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Main Articles

Audiological findings in patients with myoclonic epilepsy associated with ragged-red fibres

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Abstract
Sensorineural hearing loss is a common symptom in patients with myoclonic epilepsy associated with ragged-red fibres (MERRF), one of the mitochondrial encephalomyopathies, although the lesion causing hearing loss in such cases remains unknown. Here we describe the audiological features in three MERRF patients, all of whom exhibited a point mutation in their mitochondrial DNA at nucleotide 8344. Pure-tone threshold audiometry revealed bilateral, sloping-type, sensorineural hearing loss in all three patients. Distortion product otoacoustic emissions, electrocochleography, and auditory brainstem responses were variable, even differing between the right and left ears of the same patient. Taken together, our findings suggest that the primary lesion underlying hearing loss in MERRF patients is in the cochlea, although a retrocochlear lesion may be involved in some patients.

Key words: Hearing Loss, Sensorineural; Epilepsies, Myoclonic

Introduction

Mitochondrial encephalomyopathies are distinctive syndromes characterized by neurological dysfunction and abnormalities in structure of the mitochondria.[1,2] Sensorineural hearing loss is often a symptom in these syndromes,[3,4,5,6,] which include Kearns-Sayre syndrome (KSS),[7,8] myoclonic epilepsy associated with ragged-red fibres (MERRF),[9] and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode (MELAS).[10,11,12] Recently, specific mutations in the mitochondrial DNA (mtDNA) were shown to be associated with mitochondrial encephalomyopathies. Moreover, an adenine to guanine substitution at nucleotide 3243 of the $tRNA^{Leu(UUR)}$ gene of the mtDNA from MELAS patients has also been found in lineages showing maternally-inherited diabetes mellitus and sensorineural hearing loss, but without the typical manifestations of MELAS.[13] The lesion causing hearing loss in patients with a mtDNA mutation at nucleotide 3243 appears to vary, occurring in the cochlea in some patients and in both the cochlea and retrocochlea in others.[14,15,16]

Haring loss is also a key feature of MERRF,[17] although a detailed audiological description of patients with MERRF is not yet available. Here we report on the audiological features of MERRF patients with a mtDNA point mutation at nucleotide 8344 and on whether the lesion responsible for the observed hearing loss is cochlear or retrocochlear.

Materials and methods

Three MERRF patients with a mitochondrial $tRNA^{Lys}$ mutation at nucleotide 8344 participated in this study. DNA sequencing of the polymerase chain reaction products confirmed the mutation. The patients underwent general medical and otological examinations as well as complete audiological examinations, including measurement of pure tone audiometry (PTA) thresholds, measurement of distortion product otoacoustic emission (DPOAE), electrocochleography (ECochG) and measurement of auditory brainstem responses (ABRs), all of which were carried out in a soundproof room.

ECochG and ABR were recorded and analyzed using an ER1100 system from NEC Medical Systems (Tokyo, Japan). Extra-tympanic ECochG was carried out using an HN-5 electrode (Unique Medical, Tokyo, Japan),[18] as was the recording of compound action potentials (APs) and cochlear microphonics (CM). The acoustic stimuli used to evoke APs and CM were clicks produced by 0.1 ms rectangular electrical pulses and short tone bursts with 3 ms (at 1, 2 or 4 kHz) or 7 ms (at 0.5 kHz) durations and 1 ms

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rise and fall times. Acoustic stimuli were generated using a Nihon Kohden SSS-3200 acoustic generator (Japan); the stimuli were delivered in a free field, with a distance of 50 cm between the shielded loudspeaker and the opening of the external auditory canal. Stimulus intensities ranged from 90 dBnHL down to the response threshold, diminishing in 10 dB steps. The band-pass filters were set to be flat from 50 to 3000 Hz for APs, from 320 to 1500 Hz for 0.5 kHz-CM and 1 kHz-CM, from 320 to 3000 Hz for 2 kHz-CM, and from 320 to 6000 Hz for 4 kHz-CM. The stimulus repetition rate was 9.5 Hz. CM detection thresholds were assessed using the lowest intensities; the detection criterion was 0.2-μV. AP thresholds were detected by visually examining the recordings. AP latencies were measured from the beginning of the CM to the peaks of the APs evoked by 90-dB click stimuli.

To measure ABRs, the active electrode (silver disk) was attached to the vertex and referenced to the mastoid ipsilateral to the recorded side. Unfiltered 90 dBnHL clicks with alternating phases, generated from 0.1 ms rectangular electrical pulses, were delivered to the ear by headphones at a repetition rate of 9.5 Hz; 60 dBnHL white noise was presented to the contralateral ear for masking. The evoked potentials were passed through an 80–1500 Hz band-pass filter and averaged 1000 times. The criterion for a positive finding with respect to differences in the interpeak latencies between wave I and wave V (IPL I-V) was IPL I-V>4.4 ms.[19,20]

DPOAE analysis was carried out using a Grason-Stadler GSI 60. Recordings were made of the 2f1-f2 distortion products (DP) emitted in response to primaries of differing amplitude, ranging from 70 dB and 60 dB SPL down to the response threshold in 10 dB steps. The 2f1-f2 DPOAE were measured at a quarter-octave intervals across a frequency stimulus range of 1 kHz to 4 kHz. The frequency ratio of f2 to f1 was fixed at 1.22, and DP-grams were obtained by plotting DP levels against the geometric means of f1 and f2.

Clinical courses of patients are provided below:

Case 1: A 48 year-old male was admitted to the department of neurology in our hospital because of gait disturbance and dysarthria. These symptoms developed when he was 31 years-old. At the age of 36, he developed epileptic attacks. He presented to our out-patient clinic with a complaint of bilateral hearing loss. The onset of hearing loss has been gradual for one year. He had suffered no episodes of rotatory vertigo. On examination, there were myoclonic involuntary movement and cerebellar dysfunction (dysdiadochokinesis, finger to nose dysmetria, and saccadic ocular pursuit movement). DNA sequencing of the polymerase chain reaction products confirmed a diagnosis of MERRF.

Case 2: A 57 year-old female, with gait and speech disturbance, accompanied by episodes of tonic convulsion. She noted her hearing had been impaired for three years and had deteriorated gradually. She was an elder sister of *Case 1,* and also diagnosed to be MERRF by DNA sequencing.

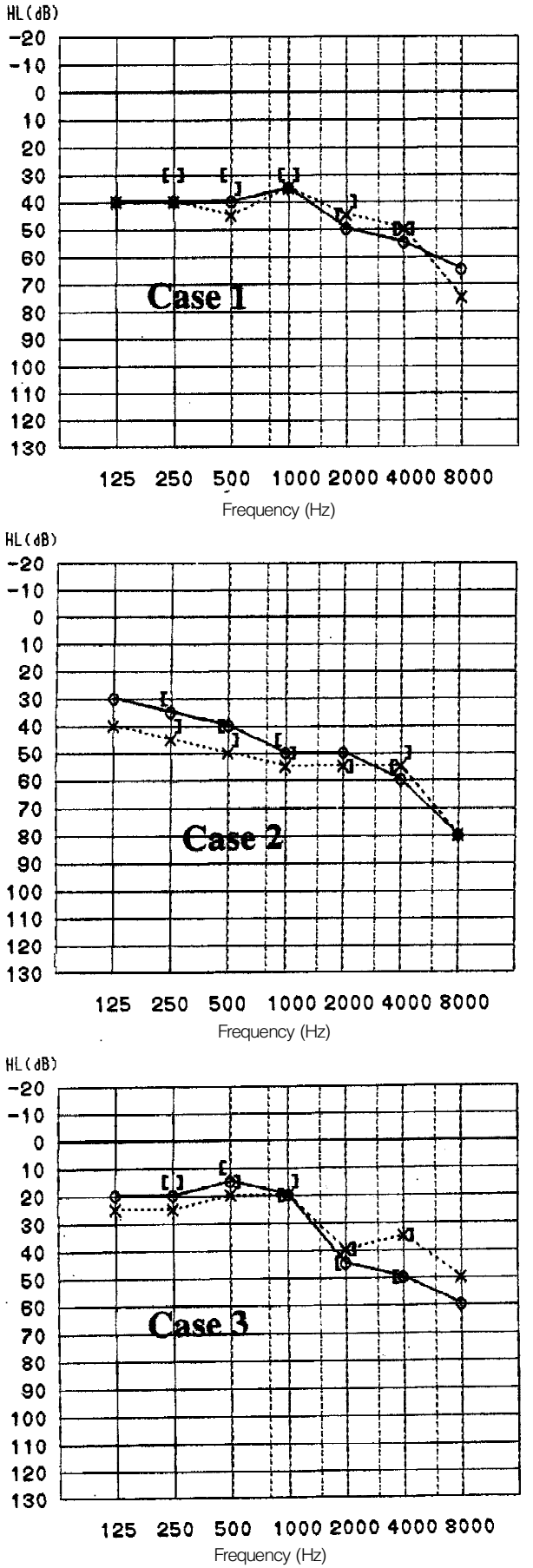

FIG. 1
Audiograms recorded from the three study participants.

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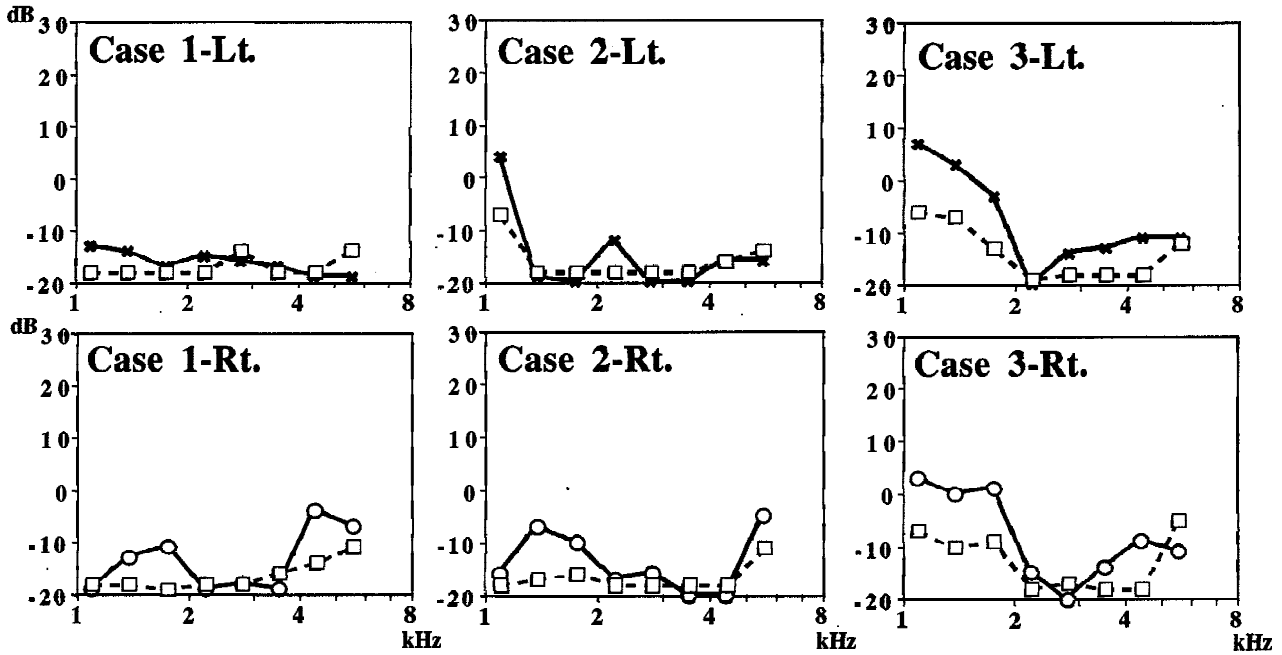

FIG. 2

DP-grams recorded from the three study participants. In each graph the abscissa is the geometric mean of f1 and f2, and the ordinate is the DP level (dBSPL). Empty squares represent the noise level.

Case 3: A 15-year-old female presented from the department of neurology, for evaluation of hearing impairment. She had developed myoclonic convulsions four years previously. DNA sequencing revealed a mitochondrial DNA point mutation as MERRF. Though there was no complaint of hearing loss, medical assessment had detected a hearing impairment four months before.

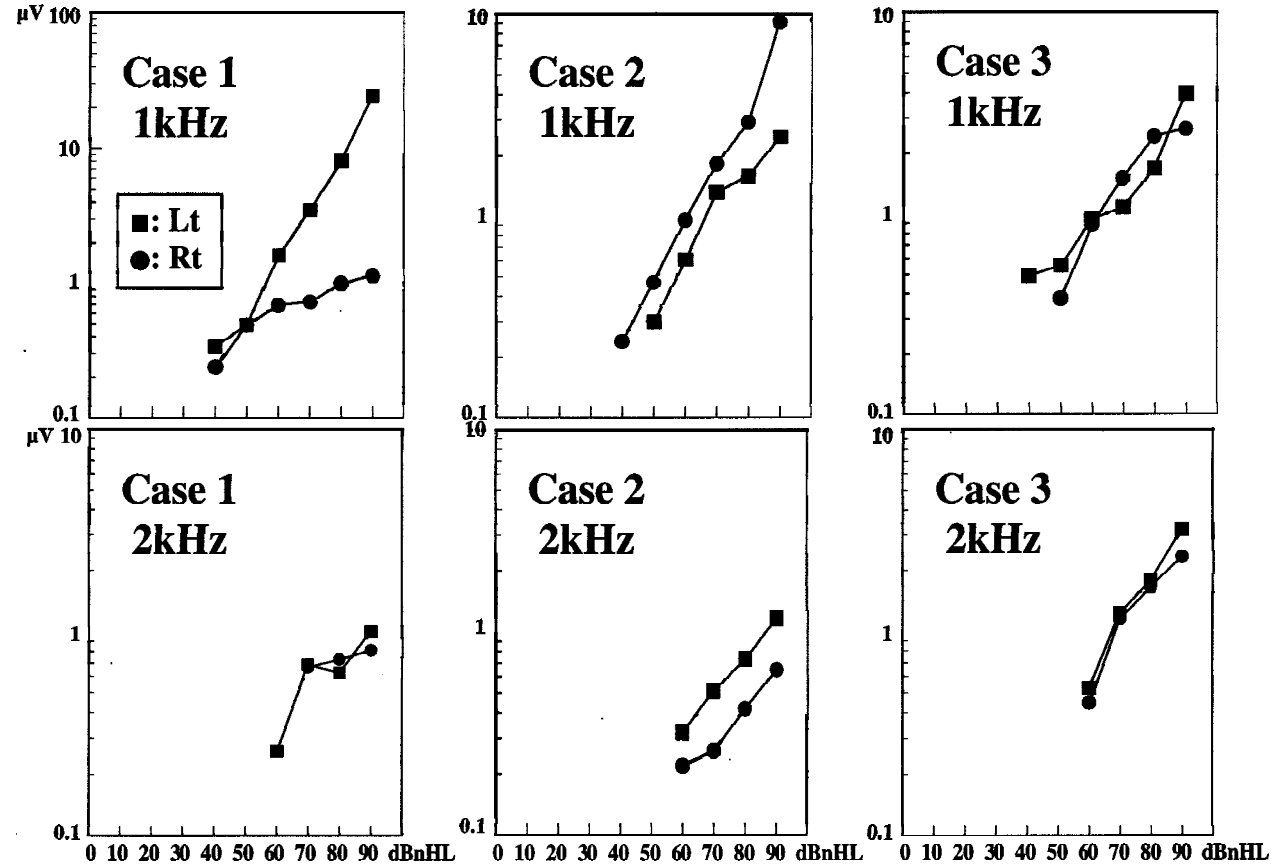

FIG. 3

CM input-output curves. In each graph the abscissa is the stimulus intensity, and the ordinate is the amplitude of CM.

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TABLE I

ECOCHG AND ABR ARE SHOWN ALONG WITH THE CLINICAL FEATURES, INCLUDING THE TYPE AND SITE OF POINT MUTATION IN THE MITOCHONDRIAL GENOME AND THE AP AND CM DETECTION THRESHOLDS IN NORMAL EARS

Case		1		2		3		Normal (n = 29)
Age at examination		48		57		15		
Sex		MERRF M		MERRF F		MERRF F		
The type of the point mutation		$tRNA^{Lys}$8344A→G		$tRNA^{Lys}$8344A→G		$tRNA^{Lys}$8344A→G		
Age at onset of hearing loss		47		53		13		
Side		Left	Right	Left	Right	Left	Right	(mean (SD)
EcochG								
Threshold (dBnHL)	AP (click)	50	60	60	60	60	60	11.7 (5.39)
	CM-0.5k	40	50	50	40			19.7 (6.26)
	CM-1k	40	40	50	50	40	50	16.2 (4.94)
	CM-2k	40	70	50	50	50	60	21.7 (7.59)
	CM-4k	60	70	60	60	60	60	50.0 (8.86)
Latency (ms)	AP (90dB-click)	1.04	1.18	1.22	1.26	1	1.16	
ABR								
Latency (ms)	I	1.66	1.58	1.74	1.64	1.66	2.14	
	V	6.54	6.48	6.14	6.38	5.6	6.16	
IPL I-V (ms)		4.88	4.9	4.4	4.74	3.94	4.02	

Results

Figures 1 and 2 show PTAs and DP-grams recorded from each of the study participants. All three exhibited a gradual form of bilateral SNHL. ECochG amplitudes were diminished in each case, and the input-output curves of CMs showed a loss of responsiveness to weaker sound stimuli (Figure 3), and non-linearity of the cochlea could not be found. The complete clinical and audiological findings are summarized in Table I, accompanied by AP and CM detection thresholds recorded from individuals in our hospital with normal hearing. Detailed audiological findings for each patient are presented below.

Case 1: DP levels were decreased bilaterally to the level of the noise; this was particularly apparent in the left ear (Figure 2). The CM detection thresholds (dBnHL) were elevated bilaterally as compared to thresholds recorded from individuals with normal hearing, and the threshold was higher in the right ear. Moreover, the CM detection thresholds were generally consistent with the pure tone audiometric thresholds at each frequency (Table I and Figure 1). ABRs showed bilateral prolongation of the I-V intervals.

Case 2: DP levels were roughly equal bilaterally (Figure 2). ECochG was also similar bilaterally, as were the AP and CM detection thresholds, except at 0.5 kHz, where the detection threshold was slightly higher on the left side (Table I). PTA thresholds were also slightly higher on the left side (Figure 1), and ABRs, showed prolongation of IPLI-V to 4.74 ms on the right side (Table I).

Case 3: DP levels were nearly equal bilaterally (Figure 2). ECochG showed bilaterally elevated CM and AP detection thresholds, the former being slightly higher on the right side (Table I). AP latency and ABR wave I were both delayed on the right side (Table I). Bilateral IPL I-Vs were within normal limits.

Discussion

Auditory dysfunction in patients with mitochondrial encephalomyopathy is reported to involve both the cochlear and retrocochlear portions of the auditory tract. Similarly, both cochlear and retrocochlear portions were affected in the MERRF patients participating in the present study. The DPOAE and elevated CM detection thresholds in *Case 1* indicate bilateral cochlear dysfunction, with the former suggesting the damage was mainly on the left side and the latter suggesting the damage was mainly on the right. In addition, the ABRs indicate retrocochlear dysfunction. The results obtained from *Case 2* suggest slightly more severe cochlear dysfunction on the left side, while the prolongation of IPL I-V indicates more severe retrocochlear dysfunction on the right side. Finally, the CM detection thresholds in *Case 3* suggest slightly greater cochlear dysfunction on the right side, and the ABR results indicate no retrocochlear dysfunction.

Cochlear dysfunction was seen in all of the study participants, while retrocochlear dysfunction was encountered in two, perhaps reflecting a higher distribution of mutated mitochondria in the cochlear than in the retrocochlear organ. That the severity of the cochlear and retrocochlear lesions even varied between the right and left ears of the same patient is consistent with the high degree of variability in level of the expression of the mutated gene in patients with homoplasmic mitochondrial diseases.[21]

CM detection thresholds were moderately increased in all three patients, which may be attributable to the absence of delayed CM.[22] In addition, CM input-output curves showed a loss of responsiveness to weaker stimuli, which may correspond to the absence of the lower portion of non-linear response and it is consistent with dysfunction of the outer hair cells.[23] We therefore suggest that, in MERRF patients, cochlear dysfunction is likely to be a consequence of disrupted outer hair cell function.

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In this series of subjects, there were no patients with MERRF but without hearing loss. In the reports of MELAS, no case report was found with detailed analysis of auditory function without hearing loss. In such a case, ABR might probably show normal waveform. However, it could be another case with abnormality of ABR which may reflect neurological dysfunction unaccompanied by any subjective auditory deficit.

Conclusions

Our analysis of the auditory function in three MERRF patients entailed performing PTA and ECochG and recording DPOAEs and ABRs. All except the PTA were objective examinations that could not be influenced by the patient's mental decline. Our findings indicate that in such cases auditory dysfunction may be a consequence of lesions at both cochlear and retrocochlear sites. The primary lesion appears to occur in the cochlea, although the site and even the side involved may vary among patients. Elevated CM detection thresholds and a lack of delayed CM in the middle frequency ranges would seem to indicate dysfunction of the outer hair cells.

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