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Clinical Record

Mitochondrial neurogastrointestinal encephalomyopathy associated with progressive hearing loss

N Hiraki, T Udaka*, H Yamamoto, Y Kadokawa*, J Ohkubo†, H Suzuki†

Abstract

Objective: We report a rare case of mitochondrial neurogastrointestinal encephalomyopathy with hearing loss.

Case report: A 46-year-old woman presented with a three-year history of progressive, bilateral hearing loss and tinnitus. She had been suffering from unexplained abdominal pain and diarrhoea for 20 years. When first seen, her otoscopic findings were normal, and pure tone audiometry showed mild and moderate hearing loss in her right and left ears, respectively. She also had: bilateral ophthalmoparesis, neck and limb muscle weakness, and hypoactive deep tendon reflexes on neurological examination; diffuse leukoencephalopathy on magnetic resonance imaging of the brain; and markedly reduced leukocyte thymidine phosphorylase activity. On the basis of these findings, the patient was diagnosed with mitochondrial neurogastrointestinal encephalomyopathy.

Conclusion: Mitochondrial neurogastrointestinal encephalomyopathy is an autosomal recessive disease caused by mutation of the thymidine phosphorylase gene, and is characterised by ophthalmoparesis, peripheral neuropathy, leukoencephalopathy, gastrointestinal symptoms and abnormal mitochondria in muscle cells. Current advances in genetic research may reveal a higher prevalence of mitochondrial disorders than had previously been thought. Otolaryngologists should be aware of mitochondrial neurogastrointestinal encephalomyopathy and other rare genetic disorders when managing patients with progressive hearing loss.

Key words: Mitochondrial Neurogastrointestinal Encephalomyopathy; Sensorineural Hearing Loss; Thymidine Phosphorylase

Introduction

Mitochondrial neurogastrointestinal encephalomyopathy is an autosomal recessive disease caused by mutations of the gene that encodes thymidine phosphorylase, located on chromosome 22q13.32-qter.[1] These mutations severely impair thymidine phosphorylase activity, and subsequently induce dramatic elevation of plasma and intracellular thymidine levels. This increase in intracellular thymidine generates imbalances in mitochondrial nucleotide stores, eventually resulting in mitochondrial DNA abnormalities. Mitochondrial neurogastrointestinal encephalomyopathy is clinically characterised by ophthalmoparesis, peripheral neuropathy, leukoencephalopathy, and gastrointestinal symptoms such as recurrent nausea, vomiting and diarrhoea.[2] Sensorineural hearing loss (SNHL) has been recognised as another important feature of mitochondrial neurogastrointestinal encephalomyopathy;[2] however, a detailed description of the audiological effects of this disease has not previously been published.

We herein report a case of mitochondrial neurogastrointestinal encephalomyopathy associated with progressive hearing loss; we also review the clinical, radiological and genetic characteristics of this disease.

Case report

A 46-year-old woman was referred to our department with a three-year history of progressive, bilateral hearing loss and tinnitus. She had also suffered unexplained abdominal pain and diarrhoea for the past 20 years. She was short in stature (155 cm), weighed 29 kg, and had no remarkable past or family history of illness.

The patient was first seen by us in March 2000, at which stage her otoscopic findings were normal, and pure tone audiometry showed mild and moderate mixed hearing loss in her right and left ears, respectively (Figure 1a). Other otological examinations showed type A tympanometry, an undetectable stapedial reflex and type two (Jerger) Bekesy audiometric findings in both ears. Although pure tone audiometry showed an air–bone gap at low to mid-range frequencies, we judged the patient's hearing loss to be sensorineural, from the findings of otoscopy, tympanometry and Bekesy audiometry. There may have been instrumental malfunction. The patient also showed bilateral ophthalmoplegia. Neurological examinations by a neurologist revealed neck and limb muscle weakness and hypoactive deep tendon reflexes. Retinopathy, cerebellar ataxia and heart block were not observed.

Contrast radiography of the gastrointestinal tract showed chronic intestinal pseudo-obstruction. Magnetic resonance imaging (MRI) of the brain revealed diffuse leukoencephalopathy (Figure 2). Electromyography showed a prolonged conduction velocity of the motor nerve with temporal dispersion. Lactate and pyruvate concentrations in the blood were 16.0 mg/dl (normal range: 4.0–16.0 mg/dl) and 1.4 mg/dl (normal range: 0.3–0.9 mg/dl), respectively,

From the Departments of Otorhinolaryngology, Hamamatsu Rosai Hospital, Hamamatsu, *Kumamoto Rosai Hospital, Yatsushiro, and †School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan.
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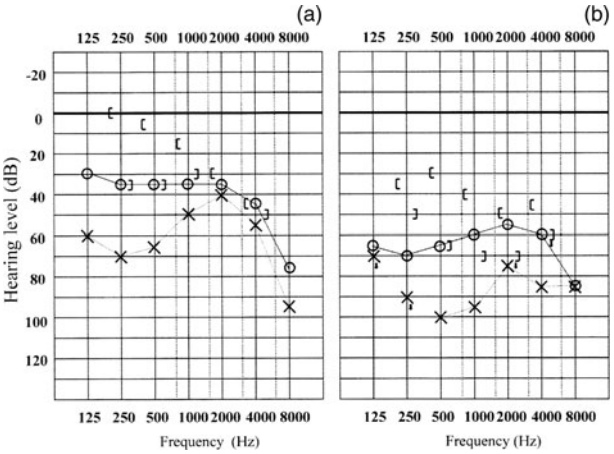

FIG. 1

The patient's pure tone audiograms (a) aged 46 years and (b) aged 50 years.

and those in the cerebrospinal fluid (CSF) were 22.0 mg/dl (normal range: 10.0–20.0 mg/dl) and 1.2 mg/dl (normal range: 0.6–1.1 mg/dl), respectively.

These findings suggested the possibility of neuromuscular disease, including a mitochondrial disorder. The patient thus underwent a thigh muscle biopsy and an assay of the thymidine phosphorylase activity in peripheral blood leukocytes. Although the muscle biopsy showed no histological abnormality, molecular genetic analysis of the muscle revealed the C4202T mitochondrial DNA point mutation. The leukocyte thymidine phosphorylase activity was markedly reduced (0.004 μmol/hour/mg protein (normal range: 0.011 ± 0.020 μmol/hour/mg)).

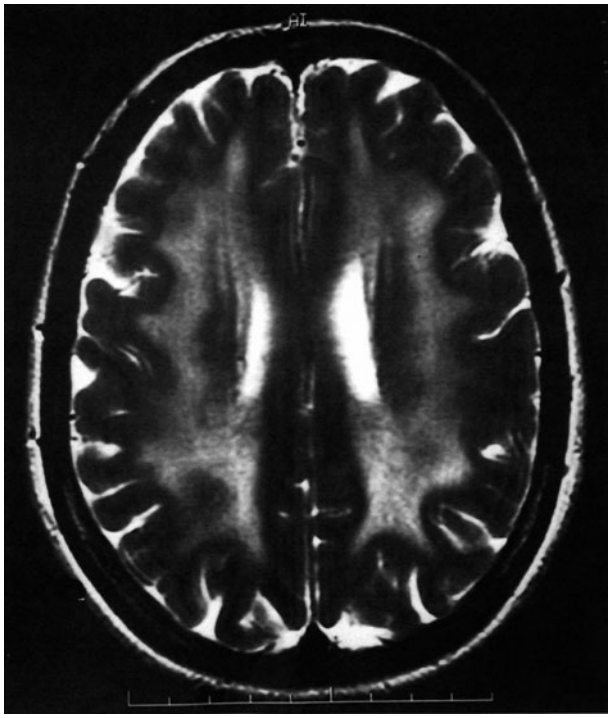

FIG. 2

Axial, T2-weighted magnetic resonance imaging scan showing diffuse high signal intensity in the white matter of the cerebrum. A = anterior

On the basis of these findings, the patient was eventually diagnosed with mitochondrial neurogastrointestinal encephalomyopathy.

Three years later, the patient complained of greater difficulty in hearing. Further objective deterioration of her hearing was demonstrated on pure tone audiometry, and an HA-70 hearing aid (RION Co., Ltd, JAPAN) was fitted to her left ear.

At the time of writing, the patient's hearing loss was gradually progressing (Figure 1b), and she was being followed up closely.

Discussion

Abnormalities in the mitochondrial genome particularly affect tissues with high energy requirements, such as those of the nervous system, skeletal muscle and inner ear. As a result, mitochondrial disorders may predispose patients to neuromuscular diseases and SNHL. Mitochondrial SNHL can be syndromic or non-syndromic, and is seen in 42 to 70 per cent of patients with mitochondrial disorders.[3,4]

A variety of mitochondrial neuromuscular syndromes exhibit progressive hearing loss,[3,5–7] including the 'mitochondrial encephalopathy, lactic acidosis and stroke-like episodes' syndrome, the 'myoclonic epilepsy associated with ragged red fibres' syndrome, the Kearns–Sayre syndrome and mitochondrial neurogastrointestinal encephalomyopathy. Hirano *et al.*[2] reported that 61 per cent (11/18) of patients with mitochondrial neurogastrointestinal encephalomyopathy had SNHL. Kaidar-Person *et al.*[7] documented a patient with rapidly progressive, bilateral SNHL associated with mitochondrial neurogastrointestinal encephalomyopathy, in contrast to our patient's slowly progressive, bilateral SNHL.

In the present case, the type two (Jerger) pattern on Bekesy audiometry suggested hearing loss of cochlear origin. Because the cochlea consumes a large amount of adenosine triphosphate (ATP) (particularly the hair cells and stria vascularis), a reduction of available ATP, caused by mitochondrial dysfunction, leads to a cochlear type of hearing loss at an early stage of the disease.[3] Advanced cases may exhibit features of retrocochlear impairment, such as a decline in speech recognition and an increase in interwave latencies with deranged waveforms in the auditory brainstem response.[3]

- **Mitochondrial disorders are the most frequent type of genetic metabolic defect, with an estimated incidence of at least one per 10 000 population**
- **This paper reports a case of mitochondrial neurogastrointestinal encephalomyopathy with sensorineural hearing loss (SNHL)**
- **Current advances in genetic research may reveal a higher prevalence of mitochondrial disorders than had previously been thought**
- **Otolaryngologists should be aware of such rare genetic disorders when managing patients with progressive SNHL**

To date, there is little prospect of effective treatment for SNHL associated with mitochondrial neurogastrointestinal encephalomyopathy or other mitochondrial disorders.[3,7,8] A hearing aid or a cochlear implant should be considered in patients with a mitochondrial disorder and progressive or profound SNHL.

Mitochondrial neurogastrointestinal encephalomyopathy generally occurs between the first and fifth decades of life, most frequently in the second decade.[2] Clinical

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manifestations of the disease include ophthalmoparesis, ptosis, SNHL, skeletal myopathy, peripheral neuropathy, gastrointestinal dysmotility and cachexia.[2,7] Gastrointestinal dysmotility, which manifests as diarrhoea and intestinal pseudo-obstruction, is the most noticeable feature of mitochondrial disorders, and one of the commonest symptoms of mitochondrial neurogastrointestinal encephalomyopathy.[2,7] Our patient showed peripheral neuropathy, ophthalmoparesis, SNHL and gastrointestinal dysmotility. Of these manifestations, gastrointestinal dysmotility, with intestinal pseudo-obstruction on contrast radiography, was the most helpful for diagnosing the disease.

Brain MRI scanning of mitochondrial neurogastrointestinal encephalomyopathy patients typically reveals leukodystrophy, while neurological investigations such as electromyography and nerve conduction studies characteristically show peripheral neuropathy with demyelination and/or axonal degeneration.[2,7,9] Skeletal muscle biopsies show histological neurogenic changes together with mitochondrial abnormalities such as 'ragged red fibres'.[2] On immunohistochemical analysis, cytochrome *c* oxidase expression is decreased, and multiple respiratory chain enzyme defects may be present.[2] In laboratory tests, lactate and pyruvate levels are elevated in the serum and CSF, as observed in the present case. Although thigh muscle biopsy in our patient did not show the characteristic histological findings of mitochondrial myopathy, a diagnosis of mitochondrial neurogastrointestinal encephalomyopathy was supported by radiological, neurological and laboratory examination findings, and was finally confirmed by detection of decreased leukocyte thymidine phosphorylase activity.

Conclusion

We report a patient with mitochondrial neurogastrointestinal encephalomyopathy who displayed progressive SNHL. Mitochondrial disorders are the most frequent type of genetic metabolic defect, with an estimated incidence of at least one per 10 000 population.[7] Current advances in genetic research may reveal a higher prevalence of mitochondrial disorders than had previously been thought. Otolaryngologists should be aware of such rare genetic disorders when managing patients with progressive SNHL.

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Address for correspondence:
Dr Nobuaki Hiraki,
Department of Otorhinolaryngology,
Hamamatsu Rosai Hospital,
25 Shogen-town, Naka-ku,
Hamamatsu, 430-8525, Japan.

Fax: +81 53 465 4380
E-mail: hiraki@med.uoeh-u.ac.jp

Dr N Hiraki takes responsibility for the integrity of the content of the paper.
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