Abstract

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

Study design: Retrospective case review

Setting: Tertiary referral center

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

Interventions: Therapeutic and rehabilitative

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

Results: Only 1.4% (5/367) of cochlear implantation cases at Kyoto University Hospital underwent cochlear implantation surgery due to syndromic mitochondrial diseases. Four of those patients showed significantly improved speech perception outcomes, and the beneficial effects of the intervention continued long after surgery. One patient could 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.

Postoperative speech perception performance test

Vowels, consonant-vowel (CV) syllables, and short sentences were phonated by a male professional announcer and digitized at a sampling rate of 44.1 kHz. These speech samples were presented via speakers at 70 dB SPL using a PowerMac PM-7300/166 computer (Apple Inc., Cupertino, California, USA) in random order; the percentage of correct answers was recorded. In the vowel perception test, 5 Japanese vowels were presented to patients. In the CV syllable perception test, 13 CV syllables—composed of 13 Japanese consonants and the vowel /a/— were presented to patients. In the phrase perception test, 10 short Japanese sentences were arranged to contain 40 different phrases. The vowel and CV syllable perception test used closed sets and the phrase perception test used an open set. These tests were administered at least 6 months after implantation. Unpaired *t*-tests were performed for the statistical analysis and *p*-values below 0.05 were considered statistically significant.

RESULTS

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

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

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

Postoperative speech perception performance test

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

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

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

CONCLUSION

Mitochondrial disease patients who underwent cochlear implantation surgery sustained gains in hearing performance even long after CI surgery. A single patient had 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 function.

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FIGURE Legends

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

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

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

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

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

The performances were well maintained 3 years after surgery.

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

and 5.

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

Figure 1

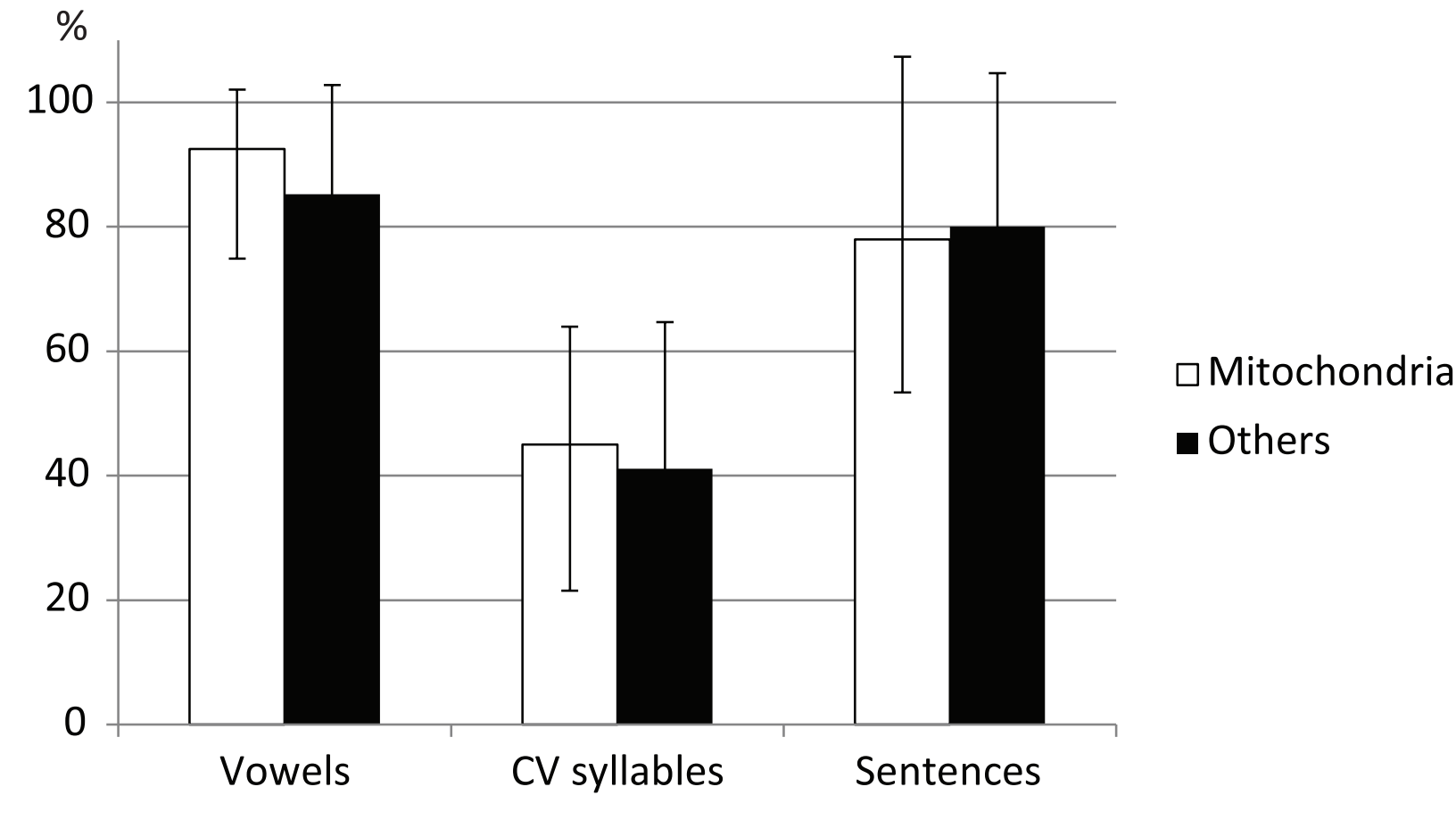
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Figure 2

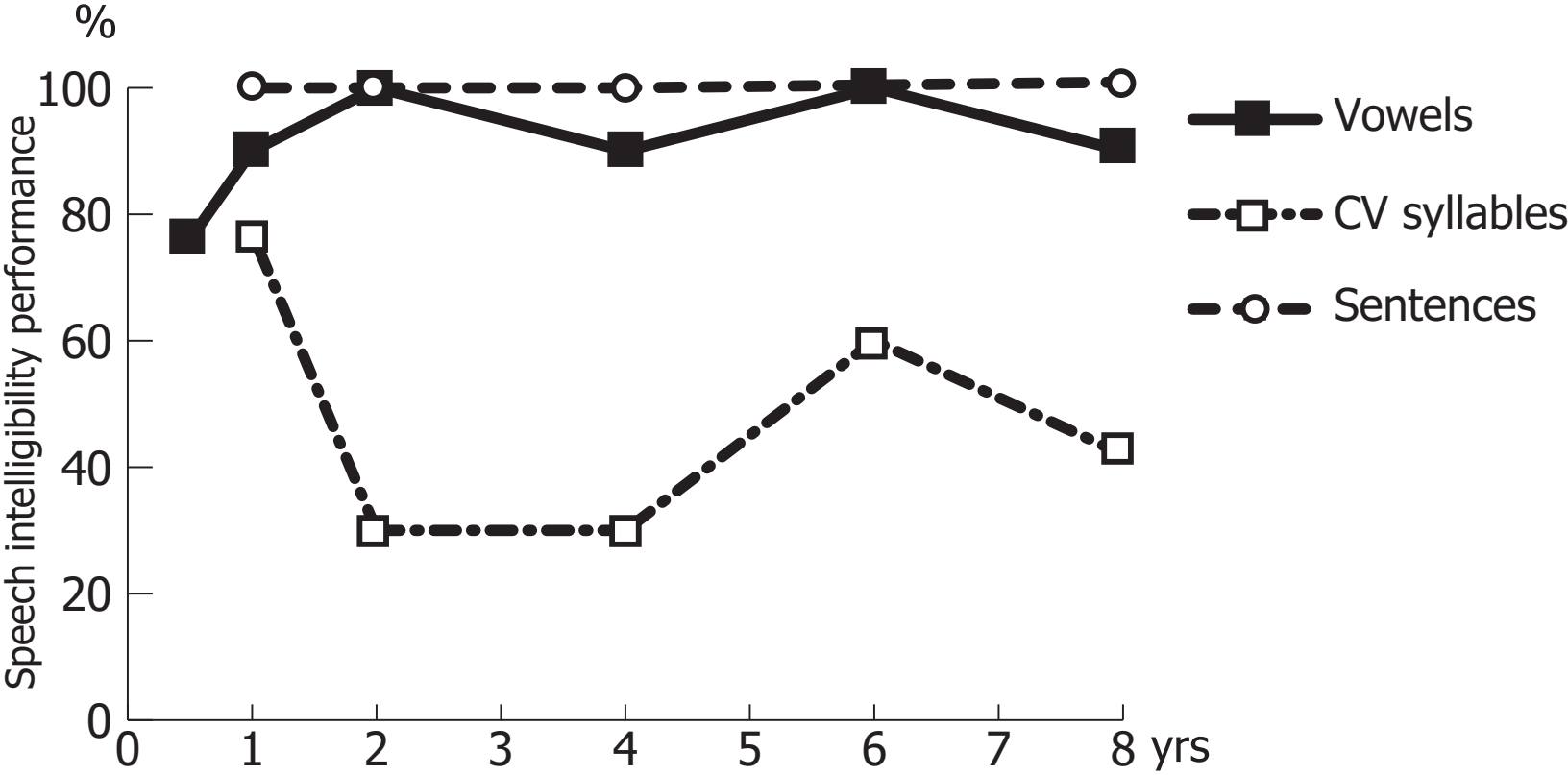
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Figure 3

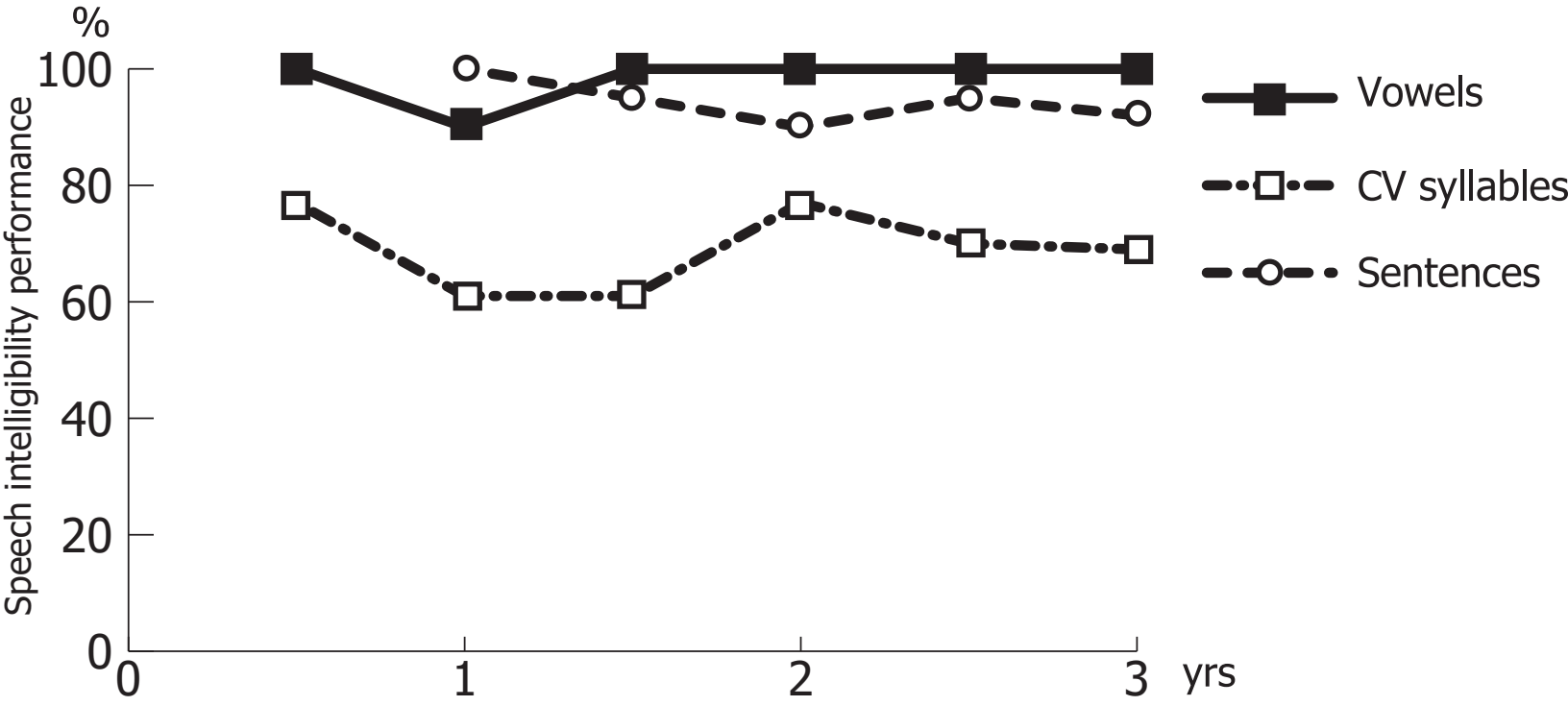
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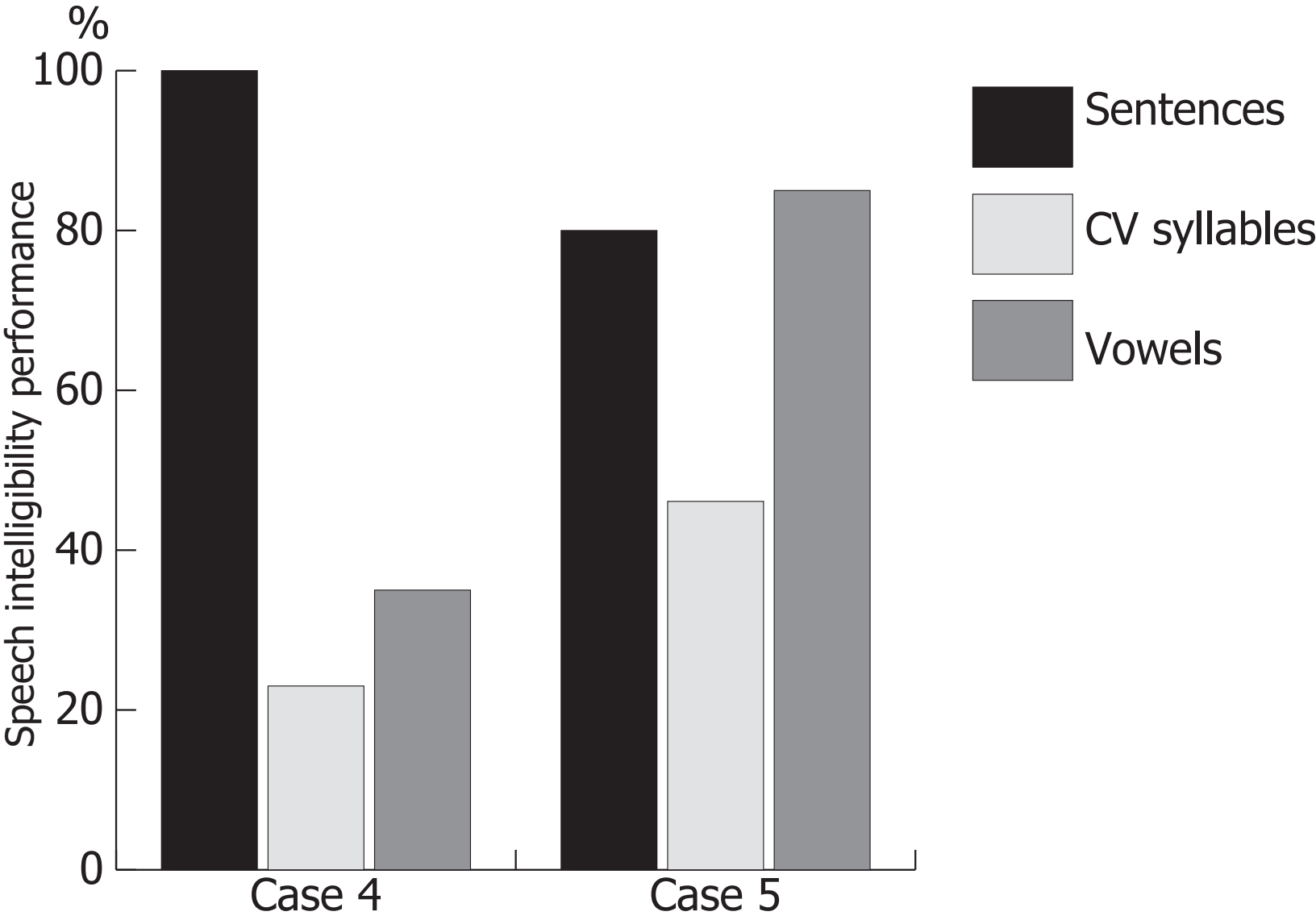
Figure 4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Speech intelligibility performance
Case 4
Case 5
Sentences
CV syllables
Vowels

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