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Clinical Records

Sudden bilateral hearing loss and sporadic mitochondrial DNA deletion

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Abstract

Several studies have indicated that a number of different mitochondrial DNA (mtDNA) mutations may be responsible for human pathologies. Sensorineural Hearing Loss (SNHL) may be associated with known syndromes (syndromal SNHL) or represent the only manifestation of mitochondrial damage (non-syndromal hearing loss). Moreover, mtDNA alterations may be responsible for aminoglycoside-induced deafness.

We describe a patient harbouring a single sporadic mtDNA deletion, who presented with sudden adult-onset bilateral, although non-simultaneous SNHL, that was partially responsive to corticosteroids. Increased values of rest, and exercise, blood lactic acid were decisive for diagnosis, prompting muscle biopsy that revealed the mtDNA deletion. The case underscores the importance of investigating a mitochondrial disease in cases of SNHL of unknown origin and points out the importance of an increased blood level of lactic acid as a screening test.

Key words: Hearing Loss, Sensorineural; DNA, Mitochondrial

Introduction

Several studies have recently showed that sensorineural hearing loss (SNHL), in both its syndromal and non-syndromal manifestations, may be associated with mitochondrial DNA (mt DNA) mutations. Various mtDNA deletions are reportedly responsible for both hereditary (0.5 to one per cent of the cases) and, more rarely, non-hereditary deafness.[1]

The mechanism by which mtDNA alterations generate deafness is still unknown. Generally speaking, there are hundreds of mitochondria in each cell serving a variety of metabolic functions, the most important being the synthesis of adenosine triphosphate (ATP) through oxidative phosphorylation.[2,3] Mitochondrial dysfunction, due to mtDNA mutations, may result in reduced cellular ATP levels, possibly determining an imbalance of ion concentrations within the cochlea.[4]

Mitochondrial mutations do not invariably lead to disease: some may do so only under certain conditions, such as a specific nuclear haplotype or the concurrent sanction of environmental agents.[2] Moreover, other factors, for the most part dependent upon cell mitochondria biogenesis, can influence the clinical expression of mtDNA mutations. Amongst these, one that must be considered is the accumulation of mutated mtDNA species in stable tissues, suh as mammalian cochlear cells.[3,5,6]

A number of pathogenic mtDNA mutations have been described in association with both isolated SNHL, as well as in a broader context involving other systems, such as the central nervous system, retina, skeletal muscle and in diabetes.[2,3,6–9]

The following presents a case of sudden bilateral SNHL, in which hearing loss in one ear predated its appearance in the other by nine months. The patient, partially responsive to corticosteroids, was found to harbour a single mtDNA deletion.

Case report

A 48-year-old male, experienced an episode of sudden right-sided hearing loss in December 1997, with no measurable improvement after institution of medical therapy with cinnarizine, acetylsalicylic acid and glycerol (250 ml 10 per cent, once a day) (Figure 1). Cranial

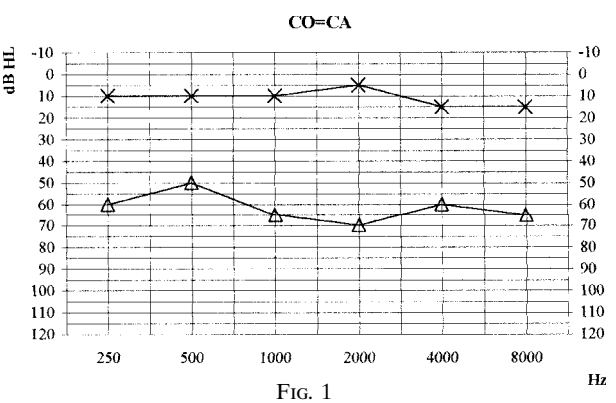

FIG. 1

Hearing threshold levels after the first episode of hearing loss (on right-side).

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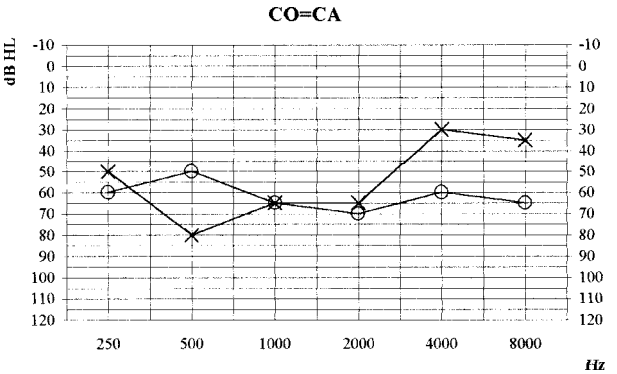

FIG. 2

Hearing threshold levels after the second episode of hearing loss (on left-side).

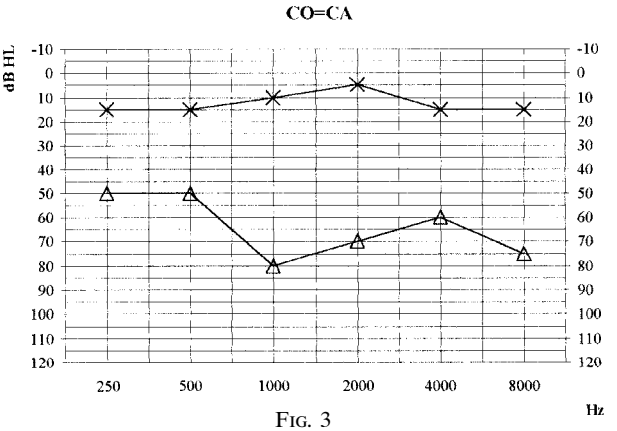

FIG. 3

Hearing threshold levels after recovery of left-side hearing.

magnetic resonance imaging (MRI) was negative. In September 1998 the patient came to our attention complaining of sudden left-sided hearing loss and autophony.

A pure-tone audiogram revealed bilateral sensorineual hearing impairment (Figure 2); tympometry was normal, acoustic reflex was present bilaterally and Metz's test was positive bilaterally. Brainstem auditory-evoked potentials showed normal central nervous conduction, and vestibular function results were normal as well.

Anamnestic data revealed no familiality for deafness. Results of ECG were normal, as were those of neurological examination, upper and lower-limb electromyography and lower limb electroneurography.

The patient underwent a complete blood and immunological evaluation for progressive SNHL.[10] (Table I); all test results were negative. The patient's serum was also assayed for antibodies against inner-ear antigen by means of a Western blot, using fresh bovine temporal-bone inner-ear antigen,[11] with no evidence of cross-reacting autoantibodies.

Blood lactic acid values at rest were increased (4.55 mmol/L; normal values: 0.67–2.47 mmol/L). The patient was therefore subjected to an ischaemic supramaximal exercise test, of the forearm muscles, that revealed abnormal lactate production.

Petrous bone computed tomography (CT) and inner ear nuclear magnetic resonance (NMR) did not show any abnormality.

The patient was started on medical therapy, consisting of intramuscular corticosteroids (1 mg/Kg/day methylprednisolone for 20 days, progressively reduced thereafter). Hearing in the left ear gradually improved and was within the normal range after seven days. On the contrary, the right-side threshold stabilized at a level of moderate-severe deafness, the U-shaped curve remaining very similar to that measured after the first episode of sudden hearing loss (Figure 3). Muscle biopsy was then performed. For the mucle biopsy, a 100 mg specimen was obtained from the left deltoid, immediately frozen in isopentane alcohol, cooled in liquid nitrogen and stored at –80°C until processing for histological, histochemical and molecular studies.

For the Southern blot analysis, total DNA (4 μg) was digested with *Pvu II* to linearize the mtDNA, electrophoresed through an 0.8 per cent agarose gel and transferred to a nitrocellulose membrane (BIO-RAD Laboratories). Four fragments of mtDNA, obtained by the polymerase chain reaction (PCR), were labelled by random-primer incorporation of digoxigenin-labelled deoxyuridine triphosphate (Boehringer-Mannheim kit) and used as the hybridization probes. The membrane was hybridized with the labelled probes overnight at 68°C, then washed and exposed to X-OMAT AR film (KODAK) for 30 minutes at room temperature. PCR analysis was then performed to assess the following point mutations: 3243 A→G, 3252 A→G, 8344 A→G, 8356 T→G.

An increased variability in fibre size and scattered pre-ragged red fibres were detected by trichrome staining. Histochemically, rare, isolated COX negative fibres were observed. PCR analysis did not reveal any of the sought for mtDNA point mutations. In addition to the 16.8 Kb

TABLE I

HAEMATOLOGICAL AND IMMUNOLOGICAL EVALUATION OF SNHL

RBC, WBC and platelet count
Glucose, cholesterol, triglycerides
Creatinine, urea, electrolytes
Total protein, albumin and globulin fractions
Bilirubin, γGT, LDH, SGOT, SGPT, **basal lactic acid**
TSH, t_3, T_4
Urine analysis
Serologic assessment for CMV, HIV, HZV, HSV, HCV, HBV, parvovirus 19, rubella virus, mumps virus.)
Serologic tests for *Toxoplasma*, syphilis (FTA), *Borrelia burgdorferi*
ESR, CRP, complement levels (CH50, C_3, C_4)
Circulating immune complexes, cryoglobulins
Immunoglobulins (Ig fractions), rheumatoid factor (Ra-test)
Antibodies; anti-nuclear (ANA), anti-extractable nuclear antigen (ENA), anti-mitochondrial (AMA), anti-smooth muscle (ASMA), anti-centromere (ACA), anti-Sc170, anti-neutrophil cytoplasm antigen (ANCA), anti-double strand DNA (CLIF test)

Abbreviations: CMV = cytomegalovirus; CRP = C-Reactive protein; ESR = erythrocyte sedimentation rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HSV = herpes simplex virus; HZV = herpes zoster virus; T_3 = tri-iodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone

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wild-type band, the Southern blot test showed an extra mtDNA band, approximately 14.1 Kb, indicating the presence of a 2.7 Kb mtDNA deletion.

Discussion

Sensorineural hearing loss is known to be one of the manifestations of mitochondrial disorders.

Over the last few years, several mtDNA mutations and deletions have been described as responsible for a large variety of syndromes, some with associated sensorineural hearing loss (syndromal SNHL). The adenine to guanine (A→G) point mutation at position 3243 of mtDNA has been found in patients affected by SNHL and MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes)[3,6,9] and by SNHL and diabetes mellitus without MELAS;[3,6,8,9] moreover the 4977 mtDNA deletion (common deletion) is a frequent finding in Kearns-Sayre syndrome (progressive external ophthalmoplegia, retinal pigmentary degeneration and heart conduction block)[9] and progressive external ophthalmoplegia .[6,9] Finally a large, 10.4-Kilobase mtDNA deletion has been found to be associated with diabetes and deafness.[1,6]

Non-syndromal SNHL has also been detected in some families presenting a striking pattern of maternal transmission[1] and attributed to mtDNA nucleotide point mutations at 1555,[7] 7455[12] and 7472[13] and to common deletion.[9]

As far as aminoglycoside-induced deafness is concerned, both familial and sporadic cases have been described,[5] in which ototoxicity occurred even after exposure to low doses, suggesting a genetic susceptibility to aminoglycoside ototoxicity.[1] The most frequent mtDNA mutation associated with aminoglycoside-induced hearing loss is the point mutation 1555A→G in the 12S rRNA gene.[1,9,14] In addition, heteroplasmic and homoplasmic mtDNA mutations at nucleotide 961 in the 12S rRNA gene have also been indicated as predisposing to aminoglycoside ototoxicity.[15]

Several authors have described the clinical features of hearing loss due to mitochondrial disorders.[7,12,13,16–18] The reported age of hearing loss onset is quite variable: some authors describe cases of hearing loss during childhood or adolescence,[7,16] while others report an extremely variable age of onset – between 14 and 50 years.[17]

Generally, hearing loss is progressive,[17] bilateral and symmetric.[18] We have found no case described in the literature of sudden hearing loss associated with an mtDNA mutation. Although the characteristics of the hearing threshold curve and the severity of the hearing loss may vary, hearing loss is generally severe-profound and affects the high frequencies more than the lower ones.[16,17] The hearing loss associated with mtDNA disorders generally presents a cochlear pattern and the vestibular function does not seem to be compromised in such patients.[16,17]

In the present case, the auditory deficit presented as sudden, bilateral hearing loss, although it did not begin simultaneously in both ears. Nor has it shown any tendency to progress. It is interesting that the left-side recovered after corticosteroid therapy.[19] The finding of partial responsiveness to corticosteroids in this case wcould have led to consideration of immune-mediated inner-ear disease, known to be sensitive to high doses of corticosteroids.[10] However, the negative results of inflammatory, immunological and rheumatological tests, including the absence of cross-reaction to inner-ear antigen, made us exclude such an aetiology. On the other hand, the increase in lactate values was suggestive of mitochondrial disorders, an hypothesis confirmed by the muscle biopsy revealing the presence of a single 2.7 Kb deletion, thus leading to the hypothesis that the SNHL was due to an mtDNA deletion. Our results present an opportunity to take into account the occurrence of mitochondrial disorders in an otherwise unexplained SNHL and, at the same time, stress the importance of performing lactate measurements as a screening test in such cases.

Conclusions

We describe the occurrence of a sporadic mtDNA deletion in a patient who presented with adult-onset SNHL, in which the hearing loss was sudden and bilateral, although not simultaneous in both ears, and at least partially responsive to corticosteroids. The findings of increased lactic acid values both at baseline and upon the anaerobic exercise revealed abnormal lactate production – a decisive factor in disclosing the mtDNA deletion. In fact, the lactate results prompted execution of a muscle biopsy, that revealed the mtDNA disorder. The case highlights the importance of testing basal and exercise lactic acid concentrations in cases of SNHL of unknown origin.

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References

1 Seidman MD, Bai U, Khan MJ, Murphy MP, Quirk WA, Castora FJ, *et al.* Association of mitochondrial DNA deletions and cochlear pathology: a molecular biologic tool. *Laryngoscope* 1996;**106**:777–83
2 Fishel-Ghodsian N. Mitochondrially determined hearing impairment. In: Martini A, Read A, Stephens D, eds. *Genetics and Hearing Impairment*, London: Whurr Publishers Ltd., 1996; 244–52
3 Oshima T, Ueda N, Ikeda K, Abe K, Takasaka T. Bilateral sensorineural hearing loss associated with the point mutation in mitochondrial genome. *Laryngoscope* 1996;**106**:43–8
4 Cortopassi G, Hutchin T. A molecular and cellular hypothesis for aminoglycoside-induced deafness. *Hear Res* 1994;**78**:27–30
5 Fishel-Ghodsian N, Prezant TR, Chaltraw WE, Wendt KA, Nelson RA, Arnos KS, *et al.* Mitochondrial gene mutation is a significant predisposing factor in aminoglycoside ototoxicity. *Am J Otolaryngol* 1997;**18**:173–8
6 Yamasoba T, Oka Y, Tskuda K, Nakamura M. Auditory findings in patients with maternally inherited diabetes and deafness harboring a point mutation in the mitochondrial transfer $RNA^{LEU(UUR)}$ gene. *Laryngoscope* 1996;**106**:49–53
7 Jaber L, Shohat M, Bu X, Fischel-Ghodsian N, Yang HY, Wang SJ, *et al.* Sensorineural deafness inherited as a tissue specific mitochondrial disorder. *J Med Genet* 1992;**29**:86–90
8 Suzuki S, Hinokio Y, Ohtomo M, Hirai M, Hirai A, Chiba M, *et al.* The effects of coenzyme Q10 treatment on maternally inherited diabetes mellitus and deafness, and mitochondrial DNA 3243 (A to G) mutation. *Diabetologia* 1998;**41**:584–8
9 Ueda N, Oshima T, Ikeda K, Abe K, Aoki M, Takasaka T. Mitochondrial DNA deletion is a predisposing cause for sensorineural hearing loss. *Laryngoscope* 1998;**108**:580–4
10 Berrettini S, Ferri C, Ravecca F, La Civita L, Bruschini L, Riente L, *et al.* Progressive sensorineural hearing impairment in systemic vasculitides. *Semin Arthritis Rheum* 1998;**27**:1–19
11 Berrettini S, Ravecca F, Bruschini L, Ursino F, Sellari-Franceschini S. Ipoacusia neurosensoriale progressiva: cause immunologiche. *Acta Otorhinolaryngol Ital* (Suppl 59):33–42

12 Sevior KB, Hataochi A, Stewart IA, Bykhovskaya Y, Allen-Powell DR. Fischel-Ghosian N, *et al*. Mitochondrial A7445G mutation in two pedigrees with palmoplantar keratoderma and deafness. *Am J Med Genet* 1998;**13**:179–85

13 Ensink RJ, Verhoeven K, Marres HA, Huygen PL, Padberg GW, ter Laak H, *et al*. Early-onset sensorineural hearing loss and late-onset neurologic complaints caused by a mitochondrial mutation at position 7472. *Arch Otolaryngol Head Neck Surg* 1998;**124**:886–91

14 Usami S, Abe S, Shinkawa H, Kimberling WJ. Sensorineural hearing loss caused by mitochondrial DNA mutations: special reference to the A1555G mutation. *J Commun Disord* 1998;**31**:423–34

15 Vernham GA, Reid FM, Rundle PA, Jacobs HT. Bilateral sensorineural hearing loss in members of a maternal lineage with mitochondrial point mutation. *Clin Otolaryngol* 1994;**19**:314–9

16 Braveman I, Jaber L, Levi H, Adelman C, Arons KS, Fischel-Ghodsian N, *et al*. Audiovestibular findings in patients with deafness caused by a mitochondrial susceptibility mutation and precipitated by an inherited nuclear mutation or aminoglycosides. *Arch Otolaryngol Head Neck Surg* 1996;**22**:1001–4

17 Elverland HH, Torbergsden T. Audiologic findings in a family with mitochondrial disorder. *Am J Otol* 1991;**12**:459–65

18 Oshima T, Ueda N, Ikeda K, Abe K, Takasaka T. Hearing loss with a mitochondrial gene mutation is highly prevalent in Japan. *Laryngoscope* 1999;**109**:334–8

19 Gubbay SS, Hankey GJ, Tan NT, Fry JM. Mitochondrial encephalomyopathy with corticosteroid dependence. *Med J Aust* 1989;**151**:100–3

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