TITLE:

The Outcome of Cochlear Implantation for Mitochondrial Disease Patients With Syndromic Hearing Loss.

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1 **Abstract**

2 Objective: To evaluate the outcome and to confirm the validity of cochlear implantation
3 for syndromic deafness in patients with mitochondrial disease.

4 Study design: Retrospective case review

5 Setting: Tertiary referral center

6 Patients: We reviewed medical charts of 367 cochlear implantation cases at Kyoto
7 University Hospital between 1987 and 2012. We identified 5 patients with syndromic
8 mitochondrial disease who underwent cochlear implantation surgery. The mean age of
9 the patients (4 women and 1 man) when they underwent surgeries was 44.4 years
10 (range 30–64years, median 41 years).

11 Interventions: Therapeutic and rehabilitative

12 Main outcome measure: In 4 out of 5 patients, speech perception performance was
13 measured using Japanese vowels, consonant-vowel syllables, and short sentences.

14 Results: Only 1.4% (5/367) of cochlear implantation cases at Kyoto University Hospital
15 underwent cochlear implantation surgery due to syndromic mitochondrial diseases.
16 Four of those patients showed significantly improved speech perception outcomes, and
17 the beneficial effects of the intervention continued long after surgery. One patient could
18 not perform speech perception test presumably due to poor cognitive function.

Conclusions: Mitochondrial disease patients who underwent cochlear implantation surgery sustained gains in hearing performance even long after surgery. A single patient showed poor postoperative speech perception associated with cognitive problems. Cochlear implantation for mitochondrial disease patients appears to be a viable treatment option in the absence of significant cognitive impairment.

INTRODUCTION

Mitochondrial diseases are caused by mutation of either mitochondrial DNA or of nuclear DNA that encodes genes related to mitochondrial function. Mitochondrial diseases result in dysfunction of the respiratory chains that are important for producing adenocine triphosphate (ATP) in eukaryotic cells (1). More than half of the known mitochondrial diseases cause various levels of sensorineural hearing loss (SNHL) (2) that is classified into either non-syndromic or syndromic hearing loss. Mitochondrial diseases with syndromic hearing loss include mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), maternally inherited diabetes with deafness (MIDD), Kearns-Sayre syndrome (KSS), and chronic progressive external ophthalmoplegia (CPEO). Some mitochondrial diseases can cause severe to profound SNHL, necessitating the use of

cochlear implants for syndromic (3-15), as well as non-syndromic (16-18), mitochondrial deafness.

Most previous case reports suggested that cochlear implantation (CI) has favorable effects in both types of mitochondrial diseases, based solely on the outcome at 1 time point or within at most 2 years after surgery. Although these results are supported by the fact that the SNHL in mitochondrial diseases is attributed to cochlear dysfunction (19,20), mitochondrial diseases with syndromic deafness can affect the central nervous system, including the central auditory pathway, or cause psychomotor regression after CI (1). Thus, the beneficial effects of cochlear implants may further change even after determination of the initial treatment outcome or within several years after surgery, since continued normal function of the central auditory pathway and stable psychological conditions are necessary for successful CI. In this study, we present the outcomes of CI on a longitudinal basis at several time points in cases of syndromic mitochondrial deafness that presented at Kyoto University Hospital and discuss the validity to perform CI for syndromic mitochondrial deafness.

MATERIALS AND METHODS

55 Patients

56 This study was approved by Kyoto University Graduate School and Faculty of Medicine,
57 Ethics Committee (E2359). Medical records of 367 patients who underwent CI at Kyoto
58 University Hospital between 1987 and 2012 were reviewed. Among these, 5 patients
59 were diagnosed with MELAS (3 patients), MIDD (1 patient), and unclassified (1 patient)
60 mitochondrial disease in the Department of Neurology at Kyoto University Hospital.

61

62 Data collection

63 Medical records of 5 patients who underwent CI surgery were reviewed and the
64 following information was extracted: age, sex, perioperative complications, and
65 postoperative speech perception performance at several time points.

66

67 Diagnosis of mitochondrial diseases

68 Mitochondrial diseases were diagnosed by neurologists at Kyoto University Hospital
69 based on genetic tests, muscle biopsies, MRI imaging of the brain, and clinical
70 symptoms—seizures, stroke-like symptoms, recurrent headache, dementia, ataxia,
71 muscle weakness, hemianopsia, diabetes mellitus, conduction disorders of the heart,
72 etc.

73

74 Postoperative speech perception performance test

75 Vowels, consonant-vowel (CV) syllables, and short sentences were phonated by a male

76 professional announcer and digitized at a sampling rate of 44.1 kHz. These speech

77 samples were presented via speakers at 70 dB SPL using a PowerMac PM-7300/166

78 computer (Apple Inc., Cupertino, California, USA) in random order; the percentage of

79 correct answers was recorded. In the vowel perception test, 5 Japanese vowels were

80 presented to patients. In the CV syllable perception test, 13 CV syllables—composed of

81 13 Japanese consonants and the vowel /a/— were presented to patients. In the phrase

82 perception test, 10 short Japanese sentences were arranged to contain 40 different

83 phrases. The vowel and CV syllable perception test used closed sets and the phrase

84 perception test used an open set. These tests were administered at least 6 months after

85 implantation. Unpaired *t*-tests were performed for the statistical analysis and *p*-values

86 below 0.05 were considered statistically significant.

87

88 **RESULTS**

89

90 Patient characteristics (Table)

Only 1.4% (5/367) of CI cases at Kyoto University Hospital underwent CI due to mitochondrial diseases. The patients—1 male and 4 females—ranged from 30 to 64 years in age. Four of the patients had m.3243A>G mutation. Three patients were diagnosed with MELAS and one patient was diagnosed with MIDD. One patient (case 4) was not diagnosed with a specific mitochondrial disease because he presented with an atypical set of symptoms (deafness, ataxia, mild cognitive deficits, and paroxysmal supraventricular tachycardia). However, he was diagnosed with a general mitochondrial disease because he showed the m.3243A>G mutation and ragged-red fibers were observed in his muscle biopsy specimens. Another patient (case 3) refused to undergo a genetic test and a muscle biopsy test. However, she was clinically diagnosed with MELAS due to typical symptoms (stroke-like episodes, seizures, hemiplegia, cognitive deficits, ataxia, short stature, and deafness) and typical MRI imaging findings (basal ganglia calcification, cerebellar atrophy, and chronic infarcts involving multiple vascular territories). Patients in cases 1, 2, and 3 died 12, 4, and 2 years after CI surgery, respectively.

Surgical findings

We did not find any inner ear anomalies and smooth and complete electrode insertion

109 was achieved in all patients. Electrically evoked compound action potential (ECAP) was
110 detected in 3 cases. The implants used in the other 2 cases (cases 1 and 3) were
111 incompatible with ECAP measurements.

112 Although susceptibility to malignant hyperthermia in patients with mitochondrial
113 diseases has been reported (21), none of the patients in our series showed malignant
114 hyperthermia. While most inhalation anesthetics and propofol can suppress complexes I
115 and II of mitochondrial respiratory chains (22), none of our patients suffered from any
116 problems.

117

118 Postoperative speech perception performance test

119 Four out of the five patients showed good performance in the speech perception
120 performance test after CI. The average performance of these 4 patients (92.5% for
121 vowels, 45.0% for CV syllables, and 78% for sentences, Figure 1) was comparable to that
122 of the other CI patients with post-lingual deafness at Kyoto University Hospital (23)
123 (85.2% for vowels, 41.1% for CV syllables, and 80.1% for sentences, Figure 1). The mean
124 speech perception results were not significantly different between those of a
125 mitochondrial disease patients group and those of a control group with p values of 0.23
126 for vowels, 0.71 for CV syllables, and 0.90 for sentences. This good performance

persisted for at least 8 and 3 years after surgery in case 1 and case 2, respectively (Figures 2 and 3). Case 4 and case 5, in which the tests were conducted only once, also showed good results in the speech perception performance test 2 years and 1.5 years after surgery, respectively (Figure 4). In case 3 the patient could not participate in the speech perception performance test even 2 years after CI surgery presumably due to the poor cognitive function. This patient's average threshold in the sound field pure-tone audiometry was 30–45 dB hearing level from 250–4000 Hz at 1 year after CI surgery.

Discussion

Possible causes of SNHL by mitochondrial diseases with syndromic hearing loss are cochlear dysfunction and retrocochlear impairment. Several studies suggested that cochlear dysfunction was the more probable cause of SNHL in mitochondrial diseases with syndromic hearing loss (19,20). However, other reports suggested the involvement of retrocochlear impairment based on the increased latency in auditory brain stem response (ABR) (24,25). Favorable outcomes of CI (3-15), including the preserved retrocochlear function shown by an electrically induced middle latency response (MLR) (5,10,12), supported the cochlear origin of SNHL in mitochondrial diseases theory. Our results were consistent with these previous reports (Figure 2–4). However, most of the

145 previous reports evaluated outcomes only once within 2 years after surgeries.

146 Since impairment of retrocochlear function may occur many years after CI surgeries

147 and may cause deterioration of CI outcomes, repeated evaluations over a longer period

148 are imperative. In this study, we performed the postoperative speech perception

149 performance test on 2 patients (cases 1 and 2) several times over 8 and 3 years,

150 respectively. These results showed the preservation of retrocochlear function in both

151 MELAS and MIDD patients over extended periods after their CI surgeries. While 5

152 years of follow-up of the CI outcome has been reported for MIDD patients (8), the

153 audiological evaluation in our study showed that even in MELAS, which is considered

154 more severe mitochondrial disease than MIDD (12), the retrocochlear function was

155 preserved over an extended period of time.

156 In addition to the dysfunction of central auditory pathways, cognitive problems should

157 be considered when deciding the indications for CI especially in severe mitochondrial

158 diseases such as MELAS. The cognitive deficit sometimes causes the limited usage of a

159 cochlear implant. The patient in case 3 had a strong desire to recover her hearing ability

160 prior to her CI surgery. However, she could not recognize the importance of using her

161 implant for the establishment of speech perception; she used her implant only several

162 hours per day. As a result, she could not undergo the speech perception performance test

163 2 year after CI surgery. This was despite her sound field pure-tone audiometry result
164 being comparable to that for the other CI users.

165 Among the 5 patients, 3 died 12, 4, and 2 years after their CI surgeries. The poor
166 prognosis of MELAS (26) raises the problem of cost-effectiveness of CI for syndromic
167 deafness due to mitochondrial diseases. Nevertheless, the long-term preferable
168 outcomes of CI in mitochondrial diseases shown in this study, and the possibility of
169 other severe symptoms caused by mitochondrial disease such as visual disturbance,
170 support the validity of CI for mitochondrial disease patients with hearing loss.

171

172 CONCLUSION

173

174 Mitochondrial disease patients who underwent cochlear implantation surgery sustained
175 gains in hearing performance even long after CI surgery. A single patient had poor
176 postoperative speech perception associated with cognitive problems. Cochlear
177 implantation for mitochondrial disease patients appears to be a viable treatment option
178 in the absence of significant cognitive function.

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243 **FIGURE Legends**

244 **Figure 1.** Comparison of post-operative speech perception performance test results.

245 The average scores in the post-operative speech perception performance test for vowels,
246 consonant-vowel (CV) syllables, and short sentences were compared between 4
247 mitochondrial disease patients (white boxes, case 1, 2, 4, and 5) and other post-lingually
248 deafened patients (black boxes) who underwent cochlear implantation. Error bars
249 indicate standard deviation. No significant difference in any test was detected between
250 mitochondrial disease patients and other post-lingually deafened patients. Error bars
251 indicate standard deviation.

252

253 **Figure 2.** Time course of post-operative speech perception performance in case 1.

254 The performances for vowels and sentences were well maintained even 8 years after
255 surgery.

256

257 **Figure 3.** Time course of post-operative speech perception performance in case 2.

258 The performances were well maintained 3 years after surgery.

259

260 **Figure 4.** The outcomes of post-operative speech perception performance test for cases 4

261 and 5.

262 The tests were performed 2 years and 1.5 years after surgery, respectively.

263

Table

Summary of patients

Case	Sex	Age	Disease	Mutation	Duration of deafness	PR	CI
1	F	41	MELAS	m.3243A>G	6 years	-	CI22
2	F	64	MIDD	m.3243A>G	1 years	-	CI24R
3	F	41	MELAS	N.D.	2 years	+++	Combi40+
4	M	30	Unclassified	m.3243A>G	20 years	+	Pulsar100
5	F	36	MELAS	m.3243A>G	2 years	-	CI24RE(CA)

N.D.: not determined; PR: psychomotor regression