

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.

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

24

## 25 **INTRODUCTION**

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

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

39 Most previous case reports suggested that cochlear implantation (CI) has favorable  
40 effects in both types of mitochondrial diseases, based solely on the outcome at 1 time  
41 point or within at most 2 years after surgery. Although these results are supported by  
42 the fact that the SNHL in mitochondrial diseases is attributed to cochlear dysfunction  
43 (19,20), mitochondrial diseases with syndromic deafness can affect the central nervous  
44 system, including the central auditory pathway, or cause psychomotor regression after  
45 CI (1). Thus, the beneficial effects of cochlear implants may further change even after  
46 determination of the initial treatment outcome or within several years after surgery,  
47 since continued normal function of the central auditory pathway and stable  
48 psychological conditions are necessary for successful CI. In this study, we present the  
49 outcomes of CI on a longitudinal basis at several time points in cases of syndromic  
50 mitochondrial deafness that presented at Kyoto University Hospital and discuss the  
51 validity to perform CI for syndromic mitochondrial deafness.

52

## 53 **MATERIALS AND METHODS**

54

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)

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

106

#### 107 Surgical findings

108 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



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

134

## 135 **Discussion**

136 Possible causes of SNHL by mitochondrial diseases with syndromic hearing loss are  
137 cochlear dysfunction and retrocochlear impairment. Several studies suggested that  
138 cochlear dysfunction was the more probable cause of SNHL in mitochondrial diseases  
139 with syndromic hearing loss (19,20). However, other reports suggested the involvement  
140 of retrocochlear impairment based on the increased latency in auditory brain stem  
141 response (ABR) (24,25). Favorable outcomes of CI (3-15), including the preserved  
142 retrocochlear function shown by an electrically induced middle latency response (MLR)  
143 (5,10,12), supported the cochlear origin of SNHL in mitochondrial diseases theory. Our  
144 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.

179

180   **REFERENCES**

- 181   1.     DiMauro S, Schon EA. Mitochondrial disorders in the nervous system. *Annual*  
182         *review of neuroscience* 2008;31:91-123.
- 183   2.     Chinnery PF, Elliott C, Green GR et al. The spectrum of hearing loss due to  
184         mitochondrial DNA defects. *Brain* 2000;123 ( Pt 1):82-92.
- 185   3.     Yamaguchi T, Himi T, Harabuchi Y et al. Cochlear implantation in a patient with  
186         mitochondrial disease--Kearns-Sayre syndrome: a case report. *Adv Otorhinolaryngol*  
187         1997;52:321-3.
- 188   4.     Cullington HE. Cochlear implantation of a deaf blind patient with mitochondrial  
189         cytopathy. *J Laryngol Otol* 1999;113:353-4.
- 190   5.     Rosenthal EL, Kileny PR, Boerst A et al. Successful cochlear implantation in a  
191         patient with MELAS syndrome. *Am J Otol* 1999;20:187-90; discussion 90-1.
- 192   6.     Counter PR, Hilton MP, Webster D et al. Cochlear implantation of a patient with a  
193         previously undescribed mitochondrial DNA defect. *J Laryngol Otol* 2001;115:730-2.
- 194   7.     Hill D, Wintersgill S, Stott L et al. Cochlear implantation in a profoundly deaf  
195         patient with MELAS syndrome. *J Neurol Neurosurg Psychiatry* 2001;71:281.
- 196   8.     Raut V, Sinnathuray AR, Toner JG. Cochlear implantation in maternal inherited  
197         diabetes and deafness syndrome. *J Laryngol Otol* 2002;116:373-5.
- 198   9.     Sinnathuray AR, Raut V, Awa A et al. A review of cochlear implantation in  
199         mitochondrial sensorineural hearing loss. *Otol Neurotol* 2003;24:418-26.
- 200   10.    Yasumura S, Aso S, Fujisaka M et al. Cochlear implantation in a patient with  
201         mitochondrial encephalopathy, lactic acidosis and stroke-like episodes syndrome.  
202         *Acta Otolaryngol* 2003;123:55-8.
- 203   11.    Karkos PD, Anari S, Johnson IJ. Cochlear implantation in patients with MELAS  
204         syndrome. *Eur Arch Otorhinolaryngol* 2005;262:322-4.
- 205   12.    Pijl S, Westerberg BD. Cochlear implantation results in patients with Kearns-Sayre  
206         syndrome. *Ear Hear* 2008;29:472-5.
- 207   13.    Li JN, Han DY, Ji F et al. Successful cochlear implantation in a patient with MNGIE  
208         syndrome. *Acta Otolaryngol* 2011;131:1012-6.
- 209   14.    Scarpelli M, Zappini F, Filosto M et al. Mitochondrial Sensorineural Hearing Loss: A  
210         Retrospective Study and a Description of Cochlear Implantation in a MELAS  
211         Patient. *Genet Res Int* 2012;2012:287432.
- 212   15.    Nishizaki K, Fukushima K, Oda Y et al. Cochlear implantation for symptomatic  
213         hereditary deafness. *Acta oto-laryngologica. Supplementum* 1999;540:34-7.
- 214   16.    Mancuso M, Filosto M, Forli F et al. A non-syndromic hearing loss caused by very low

215 levels of the mtDNA A3243G mutation. *Acta Neurol Scand* 2004;110:72-4.

216 17. Tono T, Ushisako Y, Kiyomizu K et al. Cochlear implantation in a patient with  
217 profound hearing loss with the A1555G mitochondrial mutation. *Am J Otol*  
218 1998;19:754-7.

219 18. Ulubil SA, Furze AD, Angeli SI. Cochlear implantation in a patient with profound  
220 hearing loss with the A1555G mitochondrial DNA mutation and no history of  
221 aminoglycoside exposure. *J Laryngol Otol* 2006;120:230-2.

222 19. Sue CM, Lipsett LJ, Crimmins D et al. Cochlear origin of hearing loss in MELAS  
223 syndrome. *Ann Neurol* 1998;43:350-9.

224 20. Yamasoba T, Oka Y, Tsukuda K et al. Auditory findings in patients with maternally  
225 inherited diabetes and deafness harboring a point mutation in the mitochondrial  
226 transfer RNA(Leu) (UUR) gene. *Laryngoscope* 1996;106:49-53.

227 21. Fricker RM, Raffelsberger T, Rauch-Shorny S et al. Positive malignant hyperthermia  
228 susceptibility in vitro test in a patient with mitochondrial myopathy and  
229 myoadenylate deaminase deficiency. *Anesthesiology* 2002;97:1635-7.

230 22. Lerman J. Perioperative management of the paediatric patient with coexisting  
231 neuromuscular disease. *British journal of anaesthesia* 2011;107 Suppl 1:i79-89.

232 23. Hiraumi H, Tsuji J, Kanemaru S et al. Cochlear implants in post-lingually deafened  
233 patients. *Acta oto-laryngologica. Supplementum* 2007:17-21.

234 24. Elverland HH, Torbergesen T. Audiologic findings in a family with mitochondrial  
235 disorder. *Am J Otol* 1991;12:459-65.

236 25. Zwirner P, Wilichowski E. Progressive sensorineural hearing loss in children with  
237 mitochondrial encephalomyopathies. *Laryngoscope* 2001;111:515-21.

238 26. Yatsuga S, Povalko N, Nishioka J et al. MELAS: a nationwide prospective cohort  
239 study of 96 patients in Japan. *Biochimica et biophysica acta* 2012;1820:619-24.

240

241

242

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

Figure 1

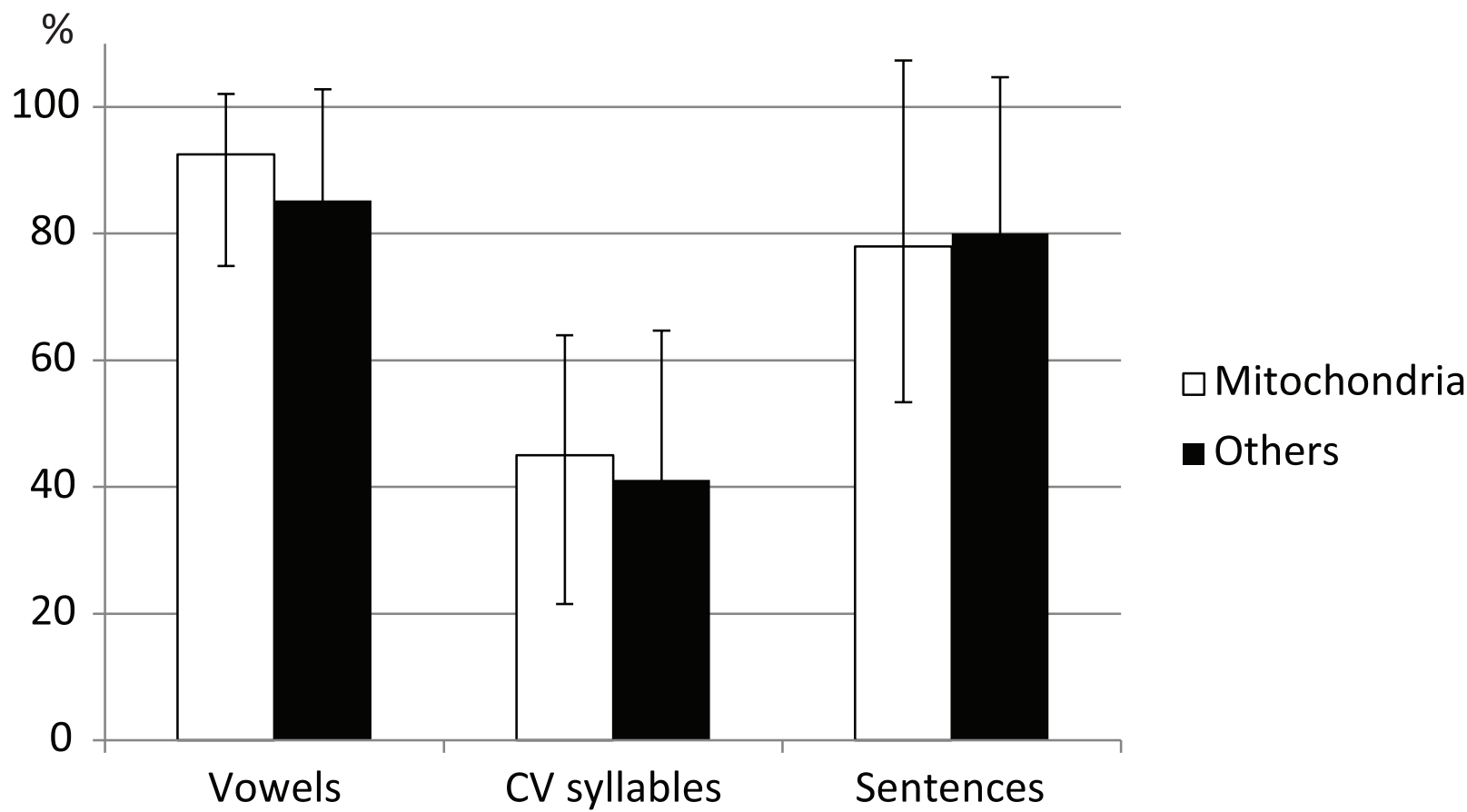




Figure 2

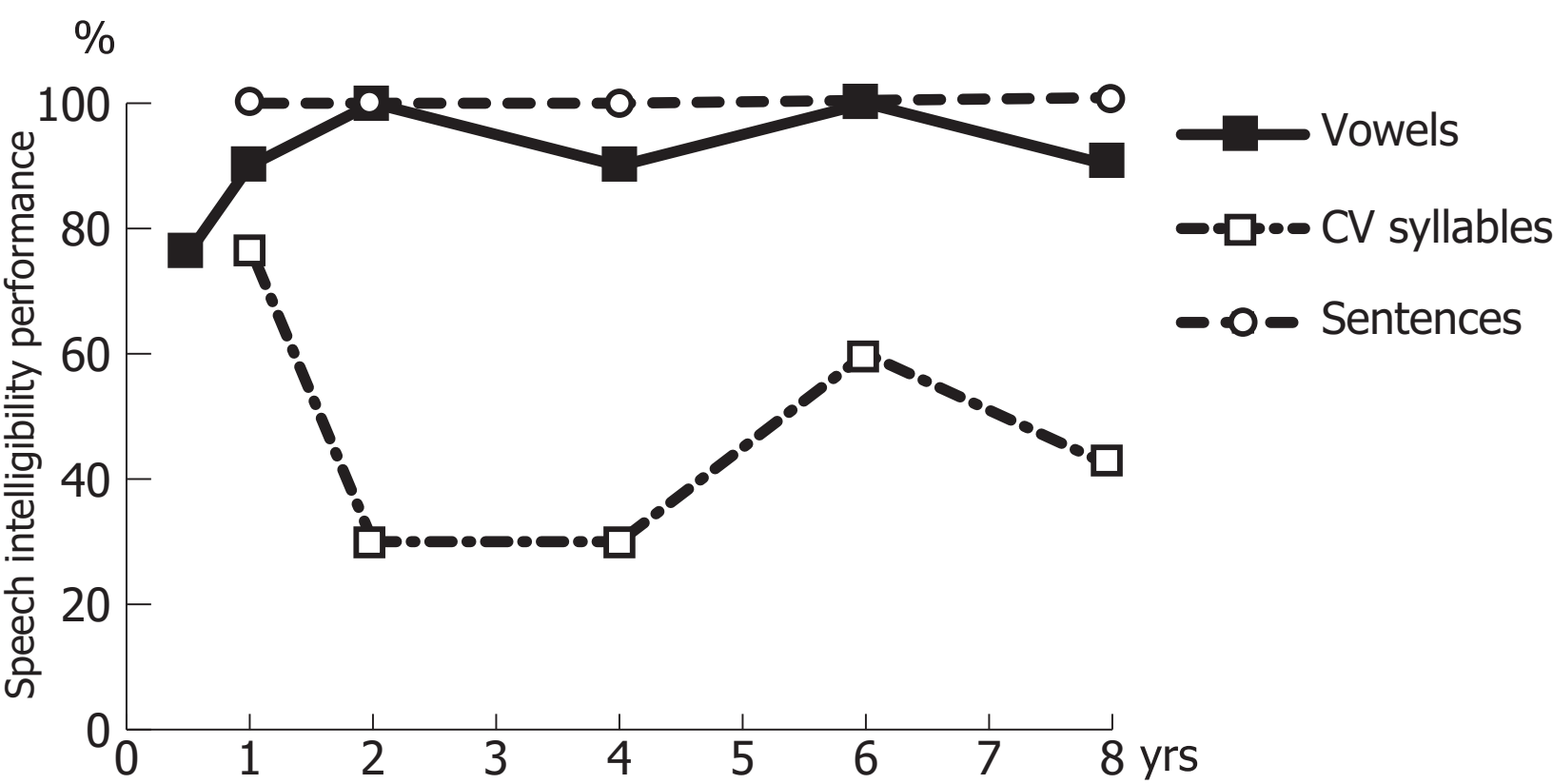


Figure 3

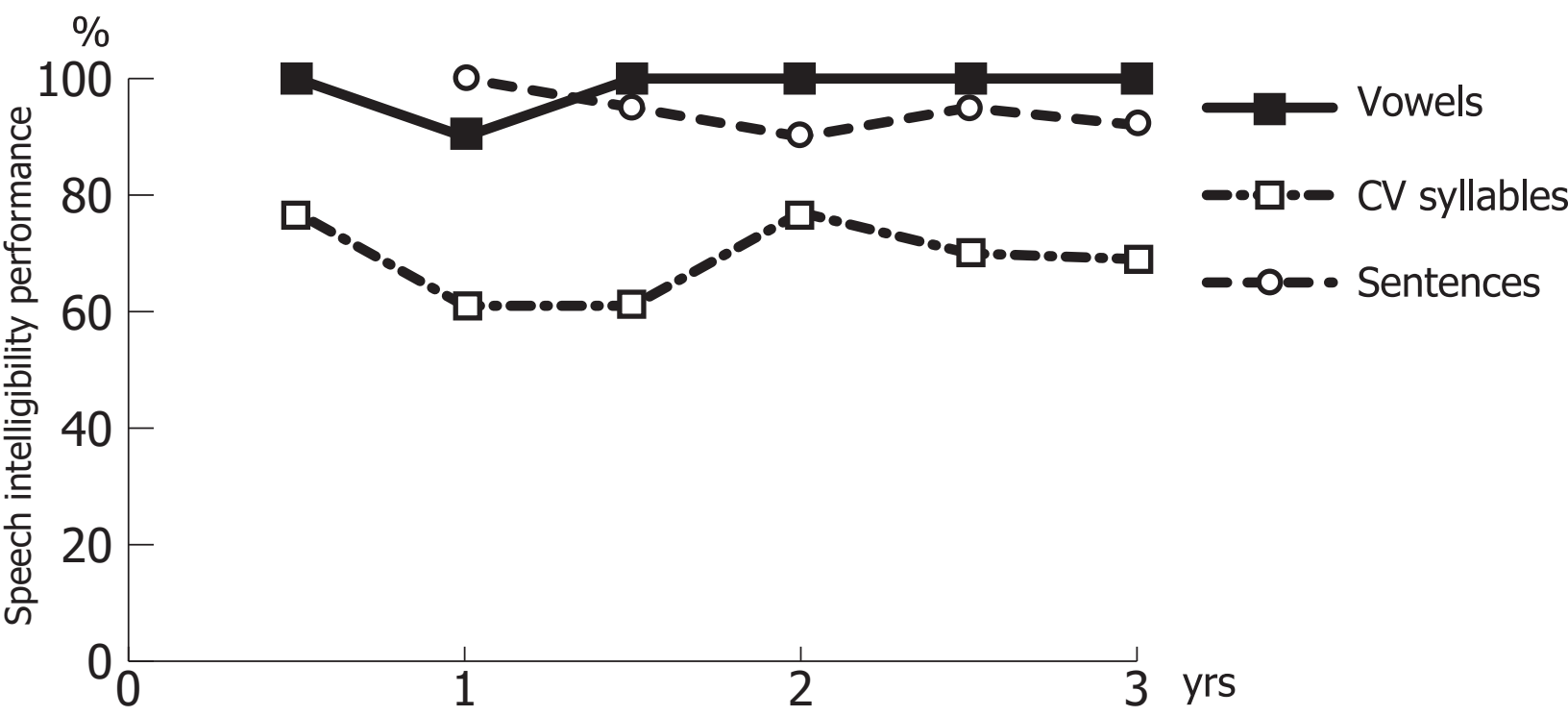
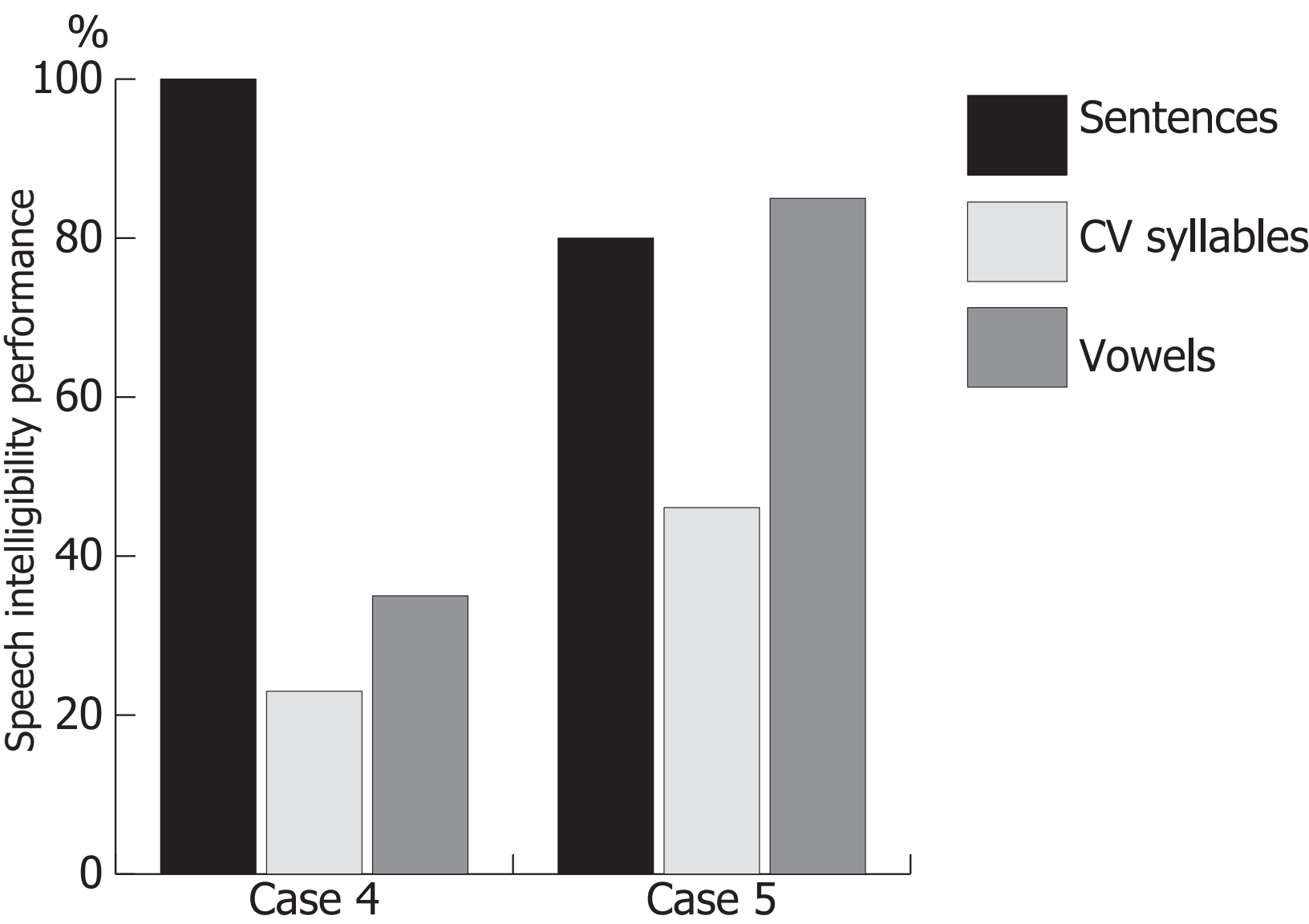


Figure 4



**Table**

Summary of patients

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

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