Ⅲ.　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表レイアウト

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
松永達雄	遺伝性難聴と遺伝カウンセリング	小川郁	よくわかる聴覚障害－難聴と耳鳴のすべて－	永井書店	東京	2010	344-348

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Mizutari K, Matsunaga T, Inoue Y, Kaneko H, Yagi H, Namba K, Shimizu S, Kaga K, Ogawa K	Vestibular dysfunction in a Japanese patient with a mutation of the gene OPA1.	J Neurol Sci	293	23-28	2010
Morimoto N, Taiji H, Tsukamoto K, Morimoto Y, Nakamura T, Hommura T, Ito Y	Risk factors for elevation of ABR threshold in NICU-treated infants.	Int J Pediatr Otorhinolaryngol	74	786-790	2010
泰地秀信、守本倫子、松永達雄	Auditory neuropathy spectrum disorder の乳幼児期における ASSR 閾値	Audiology Japan	53(1)	76-83	2010

Ⅳ.　研究成果の刊行物・別刷

CURRENT TOPICS

8. 遺伝性難聴と遺伝カウンセリング

●はじめに

遺伝性難聴は、補聴器、人工内耳といったリハビリテーション手段により大きな機能回復と言語獲得を期待できる点が特徴である。これは他の遺伝性疾患では原因が判明しても機能の改善を得る手段がほとんどないのとは大きく異なり、遺伝性難聴の遺伝カウンセリングの重要性が高い理由となっている。

しかし、今から15年前までは遺伝性難聴は遺伝形式などから漠然とその存在が知られている状況で、遺伝カウンセリングに耳鼻科医が関与するということはほとんどなかった。その後間もなく難聴遺伝子が次々と発見され出してからは、それまで原因がわからなかった目の前の多くの患者の難聴の原因や病態がわかるようになり、状況が一変した。現在では、難聴の遺伝カウンセリングは一部の医療施設で臨床の場に定着し、より多くの施設に広がりつつある。一方で、臨床に即した遺伝性難聴の研修機会はまだ乏しく、情報が不足していて実践を躊躇する場合も多いようである。そこで本稿にはそのような臨床の現場で必要な内容を記した。

遺伝カウンセリングの具体的内容

遺伝性難聴の遺伝カウンセリングは、遺伝子解析(検査)を実施することで、より正確に行うことが可能となる。そのため遺伝子解析と遺伝カウンセリングは通常はセットで行われる。多数ある遺伝性難聴の遺伝子解析を十分に実施できる専門施設は限られているので、実施する場合にはその施設に検体(血液)を送り、遺伝子解析結果の報告を受けることになる。あるいは患者を専門施設に紹介して、遺伝カウンセリングも含めてそちらで実施される場合もある。遺伝カウンセリングには、遺伝子解析前に行う事前カウンセリングと遺伝子解析結果を報告する際に行う事後カウンセリングがあり、筆者の施設での所要時間としては、事前カウンセリングは15〜30分、事後カウンセリングは結果によって異なるが30〜60分である。

事前カウンセリングの内容は、ほぼ全国共通の項目が定められた遺伝子解析用のインフォームド・コンセントを使用して、遺伝子の説明から始まり、どのような解析が行われ、どのような結果が得られ、関連して何が生じたり、わかったりする可能性があるのかなどを知ってもらうものである。事後カウンセリングの内容は、遺伝子解析の内容や結果によって大きく異なり、また施設によってもかなり違いがあると考えられる。筆者らの施設で実施している内容の典型例を**表1**にまとめた。「1．難聴の遺伝的原因について」から「7．劣性遺伝の保因者について」まで、各項目を順番に話す。また、各項目を話す前には、クライエント

表 1●難聴の遺伝カウンセリングの具体的内容と順序

1．難聴の遺伝的原因について
　a．遺伝子解析結果の簡潔な報告
　b．小児難聴や遺伝性難聴の概略(原因、頻度、遺伝形式など)の説明
　c．難聴者(児)の背景と各原因との関連の確認
　d．解析した遺伝子の選択の理由と解析結果
　e．難聴者(児)で見つかった遺伝子変異についての模式図を用いた理解しやすい説明
　f．原因遺伝子の働きと難聴となる理由についての模式図を用いた理解しやすい説明
2．難聴の特徴の予測と予後について(程度、周波数別の閾値、今後の経過など)
3．難聴の予防について(薬剤の使用、頭部への衝撃など)
4．合併症の予防と早期発見について(糖尿病、腎臓病、甲状腺腫など)
5．治療の選択について(補聴器、人工内耳の適応について)
6．再発リスクについて
　a．既に生まれている同胞の場合
　b．次の妊娠・出産の子どもの場合
　c．難聴児が将来授かる子どもの場合
7．劣性遺伝の保因者について

筆者の施設で難聴の遺伝子解析結果報告の際に行う典型的な遺伝カウンセリングの内容とその順番を一例として示した。

(カウンセリングを受ける人)が聞くことを希望するかどうかを確認する。話の間でも随時質疑などに答えるが、各項目終了後にも必ず質疑を確認する。最後に、耳鼻科医が対応する遺伝性難聴の大部分を占める劣性遺伝の難聴遺伝子の保因者(ほとんどは先天性難聴児の両親)に対しては、すべての人が8つほどあるいはそれ以上の劣性遺伝性疾患遺伝子の保因者であり、難聴児の両親が特別な遺伝的体質というわけではないこと、両親が偶然同じ遺伝子の保因者である場合に子どもに症状が出現しうること、そのためどの両親にも一定の確率で劣性遺伝性疾患の子どもが生まれうることを説明する。

カウンセリングでは、あくまでも難聴者あるいは難聴児の両親の自発的な意思決定を促すように対応する。重篤な合併症を呈しうる症候群性難聴の出生前診断など、遺伝に関するより専門的な検討を要する相談を受ける場合も時としてあるが、このような場合は原則的に各地域の遺伝医療の専門医師(主に遺伝科、産婦人科、小児科など)に紹介する。より詳細な遺伝カウンセリングの内容に関しては筆者の総説を参照されたい[1]。

遺伝性難聴に対する医療者の対応

最近では、一部の難聴者あるいは難聴児の両親はインターネットなどの情報から難聴遺伝子検査を知り、それを希望して受診される場合もある。しかし、まだ大半の方は遺伝性難聴に関して十分な情報をもたず、医療者から話を出さなければそれ以上は遺伝的原因の診断は進まない。一方、難聴診療にかかわる医療者には、遺伝性難聴の頻度が比較的高いこと、原因を知ることが診療に役立ちうること、国内でも調べることが可能であることなどの情報が徐々に普及している。初めは最も関係の深い小児難聴を専門とする医師へ普及し、次いで難聴を専門とする医師へ、そしてそれ以外の耳鼻咽喉科医師や小児科医師へという順に少しず

つ広がっている。また、学生時代に新しい遺伝学に触れた新世代の医師は、遺伝性疾患に対する医療の受け入れが速いのが特徴である。これに伴い医療者から難聴者に遺伝的原因の話をする施設も近年増えており、近い将来に難聴の遺伝カウンセリングが広く普及すると予想している。

難聴者、難聴児の両親、医療者によく聞かれる質問について

a．どのような難聴者が遺伝性難聴なのか

受診した患者のほかにも、家族の中(両親、兄弟など)に患者と類似した難聴者がいる場合は、患者側も医療者側も遺伝性難聴を意識するし、その可能性は高いといえる。一方、受診患者以外に難聴者がいない場合(孤発例)は、患者側は遺伝性とは考えない。しかし、実際には遺伝性難聴では、このように家族歴がない患者が多い。これは、難聴のみを症状とする遺伝性難聴(非症候群性難聴)では、劣性遺伝(両親は健聴でその子どもの4人に1人が難聴)が80%と多いためである。したがって、家族歴にかかわらず、原因が不明の両側性難聴が先天性あるいは若くして発症するようであれば、遺伝性難聴を疑うべきである[2]。遺伝性難聴の程度はさまざまであり、最近では新生児聴覚スクリーニングの普及により、小児の軽-中等度難聴の早期診断が促進され、その中で遺伝的原因が判明する例も増加している[3]。

b．遺伝性難聴の原因がわかると治療はできるか

先天性あるいは慢性的に経過する感音難聴を正常聴覚に戻す根本的治療法はまだない。これは遺伝性難聴についても同様である。しかし、現在の主たる医学的対応である補聴器、人工内耳の選択には役立つ場合がある。人工内耳は内耳障害による高度難聴に有効であり、早期に実施するほど効果が高いことがわかっている。しかし乳幼児などでは詳細な聴覚検査ができず、人工内耳の適応があるかどうかの判断が困難な場合がある。このような場合、遺伝子解析で難聴の原因と病態がわかることは人工内耳の適応の決定に役立つ。またAuditory Neuropathyという難聴では、人工内耳が有効な場合と有効でない場合があるが、これも原因遺伝子の解析によって鑑別できる場合がある[4]。また症候群性難聴では、合併症の治療に役立つ場合がある。例えば、A3243Gミトコンドリア DNA変異では、難聴に続いて比較的高い確率で糖尿病が出現するが、早期発見と治療で糖尿病やその合併症の悪化を予防することが可能な場合がある。

c．遺伝子解析とカウンセリングで患者の満足は得られるか、何か問題は生じないか

遺伝カウンセリングに対して患者の満足が得られるか、そして何か問題が生じないかは医療者が一般に最も懸念する点で、筆者も約10年前に開始した際に心配した。その後、約1,000人の遺伝子解析とカウンセリングの経験をしたが、事前の準備をしっかりして、遺伝

カウンセリングの原則を守ることで、これまで解決困難な問題は生じていない。そして原因の判明した難聴者と難聴児の両親の大部分から、遺伝子解析とカウンセリングを受けてよかったという反応を頂いてきた。難聴診断から1〜2年以内の患者の場合は、遺伝カウンセリングが可能であることを聞くと大部分が希望される。一方、先天性難聴で既に就学年齢に達している患者や、後天性難聴で聴力変化なく長期経過している患者あるいはその両親では、希望されない割合が高まる。

d．遺伝性難聴の遺伝子解析(検査)の内容は実施する施設によって違うのか

現時点では、費用負担、何種類の遺伝子を調べるか、遺伝子全体を調べるのか特定の変異のみを調べるのか、結果報告までの期間など、施設によってさまざまな違いがある。このため事前に内容を確認することをお勧めする。また、一施設で原因遺伝子が判明しなくても他の施設で判明する可能性があるので、そのような場合でも他の施設に相談してみる価値がある。

筆者が遺伝カウンセリングを行っている施設(国立病院機構東京医療センター耳鼻咽喉科、慶應義塾大学病院耳鼻咽喉科、国立成育医療センター耳鼻咽喉科)では、発症年齢、聴覚検査所見、家族歴などに応じて、調べるべき遺伝子の種類、遺伝子の部位あるいは特定の変異をアルゴリズムに従って決定する系統的遺伝子解析を行っており、現在は25種類の難聴遺伝子の解析を実施している[5]。多くの遺伝子は全体を調べるが、特定の部位あるいは変異のみを調べる場合もある。結果報告は遺伝子解析のための採血(年齢により5〜20 m*l*)から3ヵ月後である。難聴の遺伝的原因にはまだ不明の点も多く残されていることから、私たちは遺伝子解析を現時点では研究の一環として位置づけている。より詳細な内容に関しては筆者の総説を参照されたい[6][7]。他の施設からの検体の解析も受け付けているので、ご希望の方は筆者まで連絡されたい。(連絡先：国立病院機構東京医療センター聴覚障害研究室 松永達雄、tel 03-3411-0111、e-mail：matsunagatatsuo@kankakuki.go.jp)。

●おわりに

難聴遺伝子に限らず遺伝子とその異常に関する情報、そしてそれを解析する技術は日進月歩である。そのため診療に有用な情報を遺伝子解析からより多く、正確に、低価格で利用可能になっている[8]。遺伝性難聴はその多くが内耳障害によるものであるが、近年は外耳、中耳の奇形でも遺伝的原因の解明が進んでいる[9]。難聴の臨床にこれからますます遺伝子がかかわるのは避けることのできない流れと思われる。そのため、難聴診療にかかわる多くの皆様に遺伝子についての理解が広がり、臨床の場で活用されることを祈念している。

(松永達雄)

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Vestibular dysfunction in a Japanese patient with a mutation in the gene *OPA1*

Kunio Mizutari [a,b,*], Tatsuo Matsunaga [b], Yasuhiro Inoue [a], Hiroki Kaneko [c], Hirotaka Yagi [d], Kazunori Namba [b], Satoko Shimizu [e], Kimitaka Kaga [f], Kaoru Ogawa [a]

[a] Department of Otolaryngology, Keio University School of Medicine, Tokyo, Japan
[b] Laboratory of Auditory Disorders, National Tokyo Medical Center, Tokyo, Japan
[c] Department of Integrated Sciences in Physics and Biology, College of Humanities and Sciences, Nihon University, Tokyo, Japan
[d] VALWAY Technology Center, NEC Soft, Ltd., Tokyo, Japan
[e] Department of Ophthalmology, Teikyo University School of Medicine, Tokyo, Japan
[f] National Institute of Sensory Organs, National Tokyo Medical Center, Tokyo, Japan

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ABSTRACT

OPA1 mutations are known to cause autosomal dominant optic atrophy (ADOA), and some types of *OPA1* mutations also cause auditory neuropathy. In the present study, we evaluated the vestibular dysfunction that accompanied auditory neuropathy in a patient with an *OPA1* mutation. A caloric test failed to elicit nystagmus or dizziness in either ear. Vestibular evoked myogenic potentials (VEMPs) in the right ear were characterized by a normal biphasic waveform. In contrast, no VEMPs were evoked in the left ear. Model building suggested that the *OPA1* mutation, p.R445H, indirectly distorts the catalytic structure of the GTPase reaction center and decreases GTPase activity. The patient complained of instability while walking or moving but thought these symptoms were caused by visual dysfunction. This is the first report of a detailed evaluation of vestibular dysfunction in a patient with an *OPA1* mutation. This case suggests that vestibular dysfunction may be involved in motor instability in patients with an *OPA1* mutation, even when patients do not complain of vestibular symptoms. Based on this case, we suggest that vestibular evaluation should be performed in auditory neuropathy patients carrying an *OPA1* mutation, even if the patients are free of symptoms of vestibular dysfunction.

1. Introduction

Autosomal dominant optic atrophy (ADOA; OMIM #165500) is a dominantly inherited optic neuropathy resulting in progressive loss of visual acuity, color vision deficits, a centrocecal scotoma, and optic nerve pallor [1]. ADOA is the most common form of optic atrophy, with an estimated prevalence of 1 in 50,000 individuals [2]. Although several types of loci are known to cause ADOA, it has been reported that as many as 89% of cases may be associated with a mutation in the gene *OPA1* (3q28-29) [3]. *OPA1* encodes a dynamin-related GTPase that is located in the mitochondrial intermembrane space and plays a key role in controlling the balance of mitochondrial fusion and fission. In most cases, ADOA occurs without additional neurological symptoms. However, there are several known cases of optic atrophy associated with sensorineural hearing loss, and the Arg445His (p.R445H) mutation of *OPA1* has been reported in patients with ADOA and moderate progressive hearing loss [4]. In patients having the p.R445H mutation, progressive hearing impairment begins in childhood, and audiological examinations show features of auditory neuropathy, for which the primary lesion is located in the inner hair cells, the auditory nerve, or the synapses between them [4,5]. Recently, a detailed analysis of OPA1 protein expression in the inner ear was reported in rat, and OPA1 protein was detected in the inner hair cells, outer hair cells, and spiral ganglia in the cochlea, as well as the hair cells and ganglia in the vestibular organ [6]. Although there have been several reports of auditory function in patients with this *OPA1* mutation, the analysis of vestibular function has not yet been reported in any *OPA1* mutation. In this paper, we report the results of examinations for auditory and vestibular function in a patient who presented with both hearing impairment and vestibular dysfunction due to an *OPA1* mutation that leads to distortion of the catalytic structure of the OPA1 protein.

2. Materials and methods

2.1. Auditory function tests

2.1.1. Audiometric tests

The patient underwent standard pure-tone air- and bone-conducted audiometry (125–8000 Hz) and speech discrimination testing using an audiometer (AA-75, Rion Co., Tokyo, Japan) and the 67-S Japanese word list.

* Corresponding author. Department of Otolaryngology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan. Tel.: +81 3 3353 1211; fax: +81 3 3353 1261.
E-mail address: tari@mbf.ocn.ne.jp (K. Mizutari).

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2.1.2. DPOAEs

DPOAES were recorded and analyzed using the ILO-92 system (Otodynamics Ltd, Herts, UK). DPOAE primary tones f1 and f2 were presented at 70 dB SPL. The f2:f1 ratio was kept at 1.22, and the frequency of f2 was changed in one-third octave steps from 708 to 6299 Hz. The levels of 2f1–f2 DPOAE were recorded. DPOAE values were plotted on a DP-gram, which expresses the emission level as a function of the f2 frequency.

2.1.3. Auditory brainstem responses (ABRs)

ABRs were recorded using the Neuropack system (Nihon Kohden, Tokyo, Japan) with an electrode montage of vertex (CZ) to the ipsilateral (stimulated) ear lobe and ground to forehead (Fz). The amplifier band pass was 100–1000 Hz. Alternating-polarity click stimuli were presented monaurally at a rate of 20 Hz at 100 dB nHL. Average responses to 1024 clicks were collected in each of two experiments.

2.2. Vestibular function tests

2.2.1. Electronystagmography

The patient underwent an electronystagmography test battery consisting of spontaneous, optokinetic, positional, postural, and caloric-induced nystagmus recordings. Nystagmus was recorded using an electronystagmograph recorder (Rion, Tokyo, Japan). Caloric testing using 20 °C and ice-cold water (5 cm^3, 5 s) was used to irrigate the external auditory meatus to induce a thermal gradient across the lateral semicircular canal.

2.2.2. Vestibular evoked myogenic potentials (VEMPs)

The sternocleidomastoid (SCM) muscle was chosen as the target to record VEMPs using the Neuropack system (Nihon Kohden, Tokyo, Japan). Surface electromyographic activity was recorded from symmetrical sites over the upper half of each SCM, with a reference electrode over the sternal attachment site of the contralateral SCM. The patient was laid supine on a bed and asked to raise and orient his head contralateral to the tested ear to maximally activate the SCM ipsilateral to the stimulation. Responses to 200 short-tone bursts (105 dB nHL, 500 Hz) were recorded at 100-ms intervals over a band pass of 500–1500 Hz.

2.3. Neuroimaging studies

2.3.1. High-resolution computed tomography (HRCT)

The protocol for HRCT included scanning with a multi-slice computed tomography scanner (Sensation 64; Siemens Medical Solutions, Inc., Malvern, PA, USA). Images were acquired with direct axial sequences using a spiral scan procedure with a 1.0-mm collimation. Data were reconstructed with a slice thickness of 1.0 mm using a bone algorithm.

2.3.2. Magnetic resonance imaging (MRI)

The patient was scanned on a 1.5-T MRI machine (Signa EXITE 1.5T, General Electric, Fairfield, CT, USA) with surface and head coil. Axial three-dimensional fast imaging employing steady-state acquisition (FIESTA, repetition time, 9.3 ms/echo time, 3.3 ms; scan thickness 1.0 mm) was performed. The axial images were reconstructed in the oblique sagittal plane traversing the internal auditory canal (IAC), producing cross-sectional images that visualize the neural structures of the IAC.

2.4. Homology modeling of OPA1and ligand fitting

The crystal structure of the GTPase domain of rat dynamin 1 (PDB ID: 2AKA) was used as a template in homology modeling because the GTPase domain of rat dynamin 1 is closely related to that of OPA1 in both function and structure (32% amino acid sequence identity). A program package for protein engineering and drug design, BIOCES[E] (NEC Corp., Tokyo, Japan) [7], was used for a series of molecular modeling. This package runs on an OCATANE2 (Silicon Graphics Inc., Fremont, CA, USA). The GTP molecule of Ras-GTP (PDB ID: 5P21) was fitted into the corresponding active site of the OPA1 model using DALI (http://ekhidna.biocenter.helsinki.fi/dali_server/) [8]. The p.R445H mutation structure was superimposed on the native structure (backbone atoms only) and displayed using UCSF Chimera (http://www.cgl.ucsf.edu/chimera/) [9].

3. Case report

The patient is a 28-year-old man who first presented with sudden optic atrophy at the age of 17 years. Clinical history of vision disorder and the result of genetic test have been reported [10]. In brief, he received a detailed examination for visual function at age 21. His best corrected visual acuity was 20/200 in both eyes. He had atrophy of the optic disks, central scotoma, and generalized bilateral dyschromatopsia. As a result, the patient was diagnosed with ADOA, and a genetic examination revealed a heterozygous G-to-A substitution in the second nucleotide of codon 445 in *OPA1*, resulting in an Arg-to-His amino acid substitution (p.R445H). He had no apparent family history of either optic atrophy or hearing impairment. At that time, he was also found to have a slight bilateral hearing impairment. The patient

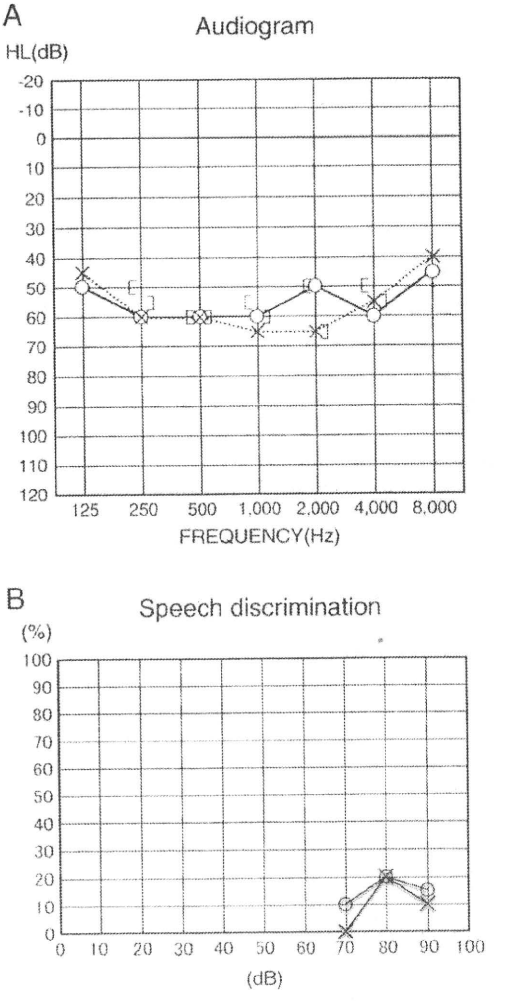

Fig. 1. Pure-tone (A) and speech (B) audiograms of a patient with an *OPA1* mutation. O = right air conduction hearing level; X = left air conduction hearing level; [= right bone conduction hearing level;] = left bone conduction hearing level.

developed progressive hearing impairment, and had particular difficulty understanding speech. He came to our department for a hearing evaluation at age 28. Although he did not initially complain of balance disorders, he stopped riding a bicycle at age 17 years because of difficulty controlling balance and also started to feel unsteady walking at that time. He thought the unsteadiness resulted from his visual dysfunction.

4. Results

4.1. Auditory function test results

Direct otoscopic observation revealed normal findings in both ears. A bilateral sensorineural hearing loss of approximately 60 dB was shown by pure-tone audiometry (Fig. 1A). The maximum speech discrimination scores were 20% in both ears (Fig. 1B), which were significantly worse than expected based on the results of pure-tone audiometry. Although no differences were observed between left and right ears, the patient reported better hearing discrimination in the right ear (Fig. 1). ABRs were absent bilaterally even at 100 dB nHL (Fig. 2A), but high-amplitude DPOAEs were present at all frequencies tested in both ears (Fig. 2B).

4.2. Vestibular function test results

No spontaneous, positioning, or pressure-induced nystagmus was found by electronystagmography. Neither 20 °C nor ice-water caloric stimulation of the labyrinth elicited nystagmus or dizziness in either ear (Fig. 3A). Short-tone burst-evoked VEMP analysis revealed a biphasic VEMP waveform in the right ear; however, the latency of n23, which is the second wave of VEMP, was delayed. No VEMPs were evoked in the left ear (Fig. 3B).

4.3. Neuroimaging studies

There were no abnormal findings by HRCT. In particular, no inner ear malformation or internal auditory canal stenosis was observed (Fig. 4A, D). By MRI, both the cochlear nerves and vestibular nerves were detected from brainstem to the inner ear in both ears in axial FIESTA slices (Fig. 4B, E). However, the diameter of the right cochlear nerve was 0.82 mm whereas that of the left cochlear nerve was 0.69 mm, and the diameter of the right facial nerve was 1.06 mm whereas that of the left facial nerve was 1.02 mm in oblique sagittal reconstructions through the IAC (Fig. 4C, F). Thus, the cochlear nerves on both sides are considered hypoplasia according to reported criteria [11].

4.4. OPA1 predicted structure

The distance between Cα of R445 of OPA1 and the GTP binding pocket is 18 Å (Fig. 5). The electric field around R445 is negatively charged due to its proximity to D450, D442, and E444. Under physiological conditions, positively charged R445 is structurally stable, and thus the mutation p.R445H reduces the electrostatic stability and indirectly distorts the structure of the GTPase catalytic

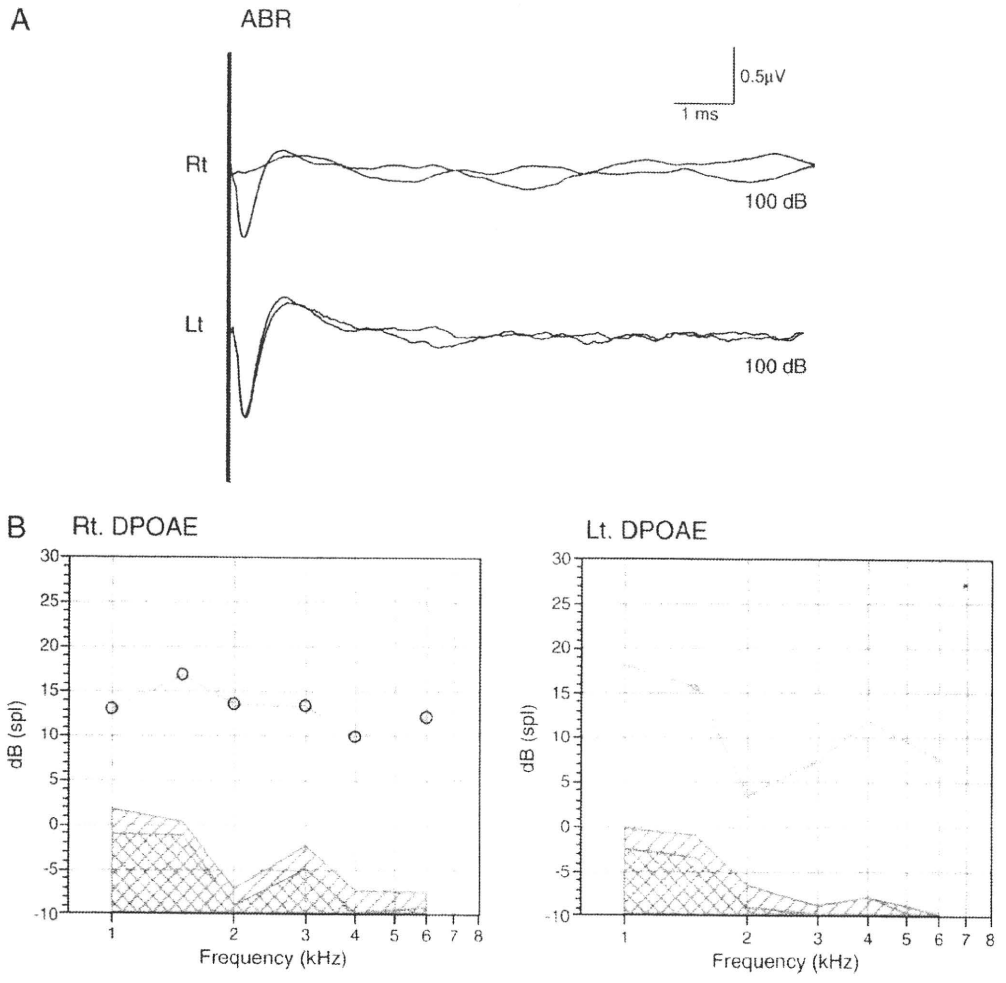

Fig. 2. (A) ABR tests revealed no ABR waveforms in this patient. (B) DPOAE recordings were normal for this patient. Residual noise levels are shown by the shaded area.

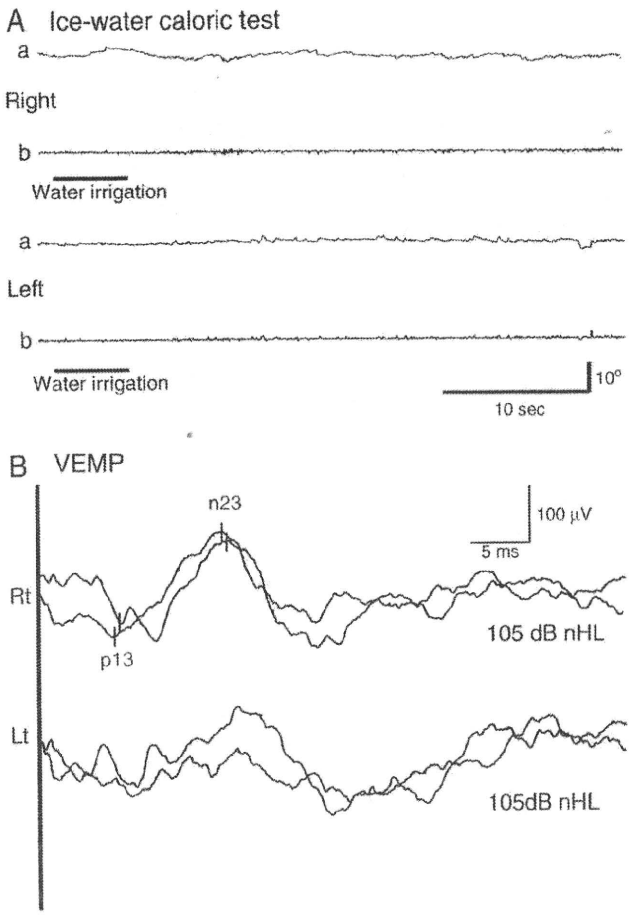

Fig. 3. (A) Horizontal record of electronystagmograph on ice-water caloric test. Time constants: a, 3.0 s; b, 0.03 s. No nystagmus were elicited in both side of ears. (B) Air-conducted VEMPs. Electromyographic responses of the right (Rt) and left (Lt) SCM to right ear stimulation. A biphasic VEMP waveform was revealed in the right ear; however, a latency of n23 was delayed. In contrast, no VEMPs were evoked in the left ear.

domain. In addition, salt bridges between R445 and D450 in the α3-helix and strong electrostatic interactions between R445 and D442/E444 are observed. The α3-helix is a key structure that constructs the common wire frame of the G-protein core fold [7,9]. Thus, the p.R445H mutation indirectly distorts the catalytic structure of the GTPase reaction center and decreases GTPase activity.

5. Discussion

Several reports have described hearing impairments associated with an *OPA1* mutation [4,12–16]. As with the case we present here, these hearing impairments were reported to result from auditory neuropathy. Common features in these patients include moderate hearing threshold elevation and a severe speech discrimination disability. No vestibular symptoms or function test results have yet been reported. To our knowledge, this is the first report of a detailed vestibular analysis in a patient with an *OPA1* mutation. Moreover, inner ear neuroimaging studies, including HRCT or 3-D MRI, have not yet been reported in patients with *OPA1* mutations. This report provides the first evidence of cochlear nerve atrophy in the IAC in a patient with an *OPA1* mutation.

OPA1 encodes a dynamin-related GTPase that is located in the mitochondrial intermembrane space and plays a key role in controlling the balance of mitochondrial fusion and fission [17]. Furthermore, release of cytochrome c from mitochondria and caspase-dependent activation of the apoptosis cascade have been observed in the down-regulation model of expression by RNA interference in HeLa cells [17]. The *OPA1* p.R445H mutation is reportedly associated with various neurological disturbances, including ataxia, peripheral neuropathy, ptosis, and cognitive impairment [18]. In cases involving the heterozygous p.R445H mutation, ADOAs associated with deafness have been reported [4], and these sensorineural hearing losses show audiological features compatible with auditory neuropathy. In normal rats, expression of OPA1 protein is seen in the inner hair cells, outer hair cells, and spiral ganglia in the cochlea, and in the vestibular hair cells and ganglia [6]. OPA1 protein expression has also been observed in membranous or submembranous compartments of vestibular ganglion cells and at the level of the calyx synapse, which typically envelopes type 1 hair cells in the vestibular epithelium [6]. Bilateral vestibular dysfunction in our present patient is probably caused by dysfunction of these parts of the vestibular organs.

An abnormality in the OPA1 protein may cause mitochondrial dysfunction, leading to insufficient energy production. Homozygous mutant mice are not viable and show impaired development as early E8.5. [19]. This study also reported that heterozygous mutants show a reduction in OPA1 protein level (about 50% compared with wild-type littermates) due to rapid degradation of the mutant polypeptide [19]. Skin fibroblasts obtained from patients carrying the heterozygous *OPA1* p.R445H mutation show hyperfragmentation of the mitochondrial network, decreased mitochondrial membrane potential, and an ATP synthesis defect [4]. Our three-dimensional structure study suggests that the p.R445H mutation reduces the electrostatic interactions and therefore the stability of the protein and indirectly distorts the structure of the GTPase catalytic center, thereby decreasing GTPase activity. According to these findings, we suggest that the OPA1 p.R445H mutation leads to severely insufficient energy production by decreasing GTPase activity in the mitochondria. This deficiency could, in turn, affect critical energy-dependent functions such as axoplasmic transport in both cochlear and vestibular nerve fibers as well as optic nerve fibers.

This patient had almost normal VEMP results in the right ear but no response in the left ear. Although the mechanisms underlying these different responses are unclear, asymmetrical hearing impairments have been reported in patients with the *OPA1* p.R445H mutation [12,13]. There was no response to caloric stimulation in either ear. The VEMP consists of myogenic potentials obtained as a response to tone-burst stimuli and is used to test the saccule and inferior vestibular nerve of the vestibular system. The caloric test, on the other hand, is used to evaluate the function of the lateral semicircular canals and the superior vestibular nerve [20]. In the right ear, there was no response in the caloric test but fare VEMPs. *OPA1* is expressed in sensory epithelia in both the saccule and the lateral semicircular canal [6]. Atrophy of the superior vestibular nerve was not detected by MRI scan. The mechanisms underlying different responses for the caloric test and VEMPs in the right ear are uncertain. In the present case, the patient reported slightly better hearing in the ear that also had good VEMP responses (the right ear). It is well established that ADOA is a progressive atrophy disease. If the main mechanism for nerve atrophy in ADOA is the same in both the eye and the inner ear, we speculate that nerve atrophy in the inner ear may develop gradually from the superior vestibular nerve to the inferior vestibular nerve in patients with the *OPA1* mutation. It has been reported that VEMPs are less affected than horizontal semicircular canal function during caloric testing in bilateral vestibulopathy [21]. We found only two reports with results of both caloric testing and VEMP analysis in auditory neuropathy patients with causes other than an *OPA1* mutation [20,22], and these revealed normal caloric responses and abnormal VEMPs in all patients ($n=4$) with auditory neuropathy. We revealed a different profile in a patient with auditory neuropathy due to an *OPA1* mutation. We speculate that the vestibule is also an organ that is sensitive to the mitochondrial dysfunction associated with the *OPA1* mutation.

In conclusion, we have presented a case of vestibular dysfunction accompanied with auditory neuropathy in a patient with an *OPA1*

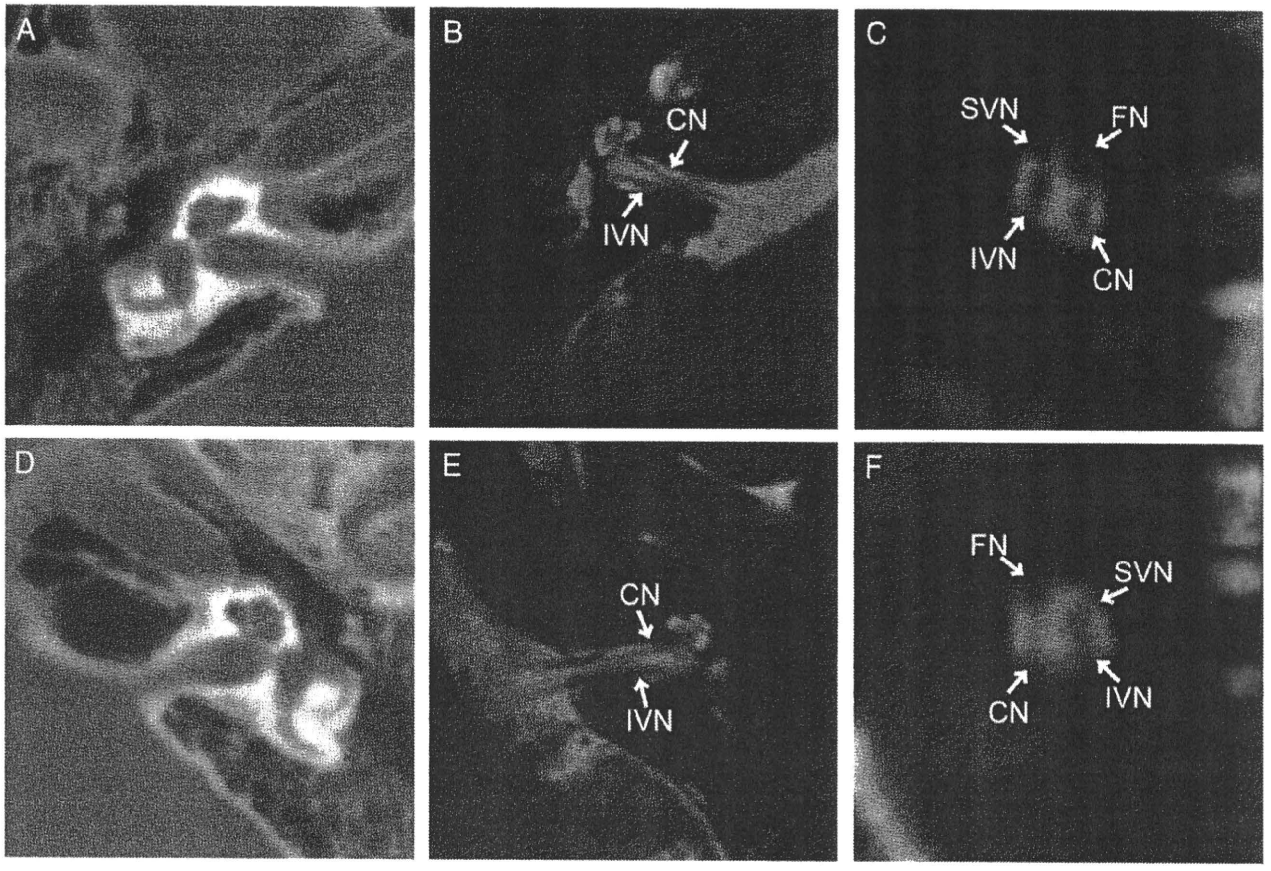

Fig. 4. Images showing the HRCT (A, D), axial MRI (FIESTA: B, E), and oblique sagittal reconstructions (C, F). The facial nerve (FN), cochlear nerve (CN), superior vestibular nerve (SVN), and inferior vestibular nerve (IVN) can be recognized in both sides of the internal auditory canal. However, the cochlear nerves in both ears were narrower than the vestibular nerves in axial FIESTA slices. Moreover, the cochlear nerves on both sides were smaller than the adjacent facial nerves in oblique sagittal reconstructions.

mutation. In a standard evaluation, this patient's balance disorder could easily have been overlooked because he attributed it to his visual dysfunction. Based on this case, we suggest that vestibular evaluation should be performed in auditory neuropathy patients carrying an *OPA1* mutation, even if the patients do not complain of balance dysfunction.

Acknowledgements

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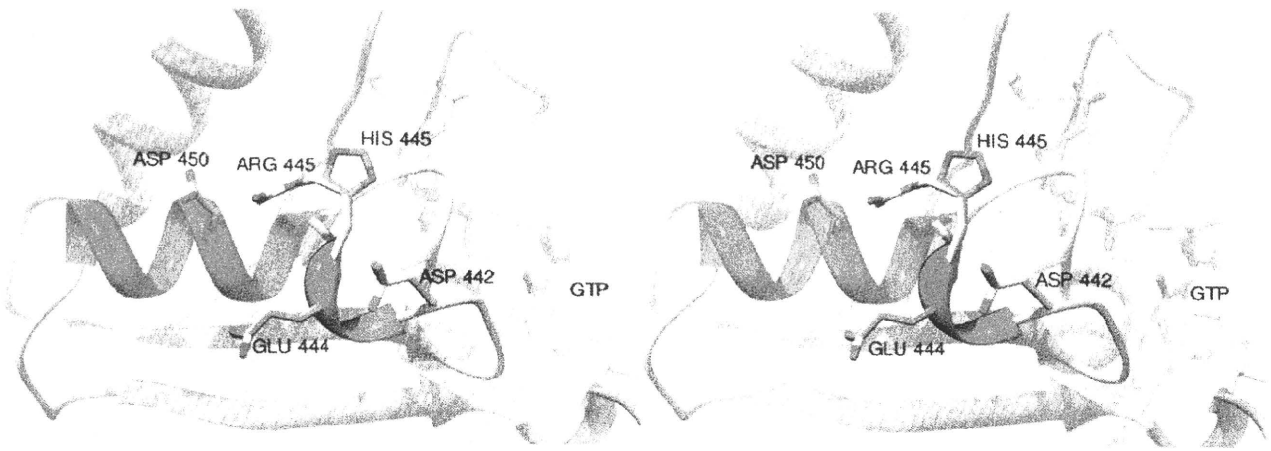

Fig. 5. Stereo view of the GTPase domain of predicted structure of human OPA1 with arginine at position 445 replaced by histidine. The electric field around R445 is negatively charged due to the proximity of D450, D442, and E444. Positively charged R445, under a physiological environment, is structurally stabilized, and thus the mutation p.R445H reduces the electrostatic stability and indirectly distorts the GTPase catalytic structure. Image produced using the UCSF Chimera package supported by NIH P41 RR-01081.

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Risk factors for elevation of ABR threshold in NICU-treated infants

Noriko Morimoto [a,*], Hidenobu Taiji [a], Keiko Tsukamoto [b], Yuji Morimoto [c], Tomoo Nakamura [b], Tomoko Hommura [a], Yushi Ito [b]

[a] Department of Otorhinolaryngology, National Center for Child Health and Development, Tokyo, Japan
[b] Division of Neonatology, Department of Perinatology and Maternal Care, National Center for Child Health and Development, Tokyo, Japan
[c] Department of Medical Engineering, National Defense Medical College, Namiki 3-2, Tokorozawa, Saitama, Japan

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ABSTRACT

Objective: Several risk factors for hearing impairment among infants treated in the neonatal intensive care unit (NICU) have been reported, but there have been few studies that show the correlation strength between the risk factors in NICU-treated infants and hearing impairment in childhood. The aim of this study was to clarify the relationship between risk factors in NICU-treated infants and a deteriolation of auditory brainstem response (ABR) threshold in their childhood.
Methods: One hundred one NICU-treated infants with ABR threshold of 50 dBnHL or more underwent 2nd ABR test at 20 months after delivery. Multiple regression analysis was performed with ABR threshold change as an objective variable and risk factors as explanatory variables.
Results: Two ABR tests of the 101 infants resulted in that 7 showed an elevation of ABR threshold by 20 dB, 70 showed a drop of ABR threshold by 20 dB, and 24 showed no significant change. Multiple regression analysis revealed that the factors contributing to the elevation of ABR threshold were congenital diaphragmatic hernia, severe respiratory disease, and a high C-reactive protein (CRP) level.
Conclusions: In the infants treated in NICU, an incidence of ABR threshold of 50 dBnHL or more was 9.0%, and 6.9% of the infants with the ABR threshold abnormality showed a significant elevation of ABR threshold in their childhood. Factors significantly related to an elevation of ABR threshold were a history of congenital diaphragmatic hernia, severe respiratory disease, and elevation of CRP. In infants with such factors, periodical examination of hearing is required.

1. Introduction

Advances in perinatal medicine have increased the survival rate of infants who are admitted to the neonatal intensive care unit (NICU). However, many infants discharge from the NICU have medical problems including communicative and/or cognitive difficulties due to hearing impairment and brainstem dysfunction. The occurrence of these auditory impairments is known to be related to risk factors [1], such as low birth weight (<1500 g), severe birth asphyxia, assisted ventilation for >5 days, administration of ototoxic drugs [2], intrauterine infection, central nervous system abnormalities, hyperbilirubinemia, and congenital syndromes [3]. However, the correlation strength between the risk factors in NICU-treated infants and hearing deterioration in their childhood has not been fully determined. Elucidation of the correlation strength can facilitate diagnosis of hearing impairment in potentially diseased infants by means of intensive hearing tests focusing on limited subjects with risk factors that are closely related to hearing deterioration. This approach would be cost-effective.

Therefore, we aimed to clarify the correlation strength between risk factors in NICU-treated infants and hearing deterioration that appeared in childhood (over 1-year old). In the present study, we defined an elevation of ABR threshold by >20 dB between two testing sessions as a significant change indicating the existence of hearing deterioration.

2. Subjects

A total of 1121 neonates were treated in the NICU of the National Center for Child Health and Development (Tokyo, Japan) from March 2002 to October 2005 and underwent an auditory brainstem response (ABR) test before discharge from the NICU for the purpose of hearing screening. Initial examination revealed that 125 infants had ABR threshold of 50 dBnHL or more in 1 or both ears. Of these 125 infants, 101 were eligible for this study after

* Corresponding author at: National Center for Child Health and Development, 2-10-1 Okura Setagaya-ku, Tokyo 157-8535, Japan. Tel.: +81 03 3416 0181; fax: +81 03 3416 2222.
E-mail address: morimoto-n@ncchd.go.jp (N. Morimoto).

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excluding 10 infants with conductive hearing loss (3 for auditory canal stenosis and atresia, 7 for otitis media with effusion) and 14 infants who were lost to follow-up.

Most infants underwent the initial ABR test within 6 months after delivery, but some infants with a poor performance status could not do so until 8 months.

3. Methods

3.1. ABR examination

The initial ABR test was conducted with a Neuropak (Nihon Koden, Tokyo, Japan) during natural sleep in the NICU before discharge and was performed at 1–33 weeks after delivery. Click stimuli were presented to alternating ears 1000 times at a rate of 9.5 Hz through headphones. The analysis time was 10 ms. To determine the hearing threshold, stimuli started from 105 dBnHL and were decreased to 30 dBnHL in steps of 20 dB. In addition, 1000 clicks were presented at 0.1 ms intervals and the threshold was defined by detection of the V wave. The infants were classified into three groups by comparison between the two ABR testing sessions: infants with a decrease of the ABR threshold by ≥20 dB in at least 1 ear (improved group), those with an increase of the threshold by ≥20 dB (worsened group), and others (unchanged group).

3.2. Distortion products otoacoustic emission (DPOAE) test

We conducted a DPOAE test in 64 of the 101 infants in which the ABR threshold was 50 dBnHL or more during stay in NICU, excluding those in whom it could not be done due to behavioral problems. An OAE analyzer (model ER32, Grason-Stadler, USA, *L1*/*L2* = 65/55 dBSPL) was employed, and infants who responded to noise levels of 2, 3, and 4 kHz with >3 dB amplitude in the DP gram were regarded as having a positive test.

3.3. Behavioral audiometric evaluation

Behavioral audiometric evaluation was performed in 101 infants in whom the ABR threshold was 50 dBnHL or more and in whom no disjunction was detected between ABR threshold and hearing threshold.

3.4. Associated risk factors

The risk factors shown in Table 2 were investigated.

Abnormalities seen in brain CT or MRI included cerebral calcification, hydrocephalus, periventricular leukomalacia and abnormal myelinization. Craniofacial malformation included premature craniosynostosis such as Crouzon's disease and Apert syndrome. EEG abnormalities included spike & sharp waves, slow dominant rhythm and diffuse slowing. C-reactive protein (CRP) elevation was determined when the maximum value measured within about 1 month after birth was more than 1 mg/dL. History of birth asphyxia (Apgar score < 4 at 1 min and ≤6 at 5 min), severe respiratory disease (pneumonia or pneumothorax), mechanical ventilation (infants requiring a ventilator for more than 5 days), hypotension (decreased urine output due to hypotension and use of vasopressors), congenital diaphragmatic hernia, and heart disease (coarctation of the aorta, patent ductus arteriosus, ventricular septal defect, etc.) were assessed. Use of ototoxic drugs such as aminoglycosides (gentamycin, amikacin, and vancomycin) and use of muscle relaxants such as pancronium bromide before the second ABR were also assessed. Chromosomal aberration such as 21-trisomy was also checked.

3.5. Statistical analysis

Multiple regression analysis was performed with a change of the ABR threshold as an objective variable and the above-mentioned risk factors as explanatory variables. A probability (p) value of less than 0.05 was considered statistically significant.

3.6. Institutional board

The study was conducted in accordance with ethical principles described in the Declaration of Helsinki and was approved by the Ethics Committee of the National Center for Child Health and Development.

4. Results

4.1. Incidence of ABR threshold elevation in NICU infants

The initial ABR test revealed that 101 of the 1121 infants had ABR threshold of 50 dBnHL or more. Of those 101 infants, 57 infants (5.1%) showed ABR threshold of 50 dBnHL or more bilaterally and 44 infants (3.9%) had a threshold of 50 dBnHL or more in 1 ear, and 20 infants (1.8%) showed ABR threshold of 90 dBnHL or more bilaterally. In the second ABR test, 28 infants (2.5%) had ABR threshold of 50 dBnHL or more bilaterally, 9 (0.8%) had ABR threshold of 50 dBnHL or more in 1 ear and 19 infants (1.7%) had a threshold of 90 dBnHL or more in both ears. When compared with the initial test, 7 of the 101 infants showed an elevation of the ABR threshold by ≥20 dB, 70 showed a decrease of the threshold by ≥20 dB, and 24 showed a change of less than 20 dB (treated as 'no change'). In the 70 infants with ABR threshold decrease, 65 infants showed a normal threshold of ABR (30 dBnHL) bilaterally in the second test. Consequently, at the second test, 65 infants had ABR threshold of 30 dBnHL in both ears and the other 36 infants had ABR threshold of 50 dBnHL or more in at least 1 ear.

Nineteen (46%) of the 41 infants with ABR threshold of 70 dBnHL or more in the initial test showed an improvement: the ABR threshold in the second test was less than 70 dBnHL (Table 1). Also, 51 (85%) of the 60 infants with ABR threshold of 50–70 dBnHL in the initial test showed ABR threshold of less than 50 dBnHL in the second test, whereas 5 (8.3%) of the 60 infants with ABR threshold of 50–70 dBnHL in the initial test showed a deterioration: the ABR threshold in the second test was 70 dBnHL or more.

Table 1
Change in ABR threshold.

		Second result				
		<50 dBnHL	≧50, <70 dBnHL	≧70, <90 dBnHL	≧90 dBnHL	
Initial result	<50 dBnHL	0 (cases)	0	0	0	0
	≧50, <70 dBnHL	51	4	1	4	60
	≧70, <90 dBnHL	10	1	4	2	17
	≧90 dBnHL	6	2	0	16	24
		67	7	5	22	101

Table 2
Risk factors for ABR threshold change.

	Improved ABR threshold (n=70)	Unchanged ABR threshold (n=24)	Worsend ABR threshold (n=7)	p-Value	Correlation coefficient
Congenital diaphragmatic hernia	0	2	3	0.000*	0.42
CRP elevation	7	10	4	0.002*	0.33
Severe respiratory disease	4	4	2	0.003*	0.29
Hypotension	28	13	2	0.082	0.19
Birth weight average (g)	2003 ± 851	1882 ± 919	2560 ± 628	0.206	0.18
Birth weeks average (weeks)	34.2 ± 4.6	33.9 ± 5.5	37.7 ± 2.0	0.305	0.14
EEG abnormality	15	10	0	0.147	0.12
Abnormality seen in brain CT or MRI	21	13	2	0.352	0.09
Use of muscle relaxants	14	7	5	0.560	0.08
Multiple pregnancy	6	4	0	0.602	0.05
Craniofacial malformation	4	0	0	0.669	0.04
Mechanical ventilation	7	17	5	0.802	0.03
Heart disease	0	3	0	0.807	0.02
Ototoxic drugs	18	16	5	0.865	0.02
Asphyxia	14	11	2	0.891	0.02
Chromosomal aberrations	8	4	2	0.889	0.01

* $P_A < 0.01$.

4.2. ABR threshold change and risk factors

Among the 7 infants with an elevated ABR threshold, 3 had congenital diaphragmatic hernia. Of those 3 infants, only 1 received extracorporeal membrane oxygenation therapy (ECMO) and the other 2 received high frequency oscillatory ventilation. All 3 had persistent pulmonary hypertension of the newborn (PPHN). Including infants who needed ventilation because of tracheo-esophageal fistula or postoperative pneumothorax, 5 of the 7 infants had a history of respiratory support and 6 had received ototoxic drugs. On brain CT or MRI, 2 infants showed brain atrophy and 1 had chronic subdural hematoma, while 1 had an abnormal electroencephalogram.

Among the 68 infants with a decrease of the ABR threshold, 25 (37%) were presumed to have central nervous system abnormalities due to changes on the electroencephalogram or brain CT scans, 22 (32%) had received ventilation, 18 (26%) had received ototoxic drugs, and 10 (15%) had an elevated CRP level.

Of the 26 infants who showed no significant change of ABR threshold (within 20 dB), 18 (69%) had a presumed central nervous disease due to abnormalities on their electroencephalograms or brain CT scans. Nineteen infants (73%) had been on a ventilator, 17 (65%) had received ototoxic drugs such as vancomycin or gentamycin, and 10 (38%) had an elevated CRP level.

Table 2 shows the results of multiple regression analysis with change of ABR threshold as the objective variable and risk factors as the explanatory variables. The risk factors contributing significantly to ABR threshold change were a history of congenital diaphragmatic hernia (standardized coefficient = 0.41; $p = 0.001$), an elevated CRP level (standardized coefficient = 0.33; $p = 0.002$), and a history of severe respiratory disease such as pneumonia or pneumothorax (standardized coefficient = 0.28; $p = 0.005$). Other risk factors did not have a significant influence.

4.3. DPOAE and ABR threshold changes

When DPOAE testing was done in 64 infants (98 ears) with ABR threshold of 50 dBnHL or more during their stay in the NICU, 29 infants (50 ears) were negative and 37 infants (48 ears) were positive.

Among the 29 infants with negative DPOAE, 22 ears of 14 infants showed a decrease in the second ABR threshold by ≥20 dB and 8 ears of 5 infants showed an elevation in the threshold by ≥20 dB. Among the 14 infants in whom the ABR threshold decreased, 5 had central nervous system abnormalities such as delayed myelinization. Five of those 14 infant had chromosomal aberrations such as 21-trisomy.

Among those 37 infants with positive DPOAE, 10 had abnormalities on brain MRI or electroencephalography, including delayed myelinization and periventricular leukomalacia in 1 infant each. In addition, among those 37 infants, 38 ears of 31 infants showed a decrease in the ABR threshold by ≥20 dB and 1 ear of 1 infant showed elevation of the threshold by ≥20 dB.

Table 3 shows a list of the infants who had positive DPOAE with ABR threshold of 70 dBnHL or more in the initial test. ABR threshold in the second test was unchanged and worse in 5 and 1 of the 6 infants, respectively. Of the 6 infants, 4 had been on a ventilator, 3 had received ototoxic drugs, and 2 and 1 had a history of hypotension and an elevated CRP level, respectively. Five of the 6 infants had suffered from hyperbilirubinemia (8.28–14.70 mg/dl) and had received phototherapy.

5. Discussion

ABR threshold elevation in the second test was seen in 7 of 101 NICU-treated infants with ABR threshold of 50 dBnHL or more in the initial test. The ABR threshold elevation was significantly correlated with congenital diaphragmatic hernia, severe respiratory disease, and a high C-reactive protein (CRP) level.

All of the 7 infants who had ABR threshold elevation were diagnosed as having definite hearing loss at 20 months after delivery by a battery of audiological tests, and 5 of the 70 infants who had a decrease in ABR threshold were also diagnosed as having definite hearing loss in at least 1 ear at 20 months after delivery. Hence, this indicates that this study did not show risk factors correlated to hearing loss but showed risk factors correlated to ABR threshold elevation. The ABR threshold elevation is considered to reflect a part of progressive hearing losses [4,5], a part of delayed-onset hearing losses [6,7] or others. The 7 infants with ABR threshold elevation probably had progressive hearing loss because their ABR threshold in the initial ABR test (before discharge from the NICU) had already been high (50 dBnHL or more).

It has been reported that NICU infants show a 10- to 20-fold increase of risk factors for impaired hearing compared with healthy newborns because of poor performance status and long-term hospitalization [8]. Possible causes of hearing impairment include congenital factors such as genetic or anatomic abnormalities and acquired factors such as use of ototoxic drugs and excessive noise in the NICU, but the contribution of each factor

Table 3
Six infants with auditory neuropathy.

Case no.	Gestational age (month)	Birth weight (g)	Initial ABR threshold		DPOAE		Brain CT or MRI	EEG	Hypotension	CRP elevation	Mechanical ventilation	Ototoxic drugs	Hyperbilirubinemia	Diagnosis
			Right	Left	Right	Left								
1	32	2152	90	90	(+)	(+)	Abnormal	w.n.l.	(−)	(−)	(+)	(−)	(−)	Hydrocephalus
2	26	709	110	110	(+)	(+)	Abnormal	Abnormal	(−)	(+)	(+)	(+)	(+)	Periventricular leukomalacia
3	28	974	70	30	(+)	(+)	w.n.l.	w.n.l.	(+)	(−)	(−)	(+)	(+)	Congenital lung disease
4	39	1850	105	105	(−)	(+)	w.n.l.	Abnormal	(−)	(−)	(−)	(−)	(+)	Beals syndrome, West syndrome
5	43	1398	110	110	(+)	(+)	Abnormal	w.n.l.	(−)	(−)	(+)	(−)	(+)	Periventricular leukomalacia
6	40	2675	110	110	(+)	(+)	Abnormal	Abnormal	(+)	(−)	(+)	(+)	(+)	Multiple carboxylase deficiency

w.n.l.: within normal limit.

remains unclear because a combination of several factors may contribute to hearing impairment. The results of the present study revealed that a history of severe respiratory disease, elevated CRP, and congenital diaphragmatic hernia were significant predictors of an elevation of ABR threshold. Severe respiratory disease can reduce oxygenation of the brain and oxygenation of the inner ear, which impair cochlear oxygenation, and cochlear hypoxia is presumed to be associated with delayed-onset hearing loss [9]. It has been reported that approximately 26–50% of infants with congenital diaphragmatic hernia suffer from delayed-onset hearing loss [7], and it has been suggested that aminoglycosides or PPHN with ECMO may be involved [10]. Yoshikawa et al. also reported a correlation with elevated CRP and ABR threshold elevation and concluded that the variable may predict hearing deterioration [11].

In the present study, ABR threshold decrease was seen in 60% of the infants who had shown ABR threshold of 50 dBnHL or more before discharge from the NICU. This suggests that abnormalities such as auditory canal stenosis or residual mesenchymal tissue due to immaturity at birth influence the initial ABR test results, so that the infants can show spontaneous improvement with growth [12]. Another reason may also be related to the decrease in ABR threshold: incomplete myelinization frequently seen infants with Down's syndrome causes immature auditory pathways [13], resulting in high threshold of ABR seen in the initial test. The incomplete myelinization mechanism can explain the cases with an elevated ABR threshold and positive DPOAE test: approximately 80% of the cases eventually showed ABR threshold decrease.

Yoon et al. [14] called for a protocol in which infants with risk factors for delayed or progressive hearing loss would be followed by periodical infant hearing tests until the age of 5 years, while infants without risk factors who show normal results of the initial hearing test would be examined again at 1 year. It was also proposed by JCIH that hearing of normal infants and hearing of NICU infants should be monitored by different methods [15]. Since NICU infants are more likely to show delayed intellectual development, they often have communication disorders that may mask hearing deterioration. Therefore, in infants with hearing deterioration-related risks clarified by this study, we should provide periodic medical evaluation and management of language and intellectual development in addition to hearing elevation [16,17].

6. Conclusion

Among 1121 infants treated in the NICU, 101 (9.0%) showed ABR threshold of 50 dBnHL or more before discharge from the NICU. Seven of those 101 infants showed an elevation of ABR threshold by ≥20 dB when ABR testing was repeated at 20 months. Risk factors for elevation of ABR threshold are a history of congenital diaphragmatic hernia, severe respiratory disease, and a high CPR level.

Conflict of interest

Authors declare no conflict of interest.

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Auditory neuropathy spectrum disorderの乳幼児例におけるASSR閾値

泰地秀信[1]，守本倫子[1]，松永達雄[2]

[1]国立成育医療センター耳鼻咽喉科

[2]国立病院機構東京医療センター耳鼻咽喉科・臨床研究センター

要旨：Auditory neuropathyは2008年の国際会議からANSDと呼称されており，今回はその定義に従って診断されたANSDの乳幼児9例について検討した。後にABRが正常化していくようなみかけ上の難聴例（auditory immaturity）は除外した。経過をみていくうちにDPOAEが消失した5例はANSDとみなした。ASSRの閾値にはかなり大きなばらつきがあり，ANSDの病態が多彩であることが推定された。良聴耳のASSR閾値とCOR閾値を比較したところ，500～4000Hzでは有意な相関が認められた。ANSDの場合も補聴器装用効果をASSRでとらえることができ，推測された利得は平均でみてCORとの差は10dB以下であった。3例はASSRの3分法平均の閾値が70dBHL未満で，その場合CORの平均閾値も88dBHL以下と他症例より良好であったが，これらはすべて基礎疾患を伴っていた。ASSRおよびCOR閾値が100dBHL以上の重度難聴の例のうち2例に*OTOF*遺伝子変異が認められた。ASSRはANSDで行動聴力検査が不確実な場合に聴力および補聴器装用効果を評価する方法になりうるものと考えられた。

－キーワード－

乳幼児聴力検査，聴性脳幹反応，歪成分耳音響放射

はじめに

Auditory neuropathyは耳音響放射（OAE）が正常で聴性脳幹反応（ABR）が無反応あるいは異常となる病態で，聴力に比し語音聴取力が低いことが特徴とされているが，その臨床像はさまざまであり，2008年に公表されたガイドラインではauditory neuropathy spectrum disorder（以下ANSDと略）と呼称されることになった[1]。ANSDについては補聴器の効果あるいは人工内耳手術の適応などまだ意見の一致がみられていない点が多いため，今回はANSDの乳幼児例についてASSR検査を行い，他の所見と対比検討したので報告する。

対象と方法

平成18年4月～平成21年3月に国立成育医療センター耳鼻咽喉科を受診した新生児・乳幼児で，DPOAEの反応が両側正常かつABR閾値が両側80dBnHL以上でANSDとして扱った症例のうち，当院で療育・聴覚管理を行うことになった9例にASSR検査を行った。NICU児では中枢系の未成熟のためにABRの閾値上昇・波形分離不良がみられることがあり，ANSDと診断されてもABRが発達とともに正常化することがある。Bergらの報告[2]ではNICU児の24%にANSDがみられているが，我々の検討[3]ではNICU児でABR閾値上昇がみられた場合，19%は1歳時に20dB以上閾値が改善している。今回はそのような例は除外するために，1