were strongly affected by the duration of auditory deprivation [1,5,6,19,20]. Since low activation of the auditory cortices with visual stimuli suggests the subject's lesser dependence on visual communication methods and substantial residual plasticity in his auditory cortices, case 2 with an *SLC26A4* mutation may be determined to be an appropriate candidate for cochlear implantation.

Accurate diagnosis of hearing loss and early cochlear implantation are important for successful spoken language development. The approach using PET could help those involved in the habilitation and education of prelingually deafened children to decide upon the suitable mode of communication for each individual.

Both of the patients received cochlear implantation after PET examination. Further follow-up of these cases may indicate that efficacy of the combination of genetic diagnosis and functional brain imaging helps to predict long-term outcomes of cochlear implantation. Examination of more cases is necessary to define the relationship of the varying cortical activation patterns with each genetic mutation.

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難聴の遺伝子診断

宇佐美真一

難聴の遺伝子診断

Molecular diagnosis of deafness

宇佐美真一

Abstract

Despite advances in discovery of deafness genes, clinical application still entails difficulties because of the genetic heterogeneity of deafness. In order to establish strategy for clinical application, we reviewed the genes responsible for hearing loss patients in Japan (Usami S et al; Acta Otolaryngol 128: 446–454, 2008), and discussed diagnostic strategy for mutation screening based on a mutation/gene database (Abe S et al; Genet Test 11: 333–340, 2007).

Our series of mutation screenings has revealed that mutations in *GJB2*, *SLC26A4*, and *CDH23*, and the 1555A>G mutation in the mitochondrial 12S rRNA, were the major causes of hearing loss in Japanese patients. Interestingly, spectrums of *GJB2*, *SLC26A4*, and *CDH23* mutations found in the Japanese population were quite different from those reported in populations with European ancestry. Our simultaneous screening of the multiple deafness mutations was based on the mutation spectrum of a corresponding population. The multicenter trial for this assay using an Invader panel revealed that approximately 40 % of congenital hearing loss subjects could be diagnosed. This assay will enable us to detect deafness mutations in an efficient and practical manner in the clinical platform.

Key words: deafness, vertigo, genetic testing

はじめに
—難聴を取り巻く環境の大きな変化—

この10年あまり難聴(特に先天性難聴)を取り巻く環境が，新生児聴覚スクリーニング，遺伝子診断，人工内耳の登場により大きく変化した．本稿ではこのうち難聴の遺伝子診断を中心に，難聴医療がどのように変わってきたかを概説する．

1. 難聴医療の進歩

a. 早期発見

先天性難聴は出生1,000人に1人生まれ，先天性疾患の中では最も高頻度に認められる疾患の一つである．難聴児の多くは難聴以外には何ら異常を示さない児であり，従来は言葉が出ない，音に対する反応がないなどをきっかけに2–3歳で発見されることが多かった．また原因も不明で，有効な治療法もなく，難聴児は補聴器を使用し，ろう学校に通学するという選択肢

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しかない時代が続いた．通常，子どもは両親の発音をまねて言語が次第に発達してくる．したがって正確な発音が聞き取れなければ正確な発音をすることは不可能である．言語発達には臨界期(2-4 歳)がありその時期に十分な音の情報が入らない場合，発音や言語発達の獲得に不利になることが明らかになり，近年，新生児聴覚スクリーニングにより難聴を早期に発見し，早期に介入や療育を行い言語発達を促そうとする流れが定着している．現在多くの自治体で新生児聴覚スクリーニングが始まり難聴児が出生直後に診断されるようになってきている．

b. 原因の特定

難聴は長い間原因不明の疾患であったが，従来の疫学的な研究から先天性難聴の少なくとも 50％は遺伝子の関与によるものと推測されていた．ヒトゲノムの解明に伴い，多くの疾患の原因遺伝子が特定されてきたが，難聴でもこの 10 年余りの間に多くの原因遺伝子が同定されてきている．原因遺伝子によって発症時期，進行性，前庭症状，随伴症状が異なることから，遺伝子診断は難聴の正確な診断，治療法の選択，予後の推測，合併症の予測，更には予防や遺伝カウンセリングといったものに関して重要な情報を提供してくれるようになってきた．今後数年のうちに難聴の分類は原因遺伝子ごとに再分類されていき，難聴患者に対する個別化医療が進んでいくと思われる．原因遺伝子の特定により，難聴のメカニズム，病態がピンポイントに理解可能になった．それに伴い近い将来難聴の医療にとって遺伝子診断は欠かせないものになることが予想される．

c. 人工内耳の発達

難聴に対する根本的な治療法の開発はこれからの課題になるが，重度の難聴患者では人工内耳が非常に効果を上げている．成人例(後天性難聴)ではいうまでもなく，現在重度の先天性難聴児に対する介入法としても人工内耳が普及し効果を上げている．従来重度難聴児に対しては補聴器では十分な補聴効果が得られない場合が多く，発音や言語発達に限界があったが，この 10 年余り先天性難聴児に対する人工内耳装用者が世界的に増え，その有効性が実証されている．

2. 原因の特定はなぜ必要か

改めていうまでもなく‘難聴’は症状名であり診断名ではない．難聴は原因不明の時代が長く続いたが，近年のヒトゲノム解析研究の発展により，多くの原因遺伝子が同定され報告されるようになり，もはや難聴は原因不明の疾患ではなくなってきている．例えば，内科医が‘腹痛’という診断名ではなく腹痛の原因を検索し患者にとって最適な治療法を考えるのと同じように，難聴の原因診断が可能になった現在，正確な診断は医療従事者側，療育関係者側，患者側からみても疾患に対するアプローチの王道であることはいうまでもなく，治療や療育を考えるうえでの出発点である．原因が異なる難聴児に対し同じ考え，同じプログラムで療育を進めていこうということ自体無理があるのは明らかで，今後は原因が異なる個々の難聴児に最適なオーダーメイドの療育プログラムが組まれていくことが望ましい．難聴児の両親にとっても，難聴の受容とともに原因を知り難聴の特徴を理解することは難聴と向き合う際の出発点であると考えられる．

3. なぜ難聴の遺伝子診断か

疫学的な研究により従来から先天性難聴の 60-70％は遺伝子の関与によるものと推測されているが(**図 1**)[1]，難聴の原因を知るためには遺伝学的検査が必要不可欠になってきている．近年，新生児聴覚スクリーニングによって難聴児が早期に発見され，人工内耳の発達によって高度難聴児でも聴覚を活用し言語発達を促すことが可能になってきた．小児難聴では早期に難聴の有無について診断がなされた後，難聴の原因診断を検索するための遺伝子診断のニーズが高まってきている．また患者サイドでも，なぜ難聴になったかということを知りたいというニーズが高まってきている．

図 1 は欧米のデータをまとめたものであるが，難聴原因遺伝子の中で特に高頻度で見いだされ

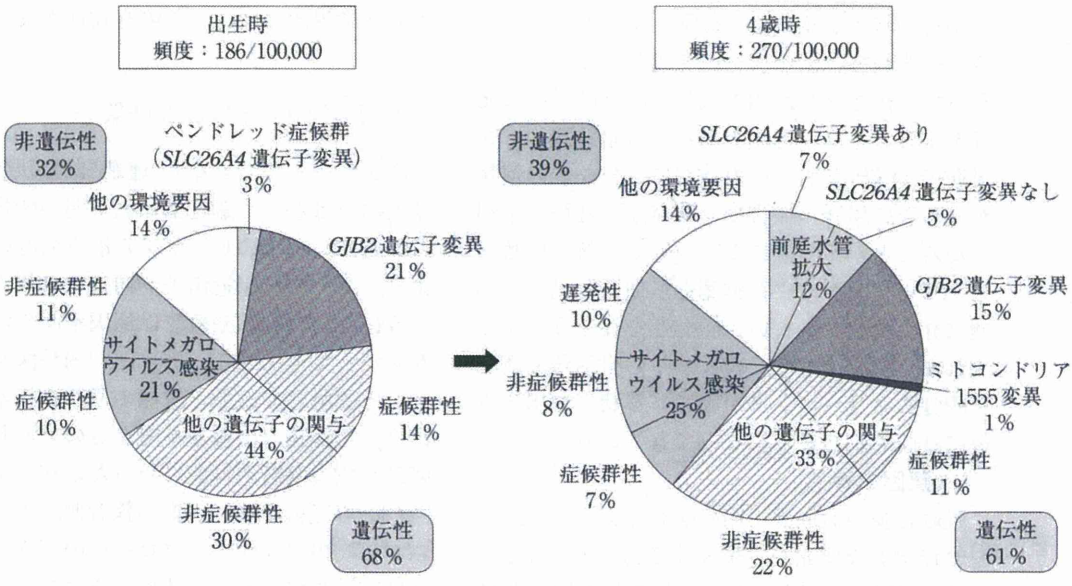

図1　小児期発症の難聴の原因(文献[1]より引用)

ているのが*GJB2*遺伝子変異による難聴で先天性難聴の約20％を占めることが知られている．次いで頻度が多いのが前庭水管拡大を伴う難聴(*SLC26A4*遺伝子変異が原因で引き起こされる)である．難聴は変動を繰り返し進行するのが特徴的であり，**図1**でも示されるように4歳時では前庭水管拡大を伴う難聴の割合が増加してくる．この2つの遺伝子で約30％を占め，その他の遺伝子が約30％を占める．このうち約1/3は'症候群性難聴'と呼ばれ，難聴のほか筋肉骨格系，腎尿路系，神経系，眼の異常，色素異常，代謝異常など種々の奇形や他の疾患を伴っている．症候群性難聴に関しては随伴する症候である程度診断が可能なものが多いが，遺伝子検索は確定診断や遺伝カウンセリングに有用となる．

4. 難聴の遺伝子診断の有用性

近年の分子遺伝学の進歩により難聴の病態が分子レベルで明らかになってきた．根本的な治療法はまだ開発されていないが，現時点でも，難聴の遺伝子診断が耳鼻咽喉科の日常臨床に応用され，次第にその有用性が認識されるようになっている[2,3]．有用性を**表1**にまとめたが，正確な診断は医師側，患者側からみても疾患に対するアプローチの王道であることはいうまでもなく，治療や療育を考えるうえでまず第一歩であり，難聴児の両親にとっても難聴の受容とともに原因を知り，難聴の特徴を理解することは難聴と向き合う際に重要であると考えられる．また，それぞれの遺伝子により臨床像が異なるので難聴の進行性の有無，変動の有無，随伴症状の有無を予測するのに有用である．また*GJB2*遺伝子などの場合，変異の種類によって難聴の程度が異なることが知られているので，介入法の選択(補聴器か人工内耳か)に有用な情報を提供してくれる．ミトコンドリア遺伝子1555変異などの場合，予防が可能であるなど，未発症の家族に対する予防が可能になっている．

表1　遺伝子診断の有用性

(1) 正確な診断
(2) 予後の推測 (難聴の進行，変動，随伴症状の予測)
(3) 治療法の選択
(4) 難聴の予防
(5) 遺伝カウンセリング
(6) 無駄な検査が省ける

(文献[2]より引用)

また遺伝形式が様々であるため遺伝カウンセリングの際の正確な情報提供に際しても原因となる遺伝子の同定が不可欠になってきた．'原因遺伝子を突き止めても治らないのであれば検査する必要はない'ということを言う患者(場合によっては医療従事者)がまだ多いのも事実である．しかしながら遺伝子治療，再生医療といった治療が近い将来可能になったときに，正確な診断ができていなければ，そのような治療が適応になるか否かもわからないこともまた事実である．

5. 難聴の原因遺伝子検索の特殊性：効率的な難聴の原因遺伝子スクリーニング

原因遺伝子の数に関しては従来から数十から100ほどの原因遺伝子が推測されているが，難聴は多種類の遺伝子が'難聴'という同じ表現型をとる(遺伝子異質性：locus heterogeneity)ために，実際に難聴を主訴に外来を受診した患者がどの原因遺伝子が関与しているかを推測することは困難である．現在までに日本人難聴患者からは合計10数種類の原因遺伝子が報告されているが(宇佐美真一'日本人難聴遺伝子データベースホームページ' http://ent.md.shinshu-u.ac.jp/deafgene.html)[4]，興味あることに，日本人で見いだされる変異は欧米人に見いだされる変異部位と大きく異なっていることが明らかになっている．これは創始者効果によるものであることが証明されており[4,5]，これらの日本人に特徴的な，あるいは頻度の高い遺伝子変異を網羅的，効果的にスクリーニングしていくことが原因を特定するために効率的であると考えられる．インベーダー法は複数の遺伝子において多数の変異を同時に検出可能なスクリーニング法として注目されているが，1回のアッセイでミトコンドリア遺伝子変異がホモプラスミーかヘテロプラスミーかも判定可能であり，従来のミトコンドリア遺伝子変異検出法と比較しても非常に優れた検査法である．日本人先天性・小児期発症難聴患者300余人における9遺伝子42変異の出現頻度の検討を行ったところ，約30％の患者で遺伝子変異の検出が可能であった[6]．多施設共同研究としてインベーダー法を用い10遺伝子47変異の有無について一次スクリーニングを実施，更に必要に応じ直接シークエンス法を用いた二次スクリーニングを行い変異確認，新規変異検索を行った結果，難聴患者の約35％(発症年齢が6歳以下の先天性難聴患者に限ると44.3％)の検出率が得られ，インベーダー法によるスクリーニングが臨床検査として有用であることが確認された(Usami et al.，投稿中)．

6. 先進医療としての難聴の遺伝子診断

多くの疾患でも同様に遺伝子解析研究が終了すると，多額の研究費を必要とする遺伝子解析自体が行われなくなるという現象が起き，費用負担の面から臨床に応用するという本来の最終目的の達成が困難になるという問題が生じている．

難聴に関しては，そのような問題点を踏まえ臨床応用の第一歩として2008年7月に'先天性難聴の遺伝子診断'が先進医療として承認され臨床診療として実施が開始されている．現在までに信州大学で実施した52症例での集計結果では約45％の症例で原因遺伝子が見いだされている(**図2**)．従来の先進医療ではすべてを自施設で行わなければならないという縛りがあり，実施可能な施設が限られていたが，2010年4月からは先進医療の共同実施(検査の受託側と委託側で共同し先進医療を実施)が可能になり，全国規模で難聴の遺伝子診断が臨床の現場で実施できるような体制作りが進んでいる．先進医療で承認された'先天性難聴の遺伝子診断'では遺伝学的検査を行い，結果を遺伝カウンセリングとともに返すまでを医療として位置づけている．後述のように各遺伝子に関して丁寧な説明と情報提供が行われている．

7. 日本人に多く見いだされる原因遺伝子

インベーダー法による網羅的な難聴遺伝子解析により，日本人難聴患者において高頻度で見いだされる遺伝子/遺伝子変異が次第に明らかになってきた．先天性難聴では*GJB2*遺伝子変

変異の見つかる頻度 44.2%(確定診断率 32.7%)

・23家系/52家系(n=134)

GJB2	劣性ホモ	2家系
GJB2	劣性コンパウンドヘテロ	8家系
SLC26A4	劣性ホモ	1家系
SLC26A4	劣性コンパウンドヘテロ	3家系
GJB2	劣性ヘテロ	4家系
SLC26A4	劣性ヘテロ	2家系
ミトコンドリア A8296G		1家系
ミトコンドリア A3243G		2家系

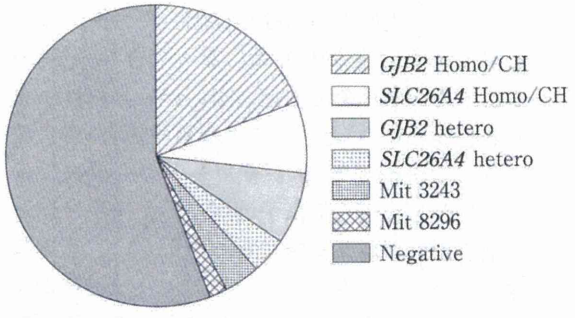

図2　信州大学における先進医療(先天性難聴の遺伝子診断)の現況

異，*SLC26A4* 遺伝子変異が多く(**図2**)，後天性難聴にはミトコンドリア遺伝子変異が多く見いだされる．それぞれの遺伝子変異による難聴について解説するとともに，実際にどのように臨床で応用されているかを紹介する．

a. *GJB2* 遺伝子変異による難聴：先天性難聴に最も多く見いだされる原因遺伝子

GJB2 遺伝子は細胞間の結合様式の一つであるギャップ結合タンパク(コネキシン26)をコードする遺伝子で，内耳のカリウムイオンのリサイクルに重要な働きを担っていると考えられている．現時点で最も高頻度で見いだされる先天性難聴の原因遺伝子として全世界で研究が進められている．日本人難聴患者1,343例について *GJB2* 遺伝子変異頻度を検討した結果では，191例(14.2%)に遺伝子変異が認められている[7]．難聴の発症年齢別(0–3歳，4–5歳，6歳–)では，0–3歳(先天性または言語獲得前難聴)の難聴患者の約25%に *GJB2* 遺伝子変異が認められ，日本人先天性難聴患者の重要な原因の一つであることが明らかとなっている[7]．

現在全世界で，100種類以上の *GJB2* 遺伝子変異が報告されており，変異の頻度および種類の分布は人種によって大きく異なっていることが報告されている[4]．日本人難聴患者には26種類の遺伝子変異が報告され，その中でも235delC変異の頻度が最も多く，次いでV37I，G45E/Y136X，R143W，176–191 del16bp変異の順に多く認められている[7](**図3**)．*GJB2* 遺伝子変異による難聴の場合，遺伝子型と難聴の程度には相関関係があることが明らかになっている[7](**図4**)．すなわち235delCをはじめ欠失，挿入変異，ストップ変異が含まれる場合，より高度の難聴になる傾向が報告されている．一方，ミスセンス変異の場合は軽度から中等度難聴の場合が多い傾向があることが報告されている．

発見年齢別に遺伝子型を検討した場合，0–3歳では235delCが58.5%と高く，発見年齢が高くなるほどその頻度は少なくなることが報告されている．一方，V37Iは発見年齢が高くなるほど頻度は高くなり，V37Iをもつ難聴患者は発見年齢が遅れることが明らかになっている[7](**図3**)．これは235delCを含む難聴患者は高度難聴を呈するのに比し，V37I変異は難聴が軽度であるため難聴の発見が遅れることが原因であると考えられている．また，V37I変異症例は日本人における *GJB2* 遺伝子変異の中では2番目に多い変異であるが，対照(正常聴力)群では最も頻度が高い変異であることが明らかになっている．これはV37I変異症例の難聴が軽度であるために患者が病院を受診しない，もしくは診療医が患者の難聴が軽度であるため遺伝学的検査を勧めない可能性があるためと考えられている．

GJB2 遺伝子変異では変異のタイプと聴力像に相関関係があることから，調整定常反応などの聴覚検査と組み合わせることにより重症度を予測し，治療法を選択する際に有用な情報となる．現在までに *GJB2* 遺伝子変異による先天性難聴患者に対する人工内耳，あるいはミトコンドリア1555変異などによる後天性難聴患者に

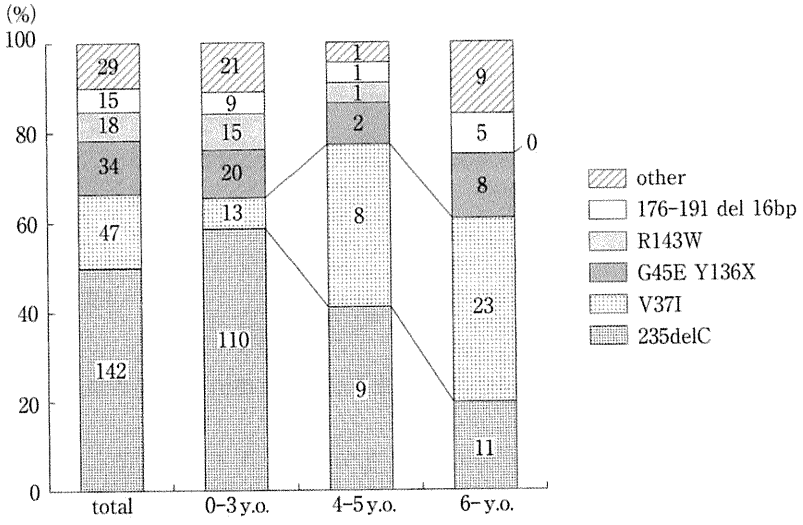

図3　*GJB2* 遺伝子変異の種類と発見年齢(文献[7]より引用)

対する人工内耳の有用性は既に報告されており，人工内耳を選択する際の情報として有用である[8,9]．

また *GJB2* 遺伝子変異症例では，耳鳴，めまい，内耳奇形の頻度が両側感音難聴患者と比較し有意に低く，*GJB2* 遺伝子変異による難聴の臨床的特徴として患者に説明可能である[7]．

b. *SLC26A4* 遺伝子変異による難聴：内耳奇形を伴い変動しながら進行する難聴

画像診断も原因遺伝子を絞りこむために重要な役割をもつ(**図5**)．先天性難聴児の数％から20％ほどに何らかの内耳奇形が見いだされると報告されているが，種々の内耳奇形の中でも‘前庭水管拡大’は頻度が高い奇形として知られ，我が国でも最近この奇形を伴った難聴症例が数多く報告されるようになり注目を集めている．一連の遺伝子解析を通じて，甲状腺腫を伴うPendred症候群の原因遺伝子(*SLC26A4*)が同時に‘前庭水管拡大を伴った難聴’の原因遺伝子になっていることが明らかにされている[10]．したがって従来2つの異なる疾患と考えられていた両疾患は今後①前庭水管拡大，②*SLC26A4* 遺伝子変異，③変動する難聴を共通の臨床的特徴としてもつ‘*SLC26A4* 遺伝子の変異が引き起こす同一の疾患群’として診断，加療されるべきだと考えられる．遺伝子診断は難聴の変動性，進行性，予想される随伴症状(めまい，甲状腺腫等)などを説明する際に有用な情報を提供してくれることが多い．

biallelic(ホモもしくは複合ヘテロ接合体)な *SLC26A4* 遺伝子変異をもつ難聴患者39人の臨床像(聴力レベル，聴力の変動，進行，めまいの有無，甲状腺腫の有無)，また遺伝子型と表現型について比較検討した結果，中等度から高度難聴であり個人差が大きかったが年齢とともに進行する傾向が認められた[11]．また，いずれの症例も言語習得前の難聴と考えられ，高率で聴力の変動(92.3％)，進行(88.0％)を認めた[11]．また24人(70.6％)の患者でめまいの合併を認めた．10人(27.8％)の患者で甲状腺腫の合併を認めたが，すべて12歳以降の発症であった[11]．遺伝子型による難聴の程度の差，随伴症状の違いは認められなかった[11]．遺伝子診断により，難聴の進行(**図5**)，めまいなど臨床症状の予後に関して，*SLC26A4* 遺伝子変異の認められた患者への適切な情報提供が可能となった．

c. ミトコンドリア遺伝子 1555A>G，3243A>G 変異：発症予防，合併症の早期治療が可能

ヒトミトコンドリアDNAは16,568塩基対か

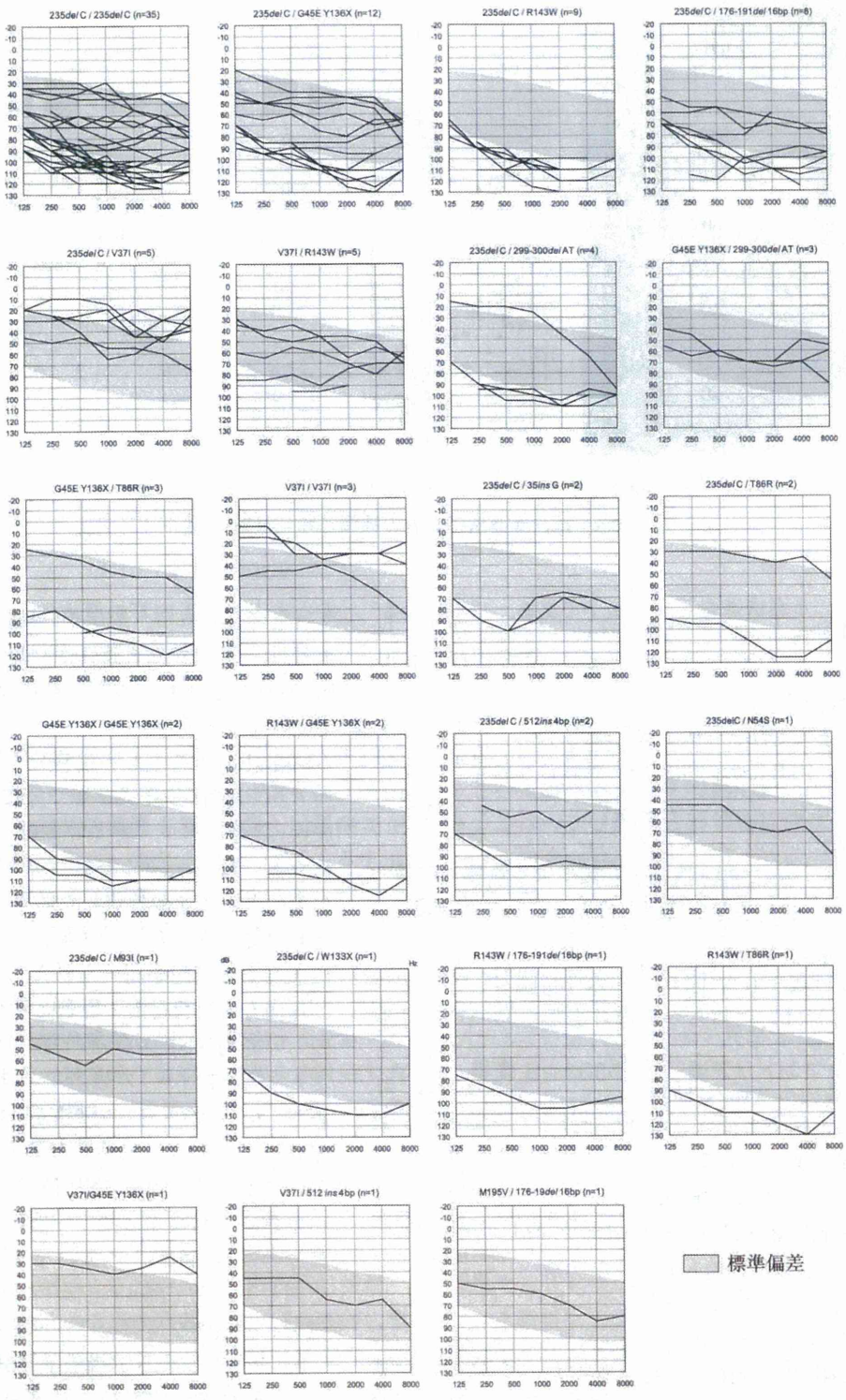

図4　*GJB2* 遺伝子変異による難聴患者の重症度予測
(文献[7]より改変)

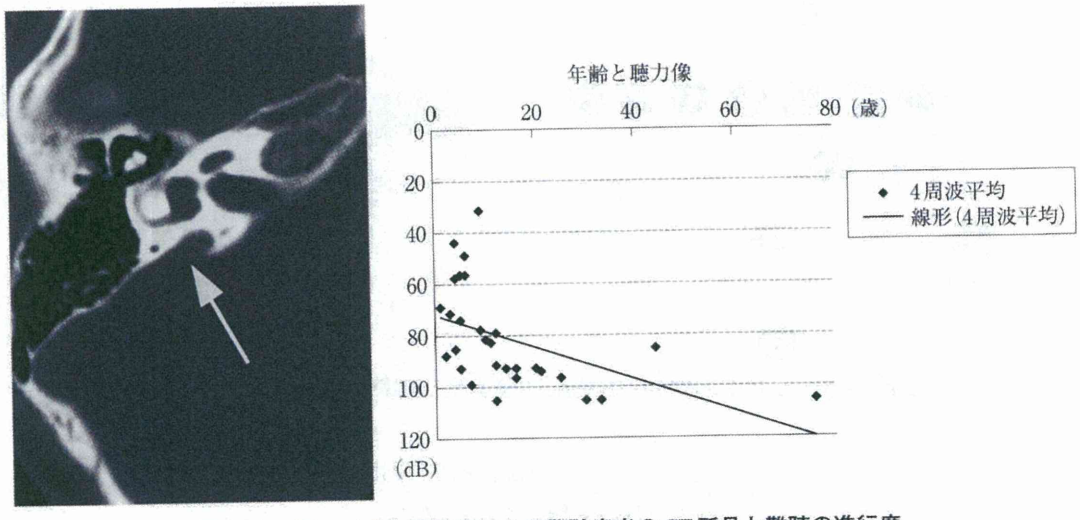

図5　*SLC26A4*遺伝子変異による難聴患者のCT所見と難聴の進行度
（文献[11]より引用）

らなる，二重環構造を示す遺伝子である．13種類の内膜の呼吸複合体遺伝子をコードし，細胞エネルギー産生にかかわっている．ミトコンドリアDNAは受精時で精子からミトコンドリアが脱落するため，ミトコンドリア遺伝子の変異による疾患は母系遺伝を呈する．種々のミトコンドリア変異が難聴と関連していることが知られているが，特に頻度が高い変異として12SrRNA領域の1555A>G変異，*tRNALeu*(*UUR*)遺伝子の3243A>G変異が知られている．インベーダー法による網羅的解析では後天性難聴の母集団に頻度が高く，成人発症の難聴の重要な原因遺伝子変異である．

1）ミトコンドリア遺伝子1555A>G変異

近年，分子遺伝学的にミトコンドリア遺伝子1555A→G変異とアミノ配糖体抗菌薬に対する高感受性との関連性が明らかとなった．この変異は外来を訪れる感音難聴患者の約3％の患者がもっていることが報告されており，この遺伝子変異による難聴患者あるいはハイリスク患者の数は，全国的にかなり多いことが推測されている[12]．またアミノ配糖体抗菌薬による難聴患者に絞ると，約30％に変異が見いだされることが明らかとなり，アミノ配糖体抗菌薬に対する高感受性と関連が深いことが確認されている[12]．また成人の人工内耳の埋め込み患者の約10％に，またアミノ配糖体抗菌薬により高度難聴をきたした人工内耳症例に限ると約60％がこの変異をもっていた[12]．したがってこの変異は日本人の言語習得後失聴の重要な原因の一つであると考えられる．

この遺伝子変異による難聴の特徴は，母系遺伝することである．したがって家族歴の聴取が診断のポイントになる．難聴の程度には個人差が大きいが，難聴は一般的に両側性，対称性，高音障害型で，耳鳴を伴うことが多い[13]．変異をもつ患者の中にはアミノ配糖体抗菌薬の投与歴がなく，いわゆる特発性難聴の形で難聴をきたす症例もあるが，難聴の程度は一般的に軽度のことが多い[13,14]．確定診断は遺伝子診断になる．現在，先進医療'先天性難聴の遺伝子診断'の一項目になっているほか，臨床検査の一つとして外注検査が可能になっている(株式会社ビー・エム・エル：受託検査項目)．

難聴は進行例も認められることから定期的に聴力検査を行い経過観察することが重要である．通常，中等度以上の難聴症例には補聴器が用いられるが，補聴効果の認められない高度難聴に関しては人工内耳の良い適応になることが多い．このミトコンドリア遺伝子1555A>G変異に伴

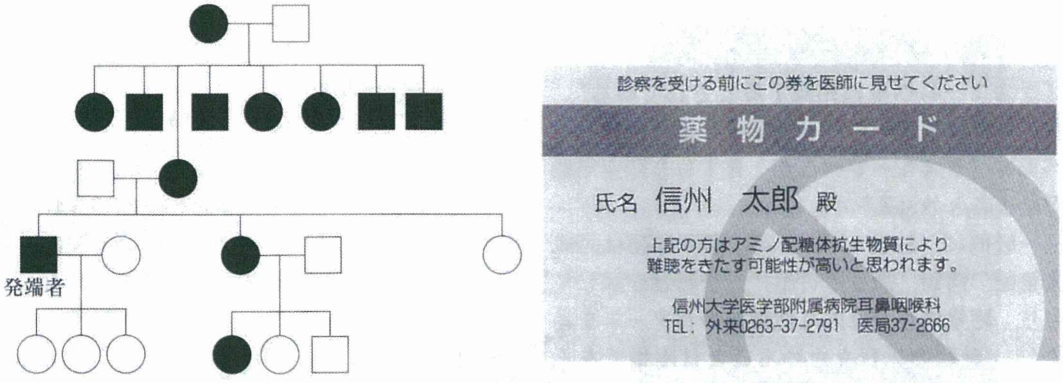

図6　ミトコンドリア遺伝子1555A>G変異患者の家系図と薬物カード(文献[15]より改変)

表2　ハイリスク患者を見つけ出すポイント

(1) 家族歴：母系に難聴者がいないか？
(2) 家族歴：アミノ配糖体抗菌薬による難聴者がいないか？
(3) 両側高音障害型難聴，進行性の難聴に注意
(4) 遺伝子検査

う難聴に関しては，アミノ配糖体抗菌薬の投与を避けることにより高度難聴はある程度予防が可能であることから，現在著者らの施設ではミトコンドリア遺伝子変異のスクリーニングシステムを確立するとともに薬物カード(**図6**)を配布し予防に努めている[15]．

表2にハイリスク患者を見つけ出すポイントについてまとめたが，最近，十分な家族歴の聴取なしにハイリスク患者に漫然と複数回のアミノ配糖体抗菌薬の投与が行われ，難聴が生じた患者・家族が病院側を訴え病院側が非を認めた事例があった．またアミノ配糖体を含んだ点耳液により感音難聴を生じ訴訟になった事例も報告されている．今後，このような事例が増えていくことが予想されるが医師サイドでも患者の遺伝的背景には十分留意することが必要である．

2) ミトコンドリア遺伝子3243A>G変異診断による合併症の早期発見

*tRNALeu(UUR)*遺伝子における3243A>G変異は糖尿病と難聴を伴う症候群の原因遺伝子として知られている遺伝子変異である[16,17]．耳鼻咽喉科外来を受診する感音難聴患者の0.3–3％に認められることが知られている[12,18]．ミトコンドリア遺伝子3243変異を同定することにより，難聴の予後(重症度，進行性の有無)が予測できるとともに合併症の予測や対応が可能になる．

この変異は，脳卒中様症状と高乳酸血症を伴うミトコンドリア筋症，脳症Mitochondrial encephalopathy，lactic acidosis and stroke-like episodes(MELAS)症例においても認められている．なぜ同じ遺伝子変異がMELAS，糖尿病，感音難聴などの多彩な障害を起こすのかは明らかにされていないが，臓器ごとでヘテロプラスミーの割合が異なっているためではないかと考えられている．ミトコンドリア遺伝子変異では，変異型ミトコンドリアと野生型ミトコンドリアがどの程度混在しているか(ヘテロプラスミー)が問題となる．ヘテロプラスミーの割合が一定以上になると(閾値を超えると)臨床症状が発症するといわれている．通常の遺伝子検査では末梢血のヘテロプラスミーの割合をみていることになるが，臓器によりヘテロプラスミーの割合は異なるとされ，一般的には神経系，筋肉，内耳などでヘテロプラスミーの割合が高いことが報告されている．理論的にはヘテロプラスミーの割合と臨床症状は相関すると考えら

れるが，必ずしも相関しない場合も多い．3243変異患者の長期間にわたる聴覚は変異型ヘテロプラスミーレベルに相関するとされている[19]．ヘテロプラスミーの程度と発症年齢は関係し，ヘテロプラスミーレベルが上昇すると発症年齢が早まるとされる[20]．

一般的に，3243A>G変異に伴う難聴は，成人発症，両側，高音障害型，感音難聴を示しており，聴覚検査では内耳性難聴のパターンを示す[18,21]．難聴の進行を止めることは困難であるが，進行した場合には補聴器や人工内耳を検討する[22]．糖尿病に関しては，定期検査を行い早期から食事療法や血糖コントロールを行い，進行や合併症を予防することが望ましい．

8. 難聴の遺伝カウンセリングのポイント

遺伝学的検査は通常の臨床検査と異なり，患者個人の遺伝情報を取り扱うという点で個人のアイデンティティに深くかかわる倫理的な側面を併せ持った検査である．遺伝子診断の結果を返す場合には遺伝カウンセリングとともに返すことが望ましい．先進医療として承認された‘先天性難聴の遺伝子診断’では遺伝学的検査を行うだけではなく，結果を遺伝カウンセリングとともに返すまでを医療として位置づけている．信州大学病院では‘遺伝子診療部’と連携して難聴の遺伝子診療を行っているが，難聴の遺伝子医療では難聴のメカニズム，予後，治療の専門知識をもつ耳鼻咽喉科医と遺伝や遺伝子のことについて正確な情報提供ができる臨床遺伝専門医との連携が重要である[2,3]．主なポイントを以下に示す．

(1) クライアントが何を求めているかを適切に判断する必要がある．難聴の遺伝子診断の際には，クライアントが難聴の今後の治療に関する情報を求める場合も多く，耳鼻咽喉科専門医とともに臨床遺伝専門医が共同して行うのが望ましい．

(2) 原因遺伝子が特定された場合，耳鼻咽喉科医が中心となりそれぞれの予後や治療法の選択に対し適切な情報や選択肢を与える．

(3) 耳鼻咽喉科医が中心となり難聴は早期診断し，補聴器や人工内耳を用いて早期療育を行えば言語習得が可能であることを説明する．

(4) 原因遺伝子が特定されない場合，臨床遺伝専門医が中心になり，考えられる遺伝形式，それに基づく一般的な再発危険率に基づき説明する．難聴の場合，遺伝性異質性がある(多種類の遺伝子が難聴という同じ表現型をとる)ことに注意して説明する．つまり常染色体劣性遺伝の場合，両親が難聴者であっても原因遺伝子が異なれば子どもが難聴になるとは限らない．また次子を考えている場合，耳鼻咽喉科医は原因は何であれ新生児聴覚スクリーニングによる早期発見，早期療育がポイントであることを説明する．

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An analysis of clinical risk factors of deep neck infection

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Abstract

Objectives: To clarify the clinical risk factors that aggravate deep neck infection.
Patients and methods: Sixty-five patients with deep neck infection (abscess or cellulitis), 42 males and 23 females, who were treated at the ear, nose, and throat department in Iwaki Kyoritsu General Hospital in the past 10 years, were retrospectively reviewed. Cases of inflammation of the upper airway including the oral cavity, laryngopharynx, palate tonsil and salivary gland, and cases of lymphadenitis were investigated. These patients were divided into five localized types and one wide range type according to the abscess locations as follows: oral cavity floor type, upper deep cervical type, submandibular type, submental type, retropharyngeal type, and wide range type.
Results: Seventeen of the 65 patients had diabetes, and significantly more diabetics had the wide range type than the localized type ($P < 0.05$, Fisher's test). Diabetes complication was more often seen in the upper deep cervical type among patients aged 61 years or older, and in the wide range type among males aged 41 years or older and elderly women aged 61 years or older. No patients with odontogenic infection or sialolithiasis had associated diabetes mellitus. Two cases developed mediastinitis, and one was caused by retrotonsillar abscess and needed thoracic drainage. More than half of the wide range type cases and more than a quarter of each of the localized type cases except the upper deep cervical type also had laryngeal edema, and eight of them needed emergency tracheotomy. Thirteen of the 40 cases had bacteria belonging to the *Streptococcus milleri* group (SMG), and all were detected in patients who underwent surgical drainage. Four of the 13 cases where SMG was detected showed drug resistance to some sorts of antibiotics.
Conclusion: Oral disorders can develop deep neck infection independently of the presence of diabetes mellitus, compared with other causes. The presence of diabetes mellitus is associated with deep neck infection, aggravating parotitis and wide spread of inflammation. Retrotonsillar abscess often spreads to the retropharyngeal and parapharyngeal spaces, causing mediastinitis, so caution is necessary. Infection due to SMG tends to form abscess independently of diabetes mellitus. Since more than half of the wide range type and more than a quarter of each of the localized types except the upper deep cervical type were associated with laryngeal edema, airway management should be considered.

Keywords: Deep neck infection; Mediastinitis; Retrotonsillar abscess; Laryngeal edema; *Streptococcus milleri* group

1. Introduction

Deep neck infection can occur at any age, and is a serious disorder that often spreads to other organs and sometimes proves fatal [1–9]. The incidence is decreasing, due to the development of antibiotics and better control of laryngopharyngitis, tonsillitis, and upper respiratory inflammation. However, once the inflammation extends to the cervical potential spaces, which are formed by the cervical fascia, the infection spreads rapidly and extensively through these spaces, causing mediastinitis, sepsis, and laryngeal edema. However, no standard protocol has been established for treating or hospitalizing the patients, because of the great variation in the causes and locations of the disease. Therefore, in order to treat such widespread infections, we must have

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extensive knowledge of the structures of the deep neck, lymphatic flow, etiology, microbiology, risks of complication, and other factors that aggravate deep neck infection [9].

The present study retrospectively reviewed 65 patients with deep neck infection treated in our department during the past 10 years, and proposes a new categorization system consisting of six groups according to the abscess location. Factors including the causes, ages, risks for mediastinitis and laryngeal edema, complication with diabetes mellitus, and bacterial analyses were analyzed to clarify the important indicators in treating deep neck infection.

2. Patients and methods

Sixty-five patients with deep neck infection (abscess and cellulitis), 42 males and 23 females with mean ages of 51 and 53 years, respectively, were treated at the ear, nose, and throat department in Iwaki Kyoritsu General Hospital from January, 1998 to August, 2007. The clinical records were reviewed retrospectively. Cases of inflammation of the upper airway including the oral cavity, laryngopharynx, palate tonsil and salivary gland, and cases of lymphadenitis were investigated. Cases of abscess limited to the peritonsillar space, isolated salivary gland infection without objective evidence of deep neck space involvement, associated with tuberculosis, or caused by foreign body, injury, or malignancy were excluded.

The cases were categorized according to the location of the abscess, as verified by computed tomography at the initial presentation, into five localized types and the wide range type as follows:

(1) Oral cavity floor type: inflammation has spread to the oral cavity floor and caused acute cellulitis in the sublingual space or just beneath the mucosa. This type includes Ludwig angina, or phlegmon of the floor of the mouth, with inflammation spreading to the submandibular and submental spaces.
(2) Upper deep cervical type: inflammation has spread to the parotid space, and in some cases, also to the masticator and the parapharyngeal spaces.
(3) Submandibular type: inflammation has spread mainly to the submandibular space, and in some cases, also to the parapharyngeal space.
(4) Submental type: inflammation has spread mainly to the submental space.
(5) Retropharyngeal type: inflammation started in the retropharyngeal space, and then spread to the parapaharyngeal space or the danger spaces.

(We did not consider whether these inflammations had spread to the parapharyngeal space or not, because the parapharyngeal space leads to both the submandibular and retropharyngeal spaces, bordering the parotid space [2,10]. Therefore, the parapharyngeal space is often inflamed, influenced by the inflammation of other potential spaces.)

(6) Wide range type was defined as inflammation extending to the deep neck at areas beyond those in (1) to (5) along the upper neck down to the lower neck including necrotizing fasciitis, or inflammation which has spread to two or more locations as specified by types (1) to (5), or in which an abscess is formed inside or outside of the cervical lymph nodes other than (1) to (5).

Bacterial culture tests were performed in 40 cases treated by surgical drainage or puncture. Inflammatory focal region, age, presence of diabetes mellitus, complication with mediastinitis or laryngeal edema, bacterial analysis, and clinical courses were analyzed.

3. Results

3.1. Clinical subgroups

Classification according to the location of inflammation showed that the wide range type was the most common (27 cases, 42%), with the other five localized types accounting for 6% to 17% (Table 1).

In the wide range type, the main sites of inflammation were located in the submandibular space and the front or inside of the sternocleidomastoid muscle, as well as the parapharyngeal space. Inflammation was seen spreading to the parapharyngeal space in 21 patients with the wide range type and 3 with the localized type, of whom two had diabetes mellitus and one was suspected of being immune-compromised.

Forty-five patients underwent urgent surgical drainage (Table 1) and 20 received only intravenous administration of

Table 1
Clinical characteristics of the 65 cases.

Type	Number of cases	Surgical drainage	Mediastinitis	Laryngeal edema	Tracheotomy
1. Oral cavity floor	11	7	0	4	0
2. Upper deep cervical	10	8	0	0	0
3. Submandibular	9	6	0	4	0
4. Submental	4	1	0	1	0
5. Retropharyngeal	4	4	0	1	1
6. Wide range	27	19	2	14	7
Total	65	45	2	24	8

broad-spectrum antibiotic agent. Two patients with wide range type were complicated with mediastinitis, and one of them required thoracic drainage.

Laryngeal edema was present in 52% of the wide range type, in 36% of the oral cavity floor type, 44% of the submandibular type, and 25% each of the submental and retropharyngeal types. Emergency tracheotomy was performed in eight patients, including one with retropharyngeal abscess. Following successful treatment, all patients improved and survived.

Distributions of each type by age, sex, and presence of diabetes mellitus are summarized in Fig. 1. Diabetes mellitus was present in 17 of the 65 patients, and was under poor control in 16 of those 17. Diabetes mellitus was present in 6 of the 38 localized type cases (16%) and 11 of the 27 wide range type cases (41%), showing a statistical difference ($P < 0.05$, Fisher's test). The presence of diabetes mellitus was more common in the upper deep cervical type among patients aged 61 years or older, and in the wide range type among males aged 41 years or older and elderly women aged 61 years or older. Diabetes mellitus was also found in the submental and retropharyngeal types. The retropharyngeal type showed a bimodal distribution consisting of infants and adults with diabetes mellitus [11]. The oral cavity floor and submandibular types tended to occur in males of all ages and particularly elderly females without diabetes mellitus.

Gas gangrene was found in three patients, and all of them were suspected of being immune-compromised.

3.2. Pathogenesis

The pathogenesis of the present cases is shown in Table 2. The oral cavity floor type was caused by odontogenic disease and sialolithiasis. The upper deep cervical and submandibular types were mainly caused by inflammation in the salivary gland. The wide range type was mostly caused by inflammation of the upper respiratory system (i.e., laryngopharyngitis, tonsillitis, retrotonsillar abscess) or lymphadenitis, but the cause was unknown in six cases. Diabetes mellitus was present in patients with laryngopharyngitis, tonsillitis, sialoadenitis, and lymphadenitis, and especially in the wide range type, all six cases had no identifiable causes. No patients with odontogenic infection or sialolithiasis had associated diabetes mellitus (Table 2). Surgical drainage was necessary in slightly more patients with diabetes mellitus than those without. Thirteen (29%) of the 45 patients treated by surgical drainage had diabetes mellitus, compared to 4 (20%) of the 20 patients who did not need drainage.

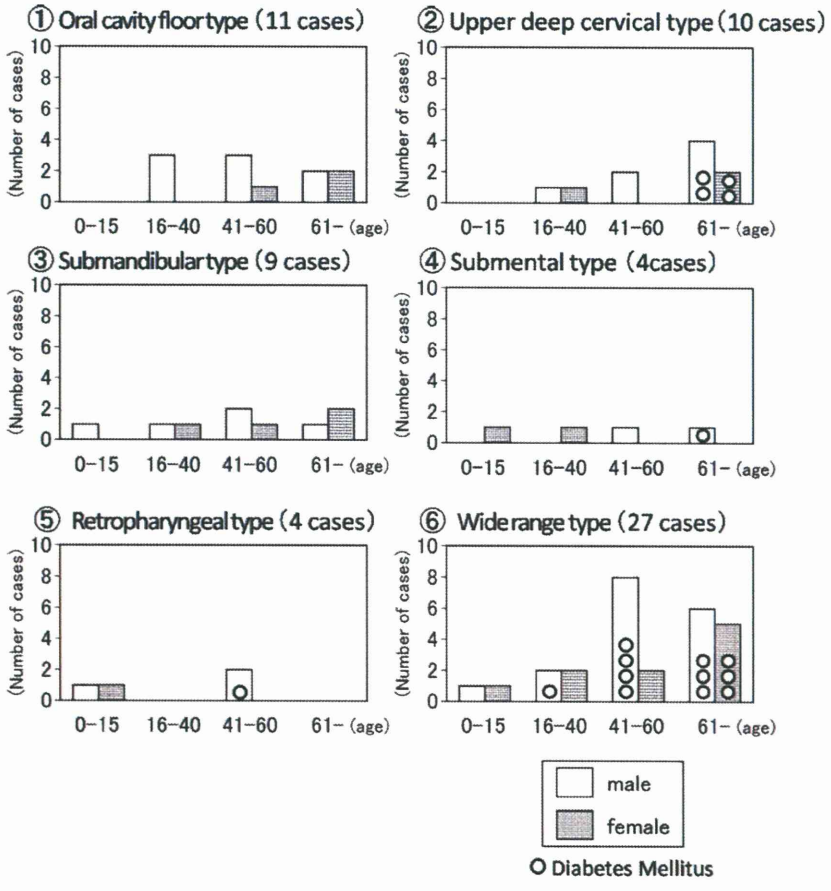

Fig. 1. Distribution of each type by age, sex, and presence of diabetes mellitus.

Table 2
Pathogenesis of the present cases. Numbers in parentheses show the numbers of cases complicated with diabetes mellitus.

Type	Number of cases	Laryngopharyngitis/tonsillitis	Odontogenic	Sialolithiasis	Sialoadenitis	Lymphadenitis	Others/unknown
1. Oral cavity floor	11	0	5	4	0	0	2
2. Upper deep cervical	10	2 (1)	1	0	7 (3)	0	0
3. Submandibular	9	1	2	0	4	0	2
4. Submental	4	1 (1)	0	1	0	0	2
5. Retropharyngeal	4	0	0	0	0	2	2 (1)
6. Wide range	27	17 (4)	0	0	0	4 (1)	6 (6)
Total	65	21 (6)	8 (0)	5 (0)	11 (3)	6 (1)	14 (7)

3.3. Bacterial analysis

Bacterial cultures of samples from the 40 patients who underwent surgical drainage or puncture detected 68 strains, 51 aerobes, 15 anaerobes, and two fungi, such as *Candida*, which could have been contaminants from the skin.

Among aerobes, genus *Streptococcus* was the most common with 30 strains, consisting of 8 *Streptococcus constellatus*, 5 alpha hemolytic *Streptococcus*, 4 *Streptococcus mitis*, 3 *Streptococcus pyogenes* (A), 3 *Streptococcus intermedius*, 3 *Streptococcus salivarius* spp, 2 *Streptococcus anginosus*, 1 *Streptococcus mobilloum*, and 1 *Streptococcus oralis*. Thirteen cases had bacteria belonging to the *Streptococcus milleri* group (SMG), and all of them were detected from the group which underwent surgical drainage. Meanwhile, none of the 5 cases treated with punctures harbored the SMG. The SMG was detected in 6 patients with deep neck infection caused by tonsillitis, including 2 with peritonsillar abscess and 4 with retrotonsillar abscess, 4 with odontogenic infection, and 3 with sialoadenitis (Table 3). Diabetes mellitus was found in only one case of the upper deep cervical type, and the presence of diabetes mellitus was unrelated to the detection of the SMG, which was more common in patients without diabetes mellitus. Four of the 13 cases with SMG infection showed drug resistance to antibiotics such as penicillins, cephems, carbapenems, penems, aminoglycosides, macrolides, and lincosamides.

Anaerobes such as *Prevotella* and *Fusobacterium* were also detected from two of the three cases of gas gangrene.

Table 3
Pathogenesis related to the type and presence of diabetes mellitus in cases with SMG infection.

Type	Pathogenesis	Cases	DM(+)
1. Oral cavity floor	Odontogenic	2	0
2. Upper deep cervical	Sialoadenitis	2	1
3. Submandibular	Odontogenic	2	0
	Sialoadenitis	1	
4. Submental		0	0
5. Retropharyngeal		0	0
6. Wide range	Peritonsillitar abscess	2	0
	Retrotonsillar abscess	4	
Total		13	1

4. Discussion

4.1. Clinical subgroup and pathogenesis

Deep neck infection often starts as cellulitis of the soft tissue in an isolated area adjacent to the source of infection [9]. Since the fascial layers of the neck and the body's natural defense mechanisms help to prevent further spread of infection, there is no typical wide spread progression, but there are various involved areas in this disease [9,12].

Some previous studies have classified deep neck infections into several types [3–5]. For example, deep neck abscess cases were classified according to the abscess locations into the submandibular space, lateral pharyngeal space (parapharyngeal space), retropharyngeal space, and Ludwig's angina groups, by investigating their frequencies and the necessities of tracheotomy [3].

Our proposed classification system is specific in differentiating not only the abscess locations for clarifying the causal relationships but also the complication risk, by adding the upper deep cervical, submental, and wide range types. The inflammation in parapharyngeal space seemed to have been caused by extension of that in localized types. Meanwhile, we thought that the wide range type is a case of a localized type which has spread widely beyond parapharyngeal space or a case of cervical lymphadenitis which has formed an abscess inside or outside the lymph node. By classifying the original sources of infection, we should be able to identify the cause of deep neck infection and the likely subsequent complications. All types occurred across all age groups, but males were more prone to develop deep neck infection (Fig. 1). Deep neck infection is well known to occur more often in males [3,5,9,13], presumably because the infection is more likely to spread to the potential spaces in males, because of the difference in the strength of connective tissue between males and females [13]. In addition, many smokers, alcohol drinkers, and drug addicts are found among deep neck infection patients [9].

Complication with diabetes is well known to exacerbate deep neck infection [3,5,6,14], but the clinical characteristic of aggravation remains unclear. In this study, complication with diabetes mellitus was more often seen in the upper deep cervical and wide range types (Fig. 1). Surgical drainage was performed in 45 cases, and 13 (29%) were complicated with

diabetes mellitus. Many cases complicated with diabetes mellitus had unclear primary regions but extensive inflammation outside the capsule which tended to spread outwards with increasing seriousness.

The present study identified three cases of upper deep neck type caused by sialoadenitis, which does not contradict the previous report that parotid abscess is strongly related to diabetes mellitus [15]. Therefore, we believe that since diabetes mellitus tends to aggravate deep neck infection, especially in the upper deep cervical and wide range types, it is also involved with aggravation of parotitis and wide expansion of inflammation.

Declining neutrophil function resulting in impaired phagocytosis and decreased bactericidal action occurs in the elderly patients requiring hemodialysis, and patients with diabetes [5,6]. Systemic hyperglycemia results in derangement of the immune system including the neutrophil function, cellular immunity, and complement function. Therefore, glycemic control is crucial in the management of diabetic infections [6]. Moreover, diabetic infections might be populated with various bacterial flora, so it is important to obtain culture and sensitivity data for their management [6].

Although the present study found little difference in the incidence rate of diabetes mellitus between patients requiring surgical drainage and those not, this result does not deny the necessity of surgical drainage. Even a patient with diabetes mellitus could probably be cured by intravenous administration of antibiotic alone, before the condition became so bad that surgical drainage was needed. However, once an abscess is formed, inflammation spreads rapidly unless surgical drainage is performed. Therefore, diagnostic imaging or immediate surgical drainage should be considered, especially in patients with diabetes mellitus or poor immune reaction associated with a high-degree of inflammation.

The causes of deep neck infections vary according to the standards or the patients surveyed [3,6], and the prevalence of cases with unknown cause has been reported from 17% to 67% [3,4,7]. The present study suggests that inflammation in some structures carries a high risk of deep neck infection as shown in Table 2. Laryngopharyngitis or tonsillitis was responsible for 21 (32%) of all cases of deep neck abscess (63% of the wide range type), and 2 cases of the upper deep cervical type were also due to the spread of inflammation around the palate tonsil to the masticator and the parotid spaces. These conditions are considered to cause deep neck infection, and if complicated with diabetes mellitus, may become even more aggravated.

Spread of inflammation in the odontogenic region caused five (45%) of 11 cases of the oral cavity floor type, and two (22%) of 9 cases of the submandibular type (Table 2). Inflammation of the second and third mandibular molars is known to drain to the submandibular lymph nodes, but odontogenic infection can also affect the submental lymph nodes [9,12,16,17]. One of our cases of the upper deep cervical type required surgical drainage, because the odontogenic infection had spread and formed an abscess around the mandibular bone, directly extending to the parotid space. Since odontogenic infection may spread to the surrounding structures, causing the danger of mediastinitis [7,18], all odontogenic infections should be treated thoroughly.

In the present study, there was no case that was obviously caused by odontogenic infection or sialolithiasis. This may indicate that oral disorders can develop deep neck infection with or without diabetes mellitus, compared with causes of other causes (Table 2). We think that unsanitary oral cavity conditions and poor immune condition are involved in deep neck infection as previously suggested [9].

Among the deep cervical structures, an understanding of the anatomy of the cervical fascia, which is the fibrous connective tissue that envelopes and divides the structures of the neck and creates potential spaces, is critical for assessing the location of a deep neck infection and predicting the extent of infection, because infections in these spaces can result from direct extensions from other spaces of the head and neck, or from the primary sites [2,8]. The parapharyngeal space is divided into the prestyloid and poststyloid compartments. The prestyloid compartment, the bottom of which is partitioned by the hyoid bone, is connected to the submandibular and sublingual spaces, and also to the retropharyngeal space [7,8,10,19]. The poststyloid compartment is the carotid space and leads to the mediastinum [10,20]. On the other hand, the danger space, which is located behind the retropharyngeal space, extends into the posterior mediastinum, and mediastinitis occurs if inflammation spreads to that area and then downward [2,11,19,21]. Infection is reported to pass through the retropharyngeal space in 70% of cases, the carotid space in 21%, and the pretracheal space in 8% [1]. Thus, there are several routes that infection can take to spread from the neck to the mediastinum. If the infection is likely to spread to these danger regions, complete and total treatment including urgent drainage will be essential.

In one of our two cases with mediastinitis, the cause was unclear and infection had spread into the mediastinum through the pretracheal space. It had a complication of diabetes mellitus. Meanwhile, the other had no complications and was caused by retrotonsillar abscess, and infection had spread through the pretracheal and retropharyngeal spaces, and thoracic drainage was needed. In fact, retrotonsillar abscess occurs close to parapharyngeal and retropharyngeal spaces (Fig. 2A), so it often spreads to these spaces, leading to life-threatening complications [22–24]. In our present study, the cause for deep neck infection was peritonsillar abscess in 7 cases, and retrotonsillar abscess in 8 cases. In addition, while 5 of the 7 peritonsillar abscess cases had complication of trismus, it was only one that had it among the 8 retrotonsillar abscess cases. This may mean that unlike peritonsillar abscess (Fig. 2B), retrotonsillar abscess does not usually cause trismus, presumably because it is anatomically far from the masticator space. However, this condition must not be overlooked as deep

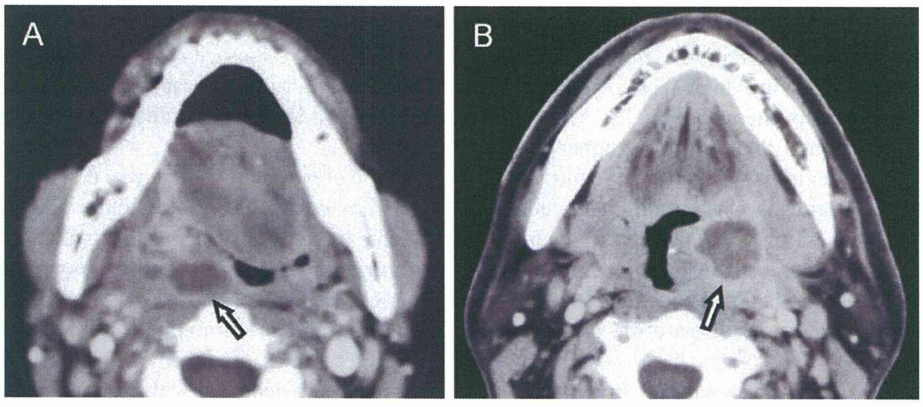

Fig. 2. (A) Representative case of retrotonsillar abscess (arrow) in a 39-year-old female. (B) Representative case of peritonsillar abscess (arrow) in a 34-year-old male.

neck infection may result. Therefore, we consider that both peritonsillar abscess and retrotonsillar abscess carry high risk of developing deep neck infection and sometimes also cause mediastinitis, so we should make an immediate diagnosis and surgical drainage.

The airway must also be examined and treated at the initial visit, because inflammation in the neck can spread to the larynx. In our series, more than a quarter of each localized type, excluding the upper deep cervical type, and more than half of the wide range type were associated with laryngeal edema (Table 1). These types are considered to carry the risk of edema of the larynx, and the complication ratio of laryngeal edema is high in patients with serious deep neck infection. Oral intubation may be difficult in patients with serious deep neck infection, because of trismus, neck swelling, mass effect, or edema of the tongue, pharynx, or larynx, but urgent airway control may become necessary. Therefore, we should not hesitate to perform emergency tracheotomy in order to immediately secure airway management. In addition, patients with neck infection who underwent tracheotomy had shorter stays in the hospital and intensive care unit compared with those who were intubated [25]. This suggests that tracheotomy provided better use of critical care resources with reduced cost.

4.2. Bacterial analysis

Various aerobic and anaerobic bacterial species causing deep neck infection have been detected [3,5,9]. The members of the SMG are normal inhabitants of the mucosal surface of the mouth capsule, and include *S. constellatus*, *S. intermedius*, and *S. anginosus*. In recent years, the SMG has been suspected to be involved in not only oral infection but also in such systematic purulent diseases as empyema, hepatic abscess, and cerebral abscess [26–29]. The SMG was responsible for 33% of the deep neck abscess cases in a previous series [28], emphasizing the importance of these bacteria. SMG infection of the mucosal surface results in production of tissue-destroying enzymes and immunosuppressive substances. As a result, the phagocytic and bacteria-killing abilities of neutrophil cells are suppressed, and the infection spreads rapidly. SMG infection also induces growth of resident anaerobes in the oral cavity, resulting in synergic infection [26–29]. In addition, it is reported that SMG caused cervical necrotizing fasciitis [29]. If the SMG is detected as the causative microorganism of oral infection, measures to prevent worsening of infection and strict control of the whole body as well as the local area are necessary [29].

In the present study, the SMG was identified in 13 (33%) of the 40 cases in which bacteria were detected. Their causes were tonsillitis (peritonsillar and retrotonsillar abscess), odontogenic infection, and sialoadenitis (Table 3), and surgical drainage was needed in all the cases with the SMG. We thought that the presence of the SMG might promote abscess formation, and consequently increase the need for surgical drainage in patients without diabetes mellitus.

Few case reports have described drug resistance to the SMG [30], but we detected some types of bacteria with resistance to beta-lactams, aminoglycosides, and lincosamides. If the SMG has similar drug resistance, we should perform surgical drainage as soon as possible and then carefully observe the subsequent course, since satisfactory improvement cannot be expected with the administration of intravenous antibiotics alone. To prevent the spread and development of inflammation and promote early improvement, identification of the causative bacteria and selection of antibiotics are as important as surgical drainage.

5. Conclusion

The present retrospective study investigated those factors that aggravate deep neck infection. Males were more prone to develop deep neck infection. Oral disorders like odontogenic infection or sialolithiasis can develop to deep neck infection independently of the presence of diabetes mellitus, presumably because of unsanitary oral cavity conditions and immunodeficiency. The presence of diabetes mellitus was

considered to aggravate deep neck infection by exacerbating parotitis and promoting wider spread of inflammation. Infection due to the SMG can form abscess independently of diabetes mellitus. Retrotonsillar abscess easily spreads to the retropharyngeal and parapharyngeal spaces and can cause mediastinitis. Additionally, those deep neck infections that have developed to anatomically dangerous areas required careful treatments including immediate diagnostic imaging and surgical drainage during the clinical course. Since more than half of the wide range type and more than a quarter of each of the localized types except the upper deep cervical type were associated with laryngeal edema, we should take airway management into consideration.

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