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Aplasia of zygomatic arch and dislocation of temporomandibular joint capsule in Treacher–Collins syndrome: three-dimensional reconstruction of computed tomographic scans

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KEYWORDS
Treacher–Collins syndrome;
Microtia;
Three-dimensional reconstruction;
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Summary Seven patients with Treacher–Collins syndrome were studied. All of patients were children or teenagers. Helical CT scanner (Toshiba) was used to reconstruct zygomatic arch and temporomandibular joint capsule on lateral aspect of temporal bone in five patients of microtia and atresia of both ears and two patients of narrow ear canals of both ears without microtia.

Three-dimensional reconstructions of computed tomography on lateral aspect of temporal bone demonstrated various congenital abnormality including aplasia of zygomatic arch in seven patients and dislocation of temporomandibular joint capsule in seven patients.

1. Introduction

Treacher–Collins syndrome (mandibulofacial dystosis) consists of certain associated congenital and familial deformities of the ears, malar bones, lips, chin and lower eyelids. The similarity between the patients is very striking [1,2].

There are various otological and maxilofacial problems such as bilateral microtia, atresia of the ear canal, middle ear anomaly and mandibular hypoplasia [3,6]. Patients affected by Treacher–Collins syndrome can show aplasia or hypoplasia of the zygomatic arch and dislocation of the temporomandibular joint capsule. These anomalies can be studied using conventional radiological procedures such as computed tomography (CT). However, CT provides only limited spatial relationships between the most important structures. In contrast, three-dimensional reconstruction of CT scans can provide more complete data of this region.

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The purpose of this study is to describe the use of three-dimensional reconstructions of microtia and atresia or bilateral narrow ear canal. This study was designed to reveal three-dimensional abnormal structures of zygomatic arch and temporomandibular joint capsule in Treacher–Collins syndrome with microtia and atresia or narrow ear canal of both ears.

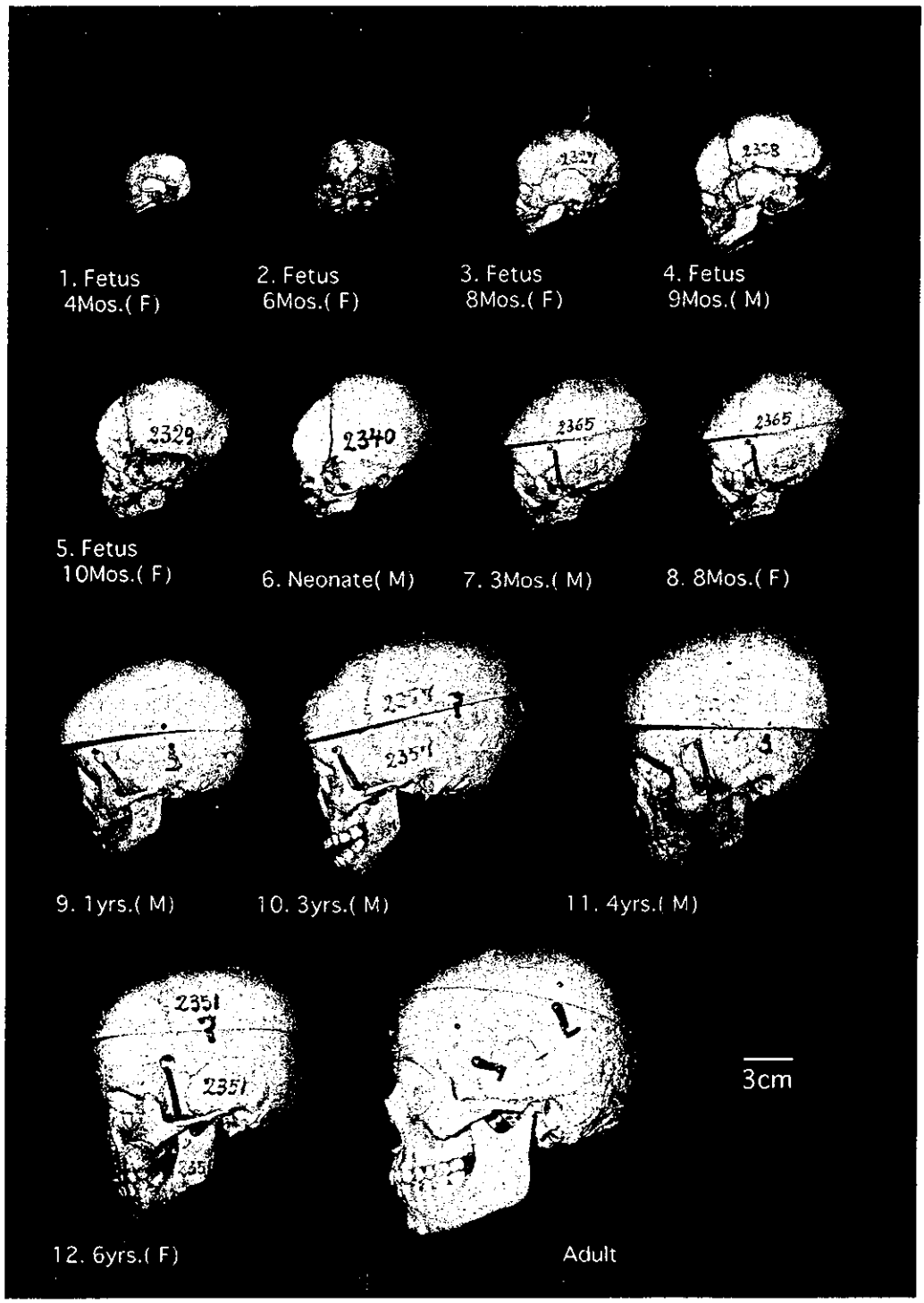

Fig. 1 The lateral view of 14 normal skulls: (1) five fetuses of different ages; (2) a neonate; (3) six infants and children of different ages; (4) an adult. Zygomatic arch and temporomandibular joint capsule can develop with age. After 1 year of age, the structures of zygomatic arch and temporomandibular joint capsule appear to be almost similar to that of adult in morphology. In the younger ages and fetuses, those of both structures can poorly develop.

2. Subjects and methods

Photographs of the lateral views of normal skulls of the following subjects were studied: five fetuses of different ages, a neonate, six children (3 and 8 months; 1, 3, 4 and 6 years of age, respectively), and an adult. The photographs were taken at the medical museum of the University of Tokyo. Also seven patients with Treacher–Collins syndrome were studied. The profiles of patients are listed in Table 1. All of these patients were children or teenagers. Helical CT scanner (Toshiba Co. Ltd.) was used for reconstructing the zygomatic arch and temporomandibular joint capsule on the lateral aspect of temporal bone. Five patients showed bilateral microtia and atresia.

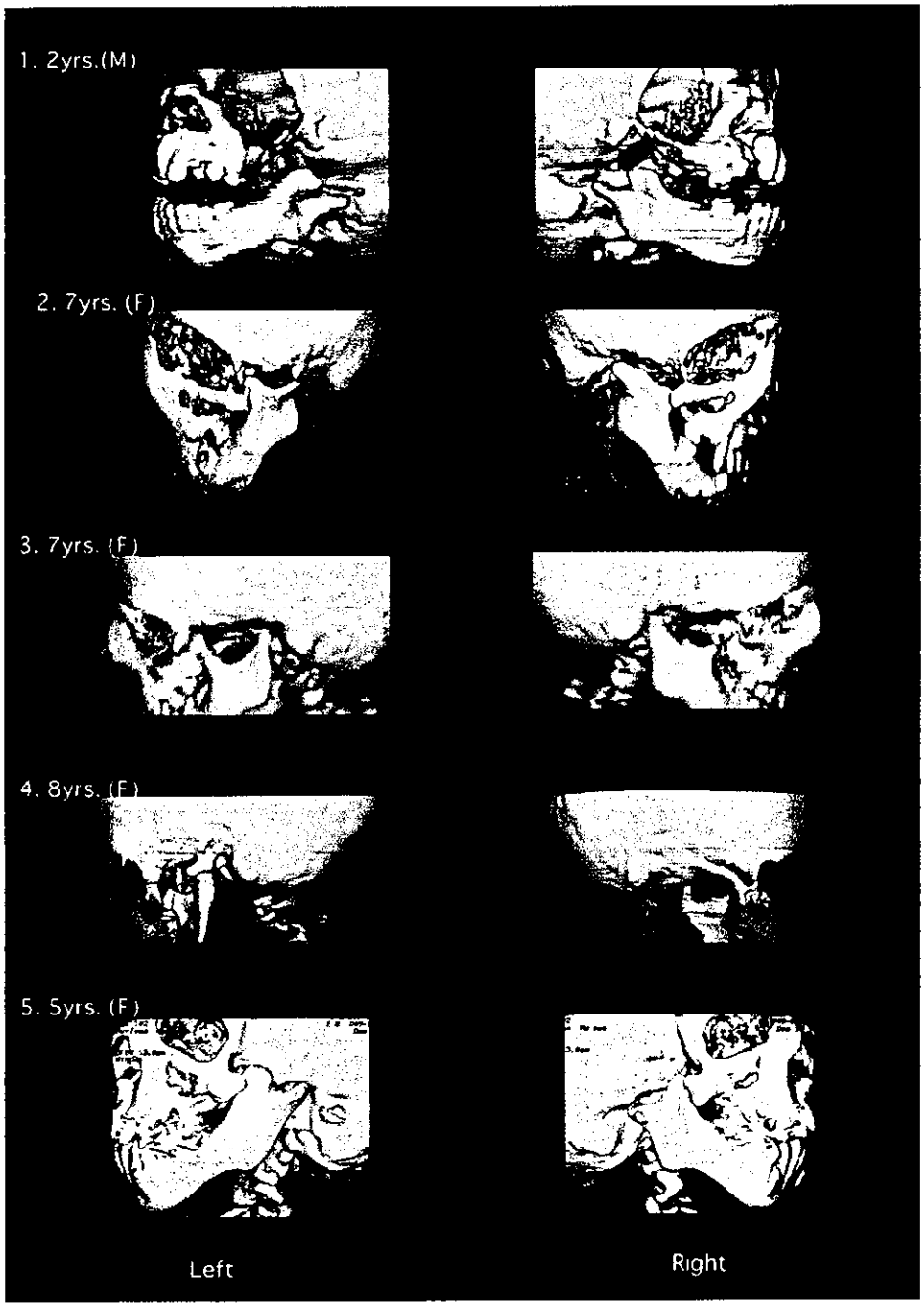

Fig. 2 Three-dimensional reconstruction on lateral aspect of temporal bone of five cases with Treacher–Collins syndrome. They showed bilateral microtia and atresia. Temporomandibular joints of Cases 1–5 with atresia of the ear canal of both ears are dislocated to the skull base and absence of bony external auditory canal are clearly demonstrated.

Table 1 The profile of seven patients with Treacher–Collins syndrome

Patient number	Sex	Age (year)	Bilateral microtia	Bilateral ear canal	Hearing aid
1	M	2	Present	Atresia	Bone conduction type
2	F	7	Present	Atresia	Bone conduction type
3	M	7	Present	Atresia	Bone conduction type
4	F	8	Present	Atresia	Bone conduction type
5	F	8	Present	Atresia	Bone conduction type
6	F	13	Absent	Narrow	Canal type
7	F	18	Absent	Narrow	Canal type

Two patients showed a narrow ear canal without microtia.

In addition, a normal child, a patient with isolated non syndromic microtia and aural atresia, and a patient with Treacher–Collins syndrome were compared to superimpose the lateral face and the lateral aspect of temporal bone by three-dimensional reconstructions of CT.

3. Results

Three-dimensional reconstructions of computed tomography on lateral aspect of temporal bone demonstrated various congenital abnormality in all patients including aplasia of zygomatic arch and dislocation of temporomandibular joint capsule.

1. Photographs of lateral view of normal skulls are shown in Fig. 1. In this picture, it is shown that even after birth zygomatic arch and temporomandibular joint capsule could develop. However, before birth development of both structures could be very poor.
2. Cases 1–5 with bilateral microtia and atresia of both ears were demonstrated to have agenesis of zygomatic arch and dislocation of temporomandibular joint capsule to the skull base (Fig. 2).
3. Cases 6 and 7 with bilateral narrow ear canal without microtia showed aplasia of zygomatic arch and also dislocation of temporomandibular joint capsule from the skull base showing bone clefts (Fig. 3).
4. Fig. 4 demonstrates a comparison of the reconstruction of the lateral view of skull,

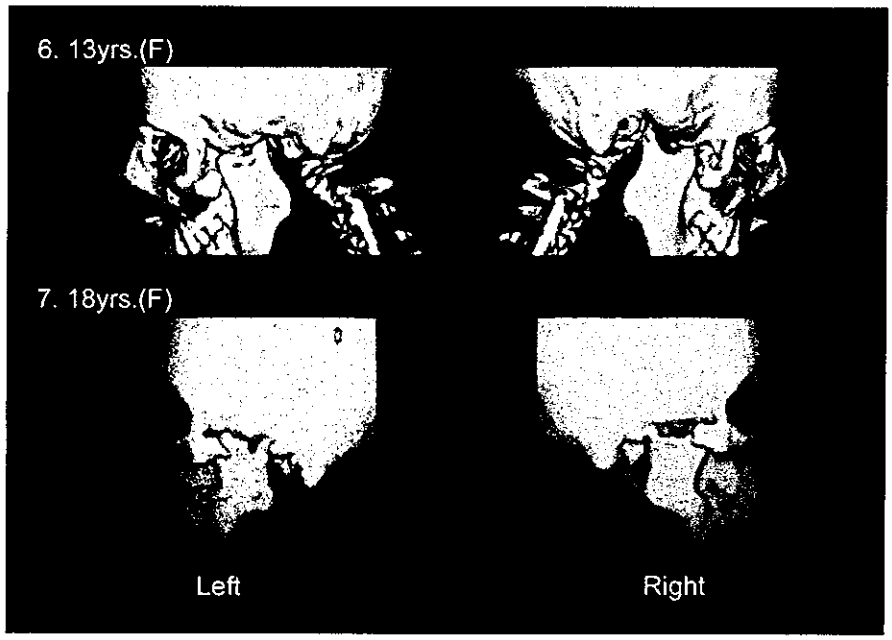

Fig. 3 Temporomandibular joints of Cases 6 and 7 with narrow ear canal without microtia are dislocated to the skull base because of aplasia of zygomatic arch.

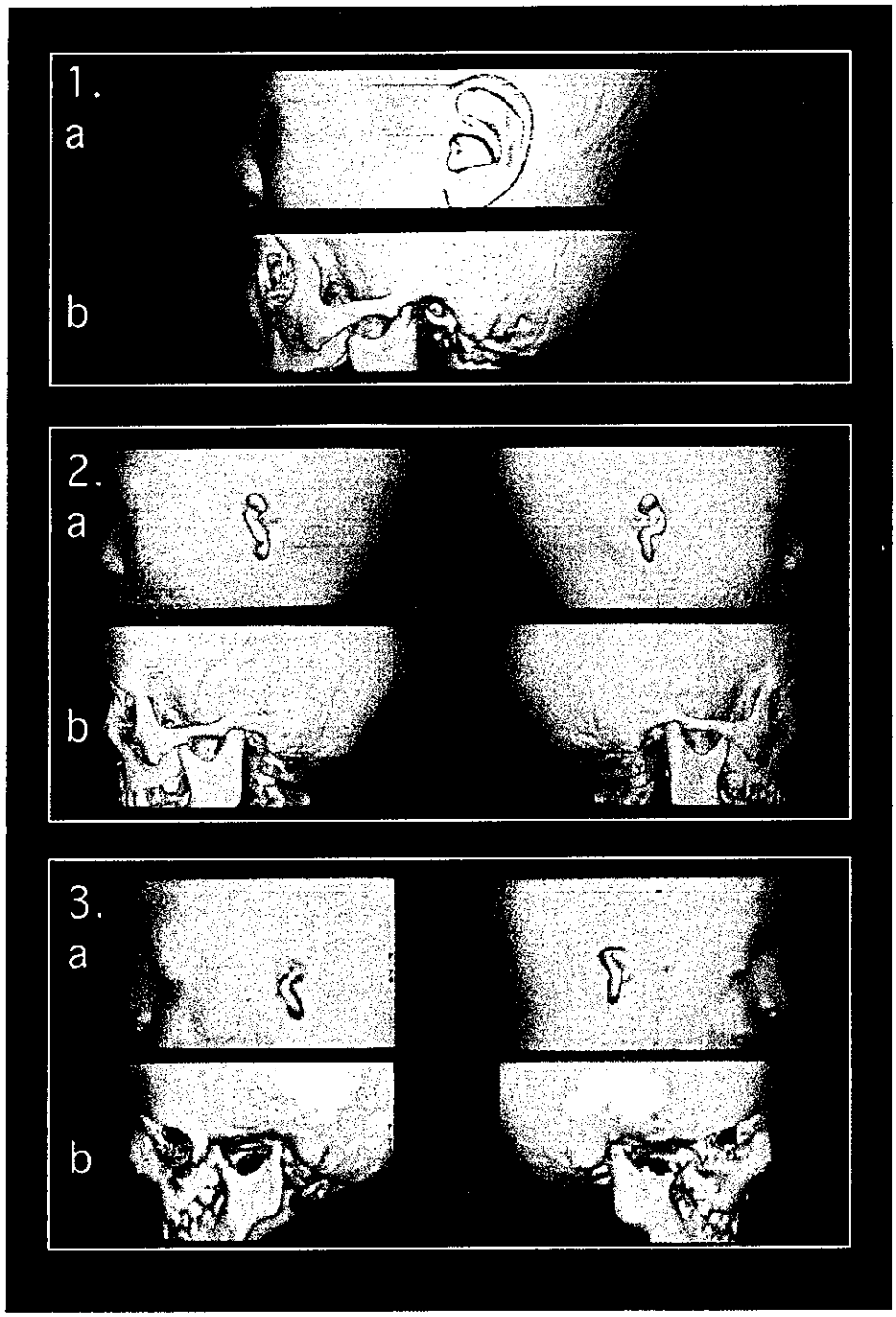

Fig. 4 A comparison of reconstruction of lateral face. Typical zygomatic arch and temporomandibular joint: (1) a and b is a 4 years old child; (2) a and b is a 7 years old child with isolated no syndromic microtia and atresia; (3) a and b is a 7 years old child (Case 2) of Treacher–Collins syndrome with microtia and atresia of both ears.

zygomatic arch and temporomandibular joint in: (1) a normal child; (2) a typical patient with isolated non-syndromic bilateral microtia and atresia; and (3) a 7 years old child (Case 2) with Treacher–Collins syndrome with bilateral microtia and atresia. This comparison revealed that only the patient with Treacher–Collins syndrome showed aplasia of zygomatic arch and dislocation of temporomandibular joint capsule.

4. Discussion

Our study using the Helical CT scanner to reconstruct lateral aspect of temporal bone in patients with Treacher–Collins syndrome demonstrated agenesis or aplasia of the zygomatic arch and that the temporomandibular joint capsule is dislocated toward the skull base according to absence of bony external auditory canal [1,3]. However, patients with

isolated non-syndromic bilateral microtia and atresia of the ear canal demonstrated normal structure at the zygomatic arch and the temporomandibular joint capsule which was located anteriorly to the mastoid [3–5,7].

In real skulls of normal young infants, the zygomatic arch and the temporomandibular joint capsule do not develop well. Moreover, in real skulls of normal fetuses, both structures' development is very poor. In normal development, around the first year of life, temporomandibular joints develop well, deciduous teeth appear and chewing abilities begin.

Embryologically, the external auditory canals starts to recanalize during the sixth intrauterine month [8]. In Treacher–Collins syndrome, this canalization and the formation of zygomatic arch are arrested prematurely. The recanalization of the external ear canal does not take place and also the underdevelopping zygomatic arch, mastoid process and mandible can cause poor temporomandibular joint and its dislocation in an abnormal direction. This is very similar to temporomandibular joints in those of normal fetuses.

In conclusion, from the results of this study, it is evident that three-dimensional reconstruction of CT scans is a safe and reliable procedure for studying patients with Treacher–Collins syndrome. Three-dimensional reconstruction of CT scans provide reliable spatial analysis of the zygomatic arch and the temporomandiabular joint capsule. The images obtained with these procedures are useful for revealing anatomical abnormalities. They are also useful for recognizing surgical landmarks and for evaluating chewing abilities.

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Auditory Agnosia in Children after Herpes Encephalitis

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Four pediatric patients whose bilateral auditory cortices were damaged by herpes encephalitis at an early age were studied. Their brain CT and MRI scans demonstrated common bilateral lesions of the auditory cortices. Their auditory perception was investigated by means of behavioral and objective hearing tests and auditory perception tests. All four patients showed mild or moderate hearing loss in the behavioral hearing test and normal auditory brainstem responses but did not manifest total deafness. Moreover, perception tests involving speech, environmental sounds and music demonstrated that most auditory perception ability had been lost in all patients. On reaching school age, the patients were enrolled in schools for the deaf or special schools for handicapped children. *Key words: auditory agnosia, auditory cortex, herpes encephalitis, school education.*

INTRODUCTION

The mechanism of hearing loss in patients with bilateral auditory cortex lesions remains controversial (1, 2). This manifestation is known as auditory agnosia or cortical deafness (3–10) and in adult patients is usually caused by two episodes of cerebral infarction. However, in pediatric cases, it is frequently caused by herpes encephalitis (11–14) and not by cerebrovascular accident. Adult cases have been extensively studied but pediatric cases have rarely been reported because the residual hearing of these patients is not well documented from the developmental and educational standpoints (14). Herein, we report four cases of children with auditory agnosia after herpes encephalitis which were studied from the neurotologic, neuropsychologic and educational standpoints, in order to determine differences from adult cases.

CASE REPORTS

Case 1

This patient was a right-handed girl whose delivery was uneventful. Her early development was normal and she responded well to auditory stimuli. When she was 6 months old she suffered from herpes encephalitis. A brain CT scan revealed bilateral lesions of the auditory cortices and a left frontal lesion (Fig. 1). Subsequently, she became indifferent to sounds and could not distinguish any sound. Conditioned orientation reflex audiometry showed threshold elevation of 60 dB HL (Fig. 2) but the auditory brainstem response (ABR) threshold was 20 dB (Fig. 3). She was diagnosed as having auditory agnosia as a sequela of herpes encephalitis. As she could still not speak at the age of 6 years, she was enrolled in a school for handicapped children during her elementary, junior high and senior high school years. She is now 19 years old.

Case 2

This patient was a right-handed boy whose delivery was uneventful. His early development was completely normal. He began to speak several words using mimicry when he was 12 months old. When he was 14 months old he suffered from herpes encephalitis, which was diagnosed based on increased serum levels of herpes simplex virus antibody. At the age of 2 years, he had spoken no intelligible words. Although he responded well to visual stimuli, he had no interest in auditory stimuli and only rarely responded to environmental sounds. Conditioned orientation reflex audiometry revealed an increased threshold to 60 dB hearing level (HL) (Fig. 2). However, ABR showed a normal threshold of 15 dB HL (Fig. 3). A brain CT scan revealed a low-density area in the bitemporal auditory cortex that was more prominent in the right as opposed to the left hemisphere. The patient was diagnosed with auditory agnosia, as manifested by destruction of the bilateral auditory cortex caused by herpes encephalitis. He was enrolled in a school for the deaf until graduation from high school. In his daily life he can hear but cannot distinguish speech, environmental sounds and music. However, he can write and can communicate using sign language. His brain MRI scan at the age of 10 years is shown in Fig. 1. He is now 28 years old.

Case 3

This patient was a right-handed boy. His development was normal until the age of 1 year and 3 months when he suffered from herpes encephalitis. Upon examination, it was found that he did not

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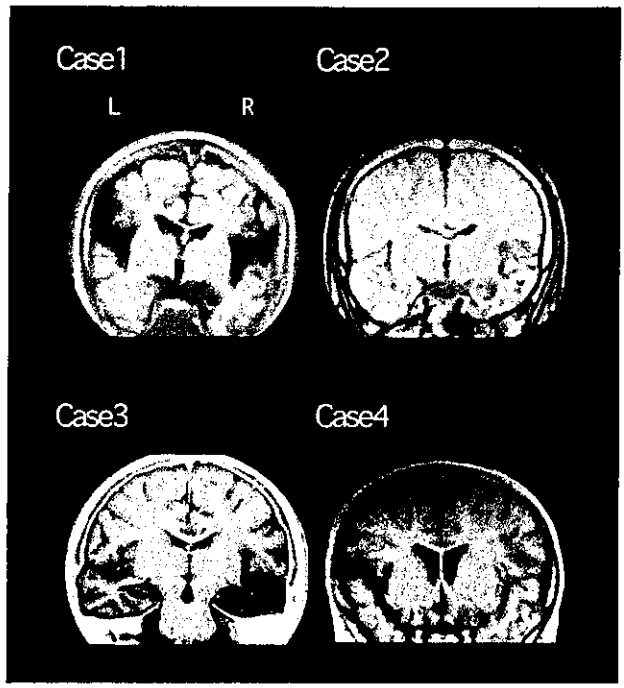

Fig. 1. Brain MRI scans of the four cases after herpes encephalitis. Note the bilateral lesions in the superior temporal gyrus, including the auditory cortex.

respond to sound and could not speak any words. His brain CT and MRI scans demonstrated bilateral lesions of the superior temporal gyrus, including the auditory cortex (Fig. 1). Conditioned orientation reflex audiometry showed threshold elevation of 50 dB HL but ABR showed a normal threshold of 20 dB HL. Speech discrimination, perception of environmental sounds and music and auditory comprehension were all totally impaired. Speech therapy was started when he was 1 year and 7 months old. When he was 3 years and 6 months old, sign language (cued speech) was introduced at a school for the deaf. At the age of 6 years, he could use >220 words and 2-word sentences for communication. He is now 17 years old and a student at a high school for the deaf; he uses sign language to communicate.

Case 4

This patient was a right-handed boy whose delivery was uneventful. His development was normal. He could hear and talk with friends of the same age until the age of 2 years and 7 months, when he suffered from herpes encephalitis. Thereafter he did not respond to any sound stimuli or speak any words. His brain CT and MRI scans demonstrated bilateral lesions of the superior temporal gyrus, including the

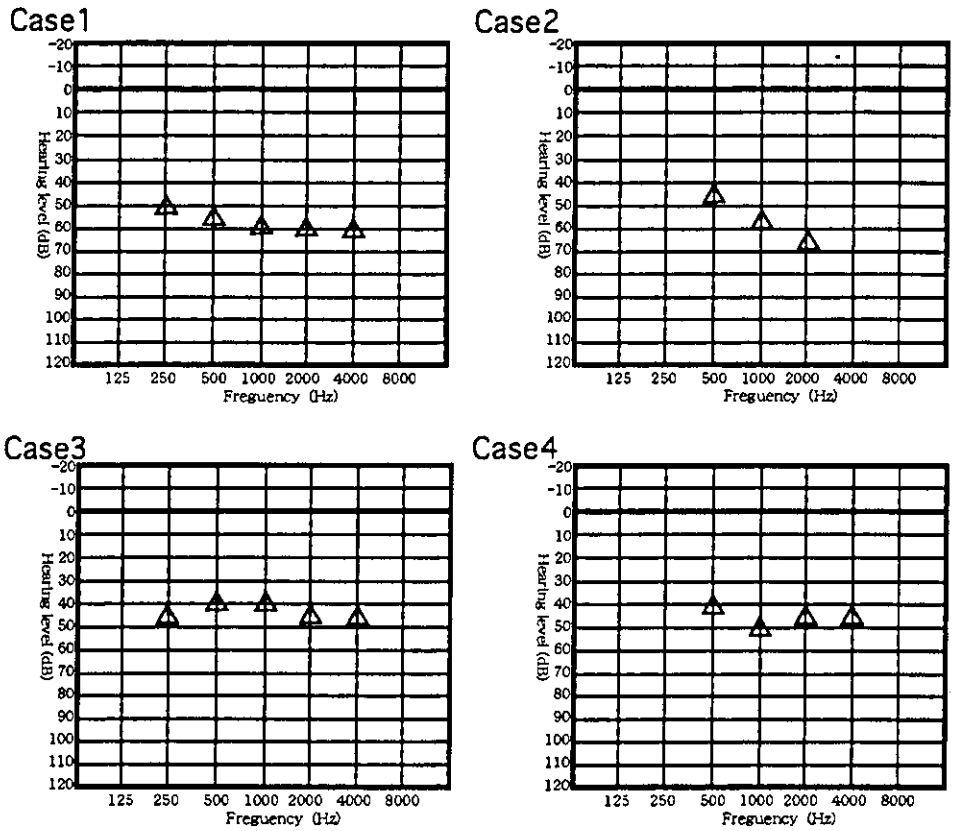

Fig. 2. Audiograms of the four cases after herpes encephalitis examined by means of conditioned orientation reflex audiometry because pure-tone audiometry was difficult. Note the threshold elevation compared to age-matched controls.

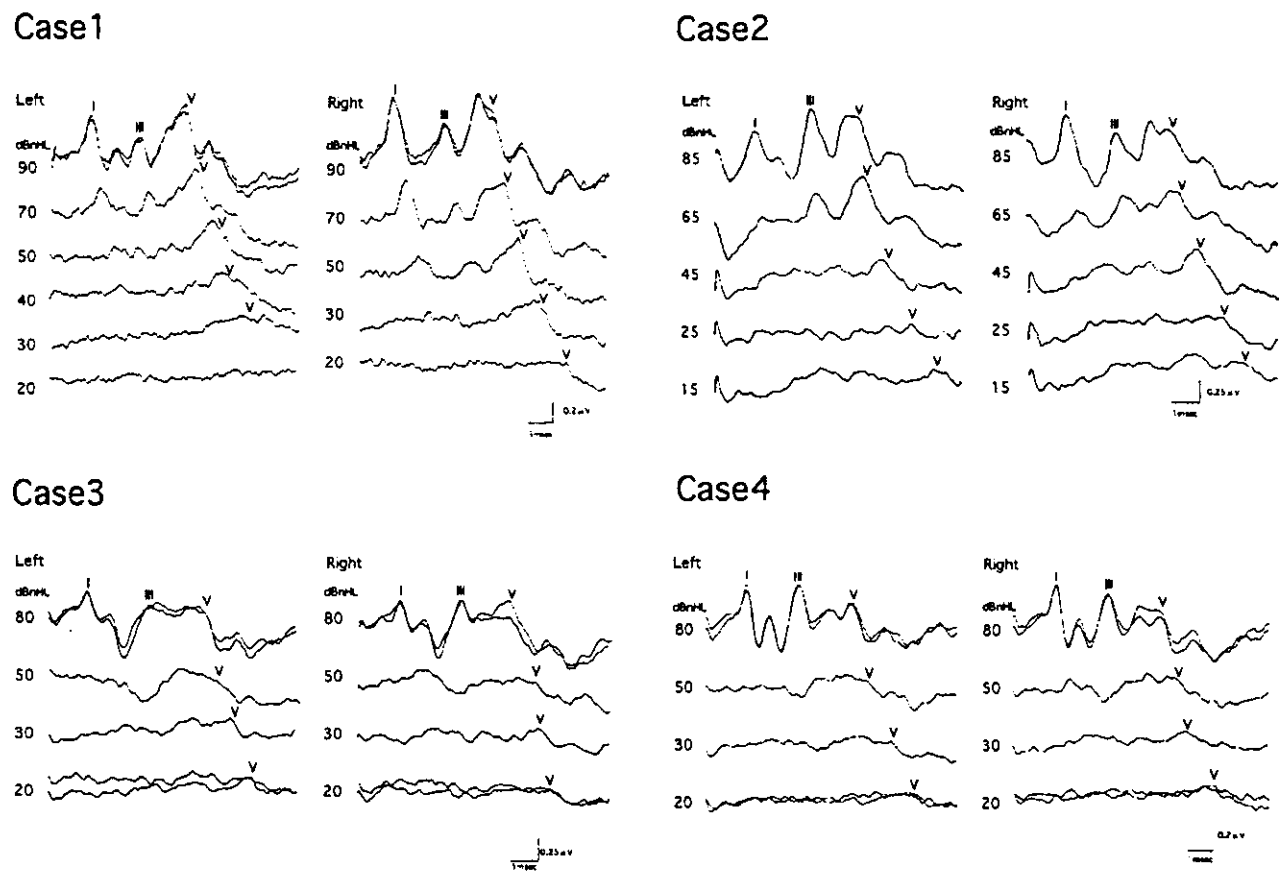

Fig. 3. ABRs of the four cases after herpes encephalitis showing normal configurations and thresholds.

auditory cortex (Fig. 1). Conditioned orientation reflex audiometry showed a threshold elevation of 50 dB HL but ABRs demonstrated a normal threshold of 20 dB HL. Subsequently, the patient responded to several environmental sounds and voices, but could not distinguish any speech or music. He was enrolled in a school for the deaf. Initially, he communicated using gestures. At the age of 5 years, sign language was introduced and he could use two- and three-word sentences for communication. However, finger spelling, letters and lip-reading remained difficult to learn. He is now 18 years old.

DISCUSSION

Severe auditory deficit due to bilateral lesions of the primary auditory cortex is very rare. The resulting hearing problem is referred to as auditory agnosia or cortical deafness. The first case of auditory agnosia due to bilateral auditory cortex lesions was reported by Wernicke and Friedlander in 1883 (3), and led to investigations of the auditory cortex in the brain. However, few histological studies have subsequently been reported in the literature concerning bilateral auditory cortex lesions in the autopsied brain (2, 4, 5, 8).

Well-known underlying diseases of auditory agnosia in children include Landau–Kleffner syndrome and cerebrovascular accidents such as moyamoya disease. However, because of the extremely low incidence of auditory agnosia in children, little interest has been paid to it and its manifestation may often be undiagnosed. Auditory agnosia as a sequela of herpes simplex encephalitis has only recently been discussed (11–14). Herpes simplex encephalitis is known to lead to focal brain necrosis, particularly in the temporal orbitofrontal regions of the brain. However, language-related sequelae in children caused by focal brain lesions are very limited. Our four patients, having being diagnosed with herpes encephalitis, showed common bilateral temporal lesions of the auditory cortices, which indicated typical auditory agnosia. The early onset of auditory agnosia made their education very difficult. Three of the patients went to schools for the deaf and one was educated at a school for handicapped children. Their audiograms showed residual hearing but they could not hear in practice. However, all of the patients can now read

and write Japanese characters, although not perfectly. Because of very slow development of the concept of grammar, they experienced difficulty in communicating effectively with others. Written communication is almost impossible, despite some writing ability. However, sign language is very useful as a communication tool.

In adult patients with auditory agnosia, the bilateral auditory cortices usually exhibit localized lesions as a result of two different episodes of cerebral infarction. Usually, adult patients with auditory agnosia have impaired central hearing but their ability to use language is not totally impaired if the language center is not involved. Thus, they can read and communicate by writing.

In the previous literature concerning autopsied cases with bilateral auditory cortex lesions, pure-tone thresholds were categorized as either mild or severe threshold elevation (1, 2, 5). However, thresholds varied across studies. For example, some cases demonstrated mild threshold elevation, while others showed thresholds that were markedly elevated. Not all audiograms were completely analyzed during the clinical course for the reported patients across cases' studies. Another problem with previous studies is that only one audiogram was analyzed for each patient. However, in our previously reported adult autopsy case (2), the pure-tone audiogram was analyzed throughout the clinical course, and progressive threshold elevation was observed. At an early stage after the onset of disease, the patient showed mild threshold elevation. Later examinations revealed that the thresholds became progressively worse and finally reached severe to profound levels 1 year before his death (2). It is very important to note that the four cases of children with auditory agnosia presented herein showed only mild or moderate threshold elevation during the developmental period, which may suggest partial damage of the auditory cortices or the auditory function of the extrageniculate pathway in each case.

Finally, we emphasize that, due to auditory agnosia, our pediatric patients showed profound communication disorder. Their present handicaps, despite early, intensive and continuous training, suggest that a more fundamental language deficit is likely to occur in the developing than the mature brain. The communication training and education of these patients can lead to some, but not complete, improvement in their communication ability. In the present educational setting, schools for the deaf are better than other schools because they cater for such very rare cases as these who require special education.

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新生児聴覚スクリーニングの発展と Auditory nerve disease (Auditory neuropathy)

加 我 君 孝 (東大耳鼻科)

第48回日本小児耳鼻咽喉科学会

＜特別講演＞

新生児聴覚スクリーニングの発展と Auditory nerve disease（Auditory neuropathy）

加 我 君 孝（東大耳鼻科）

A special lecture: Universal Newborn Hearing Screening: —Development in Japan and Auditory Neuropathy—

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In Japan, last 30 years, hearing screening of infants has been conducted regularly in the health centers at age of 3–4 months, 6 months, 9 months, 1 year and 3 years. However, last 3 years, universal newborn has been introduced to several prefectures. Thereafter, we have encountered a new problem which is absence of auditory brainstem responses but normal DPOAE. This problem is regarded as auditory nerve disease or auditory neuropathy. Auditory nerve disease was reported by us in 1996 and auditory neuropathy was reported by Starr et al in 1996. In addition, there are other new problems in universal newborn hearing screening. At present, otology and neurotology of newborns is expected to establish newly.

1. 新生児聴覚スクリーニング以前

我が国でも難聴児の早期発見には力を入れてきた。難聴児の早期発見の方法は保健所の3～4カ月健診に重点を置き，疑わしい症例は大学病院で精密検査するか，あるいは6カ月，9カ月，1歳，1歳半，3歳健診で再チェックしてから精査を依頼する仕組みである[1]。米国の新生児聴覚スクリーニングの背景は，①出産での入院は1泊2日程度に限られている。②わが国の保健所のような小児保健の監視機構がない。そのために，乳幼児の難聴をチェックし早期発見をするには新生児期に行うほかない。③audiologist や speech pathologist という難聴や言語障害の専門職があり，一度発見されると充実したアフターケアーが可能なシステムがある[2]。人工内耳手術例の増加で新しく口話療法士も生まれた。このような社会的条件の違いの他にデンバーのコロラド大学の Marion Downs 女史という1960年代より難聴児の早期発見早期教育の運動を行ってきた指導者がいたことも大きな原動力であった。歴史的には新生児の難聴を正確に判定出来るようになったのは1970年に聴性脳幹反応（ABR）が発見されてから後のことである。難聴が疑われた乳幼児・小児は ABR 検査で調べられてきた。この ABR は眠らせて検査終了まで30～60分は必要とし，聴覚の仕組みや検査装置の理解が出来て，かつ結果を判定出来るような検査技師あるいは医師が必要である。これに対しこのような専門家の不要な新しい技術の開発が行われた。

2. 自動 ABR の開発と米国における発展

ハーバード大耳鼻科の Thorton[3]は，難聴の有無を自動的にチェック可能な自動 ABR のアルゴリズムを考え，それを米国の Natus 社が製品化した。ABR が 10 dB ステップで厳密に調べるのに対し，第一段階では 35 dB で反応

の有無をチェックし，それで不合格であると第二段階で40 dBと70 dBの両方でチェックするだけの簡単な自動判定装置である。波形も描写されず，passかreferしか表示されない。この装置の信頼性は米国では10年前からよく研究されて精度が高いことが証明されている。その発表は国際ERA（Evoked Response Audiometery）学会で2年ごとに報告された。

1998年にDowns女史の弟子の日系のYoshinaga Itano[2]が，新生児期に難聴が発見され生後6カ月までに補聴器をフィティングし聴能学習をすると，その難聴が重度であれ，中等度であれ，軽度であれ，3歳になると普通の子供の90％の言語力を身につけるという論文を発表した。その結果，新生児聴覚スクリーニングは極めて意義の高いものであることが認識されるようになり，米国ではほとんどの州で実施が義務化されるに至った[3]。ヨーロッパでも各国に拡っている。中国でも北京市で全面的に導入されるに至っている。

3. 日本における新展開

我が国では，この問題は，自動ABRの輸入業者が厚生労働省を訪ね，新生児聴覚スクリーニングの意義をPRしたことがきっかけで注目されることになり，研究のための班会議が編成されたことに端を発する。班会議ではこの自動ABRを用いて約2万人の新生児聴覚スクリーニングを行い意義のあることが全国の各施設から報告された。その結果，平成12年度より厚生労働省は予算を獲得し，手上げ方式でモデル事業をスタートさせることを決めた。米国では耳鼻科，小児科，audiologist，教育者などからなる合同会議を20年以上前に編成して取り組んできたのと全く異なるスタートとなった。行政の政策としてトップダウンで行われたことが，現在大きな混乱をもたらしている。しかし，日本耳鼻咽喉科学会は精密聴力検査機関の全国のリストを作成するなど対応している。スクリーニングは産科や新生児科が担当し，つづいて耳鼻科で精密聴力検査を行っている．精密聴力検査後は難聴児通園施設やろう学校が教育を担当している。

現在，スクリーニングを経て紹介されてくる新生児の両親は，“耳は聴こえていません”と産科医や新生児科医に言われた後に，耳鼻科の幼小児の難聴の専門医へ紹介されてくる。思いがけない説明に衝撃を受け，精神衰弱のような状態で受診する母親が少なくない。この言い方は両親にとって，“何も聴こえていない”ととれるため希望を失う。この言い方は正しくはない。スクリーニングでふるいにかけられた新生児は軽～重度難聴まで幅広く含むからである。その後は専門医がよく調べ，難聴と診断されれば，身体障害者手帳の発行をし，補聴器を交付し，聴能学習，聴能訓練のための適切なところへ紹介する。

4. 現在の問題

新生児聴覚スクリーニングプログラムが始まって発見された最初の子供たちは2～3歳になっている。やはり筆者が危惧したように高度難聴の場合，早期に補聴し，熱心な教育を受けて来たにも拘わらず，言語力がYoshinaga Itanoの言うほど高いレベルに到達していない子供が目立つようになってきた。筆者の科でも平成15年夏から暮れにかけてそのような2～3才になった難聴幼児の人工内耳手術が6名予定されている。現在振り返ってみると，この新生児聴覚スクリーニングはそれ以前に人工内耳埋込術という画期的な治療が開発され，発展してきたことで大いに夢があるといえる。もし人工内耳がなければ早期発見しても昔と同様で最終的な到達度も教育も変わらなかったであろう[4]。

新生児聴覚スクリーニングでは35～40 dBがpass, referの境目である。精密聴力検査では施設でも異なるがABRは45～60 dBで正常，異常の判断をしている。新生児や乳児では，中耳腔には間葉組織や滲出液がまだ残存しているために中耳伝音機構の働きが不十分であるために軽度の伝音難聴を伴っていることが少なくない。そのために12カ月になってABRで

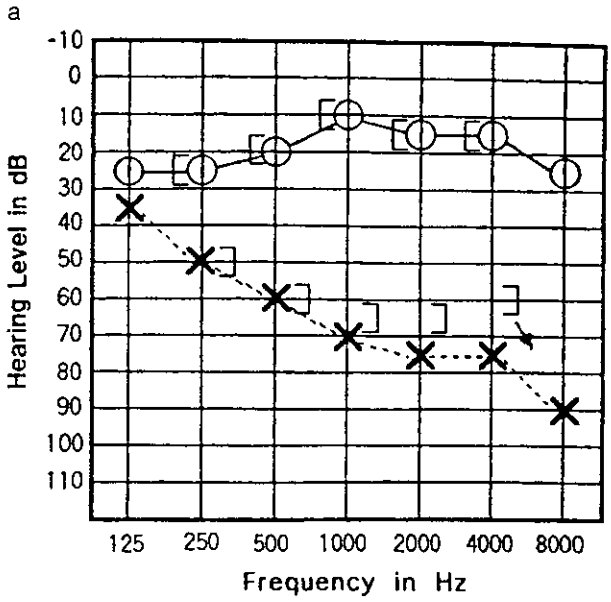
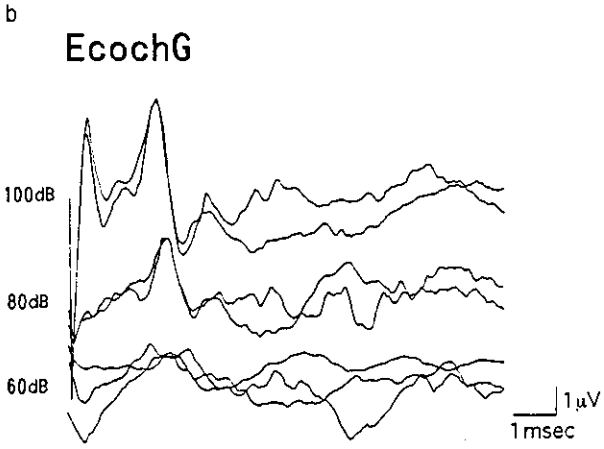
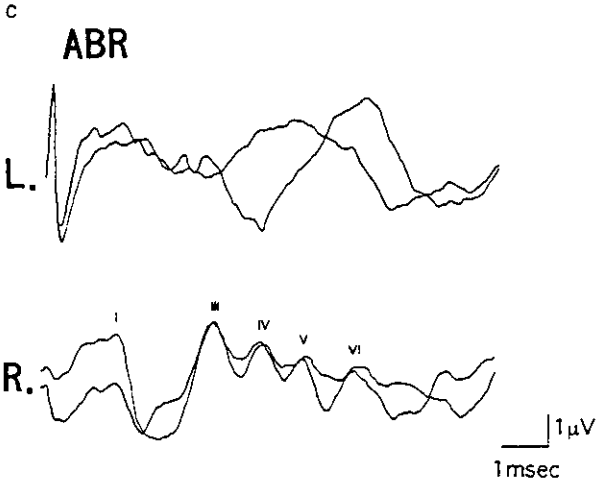
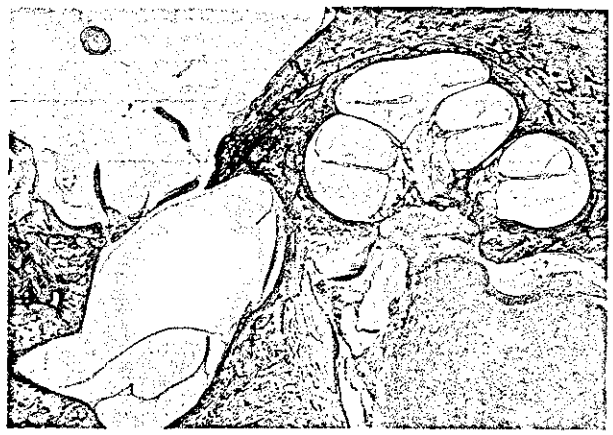
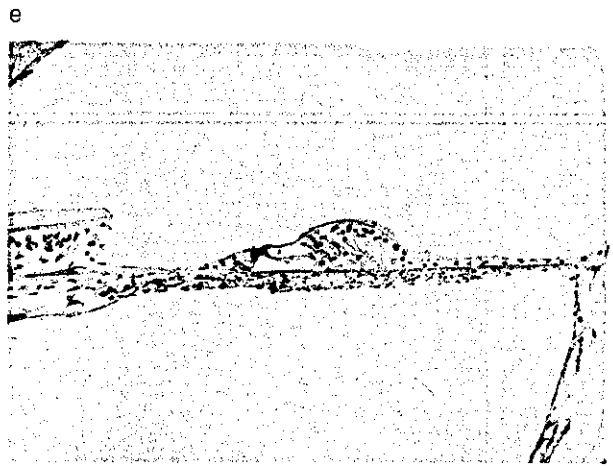


図1　左聴神経腫瘍の1例の聴覚検査所見。聴神経腫瘍が内耳道に限局している(d)。コルチ器は保存されている(e)。
a. ABRは無反応。しかしb蝸電図は出現している。









再検査すると正常化していることが多い。特にダウン症を初めとする染色体異常や奇形症候群ではこのようなことがしばしばあるので注意がいる。

さらに新しい問題は，新生児聴覚スクリーニングでは自動ABRより価格の手頃のOAEを用いるとOAEは正常であるがABRが無反応である特殊な例が存在することである。OAEかに見ると正常であるためpassとなる。OAEとABRを行って初めてこのようなOAEとABRの解離の存在することが報告された。Auditory nerve disease (Auditory neuropathy)の新生児版である。次にこの問題を詳しく解説する。

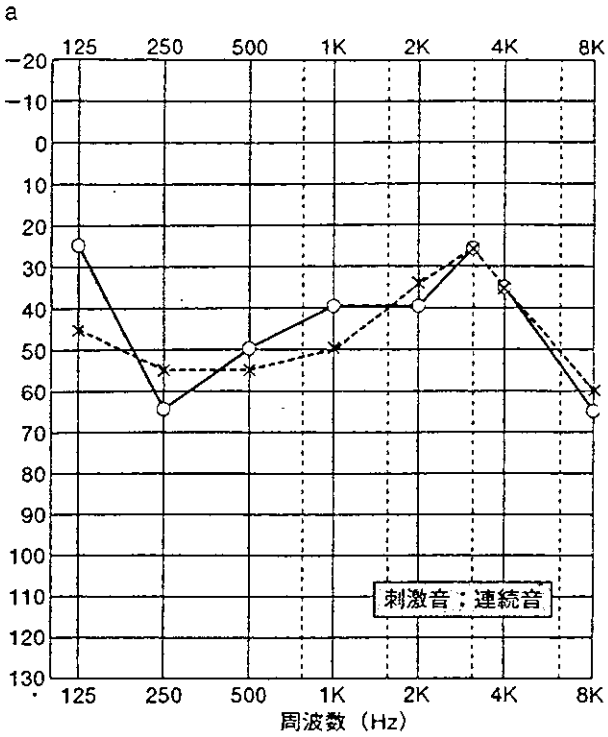
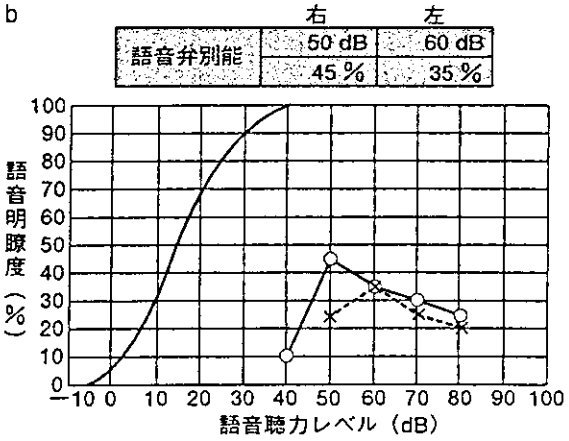


図2　後天性 Auditory nerve disease（Auditory neuropathy）の聴覚検査所見
60歳女性



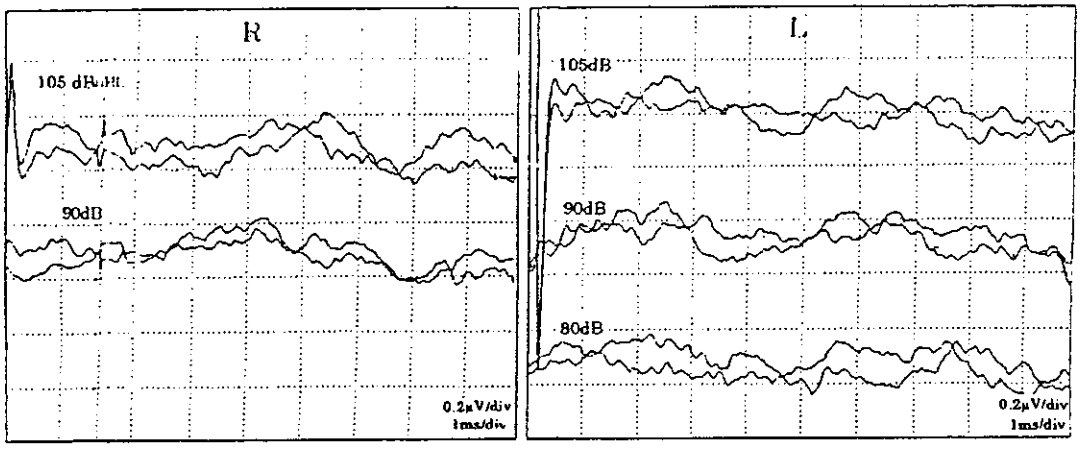
5. Auditory Nerve Disease あるいは Auditory Neuropathy

1996年，著者等は Scandinavian Audiology 誌に Auditory Nerve Disease というタイトルで新しい聴覚障害の存在することを報告した[5]。すなわち，純音聴力検査では低音部の閾値が中等度上昇し，中音域～高音域は軽度の上昇するだけにも拘わらず語音の弁別が著しく悪く20～40%程度という解離した結果を示す。他覚的検査では DPOAE は正常，蝸電図では −SP は出現するが，N_1 は欠除するかあるいは著しく小さい。ABR は無反応である。このような組合せのまとまった所見は聴神経腫瘍でも記録される（図1）。著者等は同様の検査所見を示す片側の聴神経腫瘍の側頭骨病理標本で腫瘍が内耳道に限局している例について報告した（図1）。この例では腫瘍は内耳道にあり，コルチ器も蝸牛軸のラセン神経節も正常に保たれている。ABR は無反応であるが蝸電図の記録は良好で N_1 が蝸牛軸のラセン神経節から生じていることを示している。著者等の報告した Auditory nerve disease の2例は後天性であり，言語障害はない。日常生活では1対1で話すと会話は成立するが，電話は聞き取れない。騒音のあるところでは会話は出来ない。数名の人との討論は出来ない。補聴器は効果がない。検査所見は聴神経腫瘍と数似している（図2）。これはラセン神経節よりもさらに末梢で，しかし感覚細胞より中枢側に障害部位が存在することを示唆している。

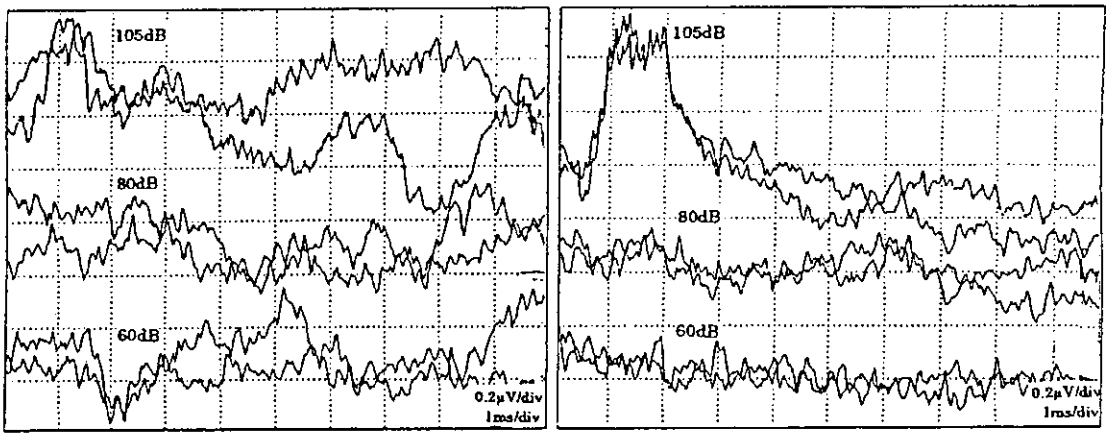
同じ1996年，Starr[6] 等は Brain 誌に Auditory neuropathy というタイトルで同様の聴覚障害を報告した。4歳～49歳までの10例の報告で，DPOAE と CM は全例で保たれ，ABR は無反応，stapedial reflex は無反応，純音聴力検査では中等度の感音難聴で，スロープが平坦型と上昇型が半々，語音明瞭度検査では0%～92%で，様々であるがほとんどが50%以下。診断名は10例中3例が Charcot-Marie-Tooth 病。5例は sporadic な症例であった。小脳変性症の Charcot-Marie-Tooth 病や Friedreich 病の側頭骨病理では，蝸牛の内外有毛細胞は保存されているにも拘わらず，蝸牛神経節は蝸牛軸でも変性していることが報告されている[5]。

Starr 等は蝸電図検査は行っていないが，著者等の報告と心理的な聴力検査や他覚的な聴力検査もほとんど同じである。ただし，遺伝性小脳変性疾患が10例中3例も含まれていることが違う。

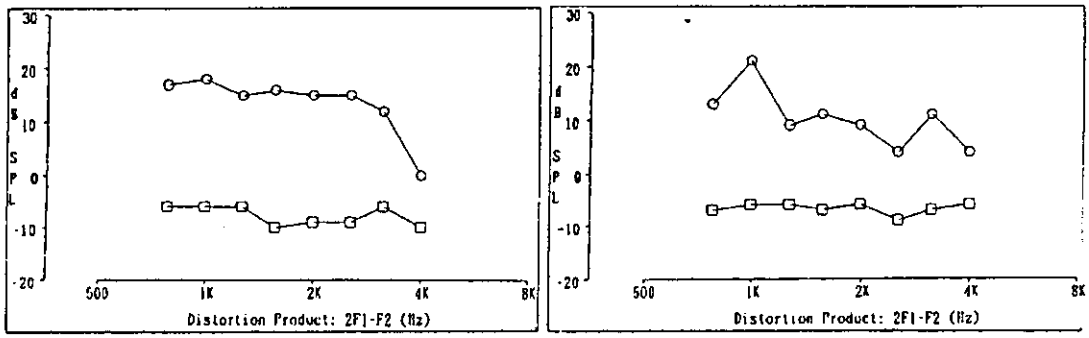
c. ABR



d. EcochG



e. Distortion Product-gram



以上の2つの報告に先立って我が国では佐藤[7]等が“本能性後迷路障害の聴力像”というタイトルで1985年に5例を報告している。軽度の感音難聴に比べ語音明瞭度検査の成績が著しく悪く，蝸電図が－SP優位でN_1を欠き，ABR無反応であった。1985年は我が国ではDPOAEはまだ検査に使われていなかった。著者等の論文も初めDPOAEなしで投稿したが採用されず，DPOAEを記録して加えて初めて掲載された。その間約3年も要した。

このAuditory nerve diseaseあるいはAuditory neuropathyはその後，思いがけない展開をするようになった。①新生児聴覚スクリーニングにDPOAEを使う施設が国内外も多くなっているが，この新しい聴覚障害をスクリーニングでは，先天性の本疾患が存在する可能性が

示唆された。②人工内耳手術で聴覚が回復する例が多いことがわかった。③遺伝子異常が報告された。④側頭骨病理が報告されたなど脚光は浴びるようになった。以下に最新の研究の動向を紹介する。

1) 小児例

Doyle ら[8]は4～15歳の8例のOAE正常でABR無反応例について報告した。3例は先天性，2例は1歳で発症(Stevens-Jonson 症候群，Friedreich's ataxia 各1例)，他については不明。この論文では内有毛細胞と蝸牛神経節を区別する方法はないこと，言語習得以前に発症すると軽度難聴にも拘わらず言語獲得が出来ないこと，治療はFM補聴器や振動装置などを使っているが，人工内耳についてはわからないと述べている。Madden ら[9]はオハイオ小児メディカルセンター過去8年の難聴児の5.1%の22例が本疾患で，平均年齢が17カ月であった。そのうち68%が周産期の異常を伴っていた(高ビリルビン血症11例，SFD 10例，耳毒性薬物使用9例，人工呼吸器使用8例，遺伝性疾患の疑い8例)。10例は補聴器を使用している。4例に人工内耳手術を行い，2例は良好な結果であった。自然軽快したものが2例ある。

Santarelli ら[10]は11カ月，12カ月，4歳，7歳の幼小児例に対し経鼓膜法で蝸電図を記録し，CM, SP が記録され，2例は broad compound action potential も記録された。蝸電図は Auditory neuropathy の診断に有用であると強調している。

小児の言語獲得前の症例は問題がある。OAE が正常で ABR 無反応であった症例では，Deltenre ら[11]によると，その後 OAE も消失する症例があり，そのような場合は補聴器が効果的であるという。OAE が乳幼児で正常でもそれから間もなく消失することがある。そのような場合，最初の OAE は本当に真の反応であるか否か迷うことが多い。小児神経学的には auditory verbal agnosia に類似しているという報告もある[12]。

2) 人工内耳手術の効果

Shallop ら[13]はメイヨークリニックでDPOAE正常反応でABR無反応，純音聴力検査で高度感音難聴，語音の認知は認められた症例を3～6歳で人工内耳埋込術を行った。その結果，3例は電話でコミュニケーションが可能となった。読話併用で聴覚を使うようになった。この報告ではEABRが出現することで，これは蝸牛神経が刺激されたことを示している。その後，Madden ら[9]，Buss ら[14]も小児の auditory neuropathy には補聴器ではなく人工内耳埋込術が聴覚の獲得のためには効果的と報告している。

現在のところ，我が国では小児のこのような人工内耳の報告はない。一方，Manson ら[15]は幼児，成人4例，の病因の異なる症例に対して人工内耳埋込術を行い，いずれも良い成績をあげている。その理由として dyssynchrony 状態の蝸牛神経に人工内耳により電気刺激を行うことで synchronous neural activity をもたらすためであろうと推測している。

3) 遺伝子

本疾患について遺伝子解析を行ったのは Varga と Starr ら[16]である。非症候群性劣性型 auditory newopathy と呼ばれる非症候群性の劣性遺伝型難聴のユニークなタイプの4家系を調べ，共通して Otoferlin（OTOF）gene を見出した。OTOF は元々非症候群劣性遺伝難聴の原因遺伝子 DFNB9 として知られていたものである[17]。Otoferlin は，成体マウスでは内有毛細胞に発現されている蛋白で，シナプス小胞のシナプス前膜への結合に関与する遺伝子と言われている。Starr[18]は2003年に，myelin protein zero（MPZ）遺伝子 Tyr145 が Ser に変位した新しい遺伝性の sensory motor neuropathy と難聴の多発する一家系を報告した。1例は側頭骨病理を得ることが出来，蝸牛内にあるラセン神経節と神経線維の著しい脱落を認めたが，外有毛細胞は頂回転で30%の脱落している以外は正常であった。

6. おわりに

新生児聴覚スクリーニングは，小児耳鼻咽喉科領域に新たに「0歳児の耳科学・神経耳科学」の研究の必要性を示唆している。現在行われている聴覚スクリーニング，その後の精密聴力検査の経験と研究から発見されると思われる。さらに先天性のauditory nerve disease (auditory neuropathy) は本当に存在するのか，存在するとすればどのような経過を経るのか。治療は人工内耳埋込術が最も適切なのか。これらの問題を解明し治療方針を検討する必要がある。最近米国の著名な小児神経医であるRapin[19]はこの問題についてreviewを書き，この診断名はこれまでの報告が医学的には様々でありすぎ，もっと病因や障害部位を狭くして使用すべきである。責任病巣をラセン神経節あるいはその神経または第8神経に限るべきであること，これまで使われている神経性難聴は脳幹から聴皮質に至る聴覚伝導路に障害が生じた場合に限って使うべきであろうと提案している。

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