大学院医学研究科，信州大学医学部）の倫理委員会の承認を得て行われたものである．

中途失聴者の脳機能

聴覚正常で出生して言語を獲得し，成長した後に何らかの原因で両側高度難聴となった中途失聴者が人工内耳で聴覚入力を再獲得すると，日常会話ではほぼ不自由しない程度の良好な語音弁別が可能になる．言語習得後失聴者の聴覚連合野は語音刺激で強く賦活される[2)～4)]が，言語習得後失聴の人工内耳装用者と健聴者の言語聴取時の脳活動を詳しく比較すると，両者には一致しない部分がある．言語習得後失聴者の画像から健聴者のものを差し引くと，人工内耳装用者では両側の上および中側頭回，ブローカ野（左半球），右半球のブローカ野相当部分，補足運動野，前帯状回において語音認知の際の賦活が有意に強い（図 1）[5)]．これは人工内耳で符号化された，通常より情報量が少なくかつ歪みのある信号をもとに語音認知を行うためには，側頭葉の聴覚連合野でより多くの情報処理が行われると同時に，通常の語音認知ではあまり用いない前頭葉の主として言語の表出に関与する言語領域も活用していると解釈できる．とくに，聴覚連合野（ウェルニッケ野）と前頭葉のブローカ野，ブローカ野と補足運動野の間には解剖学的に線維連絡があり，入力されたあいまいな言語信号をいったん保持し，多くの候補の中から前後関係や文脈に照合してもっとも適切な認知にいたる言語性のワーキングメモリ（図 2）[6)]を形成しているのではないかと推察している[5)]．

先天性高度難聴小児の脳機能検査

一方，先天性あるいは言語を習得する前の乳児期に聴力を失った小児が成長してから人工内耳手術を受けてこれを使い始めても基本的に音声言語を母語とするようにはならず，手話や読話など視覚的な言語を主に用いるようになる．言語習得前失聴者が人工内耳を介して日常会話の言語音を聞いている時の脳血流を計測すると，聴覚連合野の活動がきわめて乏しい事が観察される[4)]．たとえば 8 歳で手術を行った言語習得前失聴小児例では，術後 7 年の時点でも側頭葉の語音による賦活はきわめて低かった．この小児は人工内耳からの音入力に頼らず読話を多用していたが，PET 検査で話者の顔をビデオで呈示すると側頭葉の著明な賦活が観察された（図 3）．すなわち，この小児では，健聴者では聴覚情報処理を行う上側頭回が視覚言語処理を行う方向に発達したと考えられる[7)]．一方，特定の課題を負荷しない安静時の脳の糖代謝を FDG（fluorodeoxyglucose）-PET を用いて先天性高度難聴児で観察した Lee ら[8)]の報告を見ると，低年齢小

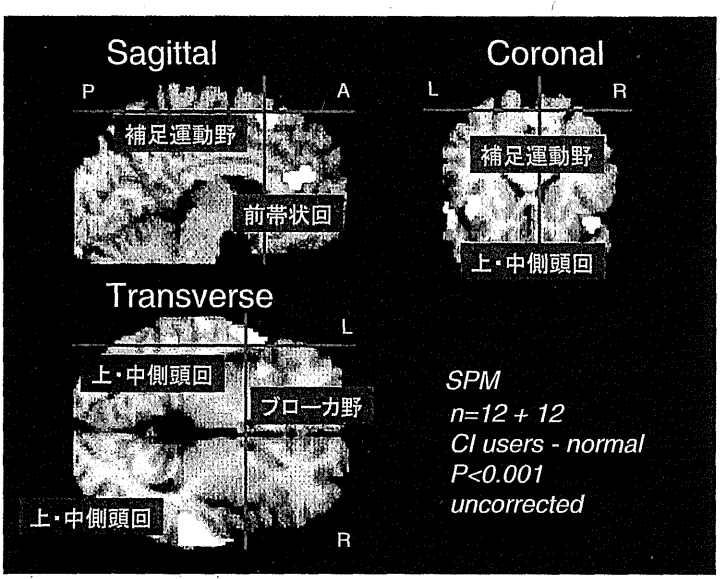

図 1　語音聴取時に言語習得語失聴の人工内耳装用者において健聴者より脳賦活が強い領域
人工内耳装用者では両側の上および中側頭回，ブローカ野（左半球），右半球のブローカ野相当部分，補足運動野，前帯状回において語音認知の際の脳賦活が有意に強い．

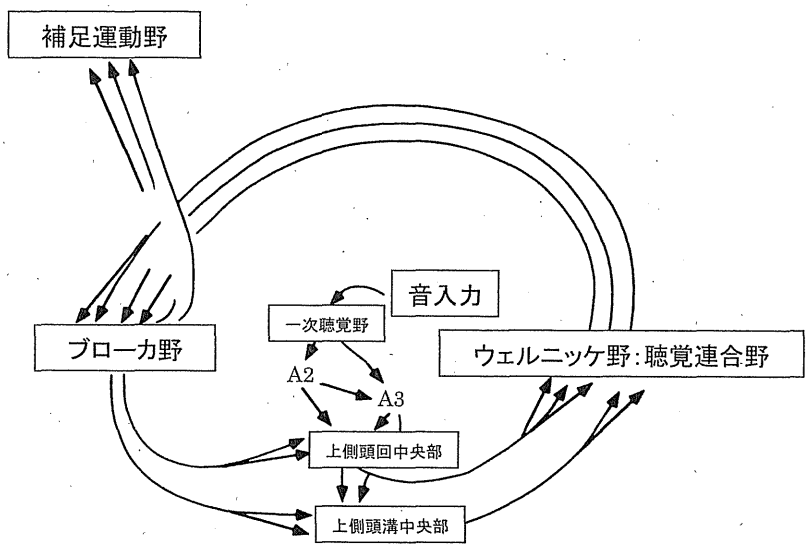

図2　言語の認知と表出を行う領域間を連絡する神経回路
聴覚連合野（ウェルニッケ野）と前頭葉のブローカ野，ブローカ野と補足運動野の間には解剖学的に線維連絡があり，入力されたあいまいな言語信号をいったん保持し，多くの候補の中から前後関係や文脈に照合してもっとも適切な認知にいたる言語性のワーキングメモリを形成しているのではないかと推察される（文献6より改変して引用）．

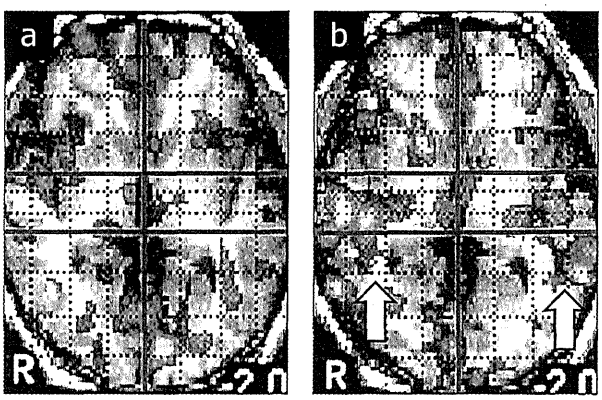

図3　先天性高度難聴児における視覚言語刺激による側頭葉の賦活
患児は8歳時に人工内耳埋め込み術を受けたが，術後7年の時点でも音声言語認知は不良で，人工内耳を介して音声を入力しても側頭葉の血流は増加しなかった（a）が，話者の顔のビデオを見ると上側頭回の血流が著明に増加した（b：矢印）．

児では側頭葉の広い範囲で通常より有意に代謝の低い領域が観察されたが，年齢が高くなるにつれて低代謝領域が小さくなり，20歳前後ではほとんどなくなり，しかも，この低代謝領域が広いほど人工内耳の効果が高い．この論文では，年齢が高くなると音が聞こえないのに聴覚連合野の活動が高くなる理由は解明されていないが，われわれは，おそらく感覚の種類を超えた可塑性（cross-modal plasticity）によって聴覚連合野で視覚情報処理が行われているためであろうと推測している．しかし，ただ「安静」と指示するだけの条件ではFDG静注後に脳がどのような情報処理をしていたかを判断することはできない．

高度難聴小児における視覚と聴覚の拮抗

FDGを静脈注射すると，投与から40分程度の間に生体内の糖代謝が盛んな細胞にFDGがトラップされてそこに留まる．脳においても，FDGの細胞内への取り込み期間中に特定の課題を負荷すると，その処理にかかわる領域にFDGが集積するので，これを脳賦活検査に用いる事もできる．この方法であれば課題負荷が脳スキャンに先行するので，低年齢小児でも覚醒した状態で言語関連課題を負荷した後に全身麻酔を施行することで安定した脳スキャンができる．われわれが幼小児の脳賦活検査にFDG-PETを用いるのは，このような理由による[9]．

高度難聴小児の言語習得方法については，音声言語を使わずに手話を母語とする方針から，聴覚と音声のみを用いる方法まで幅広い選択肢があり，難聴児とその家族は往々にしてどの方向がその児に適するのか判断に窮する．そこでわれわれは，高度難聴小児においてFDG-PET

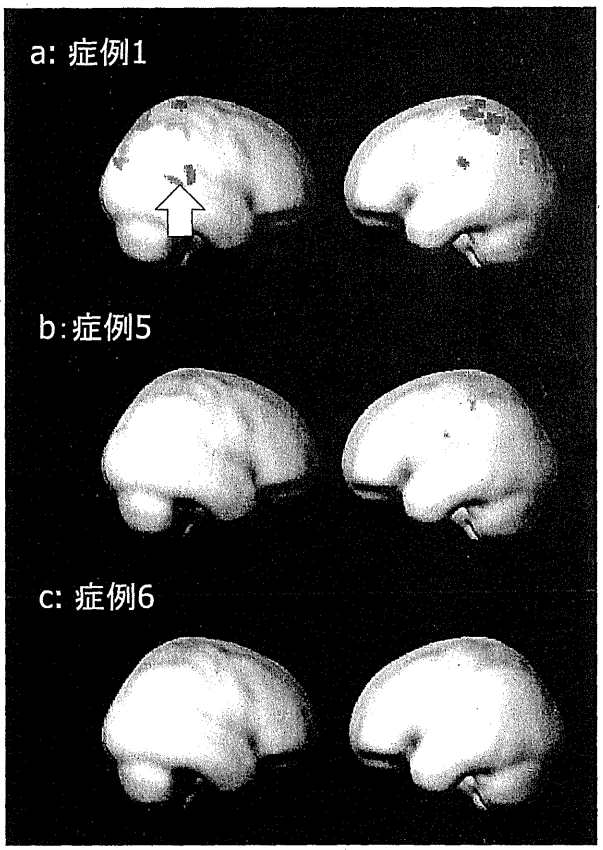

図 4　個々の難聴小児における視覚的言語課題負荷時の代謝亢進部位
聴覚と音声言語の活用が進むと過剰な脳活動が減少する．聴覚活用の程度が相対的に低い例（a：症例 1）では読話による聴覚連合野の有意な賦活がみられるが，聴覚活用の程度が進んだ例（b：症例 5）では聴覚連合野の視覚賦活がなくなっており，高度難聴があっても十分な聴覚活用ができる例（c：症例 6）では読話による脳賦活で健聴成人との間に有意な差がなくなっていた（文献 19 より改変して引用）．

で視覚的言語刺激時の脳代謝を分析することで言語発達期における聴覚と視覚の相互関係について検討した．視覚言語刺激（話者の顔のビデオ画像を無音にしたもの）の結果，難聴小児群で右中心前回（Brodmann Area：BA4），右中心後回（BA3/1/2），左上および下頭頂小葉（BA7, 40），左右の上側頭回（BA22, 42；聴覚連合野），右中側頭回（BA21；聴覚連合野）において，健聴成人より高い賦活が認められ，視覚情報処理の背側経路（上，下頭頂小葉）に加えて聴覚連合野である上および中側頭回が賦活されることが判明した[9]．言語習得前失聴小児では聴覚情報入力が少なく，外部からの聴覚情報入力がないと，側頭連合野でも相対的に視覚処理が優位になると推測される．

高度難聴小児では上記のような代謝亢進だけでなく，海馬傍回で健聴成人に比して有意に代謝が低下していることが観察された．側頭葉内側領域の海馬，海馬傍回は聴覚連合野との線維連絡がある[10]とともに，記憶，学習，言語の意味処理などに重要な役割を果たしており[11)～13)]，高度難聴児においてこの領域の活動が低いことは，難聴が記憶や言語学習に何らかの障害となっている可能性を示す所見と考える．

読話の視覚刺激効果を個々の難聴小児で分析すると[9]，聴覚活用の程度が相対的に低い例（図 4a，症例 1）ではいわゆる聴覚連合野に相当する上および中側頭回の読話による有意な賦活がみられ，側頭連合野が視覚的情報処理を行う方向に分化していることが見て取れる．一方，聴覚活用の程度が進んだ例では，そうでない例に比して代謝の亢進部分が減少して左半球優位となり，聴覚連合野の視覚賦活がなくなっており（図 4b，症例 5），さらに，高度難聴があっても十分な聴覚活用ができる例では読話による脳賦活で健聴成人との間に有意差がなくなっていた（図 4c，症例 6）．これらの結果は，側頭葉の聴覚連合野の機能は生後に使用する言語の種類に応じて分化し，聴覚と音声言語を使用しないと視覚情報処理，それらを使用すれば聴覚情報処理を主に行う領野として分化することを示唆する．

また，Moteki ら[14]は同程度の高度難聴を呈するが異なる遺伝子変異，すなわち *GJB2* および *SLC26A4* 変異に起因する成人高度難聴症例で同様の視覚課題を負荷する FDG-PET 検査を行い，前者で上側頭回の有意な賦活を観察した（図 5）．これは，この 2 者を比べると *GJB2* 変異症例の方が現在までの聴覚活用が不十分で，聴覚連合野で視覚情報処理が行われるようになっていることを示している．高度難聴においては，遺伝子変異を検査することでその病因を確定することができるが，同じ遺伝子変異でもその難聴程度には一定のばらつきがあり，また生後の聴覚活用の状況や療育方針の選択もその後の音声あるいは視覚的言語習得に大きな影響を及ぼす．脳機能画像で側頭連合野の機能分化を評価することは，遺伝子変異の検索だけでは把握できない大脳皮質の言語ネットワークの機能的病態を把握するうえで有用な情報を提供する．

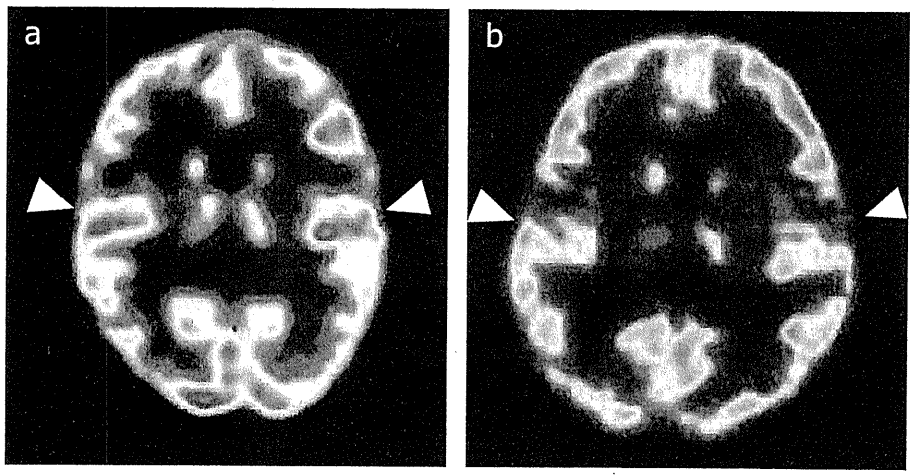

図5　異なる遺伝子変異に起因する高度難聴成人症例の視覚言語負荷による側頭葉賦活
GJB2 (a) および *SLC26A4* (b) 変異に起因する成人高度難聴症例で視覚課題を負荷する FDG-PET 検査を行うと，*GJB2* 変異例で上側頭回の強い賦活（a：矢頭）を観察した（文献 14 より改変して引用）．

まとめ

FDG-PET を用いることで，難聴小児の言語ネットワークにおける視覚と聴覚の相互関係を画像として観察，評価することができ，彼らの治療や教育の方向性を考える新たな情報が得られるものと期待される．

謝　辞

本研究は文部科学省科学研究費補助金基盤研究 C（課題番号 22591894）の援助を受けて行われた．また，本研究の要旨は第 73 回耳鼻咽喉科臨床学会総会・学術講演会サテライトシンポジウム New Trends in Hearing Implant Science—EAS and VSB Workshop in Hakuba— で発表された．

参考文献

1) 内藤　泰：難聴者の脳機能．神経内科 **68**: 456-462, 2008.
2) Naito Y, Okazawa H, Honjo I, et al. : Cortical activation with sound stimulation in cochlear implant users demonstrated by positron emission tomography. Brain Res Cogn Brain Res **2**: 207-214, 1995.
3) Okazawa H, Naito Y, Yonekura Y, et al. : Cochlear implant efficacy in pre- and postlingually deaf subjects. A study with $H_2{}^{15}O$ and PET. Brain **119**: 1297-1306, 1996.
4) Naito Y, Hirano S, Honjo I, et al. : Sound-induced activation of auditory cortices in cochlear implant users with post- and prelingual deafness demonstrated by positron emission tomography. Acta Otolaryngol (Stockh) **117**: 490-496, 1997.
5) Naito Y, Tateya I, Fujiki N, et al. : Increased cortical activation during hearing of speech in cochlear implant users. Hear Res **143**: 139-146, 2000.
6) Roland PE : Language (Chapter 9). Brain activation. pp 269-290, Wiley-Liss, New York, 1993.
7) Naito Y, Hirano S, Fujiki N, et al. : Development and plasticity of the auditory cortex in cochlear implant users: a follow-up study by PET. Adv Otorhinolaryngol (Basel) **57**: 55-59, 2000.
8) Lee DS, Lee JS, Oh SH, et al. : Cross-modal plasticity and cochlear implants. Nature **409**: 149-150, 2001.
9) Fujiwara K, Naito Y, Senda M, et al. : Brain metabolism of children with profound deafness: a visual language activation study by 18F-fluorodeoxyglucose positron emission tomography. Acta Otolaryngol **128**: 393-397, 2008.
10) Tranel D, Brady DR, Van Hoesen GW, et al. : Parahippocampal projections to posterior auditory association cortex (area Tpt) in Old-World monkeys. Exp Brain Res **70**: 406-416, 1988.
11) DeJong RN : The hippocampus and its role in memory. Clinical manifestations and theoretical considerations. J Neurol Sci **19**: 73-83, 1973.
12) Barrash J, Damasio H, Adolphs R, et al. : The neuroanatomical correlates of route learning impairment. Neuropsychologia **38**: 820-836, 2000.
13) Bartha L, Brenneis C, Schocke M, et al. : Medial temporal lobe activation during semantic language processing: fMRI findings in healthy left- and right-handers. Brain Res Cogn Brain Res **17**: 339-346, 2003.
14) Moteki H, Naito Y, Fujiwara K, et al. : Different cortical metabolic activation by visual stimuli possibly due to different time courses of hearing loss in patients with *GJB2* and *SLC26A4* mutations. Acta Otolaryngol **131**: 1232-1236, 2011.

別刷請求先：内藤　泰
〒650-0047 神戸市中央区港島南町2-1-1
神戸市立医療センター中央市民病院耳鼻咽喉科

Yasushi Naito

Kobe City Medical Center General Hospital

臨　　床

遅発性難聴をきたした先天性サイトメガロウイルス感染症例

吉岡三恵子・内藤　泰*

A Case of Delayed-onset Sensorineural Hearing Loss with Congenital Cytomegalovirus Infection

Mieko Yoshioka

(Kobe City Pediatric and General Rehabilitation Center for the Challenged)

Yasushi Naito

(Kobe City Medical Center General Hospital)

Sensorineural hearing loss (SNHL) due to congenital cytomegalovirus (CMV) infection can either be present at birth or develop later in life. We report a 3 years 7 months old boy who gradually developed speech until 3 years of age, but later showed no responses to verbal stimuli.

He was first referred to our clinic for the evaluation of motor delay at 9 months of age and was found to have left hemiparesis. Brain MRI revealed polymicrogyria in the right frontal region. Epileptic seizures began at the age of 13 months. Verbal development was assessed annually using intellectual function testing. He responded to his name at 9 months of age, and imitated words and pointed to objects when asked at 21 months. He could speak several words at 34 months of age. However, around 3 years of age, he stopped saying meaningful words. Audiologic evaluation revealed severe SNHL at 3 years 7 months old. There was no family history of hearing loss, past medical history of ototoxic medications or bacterial meningitis, or craniofacial/auditory anomalies, as possible factors related to the hearing loss. At the age of 7 years 5 months, examination of a dried umbilical cord specimen revealed the presence of CMV DNA. Thus, this patient was diagnosed as having delayed-onset SNHL with asymptomatic congenital CMV infection.

A prospective study is necessary for early detection of delayed-onset SNHL in patients with asymptomatic congenital CMV infection. Testing for the presence of CMV DNA in neonatal urine is performed in cases in which pregnant women are seronegative for CMV-IgG antibody or seropositive for CMV-IgM antibody during the first trimester of pregnancy. Infants diagnosed as having congenital CMV infection are evaluated by a newborn hearing screening test, head CT, ophthalmologic evaluations, and intellectual function testing. Follow-up hearing assessments are performed by both the auditory brainstem response and behavioral audiometry.

Keywords : delayed-onset, sensorineural hearing loss, congenital cytomegalovirus infection, intellectual function testing, dried umbilical cord

はじめに

新生児聴覚スクリーニング検査の普及によって，小児の聴覚障害は早期に発見される例が多くなった．このスクリーニング以降では，3 歳児健診における聴覚検診が

神戸市総合療育センター小児神経科
* 神戸市立医療センター中央市民病院耳鼻咽喉科

法制化されている．最近の調査によると，この3歳児聴覚検診で初めて発見される両側感音難聴児の数は，スクリーニング検査導入前と導入後でほぼ同数であり，新生児聴覚スクリーニング検査が普及しても新生児期以降に発見される難聴児は一定の割合で存在することが示唆されている[1]．

先天性サイトメガロウイルス（CMV）感染症は，非遺伝性の感音難聴をきたす原因の中で主たるものであり，小児の感音難聴の10～60％に認められている[2)~5)]．CMVによる感音難聴は，生下時すでに明らかなこともあるが，生下時には異常がなく生後数年で聴力を失う場合もある[3)~6)]．

今回，われわれは乳児期には聴力に異常がなかったか，あるいは軽度の難聴であったと考えられる症例で，3歳頃に両側高度難聴をきたした男児例を経験した．本症例では定期的な聴覚検査は行えなかったが，月1回の小児神経科での診察とほぼ年1回の発達検査によって聴性行動反応聴力検査[1]に準ずる経過観察を行うことができた．本症例は後天性難聴の原因となる薬剤の使用はなく，難聴の家族歴や難聴を引き起こす代謝性疾患・骨系統疾患・感染症・外傷・腫瘍なども認められず，7歳5ヵ月時に保存臍帯からCMV-DNAを検出して確定診断された．無症候性先天性CMV感染症の遅発性難聴の早期診断には，前方視的な対策が必要であることを強く感じたので報告する．

症　例

症例：3歳7ヵ月，男児．

主訴：聴力障害．

家族歴：難聴や腎疾患はなし．両親と妹は健康．母親は主婦であり，就労はしていない．患児の妊娠7～8ヵ月頃に嘔吐・腹痛をきたし，点滴を受けた．

既往歴：在胎36週5日，頭位自然分娩でApgarスコア7/10点，体重2,056g（－1.6SD），身長44.4cm（－1.0SD），頭囲29.4cm（－2.1SD）で出生した．生後約1時間で血糖30mg/dlであったため，輸液を開始し，以後血糖の低下はなかった．黄疸は生理的範囲で推移し，生後9日目に退院した．1ヵ月健診では体重増加は良好であった．新生児聴覚スクリーニング検査は受けていなかった．

現病歴：4ヵ月健診で頸定はみられなかったが，聴覚についての問診ではとくに異常の訴えはなかった．頸定は6ヵ月になって可能となった．9ヵ月健診で座位がとれないことから，運動発達の遅れの精査のため当センターを紹介された．来院時，寝返りは可能だが仰臥位から引き起こすと反り返りが強かった．座位はとれず，ずり這いや四つ這いによる移動もできなかったため，理学療法が開始された．このときには名前を呼ぶと振り返り，検査玩具は音を鳴らしながら提示すると，すぐに振り向いて手を伸ばして握っていた．生活場面でも興味のある玩具はガラガラや鐘などの音の出る玩具とのことであった．人への関心は高く，周囲の人が移動するとそれを追視したが，発声はアーウーと母音が中心であった（表1）．1歳1ヵ月時に左手の使用が少ないことに気づき，頭部MRIによって右多小脳回が判明した（図1）．この頃から顔面を紅潮させ，眼球を上転し体を反らせる強直発作が始まり，脳波には異常を認めなかったが，抗てんかん薬（フェノバルビタール）の投与が開始された．原因究明のため，染色体・血液および尿のアミノ酸分析，胎内感染の有無，脳波などの検査が行われたが，CMV抗体価の高値以外には著変を認めなかった（表2）．患児が1歳5ヵ月時に母の第二子妊娠が判明し，母のCMV抗体価を検査したところ，IgG，IgM抗体の上昇が認められた（表2）．2歳2ヵ月頃にけいれんが再発し，抗てんかん薬を2剤併用（フェニトインの追加）としたところ，現在に至るまで5年以上発作を認めていない．脳波では2歳11ヵ月時に入眠中，右優位の徐波や棘徐波を時に認めた（表2）．

表1　発達検査

検査時年齢	発達検査法	発達指数（DQ）	発達年齢（DA）	姿勢・運動（K式） 運動（津守式） 運動（KIDS）	認知・適応（K式） 探索・操作（津守式） 操作（KIDS）	言語・社会（K式） 理解・言語（津守式） 理解言語・表出言語（KIDS）
9ヵ月	K式	59	6ヵ月	5ヵ月	6ヵ月	7ヵ月
1歳9ヵ月	K式	49	11ヵ月	9ヵ月	10ヵ月	13ヵ月
2歳10ヵ月	津守式	35	12ヵ月	11ヵ月	12ヵ月	11ヵ月
5歳2ヵ月	KIDS	26	16ヵ月	20ヵ月	15ヵ月	11ヵ月・10ヵ月

K式：新版K式発達検査2001，津守式：津守・稲毛による乳幼児精神発達質問紙，KIDS：KIDS乳幼児発達スケール

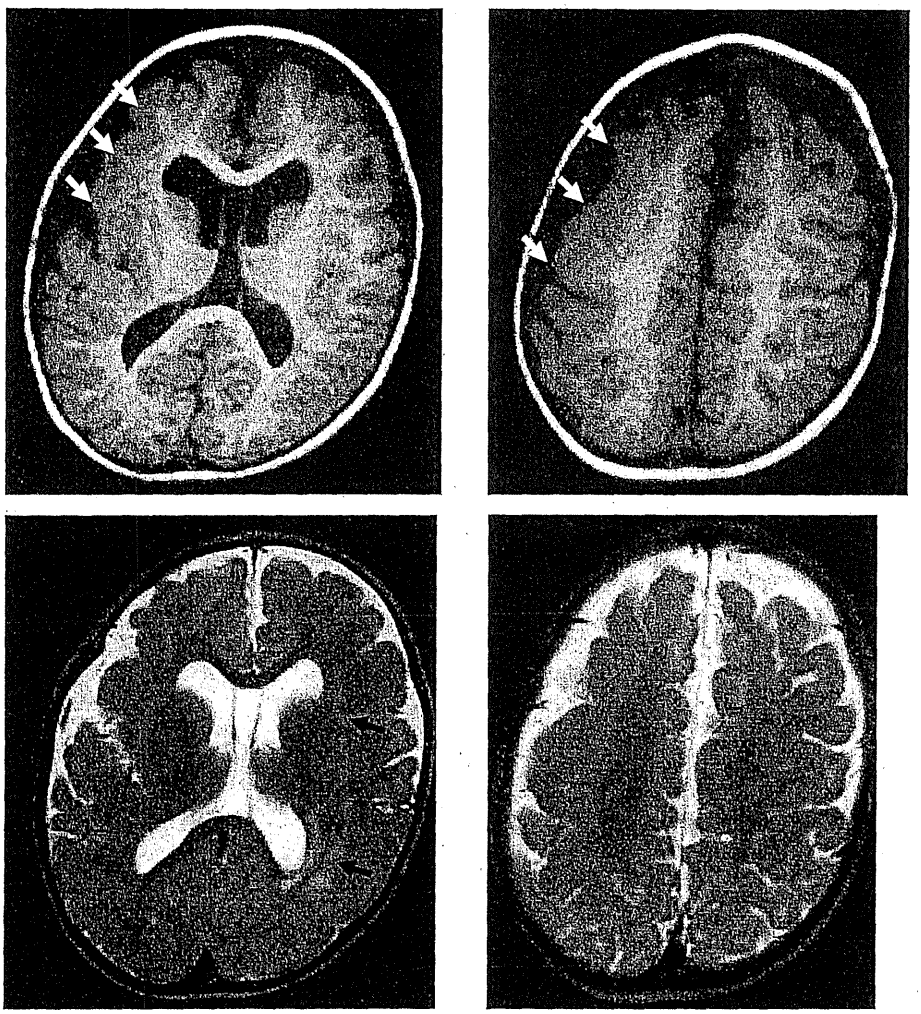

図1　1歳2ヵ月時の頭部MRI所見（上段：T1強調画像，下段：T2強調画像）
右前頭葉から島にかけて皮質は厚く，脳回は浅く，脳のボリュームは左に比べ乏しくなっていて，多小脳回と考えられる（白矢印）．両側大脳白質は一部，T2強調画像で淡い高信号域を示しており（黒矢印），髄鞘化の遅れが認められる．

以後の運動発達は，四つ這い1歳9ヵ月，独り歩き2歳11ヵ月と進んでいった．言語発達については月1回の小児神経科診とほぼ年1回の発達検査で詳しく調べられていた（表1）．1歳9ヵ月時には大人の言葉の模倣もあり，場面にあった自発的な言葉もみられていた．また，呼名で挙手し，「おいで」や禁止の指示も理解していた．定位および可逆の指差しもみられていた．2歳10ヵ月時には日常的に使う言葉は理解し，自宅では患児が2歳1ヵ月時に生まれた妹の名前を呼び，単語もいくつかみられていた．しかし，3歳頃から以前までしていた返事をまったくしなくなり，有意語も消失したため，3歳7ヵ月時に聴性脳幹反応（ABR）や聴性定常反応（ASSR）などの聴覚検査を受け，両側高度難聴が判明した（表2）．このときに尿からのCMVウイルスの分離を行ったが陰性であった（表2）．また，側頭骨CTでは内耳や内耳道には異常がなく，眼底所見を含め，眼部には器質的異常を認めなかった．以後，補聴器を装用し，音に対する反応は改善しているが，言語発達はほとんどみられていない（表1）．7歳5ヵ月時，両親の了解を得て保存臍帯からのCMV-DNAの検出を行ったところ陽性であった．同時に患児にはムンプスの既往歴はなかったが，ムンプスの血清抗体価を検査したところ上昇がみられ，不顕性感染と考えられた（表2）．

表2　検査成績

検査時年齢	検査項目
1歳2ヵ月	染色体分析（Gバンド）：異常なし 血漿・尿アミノ酸分析：異常なし 血液乳酸：14.1 mg/dl（基準値　3.0～17.0） 血液ピルビン酸：0.86 mg/dl（基準値　0.30～0.94） CMV抗体（CF法）：32倍（基準値　4倍以下） トキソプラズマ抗体（PHA法）：160倍未満（基準値　80倍未満） 単純ヘルペス抗体（CF法）：4倍未満（基準値　4倍未満） 風疹ウイルス抗体（HI法）：8倍未満（基準値　8倍未満） 脳波：基礎波に異常なく，突発波も認められない
1歳9ヵ月	母のCMV抗体価（EIA法）IgG/IgM：90.1/2.25 U/mL （基準値　2/0.8）
2歳11ヵ月	脳波：入眠中，右優位の3～4 Hzの徐波や棘徐波が散在
3歳7ヵ月	聴性脳幹反応（ABR）：両側105 dBで無反応
3歳8ヵ月	聴性定常反応（ASSR）（↑：scale out） Hz　500　1000　2000　4000 右（dB）　110↑　110↑　110↑　110↑ 左（dB）　110↑　110　110↑　110↑ 条件詮索反応聴力検査（COR） Hz　250　500　1000　2000　4000 dB　85　100↑　110↑　110↑　90↑ 尿からのCMVウイルス分離：陰性 側頭骨CT：内耳や内耳道には異常なし
4歳6ヵ月	眼底所見を含め，眼部には器質的な異常なし
7歳5ヵ月	保存臍帯からのCMV-DNAの検出：陽性 ムンプスウイルス抗体価（EIA法）IgG：14.1 U/mL （基準値　2.0未満）

注：陽性所見には下線を引いた

考　察

本症例では3歳過ぎまで聴覚検査は行われていないが，月1回の小児神経科での診察とほぼ年1回の発達検査から聴力に関する所見をみていくと，少なくとも2歳10ヵ月までは遅いながらも言語発達がみられ，軽度難聴の可能性は否定できないが，高度難聴を疑わせるような所見は認められなかった．一般に，健聴児では，言語能力は認知能力と同一の程度を示すが，難聴児では両者の差が大きく，とくに難聴の発見が生後6ヵ月以後と遅れた場合には，言語能力が認知能力に比べて著しく劣ると報告されている[7]．これは認知能力の低い児においても同様に認められている．本症例では，9ヵ月および1歳9ヵ月時の新版K式発達検査ではむしろ言語・社会領域が認知・適応領域を上回っていた（表1）．また，2歳10ヵ月時に行われた津守・稲毛式検査でも探索・操作項目と理解・言語項目の成績に大きな差はないことから，この頃まではある程度の聴力は保たれていて，以後急激に低下していったと考えられる．

以上より，本症例の難聴についてはまず後天性難聴が疑われるが，原因となる抗生剤やβ-ブロッカー，化学療法剤などの薬剤の投与はなく，脊髄小脳変性症や遺伝性運動感覚ニューロパチーなどの遺伝性神経疾患は認められなかった．また，甲状腺機能低下症などの代謝性疾患，Apert症候群・Crouzon病などの骨系統疾患はなく，3歳8ヵ月時の側頭骨CTではとくに異常はなく，外傷による錐体部分の骨折や聴神経腫瘍・コレステリン腫などは否定された．感染症としては化膿性髄膜炎によって片側性または両側性難聴が10%に起こるとされているが，本症例にはその既往はなかった．ウイルス性発疹症である水痘・ムンプス・麻疹などで急激な難聴を引き起こすことも知られているが，本症例では麻疹は乳児期にワクチン投与を受け，水痘は難聴発症後に罹患していた．ムンプスの罹患歴はないとのことであったが，念のため7歳5ヵ月時に血清抗体価を調べると上昇がみられていた．ムン

プスでは10万人に0.5～5.0人に難聴がみられるとされてきたが，最近ではより高い発生頻度を示す報告が多い[8]．通常，ムンプス難聴は一側耳に生じるが，その10～15%が両側性であるとの報告もみられる[8]．不顕性感染による難聴も報告されているが，その頻度はムンプス難聴の5～7%とされている[8]．本症例では，難聴が両側性であることや，ムンプスが不顕性感染であったこと，乳児期早期からの精神運動発達遅延や脳奇形の存在，さらにてんかんの合併などを総合的に説明する機序として，ムンプスよりも先天性CMV感染症を考えるほうが妥当と考えられる．また，患児が1歳5ヵ月時，母の第二子妊娠が判明し，母のCMV抗体価が検査され，IgG，IgM抗体の上昇が認められている．しかし，IgM抗体は初感染後6ヵ月以上高値を続けることもあるので，感染時期を決めるのには使うことはできないと考えられる．

新生児期に尿や唾液からCMVウイルスを分離して診断された無症候性先天性CMV感染症307例の聴力を経時的に観察した前方視的研究[6]では，22例（7.2%）に難聴が認められていた．このうち，50%に進行性難聴がみられ，2～70ヵ月（平均18ヵ月）で最初の進行が認められていた．一方，初回あるいは初回から数回の聴力検査では異常がなく，25～62ヵ月（平均27ヵ月）後に難聴をきたした遅発性難聴の症例は22例中に4例あり，このうち両側性難聴をきたしたのは1例であった．進行性・遅発性難聴をきたした時期については，本症例もこの報告の時期の範囲内に入っている．また，同様の報告はわが国からも行われており，新生児聴覚スクリーニング検査では両耳とも良好と判定されていたのに，1歳頃から音に対する反応が悪くなり，19ヵ月時には言語発達遅延に気づかれて，両側難聴が明らかになった例も報告されている[9]．したがって，新生児聴覚スクリーニング検査だけでは進行性・遅発性難聴の診断には不十分であり，継続的な聴力検査が必要と考えられる．

無症候性先天性CMV感染症による遅発性難聴の早期発見・早期治療のためには，前方視的な対策が必要である[6)9)10)]．すでに神戸市においても大学や一部の医療機関にて行われているが，まず全妊婦に対し，妊娠初期にCMV-IgG，IgMの検査を行い，CMV-IgGが陰性またはIgM陽性で初感染が疑われ，羊水CMVが陽性の場合には産科で妊婦および胎児にCMV高力価免疫グロブリンの投与などを行いながら経過観察を行う．また，妊婦に初感染が疑われた新生児には生後1週間以内に尿中CMV同定（DNAないしウイルス分離）を行う．これが陽性の児については，新生児聴覚スクリーニング検査，眼科的精査，頭部CTなどに加えて，継続的に必要な検査としてABRと聴性行動反応聴力検査を行っていく．さらに，新生児期に難聴などの臨床症状を示す症候性の例には，CMV高力価免疫グロブリンやバルガンシクロビル[11]が投与されている．これらの治療によって，難聴や発達などの神経学的予後の改善が示唆され，長期投与に伴う副反応も軽微であったと報告されている[11]．一方，難聴が判明した例には，難聴の程度や年齢に応じて補聴器の装用や人工内耳手術が行われている．今後，これらの対策を個々の事例だけでなく，医療圏全体において確実かつ円滑に行うためには，地域の耳鼻咽喉科・産科・小児科および保健行政の緊密な連携が必須である．このような前方視的対策により，無症候性先天性CMV感染症児の難聴の早期発見・早期治療が有効に行えると期待される．

まとめ

われわれは乳児期には聴力に異常がなかったか，あるいは軽度の難聴であったと考えられる例で，3歳頃に両側高度難聴をきたした男児例を経験した．本症例は難聴の家族歴や後天性難聴の原因となる薬物の使用や疾患も認められず，7歳5ヵ月時に保存臍帯からCMV-DNAを検出して診断された．先天性CMV感染症の大部分は不顕性であるため，新生児聴覚スクリーニング検査以後に起こる遅発性難聴の早期診断には前方視的対策が必要である．今後，全妊婦に対し妊娠早期にCMV抗体価検査を行って，CMV感染の疑われる新生児には尿CMV同定を施行し，これが陽性である例には継続的な聴力検査をして，遅発性難聴の早期発見が望まれる．

謝　辞

保存臍帯からのCMV-DNA検出を行っていただきました大阪府立母子保健総合医療センター検査科　中山雅弘先生および竹島俊一先生に深謝いたします．

本論文の要旨は第48回日本小児神経学会近畿地方会（2010年10月9日，守口市）において発表した．

参考文献

1）山下裕司，森田訓子，氏田直子：難聴児の療育．Audiol Jpn 52：139-151, 2009.
2）Cheeran MC, Lokensgard JR and Schleiss MR：Neuropatho-

genesis of congenital cytomegalovirus infection: disease mechanisms and prospects for intervention. Clin Microbiol Rev 22: 99-126, 2009.
3) Ogawa H, Suzutani T, Baba Y, et al.: Etiology of severe sensorineural hearing loss in children: independent impact of congenital cytomegalovirus infection and *GJB2* mutations. J Infect Dis 195: 782-788, 2007.
4) Tagawa M, Tanaka H, Moriuchi M, et al.: Retrospective diagnosis of congenital cytomegalovirus infection at a school for the deaf by using preserved dried umbilical cord. J Pediatr 155: 749-751, 2009.
5) 吉岡三恵子，内藤　泰：最近10年間の感音難聴児の病因と発症率について．日児誌 112: 1813-1817, 2008.
6) Fowler KB, McCollister FP, Dahle AJ, et al.: Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. J Pediatr 130: 624-630, 1997.
7) Yoshinaga-Itano C, Sedey AL, Coulter DK, et al.: Language of early- and later-identified children with hearing loss. Pediatrics 102: 1161-1171, 1998.
8) 井上泰宏：ムンプス難聴．Audiol Jpn 51: 617-623, 2008.
9) Iwasaki S, Nakanishi H, Misawa K, et al.: Cochlear implant in children with asymptomatic congenital cytomegalovirus infection. Audiol Neurootol 14: 146-152, 2009.
10) 山田秀人：D. 産科疾患の診断・治療・管理．18. 産科感染症の管理と治療．日産婦会誌 60: 132-136, 2008.
11) 藤枝憲二，森内浩幸，吉川哲史，他：全新生児を対象とした先天性サイトメガロウイルス（CMV）感染スクリーニング体制の構築に向けたパイロット調査と感染児臨床像の解析エビデンスに基づく治療指針の基盤策定．平成21年度厚生労働科学研究成果データベース（2009年7月16日公開，http://mhlw-grants.niph.go.jp/niph/search/NISR00.do）

原稿受付：2012年4月25日
原稿採択：2012年7月18日
別刷請求先：吉岡三恵子
〒653-0875 神戸市長田区丸山町2-3-50
神戸市総合療育センター小児神経科

Acta Oto-Laryngologica, 2012; 132: 420–427

informa
healthcare

ORIGINAL ARTICLE

Cochlear implantation in children with congenital cytomegalovirus infection accompanied by psycho-neurological disorders

HIROSHI YAMAZAKI[1,4], RINKO YAMAMOTO[1], SABURO MOROTO[1], TOMOKO YAMAZAKI[1], KEIZO FUJIWARA[1], MASAKO NAKAI[2], JUICHI ITO[3] & YASUSHI NAITO[1,4]

[1]*Department of Otolaryngology, Kobe City Medical Center General Hospital,* [2]*Shiga Medical Center for Children,* [3]*Kyoto University and* [4]*Institute of Biomedical Research and Innovation, Japan*

Abstract

Conclusion: Cochlear implantation was effective for deaf children with congenital cytomegalovirus (CMV) infection, but their cochlear implant (CI) outcomes were often impaired, depending on the types of CMV-associated psycho-neurological disorders. Evaluation of cognitive development and autistic tendency of implantees might be useful to predict their CI outcomes. *Objectives*: To reveal the influence of CMV-associated psycho-neurological disorders on CI outcomes. *Methods*: This was a retrospective evaluation of 11 implantees with congenital CMV infection (CMV-CIs) and 14 implantees with autosomal recessive hearing loss (genetic-CIs). *Results*: Nine of 11 CMV-CIs suffered from psycho-neurological disorders; one from attention deficit hyperactivity disorder, two from pervasive developmental disorder, and six from mental retardation. Aided hearing thresholds with CIs in the two groups did not differ, but two autistic and two mentally retarded CMV-CIs showed significantly low scores in speech discrimination tests. Language-Social (L-S) developmental quotients (DQs) evaluated by the Kyoto Scale of Psychological development were improved after the implantation in both groups, but the postoperative increase of L-S DQs was significantly smaller in the CMV-CIs than that of genetic-CIs. Interestingly, the postoperative L-S and Cognitive-Adaptive (C-A) DQs showed statistically significant correlation in all cases except for two autistic CMV-CIs whose L-S DQs were much lower than those expected from their C-A DQs.

Keywords: *Cochlear implant, pervasive developmental disorder, PDD, autistic, language development, cognitive development*

Introduction

Congenital cytomegalovirus (CMV) infection is a leading cause of developmental disability and hearing loss in children [1] and affects 0.6–0.7 of liveborn babies in the industrialized countries [2]. CMV, belonging to the herpes virus family, is widely distributed and usually innocuous in immunocompetent adults, but the primary infection or reinfection in pregnant women leads to congenital CMV infection of the infants. Approximately 10% of infants with congenital CMV infection exhibit clinically apparent signs at birth, such as growth retardation, prematurity, hepatomegaly, splenomegaly, thrombocytopenia, jaundice, petechiae, microcephaly, seizures, and abnormal neurologic findings (symptomatic congenital CMV infection). The rest are asymptomatic at birth (asymptomatic congenital CMV infection), but are at risk of CMV-associated disorders later in life. In all, 60–90% of those with symptomatic congenital CMV infection and 10–15% of those with asymptomatic infection develop long-term neurological sequelae including neurodevelopmental disorders and/or sensorineural hearing loss [3].

Hearing loss, which is a common manifestation of congenital CMV infection, is often late-onset and progressive within the first 6 years of life in children [3]. CMV-associated hearing loss is reported to

Correspondence: Yasushi Naito MD PhD, Department of Otolaryngology, Kobe City Medical Center General Hospital, 2-1-1 Minatojima Minamimachi Chuo-ku, Kobe City 650-0047, Japan. Tel: +81 78 302 4321. Fax: +81 78 302 2487. E-mail: naito@kcho.jp

(Received 4 October 2011; accepted 11 December 2011)

ISSN 0001-6489 print/ISSN 1651-2251 online
DOI: 10.3109/00016489.2011.653442

account for 15–20% of congenital and late-onset deafness and CMV is a main cause of nongenetic hearing loss [1]. In nonsyndromic genetic hearing loss, the disorders are usually limited within the inner ears, but congenital CMV infection leads to neurodevelopmental disorders including mental retardation (MR), pervasive developmental disorder (PDD), attention deficit hyperactivity disorder (ADHD), and motor dysfunction in addition to hearing loss. Cochlear implants (CIs) bypass the damaged hair cells in the inner ears, but cannot compensate the disorders of the central nervous system. Until now, the influence of CMV-associated neurodevelopmental disorders on CI outcomes has not been revealed well. Therefore, we examined implanted children with congenital CMV infection to address this question.

Material and methods

A total of 150 children who were implanted at Kobe City Medical Center or Kyoto University from 2004 to 2010 and received language rehabilitation at Kobe City Medical Center or Shiga Medical Center for Children were included in this study. Among them, 11 children were diagnosed with congenital CMV infection by the detection of CMV-DNA from their blood or urine at birth or from their dried umbilical cords using a polymerase chain reaction (PCR)-based assay [4]. We retrospectively examined these 11 implanted children with congenital CMV infection (CMV-CIs: CMV-1 to -11) and compared their CI outcomes with those of 14 implanted children with genetic hearing loss (genetic-CIs). In this study, we defined 'genetic-CI' by autosomal recessive inheritance, i.e. having parents with normal hearing as well as at least one brother or sister with hearing loss. The mean ages at implantation of CMV-CIs and genetic-CIs were 37.5 and 28.2 months, respectively, and the mean durations of deafness were 29.8 and 27.4 months, respectively. As shown below, 3 of 11 CMV-CIs had late-onset deafness and, therefore, the mean age at implantation of CMV-CIs was higher than that of genetic-CIs, but the mean durations of deafness were comparable between the two groups. In our study, only one genetic-CI was diagnosed with compound heterozygotes for GJB2 mutations using the invader assay technique [5], but the remaining genetic-CIs did not receive any genetic tests. All children underwent implantation with Nuclear devices (Cochlear Corporation).

We evaluated the CI outcomes of CMV-CIs and genetic-CIs by testing four different aspects of the auditory perceptual ability: (1) hearing threshold, (2) closed-set infant word discrimination, (3) open-set monosyllabic word discrimination, and (4) language development evaluated by Kyoto Scale of Psychological Development (K-test). Each aspect is thought to reflect a different level of the auditory perceptual ability. Speech discrimination tests were performed in a sound-controlled room with live voice or recorded stimuli presented at 70 dB SPL. In the evaluation of language development, we used the K-test, which is one of the most widely used standardized developmental tests in Japan [6]. In the K-test, three categories of a child's development including Postural-Motor (P-M; fine and gross motor functions), Cognitive-Adaptive (C-A; non-verbal reasoning or visuospatial perceptions), and Language-Social (L-S; interpersonal relationships, socializations, and verbal abilities) are assessed separately [6]. In the evaluation, we used a developmental quotient (DQ), which is determined as a percentage of the developmental age divided by the chronological age. In the K-test, developmental delay is defined by DQ below 80. We analyzed data for speech discrimination, language development and communication mode of CMV-4 at 11 months after the implantation and those of CMV-1 to CMV-9 except for CMV-4 at 2–3 years after the surgery.

The use of human subjects in this study was approved by the Research Ethics Committee of the Kobe City Medical Center General Hospital. The statistical analysis of difference in hearing thresholds and postoperative increase of L-S DQs (postoperative minus preoperative L-S DQs) between CMV-CIs and genetic-CIs was performed using the Mann-Whitney U test. Statistical analysis of difference in preoperative and postoperative L-S DQs and correlation between the L-S DQ and the C-A DQ in each implantee were performed using the Wilcoxon signed-ranks test and the Spearman rank correlation coefficient, respectively. A p value < 0.05 was considered significant.

Results

Details of CMV-CIs

Severe hearing loss of CMV-1, -3, and -4 was late-onset, while the others were deaf at birth. Their neurodevelopmental disorders, including psycho-neurological disorders and motor disorders, were assessed by pediatric neurologists. Eight CMV-CIs were delayed in motor development, which will not be discussed in this paper. CMV-1 and -2 were not diagnosed as having any psycho-neurological disorders. CMV-3 was diagnosed with ADHD, CMV-8 and CMV-9 were autistic and diagnosed with PDD. The remaining six CMV-CIs were

Table I. Details of CMV-CIs.

Subject no.	Onset of severe HL (months)	Age at implantation (months)	Duration of follow-up (months)	CMV-associated neurodevelopmental disorders		Communication mode
				Psycho-neurological	Others	
CMV-1	5	33	38			OC
CMV-2	0	25	36		Motor	OC
CMV-3	32	64	56	ADHD		OC
CMV-4	48	63	11	MR	Motor	OC
CMV-5	0	53	55	MR	Motor	TC
CMV-6	0	43	36	MR		OC
CMV-7	0	28	28	MR	Motor	TC
CMV-8	0	28	37	PDD	Motor	SL
CMV-9	0	38	24	PDD	Motor	SL
CMV-10	0	15	10	MR	Motor	not determined
CMV-11	0	23	10	MR	Motor	not determined

Severe hearing loss of CMV-1, -3, and -4 was late-onset, while the others were deaf at birth. CMV-associated neurodevelopmental disorders were divided into psycho-neurological disorders and others including motor dysfunctions. Communication mode with CI of CMV-10 and -11 were not determined because they had used CI for less than one year and they were too young for accurate evaluation. ADHD, attention deficit hyperactivity disorder; Motor, motor dysfunctions; MR, mental retardation; OC, oral communication; PDD, pervasive developmental disorder; SL, sign language; TC, total communication.

mentally retarded (Table I). The psycho-neurological disorders including ADHD, MR, and PDD accounted for over 80% in CMV-CIs, but were not identified in genetic-CIs. The incidence of neurodevelopmental disorders was significantly higher in the congenital CMV-infected children than the controls (Table II).

CI outcomes in CMV-CIs and genetic-CIs

Both CMV-CIs and genetic-CIs showed 30–40 dB of aided hearing thresholds with CIs and their hearing thresholds did not differ at tested frequencies, including 250, 500, 1000, 2000, and 4000 Hz ($p > 0.05$) (Figure 1).

In the speech discrimination and language development tests, we examined 9 of 11 CMV-CIs. Two subjects, CMV-10 and CMV-11, were under 3 years old and too young for accurate speech discrimination examinations. Among the nine CMV-CIs, two autistic CMV-CIs (CMV-PDDs) showed significantly

Table II. The proportion of each psycho-neurological disorder (%) in CMV-CIs and genetic-CIs.

Group	Psycho-neurological disorder				
	ADHD	MR	PDD	None	Total
CMV-CI ($n = 11$)	9.1	54.5	18.2	18.2	100.0
Genetic-CI ($n = 14$)	0.0	0.0	0.0	100.0	100.0

ADHD, attention deficit hyperactivity disorder; CMV-CI, cochlear implanted children with congenital CMV infection; genetic-CI, cochlear implanted children with genetic hearing loss; MR, mental retardation; PDD, pervasive developmental disorder.

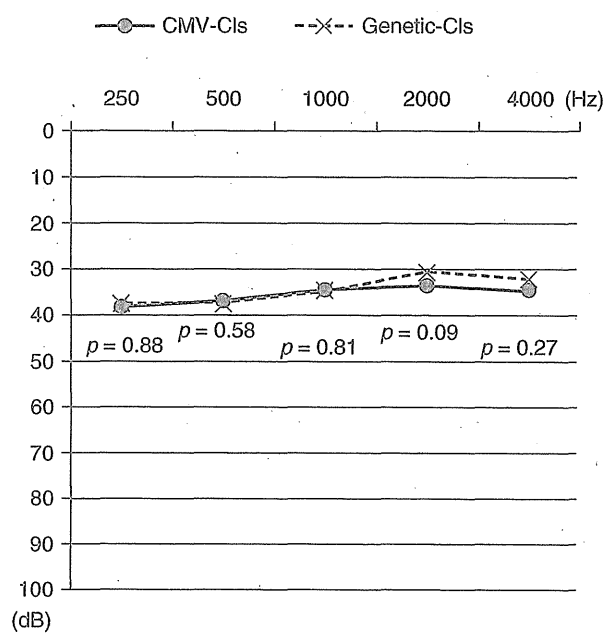

Figure 1. Aided hearing thresholds with cochlear implants (CIs) in CMV-CIs and genetic-CIs. Hearing thresholds of pure tone sounds were comparable between the two groups at all tested frequencies, 250, 500, 1000, 2000, and 4000 Hz ($p > 0.05$). CMV-CI, cochlear implanted children with congenital CMV infection; genetic-CI, cochlear implanted children with genetic hearing loss.

lower scores in both the closed-set infant word and open-set monosyllabic word discrimination tests than genetic-CIs. In addition to them, two of four mentally retarded CMV-CIs (CMV-MRs) showed low scores, 50 and chance level, only in the monosyllabic word discrimination test. The scores of the remaining CMV-CIs were comparable to those of genetic-CIs (Figure 2).

Figure 3 shows the preoperative and postoperative L-S DQs of CMV-CIs and genetic-CIs. The duration of CI usage of CMV-4 who had perilingual deafness was 11 months at the time of testing, while the others were examined at 2 or 3 years after the surgery. The L-S DQs of both groups improved significantly after implantation ($p < 0.05$ and $p < 0.01$, respectively), but the increase of L-S DQ was significantly smaller in the CMV group than the genetic group ($p < 0.05$).

Correlation between C-A DQs and L-S DQs

In Figure 4, each implantee is plotted based on their C-A DQ and L-S DQ in the K-test. Figure 4A and B show data before and after the implantation, respectively. The CMV-CIs with ADHD (CMV-ADHD), CMV-MRs, CMV-PDDs, CMV without these psycho-neurological disorders (CMV-others), and genetic-CIs are represented by different markers. Before the operation, L-S DQs varied widely, even if the C-A DQs were similar. After the implantation, however, the correlation between L-S and C-A DQs of both CMV-CIs and genetic CIs became clearer and statistically significant ($p < 0.01$).

Types of communication mode

A choice of communication mode is also important for children to achieve their best language performance [7]. As shown in Table I, both the autistic CMV-CIs used sign language, three of four CMV-MRs chose total communication, and the remaining implantees with higher L-S DQ could communicate orally.

Discussion

In this study, we examined 11 CMV-CIs and investigated (1) details of CMV-associated psycho-neurological disorders, (2) varying outcomes of CI between CMV-CIs and genetic-CIs, and (3) how to predict CI outcomes of CMV-CIs.

The percentage of congenital CMV infection among all implantees was only 7.3% (11 of 150) in our study and smaller than 15–20%, which was reported in previous studies [1]. Since newborn screening of congenital CMV infection is not yet common in Japan, it is possible that we overlooked some congenitally CMV-infected children, especially

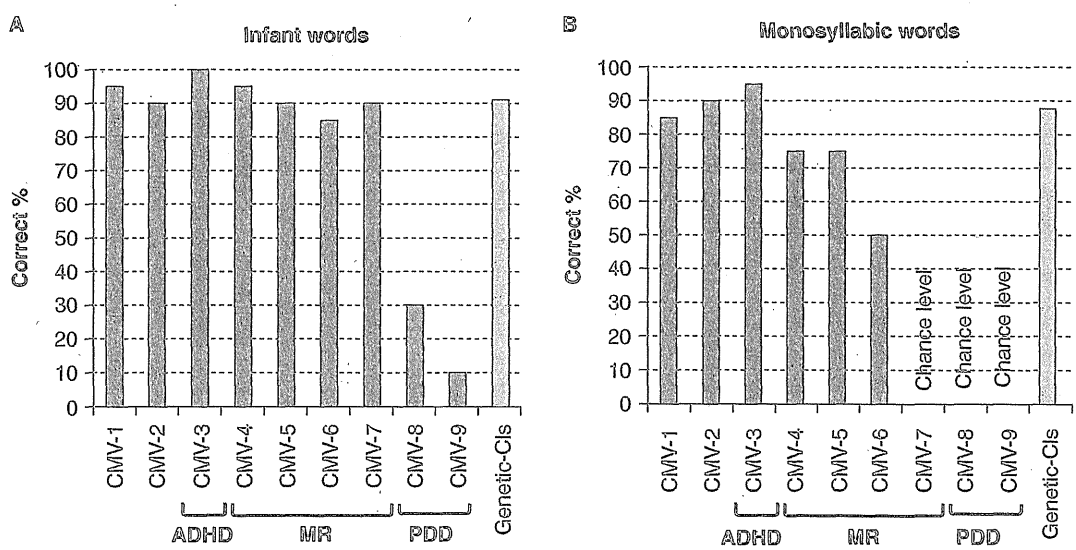

Figure 2. Scores (correct %) in speech discrimination tests using infant words (A) and monosyllabic words (B) in CMV-CIs (cochlear implanted children with congenital CMV infection) and genetic-CIs (cochlear implanted children with genetic hearing loss). The correct percentage of each CMV-CI and the mean score of 14 genetic-CIs are shown. The percentage of correct answers by chance is represented as 'chance level.' CMV-associated psycho-neurological disorders are described below the subject's numbers. The correct percentages of autistic CMV-CIs (CMV-8 and CMV-9) were extremely low, equal to or below 30 in infant word discrimination and chance level in monosyllabic word discrimination. CMV-6 and CMV-7 showed low correct percentages in monosyllabic word discrimination, 50 and chance level, respectively, but in infant word discrimination they performed as accurately as genetic-CIs. ADHD, attention deficit hyperactivity disorder; MR, mental retardation; PDD, pervasive developmental disorder.

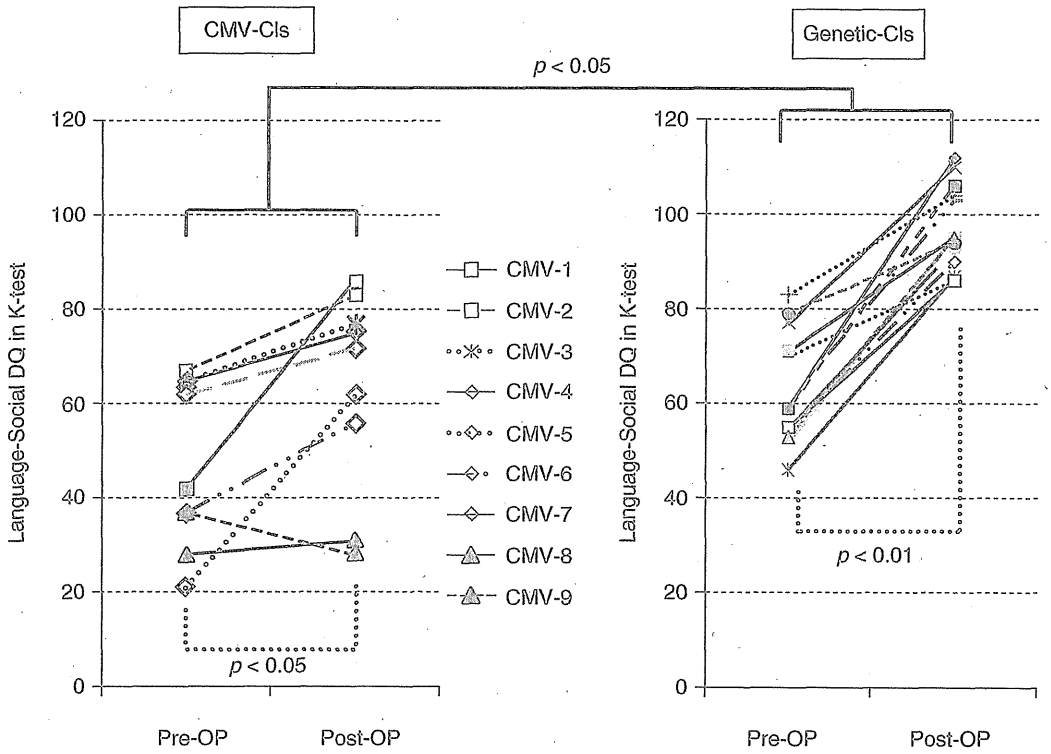

Figure 3. Changes of Language-Social (L-S) developmental quotients (DQs) in the K-test after cochlear implantation in CMV-CIs (cochlear implanted children with congenital CMV infection) and genetic-CIs (cochlear implanted children with genetic hearing loss). The preoperative (pre-OP) and postoperative (post-OP) L-S DQs in the K-test of 9 CMV-CIs and 14 genetic-CIs are plotted. L-S DQs showed statistically significant increase in both CMV-CIs and genetic-CIs ($p < 0.05$ and < 0.01, respectively), but the amount of increase in L-S DQs was significantly smaller in CMV-CIs than that of genetic-CIs ($p < 0.05$). Moreover, postoperative L-S DQs of all genetic-CIs exceeded 80 after the implantation, but all CMV-CIs except for two without any CMV-associated psycho-neurological disorders showed postoperative L-S DQs below 80.

those whose only CMV-associated manifestation was hearing loss.

A considerable proportion of CMV-CIs suffered from psycho-neurological disorders, while none of the genetic-CIs had any neurodevelopmental disorders. It is well known that congenital CMV infection leads to MR [8], but its causal relationship to ADHD and PDD has not been proven. The cause of autism has not been fully revealed, but genetic factors are proven to play an important role in the development of this disorder [9]. Other than genetic factors, environmental factors including congenital viral infection are thought to contribute to the etiology of autistic disorders in some cases and several reports showed that congenital CMV infection is sometimes associated with autistic disorder [10,11]. Therefore, it is possible that congenital CMV infection might have played a role in the development of autism in our two cases.

CMV-associated psycho-neurological disorders of CMV-CIs consisted of ADHD, MR, and PDD, all of which are known to lead to language impairment even in children with normal hearing [12–14]. Since the pathophysiology of each of these psycho-neurological disorders is different, we hypothesized that auditory perception with CIs might be impaired at different levels in the auditory processing pathway. To address this problem, we evaluated CI outcomes of CMV-CIs and genetic-CIs by four examinations, each of which is thought to assess a different level of the auditory perceptual ability. Table III summarizes the CI outcomes of the present subjects. The subtypes of the psycho-neurological disorders appeared to determine which levels of auditory perceptual ability were affected. Hearing thresholds, which show the most fundamental auditory perceptual ability, were almost the same in both CMV-CIs and genetic-CIs, but language development and monosyllabic word discrimination, which reflect higher levels of auditory processing, were impaired in CMV-CIs with MR. In autistic CMV-CIs, who showed the most devastating results, all three abilities other than hearing threshold were severely affected. These results supported our hypothesis.

As shown in Figure 3, cochlear implantation was effective in improving language development in both CMV-CIs and genetic-CIs, but congenital CMV infection impaired the rate of improvement. It was

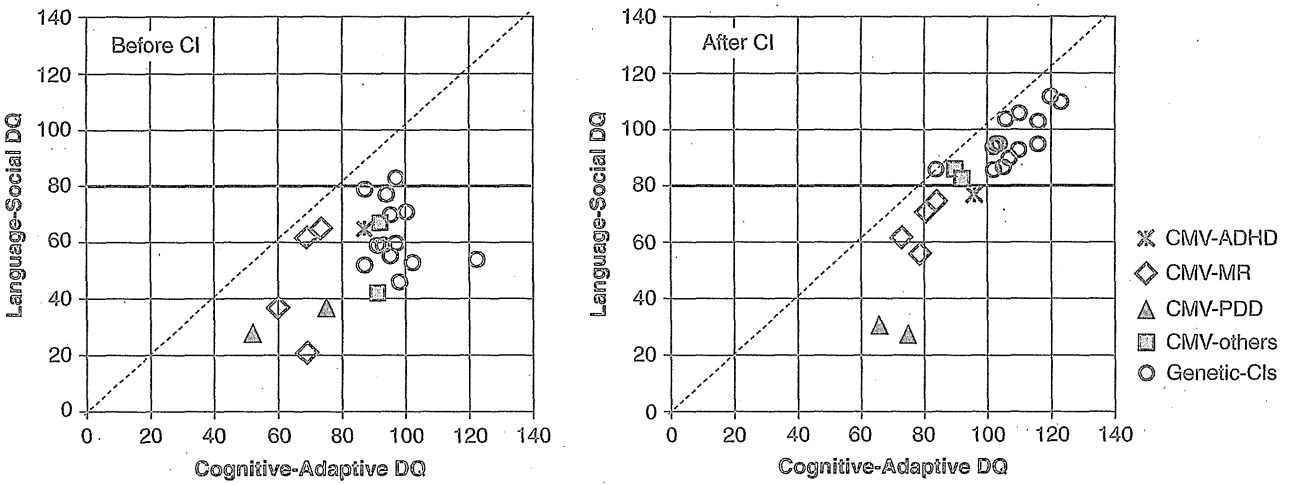

Figure 4. Correlation between Language-Social (L-S) and Cognitive-Adaptive (C-A) developmental quotients (DQs) in CMV-CIs (cochlear implanted children with congenital CMV infection) and genetic-CIs (cochlear implanted children with genetic hearing loss). Each implantee is plotted according to its L-S and C-A DQ before the surgery (A) and after the implantation (B). CMV-ADHD, CMV-MRs, CMV-PDDs, CMV-others (CMV-CIs without any psycho-neurological disorders), and genetic-CIs are represented by different markers on these scatter graphs. The dotted line in each graph means that L-S DQ is equal to C-A DQ. After the implantation, all except for two CMV-PDDs were plotted just beneath the dotted line, indicating that their L-S DQs and C-A DQs were significantly correlated, but language development of CMV-PDDs was retarded more severely than their cognitive development. ADHD, attention deficit hyperactivity disorder; MR, mental retardation; PDD, pervasive developmental disorder.

noteworthy that the developmental ages of two CMV-PDDs increased after the implantation, but their postoperative L-S DQs did not improve and never exceeded 40, indicating that their language development remained severely retarded even after the implantation. The CMV-CIs other than autistic children showed remarkable increase of L-S DQs after the implantation, but postoperative L-S DQs of CMV-ADHD and CMV-MRs were still below 80, indicating that their language development had not caught up to the age equivalent values for normal hearing. On the other hand, the L-S DQs of all genetic-CIs significantly improved to reach more than 80, within normal range. These data suggest that congenital CMV infection affected the language development and the severity of impairment was determined by the types of psycho-neurological disorders. Moreover, with respect to the communication modes, all genetic-CIs could communicate well orally after the implantation, but two CMV-PDDs and three CMV-MRs needed sign language and total communication, respectively, due to their insufficient auditory perceptual ability.

As shown above, the CI performance widely varied among CMV-CIs. Therefore, a preoperative prediction for CI outcomes is important for clinicians and parents to decide the indication for the implantation as well as to choose the most appropriate communication mode. To address this problem, we focused on the cognitive development of implantees. Our data suggest that evaluation of cognitive development and autistic tendency is important for such prediction. The level of cognitive development might define the upper limit of language development and, therefore, appropriate medical interventions including surgery and rehabilitation could achieve L-S DQ scores nearly reaching those of C-A DQs. However, if a child is autistic, the final L-S DQ would be much lower than C-A DQ (Figure 5). In general, a younger age at cochlear implantation results in better language development [15]. Although the earlier usage of CI might also have resulted in the better language DQs in our CMV-CIs, their L-S DQs would not have exceeded the C-A DQs, due to disorders of their central nervous system. The timing of surgery for the CMV-CIs in the present study varied widely, primarily due to late-onset hearing loss [3], as observed in CMV-3 and CMV-4. The high mean age at which the operation of CMV-CIs was performed might not affect the CI outcomes in this study, since the mean duration of deafness of the CMV-CIs was much the same as that of genetic-CIs.

The preoperative evaluation for autistic tendency was useful to predict CI outcomes, but the discrimination of communication disorders due to autistic disorders from those induced by deafness is difficult, especially when a child is under 3 years old. Because of the lack of a biological marker for autism, clinicians have to rely on behavioral characteristics to make a diagnosis, but both hearing loss and autistic disorder could lead similar communication difficulties.

Table III. CI outcomes of CMV-CIs and genetic-CIs.

Test		Genetic (n = 14)	CMV-others (n = 2)	CMV-ADHD (n = 1)	CMV-MR (n = 4)	CMV-PDD (n = 2)
Higher ↑ Auditory perceptual ability ↓ Lower	Language development	Good	Good	Moderate	Moderate	Poor
	Open-set monosyllabic word discrimination	Good	Good	Good	Moderate-poor	Poor
	Closed-set infant word discrimination	Good	Good	Good	Good	Poor
	Hearing threshold	Good	Good	Good	Good	Good

Auditory perceptual ability of implantees was assessed using four tests that may reflect different levels of ability. In CMV-CIs, the subtypes of the CMV-associated psycho-neurological disorders seemed to determine the levels of auditory perceptual ability that were affected. ADHD, attention deficit hyperactivity disorder; CMV-CI, cochlear implanted children with congenital CMV infection; genetic-CI, cochlear implanted children with genetic hearing loss; MR, mental retardation; PDD, pervasive developmental disorder.

Actually, autistic children with normal hearing are sometimes misdiagnosed with hearing loss in their infancy and, conversely, suspicion of autistic tendency of deaf children sometimes disappears after the long usage of CIs [16]. For accurate preoperative predictions for CI outcomes, objective and quantitative examinations for autistic tendency in the infant and toddler stage are necessary.

There have been several studies reporting the CI outcomes of implanted children with congenital CMV infection, but their results were inconsistent. Some reported that the speech perception or production of implanted children with congenital CMV infection was as high as that of control children, while the CI performance of CMV groups was poorer than that of controls in other studies [17–19]. Since our study revealed that CI outcomes varied widely depending on the psycho-neurological disorders, differences in the proportion and severity of CMV-associated psycho-neurological disorders among subjects in each study might explain the inconsistent results.

As shown above, cochlear implantation was effective for deaf children with congenital CMV infection, but their CI outcomes were impaired, depending on the types of CMV-associated neurodevelopmental disorders. Each neurological disorder varies widely in severity and manifestations, but our study design contained only 11 children with congenital CMV infection and was not sufficient to normalize the differences among individuals. Therefore, we need further examinations to reach definite conclusions. Nevertheless, in deaf children with multiple handicaps including infants with symptomatic congenital CMV infection, we have to carefully consider the aims and objectives of implantation, especially how CI contributes to improvement in a child's communication. Even though autistic CMV-CIs could not understand the meaning of spoken words or sentences, their mothers thought that CI was effective, because behaviors and family interactions of deaf children with autistic spectrum disorders were improved to some extent after the implantation, as reported previously [20]. In the case of CMV-MR, they were usually able to communicate with each other using total communication. In this way, evaluation of the cognitive development and autistic tendency of each CMV-CI might be useful for determination of an appropriate goal for language rehabilitation as well as choice of communication mode, which is critical to achieve best language outcomes and improve both children's and family's satisfaction with CIs.

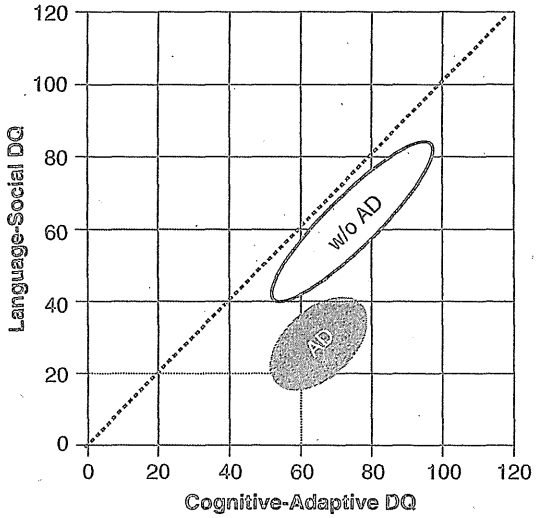

Figure 5. Prediction for language development of CMV-CIs (cochlear implanted children with congenital CMV infection). The score of Language-Social (L-S) developmental quotients (DQs) in the K-test of a CMV-CI without autistic disorder (w/o AD) might be almost same as, but slightly smaller than that of its Cognitive-Adaptive (C-A) developmental quotient (DQ). If a child has autistic disorder (AD), its L-S DQ would be lower than that expected from its C-A DQ.

Acknowledgments

We thank Dr Masahiro Nakayama at Osaka Medical Center and Research Institute for Maternal and Child Health for performing the PCR-based diagnosis of congenital CMV infection using dried umbilical cords. Dr Mieko Yoshioka at Department of Pediatric Neurology Kobe City Pediatric and General Rehabilitation Center for the Challenged gave insightful comments and suggestions about congenital CMV infection. This study was supported by a Grant-in-Aid for scientific research (C): 22591894 and 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.

References

[1] Grosse SD, Ross DS, Dollard SC. Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: a quantitative assessment. J Clin Virol 2008;41:57–62.

[2] Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007;17:253–76.

[3] Orlikowsky TW. 2011. Clinical outcomes: acute symptoms and sleeping hazards. In Halwachs-Baumann G, editor. Congenital cytomegalovirus infection: epidemiology, diagnosis, therapy. New York: Springer Wien. p 91–105.

[4] Ikeda S, Tsuru A, Moriuchi M, Moriuchi H. Retrospective diagnosis of congenital cytomegalovirus infection using umbilical cord. Pediatr Neurol 2006;34:415–16.

[5] Usami S, Wagatsuma M, Fukuoka H, Suzuki H, Tsukada K, Nishio S, et al. The responsible genes in Japanese deafness patients and clinical application using Invader assay. Acta Otolaryngol 2008;128:446–54.

[6] Koyama T, Osada H, Tsujii H, Kurita H. Utility of the Kyoto Scale of Psychological Development in cognitive assessment of children with pervasive developmental disorders. Psychiatry Clin Neurosci 2009;63:241–3.

[7] Venail F, Vieu A, Artieres F, Mondain M, Uziel A. Educational and employment achievements in prelingually deaf children who receive cochlear implants. Arch Otolaryngol Head Neck Surg 2010;136:366–72.

[8] Pass RF, Stagno S, Myers GJ, Alford CA. Outcome of symptomatic congenital cytomegalovirus infection: results of long-term longitudinal follow-up. Pediatrics 1980;66:758–62.

[9] Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics 2004;113:e472–86.

[10] Engman ML, Lewensohn-Fuchs I, Mosskin M, Malm G. Congenital cytomegalovirus infection: the impact of cerebral cortical malformations. Acta Paediatr 2010;99:1344–9.

[11] Yamashita Y, Fujimoto C, Nakajima E, Isagai T, Matsuishi T. Possible association between congenital cytomegalovirus infection and autistic disorder. J Autism Dev Disord 2003;33:455–9.

[12] Cohen NJ, Vallance DD, Barwick M, Im N, Menna R, Horodezky NB, et al. The interface between ADHD and language impairment: an examination of language, achievement, and cognitive processing. J Child Psychol Psychiatry 2000;41:353–62.

[13] Holt RF, Kirk KI. Speech and language development in cognitively delayed children with cochlear implants. Ear Hear 2005;26:132–48.

[14] Stefanatos GA, Baron IS. The ontogenesis of language impairment in autism: a neuropsychological perspective. Neuropsychol Rev 2011;21:252–70.

[15] Niparko JK, Tobey EA, Thal DJ, Eisenberg LS, Wang NY, Quittner AL, et al. Spoken language development in children following cochlear implantation. JAMA 2010;303:1498–506.

[16] Teplin SW. 1999. Autism and related disorders. In: Levine MD, Carey WB, Crocker AC, editors. Developmental-behavioral pediatrics. 3rd edition. Philadelphia: Saunders. p 589–605.

[17] Yoshida H, Kanda Y, Takahashi H, Miyamoto I, Yamamoto T, Kumagami H. Cochlear implantation in children with congenital cytomegalovirus infection. Otol Neurotol 2009;30:725–30.

[18] Malik V, Bruce IA, Broomfield SJ, Henderson L, Green KM, Ramsden RT. Outcome of cochlear implantation in asymptomatic congenital cytomegalovirus deafened children. Laryngoscope 2011;121:1780–4.

[19] Ciorba A, Bovo R, Trevisi P, Bianchini C, Arboretti R, Martini A. Rehabilitation and outcome of severe profound deafness in a group of 16 infants affected by congenital cytomegalovirus infection. Eur Arch Otorhinolaryngol 2009;266:1539–46.

[20] Donaldson AI, Heavner KS, Zwolan TA. Measuring progress in children with autism spectrum disorder who have cochlear implants. Arch Otolaryngol Head Neck Surg 2004; 130:666–71.

Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Ras/p38 and PI3K/Akt but not Mek/Erk signaling mediate BDNF-induced neurite formation on neonatal cochlear spiral ganglion explants

Lina M. Mullen[b], *Kwang K. Pak*[a], *Eduardo Chavez*[b], *Kenji Kondo*[b], *Yves Brand*[b,d,1], *Allen F. Ryan*[a,b,c,*,1]

[a]San Diego VA Medical Center, 3350 La Jolla Village Drive, San Diego, CA 92161USA
[b]Surgery/Otolaryngology, UCSD School of Medicine, 9500 Gilman Drive MC0666, La Jolla, CA 92093, USA
[c]Neurosciences, UCSD School of Medicine, 9500 Gilman Drive MC0666, La Jolla, CA 92093, USA
[d]Department of Biomedicine and Clinic of Otolaryngology, Head and Neck Surgery, University Hospital Basel, Hebelstrasse 20, 4031 Basel, Switzerland

ARTICLE INFO

Article history:
Accepted 30 October 2011
Available online 6 November 2011

Keywords:
BDNF
Neuritogenesis
Ras/P38
Spiral ganglion
Signal transduction
TrkB receptor

ABSTRACT

Neurotrophins participate in regulating the survival, differentiation, and target innervation of many neurons, mediated by high-affinity Trk and low-affinity p75 receptors. In the cochlea, spiral ganglion (SG) neuron survival is strongly dependent upon neurotrophic input, including brain-derived neurotrophic factor (BDNF), which increases the number of neurite outgrowth in neonatal rat SG in vitro. Less is known about signal transduction pathways linking the activation of neurotrophin receptors to SG neuron nuclei. In particular, the p38 and cJUN Kinase (JNK), mitogen-activated protein kinase (MAPK) pathways, which participate in JNK signaling in other neurons, have not been studied. We found that inhibition of Ras, p38, phosphatidyl inositol 3 kinase (PI3K) or Akt signaling reduced or eliminated BDNF mediated increase in number of neurite outgrowth, while inhibition of Mek/Erk had no influence. Inhibition of Rac/cdc42, which lies upstream of JNK, modestly enhanced BDNF induced formation of neurites. Western blotting implicated p38 and Akt signaling, but not Mek/Erk. The results suggest that the Ras/p38 and PI3K/Akt are the primary pathways by which BDNF promotes its effects. Activation of Rac/cdc42/JNK signaling by BDNF may reduce the formation of neurites. This is in contrast to our previous results on NT-3, in which Mek/Erk signaling was the primary mediator of SG neurite outgrowth in vitro. Our data on BDNF agree with prior results from others that have implicated PI3K/Akt involvement in mediating the effects of BDNF on SG neurons in vitro, including neuronal survival and neurite extension. However, the identification

* *Corresponding author at:* Neurosciences, UCSD School of Medicine, 9500 Gilman Drive MC0666, La Jolla, CA 92093, USA. Fax: +1 858 534 5319.
E-mail address: afryan@ucsd.edu (A.F. Ryan).

Abbreviations: ANOVA, one-way analysis of variance; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; HC, hair cells; JNK, cJUN Kinase; MAPK, mitogen-activated protein kinase; NT-3, neurotrophin-3; PI3K, phosphatidyl inositol 3 kinase; PVDF, polyvinylidene difluoride; SCs, supporting cells; SG, spiral ganglion

[1] Drs. Ryan and Brand contributed equally to the supervision of this work.

0006-8993/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.brainres.2011.10.054