効であり，適切な徐放システムを使用すれば高い有効性と副作用の軽減が期待できる。今後さらに基礎的研究開発を進め，使用できる薬物の選択肢を増やすとともに，積極的に臨床応用の可能性を探っていきたい。本稿で紹介した治療法は，内耳の細胞を細胞死から保護することにより，いったん障害された聴力を回復させるものであるが，今後消失した細胞を再生させる方向性での研究にも，今回開発した内耳への神経栄養因子や細胞増殖因子の徐放システムを応用していきたい。

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用語解説

1. **有毛細胞**：聴覚の感覚器である蝸牛および平衡感覚をつかさどる前庭の感覚上皮に存在する。細胞の頂部にある感覚毛の偏位により，脱分極し，細胞底部にある神経終末から神経伝達物質を放出することにより，振動刺激を神経刺激に変換する。
2. **ラセン神経節**：聴覚の感覚器である蝸牛はらせん状の渦巻き構造を有するが，蝸牛の中心にある蝸牛軸に局在し，有毛細胞からの神経刺激を脳幹にある蝸牛神経核に伝達する。
3. **人工内耳**：人工内耳はマイクロホン，音声分析装置，刺激電極，電波の送受信機からなる。刺激電極は蝸牛内に挿入され，ラセン神経節細胞を直接電気刺激することにより，脳へ聴覚刺激を伝達する。2006年で国内での装用者は4150人を超えている。
4. **正円窓**：聴覚の感覚器である蝸牛は骨で囲まれた器官であるが，正円窓でのみ膜で中耳との境界が形成されている。中耳から内耳への薬物や遺伝子の投与経路として用いられる。
5. **突発性難聴**：急激に片側の聴力が低下する原因不明の難聴と定義されている難治性疾患であり，厚労省で班研究が行われている。蝸牛有毛細胞の障害が主因の1つと考えられている。中年に多く，年間35000人に発症する。

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・ゼラチンハイドロゲルによるIGF1内耳投与臨床試験
http://www.kuhp.kyoto-u.ac.jp/~ent/ClinicalTrial/GelforMedipro.html

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ORIGINAL ARTICLE

Changes in the characteristics of definite Meniere's disease over time in Japan: a long-term survey by the Peripheral Vestibular Disorder Research Committee of Japan, formerly the Meniere's Disease Research Committee of Japan

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Abstract

Conclusion. The incidence of new cases of Meniere's disease (MD) in elderly patients aged 60 years or more was found to have increased over time after correction for age distribution in the overall population. Job- and care-related fatigue may be involved in the recent increase in elderly-onset cases because physical and mental fatigue can induce onset of the disease. *Objectives.* Changes over time in the epidemiologic characteristics of MD in Japan were analyzed. *Materials and methods.* Between 1975 and 2006, four nationwide, multi-center surveys of MD were conducted by the Meniere's Disease Research Committee of Japan (1975–1976) and the Peripheral Vestibular Disorders Research Committee of Japan (1982–1984, 1990, and 2001–2006). Information was collected by the committee members on a total of 1368 de novo cases of definite MD, 520 reported in the first survey, 290 in the second survey, 148 in the third survey, and 410 in the fourth survey. *Results.* Clear changes were seen over time in the population-adjusted sex distribution of the disease and population-adjusted age at onset. The number of definite MD cases in females increased over time relative to the number of cases in males. The proportion of cases in which onset occurred at 60 years of age or more increased over time when the number of cases in each age group was adjusted for changes in age distribution of the population over time. From the time of the third survey, there was a slight increase in the proportion of cases with bilateral involvement.

Keywords: *Meniere's disease (definite), onset age, sex distribution, aging*

Introduction

Basic demographic characteristics of Meniere's disease (MD) have been reported from many places worldwide [1–7]. Most such reports present epidemiologic data representing a single brief period, without addressing secular trends. The Meniere's Disease Research Committee of Japan was organized by the Ministry of Health and Welfare of Japan in 1974 and continued after reorganization in 1980 as the Peripheral Vestibular Disorders Research Committee. Between 1974 and the end of 1990, the committee conducted three nationwide, multi-center surveys to investigate the epidemiologic and clinical characteristics of MD, surveying patients admitted to hospitals with which members of the committee were affiliated [8–10]. Because the same diagnostic criteria have been used consistently [8], these epidemiologic surveys provide a unique opportunity to evaluate long-term trends in the epidemiologic characteristics of MD. We analyzed basic epidemiologic characteristics of MD as found in the fourth nationwide survey of Japan conducted from

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2001 to 2006 and compared the recent data with data from the three previous surveys.

Materials and methods

The first nationwide survey was conducted from April 1975 to December 1976 by 17 committee members at 14 university and 3 general hospitals located in various districts or areas of Japan [8–10]. Data collected from 520 patients with definite MD included age, sex, and occupation; mode of onset; and whether symptoms were bilateral or unilateral. The second nationwide survey was conducted from January 1982 to December 1984 by 24 committee members in 22 university and 2 general hospitals [9,10]. Data similar to those collected in the first survey were collected from 290 patients with definite MD. The third survey was conducted from January to December 1990 by 16 committee members at 13 university and 3 general hospitals [9,10]. Data similar to those collected in the first and second surveys were collected from 148 patients with definite MD. The fourth survey was conducted in 2001 and from January 2004 to December 2006 by 14 committee members at 14 university hospitals. Data were collected from 410 patients with definite de novo MD (i.e. patients who had undergone their first medical examination for definite MD symptoms) and were similar to data collected in the three previous surveys.

The diagnostic criteria for MD, decided on in 1976 by the committee conducting the first survey, are as follows: (1) repeated attacks of whirling vertigo; (2) fluctuating cochlear symptoms synchronized with attacks of vertigo; and (3) exclusion of central nervous system involvement, eighth nerve tumor, and other cochleovestibular diseases [8]. Cases fulfilling all 3 criteria were diagnosed as cases of definite MD, whereas cases fulfilling only criteria 1 and 3 or criteria 2 and 3 were considered cases of suspected MD. In 1991, the committee decided on diagnostic criteria for MD with bilateral fluctuant hearing loss as follows: (1) repeated attacks of whirling vertigo; (2) fluctuating bilateral cochlear symptoms synchronized with attacks of vertigo; and (3) exclusion of central nervous system involvement, eighth nerve tumor, and other cochleovestibular diseases [11]. Because the cochlear symptoms sometimes fluctuate, and the severity of symptoms is not the same in each ear, some patients complain of severe unilateral, not bilateral, symptoms. Cases fulfilling all three criteria were diagnosed as cases of definite bilateral MD. Use of the glycerol test and/or frequently repeated pure tone audiometry is highly recommended to diagnose bilateral involvement more precisely. Only patients who had undergone their first medical examination for MD symptoms were surveyed. All of the cooperating committee members were ear, nose, and throat physicians.

Survey data were stored and analyzed by database software at the Department of Otolaryngology at the University of Toyama. Data from the fourth survey on the sex distribution of definite MD, unilateral vs bilateral involvement, and age at onset per sex were analyzed. The distribution of bilateral involvement and of age at onset per sex was compared between the four surveys to investigate changes over time. The sex ratio and onset age for definite MD from the first, second, and third surveys were adjusted for sex and age ratios of the general population calculated with the use of denominators interpolated from census data between census years. Data from the national census for 1980, 1985, 1990, and 2005 were used to correct the data from the first, second, third, and fourth survey, respectively. For statistical analysis, chi-squared tests were performed on a personal computer with StatView for Windows (version 4.5, Abacus Concepts, Berkeley, CA, USA). Some of the data in this study were analyzed in previous studies [8–10].

Results

At the time of the first survey, nearly equal numbers of males and females, i.e. 259 males (49.8%) and 261 females (50.2%), were diagnosed with definite MD (Table I). The second to fourth surveys showed a progressive increase with time in the proportion of definite MD cases occurring among females. At the time of the fourth survey, 256 females (62.4%) and only 154 males (37.6%) were diagnosed with definite MD. The percentage of females in the population of Japan did not change between 1975 and 2005; it was 50.8% in 1975 and 51.2% in 2005, according to national census data. The population-adjusted proportion of female patients in the fourth survey was significantly greater than that in the first survey ($p < 0.01$; Table II).

Proportions of cases with bilateral involvement during the time of each survey are shown in Table III. At the time of the first survey, 48 of the 520 cases of definite MD (9.2%) were diagnosed as bilateral.

Table I. Sex distribution of definite MD per survey period.

	1975–76	1982–84	1990	2001–2006
Males	259 (49.8)	126 (43.4)	63 (42.6)	154 (37.6)
Females	261 (50.2)	164 (56.6)	85 (57.4)	256 (64.4)
Total patients	520 (100)	290 (100)	148 (100)	410 (100)

Number (and percentage) of patients are shown.

Table II. Population-adjusted sex distribution of definite MD per survey period.

	1975–76	1982–84	1990	2001–2006
Males	257 (49.4)	125 (43.1)	63 (42.6)	154 (37.6)
Females	263 (50.6)	165 (56.9)	85 (57.4)	256 (64.4)
Total patients	520 (100)	290 (100)	148 (100)	410 (100)

Number (and percentage) of patients are shown.

The proportion of cases showing bilateral involvement fluctuated over time, declining slightly from the first to the second (7.9%) survey, then increasing between the early surveys and the third (16.2%) and fourth (13.8%) surveys. The proportions of definite bilateral MD cases reported during the third and fourth surveys were significantly greater than those in the first and second surveys ($p < 0.01$).

Age at onset of definite MD peaked in the fourth decade in males and in the third decade in females at the time of the first survey (Tables IV and V). At the time of the second survey, age at onset peaked in the third decade in males and in the fifth decade in females. At the time of the third survey, onset age peaked in the fourth decade in males and in the third decade in females. At the time of the fourth survey, onset age peaked in the fifth decade in males and in the sixth decade in females. Population-adjusted onset age peaked in the fourth decade in males and the fifth decade in females at the time of the first survey and in the fifth decade in males and the sixth decade in females at the time of the fourth survey (Tables VI and VII).

The population-adjusted proportion of patients with definite MD for whom age at onset was 60 years or more increased slightly from the first to the fourth survey (Tables VI and VII, and VIII). During the time of the first survey, the percentage of male patients with onset age of 60 years or more was 15.7%, the percentage of female patients was 12.7%, and the percentage of total patients for whom onset age was 60 years or more was 13.5%; these values increased to 20.1% in males, 31.1% in females, and 26.9% in total by the time of the fourth survey. Differences between the first survey and fourth survey in population-adjusted age at onset of 60 years or more among female patients and among the total patients were significant ($p < 0.05$).

Table III. Unilateral and bilateral involvement of definite MD per survey period.

	1975–76	1982–84	1990	2001–2006
Unilateral	472 (90.8)	267 (92.1)	124 (83.8)	343 (86.2)
Bilateral	48 (9.2)	23 (7.9)	24 (16.2)	55 (13.8)
Total	520 (100)	290 (100)	148 (100)	398 (100)
Unclear	0	0	0	12

Number (and percentage) of patients are shown.

Table IV. Onset age in males with definite MD per survey period.

Age (years)	1975–76	1982–84	1990	2001–2006
≤19	12 (4.7)	5 (4.1)	1 (1.7)	6 (3.9)
20–29	36 (14.1)	13 (10.7)	4 (6.7)	17 (11.0)
30–39	65 (25.5)	32 (26.2)	14 (23.3)	32 (20.8)
40–49	88 (34.5)	31 (25.4)	20 (33.3)	27 (17.5)
50–59	34 (13.3)	28 (23.0)	17 (28.3)	41 (26.6)
60–69	15 (5.9)	10 (8.2)	4 (6.7)	23 (14.9)
≥70	5 (2.0)	3 (2.5)	0 (0.0)	8 (5.2)
Total	255 (100)	122 (100)	80 (100)	154 (100)
Unclear	4	4	3	0

Number (and percentage) of patients are shown.

Discussion

In this study, changes over time in the sex ratio, proportion of unilateral vs bilateral definite MD, and age at onset of definite MD were examined on the basis of data collected during four nationwide, multi-center surveys conducted by the Peripheral Vestibular Disorders Research Committee of Japan (formerly the Meniere's Disease Research Committee of Japan) between 1975 and 2006. Clear changes were seen over time in the population-adjusted sex distribution of the disease and population-adjusted age at onset. The number of definite MD cases in females increased over time relative to the number of cases in males. The proportion of cases in which onset occurred at 60 years of age or more increased over time when the number of cases in each age group was adjusted for changes in age distribution of the population over time. From the time of the third survey, there was a slight increase in the proportion of cases with bilateral involvement.

The sex distribution of patients with MD has varied among other such regional surveys. In Scandinavian countries, the majority of cases of MD have been reported in females. Stahle et al. [1] found in a year-long 1973 survey that 60% of MD patients in the Uppsala region and the county of Skane in

Table V. Onset age in females with definite MD per survey period.

Age (years)	1975–76	1982–84	1990	2001–2006
≤19	15 (5.9)	7 (4.5)	3 (3.6)	2 (0.8)
20–29	34 (13.3)	19 (12.2)	11 (13.1)	29 (11.4)
30–39	72 (28.2)	29 (18.6)	23 (27.4)	43 (16.9)
40–49	64 (25.1)	43 (27.6)	20 (23.8)	45 (17.7)
50–59	52 (20.4)	38 (24.4)	19 (22.6)	56 (22.0)
60–69	16 (6.3)	13 (8.3)	8 (9.5)	64 (25.2)
≥70	2 (0.8)	7 (4.5)	0 (0)	15 (5.9)
Total females	255 (100)	156 (100)	84 (100)	254 (100)
Unclear	6	8	1	2

Table VI. Population-adjusted onset age among males with definite MD.

Age (years)	1975–76	1982–84	1990	2001–2006
≤19	7 (2.6)	3 (2.5)	1 (1.2)	6 (3.9)
20–29	23 (9.2)	11 (9.4)	4 (6.1)	17 (11.0)
30–39	56 (21.9)	27 (22.1)	15 (25.3)	32 (20.8)
40–49	73 (28.7)	26 (20.9)	16 (26.2)	27 (17.5)
50–59	56 (21.9)	32 (26.6)	20 (33.1)	41 (26.6)
60–69	27 (10.5)	17 (13.6)	5 (8.4)	23 (14.9)
≥70	13 (5.2)	6 (4.9)	0 (0.0)	8 (5.2)
Total males	255 (100)	122 (100)	80 (100)	154 (100)

Table VIII. Population-adjusted onset age among all patients with definite MD 4 Surveys.

Age (years)	1975–76	1982–84	1990	2001–2006
≤19	15 (3.0)	7 (2.7)	3 (2.0)	8 (2.0)
20–29	46 (9.0)	28 (10.1)	13 (9.3)	48 (11.3)
30–39	119 (23.4)	51 (15.5)	39 (27.2)	75 (18.4)
40–49	127 (25.0)	61 (21.9)	31 (21.5)	72 (17.6)
50–59	133 (26.0)	76 (27.3)	42 (29.2)	97 (22.0)
60–69	52 (10.3)	35 (12.4)	16 (11.1)	87 (25.2)
≥70	17 (3.2)	20 (7.2)	0 (0.0)	23 (5.9)
Total patients	510 (100)	279 (100)	144 (100)	408 (100)

Sweden were females. Havia et al. [6] found in a 2005 survey that 67% of definite MD patients in the Helsinki University hospital area in Finland were females. In 2007, Klockars et al. [7] reported that 70% of MD patients in Finland were females. According to surveys conducted in Italy and the United States, however, the proportion of MD cases in males and females has been almost equal. After a year-long 1992 survey in the region of Tuscany in Italy, Nuti et al. [5] reported that 53.9% of MD patients were females. In a 13-year survey (1973–1985) of southeastern Latium, the adjusted sex distribution was found to be almost equal (males, 48.9%; females, 51.1%) [4]. In the United States, Wladislavosky-Waserman et al. [2] reported changes in the sex distribution of MD between 1951 and 1980 in Rochester, Minnesota. In the first decade, a slight but not significant preponderance of female patients was observed. In the following two decades, the number of female MD patients declined over time, and the number of male MD patients exceeded the number of female patients, although not significantly, in the third decade.

In Japan before 1965, MD occurred more frequently in males than in females. In 1973, Naito reported that the male:female ratio was about 1.5 from 1934 to 1960, although after that time, the number of female patients with MD increased more rapidly than the number of male patients, and the difference between the two sexes almost disappeared [12]. Most of the subsequent Japanese surveys showed a preponderance of female patients [9,10,13,14]. In a year-long 1991 survey, 68.4% of MD patients in Toyama prefecture were found to be females [13], and in a 1994 survey, 79.2% of MD patients in the Hida district of Gifu prefecture were found to be females [10]. The sex distribution of definite MD was almost equal in our committee's first survey, but there was a preponderance of female cases of MD in the subsequent surveys. In recent times, the number of cases of definite MD has been greater among females than among males in Japan.

Table VII. Population-adjusted onset age among females with definite MD.

Age (years)	1975–76	1982–84	1990	2001–2006
≤19	9 (3.4)	4 (2.8)	2 (2.4)	2 (0.8)
20–29	22 (8.8)	17 (10.7)	9 (11.2)	29 (11.4)
30–39	63 (24.8)	24 (15.7)	24 (26.5)	43 (16.9)
40–49	55 (21.5)	35 (22.5)	15 (18.1)	45 (17.7)
50–59	73 (28.8)	43 (27.9)	22 (26.5)	56 (22.0)
60–69	27 (10.4)	18 (11.5)	12 (13.8)	64 (25.2)
≥70	6 (2.3)	14 (9.0)	0 (0.0)	15 (5.9)
Total females	255 (100)	156 (100)	84 (100)	254 (100)

In the present study, the proportion of MD cases with bilateral involvement was significantly higher at the time of the third and fourth surveys than at the time of the first and second surveys. The Peripheral Vestibular Disorders Research Committee of Japan prepared a draft of the diagnostic criteria for bilateral MD between 1988 and 1990 and published the criteria in 1991 [11]. The establishment and spread of the diagnostic criteria for bilateral MD may have influenced the reported incidence of bilateral involvement starting at the time of the third survey in 1990. A patient with bilateral MD often does not notice the bilateral fluctuant cochlear symptoms, and thus the physician in charge sometimes thinks that the patient is suffering from unilateral MD. Use of the unilateral glycerol test or frequently repeated pure tone audiometry is recommended for accurate diagnosis of bilateral involvement.

MD was once considered to be quite rare in the elderly [12]. However, in 1984, Wladislavosky-Waserman et al. [2] reported a high annual incidence of MD in the elderly in the United States. In 2002, Ballester et al. [15] pointed out that MD is not at all uncommon in the elderly. Several investigations have revealed that cases of MD in the elderly constitute between 10.8% and 37.8% of the total number of MD cases [1–3,13,16]. Because MD is not usually a life-threatening disease, cases of MD in the elderly comprise both long-standing cases that are reactivated and de novo cases. One may therefore think that the increased number of elderly MD

patients is associated with recent increases in life-span. However, we found that the proportion of MD cases in which onset age was 60 years or more during the time of the fourth survey was greater than in previous surveys when we corrected for age distribution of the overall population. This nationwide trend is similar to the increase in elderly-onset MD found in a recent regional survey [17]. In Japan, it appears that the recent increase in de novo MD cases exceeds the increase in the elderly population.

Elderly individuals are healthier now than those of previous generations. According to the 2005 census, 22.2% of elderly persons in Japan are working. This percentage is higher than that in France (1.2%), Italy (2.5%), Finland (2.7%), Germany (3.3%), and the United States (15.1%) in 2005 [18]. The larger population of working elderly persons in recent years might explain the trend in MD in Japan. Ikeda and Watanabe [19] reported 11 patients who had their first vertiginous attack after the age of 69 years (9 males, 2 females). Six of the nine elderly male patients with de novo MD were working. Four of them had managerial jobs. Only one male patient was out of work, and employment status was unclear in two male patients. Two female patients were housewives. Because physical and mental fatigue can induce onset of the disease [10], job-related fatigue may be involved in the recent increase in elderly-onset cases.

Today, 33% of the population is aged 65 years or more. In 2004, the number of persons aged 65 years or older was 24.88 million, the number of persons aged 65 years or older certified as requiring long-term care or support was 3.94 million [20]. Such individuals are generally looked after at home mainly by a family member, usually a female or someone aged 60 years or older. Care-related fatigue may also be involved in the increase in elderly-onset cases of MD. Ikeda and Watanabe [19] reported three elderly patients aged 69 years or older with de novo MD who had looked after a sick, elderly family member. Two of them were housewives and one was a man out of work.

Compared with other countries, the rate of the elderly populations of Japan increased rapidly. In such a rapidly aging society as Japan, elderly persons often experience various stressful events. Investigation of the variety and grade of the stress among the patients with MD may be useful for clarifying the reason why the elderly-onset MD cases have increased recently in Japan.

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論　　説

耳鼻咽喉科手術トレーニング

伊　藤　壽　一

Surgical Training in Otorhinolaryngology

Juichi Ito

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It is very difficult to master surgical skills in Otorhinolaryngology because of the anatomical complexixy of the field. There are several ways to gain surgical skills before being involved in surgery on humans, especially for young surgeons.

This paper introduces the concept of surgical dissection in the field of nasal surgery using a human cadaver and points out certain problems with using human cadavers. Future surgical training systems such as computer-simulated surgical training system are also described.

Key words : surgical training, nasal surgery, cadaver, computer-simulated surgical training system

はじめに

外科手術手技の習得には分野を問わず困難と時間を伴うものである．耳鼻咽喉科の分野でも事情は同じで，手技によって異なるが数年から10年程かけて一つの手技を習得することになる．このことは以前に本誌にて「耳科トレーニング」について述べた[1]．耳科手術は耳鼻咽喉科・頭頸部外科学領域の手術の中で習得に非常に時間がかかり，また困難なものである．従来，耳科手術の習得には熟練した術者の助手を務めたり手術ビデオを見たりして徐々にその技術を向上させるという方法が取られてきた．耳科手術など，顕微鏡を使用する手術と他の手術との決定的な違いは，手術は術者一人に委ねられるということであり，モニターを使っても上級者が同じ術野で直接指導するのが困難な点にある．顕微鏡下での手術と同様，内視鏡下の手術も手術が術者一人に委ねられるという点では同様に指導・習熟に困難をきたす．耳鼻咽喉科領域では主に鼻副鼻腔手術に対し内視鏡を用いる．内視鏡下鼻副鼻腔手術（Endoscopic Sinus Surgery：以下ESSと略す）は耳科手術に比べ比較的経験の浅い医師が手術を始めることが多いが，また手術に伴う事故の多いことも事実である．これはトレーニングもそこそこに実際の手術を行ってしまうことが多かったことにもよると思われる．内視鏡下の手術でも何らかの手術トレーニングを行ってから実際の手術を始めることが必須であるが，顕微鏡下の耳科手術同様これまでこのようなトレーニングを行っている施設はわが国では非常に限られた施設のみであった．本稿では京都大学耳鼻咽喉科・頭頸部外科学のヒトcadaverを用いたESS手術実習プログラムを紹介するとともに，耳科手術トレーニングもあわせ，これからの耳鼻咽喉科手術トレーニングシステムのありかたについて言及したい．

鼻・副鼻腔手術実習マニュアル

鼻・副鼻腔手術実習を行うためには側頭骨手術実習[2]の場合と同様，優れた実習マニュアルが不可欠である．欧米では各施設で優れた鼻・副鼻腔手術マニュアルを作

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表1　鼻・副鼻腔手術講習会マニュアル

1) 準備
　実習室の機器の点検
　手術器具の点検
　Cadaverの状態の確認
2) CT読影と基本構造の観察
　3DCTでの読影
　1. 鼻前頭洞管とAgger Nasi Cell鉤状突起の位置関係
　2. 中鼻甲介水平部，上鼻甲介の同定
　3. 前篩骨動脈，後篩骨動脈の位置関係
　4. 視神経管，翼口蓋管の位置
　5. 基本構造の確認
　①下鼻甲介
　②鉤状突起（天蓋，眼窩内側壁の付着部，上顎自然口の探索）
　③中鼻甲介（篩骨洞ブラ）
　④上鼻甲介
　⑤蝶形骨洞自然口
3) 鼻中隔矯正術
4) 前部篩骨洞開放
5) 後部篩骨洞，蝶形骨洞開放
6) 後鼻神経切断術
7) 下垂体，頸動脈
8) 斜台部
9) 前頭洞の解放，Modified Lothrop
10) Medial Maxillectomy
11) 前頭蓋底開放

成しそれによって実習を行っている．実習書は図を多用し，よく工夫されているが，側頭骨実習マニュアルに比べその数はそれ程多くはない．頭蓋内部の記載がやや不十分なものや必ずしも実際の手術を想定していないものなども多い．われわれは独自の鼻・副鼻腔手術実習マニュアルを作成しそれに沿って実習を行っている[3]．表1にわれわれの作成した実習書を紹介する．

鼻・副鼻腔手術実習の問題点

鼻副鼻腔手術実習の必要性はいうまでもないが，実習室の整備には当然費用がかかる．われわれは側頭骨実習の際と同様の実習室を使用しているが，使用する内視鏡機器を整備するには側頭骨実習に比べさらに費用を要する．また，機器の多様化のため実習室のみで収容できる人数に限りがある．

しかし，もっとも大きな問題点はヒトcadaverの入手の問題である．ヒト側頭骨（cadaver）に比べ鼻・副鼻腔手術実習で使用するcadaverはwhole head cadaverであり，またその使用目的のため，一般の学生実習で用いられるようなホルマリン固定ではなく，凍結のものを用いることが多い．このためcadaverの入手だけでなく保存にもかなりの設備とスペースが必要となる．Cadaverの入手に関しては限られた数であれば各大学の解剖学教室，病理学教室の協力のもとに，ホルマリン固定のcadaverを使用する方法があり，実際このような方法で実習を行う場合もある．しかし，それでは実際必要とする数に対して大きく不足する．京都大学では海外から輸入したヒトwhole head cadaverを使用する場合が多いが，かなり費用がかかる（1個のwhole head cadaverで1000ドル位必要な場合もある）．さらに輸入元の米国でも多くの施設でヒトcadaverを使用するため，絶対数が不足する傾向にある．

一方，このような実習に対する倫理的，法的問題は解決されていない．学生の解剖学実習で使用する屍体は以前は身元不明者，また有志からの献体であったが，いずれにせよ学生実習のためのものであり，法的に定められた実習室で行うことが義務付けられている．屍体をその一部であれ，解剖学実習室以外で，手術実習のため行うことに対する法的正当性は認められていないのが現状である．またわれわれの行っているような輸入cadaverを使用することに対しては，その是非に関しての規定もあいまいな状態である．

耳鼻咽喉科以外の外科系領域でも手術トレーニングの必要性が論議されている．脳神経外科領域では耳鼻咽喉科の側頭骨実習と同様にcadaverを使用した実習を行っている施設もある．また一般外科でも昨今の医療事故の問題からもcadaverを使用しての実習の必要性が論議されている．いずれの分野においてもcadaverを使用する限り，耳鼻咽喉科領域での実習と同様の問題，とくにcadaverの入手問題と法的問題は解決されていない．最近では外科系全体がまとまってこれらの問題につき討議し，解決への道を模索しようとする動きがある．いずれにせよこのような手術手技トレーニングが必須であることは議論の余地がないので法的整備も早急にする必要がある．

今後の方向性

側頭骨実習の際にも述べたが，現在行われているようなcadaverを用いての実習は，費用の問題，cadaver入手が困難な点，倫理的な問題もあろうが，手術のスキルアッ

プ，医療事故などを避けるためにも必須であり，少数の施設だけでなくできるだけ多くの施設で行うべきであろうと思われる．

一方 cadaver を使用せずに手術手技トレーニングを行う機器なども開発されている．側頭骨実習の場合は3次元 CT を元にして，合成樹脂などで実際の側頭骨と解剖学的にもまた骨削開用ドリルでの削開感触もかなり類似したものが作成でき，それによって実習を行うことが可能となっている．本トレーニング素材は非常に有用であるが，血管，神経などの軟部組織を構築できないという欠点も有する．また最近では手術術野をコンピューターで再現し，バーチャル手術トレーニングを行うソフト，機器も開発されている．このようなソフトを使用すると解剖学的知識の習得には有用であるが，この機器の欠点は，実際の骨削開，軟部組織の操作などの感触を得ることができない．近い将来にはこのような機器を利用した手術トレーニングが cadaver を使用したトレーニングに代わっていくものと思われるが，現時点ではまだ cadaver を使用したものには遠く及ばない．

前回も述べたが，手術トレーニングに対する学会認定も必要となってくると思われる．

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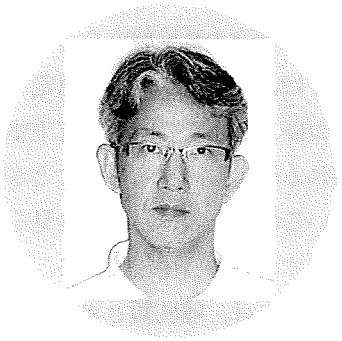
長寿フロントライン

内耳有毛細胞の再生による難聴治療



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●専門分野：耳鼻咽喉科学、医学博士

研究にあたってのエピソード

複雑な構造と脆弱性を併せ持つ内耳に対するポンプ埋め込みなど手術手技の開発には、多大な時間と労力を要した。研究開発に関係した学生、大学院生、スタッフにこの場を借りて、深謝したい。

内耳有毛細胞と感音難聴

音は空気の疎密波、簡単にいうと空気の振動ということができる。この空気の振動は、外耳道を通って、鼓膜を振動させる。鼓膜の振動は、耳小骨という小さな3つの骨を介して、内耳に伝えられる（図1）。

空気の振動を内耳に伝えるまでに障害があり、聞こえが悪くなることを伝音難聴という。伝音難聴を起こす代表的な疾患として中耳炎がある。中耳炎が慢性化して鼓膜に大きな穴ができると、うまく空気の振動を耳小骨に伝えることができなくなる。したがって、鼓膜などの空気の振動を伝えるしくみを治すことで、このタイプの難聴は治療することができる。

一方、内耳に音刺激が伝わっているにもかかわらず、内耳で音を感じることがうまくできない状態を感音難聴という。内耳に大きな障害がなく、内耳から脳に音の信号を伝えることがうまくできない場合も感音難聴に含まれる。感音難聴の多くは、内耳に原因がある。内耳に存在し、音刺激を神経刺激に変換する細胞が内耳有毛細胞といわれる細胞であり、内耳有毛細胞の障害が多くの感音難聴を引き起こしている。したがって、内耳有毛細胞は感音難聴治療開発の重要なターゲットということができる。

内耳有毛細胞の障害は、さまざまな要因で引き起こされる。内耳有毛細胞は音刺激を感じ取る細胞であるが、この音刺激が強すぎる場合、内耳有毛細胞が破壊されてしまう。強大音響曝露がこの状態である。ある程度以上の大きな音を日常的に聞いていても、同様に内耳有毛細胞は傷害される。ある種の抗生物質や抗がん剤も内耳有毛細胞の障害を引き起こすことがよく知られている。結核の治療薬であるストレプトマイシンに代表されるアミノ配糖体と呼ばれる抗生物質が、内耳有毛細胞を細胞死においやることは広く知られている。また、最も広く用いられている抗がん剤の一つである白金製剤も内耳有毛細胞障害を起こすことが知られている。

臨床の現場で最も高頻度に遭遇する内耳有毛細胞障害の原因は老化である。加齢とともに内耳有毛細胞の数が減少し、老人性難聴の原因の一つとなっている。遺伝子異常も内耳有毛細胞障害と関係している。内耳有毛細胞の障害に関わる遺伝子も数多く報告されている。これらの多くは、先天性難聴に関与している。

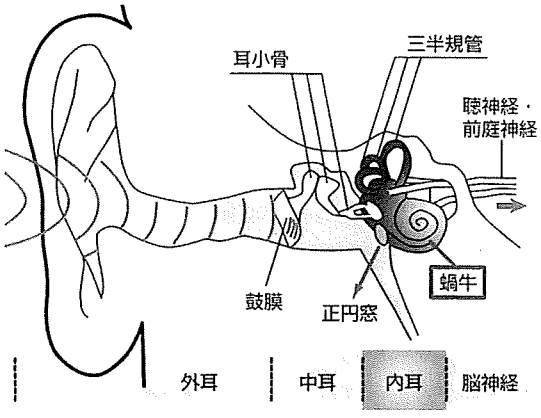

図1．音刺激の伝達機構

感音難聴治療の現況

感音難聴は、急激に起こる急性タイプと緩徐に進行する慢性タイプに分けることができる。急性タイプの代表例が突発性難聴である。突発性難聴は、原因不明に急激に片側の聞こえが悪くなる疾患であるが、ステロイド治療が一般に用いられている。3分の1の患者さんでは、聴力が回復するが、3分の1の患者さんでは完全に回復するには至らない。さらに、残りの3分の1の患者さんではまったく回復が認められない。また、老人性難聴に代表されるじわじわと悪くなるタイプの感音難聴では、まったく有効な治療法がなく、損なわれた聴力を補聴器で補う以外に道は残されていない。

ここまでに述べた感音難聴は、すべていったん聞こえを獲得した後に起こる感音難聴であるが、先天障害においても感音難聴は最も頻度が高いものの一つである。生まれながらに聞こえが悪い先天性難聴は、出生1000人に1人の割合で認められる。難聴の程度に応じて、補聴器、あるいは、内耳に電極を埋め込む人工内耳が聴力獲得への道となる。

このように、感音難聴の根本的治療はきわめて限られているのが現状であり、新しい治療法の開発が切望されている。上述した感音難聴のすべてが、内耳有毛細胞の障害のみに起因するものではないが、内耳有毛細胞障害が関与している病態は少なくない。したがって、内耳有毛細胞の障害を克服することができれば、新しい治療法開発の道が拓ける。内耳有毛細胞障害の克服には、内耳有毛細胞が死に至る前に細胞死を防御する方法と、いったん喪失してしまった内耳有毛細胞を再生させる方法が考えられる。内耳有毛細胞は、哺乳類ではいったん失われると再生しないとされている。したがって、細胞死の防御方法を開発する方が現実的な戦略といえる。

われわれは、内耳有毛細胞の死を防御する方法として、内耳に持続的、かつ、直接的に薬物を投与する方法を開発した。この方法を用いて、インスリン様細胞増殖因子1を内耳に投与する治療法は、厚生労働省感覚器障害事業としての基礎的研究開発を経て、臨床試験を行う段階にある。しかし、細胞死の防御では、治療が有効と想定される期間は、細胞が死んでしまうまでの発症後限られた時間となる。つまり、すでに症状が固定した感音難聴や慢性に進行した感音難聴に対する有効性を期待することはできない。一方、内耳有毛細胞再生はきわめて困難な課題であるが、実現することができれば、聴力を失った多くの患者を救うことができる可能性がある。このような観点から、困難な課題ではあるが、内耳有毛細胞再生をわれわれが取り組むべき重要な研究課題の一つと位置づけている。

内耳有毛細胞再生への戦略

いったん失われた内耳有毛細胞は、われわれ人類を含めた哺乳類では通常再生しない。これまでの研究成果から、哺乳類で再生能力が乏しい原因として、再生を抑制する因子が働いている、あるいは、再生する能力がある細胞が乏しいということがわかってきた。われわれは、2つのアプローチ、すなわち、再生を抑制している因子を解除する方法と再生能力がある細胞を内耳に移植する方法で研究開発を行っている。内耳への細胞移植治療については、ES細胞やiPS細胞を含め、種々の幹細胞を用いた難聴治療の可能性について研究展開し、一部霊長類での実験にも着手している。本稿では、もう一つの戦略、再生を抑制するメカニズムを操作して、内耳有毛細胞を再生する試みについて紹介したい。内耳に残っている細胞を使って、なんとか有毛細胞再生ができないかを研究するアプローチと言い換えることもできる。

内耳有毛細胞の再生戦略を考えるにあたっては、2つの方向性が想定できる。一つは、哺乳類の内耳で有毛細胞が作られる発生段階にどんなことが起こっているのかを調べ、その知見を再生に応用するという手段である。もう一つの考え方は、哺乳類と異なり、内耳有毛細胞の再生能力がある鳥類や両生類では、どのようなメカニズムで再生が誘導されているのか、哺乳類との違いは何かを調べて、再生に応用しようとする考え方である。

内耳感覚上皮は、感覚細胞である有毛細胞と支持細胞からなる。支持細胞は、通常、有毛細胞の周囲に存在し、構造的に有毛細胞を支えているだけではなく、聴覚に不可欠な重要な役割も数多く果たしている。哺乳類内耳の発生に関する研究から、有毛細胞と支持細胞は同じ起源(元になる細胞)から生まれていることが明らかにされている。言い換えれば、少し前の段階に遡れば、支持細胞と有毛細胞は同じ種類の細胞であったということである。そこから、なんらかの因子が作用して、有毛細胞になる細胞と支持細胞になる細胞へと分別作業が行われているわけである。すべてのメカニズムが明らかにされているわけではないが、近年の分子生物学的な研究手法の発展から、多くの重要な知見が得られている。後述するノッチ情報伝達系に関する知見もこのような発生に関する研究に端を発している。

一方、鳥類では、いったん有毛細胞

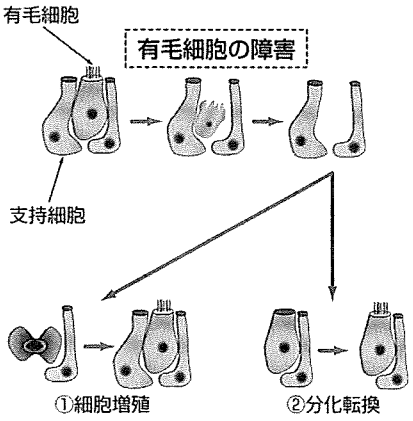

図2. 有毛細胞再生のメカニズム

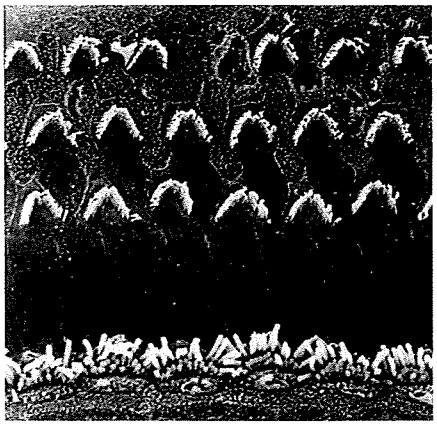
図3. 哺乳動物蝸牛における有毛細胞の配列

を喪失しても、有毛細胞が再生できる。鳥類では2つの方法で支持細胞から有毛細胞が再生される(図2)。一つは、有毛細胞喪失後、周囲の支持細胞が分裂、増殖し、新しい有毛細胞に分化するというメカニズムである。この方法は、支持細胞の数を減らすことなく、有毛細胞を再生できるので理想的であるが、支持細胞の増殖、増殖した細胞の有毛細胞への分化という2つのステップが必要となる。もう一つの再生機構は、支持細胞が直接的に有毛細胞に変身(分化転換)するというメカニズムである。この方法では、有毛細胞再生のために支持細胞がひとつ減ることになるが、支持細胞の有毛細胞への分化転換という一つのステップで有毛細胞が再生できる。

支持細胞から有毛細胞への分化転換

もともと同じ起源となる細胞から支持細胞と有毛細胞はどうように作り分けられているのだろうか。将来的に支持細胞と有毛細胞になる部分は、発生の比較的早い段階で決定されて、内耳全体の中でも早く細胞増殖が停止する。ほぼ同時に、有毛細胞と支持細胞に明確に区別され、細胞の分化が開始される。音を感じ取る蝸牛の感覚上皮では、有毛細胞と支持細胞が整然とした配列で交互に並んでいる(図3)。この整然とした配列と隣り合う細胞を有毛細胞と支持細胞に分けていく機構として、ノッチ情報伝達系というメカニズムが働いていることが明らかにされている。

ノッチ情報伝達系は、身体が形作られる過程や幹細胞の維持機構など、生体で数多くの重要な働きをしている。有毛細胞と支持細胞の作り分けについても、ノッチ情報伝達系が働いている。有毛細胞になる運命が決まった細胞は、自らの周囲の細胞が有毛細胞にならないように指令を出す。この指令を受けた細胞では、ノッチ情報伝達系が活性化されて、有毛細胞にならずに支持細胞になるようスイッチがオンになり、支持細胞となる。このように、有毛細胞の隣には、支持細胞が存在する仕組みが存在する。支持細胞となるスイッチがオンとなると細胞内で作られる物質として、Hesファミリーというタンパクが存在する。

Hesファミリータンパクは、有毛細胞に分化するために必要なAtoh 1というタンパク質の発現を抑制する働きがあり、支持細胞が有毛細胞になるのを防止している。Hesファミリータンパクの一部を欠損させると、本来、支持細胞があるべき場所にも有毛細胞が出現する。また、ウイルスベクターを使った遺伝子導入により、強制的にAtoh 1を支持細胞で発現させると、支持細胞が有毛細胞に分化転換することが示されている。すなわち、有毛細胞がなくなってしまっても、支持細胞が残存している状況であれば、残存している支持細胞にAtoh 1を発現させることによって、有毛細胞を再生することができる可能性があるといえる。

薬物治療による内耳有毛細胞再生のコンセプト

実際の難聴治療を考えると、人間の内耳にウイルスを入れるには、いろいろと解決すべき問題がある。ウイルスを用いないで、内耳に遺伝子を入れる試みがなされているが、残念ながら、内耳の細胞にはなかなか遺伝子が入りにくいのが現状である。また、人間の内耳に障害を起こさないようなウイルスを使うことを考えた研究開発も行われている。いずれにせよ、実際の治療法として開発するためには、解決すべき問題が数多く残されている。

われわれは、遺伝子導入を行わずに、薬物で支持細胞でのHesファミリーを抑制して、HesファミリーによるAtoh 1発現抑制を解除すれば、支持細胞内でのAtoh 1発現を誘導できるのではないかと考えた。薬物で、Hesファミリーを抑制できれば、支持細胞でのAtoh 1を促し、有毛細胞への分化転換が誘導できる可能性がある。Hesファミリーの発現をコントロールしているノッチ情報伝達系では、隣の細胞からノッチ関連するシグナルが細胞膜を介して伝えられると、細胞膜の内側にあるNICD (Notch intracellular domain)という物質が細胞膜から切り離され、細胞の核に移行し、Hesファミリーなどが作られる。この細胞膜の内側にあるNICD

の切り離しに、γセクレターゼという酵素が必要なことが知られている。

われわれは、γセクレターゼの働きを止めてしまうγセクレターゼ阻害薬を使って、支持細胞でのノッチ情報伝達系を阻害することにより、Hesファミリーを抑制し、相対的にAtoh 1の発現を増加させることができれば、支持細胞から有毛細胞への分化転換が誘導できる可能性があると考えた。この方法が実際の内耳で可能かどうかを調べるために、蝸牛感覚上皮の培養系での実験を行った。蝸牛感覚上皮を取り出し、培養系に移し、γセクレターゼ阻害薬を投与し、支持細胞から有毛細胞への分化転換が誘導されるのかを調べた。結果、γセクレターゼ阻害薬投与により、支持細胞から有毛細胞への分化転換が誘導できること、発生段階の内耳と生後の内耳では有効な薬物が異なることがわかった。この知見に基づき、生後の内耳に有効なタイプのγセクレターゼ阻害薬を用い、実際にモルモット内耳にγセクレターゼ阻害薬を投与する実験を行った。

γセクレターゼ阻害薬の内耳投与による内耳有毛細胞再生

γセクレターゼ阻害薬は、比較的短期に体内で活性を失うことが知られているので、十分に効果が発揮されるためには持続的に内耳に投与することが必要となる。確実に持続的投与を行うとの観点から、埋め込み型ポンプを薬物投与方法として用い、モルモット内耳へのγセクレターゼ阻害薬投与を行った。培養系の実験では、胎生期および新生マウス蝸牛を用いたが、本研究では成獣モルモットを用いることにより、臨床応用への外挿性を評価することとした。

第一に、とくに傷害を与えていないモルモットを用いて、γセクレターゼ阻害薬内耳局所投与の効果を評価した。しかし、成熟した蝸牛感覚上皮では、支持細胞から有毛細胞への分化転換は観察されなかった。正常モルモットにおけるノッチ情報伝達系関係分子の発現を調べたところ、蝸牛感覚上皮ではほとんど活性が認められないことがわかった。つまり、完成された蝸牛感覚上皮ではノッチ情報伝達系が活性化されていないため、ノッチ情報伝達系を阻害しても何の効果も認められないというわけである。

次に、広範な有毛細胞脱落を惹起したモルモット感覚上皮を調べると、正常蝸牛では認められなかったノッチ情報伝達系の活性化が残存支持細胞で認められた。この結果は、他施設での解析結果とも合致するものであり、有毛細胞脱落を伴う内耳障害後、蝸牛感覚上皮で一時的にノッチ情報伝達系が活性化されているといえる。γセクレターゼ阻害薬は、ノッチ情報伝達系が活性化されている状態で、初めて効果が発現されると考え、ノッチ情報伝達系が最も活性化されている傷害4日後のモルモット蝸牛に2週間γセクレターゼ阻害薬を投与した。すると、一部本来支持細胞が存在する部位に有毛細胞様の細胞を認められた。したがって、成熟した蝸牛組織であっても、傷害後の適切な時期にγセクレターゼ阻害薬を投与することにより、有毛細胞再生が誘導できる可能性が示されたこととなる。残念ながら、今回の検討では、新生有毛細胞の数が少ないことから、新生された有毛細胞の機能的な側面の評価を十分に行うことはできなかった。

今回の実験では、新生有毛細胞をいかにして、残存している有毛細胞と区別するのかという問題があった。傷害された有毛細胞と新生された未熟な有毛細胞は、形態学的には判別できない。そこで、今回はかなり強い有毛細胞喪失が引き起こされる障害モデルを用い、新生された有毛細胞が識別しやすくなる工夫を行った。このため、蝸牛感覚上皮全体の傷害もかなり強いものとなり、機能的な再生はかなり困難な状況であった。

今後の展開

今回の検討から、γセクレターゼ阻害薬の内耳局所投与は、有毛細胞再生に有効な手段となる可能性が呈示されたが、聴覚機能の回復には至っていない。今後、聴覚機能再生の観点からの、研究が望まれる。具体的には、傷害の程度がもう少し軽度でなおかつ傷害される蝸牛感覚上皮の部位が限定されたモデルを使って、有毛細胞再生効率および聴覚機能再生について調べている。さらに、次のステップの課題ともいえるが、γセクレターゼ阻害薬の投与方法として、埋め込み型ポンプではなく、バイオマテリアルを用いたドラッグデリバリーシステムによる内耳への持続的な投与法開発が望まれる。臨床応用を考えた場合、埋め込み型ポンプでは、かなりの手術侵襲が加わるが、バイオマテリアルを用いたドラッグデリバリーシステムであれば、鼓膜切開と同等の手術侵襲を伴うのみである。現在、γセクレターゼ阻害薬を徐放できるドラッグデリバリーシステムを開発し、培養系実験でその有効性を検証している。

感音難聴に対する治療法がきわめて限られている現状を打破すべく、先駆的な治療法開発に取り組むと同時に、耳鼻咽喉科臨床医としての立場から、速やかな臨床応用に関連する研究開発を並行して行っていきたいと考えている。

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Abnormal auditory cortex with giant N100m signal in patients with autosomal dominant lateral temporal lobe epilepsy

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ABSTRACT

Objective: Lateralization of functionally abnormal cortical area in autosomal dominant lateral temporal lobe epilepsy (ADLTE).
Methods: A sound pulse of pure tone was delivered monaurally to the ears alternately. Auditory evoked magnetic fields (AEF) were measured by using whole-head magnetoencephalography (MEG) system.
Results: Significantly large N100m signals (a magnetic counterpart of N1/N100 in EEG) were detected in three out of five patients, either in the left or in the right hemisphere, contralateral to the auditory stimulation. The peak latency, location and orientation of distinct N100m exhibited no clear difference from those of normal controls.
Conclusions: Unilateral cortical abnormality exists in some of the patients in ADLTE. Patients with abnormally large N100m had seizures apparently provoked by auditory stimuli, suggesting that the appearance of significantly large N100m is associated with the epileptogenicity. Based on the detailed examination using MRI and FDG-PET for two of the patients, the authors hypothesize hyperexcitability caused by the decreased inhibitory functions, larger number of synchronously activated neurons, or the elongation of neuronal firing in the pathological temporal cortex in ADLTE.
Significance: The present study revealed clear abnormalities in the auditory cortex that have not been well detected by conventional EEG in patients with ADLTE.

1. Introduction

Direct evidence that the seizures originate from a specific region is obtained only when epileptic cortical activities are recorded in that particular region. Epileptic seizures usually occur sporadically and, in most cases, little neurological deficit is found during the interictal period. EEG is useful to find the abnormal cortical activities during seizures. In the interictal period, however, abnormal activities are sometimes not found in EEG. Evoked potentials (EPs) have been used to evaluate abnormality in various neurological diseases. In epileptic syndromes, it is known that somatosensory evoked potentials (SEPs) or their magnetic counterparts are extremely large in patients with progressive myoclonic epilepsy (Dawson, 1946; Watson and Denny-Brown, 1955; Halliday, 1967; Chadwick et al., 1977; Shibasaki et al., 1978; Hallett et al., 1979; Karhu et al., 1994). In other types of epilepsy, however, EPs have rarely been used to investigate latent cortical abnormality.

Autosomal dominant lateral temporal lobe epilepsy (ADLTE) is one of the rare genetic epilepsies that exhibit partial seizures (Ottman et al., 1995; Ikeda et al., 2000, 2007; Michelucci et al., 2003). Since ADLTE is characterized by recurrent auditory auras, it is assumed that the seizure onset or the irritative zone is on the lateral temporal lobe, and that the auditory cortex or its association areas are involved in the epileptic activities. Functionally abnormal cortical area, however, has not yet been clearly localized due to the fact that ictal EEG is scarcely recorded in the cases of ADLTE, and that interictal abnormality observed in EEG is also rare (Ikeda et al., 2000, 2007; Michelucci et al., 2003).

In the present study, we employed evoked magnetic field (AEF) measured by using magnetoencephalography (MEG), a magnetic version of evoked potential technique, for the investigation of interictal abnormality in the cortex in ADLTE. We investigated interictal abnormality in the cortex in ADLTE. MEG picks up

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cortical activities right beneath the magnetic sensors with high spatial and temporal resolutions, and thus enabled us to evaluate the cortical function of the left and right temporal lobes separately (Hari, 1990). The content of this paper did not appear elsewhere except for an abstract (Ikeda et al., 2007)

1.1. Subjects and methods

1.1.1. Subjects

Five right-handed patients from three families with ADLTE participated in the present study. Table 1 shows their clinical profile. The clinical details of the patients, have been reported elsewhere (Ikeda et al., 2000, 2007; Kawamata et al., in press; Fujita et al., 2009). Families U and O were genetically diagnosed as ADLTE (Ikeda et al., 2007; Kawamata et al., in press; Fujita et al., 2009). All patients had auditory auras and three of them (Patients 2, 4 and 5) had seizures triggered by specific sound. In interictal period, no neurological deficits and hearing disturbance were observed. In all patient EEG showed no definite epileptic discharges in interictal period.

3-Tesla or 1.5-Tesla MR images were taken in all patients. MRI showed volume reduction in unilateral temporal lobe in two patients (Patients 4 and 5) and the left hippocampal sclerosis in one patient (Patient 3). [F-18]fluorodeoxyglucose-positron emission tomography (FDG-PET) showed glucose-hypometabolism in the same temporal lobes with MRI abnormality in Patients 3, 4 and 5.

Ten healthy volunteers (2 females) of the age between 20 and 43 y.o. (mean (SD), 30.9(6.1)) with no neurological deficits and hearing disturbance were recruited in the study as normal control. All the procedures were approved by Kyoto University Graduate School and Faculty of Medicine, Ethics Committee and written informed consent was obtained from all patients and normal volunteers.

1.1.2. MEG measurement and analysis

AEFs were measured by using a 306-channel whole-head system (VectorView, Elekta Neuromag, Finland). It was confirmed that the patients with ADLTE had no seizures within 12 hours before the AEF recording. No seizure occurred during the recording. A sound pulse of pure tone of 1000 Hz was delivered through ear tubes monaurally to the right and left ears alternately. Level of the sound pulses was controlled so that both patients and normal volunteers were given auditory stimuli at SL (sensation level) of 50 dB above his or her hearing threshold. Output of the sound pulse generator was individually set at SL (sensation level) of 50 dB above the hearing threshold of each subject or normal controls. The duration of the pulse was 130 ms (the rise and fall time of 10 ms each) with 1000 ± 70-ms intervals.

MEG were recorded with bandpass filter of 0.1–330 Hz and with sampling rate of 997 Hz. Epochs for on-line averaging started 100 ms before the onset of each stimuli and terminated 400 ms after the onset. Each stimulus given to the right or left ear were averaged separately. Epochs containing blinks and/or other artifacts were automatically excluded from averaging. More than 100 epochs for each right- and left ear stimulation were averaged in one measurement. Two or three measurements were performed in each subject in order to confirm that auditory magnetic responses were reproduced.

N100m, a magnetic counterpart of N1/N100 in EEG, which is the most prominent component of AEFs (Pantev et al., 1995; Lutkenhoner and Steinstrater, 1998), were analyzed. The activated brain areas were modeled as equivalent current dipoles (ECDs) (Hamalainen et al., 1993). A spherical model, which is made from each subject's anatomical 0.5-Tesla 3-dimensional MR images (Signa, General Electric, USA), was used for describing the conductivity profile of the brain. The ECDs were estimated from at least 27 channels (= 9 set of sensors), that covered the field pattern of 100 ms component in auditory magnetic fields over each hemisphere. The ECDs with goodness of fit (GOF) more than 80% and confidence volume (CV) less than 1000 mm^3 were used for further analysis.

The mean and standard deviation (SD) of ECD moment and peak latency of N100m were obtained from the control subjects. The data of patients and of control group were compared, and the values that surpassed the mean + 2.5 SD of those obtained from control group were regarded as significantly large.

2. Results

Fig. 1 shows representative magnetic responses of a patient (Patient 4) to the auditory stimuli given to the left and right ears. Shown in this figure are waveforms in 306 channels (A and D), largest responses detected by planar gradiometer in the contralateral hemisphere to the stimuli (insets of A and D), magnetic field maps and estimated ECDs at 97 ms from stimulus onset in the contralateral hemisphere (B and E), and the ECDs superimposed on the patient's anatomical MR images (C and F). The latency and estimated ECD moment (strength) of N100m peak in each patient are shown in Table 2 in comparison with the mean (SD) of those in normal controls. In all patients, the peak latency of N100m showed no significant difference from those of the control group. The sources of N100m were localized in the temporal plane in each hemisphere of both patients and control subjects, and no significant difference in the location and orientation of sources was identified.

As for the ECD moment, significantly large response was recorded in three patients either in the left (Patients 2 and 4) or in the right (Patient 5) hemisphere, contralateral to the auditory

Table 1
Clinical profile of patients with ADLTE.

Patient	Age	Sex	Family	Types of aura	Seizure types	Inducing factors of seizures	Findings in MRI and/or FDG-PET
1	31	M	U	Auditory, deja vu	SPS, CPS, *n*-GTCS	None	No abnormal findings
2	56	M	U	Auditory	SPS, CPS, *n*-GTCS	Ringing of phone	No abnormal findings
3	27	F	U	Auditory	SPS, CPS, *n*-GTCS	None	Left hippocampus: sclerosis suspected Left temporal lobe: mild hypometabolism suspected
4	27	F	O	Auditory, deja vu	SPS, CPS	Specific sound, conversation	Left superior temporal gyrus: small in volume Left temporal lobe: hypometabolism
5	36	F	H	Auditory, deja vu	SPS, CPS	Specific music	Right inferior horn of lateral ventricle: enlargement Right temporal lobe: hypometabolism

SPS, simple partial seizures; CPS, complex partial seizures; *n*-GTCS, nocturnal generalized tonic–clonic seizures.

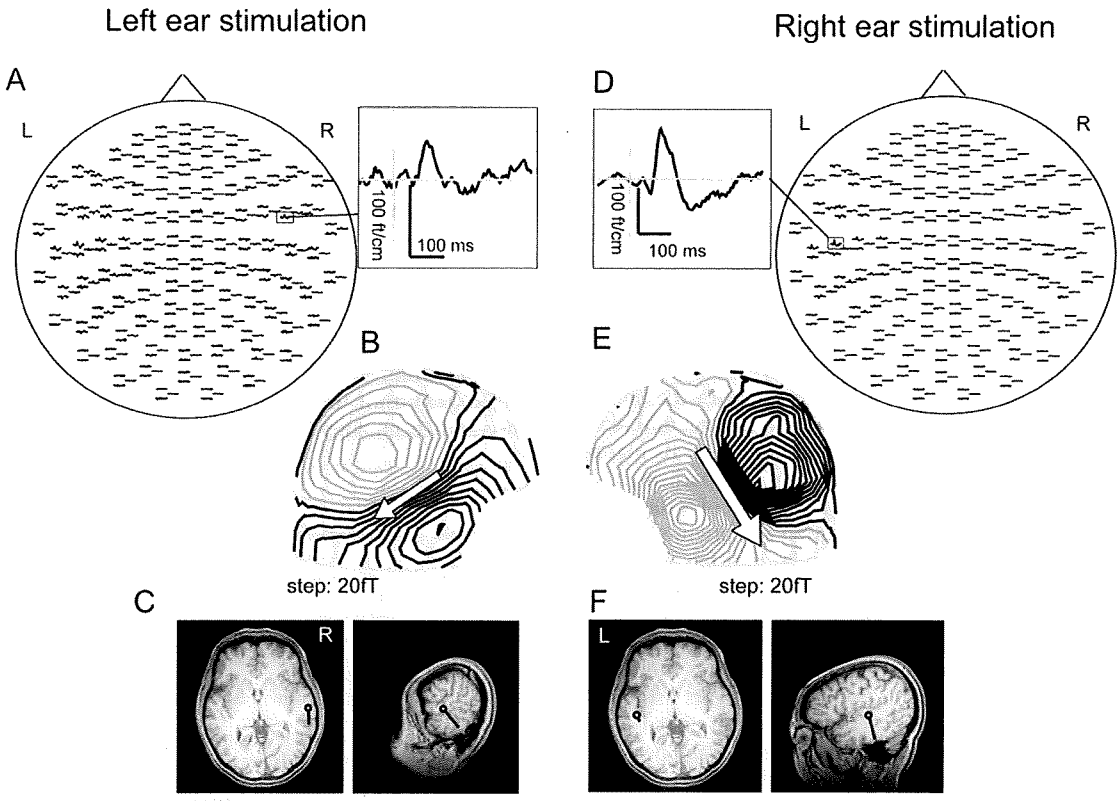

Fig. 1. Auditory evoked magnetic fields of Patient 4. Magnetic responses to the left ear stimulation are shown in the left and the responses to the right ear stimulation in the right. Upper panels (A and D) show responses in all channels. The traces show a 500 ms time period starting 100 ms before the stimulus onset. The insets show the magnified largest responses in the contralateral hemisphere to the stimuli. Lower panels show field map and ECD of N100m. Field patterns in the contralateral hemisphere to the stimuli at the peak latency (97 ms from stimulus onset) are shown in panels (B) and (E). The maps were drawn over the helmet-shaped sensor array. The step between the isocontour lines is 20 fT. The areas with black lines indicate the magnetic field out of the head and the areas with gray lines indicate the field into the head. The arrows show the estimated location of the ECDs projected onto the subject's head surface. Panels (C) and (F) show the ECD location superimposed on the subject's 3-dimensional MR images.

Table 2
Peak latency and ECD moment of N100m in the contralateral and ipsilateral hemispheres to unilateral auditory stimuli.

Subject	Lt ear stimulation				Rt ear stimlation			
	Contralateral (Rt)		Ipsilateral (Lt)		Contralateral (Lt)		Ipsilateral (Rt)	
	Latency (ms)	Moment (nAm)	Latency (ms)	Moment (nAm)	Latency (ms)	Moment (nAm)	Latency (ms)	Moment (nAm)
P1	98	40.8	112	13.0	103	12.2	108	27.5
P2	106	51.2	127	37.7*	114	88.0*	114	45.5
P3	94	21.2	104	13.8	98	17.7	118	24.8
P4	97	18.5	96	30.6	97	44.2*	104	13.1
P5	97	83.7*	111	7.6	105	15.8	114	42.3
Control (n = 10)	Latency(SD) 97.3 (5.7)	Moment(SD) 35.4 (14.1)	Latency(SD) 108.9 (11.8)	Moment(SD) 18.5 (6.6)	Latency(SD) 98.2 (10.5)	Moment(SD) 23.6 (7.3)	Latency(SD) 105.7 (8.6)	Moment(SD) 27.5 (12.0)

P, patient; Lt, left; Rt, right. The data of control group are shown as the mean (SD).
* >The mean + 2.5 SD of control group.

stimulation. In the left hemispheres of Patients 2 and 4 and the right hemisphere of Patient 5, large N100m was also evoked in response to the ipsilateral stimuli and the ECD moment was significantly large for Patient 2. In the remaining patients (Patients 1 and 3) the ECD moment of N100m was not different from those of the control group.

3. Discussion

Morphological and/or functional abnormality in ADLTE has been reported predominantly on the left hemisphere in the literature so far. In one study, for example, it was reported that morphological abnormality lateralized on the left hemisphere existed in 45% of 22 patients with ADLTE (Kobayashi et al., 2003). Another study reported abnormality in auditory evoked potentials (AEPs) lateralized on the left (Brodtkorb et al., 2005).

Epileptogenicity and functional deficit, however, are caused not only by visually detectable malformations but also by some other abnormalities. In addition, AEP evaluation using EEG and binaural sound presentation are not appropriate to distinguish left and right auditory responses separately. It is, therefore, uncertain how much the causes of ADLTE is associated with morphological abnormality that is localized on the left hemisphere.

In this study using AEF, ECD moment of N100m can be classified into two groups: one with the values larger than +2.5 SD, and the other with the values smaller than +2.5 SD. For brevity, we call the former "large signal" and the latter "small signal". N100m

signals of three patients were clearly larger than those of other patients. The results of these three exhibit unique features that should be mentioned. First noticeable feature is that these larger signals were observed in the left hemisphere for two patients and in the right for the other patient.

Second noticeable and striking feature is that the N100m in the right hemisphere of the two patients who exhibited large signals in the left was small. It is also found that the N100m in the left hemisphere of the other patient who exhibited large signal in the right was small. The fact that the significantly large N100m signals were detected in either left or right hemisphere in three patients, and that the N100m in the opposite hemisphere of all these three patients were small is a clear indication that unilateral cortical abnormality exists, at least in some patients, in ADLTE.

Third noticeable feature is that, as compared with the normal subjects, the latency of large N100m showed no distinct difference in the case of ADLTE patients. This result strongly suggests that no disturbance in both peripheral and central auditory pathways.

Fourth feature is that, although the ECD moment of N100m was distinctively large in the patients, the location and orientation was similar to those in control subjects. The similar location and orientation of the ECD suggested that the center of neuronal populations underlying N100m response are supposed to be the same, or, at least, very close in the giant and normal AEFs. (For detailed mechanism see Eggermont and Ponton, 2002 and references therein)

Further detailed examination for two of the patients using MRI and FDG-PET showed the anatomical and functional deficit localized in the temporal lobes. The volume of the temporal lobe which generated the giant N100m was reduced (possibly due to malformation or atrophy) and glucose-hypometabolism was detected. Volume reduction and hypometabolism usually suggest cortical hypofunction, which is supposed to lead weak signals. The two patients with ADLTE, whose cortical area was reduced in volume, by contrast, generated larger N100m than those with cortices of normal volume.

Since there is no way to reveal the underlying mechanism of the distinctively large ECD moment or the strength of MEG response with concrete experimental evidence in our study so far, we present the hypotheses. One possible explanation is the hyperexcitability of the neurons: the amount of the neurons is the same but the neurons of the patients are hyperreactive. If the neuronal population producing N100m is hyperexcited, the signals would be apparently larger than those of normal activity. Large dipole moment may also indicate highly coordinated activity. If the amount of synchronously activated neurons is larger in the patients with ADLTE than in the normal controls, the signals would be apparently larger. Other possible explanation may be the elongation of neuronal firing. To clearly distinguish the factors affecting the N100m signal, microscopic invasive study using depth or subdural electrodes is needed.

Our investigation found that three patients exhibited distinctively large N100m and the remaining two patients exhibited comparatively small N100m. The difference observed between two groups of patients was that the former had seizures apparently provoked by auditory stimuli, such as specific sound or music, while the latter did not. These facts suggest that the appearance of significantly large N100m in the auditory cortex, which indicates abnormally large response to sound, may be closely associated with the epileptogenicity in these patients, just as giant SEPs in patients with progressive myoclonic epilepsy.

In summary, the present study using auditory magnetic fields showed that significantly large N100m signals are supposed to be an indication of auditory induced seizures. Our result is also a clear demonstration of significant usefulness of AEF in the detailed studies to address the issue of whether unilateral or bilateral temporal lobes are involved. This technique enables these evaluations even for the interictal period.

Conflict of interest

The authors have no financial conflicts to report.

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OTOLOGY

Efficiency of a transtympanic approach to the round window membrane using a microendoscope

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Abstract There has been increasing interest in cochlear drug delivery through the round window membrane (RWM). However, placing drugs on the RWM is difficult because of anatomical barriers. We examined the efficacy of a microendoscope for a transtympanic approach to the RWM. We evaluated the visibility of the RWM using four approaches: transtympanic microendoscopic, transtympanic microscopic, transmastoid microendoscopic, and transmastoid microscopic in ten human temporal bones. For the transtympanic approach, we made a fenestration (2 × 1 mm) in the postero-inferior quadrant of the tympanic membrane. For the transmastoid approach, conventional posterior hypotympanotomy was performed. The transtympanic microendoscopic approach enabled visualization of the RWM in all specimens, whereas the transtympanic microscopic approach only permitted visualization in three specimens. Through the transmastoid approach, the RWM was visible in all specimens using either a microendoscope or a microscope. The transtympanic microendoscopic approach can be utilized for cochlear drug delivery through the RWM.

Keywords Microendoscope · Round window membrane · Cochlea · Drug delivery

Introduction

Sensorineural hearing loss (SNHL) is one of the most common disabilities in industrial countries. Systemic administration of steroids has been widely used for the treatment of acute profound hearing loss [1]; however there are limitations in their clinical efficacy [2]. At present, therapeutic strategies are limited to hearing aids and cochlear implants for patients with chronic SNHL. Based on this background, basic investigations have elucidated several agents that are effective for the treatment of SNHL. However, the problem of how to deliver drugs to the inner ear has been a considerable obstacle to the development of treatments for SNHL. The blood-inner ear barrier prevents the transportation of serum drugs to the inner ear, and the blood flow to the inner ear is very limited.

Drug transduction through the round window membrane (RWM) is one option for delivering drugs into the inner ear. Continuous infusion of RWM with an osmotic pump and microcatheter has been reported as an effective and safe approach [3]. However, it requires surgery and the invasion cannot be overlooked. Recently, new local drug application procedures using biodegradable substances are gaining interest [4, 5]. The inner ear is one of the targets for local drug administration using biodegradable gelatin hydrogels [6, 7]. In this drug delivery system, positively charged proteins or peptides are electrostatically trapped in negatively charged gelatin polymer chains. As the gelatin polymer chains degrade, proteins or peptides are released from the hydrogel. The released protein is conveyed through the RWM into the inner ear via a concentration gradient. Therefore, close contact of biodegradable hydrogels with the RWM is critical for efficient drug delivery to inner ear fluids.

The RWM is situated perpendicular to the tympanic membrane and deep in the round window niche. In some cases, a false membrane covers the RWM. For safe and certain drug administration, hydrogels containing drugs should be placed on the RWM under direct visualization. Use of a

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