4. 補聴器の装用

Clinical Question
AN の補聴器のフィッティング

【推奨文】

　補聴器は音声を増幅して聞き取り難くなった聴力を補助するものである。したがって、AN の小児難聴の場合も、閾値上昇があり音声が聞き取り難い場合であれば、補聴器の適応がある。なお補聴器の選択と調整は、他の聴覚障害児への対応と何ら違いはないと考えられる。ただし、AN の障害では、閾値の上昇とともに時間分解能などが低下しており、騒音下での語音聴取が困難であるため、補聴器の調整と活用における課題は、騒音の制御となる。この具体的な対応としては、まず音環境の整備、すなわち騒音の除去を心がける。幼児期では FM 補聴援助用システムの活用も試みたい。また、近年のデジタル補聴器の雑音抑制機能、指向性機能の有用性には期待されているものの、現在のところは検討を重ね慎重な対応が望ましい。

【担当】

　　杉内　智子

5. 人工内耳の装用

Clinical Question
小児 AN 症例に対して、人工内耳は有用か
【推奨文】

　基本的には、日本耳鼻咽喉科学会の小児人工内耳適応基準に則った適応患者に対して手術が施行される。術前検査にて、画像検査（CT、MRI）で明らかな異常が無いこと（蝸牛の形態は正常で、蝸牛神経が確認される）、Electrically evoked ABR (EABR)にて正常反応であること１）は、人工内耳が有用である可能性を示唆させる。また、遺伝子検査にて OTOF 遺伝子変異が認められる症例は人工内耳が有用である可能性が高い。少なくとも補聴器での効果が限定的な場合は、人工内耳は有益な選択肢の一つと考えられる。

【文献】

　Gibson WP, Sanli H. Auditory neuropathy: an update. Ear Hear. 2007 Apr;28(2 Suppl):102S-106S.

【担当】

　新田　清一

6. コミュニケーション発達のリハビリテーション

Clinical Question
どのようなコミュニケーションモダリティを選択すればよいですか

【推奨文】

　乳児期にはその後の聴取能力や言語発達の推定が困難である。このため、初期介入期においてはあらゆるコミュニケーションモダリティに関する情報を提供すべきである。子どもの聴性行動や言語発達の経過を観察した上で、補聴器や人工内耳を検討するのか、又は視覚的手段（読話、手指法など）を選択していくのかについて総合的に判断する。

　補聴器や人工内耳による聴覚活用を行う場合にも、視覚的手段の併用が有効な場合もあるため、積極的に併用、活用すべきである。

【解説】

　AN と診断された児においては、補聴器や人工内耳により効果のある児や効果のない児、介入がなくとも年齢相応の言語力が獲得できる児など、その症状や経過は多様である (Berlin et al, 2010)。このため、乳幼児期には、子どもの聴性行動や言語発達経過について評価した上で、適切なコミュニケーションモダリティが選択できるようにする。このためには、聴覚障害児と同様、あらゆる可能性を検討した情報提供が必要となる。

　また、AN 児においては、補聴器や人工内耳を用いても十分な効果がみられない児がいることを考慮し、指導においては、視覚的な手段を積極的に取り入れること（Berlin, 2003）は重要といえる。

【文献】

1)Berlin, Hood, Morlet, Rose & Brashears. Auditory neuropathy/dys-synchrony: diagnosis and management. Ment Retard Dev Disabil Res Rev. 9, 225-231, 2003.
2) Berlin, Hood, Morlet, Wilensky, Li, Mattingly,Taylor-Jeanfreau, Keats, John, Montgomery, Shallop, Russell, & Frisch. Multi-site diagnosis and management of 260 patients with auditory neuropathy/dys-synchrony (auditory neuropathy spectrum disorder). International Journal of　Audiology. 49, 30-43, 2010.

【担当】

　　小渕　千絵

Clinical Question

どのようなハビリテーション内容で指導を行えばよいですか

【推奨文】

　基本的な指導方法は、聴覚障害児に対するハビリテーションと同様といえる。ただし、聴覚活用のみにこだわらず、様々な視覚的手段を有効に活用しながら指導を行うべきである。

　また、言語や読み書きだけでなく、社会での自立に向けた発達全般への関わりが重要である。

　医師、言語聴覚士、特別支援学校教諭などの多職種間での協力が不可欠といえる。

【文献】

Berlin, Hood, Morlet, Wilensky, Li, Mattingly,Taylor-Jeanfreau, Keats, John, Montgomery, Shallop, Russell, & Frisch. Multi-site diagnosis and management of 260 patients with auditory neuropathy/dys-synchrony (auditory neuropathy spectrum disorder). International Journal of Audiology. 49, 30-43, 2010.

【担当】

　小渕　千絵

Clinical Question

コミュニケーションや発達面を評価する上では、どのようなことに配慮すればよいですか

【推奨文】

　音声言語のみでの教示では理解できないことがあるため、口型を見せる、手指法を併用する、学童期以降では文字を見せる、などの配慮を行った上で、評価を実施する必要がある。

【解説】

　AN の診断を受けて、補聴器もしくは人工内耳を装用しても、聴覚のみでの語音聴力には個人差が大きい。このため、評価においては、手指法や文字、口型など様々な情報を利用した上で行うことが重要と考えられる。

【文献】

Berlin, Hood, Morlet, Wilensky, Li, Mattingly,Taylor-Jeanfreau, Keats, John, Montgomery, Shallop, Russell, & Frisch. Multi-site diagnosis and management of 260 patients with auditory neuropathy/dys-synchrony (auditory neuropathy spectrum disorder). International Journal of Audiology. 49, 30-43, 2010.

【担当】

　小渕　千絵

7. 新生児の AN スクリーニング

Clinical Question

新生児聴覚スクリーニングで AN を検出するにはどうすればよいですか

【推奨文】

　新生児聴覚スクリーニングを自動 ABR で実施し、refer となった場合に OAE を行います。OAE が pass であれば AN が疑われます。OAE が refer の場合には滲出性中耳炎などで refer になっていないか確認が必要です。

【解説】

　AN は ABR が無反応か難聴を示しますが、OAE は正常を示します。新生児聴覚スクリーニングが OAE にて行われますと pass となり、AN は検出されません。新生児聴覚スクリーニングが自動 ABR にて行われますと AN があれば refer となります。refer 児はさらなる検査として OAE が行われ、OAE が正常に出れば AN が疑われます。OAE が陰性の場合には滲出性中耳炎などで反応が陰性になっていないか確認が必要です。

　新生児聴覚スクリーニングが OAE で行われ pass となった場合は、AN に関してのハイリスク児であれば自動 ABR や耳小骨筋反射検査が行われるべきです。耳小骨筋反射が陰性または閾値上昇であれば AN が疑われます。

　AN の早期検出・早期介入のために新生児聴覚スクリーニングは自動 ABR と OAE の両方で行うのがよいとの意見もあります。

【担当】

　小河原　昇

Clinical Question

新生児の AN に関してのハイリスク要因にはどのようなものがありますか

【推奨文】

　早産、低出生体重、anoxia、高ビリルビン血症、敗血症、ゲンタマイシン・バンコマイシン・フロセマイド使用、血族結婚、難聴の家族歴、人工授精などは AN のリスクファクターと考えられています。NICU 児は AN が高頻度です。

　これらの要因を持つ新生児の聴覚スクリーニングは自動 ABR でなされるべきです。

【担当】

　小河原　昇

8. 一過性 AN の経過観察

Clinical Question
一過性 AN では ABR はいつ頃改善することが期待できるか
【推奨文】
　ハイリスク児では生後 6－8 ヶ月以内に少しは改善することが期待できる。

【解説】
　ハイリスク児の一過性 AN では ABR の改善が見られるのが、生後 4-6 カ月（平均 5.5 カ月）(Psarommatis)や平均 5.8 カ月（Madden)との報告が多い。時にもっと時間がかかる例も認められるが、一般的には 1 歳未満のうちに改善しなければ、一過性の可能性は低い。

【文献】
　Psarommatis I,et al:Transient infantile auditory neuropathy and its clinical implications. Int. J. Pediatr Otorhinolaryngol 2006, 1629-1637

【担当】
　守本　倫子

Clinical Question
ABR が改善する可能性が高いリスクファクターは何か
【推奨文】
　高ビリルビン血症と低出生体重児では ABR 改善の見込みが高い。

【解説】
　統計のレベルであるが、ABR 改善した群の平均体重 1.89kg に対し、改善しなかった群は 3.00kg であり、改善した群ではビリルビン値も高く治療を要した例が多かったとされている。ただし、ビリルビン値と ABR 閾値には相関がないとされている。

【文献】
　Madden C, et al: Clinical and audioogica features in auditory neuropathy. Arch Otolaryngol Head neck Surg 128, 1026-1030,2002

【担当】
　守本　倫子

8. 一過性 AN の経過観察

Clinical Question
AN のうち一過性の AN の頻度は

【推奨文】
　40%から 80%, 90%までさまざまであり、おそらく AN の定義が共通に定まらないと頻度も明らかにならないと思われる。

【解説】
　AN 診断の定義である ABR 閾値が 75dB＜（psarommatis）、70dB<（morimoto）、absent(Rance G)と異なり、それぞれ一過性の頻度は 90%、80%、40%であった。このため最終的な頻度を明らかにすることが困難である。

【文献】
1)Rance G,et al:clinical findings for a group of infants and young children with auditory neuropathy. Ear Hear 1999,20:238-252
2)Psarommatis I, et al:Transient infantile auditory neuropathy and its clinical impications. Int J pediatr otorhinoaryngol 2006,70:1629-1637
3)Morimoto N, et al:Risk factors for elevation of ABR threshold in NICU treated infants.Int J pediatr otorhinoaryngol2010,74,786-790

【担当】
　守本　倫子

9. 家族へのカウンセリング

Clinical Question
家族に対するカウンセリングは、誰が行うべきでしょうか
【推奨文】
　小児の全体的な発達評価も含めたフォローが必要となるため、耳鼻咽喉科医、言語聴覚士だけではなく、小児神経科医師、Social Worker、療育担当者など、児に係わるすべての職種が情報を共有した上で、複数の職種が参加することが理想的である。
　可能であれば、家族が自由に相談できる窓口を医療機関内に設けることが望ましい。

【担当】
　　安達　のどか

Clinical Question
家族へのカウンセリングで留意すべき点は
【推奨文】
　AN は、聴覚閾値、聴覚補償の効果、言語およびコミュニケーション発達など個人差が大きく、最初の診断の時点では予測することができない。更に小児の場合どれだけの支障があるかの判断が大変難しい為、慎重な観察が必要である。そのため、画一的な説明は避けるべきである。各時点で想定される全ての可能性（①補聴器など何もなくて問題ない②補聴器で効果がある③人工内耳で効果がある④補聴器や人工内耳での効果がない）、コミュニケーションモードの選択（聴覚情報のみならず視覚情報を取り入れるかなど）、療育先やその後の進路（聾学校、難聴療育施設、普通幼稚園、難聴学級、普通小学校など）の情報を提示し、発達段階ごとに親と共に考え選択する形がよい。

【担当】
　　安達　のどか

Clinical Question
発達の評価は誰が行うのでしょうか
【推奨文】
　可能な限り、全体の発達の評価は小児の発達評価の専門家（小児神経科医）が、言語の発達の評価は、言語聴覚士によるものが推奨される。特に就学時に進路先を迷うケースは、患児の発達評価などのより多くの情報が必要となる。

【担当】
　　安達　のどか

Clinical Question
家族が家庭生活上できることがあるか
【推奨文】
　家族が家庭生活上においてできる事柄としては、基本的には中等度・高度難聴児に対する児への関わり方が理想である。通常よりも大きめで、抑揚をつけ、はきはきした発音での声かけ、ややオーバーなリアクション等、難聴療育者が工夫して行うような事を家庭でも実践できるようにすすめる。小児の発達を促す上では、聴こえのみだけでなく全体的な発達を重視し、五感刺激を意識した療育が望ましい。

【担当】
　　安達　のどか

Ⅱ．　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表レイアウト

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Matsunaga T	Trends in genetic research on auditory neuropathy.	Kaga K, Starr A	Neuropathies of the Auditory and Vestibular Eighth Cranial Nerves.	Springer	London	2009	43-50
		Kaga K, Starr A	Neuropathies of the auditory and vestibular eighth cranial nerves.	Springer	London	2009	1-159

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Matsunaga T	Value of genetic testing in determination of therapy for auditory disorders.	Keio J Med	58(4)	216-222	2009
Mizutari K, Matsunaga T, Inoue Y, Kaneko H, Yagi H, Namba K, Shimizu S, Kaga K, Ogawa K	Vestibular dysfunction in a Japanese patient with a mutation of the gene OPA1.	J Neurol Sci	293	23-28	2010
Morimoto N, Taiji H, Tsukamoto K, Morimoto Y, Nakamura T, Hommura T, Ito Y	Risk factors for elevation of ABR threshold in NICU-treated infants.	Int J Pediatr Otorhinolaryngol	74	786-790	2010
泰地秀信、守本倫子、松永達雄	Auditory neuropathy spectrum disorder の乳幼児期における ASSR 閾値	Audiology Japan	53(1)	76-83	2010
松永達雄	Auditory Neuropathy の遺伝子	Clinical Neuroscience	29(12)	1409-1411	2011
大原卓哉、泰地秀信、守本倫子、本村朋子、松永達雄	OTOF遺伝子変異を認めるAuditory neuropathy spectrum disorderの乳幼児例における人工内耳装用効果	Audiology Japan	54(4)	289-297	2011
泰地秀信	乳幼児難聴の聴覚医学的問題「聴覚検査における問題点」.	Audiology Japan	54	185-196	2011
仲野敦子、有本友季子、松永達雄、工藤典代	Otoferlin遺伝子変異が確認された小児難聴症例の検討	Otol Jpn	22(1)	47-52	2012

Ⅲ． 研究成果の刊行物・別刷

Reprint from

Kimitaka Kaga, Arnold Starr (Eds.)
Neuropathies of the Auditory and Vestibular Eighth Cranial Nerves

Springer

Trends in Genetic Research on Auditory Neuropathy

Tatsuo Matsunaga

Summary

Various etiologies of auditory neuropathy (AN) have been reported, including genetic causes. Genes such as *OTOF* and *pejvakin* cause AN without other associated symptoms, that is, nonsyndromic auditory neuropathy. Syndromic AN, in which AN is associated with other related symptoms, has been frequently reported in hereditary neurological disorders such as Charcot–Marie–Tooth disease and mitochondrial disease. In these neurological disorders, specific genes and mutations that are related to AN are being revealed. AN may be caused by dysfunction of synapses in inner hair cells. For an example, function of inner hair cells is impaired but that of spiral ganglion cells is maintained in knockout mice of the *OTOF* gene. This finding implies that surgery for cochlear implants may be indicated in patients with AN caused by *OTOF* gene mutations because the spiral ganglion cells are preserved.

Key words Auditory neuropathy, Cochlea, Spiral ganglion, Hereditary hearing loss, Genetic test

History of Genetic Research on Auditory Neuropathy

Auditory neuropathy (AN) is a novel clinical concept of auditory disorder that is distinguished from general sensorineural hearing loss and is characterized by audiological test results indicating normal function of outer hair cells and impairment of auditory neurons [1,2]. Various causes have been reported for AN. In approximately half of AN patients, hearing loss is syndromic as a part of symptoms associated with known causes such as hyperbilirubinemia, anoxia, viral infection, high

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Table 1. Genetic causes related to nonsyndromic auditory neuropathy (AN)

Autosomal recessive	*OTOF*
	Pejvakin
	GJB2
Autosomal dominant	AUNA1 locus (13q14–21)
X related	AUNX1 locus (Xq23–27.3)
Mitochondrial	T1095C in12S ribosomal RNA

fever, hereditary neurological disorders, and immunological disorders [3]. In the other half, hearing loss is nonsyndromic, that is, the symptom is isolated. In some of the latter patients, autosomal recessive inheritance has been noted. Recently, *OTOF* gene mutations were found as the cause of such autosomal recessive non-syndromic AN [4]. Then, various mutations, genes, or loci such as the *pejvakin* gene [5], *GJB2* gene, T1095C mutation in mitochondrial 12S ribosomal RNA gene, and AUNA1 locus (13q14–21), were also found to be related to nonsyndromic AN (Table 1).

Some types of hereditary neurological disorders are known to be associated with AN, and these include Charcot–Marie–Tooth disease, Friedreich's ataxia, Refsum syndrome, Mohr–Tranebjaerg syndrome, mitochondrial disease, and autosomal dominant optic atrophy (ADOA). Recent progress in genetics has changed the classification of these neurological disorders. Details about subtypes of neurological disorders in association with AN are now becoming clear. As an instance, *peripheral myelin protein 22 (PMP22), myelin protein zero (MPZ), gap junction protein beta-1 (GJB1), early growth response 2 (EGR2)*, and *N-myc downstream regulated gene (NDRG1)* were found as the genes causing Charcot–Marie–Tooth disease [6]. *PMP22, MPZ*, and *NDRG1*, at least, have been reported to be associated with AN.

Epidemiology of Genetic AN

The prevalence of AN in children with severe or profound hearing loss has been reported to be 7% to 15%. AN occurs in bilateral ears in most patients. According to a study about the causes of AN, 42% of patients are associated with hereditary neurological disorders, 10% with toxic, metabolic, immunological, and infectious causes (anoxia, hyperbilirubinemia, drug reaction, demyelination, viral infection), and 48% with no known causes [3]. Many nonsyndromic AN cases with no known causes probably have a genetic basis. The inheritance pattern of such AN is mostly sporadic or autosomal recessive [4], rarely X-linked or autosomal dominant.

Pathophysiology, Diagnosis, and Treatment for Genetic AN

Pathophysiology

Because AN is diagnosed on the basis of audiological test results showing normal function of outer hair cells and impairment of auditory neurons, the pathophysiology of AN may be impairment of synapses in inner hair cells, auditory neurons, or both. In addition, impairment of central auditory pathways may be associated with such disorders. Hearing loss caused by impairment of inner hair cells is not compatible with the term "auditory neuropathy." However, impairment of inner hair cells is usually referred to as auditory neuropathy because current clinical tests cannot discriminate impairment of synapses in inner hair cells and auditory neurons.

Among nonsyndromic AN, some mutations in the *OTOF* gene cause impairment of inner hair cells [7], some mutations in the pejvakin gene may cause impairment of the organ of Corti and peripheral and central auditory neurons [5], and some mutations in the *GJB2* gene may cause impairment of inner hair cells and nerve endings beneath the hair cells. Among syndromic AN, studies on temporal bones from Friedreich's ataxia and Charcot–Marie–Tooth disease showed degeneration of spiral ganglion cells with or without degeneration of inner hair cells and demyelination of auditory neurons. A recent study on the temporal bones from an AN patient having a mutation in the *MPZ* gene revealed prominent loss of spiral ganglion cells and auditory neurons, and incomplete remyelination, as well as almost normal inner and outer hair cells. In this patient, detailed audiological evaluation demonstrated that hearing loss is mainly caused by decreased auditory input through a diminished number of auditory neurons [8].

Diagnosis

In clinical diagnosis of genetic AN, patients first undergo audiological evaluation to detect AN, followed by otological, genetic, and neurological evaluation of the etiology of AN. For audiological evaluation, diagnosis of sensorineural hearing loss is made by pure tone audiometry. A loss of speech comprehension that is out of proportion with pure tone hearing thresholds raises a suspicion of AN. Identification of preserved outer hair cell function by transient evoked otoacoustic emissions (TEOAE) or distortion product otoacoustic emissions (DPOAE), and confirmation of absent or prominently abnormal auditory brainstem response (ABR), lead to the diagnosis of AN. For diagnosis of etiology, patients or parents of AN children are first carefully asked about nongenetic factors, that is, risk factors during pregnancy, delivery, and neonatal and infantile periods such as anoxia, hyperbilirubinemia, prematurity, low birth weight, use of drugs, demyelinating disorders, or viral infection. Then, hereditary neurological disorders such as Charcot–Marie–Tooth disease,

Friedreich's ataxia, and mitochondrial disease are evaluated by neurological examination to make diagnosis of syndromic AN or nonsyndromic AN. Genetic tests for appropriate genes are conducted to identify genetic cause after obtaining informed consent.

Treatment

There has been no fundamental treatment for AN. Thus, auditory rehabilitaton using hearing aids or cochlear implants plays a central role for most AN patients. However, hearing aids are not as effective in AN patients compared to non-AN patients with equivalent level of pure tone thresholds because of poor speech comprehension, which is a characteristic feature of AN. Furthermore, in general, cochlear implants have also been thought to be ineffective for AN patients because auditory neurons cannot respond correctly upon stimulation. However, this is not the case for AN caused by *OTOF* gene mutations because the auditory neurons are normal in this type of AN. Theoretically, a cochlear implant, which directly stimulates auditory neurons within the cochlea, should be effective in AN caused by *OTOF* gene mutations. In fact, successful results of cochlear implants have been reported in this type of AN [4,9]. Cochlear implant was also reported to be effective for a family with AN mapping to the AUNA1 locus.

Representative Genes Causing Nonsyndromic Auditory Neuropathy

OTOF Gene

The *OTOF* gene is the first gene identified as the cause of nonsyndromic AN. The *OTOF* gene was originally found as a locus (DFNB9: 2p22–23) that is linked to autosomal recessive, congenital, severe to profound hearing loss. Then, it was identified as a gene coding the cell membrane protein otoferlin, which is expressed in the cochlea, vestibule, and brain [10]. *OTOF* consists of 48 exons, and has multiple isoforms, by alternative splicing combined with the use of several translation initiation sites. Otoferlin belongs to a family of membrane-anchored cytosolic proteins containing six repeats of a structural module that binds calcium (the C2 domain), and they are involved in vesicle membrane fusion.

   Mutant mice lacking otoferlin are profoundly deaf, with no detectable ABR across all sound frequencies tested. However, DPOAE show that outer hair cell function is maintained, as was seen in human AN patients. In these mice, the structure of the inner ear including hair cells and spiral ganglion cells is normal, but complete abolition of inner hair cell synaptic exocytosis in response to cell depolarization is detected, which is consistent with a failure of inner hair cell neurotransmitter release.

Genetic tests of *OTOF* gene were conducted in 65 American families with autosomal recessive nonsyndromic hearing loss, including 9 families with AN. Eight mutations that were related to hearing loss were found in 6 families, including 5 families with AN. One of these families, which had the I515T mutation, showed temperature-sensitive AN in which hearing loss is aggravated with elevation of body temperature and returns to mild hearing loss with normalization of the temperature. A nonsense mutation Q829X in *OTOF* gene was first identified in a Spanish population and was found in approximately 3% of autosomal recessive hearing loss in Spanish children, making it the third most frequent mutation in this population [11]. Later studies in other populations showed that the Q829X mutation also caused dysfunction of outer hair cells. Thus, it is necessary to explore the significance of this frequent mutation in both AN and non-AN sensorineural hearing loss.

Pejvakin gene

Pejvakin gene is the second gene to be identified as the cause of nonsyndromic AN [5]. This gene was identified in the DFNB59 (2q31.1-q31.3) locus by linkage analysis in two Iranian families with autosomal recessive, severe to profound, congenital hearing loss, in which T54I and R183W missense mutations were detected. Pejvakin protein consists of 352 amino acids, but its function has been unknown. Pejvakin protein is localized in the cochlear hair cells, supporting cells, spiral ganglion cells, and the first three relays of the central auditory pathway. On the other hand, dysfunction of outer hair cells was reported in a Moroccan family with insertion of T at 113–114 as well as in a Turkish family with homozygous nonsense mutation R167X and another Turkish family with homozygous missense mutation R183W which is the same mutation as in the Iranian family with non-syndromic AN. Furthermore, mutant mice that have an abnormal *pejvakin* gene demonstrated progressive hearing loss with or without the loss of otoacoustic emissions (OAE), depending on the mutation introduced in the pejvakin gene. These findings indicate that the *pejvakin* gene may cause both AN and non-AN sensorineural hearing loss, depending on the type of mutation and different background factors.

Representative Genes Causing Syndromic Auditory Neuropathy

Charcot–Marie–Tooth Disease

Charcot–Marie–Tooth disease is the most common hereditary peripheral neuropathy, characterized by slowly progressive weakness, muscle atrophy, and sensory impairment, all most marked in the distal part of the legs. Charcot–Marie–Tooth disease is classified into subtypes based on clinical features and causative genes, and hearing loss has been known to be associated with some of these

subtypes. Recently, AN was found in some of such Charcot–Marie–Tooth disease patients with hearing loss and established as a syndromic AN. The following three subtypes of Charcot–Marie–Tooth disease have been reported in association with syndromic AN.

Mutations in *PMP22* genes cause the CMT1A subtype of Charcot–Marie–Tooth disease, which shows autosomal dominant inheritance. PMP22 protein encoded by *PMP22* gene is a cell membrane protein that consists of approximately 5% of components of myelin sheath. AN has been reported in an American CMT1A family in which the A67P mutation was identified [12].

Mutations in the *MPZ* gene cause the CMT1B subtype of Charcot–Marie–Tooth disease, which shows autosomal dominant inheritance. MPZ protein coded by *MPZ* gene is a glycoprotein specific to Schwann cells, consists of approximately 50% myelin sheath components, and constitutes the myelin sheath as a complex with myelin basic protein and PMP22 protein. AN with an onset after 40 years of age has been reported in an American CMT1B family in which the Y145S mutation was identified. A study of temporal bone pathology in one member of this family revealed prominent loss of spiral ganglion cells and auditory neurons as well as well-preserved inner and outer hair cells [8].

Mutation in the *NDRG1* gene causes the CMT4D subtype of Charcot–Marie–Tooth disease, which shows autosomal recessive inheritance [13]. The *NDRG1* gene is highly expressed in Schwann cells and is expected to play a role in inhibition of mitosis and promotion of differentiation. R148X mutation in the *NDRG1* gene was identified in many European families in which AN was also found. In a CMT4D family, 25 of 39 family members complained of hearing loss that developed between 13 and 26 years of age.

Autosomal Dominant Optic Atrophy (ADOA) with Sensorineural Deafness

ADOA is a dominantly inherited disorder characterized by symmetrical optic atrophy, central visual impairment, and color vision defect. Although ADOA generally appears as an isolated disorder, it is sometimes associated with sensorineural deafness. Furthermore, some ADOA patients may be associated with not only sensorineural deafness but also several other phenotypes such as ataxia and peripheral neuropathy. Mutations in the *OPA1* gene have been found in a majority of patients with ADOA, and such mutations have also been reported in ADOA with sensorineural deafness and ADOA with deafness and other phenotypes.

The *OPA1* gene encodes a dynamin-related GTPase, which is targeted to mitochondria by an N-terminus import sequence motif and is anchored to the inner ear membrane facing the intermembrane space [14,15]. OPA1 protein is involved in the regulation of mitochondrial fusion and remodeling of mitochondrial cristae, the apoptotic process through the control of cytochrome C redistribution, and the

maintenance of mitochondrial DNA [16]. The OPA1 protein is expressed in all tissues examined, but most strongly in the retina and brain. In the ear, OPA1 protein was found to be widely expressed in the sensory and neural cochlear cells. Although the exact pathological mechanism is unknown, an abnormality of the OPA1 protein may cause an abnormality of the mitochondria, leading to insufficient energy support. This lack could then result in a dysfunction of axoplasmic transport in the nerve fibers.

In patients with ADOA and sensorineural deafness, AN was first identified in two subjects by audiological evaluation including OAE and ABR in a study of five subjects from four families having this disorder [17]. Skin fibroblasts from these subjects showed hyperfragmentation of the mitochondrial network, decreased mitochondrial membrane potential, and ATP synthesis defect, indicating that AN in these patients may be related to energy defects caused by a fragmented mitochondrial network.

References

1. Kaga K, Nakamura M, Shinogami M, et al (1996) Auditory nerve disease of both ears revealed by auditory brainstem responses, electrocochleography and otoacoustic emissions. Scand Audiol 25:233–238
2. Starr A, Picton TW, Sininger Y, et al (1996) Auditory neuropathy. Brain 119:741–753
3. Starr A, Sininger YS, Pratt H, et al (2000) The varieties of auditory neuropathy. J Basic Clin Physiol Pharmacol 11:215–230
4. Varga R, Kelley PM, Keats BJ, et al (2003) Non-syndromic recessive auditory neuropathy is the result of mutations in the otoferlin (OTOF) gene. J Med Genet 40:45–50
5. Delmaghani S, del Castillo FJ, Michel V, et al (2006) Mutations in the gene encoding pejvakin, a newly identified protein of the afferent auditory pathway, cause DFNB59 auditory neuropathy. Nat Genet 38:770–778
6. Boerkoel CF, Takashima H, Garcia CA, et al (2002) Charcot-Marie-Tooth disease and related neuropathies: mutation distribution and genotype-phenotype correlation. Ann Neurol 51: 190–201
7. Roux I, Safieddine S, Nouvian R, et al (2006) Otoferlin, defective in a human deafness form, is essential for exocytosis at the auditory ribbon synapse. Cell 127:277–289
8. Starr A, Michalewski HJ, Zeng F, et al (2003) Pathology and physiology of auditory neuropathy with a novel mutation in the MPZ gene (Tyr145->Ser). Brain 126:1604–1619
9. Rouillon I, Marcolla A, Roux I, et al (2006) Results of cochlear implantation in two children with mutations in the OTOF gene. Int J Pediatr Otorhinolaryngol 70:689–696
10. Yasunaga S, Grati M, Cohen-Salmon M, et al (1999) A mutation in OTOF, encoding otoferlin, a FER-1-like protein, causes DFNB9, a nonsyndromic form of deafness. Nat Genet 21:363–369
11. Migliosi V, Modamio-Hoybjor S, Moreno-Pelayo MA, et al (2002) Q829X, a novel mutation in the gene encoding otoferlin (OTOF), is frequently found in Spanish patients with prelingual non-syndromic hearing loss. J Med Genet 39:502–506
12. Kovach MJ, Lin J, Boyadjiev S, et al (1999) A unique point mutation in the PMP22 gene is associated with Charcot-Marie-Tooth disease and deafness. Am J Hum Genet 64: 1580–1593
13. Kalaydjieva L, Gresham D, Gooding R, et al (2000) N-myc downstream-regulated gene 1 is mutated in hereditary motor and sensory neuropathy-Lom. Am J Hum Genet 67:47–58

14. Delettre C, Lenaers G, Griffoin J, et al (2000) Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy. Nat Genet 26:207–210
15. Alexander C, Votruba M, Pesch UEA, et al (2000) OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28. Nat Genet 26:211–215
16. Zeviani M (2008) OPA1 mutations and mitochondrial DNA damage: keeping the magic in shape. Brain 131:314–317
17. Amati-Bonneau P, Guichet A, Olichon A, et al (2005) OPA1 R445H mutation in optic atrophy associated with sensorineural deafness. Ann Neurol 58:958–963