はじめに

最近、新生児聴覚スクリーニングの導入に伴い、早期に一側性難聴が診断されるようになり、一側性難聴児の1/4が新生児聴覚スクリーニングで発見されている[1]。一側性高度難聴の場合、患側からの聞き取りの困難、騒音下の聞き取りの低下、音源定位の困難が言われている。また、言語発達遅滞や学業成績への影響を指摘する者もあり、一側性難聴であっても日常生活に支障をきたすことがある[2]。一側性難聴を生じる疾患としては、ムンプスウイルスやサイトメガロウイルス（以下CMV）を代表とするウイルス感染や内耳・内耳道奇形、細菌性髄膜炎、auditory neuropathy spectrum disorder（ANSD）などが上げられている。近年画像技術が向上し、MRIにより内耳道内の神経が個別に描出できるようになり、蝸牛神経の無～低形成が先天性一側高度難聴で高頻度に認められている[3]。

CMVは胎内感染する病原体の中で最も頻度が高く、妊娠中に初感染した場合20～40%に胎盤感染し、先天性CMV感染症は出生児の0.2～2.5%にみられる[4),5]。先天性CMV感染した出生児の約1割が低出生体重・肝脾腫・脳室周囲石灰化、小頭症、DICなどの症候を示し、運動発達遅滞・精神発達遅滞を伴い、その半数に難聴を生じるとされている。それ以外の約9割の出生児は何ら症状を示さない無症候性感染症として経過するが、その後1～3割に難聴や精神発達遅滞などの神経症状を伴ってくる[6),7]。難聴は中等度から高度の聴力障害から、遅発性・進行性など臨床症状は様々である[8),9]。また、両側性難聴が25%で一側性難聴が75%であったとの報告もみられている[10]。しかし、先天性CMV感染症の診断法には免疫学的検査（妊婦のIgG・IgM、新生児のIgM）、新生児の尿やガスリーカードの血液や臍帯の組織を使ったCMV DNA検査法があるが、先天性CMV感染を診断するための実用的なスクリーニング検査法はないため広く行われているわけではない。また新生児の尿検査は出生後2ないし3週以内に実施する必要があり、それ以降に先天性CMV感染を診断するためにはガスリーカードの血液や臍帯の組織を使ったCMV DNA検査が必要となるため、先天性CMV感染が一側性難聴の原因に占める頻度や先天性CMV感染による難聴で一側性難聴を生じる頻度などについて厳密に調べた報告はない。今回我々は一側性難聴児に対して保存臍帯を使用してCMV DNA検査を実施し、検討したので報告する。

対象と方法

対象は、2008年5月から2012年4月までの48ヶ月間に信州大学附属病院耳鼻咽喉科小児難聴外来を受診した感音難聴児134例のうち、一側性感音難聴を認めた88例（65.7%）とした（表1）。対象児は難聴以外に合併症はなく、難聴と診断された年齢は生後1ヶ月から12歳（平均40.8ヶ月）、男児39例、女児49例であった。難聴耳側は右が43例、左が45例であった。難聴耳の平均聴力は89.5dB、良聴耳は平均13.6dBで、平均聴力70dB以上の一側高度難聴が73例（83.0%）、平均聴力20dBから69dBの一側軽度～中等度難聴が15例（17.0%）であった。

表1　一側性感音難聴88児の内訳

性別	男児	39例（44.3%）
	女児	49例（55.7%）
平均聴力レベル	難聴耳	89.5dB
	良聴耳	13.6dB
難聴耳側	右耳	43例（48.9%）
	左耳	45例（51.1%）
高度・重度難聴	例数	73例（83.0%）
	診断時月齢	41.2±36.3ヶ月
軽度・中等度難聴	例数	15例（17.0%）
	診断時月齢	40.3±36.8ヶ月

平均聴力レベルは4分法。高度・重度難聴：70dB以上。軽度・中等度難聴：20dBから69dB。

難聴の診断は純音聴力検査（年齢によっては遊戯聴力検査）とASSR（auditory steady-state evoked response）検査（Master 580-Navpro; Nihon Kohden Co. Ltd, Tokyo, Japan）によって行った。平均聴力は500、1000、2000、4000Hzの4分法とした。聴力検査は6～12ヶ月おきに実施し、複数の周波数で10dB以上の閾値上昇が見られた場合を進行性とし、10dB以上の閾値の悪化、改善がみられた場合を変動性と定義した。

両親の同意を得た上で、難聴遺伝子検査（インベーダー法：13遺伝子46変異）と保存臍帯の一部（5 mm片）を採取（図1）し、CMV DNA検査を実施した。採取した保存臍帯からQIAGEN-QIAamp DNA Miniを用いてDNAを抽出し、定量的PCRにてCMV DNAの有無を診断した。なお、ポジティブコントロール、ネガティブコントロール、解析方法の詳細は引用文献[11]に記載した方法と同様である。今回は保存臍帯からのCMV

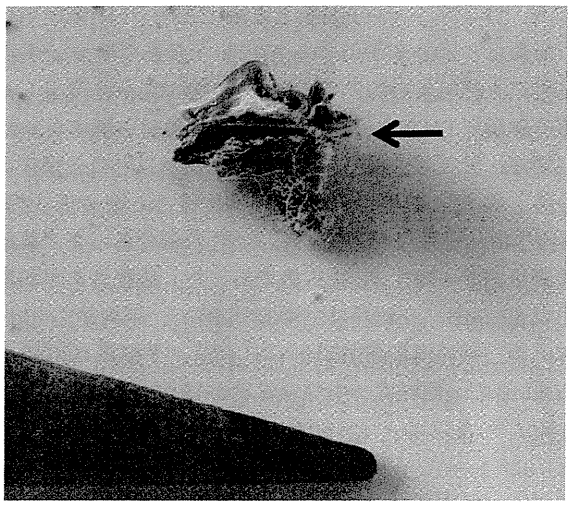

図1　CMV DNA検査のために採取した保存臍帯片

CMV（cytomegalovirus）DNA検査のために必要な約5 mm大に採取した保存臍帯片（矢印）。

DNA検査のみで先天性CMV感染の有無を判断した。

結　果

CMV DNAが陽性であったのは、一側性感音難聴児88例中8例（9.1%）に認められた。一側高度難聴は73例中の7例（9.6%）であり、一側軽度～中等度難聴は15例中の1例（6.7%）であった。CMV陽性であった8例の聴力図を図2に示す。難聴遺伝子の変異は一側性感音難聴児には1例も確認されなかった。表2にCMV DNA陽性を認めた8例の臨床症状の特徴を示す。男児が4例、女児が4例で、難聴の診断時の年齢は生後2ヶ月から98ヶ月、平均50ヶ月であった。難聴耳側は右耳が3例、左耳が5例で、高度難聴の平均聴力は96.3dB、中等度難聴の1例は58.3dBであった。出生児体重は2児以外は不明であったが、1児は2395gと狭義の低出生体重児（2500g未満）であった。しかし、全例頭部MRI検査では異常所見はなく、発達障害もみられていない。難聴の発症時期は新生児聴覚スクリーニング検査で一側REFERと判定された先天性が2例、新生児聴覚スクリーニング検査でPASSが確認されている遅発性発症が2例、不明が4例であった。一側中等度難聴であった1例（12.5%）において変動する聴力が確認された。遅発性発症例、変動＋進行例ともに今回は特に治療は行っていない。CMV DNA陽性が確認された8例においてはCT検査で内耳奇形は認められなかった。

考　察

一側性難聴は日常生活や学校教育においてほとんど支障がないといわれ、自ら訴えができ、左右別の聴力検査ができる就学時頃に発見される事が多かったが、最近、新生児聴覚スクリーニングの導入に伴い、早期に一側性難聴が診断されるようになった。新生児聴覚スクリーニング後の精密検査で一側性難聴と診断される頻度は24.5%～36.8%で、全出生児中の0.07%と報告[12]されている。一側referであっても一側性難聴と診断される頻度は50%前後で、経過観察中に良聴耳が悪化（6%）する例や両側passが最終的に一側性難聴と診断（3～8%）される例がある[13]。信州大学附属病院耳鼻咽喉科小児難聴外来を受診した感音難聴児134例のうち、65.7%に一側性感音難聴を認め、両側性難聴よりも頻度が多かった。

守本ら[14]は94例の一側性難聴児を検討し、36.2%が感音難聴であったが、そのうちの52.9%が原因不明であったと報告している。また、茂木ら[15]（2009年）は2001年から2008年までに信州大学耳鼻咽喉科小児外来を受診した120例の一側性難聴児の原因を調査し、内耳・内耳道奇形が15%、ムンプス難聴が6%、先天性CMV感染症が3%、髄膜炎が2%、突発性難聴が3%、ANSDが4%、原因不明が67%であったと報告している。この時の検討では、120例中20症例のみに保存臍帯からのCMV DNA検査の実施であったため、88例全例に検査を実施した今回の検討に比べると頻度が低くなったと思われる。今回の検討ではCMV DNAが陽性であったのは、一側性感音難聴児の9.1%に認められた。一側高度難聴児にかぎると9.6%であり、一側軽度～中等度難聴にかぎると6.7%であった。一側性難聴における先天性CMV感染児の比率に関してはこれまで25%（1/4例）[16]と19%（8/42例）[17]の報告がみられる。これらの報告より対象者の数は多かったが、頻度は低い結果となった。より正確な頻度を導くには、先天性CMV感染のスクリーニング検査法の確立と普及、さらに前向き研究を実施して行く必要がある。

先天性CMV感染した出生児の約9割は何ら症状を示さない無症候性感染症として経過するが、その後1～3割に難聴や精神発達遅滞などの神経症状を伴ってくる[6),7)]。難聴は中等度から高度の聴力障害がみられ、遅発性（11～18%）・進行性（23～62%）、また難聴が改善する（23～47%）報告[8),9)]がみられている。今回の検討では、先天性CMV感染による一側性難聴の場合、高度難聴が87.5%（7/8例）と高率であった。25%（2/8例）が新生児聴覚スクリーニング検査で一側REFERで

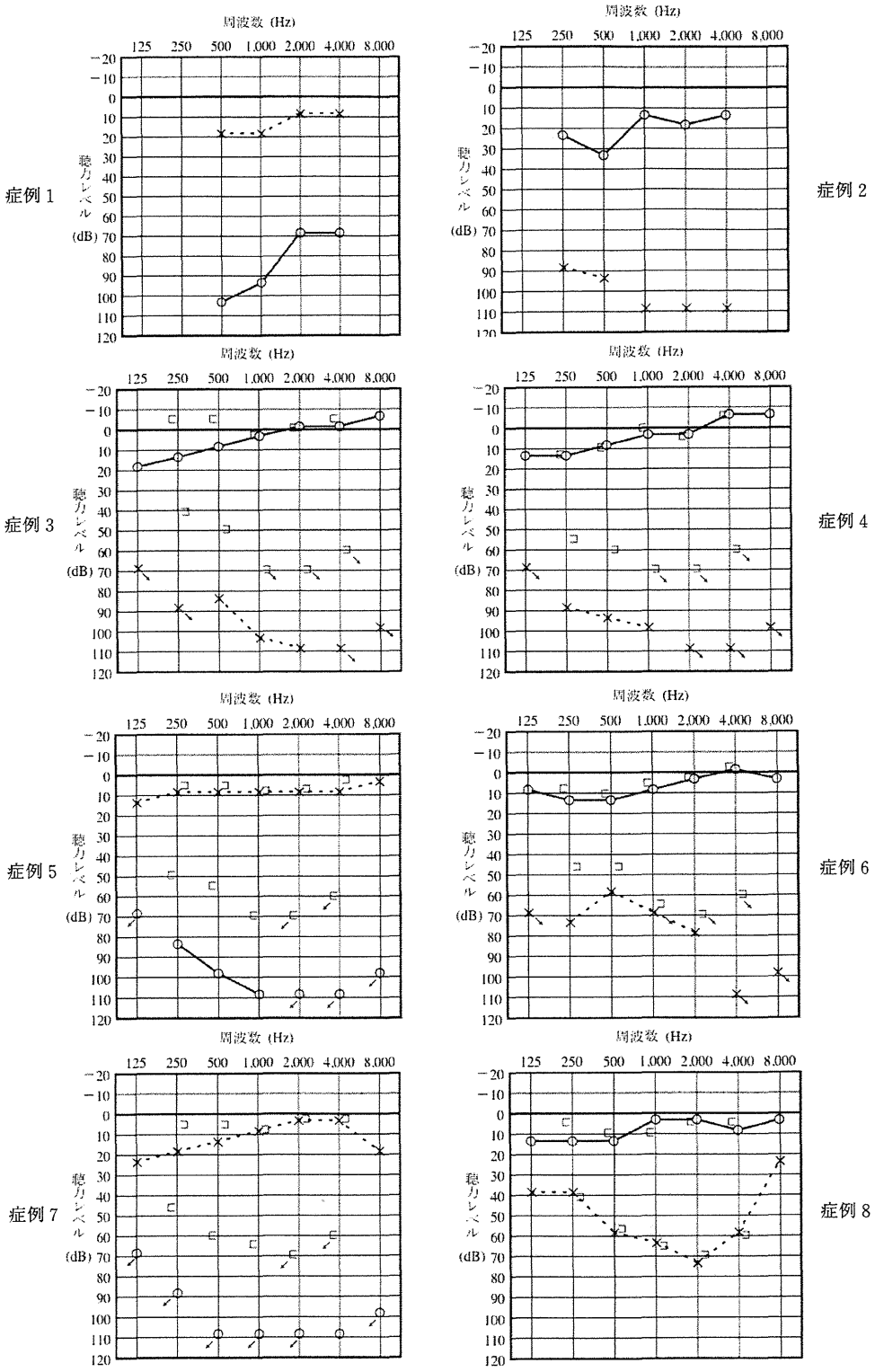

図2　CMV DAN陽性であった一側性感音難聴8例の聴力図

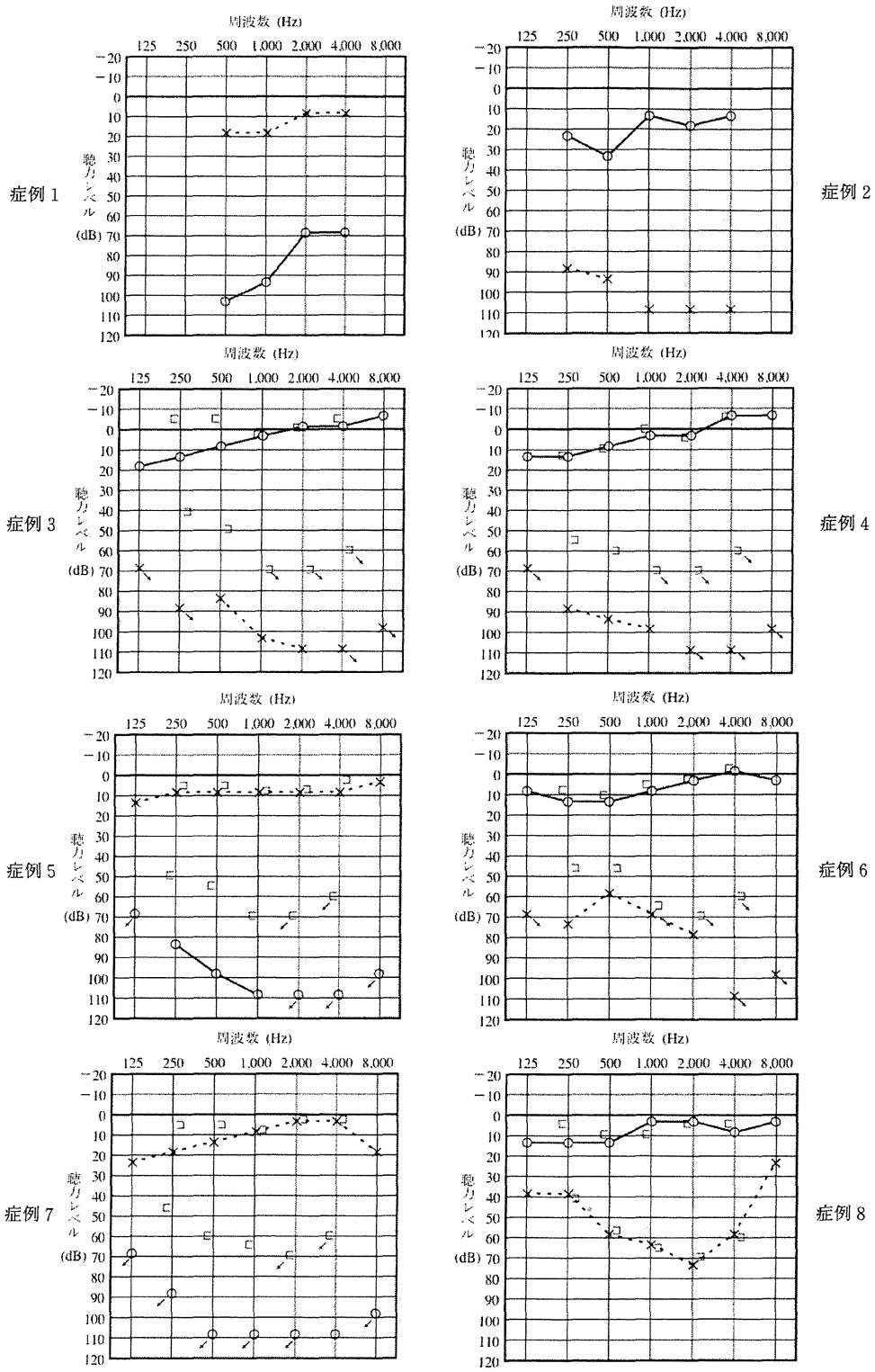

図 2　CMV DAN陽性であった一側性感音難聴 8 例の聴力図

表2　CMV DNA（+）の8児の臨床症状

症例	性別	難聴耳側	出生時体重	難聴診断月例	平均聴力レベル	先天性／遅発性	変動の有無	難聴遺伝子	NHSの結果	発達異常の有無
1	女児	右耳	2395g	2ヶ月	90.0dB	先天性	不明	(—)	Refer	無
2	男児	左耳	不明	6ヶ月	103.8dB	先天性	(—)	(—)	Refer	無
3	男児	左耳	不明	50ヶ月	100.0dB	不明	(—)	(—)	未実施	無
4	女児	左耳	不明	55ヶ月	92.5dB	遅発性	(—)	(—)	Pass	無
5	男児	右耳	2614g	65ヶ月	107.5dB	不明	(—)	(—)	未実施	無
6	男児	左耳	不明	80ヶ月	70.0dB	不明	(—)	(—)	未実施	無
7	女児	右耳	不明	98ヶ月	110.0dB	不明	(—)	(—)	未実施	無
8	女児	左耳	不明	44ヶ月	58.3dB	遅発性	変動＋進行性	(—)	Pass	無

CMV：cytomegalovirus。NHS: Newborn hearing screening（新生児聴覚スクリーニング）。

あったことから先天性と思われ、25%（2/8例）が遅発性で、進行性が確認できたのは12.5%（1/8例）であった。両側性難聴の場合と比べると、遅発性の頻度が高く、高度難聴として発症するため進行性が少ない傾向があると思われた。先天性CMV感染による聴覚障害の発症機序に関しては血行性感染が主体であると考えられているが、動物実験とヒト側頭骨病理所見も異なっており、発症機序は不明である[18]。一側性難聴として発症する機序や遅発性の頻度が多い理由に関しては今後の課題と考える。

最近は画像診断技術の向上が関与しているのかもしれないが、一側性難聴児における内耳・内耳道内の奇形の頻度は最近の報告では57.1%～66.7%と高く[3),19)]、両側性難聴よりも奇形の頻度は高い。先天性の一側性難聴に限るとCTで診断される内耳・内耳道奇形は30～35%にみられ[19)]、MRIによる蝸牛神経の無～低形成は65%～71%と高頻度に認められている[3)]。一側性難聴の場合は難聴遺伝子の変異は認められなかったので、原因精査には画像検査と先天性CMV感染の診断のための検査が重要と考える。

一側性難聴は患側からの聞き取りの困難性、騒音下の聞き取りの低下、音源定位の困難がよく指摘されている。言語発達に関しては正常聴力の児と変わりがないとする者もいれば、2語文の発語が平均5ヶ月ほど遅延する[20)]、学童期で30～40%の言語が遅れる[2)]など、言語発達遅滞や学業成績への影響を指定する報告もあるが、先天性CMV感染症による一側性難聴児に限定した言語発達遅滞や学業への影響を検討した報告はない。非症候性の先天性CMV感染症では難聴の遅発発症だけではなく、精神発達障害の遅発発症もあるため[21)]、今後先天性CMV感染による一側性難聴の言語発達の経時的な評価を行っていく事も重要と考える。そのためにも先天性CMV感染のスクリーニング検査、確定診断の流れを確立して行く必要がある。

まとめ

信州大学附属病院耳鼻咽喉科小児難聴外来を受診した感音難聴児134例のうち、一側性感音難聴を認めた88例（65.7%）に対し、難聴遺伝子検査と保存臍帯からのCMV DNA検査を実施し、他の一側性難聴の原因との頻度について検討した。

CMV DNAが陽性であったのは、一側性感音難聴児88例中8例（9.1%）で、一側高度難聴は73例中の7例（9.6%）、一側軽度～中等度難聴は15例中の1例（6.7%）であった。難聴遺伝子の変異は1例も確認されなかった。遅発性の頻度（25%）が高く、高度難聴として発症（87.5%）するため進行性が少ない傾向（12.5%）にあった。

付記

本研究は、平成23～24年度文部科学研究費補助金基盤研究（C）と平成24年度厚生労働科学研究費補助金障害者対策総合研究事業（感覚器障害分野）の研究助成を受けて行った。

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論文受付　25年5月10日
論文受理　25年7月17日

別刷請求先：〒390-8621　長野県松本市旭3-1-1
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あらゆる可能性を考え，薬物療法，補聴器（希望により音響療法）を試み，患者サイドに立った治療の提案を行うことが重要である．

耳閉感

診断

A 病態

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

B 診断

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

治療方針

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

高度難聴（補聴器，人工内耳）

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

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診断

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

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

治療方針

A 補聴器

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

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

B 人工内耳

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

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

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

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

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

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

患者説明のポイント

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

看護・介護のポイント

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

めまい，平衡障害
vertigo and dysequilibrium

肥塚　泉　聖マリアンナ医科大学教授・耳鼻咽喉科

病態と診断

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

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

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

治療方針

A めまい急性期の治療

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

International Journal of Pediatric Otorhinolaryngology 78 (2014) 285–289

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Evaluation of cortical processing of language by use of positron emission tomography in hearing loss children with congenital cytomegalovirus infection☆

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ARTICLE INFO

Article history:
Received 24 May 2013
Received in revised form 22 November 2013
Accepted 24 November 2013
Available online 2 December 2013

Keywords:
FDG-PET
CMV
Hearing loss
Visual language task

ABSTRACT

Objective: To predict cochlear implant efficacy and investigate the cortical processing of the visual component of language in profoundly deafened patients with asymptomatic congenital cytomegalovirus (CMV) infection.

Methods and cases: The cortical activity of two children with CMV-related hearing loss was evaluated with fluorodeoxyglucose-positron emission tomography (FDG-PET) with a visual language task before cochlear implantation. Total development and auditory perception ability were assessed one year after implantation.

Results: The two children with CMV-related hearing loss showed activation in the auditory association area where no activation was found in the controls, and exhibited nearly identical cortical activation patterns to those seen in patients with profound congenital hearing loss. In contrast, differences in total development in verbal ability and discrimination of sentences between the two cases were revealed one year after implantation.

Conclusion: These results might indicate that the differences of cortical activities according to hearing abilities could have been influenced by CMV infection that involves higher function of the brain directly and/or affects the cochlea peripherally. Additionally, if CMV infection might have affected only the cochlea, these cortical activation patterns were influenced secondary by the time course of hearing loss characterized by CMV infection, which had varied manifestations.

Accurate diagnosis and cochlear implantation at the appropriate time are important for successful speech development, and each patient needs a personalized habilitation program based on their etiology and brain function.

1. Introduction

Functional brain imaging provides important evidence of the plasticity of the central auditory pathway following a profound loss of hearing, and is one of the effective methods for investigating the cortical processing of language [1,2]. Previous studies have shown low levels of auditory cortical activity in subjects with profound deafness, i.e. lower levels of activity are observed with longer durations of deafness [3,4]. The importance of early hearing inputs by hearing aids or cochlear implantation (CI) has also been shown. Children with prelingual deafness can acquire spoken language by CI, but this approach is less effective in older children who have not acquired language during the critical language acquisition periods [5,6]. The development of the auditory cortex is believed to depend on the patient's auditory experience within 'critical periods' in the early lifetime. Positron emission tomography (PET) activation study by visual language task has shown that low glucose metabolism in the temporal auditory cortex predicts a good CI outcome in prelingually deafened children, which suggests that low metabolism in the

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http://dx.doi.org/10.1016/j.ijporl.2013.11.025

auditory cortex may indicate its potential of plasticity for spoken language acquisition [7].

Congenital cytomegalovirus (CMV) infection is the most common environmental cause of developmental disability and sensorineural hearing loss (SNHL) in children [8]. Approximately 90% of infected infants are born with no clinical symptoms of congenital CMV infection, such as microcephaly, growth retardation, hepatomegaly, jaundice, or abnormal neurologic findings. SNHL is found in 6–23% of these asymptomatic infection cases and is often late-onset, fluctuating and progressive in nature within the first 6 years of childhood [9,10]. Hence, newborn hearing screening often does not detect problems in children with asymptomatic congenital CMV infection, and at the time of eventual SNHL diagnosis, the exact time course and manifestations cannot be determined [11]. The development of auditory skills and experiences of children with congenital CMV infection with associated hearing loss are unclear due to various clinical histories. Hearing impairment resulting from (even asymptomatic) congenital CMV infection might be not only of cochlear origin but also have central nerve involvement and entail possible risk of CMV-associated disorders later in life. Brain function and CI outcomes have not been examined in asymptomatic congenital CMV-associated hearing loss. In this study, we used ^{18}F-fluorodeoxyglucose (FDG)-PET to measure cortical glucose metabolism with a visual language task before CI in two profoundly deaf children with asymptomatic congenital CMV infection in order to assess the activities of the auditory cortex and predict the CI outcomes.

2. Methods and cases

2.1. Diagnosis of congenital CMV infection

To analyze congenital CMV infection, we used CMV DNA quantitative PCR (qPCR) analysis. Before qPCR analysis, total DNA including genomic DNA and CMV DNA was extracted from preserved dried umbilical cords. Each 10 pg total DNA was analyzed by a Step One Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) using a TaqMan Universal Master Mix II (Applied Biosystems). The detailed methods of qPCR have been described previously (Furutate et al.) [12].

2.2. FDG-PET scanning and image analysis

FDG-PET scanning and image analysis were performed using the methods described by Fujiwara et al. [7]. During the time period between the intravenous injection of 370 MBq 18 F-FDG (the dose was adjusted according to the body weight of each subject) and the PET scanning of the brain, the patients were instructed to watch a video of the face of a speaking person reading a children's book. The video lasted for 30 min, and several still illustrations taken from the book were inserted (for a few seconds each) to help the subjects to follow the story. The subjects were video-recorded to confirm that they were watching the task video. PET images were acquired with a GE ADVANCE NXi system (General Electric Medical Systems, Milwaukee, WI, USA). The patients were then sedated by an anesthesiologist, and their heads were immobilized with a bandage during the scan. Spatial preprocessing and statistical analysis were performed with SPM2 (Institute of Neurology, University College of London, UK) implemented in Matlab (Mathworks, MA, USA). The cortical radioactivity of each deaf patient was compared with that of a control group by a t test in the basic model of SPM2. The control group consisted of six normal-hearing (pure tone average hearing levels within 20 dB HL) right-handed adult (27.5 ± 3.8 years) subjects. The statistical significance level was set at $p < 0.001$ (uncorrected).

2.3. Measurement of language and total development

Before CI, we evaluated the patients' mental development by the Kyoto scale of psychological development (K-test) in which Cognitive-Adaptive development [13] that consists of non-verbal reasoning or visuospatial perceptions is measured. This test is used commonly to assess developmental status for Japanese language users and the results are described as a developmental quotient (DQ) in comparison to normal controls. In the K-test, developmental delay is defined by DQ below 80.

One year after CI, auditory perception ability was assessed by word and sentence discrimination tests, which are components of the CI2004 test battery for children. Audible word discrimination tests were administered by a speech therapist with live voice stimuli presented at 70 dB in a soundproof room. We also evaluated intellectual development using the Japanese version of the WISC-III that corresponds to the Wechsler Intelligence Scale for Children (WISC) and contains non-verbal and verbal ability components. The Japanese WISC-III includes five subsets for performance IQ (PIQ) (picture completion, picture arrangement, block design, object assembly and coding) and five subsets for verbal IQ (VIQ) (information, comprehension, similarities, arithmetic and vocabulary).

This study was approved by the Ethics Committee of Shinshu University School of Medicine and prior written consent was obtained from the parents of both children after a full explanation of the study.

2.4. Details of cases

2.4.1. Case 1

This case was a 5-year-old girl. She had no particular events in the perinatal period and passed the newborn hearing screening. However at age 4 years 11 months, her mother suspected hearing loss because of poor response to sound. She only had mild expressive language impairment; her fine motor skills were unaffected. An auditory steady state response (ASSR) test showed bilateral hearing loss (approximately, right: 60 dB, left: 110 dB) (Fig. 1A). She was promptly fitted for bilateral hearing aids. After one month, a follow-up ASSR test indicated deterioration of hearing in her right ear to over 110 dB (Fig. 1C). At this point, DNA testing for hereditary hearing loss e.g. screening for mutations in the *GJB2* and *SLC26A4* genes, and checking for congenital CMV infection using preserved dried umbilical cord (above mentioned) was performed to diagnose the cause of hearing loss. These tests revealed that there were no pathological mutations causing hearing loss, but there were positive results for CMV infection. It was suspected that this late-onset, and rapidly progressive for one month, hearing loss was due to asymptomatic congenital CMV infection. Computed tomography (CT) findings of the middle and inner ear were normal. Hearing aids were not expected to be adequate to acquire spoken language, therefore CI was performed in the left ear at the age of 5 years 5 months.

2.4.2. Case 2

This 4-year-old girl had no particular events in the perinatal period and had not undergone newborn hearing screening. Her parents noticed that she did not respond to their voices when she had just turned 3 years old. She visited a hospital for a checkup where she was diagnosed by ASSR test at the age of 3 years 6 months with hearing loss that was approximately right: 60 dB, and left: 110 dB (Fig. 1B). She attended rehabilitation for hearing, using a combination of finger signing and gestures. In the following year, her hearing deteriorated further to right: 90 dB, left: 110 dB at the age of 4 years five months and her speech development was not

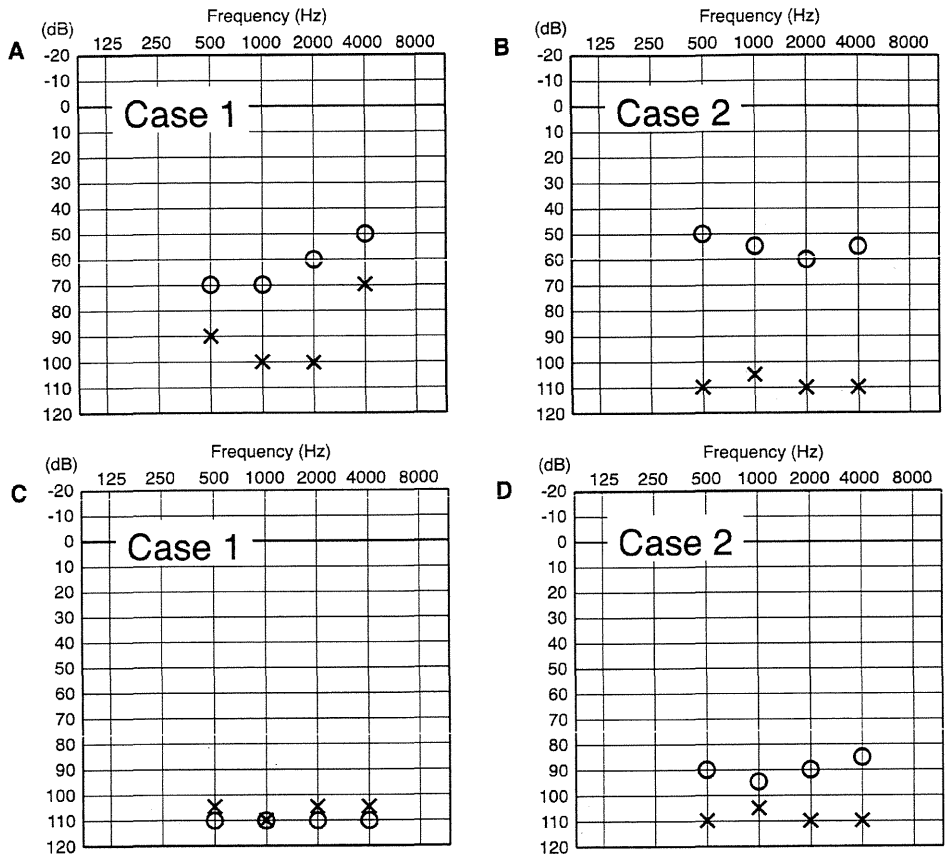

Fig. 1. (A) Case 1; a 5-year-old girl with asymptomatic congenital CMV infection (threshold using ASSR test). (B) Case 2; a 5-year-old girl with asymptomatic congenital CMV infection. These were results of first diagnosed with hearing loss. (C and D) Deterioration in hearing, for one month and for one year, respectively.

significant (Fig. 1D). She was referred to our hospital for further examinations, and her preserved umbilical cord demonstrated a positive result for congenital CMV infection. Late-onset and slowly progressive hearing loss for one year was suggested. There were no inner ear abnormalities seen in the CT findings. She underwent CI surgery in the left ear at the age of 4 years 9 months.

Each child received the same rehabilitation according to auditory oral method by the same speech therapist after implantation.

Table 1
The activated areas of the brain in profoundly deaf individuals during speech-reading.

Case	Gender/age (years)	Activated areas	
		Right hemisphere	Left hemisphere
1	Female/5	Superior temporal gyrus [BA22] Cingulate gyrus [BA31] Middle frontal gyrus [BA9]	Middle temporal gyrus [BA21] Inferior parietal lobe [BA40] Occipital gyrus [BA19] Precueus [BA7]
2	Female/5	Middle temporal gyrus [BA21] Postcentral gyrus [BA3/1/2] Middle occipital gyrus [BA20] Middle frontal gyrus [BA9]	Precentral gyrus [BA4] Precuneus [BA31] Precuneus [BA19] Cingulate gyrus [BA24]

3. Results

3.1. Brain imaging with PET

Table 1 and Fig. 2 show the areas that were activated in each child during a speech-reading task. The following cortical areas showed significantly higher metabolism during speech-reading in the children compared to normal hearing control subjects. In Case 1, the activated areas were the bilateral auditory association area [BA21], the bilateral precuneus, somatosensory cortex [BA7], the left secondary visual area [BA19], and the left inferior parietal lobule [BA40].

The activated areas in Case 2 were similar to those in Case 1, but the activation of the visual association areas in the parietal lobe were lower and smaller than in Case 1.

3.2. Assessment before cochlear implant, and outcome

Table 2 shows the children's scores in the *K*-test before CI, in the word and sentence discrimination tests, and in the Japanese WISC-III at one year after implantation. *K*-test scores that assessed Cognitive-Adaptive development of each child were almost similar. Both cases showed 30–40 dB of aided hearing thresholds at all frequencies with CI. One year after CI, the results of the Japanese WISC-III showed a clearer difference in VIQ than PIQ, in which Case 1 had a better score compared with Case 2. Case 1 did

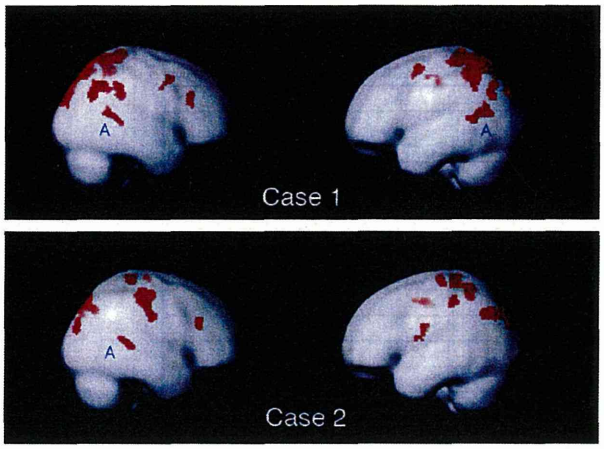

Fig. 2. Cortical activation by language-related visual stimuli in two profoundly deafened with congenital CMV infection cases. Case 1 and 2 showed significant activation in auditory association areas (A) (SPM2, $p < 0.001$, uncorrected).

Table 2
The results of total development before and after cochlear implant, and auditory assessment.

	Before CI	One year after CI	
	K-test (Cognitive-Adaptive)	WISC-III (Japanese version)	Infant word and sentence discrimination
Case 1	99	PIQ 101 VIQ 84	Word 98% Sentence 90%
Case 2	93	PIQ 93 VIQ 56	Word 100% Sentence 53%

CI, cochlear implant; *K*-test, Kyoto scale of psychological development; WISC, Wechsler Intelligence Scale for Children; PIQ, performance IQ; and VIQ, verbal IQ.

better as well in the sentence discrimination component of the auditory perception ability assessment while their results were similar regarding words in the word and sentence discrimination test for children.

4. Discussion

This is the first report on the evaluation of cortical processing of language in hearing loss children with congenital CMV infection. In infants with congenital CMV infections, as many as 20% will suffer from some degree of SNHL, either fluctuating or progressive [14]. This may present a late onset hearing loss, even if the results of newborn hearing screening were normal. The clinical courses of hearing loss in Cases 1 and 2 were typical for asymptomatic congenital CMV infection. Performance and outcome of children with CIs have a strong relation to hearing variables such as onset and course of hearing loss, age of hearing aids fitting, and social background variability, which depends on habilitation and education. According to Fukushima et al. and Kawasaki et al., children with *GJB2* mutations as the etiology for hearing loss have an advantage in their CI outcomes and speech acquisition with normal cognitive development compared with children with unknown etiologies, but this is because the hearing loss is of cochlear origin [15,16]. On the other hand, widely varying conclusions regarding CI outcomes with congenital CMV infection have been reported. Some studies reported the efficacy being not inferior to that of other CI recipients, while others reported it being much poorer [9,17–20]. Accordingly, prediction of CI outcomes for hearing loss with CMV infection is still difficult, unclear, and inconsistent because of various manifestations, progression and the possibility of involvement of higher brain function. Yamazaki et al. suggested that CI with CMV infection outcomes vary widely depending on the psycho-neurological disorders, with their differences in proportion and severity [19].

In this study, the auditory association area in the temporal lobe was activated bilaterally in Case 1 and unilaterally in Case 2. Fujiwara et al., in a FDG-PET study using the same methods and tasks as the present study, showed that subjects with better spoken language skills had less temporal lobe activation [7]. These cases exhibited nearly identical cortical activation patterns to those of congenitally deafened children, suggesting that they did not have enough hearing to develop the cortical network for audition. Previous studies have suggested that plastic changes in auditory cortices were strongly determined by the duration of auditory deprivation [21,22]. However, our two cases of children with CMV-related hearing loss were affected with severe bilateral hearing loss over a short period and were able to acquire spoken language with only a little delay for their age group. It is an interesting but unsolved question why they exhibited results that were the same as previous reports of pre-lingually deafened patients who did not receive sufficient auditory signals and therefore depended on visual cues. One possibility was that high speech-reading activation in the temporal auditory area might be linked to the condition of lacking auditory speech skills at that point, rather than reflecting a consequence of replacement by visual cross-modal plasticity due to a hearing loss of long duration. Besides, visual language activation in the auditory area may change even if affected by hearing loss of a short duration, or it might be influenced by the age-related metabolic changes during the critical period for spoken language acquisition. Another possibility was that these results might indicate that both cases had not received sufficient hearing stimulation as a foundation of language during their early years, which may be attributed to the central nervous system impairment of CMV infection.

Regarding the results of assessment after CI, there was a difference of cognitive ability with VIQ and hearing ability of sentence discrimination, with Case 1 having better CI performance than Case 2 (Table 2). In the assessment of auditory performance, Case 2 especially had difficulty in sentence discrimination despite having the same score in word discrimination as Case 1, who had better CI performance. Sentence discrimination tests require not only audible sound coded by CI, but also recognition of semantics and syntax that would be developed and established with hearing experiences during growth. Indeed, because of the differences between our two cases of the brain imaging, especially in the auditory cortex, we were uncertain whether it might be affected by CMV infection or the onset of their hearing loss itself. However, it raised the possibility that involvement of central nerve and high brain function relevant to CMV infection may lead to retardation of sentence discrimination and speech acquisition in Case 2. On the other hand, there was a difference of activation patterns in the parietal visual association areas. Case 2 showed lower and smaller than in Case 1. Fujiwara et al. predicted that the children with deafness were likely to depend more on vision than normal hearing children do. In Case 1, when someone talked to her, she might have been able to pay much more attention to their facial expression, gestures and visual cues for understanding better than Case 2. Lee et al. reported the comparison of brain metabolic activity between good and poor CI outcomes [23]. The activity patterns in the parietal regions of those with good CI outcomes in their study were similar to our result in Case 1.

We considered that these results might indicate that the differences of cortical activities according to hearing abilities could have been influenced by CMV infection that involves higher function of the brain directly and/or affects the cochlea peripherally. Additionally, if CMV infection might have affected only the

cochlea, these cortical activation patterns were influenced secondary by the time course of hearing loss characterized by CMV infection, which had varied manifestations.

Accurate diagnosis of hearing loss and early cochlear implantation are important for successful speech development. The approach using PET could help those involved in the habilitation and education of pre-lingually deafened children to decide upon the appropriate mode of communication for each individual. Brain imaging technologies to evaluate the neural basis for auditory speech skills have been developed and much evidence has been reported; however, correlation with hearing loss etiology, pathology and cross-modal plasticity of auditory cortex remains contentious. Further evaluations of the cortical metabolism before and after implantation are necessary for establishing appropriate personalized audiologic rehabilitation programs for individuals based on their etiology and brain function.

Conflicts of interest statement

We, the authors, declare that there were no conflicts of interest in conjunction with this paper.

Acknowledgements

We thank A.C. Apple-Mathews and Nora Prachar for help in preparing the manuscript. We also thank Masanori Sakaguchi, M.D. and radiologic technologists, Kouichi Anraku and Hiroyuki Fujimoto, for excellent technical assistance.

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Acta Oto-Laryngologica. 2014; 134: 58–65

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ORIGINAL ARTICLE

Clinical features of rapidly progressive bilateral sensorineural hearing loss

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Abstract

Conclusion: Rapidly progressive bilateral sensorineural hearing loss (SNHL) often develops as a symptom of intracranial diseases or systemic vasculitis. For early diagnosis and treatment of these potentially fatal diseases, a history of hearing deterioration within 2 months and associated symptoms may be important. *Objectives:* To reveal clinical features and causative diseases for rapidly progressive bilateral SNHL. *Methods:* The inclusion criterion was patients with bilateral progressive SNHL, who had experienced difficulty in daily conversation within 4 days to 1 year after the onset of hearing loss awareness. This study was a retrospective evaluation of 12 patients with rapidly progressive bilateral SNHL who visited our hospital between 2007 and 2011. *Results:* The causative disease for hearing loss was identified in 11 of 12 patients; intracranial lesions including nonbacterial meningitis, meningeal metastasis of lymphoma, and superficial siderosis in 4 patients, systemic vasculitis in 2, auditory neuropathy spectrum disorder in 1, and an isolated inner ear disorder in 4. Relatively rapid hearing deterioration within 2 months showed a significant association in six patients with an intracranial lesion or systemic vasculitis. Moreover, all these six patients complained of dizziness and/or non-cochleovestibular symptoms such as fever, headache, and/or altered mental state in addition to hearing loss.

Keywords: *Auditory perception, intracranial disease, systemic vasculitis, magnetic resonance imaging, hearing threshold*

Introduction

Sensorineural hearing loss (SNHL) is caused by various disorders, including sudden deafness, presbycusis, hereditary hearing loss, drug-induced hearing loss, and Meniere's disease. Various clinical data are used to diagnose the cause of SNHL, of which the time course of hearing deterioration may be particularly important for estimating the nature of the disorder. For example, sudden deafness has an onset period of < 72 h [1], while presbycusis deteriorates by 1–2.5 dB per year over a long period of time. We also encounter patients with bilateral SNHL whose hearing deteriorates more slowly than that in sudden deafness but more quickly than that in presbycusis. Such patients often have serious complicating diseases, although only a few studies have examined this type of hearing loss. In this study, we report 12 cases of rapidly progressive bilateral SNHL and analyze the clinical features and causative diseases for hearing loss.

Material and methods

The study was a retrospective review of medical records. Of the 908 patients diagnosed with bilateral SNHL who visited the Department of Otolaryngology at Kobe City Medical Center General Hospital from

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(Received 17 June 2013; accepted 30 July 2013)

ISSN 0001-6489 print/ISSN 1651-2251 online
DOI: 10.3109/00016489.2013.831993

Table I. Characteristics of 12 patients with rapidly progressive bilateral sensorineural hearing loss.

Case no.	Onset (age in years)	Time from onset to difficulty in daily life (days)	Gender	Causative disorder	Category of causative disorder	Worst hearing (dB)		Hearing after treatment (dB)		Clinical symptoms
						R	L	R	L	
1	33	4	M	Cryptococcal meningitis	Intracranial lesion	115	115	68.3	25	Fever, headache, altered mentation, dizziness
2	45	60	M	Chronic herpes meningitis + labyrinthitis		115	108.3	No improvement		Fever, tinnitus
3	60	6	M	Meningial metastasis of lymphoma		75	50	45	48.3	Fever, dizziness
4	79	30	F	Superficial siderosis		65	61.7	No improvement		Dizziness, tinnitus
5	73	45	F	Cogan's syndrome	Systemic vasculitis	115	115	No improvement		Fever, headache, dizziness
6	44	4	F	Vasculitis syndrome		93.3	81.7	51.7	38.3	Fever, headache, altered mentation
7	26	7	F	Auditory neuropathy	ANSD	115	113.3	No improvement		Tinnitus
8	63	120	F	Isolated inner ear disorders	Isolated inner ear disorder	65	56.7	No improvement		Tinnitus
9	67	90	M	Isolated inner ear disorders		103.3	103.3	No improvement		Tinnitus
10	69	360	M	Isolated inner ear disorders		95	115	No improvement		Tinnitus
11	69	360	F	Isolated inner ear disorders		80	73.3	No improvement		Tinnitus
12	61	14	F	Undefined disorder	Undefined	53.3	55	41.7	41.7	Fever, backache

January 2007 to December 2011, 12 (1.3%, 5 males and 7 females; Table I) who met the following criteria for rapidly progressive bilateral SNHL were selected: (1) pure-tone audiometry data showing bilateral SNHL and average hearing thresholds at 500, 1000, and 2000 Hz of ≥ 50 dB; (2) difficulty in daily conversation without lip-reading or sign language within 4 days to 1 year after the onset of hearing loss awareness; and (3) exclusion of cases with bilateral Meniere's disease or functional hearing loss. Wegener's granulomatosis [2], Churg-Strauss syndrome [3], and eosinophilic otitis media [4], are also known to induce progressive hearing loss, but were excluded from this study because these diseases lead to mixed hearing loss rather than SNHL. The median age at onset of hearing loss was 62 years (range 26–79 years). The precise deterioration speed of the patients' pure-tone audiometric thresholds could not be calculated because most of them came to our hospital after having moderate or severe SNHL and their initial pure-tone audiometry thresholds before the onset of hearing loss had not been tested. Therefore, we defined progressive bilateral SNHL on the basis of subjective time course of deterioration in auditory perception.

The diagnoses of causative diseases of rapidly progressive bilateral SNHL were based on medical interviews, physical findings, and examinations by otologists, internal medicine specialists, and radiologists. The examinations included blood autoantibody tests, microbiological culture tests, radiographic examinations (CT and MRI), and cerebrospinal fluid (CSF) tests, as well as conventional otological examinations including pure-tone audiometry, distortion product otoacoustic emissions (DPOAEs), and auditory brainstem response (ABR). The causative diseases were categorized into five groups: (1) an intracranial lesion for which CT, MRI, and/or CSF tests revealed an abnormality in the central nervous system; (2) systemic vasculitis, diagnosed by positive blood tests for autoantibodies and systemic inflammation and vasculitis-specific skin lesion, retinal vasculitis, or non-syphilitic interstitial keratitis; (3) auditory neuropathy spectrum disorder (ANSD), diagnosed on the basis of good responses in DPOAE and a lack of obvious responses in ABR; (4) isolated inner ear disorder, with no abnormality on CT or MRI scans and no symptoms other than cochleovestibular symptoms; and (5) an undefined disorder with symptoms other than cochleovestibular symptoms.

The time course of hearing deterioration was evaluated using subjective manifestations. The time course was defined as the time period from the onset of hearing loss awareness to the onset of difficulty in understanding speech in daily life, and it was classified as follows: (1) 4 days to 1 week, (2) 1 week to 1 month, (3) 1–6 months, and (4) 6 months to 1 year. We also focused on clinical manifestations other than hearing loss, which were divided into cochleovestibular symptoms including tinnitus and dizziness and noncochleovestibular symptoms including fever, headache, and altered mental state.

Results

Clinical manifestations

The time course of hearing deterioration was from 4 days to 1 week in four patients, from 1 week to 1 month in two patients, from 1 to 6 months in four patients, and from 6 months to 1 year in two patients. The median hearing level (i.e. the worst value for each patient) of the 12 patients was 94 dB for the right ear and 93 dB for the left ear (Table I). With respect to manifestations related to noncochleovestibular disorders, fever was the leading symptom and was observed in six patients (50%). Among these patients with fever, three also complained of severe headache and two of these further suffered from altered mental state. Tinnitus was observed in seven patients including all six patients without noncochleovestibular symptoms. Dizziness was reported in four patients and three of these were also associated with a noncochleovestibular symptom, but the other complained of only tinnitus and dizziness (Table I).

MRI findings

Brain MRI was performed in nine patients including all six with a noncochleovestibular symptom, one with both tinnitus and dizziness, and two with tinnitus. Association of noncochleovestibular symptoms and dizziness with bilateral SNHL suggests the presence of systemic or intracranial lesions in the former and a retrocochlear or unusual inner ear disease in the latter. In fact, the diagnosis of an intracranial lesion or systemic vasculitis was confirmed or supported by MRI in five of seven patients with a noncochleovestibular symptom or dizziness (Figure 1). In case 4, T2-weighted MRI revealed superficial hypointensity on the surface of the brainstem and cerebellum, which was diagnosed as superficial siderosis. In the other four patients, gadolinium-enhanced T1-weighted MRI showed abnormal enhancement in the inner ear or internal auditory canal. In five cases complaining solely of tinnitus in addition to hearing loss, only two underwent brain MRI. In the other three cases, results of neurological examinations implied that the lesion was restricted in the cochleae and, therefore, careful follow-up of pure-tone audiometry, ABR,

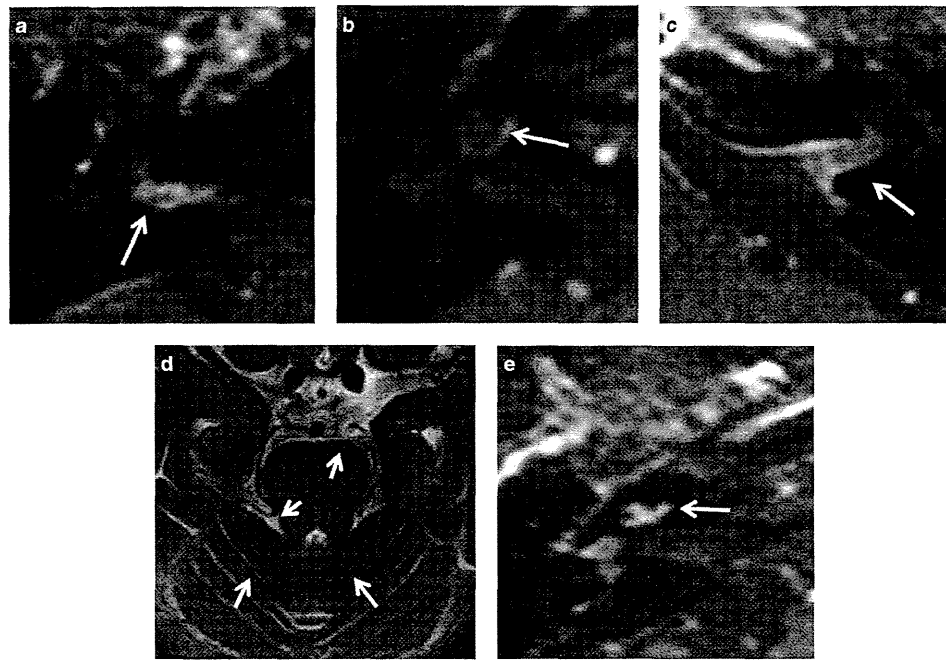

Figure 1. (a) Case no. 1. Cryptococcus meningitis with enhancement of bilateral internal auditory canal (IAC) on gadolinium-enhanced MRI. The enhanced right IAC is shown. (b) Case no. 2. Chronic viral meningitis plus labyrinthitis with enhancement of bilateral cochlea on gadolinium-enhanced MRI. The enhanced basal turn of the right cochlea is shown. (c) Case no. 3. Meningeal metastasis of lymphoma with enhancement of bilateral IAC on gadolinium-enhanced MRI. Enhanced left IAC is shown. (d) Case no. 4. Superficial siderosis with hypointensity along the brainstem and cerebellum on T2-weighted MRI. (e) Case no. 5. Cogan's syndrome with enhancement of bilateral cochlea on gadolinium-enhanced MRI. The right whole cochlea is enhanced.

DPOAE, and/or blood tests for autoimmune antibodies rather than brain MRI were conducted to evaluate cochlear disorders.

Categories of causative diseases

The causative diseases for hearing loss are shown in Table I. Systemic evaluation showed abnormalities restricted to the inner ear in four patients (isolated inner ear disorder). Intracranial lesions were detected in four patients and systemic vasculitis in two, with these disorders diagnosed as the causes of bilateral SNHL. The intracranial lesions included Cryptococcus meningitis, chronic meningitis due to herpes simplex virus, meningeal metastasis of lymphoma, and superficial siderosis. The two patients with systemic vasculitis were diagnosed with Cogan's syndrome and Sjögren syndrome with aseptic meningitis, retinal vasculitis, and skin lesions.

Relationship between category of causative diseases and clinical manifestations

The time course for deterioration in auditory perception was ≤ 60 days in the six patients with an

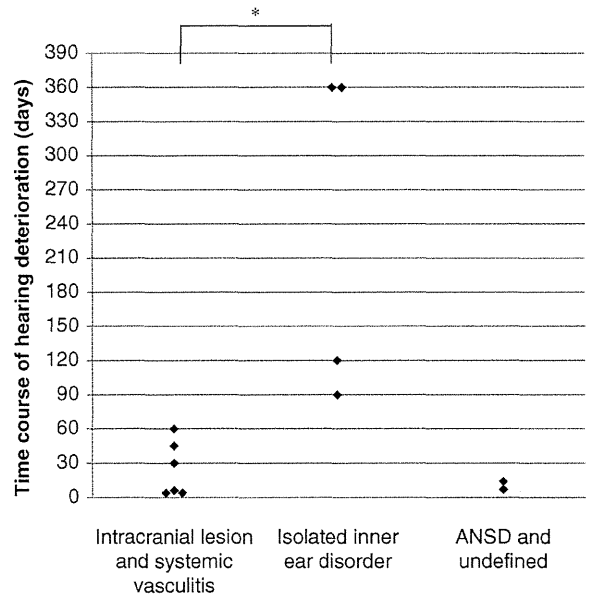

Figure 2. Time course of hearing deterioration in different categories of causative disorders. There was a significant difference between patients with intracranial lesion and systemic vasculitis, and those with an isolated inner ear disorder.
*: $p < 0.05$

Table II. Characteristics of six patients with an intracranial lesion or systemic vasculitis.

Case no.	Diagnosis	Treatment	Time before treatment (days)	Hearing improvement
1	Cryptococcal meningitis	Antifungal drug	3	Improved
2	Chronic herpes meningitis + labyrinthitis	Steroid and anti-HSV agents	Unknown	Not improved
3	Meningial metastasis of lymphoma	Steroid and anticancer drug	6	Improved
4	Superficial siderosis	No treatment		Not improved
5	Cogan's syndrome	Steroid	90	Not improved
6	Sjögren syndrome	Steroid	4	Improved

intracranial lesion or systemic vasculitis and ≥ 90 days in the four patients with an isolated inner ear disorder. The Mann–Whitney U test showed a significant difference ($p < 0.05$) between these groups (Figure 2). As shown in Table I, all patients with an intracranial lesion or systemic vasculitis complained of dizziness and/or noncochleovestibular symptoms in addition to hearing loss. Four of these six patients had dizziness and five of them had fever, headache, or altered mental state. These symptoms were not observed in patients with ANSD or an isolated inner ear disorder, who had only tinnitus as an associated symptom.

Hearing improvement after treatment for the causative diseases

The causative disease was treated in five patients with an intracranial lesion or systemic vasculitis, except in case 4 who had superficial siderosis (Table II). Hearing improved in three patients, who did not require hearing aids in daily life. The delay from the onset of hearing loss awareness to the beginning of treatment was within 1 week in cases 1, 3, and 6, who showed an improvement in hearing. However, it took as long as 90 days in case 5, who showed no change in hearing threshold after treatments. In case 4, the origin of bleeding that caused hemosiderosis was not determined despite radiographic evaluations, including brain and spinal MRI, and the patient showed no improvement in hearing at follow-up. Improvement in hearing loss did not occur in any of the patients with ANSD or an isolated inner ear disorder, despite systemic administration of steroids and/or circulation activators.

Discussion

This study was performed as a retrospective review of 12 cases with progressive bilateral SNHL who complained of difficulty in daily conversation within 4 days to 1 year after the onset of hearing loss awareness. The patients with bilateral SNHL presenting this time course of deterioration were relatively rare and accounted for only 1.3% of those with bilateral SNHL in this study. However, retrospectively, distinguishing this type of SNHL from others was meaningful because 6 of these 12 patients (50%) developed SNHL from an intracranial lesion or systemic vasculitis, which can be fatal without appropriate treatment. It is also noteworthy that all three patients with an intracranial lesion or systemic vasculitis, who showed improvement in hearing, underwent early treatment of the causative diseases, suggesting that accurate diagnosis and appropriate treatments for the causative disease at its early stage may be important to restore hearing as well as to lower the mortality. In the present study, the rapidly progressive SNHL was also caused by ANSD or an isolated inner ear disorder, but clinical manifestations of intracranial lesions and systemic vasculitis were different from those observed in other categories of causative diseases. Our study showed that in patients with intracranial lesions and systemic vasculitis, the time from onset of hearing loss to difficulty in daily life was within 2 months and significantly shorter than that in patients with an isolated inner ear disorder. In addition to the rapidly progressing hearing loss, noncochleovestibular symptoms and/or dizziness were always associated with intracranial lesions and systemic vasculitis, while all five patients with an isolated inner ear disorder or ANSD complained of only tinnitus. Among noncochleovestibular symptoms, fever was the leading symptom (6 of 12 patients), followed by headache and an altered mental state. In all cases with fever, the origin of fever was difficult to identify at first and systemic inflammation or intracranial infection was identified later based on systemic evaluations by otologists, internal medicine specialists, and radiologists. The presence of headache and an altered mental state also suggests that lesions may

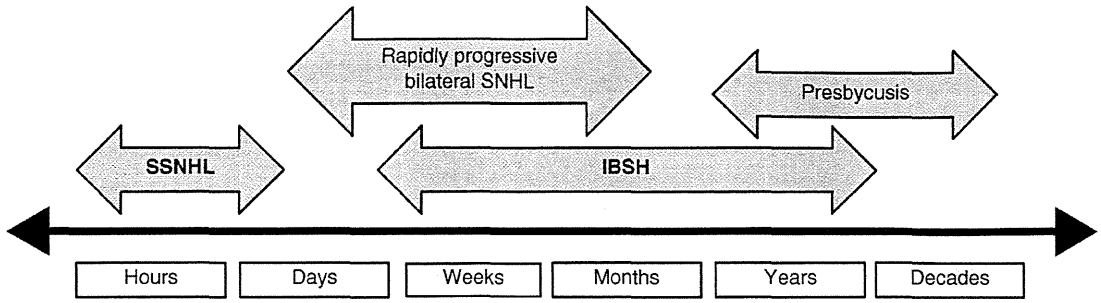

Figure 3. The time course in various types of bilateral sensorineural hearing loss (SNHL). IBSH, idiopathic bilateral SNHL; SSNHL, sudden SNHL.

involve other areas of the central nervous system in addition to the auditory neural pathway. Interestingly, obvious vestibular dysfunction was not observed in patients with an isolated inner ear disease, although four of the six patients with an intracranial lesion or systemic vasculitis had dizziness. The inner ear lesions in the present series may have been limited to the cochlea, with central compensation possibly making the vestibular symptoms less prominent despite the presence of some vestibular involvement.

We performed brain MRI in nine patients including all seven with a noncochleovestibular symptom or dizziness. Headache, altered mental state or other abnormal neurological findings in addition to the eighth cranial nerve dysfunction suggests the presence of an intracranial lesion. In this situation, brain MRI is necessary to evaluate intracranial diseases. Even though the neurological disorders were limited to the eighth cranial nerve, association of dizziness with SNHL might be caused by labyrinthitis or lesions in internal auditory canals and brain MRI may be recommended. Prolonged unknown origin of fever associated with bilateral SNHL is also an indication for brain MRI to evaluate labyrinthitis and nonbacterial meningitis.

In the present study, pure-tone hearing thresholds were improved in case 1 with Cryptococcus meningitis and case 3 with meningeal metastasis of lymphoma after the intracranial administration of antifungal and anticancer drugs, respectively. Hearing recovery is usually difficult in patients with Cryptococcus meningitis [5], although a patient with this disease was reported to show partial recovery of hearing after treatment [5]. Hearing improvement after treatment has also been reported in patients with bacterial and viral meningitis [6,7]. Vasculitis causes SNHL in patients with connective tissue diseases such as systemic lupus erythematosus and polyarteritis nodosa [8], with this type of hearing loss reported to improve following plasmapheresis or immunosuppressive therapy using steroids or cyclophosphamide [2,9]. In our study, case 6, who had Sjögren syndrome, showed hearing improvement after steroid treatment. In contrast, hearing loss in case 5, who had Cogan's syndrome, was not improved by steroids. Although hearing improvement has been described in a patient with Cogan's syndrome [10], it is often difficult to improve hearing loss in such patients.

Previous case reports indicate that the etiology of bilateral SNHL, which deteriorates more slowly than sudden deafness and more quickly than presbycusis, also includes meningeal carcinomatosis [11], metastasis of carcinoma in the bilateral internal auditory canal [12], mitochondrial neurogastrointestinal encephalopathy (MINGIE) [13], and polyarteritis nodosa [14]. These diseases were not found in the present study due to the small size of the study. The rapidly progressive bilateral SNHL can be induced by various types of diseases with different etiologies described above and, moreover, within each type of a disease, severity of symptoms may vary widely between patients. Therefore, further study investigating more patients with rapidly progressive bilateral SNHL is needed to lead to definite conclusions about the importance of clinical manifestations and indications for MRI for diagnosis of the causative diseases.

The definition of rapidly progressive SNHL in previous reports varies, including SNHL deteriorating in days [15] or in weeks to months [14,16–18]. However, the disease entity described in these reports is almost identical, which is the SNHL that progresses more slowly than sudden deafness and more rapidly than presbycusis. Thus, in line with those previous reports, we defined rapidly progressive SNHL as the one that deteriorates in days to months. The time course of rapidly progressive bilateral SNHL compared with that of other types of common bilateral SNHL is illustrated in Figure 3. Idiopathic bilateral SNHL (IBSH) is a progressive bilateral SNHL of unknown etiology and

was proposed as a clinical entity in 1976. In IBSH, hearing loss usually progresses over several years; therefore, deterioration in hearing loss is slower than that observed in the current patients [19], suggesting different etiologies. In the current study, the four patients with isolated inner ear disorders showed a significantly slower deterioration in hearing loss compared with the other patients. IBSH sometimes shows rapid progression of hearing loss within several days or weeks; therefore, patients with similar pathology to that observed in IBSH could meet our criteria for rapidly progressive bilateral SNHL if they visit a hospital in the rapid phase of the disease.

A noteworthy aspect of the patients reported in this study was that early treatment of intracranial lesions and systemic vasculitis improved hearing loss, suggesting the importance of early diagnosis of the causative disease, although further investigation of large numbers of patients is necessary to prove the effectiveness of early treatment. Early diagnosis is also important because the causative diseases for rapidly progressive bilateral SNHL include fatal conditions such as meningitis or malignant diseases, or diseases that may result in irreversible neurological deficits such as superficial siderosis. In patients with superficial siderosis, decreasing the risk for a poor outcome requires early diagnosis of the disease and identification and ablation of the bleeding source [20].

Conclusion

Rapidly progressive bilateral SNHL is rare, but it often develops as a symptom of intracranial disease or systemic vasculitis, both of which are potentially fatal. Hearing may recover in patients who undergo treatment at an early stage of the causative disease. This indicates that early diagnosis followed by appropriate treatment of the causative disease is critical for the management of these patients.

Acknowledgments

We would like to thank Dr Michi Kawamoto and Dr Nobuo Kohara in our institute for advice about diagnosis and treatment of patients. This study was supported by a Grant-in-Aid for Scientific Research (C) (22591894) and a Grant-in-Aid for Young Scientists (B) (22791642) from the Japanese Ministry of Education, Culture, Sports, Science, and Technology.

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

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