で検出される．点変異の検出は，それぞれの変異に応じたミスマッチプライマーを作製し，PCRの後に制限酵素切断をすることで変異の有無を調べる方法が一般的である[13]（図3）．

5. 蛋白質コード領域の変異（図4）

蛋白質コード領域で最初に報告された点変異は，母系遺伝する夜盲を主症状とするLeber視神経萎縮症の患者からのものである[15]．ND4領域の11778位のGがAに変異していた．この変異はホモプラスミーで検出され，筋病理では特徴的なミトコンドリア形態変化はない．ただ，ND4を含む複合体Ⅰの機能低下を組織化学的に検出できる方法が開発されれば，形態学的に異常をとらえられなくはないだろう．同様なことは，乳児期に精神発達遅滞で発症する重症のLeigh脳症で認められるATP6領域の点変異である8993変異でもいえる[16]．現在のところ，筋病理学的には明らかな異常をとらえられていない．したがって，このような例ではmtDNA検査が必須になる．また，COXのサブユニットの中に病的点変異が存在する場合は，COX染色で活性低下を認めるはずであり，この場合は筋病理検査が有用な情報を提供する．

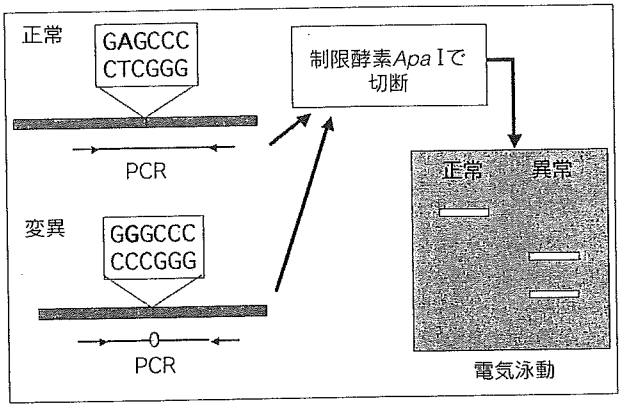

図3　PCR制限酵素切断法による点変異の検出

もっとも頻度の高い3243変異を検出する方法で，3243位の塩基がA（アデニン：正常）からG（グアニン：変異）に変化している場合，その部分を含むDNA領域をPCR法で増幅し，制限酵素*Apa* Iで切断すると，変異をもつDNAだけ切断される．切断されると電気泳動で簡単に検出できる．

6. 核DNA上の遺伝子変異

電子伝達系酵素複合体の核DNA由来のサブユニット遺伝子変異は，複合体Ⅰの*NDUFV1*，*NDUFS4*，*NDUFS7*，*NDUFS8*，*NDUFS2*，*NDUFS1*の6個に発見された[17]．複合体Ⅰの核由来サブユニットは三十数個知られており，これ以外のサブユニット遺伝子の変異の存在することは否定できない．しかし，すべての複合体Ⅰ欠損症に対して，30個以上の遺伝子を網羅的に検索することは困難であり，いまのところ遺伝子診断に臨床応用することはできていない．これらの多くは，生化学的には複合体Ⅰ欠損を示し，臨床的にはLeigh脳症，心筋症のあるのが特徴である．また，あるLeigh脳症患者では，複合体Ⅱのフラボプロテインサブユニットをコ

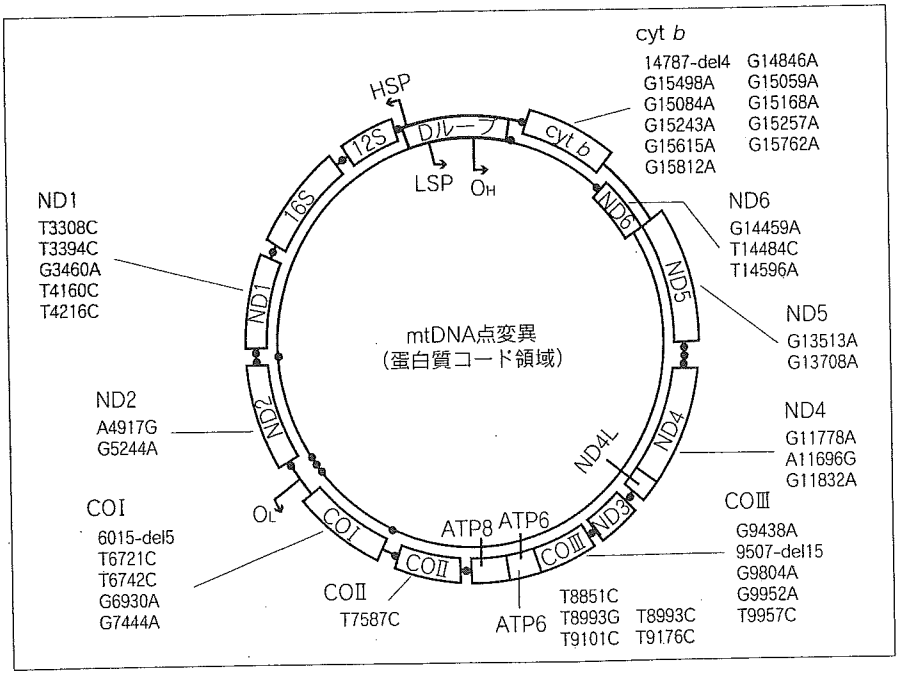

図4　蛋白質コード領域の病的点変異

ミトコンドリアDNAのなかで，蛋白質をコードしている部分に存在する点変異を示す．

ードしているSDHA遺伝子の変異が報告された[18].

電子伝達系酵素複合体サブユニットそのものではなく,集合にかかわる因子の遺伝子異常も報告されている.その代表は,COX欠損を伴うLeigh脳症で認めるSURF-1変異である[19].この遺伝子産物の機能はまだ明らかにされていないが,欠損するとCOX集合に障害の起こることが示されている.また,同じCOX欠損を示す患者で,心筋症を伴う脳筋症患者でSCO2[20],肝不全を伴う脳筋症患者でSCO1[21],また別の脳筋症患者でCOX10の遺伝子変異が報告された[22].また複合体Ⅲ欠損患者で,集合因子であるBCS1L遺伝子の変異が同定されている[23].

ミトコンドリアDNAの維持・複製にかかわる核DNA由来因子の遺伝子変異も次々と明らかにされている.この場合,mtDNA側の異常としては,多重欠失と欠乏状態が惹起される.これらはすでに,多重欠失と欠乏状態の項で述べた.

■おわりに■

mtDNAの異常は,ここで述べたミトコンドリア病に留まらず,癌組織でmtDNA変異が蓄積しているとか,老化現象の原因になっているとか,新たな知見が出てきている.今後も種々の病態にmtDNA異常がかかわっていることが明らかになっていくと考えられ,その研究の重要性は疑いない.

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遺伝子診療学

—遺伝子診断の進歩と遺伝子治療の展望—

A. 遺伝子診断（genetic diagnosis）

（遺伝学的検査 genetic testing，遺伝子検査 gene-based testing，
核酸検査 nucleic acid-based testing）

I. 総　　論

遺伝疾患の分類と分子遺伝学的発症機構

ミトコンドリア遺伝病

後藤雄一

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ミトコンドリア遺伝病

Mitochondrial genetic diseases

後藤雄一

Key words：ミトコンドリアDNA，母系遺伝，ボトルネック効果，ヘテロプラスミー，閾値効果

はじめに

ミトコンドリア病は細胞小器官であるミトコンドリアの機能異常に起因する病気であり，多種多様な症状を引き起こす．その理由は，ミトコンドリアが成熟赤血球とケラチノサイト以外の細胞に必ず存在しており，ミトコンドリア機能異常が細胞死や細胞のもつ機能に障害を与えるからである．特に，エネルギー依存度の高い細胞(筋細胞，神経細胞，心筋細胞など)はその障害が現れやすく，骨格筋，中枢神経，心などはその代表である．

本稿では，ミトコンドリア病の中でも，ミトコンドリアDNA(mtDNA)異常によって起きる病気をミトコンドリア遺伝病としてとらえ，その解説を行う．

1. ミトコンドリア病を起こす遺伝子異常

ミトコンドリア病の原因は，大きく分けて，mtDNA異常によるものと核DNA上にコードされている遺伝子変異によるものとがある(図1)．

a. mtDNAの異常

実際の患者に認められるmtDNA異常には，量的異常と質的異常がある．量的異常とは，mtDNA欠乏状態のことである．この病因は遺伝的な場合と後天的な場合との2つがあり，遺伝的には乳幼児期に肝不全や腎不全で死亡した家系や，また後天的にはAIDSの治療に用いられるAZTによるものが有名である．

mtDNAの質的異常には，点変異と構造異常(欠失/重複)がある．点変異は，存在する領域によって，転移RNA領域とそれ以外(リボソームRNAおよび蛋白領域)とに分けられる．転移RNA領域に変異をもつ患者では，筋病理学的にragged-red fiber(RRF)などの形態異常を示すことがほとんどであり，比較的診断が容易であったことが多くの変異が同定された要因である．臓器症状が多彩で，症例ごとで違いが著しいという特徴を有している．一方，転移RNA以外の領域の点変異は，筋病理学的に異常所見が乏しく，ミトコンドリア異常を確実に証明することが困難であったことから，病因としての点変異の確認数は少なかった．しかし，最近の研究により病因的変異の確定は不十分のものはあるものの，この領域に数多くの点変異が報告されている．その代表はLeigh脳症とLeber遺伝性視神経萎縮症で認められる点変異であり，これらの患者は比較的均一の臨床症状を示す．

点変異と異なり，構造異常の欠失と重複は，その遺伝形式が複雑である．欠失には，単一欠失と多重欠失があるが，単一欠失は，ヒトの病気で発見された最初のmtDNA異常で，慢性進

Yu-ichi Goto: National Institute of Neuroscience, NCNP　国立精神・神経センター神経研究所

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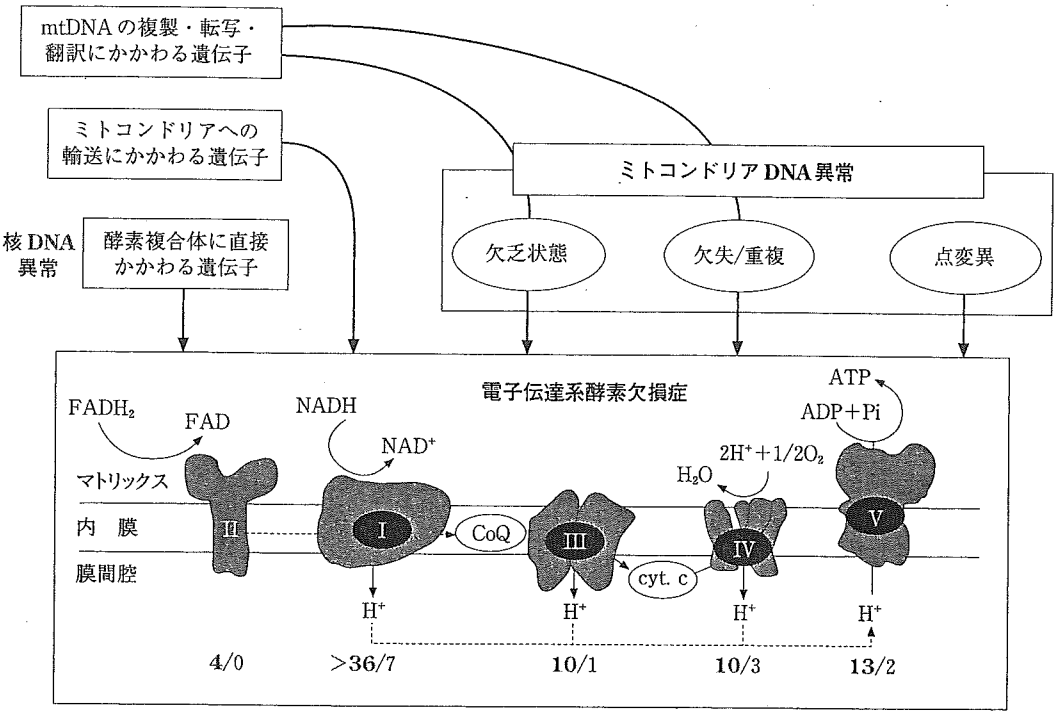

図1 ミトコンドリア病の病因

ミトコンドリア病の病因には核DNAとmtDNAがある．mtDNAは，電子伝達系酵素複合体のうち，複合体IIを除く4つの複合体サブユニットの一部をコードしているので，mtDNA異常は電子伝達系酵素欠損症として表現される．mtDNAの異常には量的異常の欠乏状態と質的異常の欠失/重複と点変異がある．また，興味深いことに，mtDNAの複製や維持にかかわる核DNA上の遺伝子変異により，2次的にmtDNA異常（多くは欠乏状態，多重欠失）が起き，それが病気の原因となるという病態もある．この場合は，上位の核DNA上の遺伝子変異の遺伝形式となるため，常染色体優性もしくは劣性遺伝となる．

行性外眼筋麻痺症候群（chronic progressive external ophthalmoplegia: CPEO）やKearns－Sayre症候群の臨床症状をもつ患者で認められる．これらの患者は散発性で，恐らく突然変異によるであろうと考えられた．しかし，多重欠失を認める常染色体優性遺伝の大家系が報告され，この場合はmtDNAの安定性や複製機構に障害を及ぼす核DNA異常が想定された（後述）．

また，重複をもつ患者が報告され，この場合も当初は突然変異であろうと考えられていたが，後になって母と子が同じ重複をもっている家系が報告され，一部の重複例は母系遺伝したものと考えられている．しかし，なぜ重複が子に伝わりやすいのかの機序は今のところ不明である．

b. 核DNA上の遺伝子変異

ミトコンドリア内に存在している電子伝達系酵素蛋白をコードする核DNA上の遺伝子変異が報告されている．複合体IIのサブユニットである*SDHA*遺伝子変異（複合体II欠損症），複合体Iのサブユニットである*NDUFS4*，*NDUFS7*，*NDUFS8*，*NDUFV1*などの遺伝子変異（複合体I欠損症），ミトコンドリア輸送蛋白の一つである*DFN1*遺伝子変異（ジストニア，難聴症候群）などである．また複合体IVのアッセンブリーにかかわると考えられている*SURF1*，*SCO1*，*SCO2*，*COX10*遺伝子の変異（複合体IV欠損症）が報告された．

更にmtDNAの維持や複製に直接影響を与える核DNA上の遺伝子の変異が次々と明らかにされている．重篤な消化管症状を伴うミトコンドリア脳筋症で常染色体劣性遺伝とmtDNAの多重欠失を伴うMNGIE（mitochondrial neu-

rogastrointestinal encephalomyopathy)では，thymidine phosphorylase 1(*TP1*)内の遺伝子変異と活性低下が示されている．また，常染色体優性遺伝形式のmtDNA多重欠失を示す家系から，adenine nucleotide translocator 1(*ANT1*)遺伝子，DNAポリメラーゼγ遺伝子(*POLG*)，*Twinkle*遺伝子に変異が同定されている．これらでは，核DNA変異とmtDNA異常が同時に存在することになる．

2. mtDNAの特徴と遺伝形式

mtDNAは，約16,500余りの塩基からなる環状二本鎖DNAであり，ミトコンドリア内で蛋白を合成するための2個のリボソームRNA，22個の転移RNAをコードしている．更に，電子伝達系酵素群のサブユニットの一部を構成する蛋白を計13個コードしている．核DNAと大きく異なる性質として以下の3つがあげられる．

a. マルチコピー性

1つの細胞内に数十～数百個存在する個々のミトコンドリア内に，mtDNAは5～10個ずつ存在しているため，1細胞では数百～数千個存在することになる．このマルチコピー性という性質は，患者で認める野生型と変異型が細胞内に混在するヘテロプラスミーという現象と密接に関係がある．また，ミトコンドリアは成熟骨格筋細胞のように筋原線維の構造に取り込まれその存在場所が固定されているが，そうでなければ，ミトコンドリアは細胞内で融合と分離を常時繰り返しており，1細胞内のヘテロプラスミーの比率はほぼ平均化されていると考えられている．

b. 易変異性

mtDNAは，核DNAに比べ変異の起こりやすさが5～10倍高いとされている．その理由は，ミトコンドリア内で変異原性のある活性酸素に曝露されていること，DNA損傷に対する修復機構が核に比べて弱いことなどがあげられている．したがって，この易変異性は，実際の患者においては突然変異という形で現れてくる．その代表例がmtDNAの欠失であり，その多くが散発性である．また，欠失がどの時点で起こったのかについては明らかにできていないが，健常女性から採取した未受精卵を用いた研究で，その卵からも欠失がわずかながら検出されたという報告がある．一方で，すべての卵に欠失が存在すると仮定すると，欠失をもつ患者がなぜこれほど頻度が少ないのかが新たな疑問になり，この点を明らかにするような欠失の出現，増幅，維持に関する研究が今後重要になると考えられる．

c. 細胞質遺伝

細胞分裂の際，核DNAは正確に複製が行われ，娘細胞には同一のDNAが伝わっていくのが原則である．それとは違って，mtDNAはミトコンドリア内に存在し，もしmtDNAのヘテロプラスミーがある場合は娘細胞に伝わる変異型mtDNAの割合は予測不能で，統計学的な分離(stochastic segregation)が起きる．また，遺伝物質が細胞質に存在するミトコンドリアにあるという意味で細胞質遺伝という用語も用いられる．

この細胞質遺伝が生殖細胞ではどのような現象になるかを考える．未受精卵には約10万個のmtDNAが存在する．一方，精子にはわずかのミトコンドリア(とmtDNA)しか存在していない．よって受精の際には，精子由来のミトコンドリアは卵の中に侵入しないか，もし侵入したとしてもそのミトコンドリア自体が消失する現象が知られている．この精子(父)由来ミトコンドリアの消失機序の詳細は不明である．結局，受精卵のミトコンドリア(とmtDNA)はすべて卵(母)由来となり，もしもともと未受精卵の中に変異mtDNAが存在し，その後の発生段階で有意な比率になれば病気を発症することになる．これが母系遺伝である．

このようにヒトでは母系遺伝はあっても，父系遺伝はないとされているが，実はハエやマウスなどでは父系遺伝の例が報告されている．そしてつい最近になって，ヒトのミトコンドリア病患者で父系遺伝と考えられる症例の報告があった[1]．症例は，軽い運動でも乳酸値が上昇する強い易疲労性を訴える男性(28歳)で，両親，妹は健康である．筋生検でRRFを15％認め，

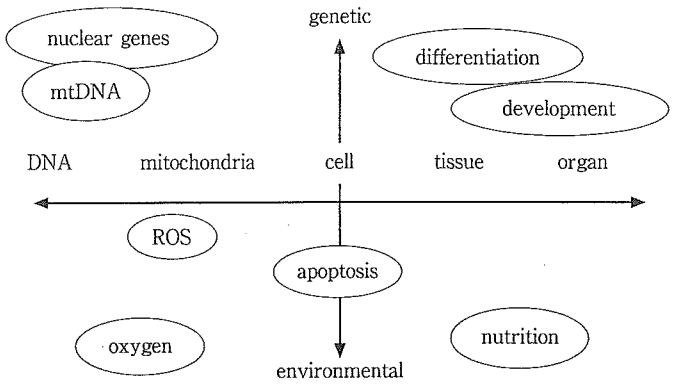

図2　変異率の変動にかかわる因子
変異率の変動にかかわる主な因子をDNAから個体までの形態レベルの軸と遺伝か環境かという要因による軸上に表現した．ROS：活性酸素．

生化学的に複合体I欠損を示した．mtDNA検査の結果，ND2遺伝子内に2塩基の欠失が見つかり，この変異は血液で10％，筋肉で90％のヘテロプラスミーであった．そして，この部位以外の領域の塩基配列を調べたところ，筋肉のmtDNAでは父と同じ多型が見つかり，血液のmtDNAでは母と同じ多型が見つかった．すなわち，病因と考えられる2塩基の欠失は父由来のmtDNA上に存在していたと考えるのが妥当であった．なぜ，筋肉だけに父由来のmtDNAが存在したのかについては全く不明であるが，著者らは，受精した精子のmtDNAにはもともと2塩基の欠失が生じており，それが受精時に消失せずに残り，しかもそれらが筋肉で有意な比率で存在したというメカニズムを推測している．しかし，その根拠は明確ではないし，その後の別の複数のグループの研究でも同様な例は見つかっておらず，現状では極めてまれな現象であると考えられる．

3. 変異mtDNAの蓄積とその効果

a. 閾値効果と細胞障害性

ヘテロプラスミーの状態で存在している変異mtDNAは，その比率が低いときはミトコンドリア機能に影響を与えない．しかし，ある一定の値（閾値という）以上になると，機能障害が現れてくる．このような閾値効果は，生化学的にも，病理学的にも確かめられており，逆にいうと閾値以下の変異率であれば変異mtDNAを有していても機能障害を免れていることを意味する．これは臨床的にも重要な所見であり，遺伝子検査で変異mtDNAが検出されても，病気と関係ない場合もあり得るということである．

一方で，これまでのミトコンドリア機能といえばエネルギー産生能を調べることであったが，実際のミトコンドリアにはそれ以外に活性酸素産生やカルシウムイオン調節などの働きがあり，これらの現象における閾値がどの程度であるかはまだよくわかっていない．エネルギー産生が低下する場合より低い閾値でこれらに影響が出ている可能性が否定できない．その意味で，ミトコンドリア病以外のParkinson病，Alzheimer病などの神経変性疾患，糖尿病，高血圧などの生活習慣病にもミトコンドリア機能異常がかかわっていることが次第にわかってきている．

b. 変異率変動要因とボトルネック効果

変異mtDNAの比率を変動させるものとして，形態的なレベルと遺伝/環境レベルという2つの軸からなる場に位置づけられる種々の要因があげられる（図2）．これらの要因が細胞内の変異mtDNAの比率の変動に効いてくるには，変異mtDNAの優先的増幅やmtDNAの損傷出現などのDNAレベルの効果や，細胞分裂や細胞死などの細胞レベルの効果などに直接的または

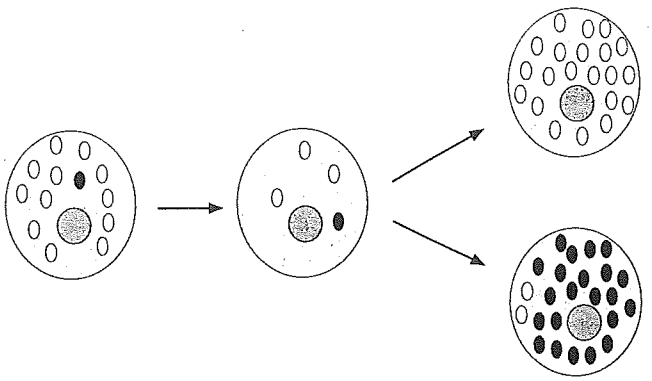

図3 ボトルネック効果
通常のミトコンドリア(とmtDNA)の数が著しく減少すると，その後の数の回復過程で変異mtDNAが爆発的に優位になる可能性がある．このような現象をボトルネック効果という．

間接的にかかわることが必要である．この比率決定に関する要因の研究は，ミトコンドリアの病理を理解し治療法を開発することに極めて重要であるものの，まだよくわかっていないことが多い．最近，細胞特異的にある種のmtDNAを優先的に増殖させる因子の存在が示されたり[2]，活性酸素が欠失mtDNAの増加を促す証拠などが得られたりしている[3]．

その中でも，比率を大きく変動させる要因として最も知られているのがボトルネック効果である(図3)．これは，細胞内のミトコンドリア(とmtDNA)の数が減少すると，通常ではほとんど比率に影響を与えないわずかな変異率の変化がその後の比率変動に大きく影響するというものである．例えば，1,000個あるmtDNAの中の1個のmtDNAに新たな変異が生じても0.1%の変化であるが，もし50個のmtDNAであれば2%の変化となり，その後のmtDNA数の回復の過程で変異mtDNAが何らかの理由でより優先的に増えると比率が大きく上昇する可能性がある．臨床的にも，Leigh脳症を起こす8993変異が1人の母から複数の子に種々の比率で伝わることが示されている．この場合，卵母細胞が著しくその数を増やすときに遺伝的なボトルネックがあると考えられており，成熟排卵前卵子には種々の比率を有するものが存在し，どの卵が受精するかで子に伝わる比率がほぼ決まってしまう．

4. 病型と遺伝形式

ミトコンドリア病の臨床病型は様々なものがあり，ここで詳細を解説できないが，主なものとしてMELAS(mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes)，MERRF(myoclonus epilepsy associated with ragged-red fibers)，CPEO，Leigh脳症などがある．これらの病型を示す遺伝子異常は一定していないが，まとめると表1のようになる．このように，臨床病型から遺伝形式が判明しないという点はミトコンドリア病の特徴であり，遺伝形式が明らかになるのでmtDNA検査を含めた遺伝子検査の臨床的意義は大きいと考える．ただし，母系遺伝については，その臨床的意義を患者やその家族に正確に説明する必要があり，言葉が一人歩きして，母や母方親族に無用な不安や負担をかけることのないように努めるべきである．その意味で検査前遺伝カウンセリングの必要性と重要性を再確認すべきである．

5. 今後のmtDNA検査の方向性と遺伝子治療の可能性

a. 今後のmtDNA検査

ミトコンドリア病の臨床症状の多様性，類似

表1 主な臨床病型の遺伝形式

MELAS	→	80％以上は母系遺伝，残り核性？
MERRF	→	80％以上は母系遺伝，残り核性？
慢性進行性外眼筋麻痺症候群（CPEO）	→	単一欠失：ほとんどが突然変異 重複あり：ほとんどが突然変異 ときに母系遺伝 多重欠失：大部分が突然変異 ときに常染色体優性/劣性
Leigh脳症	→	mtDNA点変異：母系遺伝，まれに突然変異 核遺伝子判明：常染色体劣性，X連鎖劣性 核遺伝子不明：恐らく常染色体劣性

した病型でもいろいろな遺伝子異常があり得ることなどから，mtDNA検査はより網羅的に行わなければならなくなるであろう．そうなると多数の変異を同時に検出できる安価な検査法を開発することが必要になる．

一方で，変異mtDNAはヘテロプラスミーで存在していることが多く，しかも罹患臓器ではない血液を用いた検査を行わなければならない場合，その変異率はかなり低い可能性がある．また，罹患臓器を検査対象とする場合でも変異率をある程度正確に求めることが必要になる．その意味で，検出限界を下げることと同時に，変異率の正確な測定ができる方法が必要になるであろう．

出生前診断は，基本的にヘテロプラスミーで発症するMELASやMERRFではその適応ではない．なぜなら，絨毛細胞や羊水細胞での変異率からその後の発症を予測することが不可能であるからである．しかしながら，ほぼホモプラスミーで発症する8993変異によるLeigh脳症の場合は適応になる．

b. 遺伝子治療の可能性

mtDNAはミトコンドリア内に存在するという現実のために，なかなかmtDNAを直接改変させる方法が確立できないでいる．しかもmtDNAの複製やmtDNA数の調節を行っている機構についても未知の部分が多い．変異mtDNAを正常に復する方法を獲得するには，更なる基礎研究が必要である．一方で，ヘテロプラスミーで発症している病気の場合，その変異率を人為的に低下させることができれば，理論的に治療と発症予防が可能になる．この方針の下で，変異率変動因子の全容を解明し，変動因子の調節を行う方法を臨床に応用する研究が重要であると考える．

おわりに

ミトコンドリア病は核DNA上の遺伝子とmtDNAの双方の異常で起きるが，mtDNAのもつ特殊性から核DNAとは全く異なるアプローチが必要になる．しかし，基礎研究と臨床研究とのタイアップで，新たな診断法や治療法の開発が可能になるものと期待する．

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Neuro-Otologic Findings in Unilateral Isolated Narrow Internal Auditory Meatus

Ken Ito, Sayaka Suzuki, Toshihisa Murofushi, Shin-ichi Ishimoto, Shinichi Iwasaki, and Shotaro Karino

Department of Otolaryngology, Faculty of Medicine, University of Tokyo, Tokyo, Japan.

Objective: To report neuro-otologic findings concerning the four nerves in the internal auditory meatus (IAM) in patients with isolated congenitally narrow IAM and explore the implications regarding ontogeny of the nerves in the IAM.
Design: Retrospective case series study.
Setting: University hospital.
Subjects: Five consecutive patients between 1997 and 2002 with unilateral isolated narrow IAM demonstrated by high-resolution computed tomography whose chief complaint was hearing loss (1 male and 4 females, 4 right sides and 1 left; age range 5–37 years, mean 20 years; IAM diameter at the porus: 26–33% of that on the normal side).
Main Outcome Measures: Functional studies concerning the VIIth cranial nerve and the three branches of the VIIIth cranial nerve.
Results: In all ears, auditory brain stem responses were absent, the speech discrimination score was 0%, and otoacoustic emissions were absent or markedly reduced compared with those on the normal side. Caloric responses were absent in two ears, reduced in two ears, and normal in one ear. Galvanic body sway tests showed no responses in the two ears in which caloric responses were absent. Inferior vestibular nerve function was estimated as normal in all ears on the basis of vestibular evoked myogenic potential recordings. Facial nerve functions were normal in all patients.
Conclusions: In isolated congenital stenosis of IAM, dysfunction of each nerve in the IAM can occur independently. In the ontogeny of the VIIIth cranial nerve, the cochlear and superior vestibular nerves tended to be involved together, whereas the cochlear and inferior vestibular nerves appeared independent of each other. **Key Words:** Narrow internal auditory meatus—Facial nerve—Cochlear nerve—Vestibular nerve—Ontogeny—Neuro-otological findings.
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Nonsyndromic congenitally narrow internal auditory meatus (IAM) is rare, especially as an isolated finding without inner, middle, or external ear anomalies (1–5), whereas acquired stenoses of IAM were more frequently reported, such as osteomas, exostoses, and fibrous dysplasias (6–8). Although single case reports have appeared recently, neuro-otologic dysfunctions have not been well elucidated. It is known that cochlear nerve atrophy sometimes causes a problem after cochlear implant surgery.

Because it is not possible to conduct experimental research on human development, congenital anomalies are very important in giving us a clue to understanding the processes that occur in ontogeny. This study is to report neuro-otologic findings of five cases in our institution and to deduce what occurs during ontogeny of the four nerves in the IAM.

Address correspondence and reprint requests to Dr. Ken Ito, Department of Otolaryngology, Faculty of Medicine, University of Tokyo, 7–3–1 Hongo, Bunkyo-ku, Tokyo 113–8655, Japan; E-mail: itoken-tky@umin.ac.jp

SUBJECTS

Study comprised five consecutive patients between 1997 and 2002 with isolated congenitally narrow IAM demonstrated by high-resolution computed tomography (HRCT) whose chief complaint was hearing loss (1 male and 4 females, 4 right sides and 1 left, age range 5–37 years, mean 20 years). All patients had unilateral narrowing of the IAM. No other osseous anomalies of the body and no other developmental problems were found in any patient.

METHODS

Dimensions of IAM

Measurements were obtained after McClay et al. (9). Diameter of IAM at the porus (average of height and width) and length of IAM were measured using HRCT.

Functional Studies

In all patients, the following tests/recordings were performed: pure-tone audiograms, auditory brainstem responses, speech discrimination scores, distortion product otoacoustic emissions (DPOAEs), caloric responses (ice water, recorded by electronystagmograph), vestibular evoked myogenic

responses (VEMPs), facial nerve scores (House-Brackmann grade), and stapedial reflexes (contralateral stimulation on the normal side). Patients without caloric responses on the affected side underwent galvanic body sway tests (GBSTs). The GBST directly stimulates the vestibular nerves and presumably represents the function of the superior vestibular nerve innervating the utricle because this test evaluates the lateral sway of the center of foot pressure (10). In patients without VEMPs, electrically evoked myogenic potentials (galvanic-VEMPs) were also recorded. The galvanic-VEMP test, a counterpart of the GBST, also stimulates the vestibular nerves directly and presumably represents the function of the inferior vestibular nerve innervating the saccule because it records the muscular responses similar to the VEMPs of the saccular origin (11,12).

None of the patients had any complaint other than hearing loss. In Cases 1 to 4, profound hearing loss appeared to have been fixed from birth. Case 5 reported episodes that suggested progression of hearing loss. No patients experienced tinnitus or vertigo. On examination, all patients had normal ear drum with type A tympanograms, and none of the patients had nystagmus. A detailed description of Case 1 was published elsewhere (13). Case 5, whose course of hearing loss appeared somewhat atypical compared with the other four cases, is presented below.

CASE PRESENTATION (CASE 5)

A 17-year-old woman was referred to the University Hospital complaining of hearing loss on the right side. When she was 3 years old, she underwent paracentesis for otitis media with effusion. Although right-sided hearing impairment had already been pointed out at that time, there was no further examination. At the age of 15, she noticed right ear fullness and exacerbation of hearing loss. One year later, ear fullness on the right recurred, and she consulted a primary physician. Although she underwent steroid administration therapy under a diagnosis of sudden deafness, there was no improvement in hearing. She did not experience tinnitus, vertigo, or fluctuation of hearing level. Except for hearing impairment, her past history was unremarkable. No one in her family had suffered hearing impairment. Physical examination findings in the head and neck were normal, including the tympanic membranes.

Imaging Study

HRCT

There were no abnormalities found in the external auditory meatus or the middle ear on either side (Fig. 1). The IAM, cochlea, vestibule, and semicircular canals were normal on the left side. Although the inner ear structures were also normal on the right, the right IAM was very narrow, and at the periphery, branched small canals for the four nerves in the IAM were identified.

Magnetic Resonance Imaging

On the left side, inner ear structures were normal, and the cochlear and superior vestibular nerves in the IAM were clearly identified (Fig. 2). On the right side, the cochlea, the vestibule, and the semicircular canals were normal. However, the right cochlear nerve was not identified, whereas the right superior vestibular nerve was clearly visible.

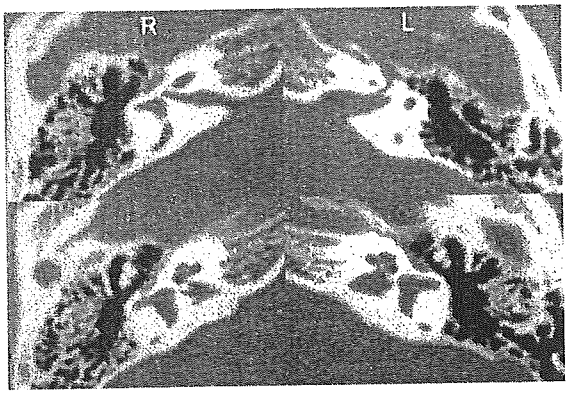

FIG. 1. Axial high-resolution CT scans of the internal auditory meatus (IAM). Compared with the normal left IAM (L), the right IAM (R) is much narrower, and shows branching in the IAM.

Neuro-Otologic Findings

Auditory

Pure-tone audiometry demonstrated sensorineural hearing impairment of the right ear (pure-tone average 73 dB) and normal hearing in the left ear (Fig. 3*A*). DPOAE studies confirmed normal responses in the left ear but very poor responses in the right ear, indicating severe impairment of the outer hair cell (OHC) function (Fig. 3*B*). Auditory brainstem response showed a normal response in the left ear but no response in the right ear.

Vestibular

The patient did not demonstrate nystagmus, dysequilibrium, or ataxia. Caloric responses were normal on the left but absent on the right side. GBSTs showed normal responses (deviation of 11 mm) on the left, but there were no responses on the right side. VEMPs (click) were normally recorded on the left but were absent on the

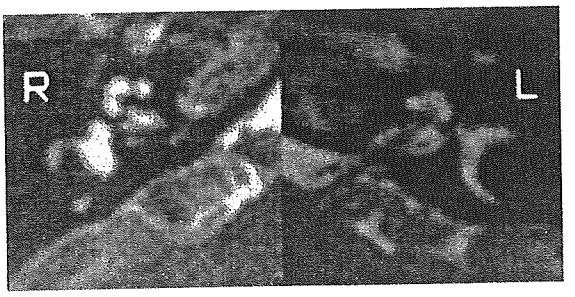

FIG. 2. Axial three–dimensional-constructive interference on steady state (3d-CISS) MRIs. On the left side, cochlear and superior vestibular nerves are identified in the fluid (high) intensity in the IAM. However, on the right, only the superior vestibular nerve can be identified, and the narrow route to the cochlea, seen in the CT, is filled with the fluid intensity.

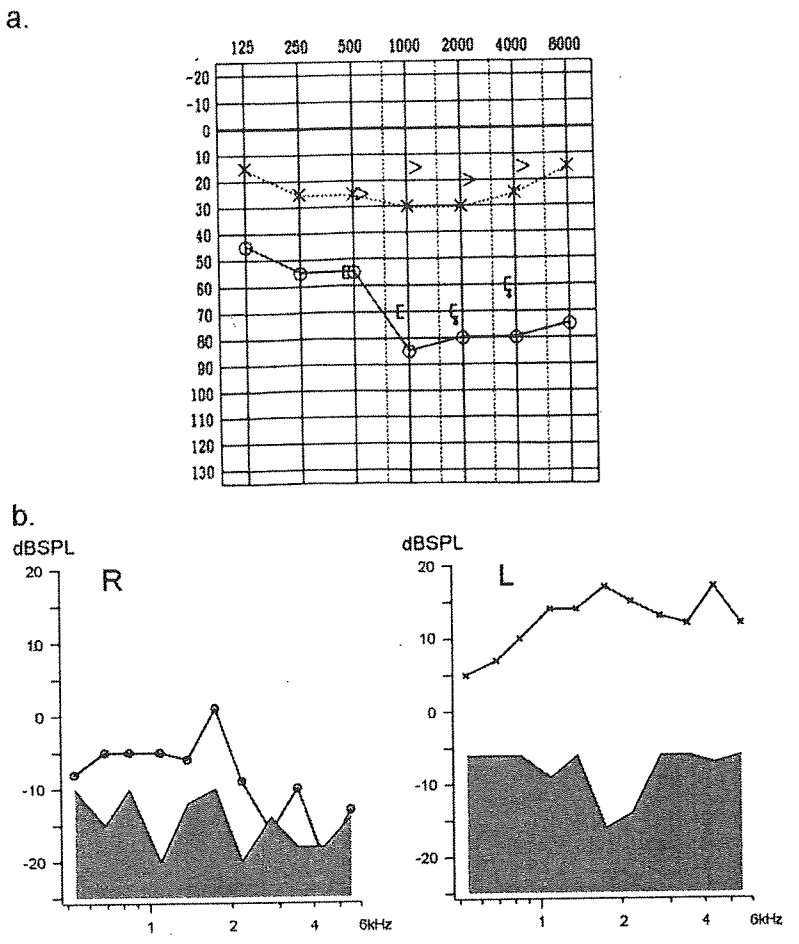

FIG. 3. (*A*) Audiograms. (*B*) DPOAEs.

right side (Fig. 4*A*). However, galvanic VEMPs (3 mA, 1 ms) were normally recorded on both sides (Fig. 4*B*).

Other

Type A tympanograms were recorded on both sides. SRs were normally recorded on the right ear when the tones were delivered to the left ear, indicating normal facial nerve function on the right side. Physical examinations of facial nerve functions were normal. Other cranial nerve tests demonstrated the absence of abnormalities.

RESULTS

Dimensions of IAM

The diameter of the IAM on the affected side was 1.4 to 2.2 mm, mean 1.8 mm (26–33% of that on the normal side), and the length was 12 to 17 mm, mean 14 mm (93–109% of that on the normal side).

Functional Studies

The test results are summarized in Table 1. Pure-tone average was immeasurably high, and no DPOAE responses were found in four patients (Cases 1–4). One patient (Case 5) had severe sensorineural hearing loss with markedly reduced DPAOE responses compared with the normal side. In all ears, auditory brain stem responses were absent, and the speech discrimination score was 0%. Caloric responses were absent in two ears, reduced in two ears (canal paresis 30–40%), and normal in one ear. GBSTs did not show any responses in the two ears in which caloric responses were absent, whereas the normal sides showed normal responses. VEMPs were normally recorded in four ears. In one patient (Case 5) in whom VEMPs were absent on the affected side, galvanic-VEMPs were normally recorded on the same side, suggesting that inferior vestibular nerve function was normal and that the lesion existed in the inner ear (i.e., saccule). Facial nerve functions were normal in all patients.

DISCUSSION

Table 2 shows functional findings in each of the four partitions in the IAM (cochlear, superior vestibular,

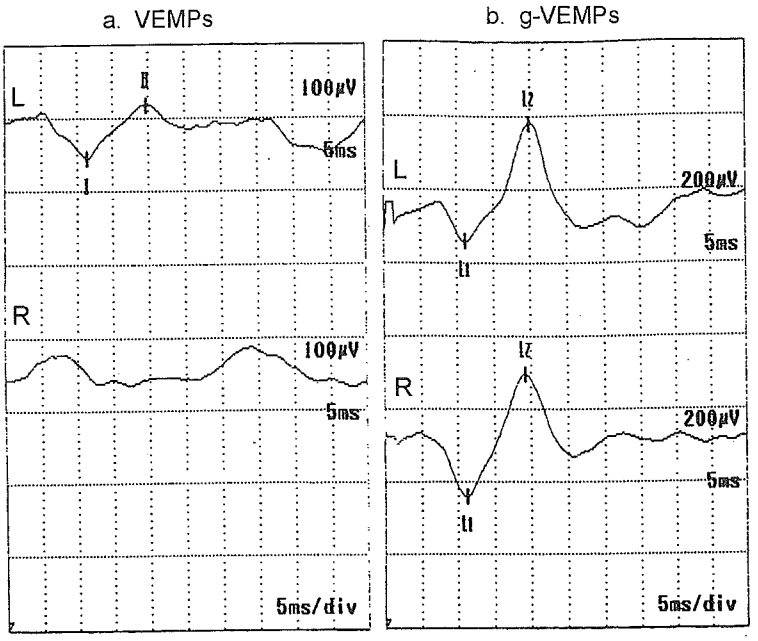

FIG. 4. Recordings of vestibular evoked myogenic potentials (*A*) and galvanic VEMPs (*B*). Stimuli were ipsilaterally delivered as rarefaction clicks of 95 dBn HL for VEMPs (stimulation rate 5 Hz, analysis time 50 ms, averaging 200 traces) and ipsilaterally delivered 3 mA current for 1 ms for g-VEMPs.

inferior vestibular, and facial partitions). In the cochlear partition, OHC damage and impairment of cochlear nerve or inner hair cells can be discriminated by functional tests. In the inferior vestibular partition, nerve damage can be detected by galvanic-VEMPs. However, in the superior vestibular partition, labyrinthine and retrolabyrinthine damage cannot be discriminated at present. GBST is a candidate for detecting superior vestibular nerve damage because body sway is considered to reflect utricular responses. As to the cochlear partition, severe inner ear or cochlear nerve dysfunction was found in all ears. Superior vestibular partition was variably impaired: severe impairment in two ears, moderate impairment in two ears, and normal function in one ear. Inferior vestibular partition was principally not impaired, with one exception (Case 5), in which saccular impairment, but not inferior vestibular nerve dysfunction, was found. The facial nerve was not affected.

Not many articles reported vestibular findings in narrow IAM (1,14–19). OHC function was poor or absent in all four ears in which otoacoustic emission responses were measured, caloric responses were present in three of the seven ears tested, and VEMPs were normally evoked in one ear tested. These reports are in accordance with the present findings.

Our results showed that dysfunction of each nerve in the IAM can occur independently. In the ontogeny of the VIIIth cranial nerve, the cochlear and superior vestibular nerves tend to be involved together, whereas the cochlear and inferior vestibular nerves appear independent of each other. This is in clear contrast with congenital inner ear anomalies, in which cochlea and saccule (pars inferior) tend to be coinvolved, and utricle and semicircular canals (pars superior) tend to be preserved (20). The reason for this discrepancy between the inner ear and the primary sensory nerves in terms of developmental coupling among partitions (cochlear, superior vestibular, and inferior vestibular) is unknown. One possible explanation is the difference of neurotrophic factors involved. It is shown that brain-derived neurotrophic factor is the major survival factor for vestibular ganglion neurons, and neurotrophin-3 for spiral ganglion

TABLE 1. *Results of neuro-otologic tests concerning the VIIth and VIIIth cranial nerves*

Case	Age/sex/side	PTA	SDS	OAE	ABR	CP	GBST	VEMP	g-VEMP	FM, SR
1	31/F/R	>110 dB	0%	no	no	0%		normal		normal
2	5/F/R	>110 dB	0%	no	no	30%		normal		normal
3	9/F/L	>110 dB	0%	no	no	40%		normal		normal
4	37/M/R	>110 dB	0%	no	no	100%	(−)	normal		normal
5	17/F/R	73 dB	0%	poor	no	100%	(−)	(−)	normal	normal

Dark gray indicates afunction, and light gray dysfunction.

PTA, pure-tone average; SDS, speech discrimination score; OAE, distortion product otoacoustic emission; ABR, auditory brain stem response; CP, canal paresis; GBST, galvanic body sway test; (g-)VEMP, (galvanic) vestibular evoked myogenic potential; FM, facial movement; SR, stapedial reflex.

TABLE 2. *Functional findings of each partition of the four nerves in the internal auditory meatus*

Case	Cochlear partition		Superior vest. partition	Inf. vest. partition		
	OHC	IHC and/or nerve	LSCC and/or nerve	Saccule	Nerve	Facial nerve
1	(++)	(++)	(−)	(−)	(−)	(−)
2	(++)	(++)	(+)	(−)	(−)	(−)
3	(++)	(++)	(+)	(−)	(−)	(−)
4	(++)	(++)	(++)[a]	(−)	(−)	(−)
5	(+)	(++)	(++)[a]	(++)	(−)	(−)

[a]Superior vestibular nerve dysfunction was confirmed by galvanic body sway test.
Dark gray indicates afunction, and light gray dysfunction.
(++) Afunction or severe dysfunction; (+) Impaired function; (−) Normal function.
OHC, outer hair cell; IHC, inner hair cell; LSCC, lateral semicircular canal.

neurons (21). However, the difference between superior and inferior vestibular ganglion neurons has not yet been elucidated. For example, this coupling between cochlear and superior vestibular partitions could be accounted for if the superior vestibular ganglion neurons also depended partly on neurotrophin-3 as well as on brain-derived neurotrophic factor.

In this study, we used CT to evaluate the abnormality of the IAM because magnetic resonance imaging is of limited use with a narrow IAM in contrast with the cochlear nerve aplasia with a normal-sized IAM in which nerve bundles can be visualized in the high-intensity IAM space with T2-weighted images (22). Although magnetic resonance imaging was useful in a certain, rather exceptional, occasion with a narrow IAM (13), it is usually not possible to discriminate between cochlear nerve aplasia and hypoplasia even with the highest resolution because nerve bundles are not well visualized in the small IAM space with T2-weighted images and because it is difficult to identify a very thin nerve bundle using T1-weighted images.

From the smooth outlines of the narrow bony canals, it is supposed that the narrowing was formed congenitally by the excessive bone proliferation around the atrophic nerves in the course of ontogeny. Acquired stenosis such as fibrous dysplasia or osteoma causes the outlines of the stenotic canal to look irregular, showing constriction only at the portion where the lesion existed (6,7). Neural growth factors excreted from the developing otic capsule induce the VIIIth cranial nerve, and the mesoderm eventually transforms into cartilage and ultimately ossifies around the VIIth and VIIIth cranial nerve, forming the IAM. Therefore, it is assumed that IAMs can normally be formed around normal VIIIth nerves only (1,3). Although the normally shaped cochlea demonstrated by imaging studies suggests that the cochlea was formed during ontogeny, impairment of the organ of Corti in all affected ears of the patients, demonstrated by otoacoustic emission testings that showed OHC dysfunction, supports this hypothesis.

A question remains regarding the onset of hearing loss in Case 5. In addition to the congenital hearing loss caused by the hypoplastic VIIIth nerve, there is a possibility of progression. The cochlea and the hypoplastic cochlear nerve might have been further damaged postnatally for certain reasons (e.g., a sudden decrease in cochlear blood supply caused by inflammation, edema and so on) because the cochlear artery is an end artery. In this relation, acquired facial palsy in a case of IAM stenosis was previously reported (15). Therefore, when this disorder is encountered, we suggest that the thorough neuro-otologic examination, preferably including inferior vestibular nerve evaluation, should be performed and that the patient should be followed up on a regular basis (e.g., once per 1–2 years).

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Correlation Between Microtia and Temporal Bone Malformation Evaluated Using Grading Systems

Shin-ichi Ishimoto, MD; Ken Ito, MD; Tatsuya Yamasoba, MD; Kenji Kondo, MD; Shotaro Karino, MD; Hideki Takegoshi, MD; Kimitaka Kaga, MD

Objective: To evaluate the relationships between temporal bone abnormalities and the severity of microtia in Japanese patients using objective grading systems.

Design: Retrospective case series study conducted between 1992 and 2003.

Setting: Academic, tertiary care, referral medical center.

Patients: One hundred forty-two ears of 109 Japanese patients (85 male and 24 female patients; mean age, 12.8 years [range, 2-36 years]) with microtia.

Main Outcome Measures: The severity of microtia was classified according to Marx classification. Developmental abnormalities of the temporal bone were evaluated by a computed tomographic (CT) scoring system modified after the system used by Jahrsdoerfer and colleagues, using high-resolution CT scans of the temporal bone. Correlations between the scores obtained from these 2 grading systems were evaluated using a nonparametric statistical method.

Results: Male preponderance and incidence of bilateral cases of approximately 30% were observed in our Japanese patients with microtia. There was no significant difference in the severity of microtia between unilateral and bilateral cases. The mean±SEM total points in the CT scoring system (full marks, 10) was 7.9±0.4 for grade I microtia, 6.6±0.6 for grade II, and 6.4±0.3 for grade III; the total points correlated inversely with the microtia grade. Development of the auricle correlated significantly with aeration in the middle ear spaces but not with ossicular development or formation of the oval/round windows. Proportion of acceptable surgical candidates according to the CT scoring system (>5 points) was 79% for grade I microtia, 52% for grade II microtia, and 65% for grade III microtia.

Conclusion: The principle "the better developed the auricle, the better developed middle ear" was confirmed in Japanese patients with microtia; however, even with grade II/III microtia, more than half of the patients were considered suitable for atresia surgery.

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Author Affiliations:
Department of Otolaryngology, Faculty of Medicine, University of Tokyo, Tokyo, Japan (Drs Ishimoto, Ito, Yamasoba, Kondo, Karino, and Kaga); and Department of Otolaryngology, Saitama Medical Center, Kawagoe, Saitama, Japan (Dr Takegoshi).
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THE INCIDENCE OF CONGENital aural atresia ranges from 1 in 10000[1] to 1 in 15000[2] births. Congenital aural atresia is a serious birth malformation in which the auricle, the external auditory canal (EAC), middle ear structures, and the inner ear may fail to develop. The degree of microtia ranges from smaller pinna with a normal shape to almost complete absence of pinna with rudimentary soft tissue. The state of the auricle can be classified into 3 types using the classification described by Marx.[3] The EAC anomaly varies from slightly narrow canal to complete atresia.[4-8] Abnormalities of the middle ear structure include stapes deformity, absence of oval and/or round windows, aberrant course of facial nerve, poor pneumatization of the middle ear space, and fusion of malleus and incus.[4-6,9-13] The incidence of inner ear abnormalities associated with microtia is estimated between 10% and 47%.[14]

Surgery for congenital aural atresia is one of the most challenging and difficult procedures in otology because this condition is often accompanied by various temporal bone anomalies, such as aberrant facial nerve, deformity of ossicles, defect of oval window, and lack of mastoid pneumatization.[4,5,7,8,13,15] Preoperative high-resolution computed tomography (HRCT) is indispensable for the surgical planning because it provides important anatomical information. For determining good surgical candidacy, Jarhsdoerfer et al[8] developed a grading system based on preoperative temporal bone HRCT and appearance of the auricle. This computed tomographic (CT) scoring system consists of 9 parameters related to temporal bone anatomy. The presence of a well-defined stapes scores 2 points, whereas all other parameters are assigned 1 point

Table 1. Distribution of 142 Microtic Ears With External Ear Anomalies According to the Criteria of Marx[3] Classification

	Bilateral			Unilateral			
Grade	Right, No.	Left, No.	Subtotal, No. (%)	Right, No.	Left, No.	Subtotal, No. (%)	Total, No. (%)
I	4	7	11 (17)	10	12	22 (29)	33 (23)
II	6	4	10 (15)	3	8	11 (14)	21 (15)
III	23	22	45 (68)	26	17	43 (57)	88 (62)
Total	**33**	**33**	**66 (100)**	**39**	**37**	**76 (100)**	**142 (100)**

each.[8] A presurgical rating of 8 points or more translates into an 80% chance of restoring hearing to near-normal levels.[8,9] This grading system allows accurate prediction of the surgical outcome, and patients with scores less than 6 are considered unsuitable for surgical correction.

The correlation between microtia grade and severity of middle ear abnormalities has been reported.[10] Better developed auricles have more developed middle ear structures and, therefore, the severity of microtia may be used as an indicator of middle ear development in microtia.[10] However, previous studies only examined white patients, and to our knowledge, no studies have yet examined Asian patients. Moreover, the correlation between individual parameters of the CT scoring and microtia grades has not been evaluated. In the present study, we investigated the relationship between severity of microtia and temporal bone abnormalities in a Japanese population.

METHODS

The subjects included 142 ears of 109 patients with microtia (85 male and 24 female patients; mean age, 12.8 years [range, 2-36 years]), who were seen between August 1992 and October 2003 and underwent HRCT examination of the temporal bone at the University of Tokyo Hospital, Tokyo, Japan. Those who had other anomalies associated with systemic syndromes, such as Treacher Collins and Goldenharr syndromes, were excluded from this study.

The severity of microtia was classified into grades I, II, or III according to the classification used by Marx.[3] In brief, grade I microtia exhibits only mild deformity, with the auricle being slightly smaller than normal, each part of which can be clearly distinguished. In grade II microtia, the size of the auricle is one half to two thirds of the normal size and its structure is only partially retained. In grade III microtia, the auricle is severely malformed and usually exhibits a peanut shape.

The HRCT images of the temporal bone were obtained using the Aquilion Multi CT system (Toshiba, Tokyo, Japan). Continuous slices of 1.0-mm thickness were obtained in both axial and coronal planes at 120 kV (peak) and 160 mA. The anomalies of the temporal bone were graded according to the CT scoring system used by Jahrsdoerfer et al,[8] with slight modification, in which the parameter "appearance of external ear" in the original grading system was replaced with the parameter "external ear canal present." The original grading system used by Jahrsdoerfer and colleagues[8] is useful for selection of candidates for atresia surgery. The relationship between the development of the auricle and the structures of the temporal bone was evaluated in the present study. The replacement of the parameter of the "external ear canal present" was more appropriate for this study because the parameter of "appearance of external ear," which is one of the most important elements, was included in the Marx classification.[3] If the external auditory ear was absent or not more than a small mound of skin and cartilage on the face (ie, grade III according to Marx classification[3]) no point was assigned in the classification used by Jahrsdoerfer and colleagues[8]). No other changes were made to the other parameters including their assigned scores.

Table 2. Sex of 109 Patients With Microtia

		Unilateral		
Sex	Bilateral	Right	Left	Total
Male, No.	28	27	30	85
Female, No.	5	12	7	24
Total	**33**	**39**	**37**	**109**

The distribution of parameters of the CT scoring system was examined in relation to the grade of microtia. We also evaluated the correlation between the CT scoring and Marx classification. For correlational analyses, Spearman nonparametric rank correlation coefficient was calculated for Marx classification and total scores of the CT scoring (full mark, 10 points) and between Marx classification and the following 3 subtotal scores reflecting specific development: (1) subtotal of parameters related to ossicular development (sum of "stapes present," "malleus/incus complex," and "incudostapedial connection"; full mark, 4 points); (2) subtotal of parameters related to windows connected to the cochlea (sum of "oval window open" and "round window"; full mark, 2 points); and (3) subtotal of parameters related to aeration of the middle ear cavity (sum of "middle ear space" and "mastoid pneumatization"; full mark, 2 points).

RESULTS

Table 1 gives the distribution of microtic ears according to the side and severity as classified using the Marx classification.[3] The distribution according to the side and sex is given in **Table 2**. There was no significant difference in the severity of microtia between unilateral and bilateral cases (t test, 2-tailed). Male patients were predominant in our sample. Moreover, there was no significant difference in the severity of microtia between male and female patients. The inner ear anomalies such as agenesis of the cochlea and the enlarged vestibular aqueduct were not found in these patients.

Table 3 demonstrates the distribution of parameters of the CT scoring system in relation to the grade of microtia. Correlations with Marx classification were evalu-

Table 3. Distribution of Each Parameter of the Computed Tomographic Scoring System*

Parameter	Assigned Point	Marx Classification, %		
		I	II	III
Related to ossicles				
Stapes present	2	70	52	59
Malleus/incus complex	1	94	100	88
Incudostapedial connection	1	67	48	48
Related to the window's connection to the cochlea				
Oval window open	1	85	71	76
Round window	1	94	95	85
Related to aeration development of middle ear				
Middle ear space	1	100	90	85
Mastoid pneumatization	1	85	62	63
Facial nerve	1	64	57	60
External ear canal present†	1	58	33	9

*Modified after the system used by Jahrsdoerfer and colleagues[8] in relation to the Marx classification.[3]
†$P<.001$.

Table 4. Correlation Between Total/Subtotal Points and the Marx[3] Classification*

Variable	Points, Full Mark	Marx Classification			r	P Value
		I	II	III		
Total points	10	7.85	6.62	6.35	−0.251	.003
Subtotal points related to development of ossicles, windows, and aeration						
Ossicles	4	3.00	2.52	2.53	−0.136	.11
Windows	2	1.79	1.67	1.61	−0.119	.16
Aeration	2	1.85	1.52	1.48	−0.189	.03

*Data are given as average points and Spearman rank correlation coefficient (r) with P values.

ated in total points and 3 subtotal points related to ossicles, windows open to the inner ear, and aeration of middle ear (**Table 4**).

Total points correlated significantly with the microtia grade, indicating that better developed auricles have better developed middle ear spaces that are more suitable for surgery. For comparison between microtia grades, 1-way analysis of variance showed a significant difference between mean values by grades ($P=.02$), and the Sheffe test, a post hoc test suitable for multiple comparison, showed a significant difference between grades I and III ($P=.02$). The differences between the other pairs (grades I and II, $P=.23$; grades II and III, $P=.91$) failed to reach statistical significance.

With regard to the 3 subtotal points, only the sum points of aeration of the middle ear correlated significantly with the microtia grade. One-way analysis of variance for intergrade comparison revealed significant difference only with sum points regarding aeration ($P=.02$) and not with sum points regarding ossicles ($P=.29$) or windows ($P=.34$). In the intergrade comparison for sum points regarding aeration, the Sheffe test showed significant difference only between grades I and III ($P=.03$) but not between the other pairs (grades I and II, $P=.22$; grades II and III, $P=.96$). These results indicate that the difficulty of ossicular reconstructive surgery, which is closely related to the existence of oval/round windows and deformity of ossicles, does not necessarily depend on the microtia grade.

The proportion of candidates suitable for surgery according to the CT scoring system (>5 points) was 79% for grade I microtia, 52% for grade II microtia, and 65% for grade III microtia.

COMMENT

Microtia has been reported to occur predominantly in male individuals (male-female ratio, 2:1). Furthermore, the incidence of bilateral microtia is reported at 10% to 30%, with right ear involvement in 55% to 65% of unilateral cases.[1,6,16,17] The findings of the present study in Japanese individuals were similar to the aforementioned data (male-female ratio, 4:1; incidence of bilateral case, 30%; and incidence of right-sidedness in unilateral cases, 51%). The severity of microtia was not different between unilateral and bilateral cases.

A previous study reported that the average atresia score according to CT grading system correlates with the severity of microtia,[10] in which the average atresia score was 8.5 in grade I microtia, 7.2 in grade II microtia, and 5.9 in grade III microtia. Similarly, in our patients, total points of the CT scoring system correlated inversely with the severity of microtia. These results support the principle

"the better developed the auricle, the better developed middle ear."

To our knowledge, the correlation between microtia grades and CT parameters (subtotals) regarding development of specific components of the middle ear has not been reported previously. Our study indicates that auricular development correlated significantly with the aeration in the middle ear spaces but not with the ossicular development or formation of the oval/round window. The auricle, middle ear epithelium lining the air cells, ossicles, and stapes footplate capping the oval window are thought to arise from neural crest cells of the first branchial arch, endodermal cells of the first branchial arch, neural crest cells of the first and second branchial arches, and mesodermal cells of the otic capsule, respectively.[18,19] Differences in correlation among specific components may reflect differences in their origin during development.

Takegoshi and colleagues[15] performed a similar study on patients with mandibulofacial dysostosis and found a positive correlation between attic formation and microtia severity. The antrum and the mastoid air cells were absent in the patients with mandibulofacial dysostosis. In our study, the mastoid air cells were not necessarily absent. The mastoid pneumatization were 85% in grade I, 62% in grade II, and 63% in grade III in these patients with microtia, except for those with systemic syndromes.

Microtia is usually accompanied by atresia or stenosis of the EAC. Abnormal EACs can be classified into 3 types: almost normal; narrowing of the fibrocartilaginous canal; and narrowing and tortuosity of both the fibrocartilaginous and bony parts of the canal. Surgical reconstruction of the EAC and ossicular chain is much easier when the EAC is present, even when it is very narrow and tortuous, because this acts as a landmark to help the surgeon to reach the tympanic cavity more safely. In addition, the presence of the EAC is very closely related to the formation of the manubrium.[20] The presence of the manubrium helps to reconstruct the tympanic membrane in its original position. These were the reasons why we replaced the parameter of "appearance of the auricle" in the original scoring system used by Jahrsdoerfer and colleagues[8] with "existence of EAC." As is evident from the distribution shown in Table 3, the parameter "existence of EAC" correlated significantly with the microtia grade ($P<.001$), confirming that replacement of the parameter in the overall scoring system would be beneficial in determining the candidacy for atresia surgery.

In conclusion, the principle "the better developed the auricle, the better developed middle ear" was confirmed in Japanese cases of microtia; however, even with grade III microtia, more than half of the patients were acceptable candidates for atresia surgery. Auricular development correlates significantly with aeration in the middle ear spaces.

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Correspondence: Shin-ichi Ishimoto, MD, Department of Otolaryngology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan (shinchan-tky@umin.ac.jp).

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Friedman et al. criticize the use of Muller's maneuver, questioning its reproducibility and validity as predictive tool.[3] They argue that assessment with Muller's maneuver can identify palatal obstruction preoperatively and that elimination of palatal obstruction will increase the airflow postoperatively. Eliminating palatal obstruction may result in increasing negative pressures with subsequent obstruction at a lower level. We fully agree that Muller's maneuver is not a very valuable test to predict the obstruction site. Remodelling the upper airway does have consequences for its dynamics and airflow patterns, which may result in obstruction at tongue base level rather than at hypopharyngeal level. Changing the architecture of the upper airway might be an additional reason why we cannot predict surgical outcomes preoperatively.

Anatomical staging has a large cost-benefit when compared to sleep endoscopy, but we believe that combining the two tests may help improving surgical outcomes even more, since both policies lead to fewer UPPP failures. In case the outcome of both screening tests is equal, there is little reason for concern. In case of conflicting outcome, however, it remains unclear which of the screening modalities is superior. In this respect, more research is mandatory.

CINDY DEN HERDER, MD
Resident of ENT, St. Lucas Hospital Amsterdam
Amsterdam, Netherlands

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Bent (Head-Down) Posture and Aberrant Common Carotid Arteries of the Neck: Another New Risk Factor for Stroke?

Dear Editor:

We previously suggested the possibility that aberrant carotid arteries in the area of the mouth are a new risk factor for atherosclerotic stroke.[1,2] We then speculated that stroke is associated with aberration of the internal carotid artery as follows: if the neck is bent forward, the distance between the central carotid artery and the skull base becomes shorter. To adjust to this shorter distance, a vein shortens and widens. An artery, however, cannot do so if it is atherosclerotic. Because it cannot shorten, the internal carotid artery is forced to bend. The internal carotid artery is located within the parapharyngeal space, the only nonrigid borders of which are the medial and inferior areas. For these reasons, the mouth is anatomically the most likely site for aberration of the internal carotid artery to occur. Marked aberration in patients with severe atherosclerosis causes turbulent blood flow that produces plaque and leads to brain infarctions.

After our previous reports, we performed routine examinations to detect signs of aberrant carotid arteries in aged patients with chronically bent (head-down) posture. We encountered five patients with bent posture without aberrant carotid arteries in the mouth region. The necks of those patients were chronically bent forward, and thus the distance between the central carotid artery and the skull base was shortened. However, even though the distance was shortened, we did not find any aberration inside the mouth, pharynx, and larynx even with fiberscopic examination by way of the nasal route. Finally, we determined that the common sign in these patients was aberration of the common carotid artery in the neck.

In general, the common carotid arteries are covered not only by the layers of the fascia but also by the sternocleidomastoid muscle (SCM) and the strap muscles of the neck. We realized that the carotid arteries were bent under the SCM in our patients. (Fig. 1) On ultrasonography, no difference in blood flow was seen between the two common carotid arteries; plaque was found inside both. Magnetic resonance imaging studies showed asymptomatic or symptomatic cerebral infarctions in all cases.

Advanced age with bent posture (cervical kyphosis) increases not only the incidence of aberration of the inter-

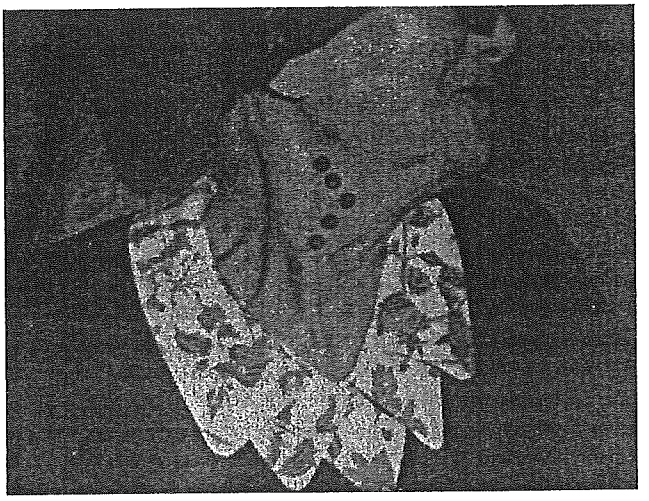

Fig. 1. The carotid arteries (red dots) were bent under the sternocleidomastoid muscle in a 74-year-old female. She had a history of stroke and atherosclerosis, with bent posture.