However, he could play various sports at school age. By the age of twenty, he can enjoy skiing, ski jumping, and riding bicycles without holding on with both hands, which requires higher balance functions (Figure 13).

Eventually, these two cases overcame vestibular failure.

The evidence to date would suggest that the ceiling for central compensation in cases with congenital vestibular failure may be unlimited, but more longitudinal follow-up studies must be undertaken.

## Conclusion

In general, congenitally deaf children with hypoactive or absent vestibular function are frequently misdiagnosed with psychomotor retardation or brain damage. However, in our studies, we conclude that in congenitally deaf children with vestibular loss, central vestibular compensation can overcome delayed motor function very well, such that the children may develop exercises and sports activities with great skill.

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**ORIGINAL ARTICLE**

# Vestibular evoked myogenic potentials evoked by multichannel cochlear implant – influence of C levels

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**Abstract**

*Conclusions.* This study showed that vestibular evoked myogenic potentials (VEMPs) evoked by cochlear implant (CI), could be related to the comfortable level (C level), particularly in the channels that are closer to the apical turn of the cochlea. *Objective.* The purpose of this study was to investigate the correlation between VEMPs and C level of each channel. *Subjects and methods.* We investigated 24 children who underwent cochlear implantation. VEMPs were recorded from the operated ears with the CI switched 'off' or 'on'. To investigate the correlation between VEMPs and C level, we selected 13 patients with Nucleus 24 (SPrint), and divided them into group A (normal VEMPs) and B (absence of VEMPs). In these children, all the 22 electrodes were active, and were mapped in the same frequency range for each channel. *Results.* Twenty children (83%) showed no VEMPs with the CI 'off'. Among them, 10 elicited VEMPs with the CI 'on', but the other 10 did not. In all channels, the mean C levels of CI were higher in group A than in group B. The $p$ values in channels 1–12 were >0.10, in channels 13–16 were 0.06–0.09, and in channels 17–22 were 0.05–0.06, which were lower but not statistically significant.

**Keywords:** *Children, cochlear implant (CI), VEMPs, electrical stimulation, inferior vestibular nerve, C level*

## Introduction

In patients with a multichannel cochlear implant (CI), electrical stimulation may not only stimulate the cochlear nerve, but may also partially spread to the facial nerve [1,2] or vestibular nerve [3]. Vestibular evoked myogenic potentials (VEMPs) are considered to be useful for evaluating the functions of the saccular [4], inferior vestibular nerve [5] and the tonus of the sternocleidomastoid muscle (SCM). In our previous study, we reported that there were no VEMPs during CI stimulation in eight children, but there were VEMPs in the other four children [3]. However, the differences in VEMPs in that study were still unclear.

The surgical procedures, CI devices, current intensity, stimulation schemes and testing paradigms used may be important for eliciting VEMPs. In this study, we selected 13 children with Nucleus 24 (SPrint), all the 22 electrodes of which were active and mapped in the same frequency range, and investigated the correlation between VEMPs and the C level of each channel.

## Subjects and methods

### *Subjects*

The patients were 24 children who underwent CI surgery at the University of Tokyo Hospital. The mean age at VEMP recording was 5.4 ± 3.0 years (range 2–14 years). All the patients had normal inner ear structures, as demonstrated by computed tomography (CT) of the temporal bone. All the children showed improved hearing after surgery.

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### *Procedures and VEMP recordings*

The children were placed in the supine position. The active electrode was placed on the upper half of SCM, the reference electrode on the upper sternum and the ground electrode on the midline of the forehead. During VEMP recording, the children were instructed to lift their head up or to turn their head to the contralateral side to induce hypertonicity in the SCM.

The electromyography signal from the stimulated side was amplified and averaged using a Neuropack evoked-potential recorder (Nihon Kohden Co. Ltd, Tokyo, Japan). Electromyographic activities at a constant level were recorded for each child. The head-phone was placed over the microphone of the CI behind the ear. Rarefaction clicks (0.1 ms; 95 dB normal hearing level) were presented through the head-phone (type DR-531; Elega Acous Co. Ltd, Tokyo, Japan) and were used to evoke the VEMPs. The stimulation rate was 5 Hz, the band-pass filter intensity was in the range of 20–2000 Hz and the analysis time was 50 ms. VEMPs in response to 100 stimuli were averaged twice. After the CI surgery, the VEMPs of all the 24 children were recorded from the operated ear with the CI switched 'off' or 'on'.

### *Definition of VEMP*

We classified VEMP recordings into three types as follows. Type 1, normal: the amplitudes of VEMPs were $>50\ \mu V$. Type 2, small: the amplitudes of VEMPs were higher than $0\ \mu V$, but lower than $50\ \mu V$. Type 3, absent. Types 2 and type 3 were regarded as abnormal VEMPs.

### *Characteristics of CI device*

The characteristics of CI devices are summarized in Table I.

*CI device.* All patients received multichannel cochlear implants; 21 children had Nucleus 24 and 3 children had Nucleus 22.

*Speech coding strategy.* All patients with Nucleus 24 were coded with ACE and all patients with Nucleus 22 were coded with SPEAK.

*Speech processor.* Two patients used ESPrit, and one child used Spectra. Among patients with Nucleus 24, 18 patients used SPrint, one used ESPrint and 2 used ESPrit 3G. Among patients with Nucleus 24, the electrodes of all the channels were active in

Table I. Profile of patients.

| Patient no. | Sex | Age (years) | CI type | Speech processor | Strategy | Active electrode number | VEMP | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Off | On |
| 1 | M | 2 | 24M | SPrint | ACE | 22 | – | + |
| 2 | F | 2 | 24M | SPrint | ACE | 22 | – | + |
| 3 | F | 4 | 24M | SPrint | ACE | 22 | Small | + |
| 4 | F | 5 | 24M | SPrint | ACE | 22 | – | + |
| 5 | F | 7 | 24M | SPrint | ACE | 22 | – | + |
| 6 | M | 3 | 24M | SPrint | ACE | 22 | Small | + |
| 7 | M | 3 | 24M | SPrint | ACE | 22 | Small | Small |
| 8 | M | 2 | 24M | SPrint | ACE | 22 | Small | Small |
| 9 | M | 6 | 24M | SPrint | ACE | 22 | – | – |
| 10 | F | 4 | 24M | SPrint | ACE | 22 | – | – |
| 11 | M | 6 | 24M | SPrint | ACE | 22 | – | – |
| 12 | F | 4 | 24M | SPrint | ACE | 22 | – | – |
| 13 | F | 5 | 24M | SPrint | ACE | 22 | – | – |
| 14 | F | 3 | 24M | SPrint | ACE | 22 | – | – |
| 15 | F | 3 | 24M | SPrint | ACE | 22 | – | – |
| 16 | F | 7 | 24M | SPrint | ACE | 22 | – | – |
| 17 | M | 4 | 24M | SPrint | ACE | 21 | – | – |
| 18 | F | 3 | 24M | SPrint | ACE | 18 | – | + |
| 19 | F | 11 | 24M | ESPrit | ACE | 20 | – | + |
| 20 | M | 7 | 24M | ESPrit 3G | ACE | 20 | – | + |
| 21 | M | 7 | 24M | ESPrit 3G | ACE | 20 | – | – |
| 22 | F | 9 | 22M | ESPrit 22 | SPEAK | 18 | – | + |
| 23 | M | 14 | 22M | ESPrit 22 | SPEAK | 17 | – | + |
| 24 | F | 8 | 22M | Spectra | SPEAK | 16 | – | + |

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16, and electrodes of a part of channels were active in 5 patients.

### *Correlation between VEMP and C level*

To investigate the correlation between VEMP and C level, we selected patients with the same CI device, coded with the same strategy and programmed with the same frequencies in each channel. All of these patients had Nucleus 24 CI devices (SPrint) and were coded with ACE strategy, and programmed with the same frequency ranges in each channel. In these patients, the electrodes of all the channels were active. We divided these patients into group A (normal VEMP; $n=6$) and group B (absence of VEMP; $n=7$) when the CI was switched on. Groups A and B were compared in terms of the C levels of each channel. However, two patients with small VEMPs were excluded, and one patient who used a different stimulation rate was also excluded from this study.

### *Procedures for obtaining C level data*

MAPs were created by audiologists for each subject using Cochlear Corporation's Nucleus R126 ver.2.1. All MAP data of Nucleus 24 were created using ACE of monopolar stimulation at a duration of 25 μs/phase. The default stimulus for the ACE processor is a 500 ms burst of 250 Hz biphasic pulse train. The 'current level' used in both the NRT software (for masker and probe levels) and the R126 programming software were represented in units that vary from 1 to 255 and span a nominal range of approximately 10.2 μA to 1.75 mA, respectively. To avoid confusion between actual current level of microamps and Cochlear Corporation's 'current level' units, we refer to the stimulus level in 'programming units', which correspond to Cochlear Corporation's 'current level' units [6].

The child would indicate threshold and the maximum stimulus level that was comfortable for each electrode stimulated. For younger children (approximately aged 2–6 years), minimal response levels were obtained using play audiometry. These levels were used to measure T level. T level would be set at a level that evoked a consistent change in behaviours, such as quieting or head turn. At connection, C levels were typically set from above T level uncomfortable level for each of the three or four MAPs loaded onto the speech processor. The child was sent home wearing the softest MAP, and the parents were instructed to work their child through each of the progressively louder programs during the first few weeks of implant use until they returned for the next programming session. This was done to ensure that the initial MAP would be comfortable for the first day of use. To investigate the correlation between VEMP and C level, we selected the data of C level at the same time as VEMP recording.

### *Statistical analysis*

Data were analysed statistically using unpaired *t* test. A difference was considered to be statistically significant at $p<0.05$.

## Results

### *VEMPs appearance rate with CI off and on*

When patients were tested with CI off, VEMPs were absent in 20/24 and small in 4/24 children. When patients were tested with CI on, VEMPs were normal in 12/24, small in 2/24 and absent in 10/24 children (Figure 1).

### *Comparison of VEMPs in the same patients with CI off and on*

The comparison showed the following results: 10/24 children among those with absent VEMPs with CI off showed VEMPs with CI on (Figure 2); 10/24

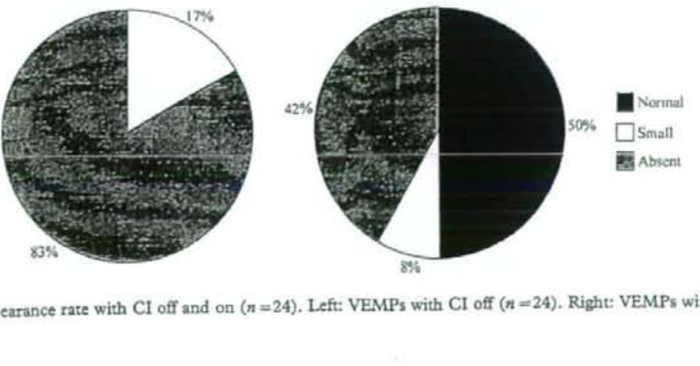

Figure 1. VEMPs appearance rate with CI off and on ($n=24$). Left: VEMPs with CI off ($n=24$). Right: VEMPs with CI on ($n=24$).

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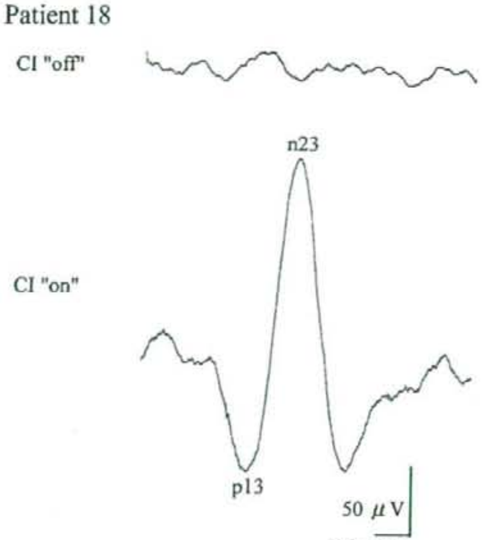

Figure 2. VEMPs of patient 18. This patient was fitted with a Nucleus 24 (SPrint), coded with ACE strategy. Electrode numbers 1–4 were not active, but numbers 5–22 were active. Top: absent VEMPs with CI off. Bottom: normal VEMPs with CI on.

among those with absent VEMPs with CI off showed absent VEMPs with CI on; 2/24 among those with small VEMPs with CI off showed VEMPs with CI on; 2/24 among those with small VEMPs with CI off showed small VEMPs with CI on.

The changes in VEMP amplitude before and after turning CI on are summarized in Figure 3. The mean amplitude with CI off and CI on were 6.5±15.4 and 83.9±102.9 μv, respectively.

### *Effect of C level on VEMPs*

The mean time lapse after CI surgery in groups A ($n = 6$) and B ($n = 7$) were 13.3±17.7 and 11.1±10.1 months, respectively. There was no significant difference in the time lapse after CI surgery between groups A and B ($p = 0.7843$).

The VEMPs in groups A and B are illustrated in Figure 4.

The lower and upper frequencies in each channel in group A (normal VEMP) and group B (absence of VEMP) are illustrated in Figure 5a.

Mean C levels in each channel in group A and B are illustrated in Figure 5b. In all channels, each mean C level was higher in group A than in group B. The $p$ values in channels 1–12 were $>0.10$, in channels 13–16 were 0.06–0.09, and in channels 17–22 were 0.05–0.06. Then, it was revealed that the C level that elicited VEMPs in group A was higher than in group B. The C level was higher than among those who had normal VEMPs (with CI on) and those who had no VEMPs, due to differences in channels 17–22.

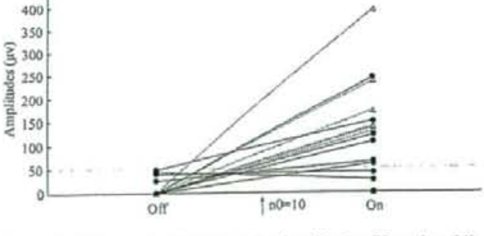

Figure 3. Changes in VEMP amplitude with the CI on ($n = 24$). Solid circle, patients have Nucleus 24 and all the 22 electrodes were active; empty triangle, other kinds of patients. n0 = 10: absent VEMPs with both CI off and on ($n = 10$).

## Discussion

As regards saccular function after CI surgery, the insertion of an intrascalar electrode array causes immediate damage to the inner ear [7,8] and over time may cause additional changes, which can interfere with neuronal stimulation [9,10]. The postoperative dysfunction of the vestibular system in multichannel CI patients has been reported, such as dizziness [11], and reduction of caloric responses [12], and a vestibule-ocular response to rotation chair [13]. A decrease in VEMPs after CI surgery has also been reported [3,14]. In our previous study, we compared the VEMPs of the operated ear before and after CI surgery, and found that in 7 of the 12 children (58%), the VEMPs were abolished postoperatively without CI stimulation [3]. Ernst et al. demonstrated that VEMPs induced by bone-conducted acoustic stimuli are absent in 36% of patients before implantation, and that this percentage increases to 78% after the CI surgery [14]. These reports suggested that the saccule of these children must have been damaged after CI surgery in the operated ear.

In this study, we found that 20 patients (83%) did not show VEMPs without CI stimulation after surgery. This result is in agreement with those of previous studies [3,14]. In a pathological study of the human temporal bone, saccule collapse occurred in the operated ear [15,16], but the hair cell densities were the same as those in the non-operated ear [15]. Direct damage to the ductus reunions [17] or cochlear duct as a result of it being blocked externally by fibrous tissue or bone and internally by debris may result in saccule collapse [15]. Our

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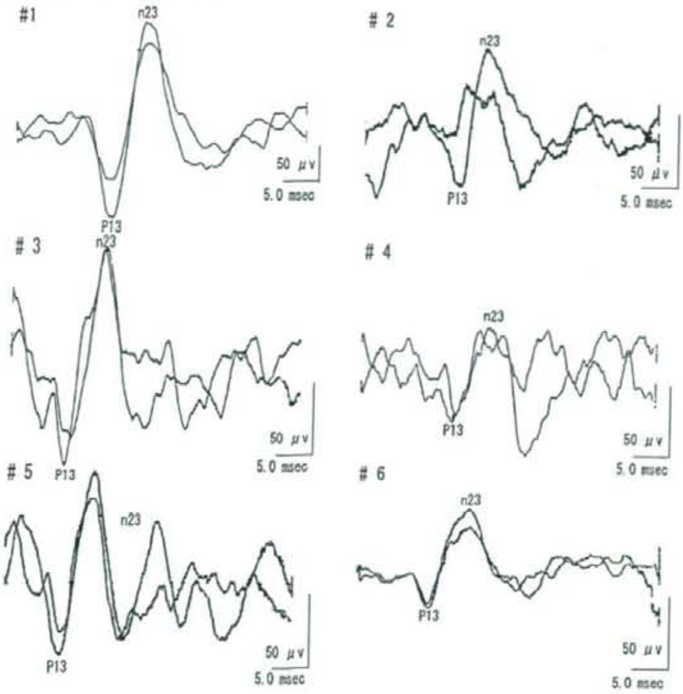
(a) VEMP in group A (n=6)



(b) VEMP in group B (n=7)

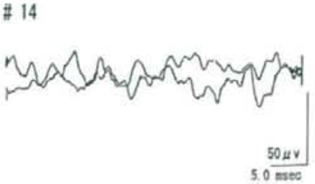


Figure 4. VEMPs in groups A and B. (a) VEMPs in group A ($n = 6$); (b) VEMPs in group B ($n = 7$).

results also revealed that the functions of the saccule are lost after CI surgery.

Galvanic stimulation of the mastoid can stimulate the vestibular nerve [18,19], and elicit a sway response [20], eye movement [21] and VEMPs (galvanic VEMPs) [22,23]. Watson et al. reported that galvanic VEMPs are abolished by selective vestibular nerve section [22]. These studies suggest that galvanic VEMPs can stimulate the vestibular nerve and vestibular nucleus and elicit myogenic potentials in the SCM.

In our study, 20 children (83%) showed no VEMP response with the CI off, but 10 of these patients showed normal VEMP responses with the CI switched on. With the CI off, children with a CI were given only acoustic stimulation, but with the CI on, the acoustic stimulation changed to electrical stimulation. The VEMPs evoked by CI must be caused by the electrical stimulation of CI, which probably stimulates the inferior vestibular nerve. A human temporal bone pathological study demonstrated that Scarpa's ganglion cell count in the operated ear was the same as that in the non-operated ear [15]; however, collapse was only seen in the operated ear [15,16]. It is suggested that the vestibular nerve must be intact, although the functions of the saccule were lost in CI patients.

The basilar membrane of the inner ear is responsible for analysing the input signals into different frequencies. Low-frequency sounds create travelling waves in the fluid of the cochlea that cause the basilar membrane to vibrate, with the largest

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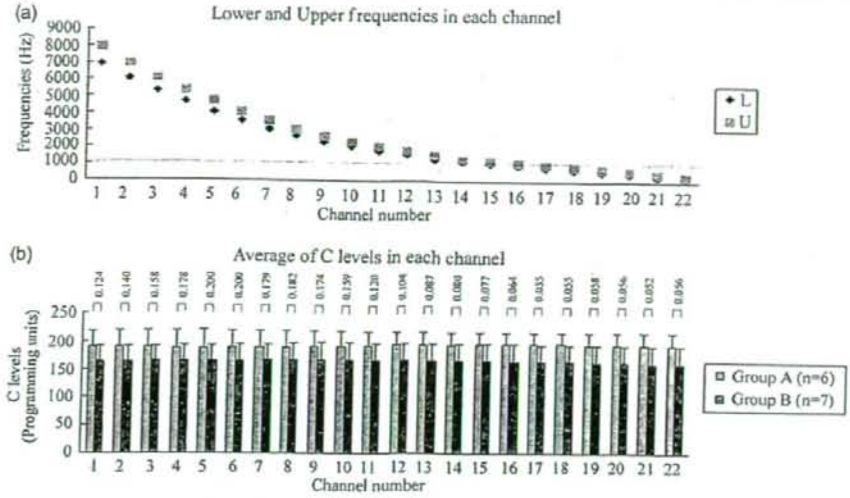

Figure 5. Average of C levels in each channel in group A ($n = 6$) and B ($n = 7$). (a) Lower and upper frequencies in each channel; L, lower frequency; U, upper frequency. (b) Average of C levels in each channel in group A ($n = 6$) and B ($n = 7$).

amplitude of displacement occurring at the apex of the basilar membrane. On the other hand, high frequency sounds create travelling waves with the largest amplitude of displacement occurring at the base of the basilar membrane. If the signals are composed of multiple frequencies, then the resulting travelling wave will show its maximum displacement at different points along the basilar membrane. This place theory for coding frequencies has motivated scientists to consider studying multichannel CIs and VEMPs. In multichannel CIs, the electrodes are located at different distances from the round window, and every channel shows different sensitivities to frequencies.

This study demonstrated that the C levels of CI were higher in group A than in group B. VEMPs stimulated by clicks are more sensitive to higher intensities, and the amplitudes of VEMPs increase with stimulus intensity [24,25]. The amplitudes of galvanic VEMPs also increase with current intensity [26]. It is suggested that the amplitudes of VEMPs are related to the current intensity of the C level.

In this study, the C level was higher among those who had VEMP (with CI on) than among those who had no VEMP, because of differences in channels 17–22 ($0.05 < p < 0.06$). The frequencies of channels 17–22 were 188–938 Hz. This difference in frequency range revealed that VEMPs evoked by CIs are easily elicited in the low frequency range. McCue and Guinan [27] reported that sound-sensitive vestibular afferents showed a broad, V-shaped tuning curve, with the ideal frequencies in the range of 500–1000 Hz. VEMPs evoked by short tone bursts (STBs) of 500 Hz, are used in clinical tests. These suggest that the saccular macula has its preferred stimulus frequency in the low frequency range. Our results suggest that the inferior vestibular nerve could be more sensitive to lower frequency ranges. The anatomic factor should be also considerable. Our results demonstrated that the $p$ values in channels 1–12 were $>0.10$, in channels 13–16 were 0.06–0.09, and in channels 17–22 were 0.05–0.06. Channels 17–22 and channels 13–16 were further away from the inferior vestibular nerve endings than channels 1–13, so it may be that higher current intensities are needed to stimulate the inferior vestibular nerve in channels 17–22. This suggests that VEMPs evoked by CIs were correlated with C level, especially in the channels that are closer to apical turn of the cochlea.

In our study, 10 of the 24 patients showed no VEMP responses with the CI on. These patients may require higher current intensities to elicit VEMP responses. However, in children, it is difficult to increase the current intensity. Children feel pain or facial nerve stimulation when the current intensities are increased higher than those of the C level.

In conclusion, the presence or absence of VEMPs in children with CIs depends on the larger current intensities of the C level, particularly in the channels that are closer to the apical turn of the cochlea.

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# Advancement in singing ability using The YUBA Method in patients with cochlear implants

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**Abstract**

*Conclusion.* Although overall improvement was not so dramatic due to a lack of retention, session by session advancement of matching pitch for targeted MIDI (Musical Instrument Digital Interface) sound was predominantly obvious. It was proved that The YUBA Method worked to improve singing ability for patients with cochlear implants. *Objectives.* This study sought to verify whether or not the Yuba theory and method improved the singing ability of patients with cochlear implants. *Subjects and methods.* Based on diagnosis, the instructor experimented to improve matching pitch of singing for three patients with cochlear implants using The YUBA Method. The mean fundamental frequencies and standard deviation of singing were then compared with before and after instructions to patients. The instruction was given for over 40 days at the University of Tokyo Hospital. *Results.* For each patient, the mean fundamental frequencies of their singing approached the mean MIDI specified frequencies as references for tests done in all three songs. Overall, the SD between fundamental frequencies of their singing and reference MIDI sounds became smaller.

**Keywords:** *Vocal folds, falsetto voice, vocal register shock, natural voice, vocal functional physiology, Yuba theory, tone deafness, music education, speech therapy*

## Introduction

It is known that people with cochlear implants tend to sing off-key, monotonously, and flat [1]. Earlier results are the work of two separate research groups using the same unique technological singing voice method, The YUBA Method. One group tested 60 normal hearing subjects and found that the main effect of treatment was at the $p < 0.0001$ significance level [2,3]. Another group's results indicated a clear improvement in the singing ability of eight children with cochlear implants through the same method at the $p < 0.02$ significance level. The mean fundamental frequencies of their singing approached the mean MIDI specified frequencies as references. Secondly the deviation between fundamental frequencies of their singing and reference MIDI sounds decreased [4].

There are varying factors among the subjects that influence their singing ability, i.e. device and program of cochlear implants, the inner shape of the cochlea and the condition of the hair cells, musical background, implantation circumstances, cause of hearing loss or strong bradyacusia, and age at implantation. Therefore, it is necessary to evaluate the development of singing skills in individual cases rather than trying to examine their singing by standardizing the subjects' conditions.

In this study, we gave subjects several courses of individual singing voice instruction to teach them whole songs, while gradually increasing the degree of difficulty, so as to understand their singing ability.

This study asserts that if cochlear implant patients can recognize falsetto and natural voices, their singing ability, specifically pitch adjustment, can improve with the application of The YUBA Method. This method facilitates the subjects' intrinsic laryngeal muscular activities, which control their vocal folds, resulting in improved ability in matching pitch.

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With regards to the mechanism of pitch adjustment and pitch control in voicing, pitch is determined by the number of vibrations of the vocal folds. The main factor determining pitch is the function of intrinsic laryngeal muscles that control the length and thickness of vocal folds and the opening and closing of the glottis. Breathing muscles which adjust expiratory pressure can also influence pitch [5]; however, the influence of intrinsic laryngeal muscles is much stronger [6]. In the intrinsic laryngeal muscles there are specific functions of muscles such as the cricothyroid muscle which stretches the vocal folds and the closing muscle group which closes the glottis (interior thyroarytenoid muscle, posterior thyroarytenoid muscle, lateral cricoarytenoid muscle, transverse muscle, oblique muscle) [7–9]. In the production of the falsetto voice the cricothyroid muscle is more active than the closing muscle group, and in the production of the natural voice the closing muscle group is more active [10].

The contraction of the cricothyroid muscle narrows the distance between the cricoid cartilage and the thyroid cartilage; this results in stretching of the vocal folds. The number of vibrations increases not only because of the contraction of the cricothyroid muscle, but also because of the increase in expiratory pressure which elevates the subglottic air pressure [5–9]. The contraction of the closing muscle group closes the glottis, and as the cricothyroid muscle relaxes, the vocal folds are shortened. The number of their vibrations decreases not only because of the contraction of the closing muscle group but also because of decreasing expiratory pressure, which lowers the subglottic air pressure [5–9].

The mechanism for lowering pitch has not been fully revealed [10] in speech physiology. However, past experiments succeeded in lowering pitch by decreasing expiratory pressure, resulting in production of the natural voice [11,12].

## Subjects and methods

Three young outpatients of the University of Tokyo Hospital were given therapeutic vocal instruction by The YUBA Method. Table I presents relevant information regarding the patients.

This study was conducted at a language training laboratory in the University of Tokyo Hospital. The mean laboratory base level during the treatment was around 40 dB. The patients were treated four times between 1 April and 13 May 2006. The patients did not have any medical illness that would affect singing performance (i.e. flu, cold, cough) during the treatment.

Subjects were each given copies of three musical figures and three songs on separate sheets, totaling six sheets. We used a Sony PCM-D1 hard disk recorder to record singing data, instructions, and singing diagnosis, and an electric piano for melody and harmony accompaniment.

The nursery songs chosen for use in this study are well known to most Japanese people, including the subjects. We started out at an easy level and gradually worked up to higher levels. Song 1 'Frog chorus' and song 2 'Twinkle, twinkle little star' have an interval within the major 6th. Song 2 is a little more difficult than song 1, because in song 1, they can sing along with the scale, but song 2 has two jumps in the melody and is much longer than song 1.

Table I. Profile of patients.

| Subject | Gender | Age | Device | Medical history | Speech perception test score | Musical background |
|---|---|---|---|---|---|---|
| Case 1 | Female | 23 | Med-El Combi 40+ | (Congenital bradyacusia)<br>Hearing aid from 1 year 8 months until implantation of CI Cause of anacusis: vestibular aqueduct dilatation<br>CI: since 20 years 3 months | Single note: 7%<br>Single word: 20%<br>Short sentence: 18%<br>Post surgery time period to test: 1/2 years | No prior singing or instrument experience except school standard lessons. Violin lessons from 5 to 9 years |
| Case 2 | Male | 20 | Cochlear Nucleus 22 | (Congenital bradyacusia)<br>Cause of anacusis: cold<br>Hearing aid until 11 years<br>CI: since 13 years 1 month | Single note: 60%<br>Single word: 80%<br>Short sentence: 88%<br>Post surgery time period to test: 4 years | No prior singing or instrument experience except school standard lessons |
| Case 3 | Male | 20 | Cochlear Nucleus 22 | (Acquired anacusis)<br>Age of loss: 9 years 4 months<br>Cause of anacusis: Mycoplasma pneumoniae infection<br>CI: since 10 years 5 months | Single note: 45% Single word: 72% Post surgery time period to test: 1 year | No prior singing or instrument experience except school standard lessons |

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Song 3, 'Sea', is much more difficult than the other two because it has a wider range and skips more frequently. The tonal range of the songs for a male voice is 131–294 Hz, and for a female voice is 262–587 Hz. To ensure consistency due to differences in vocal range, the key was adjusted according to individual vocal range.

### *Yuba theory and method*

The Yuba theory is based on the 'Vocal functional physiology', which deals with the anatomic function of voicing in humans. This theory was originated by Toru Yuba, who has also named this field. It is mainly about controlling intrinsic laryngeal muscular activities, which in turn control the movement of the vocal folds in an effective and original way.

A part of this theory and method comes from the studies of Cornelius L. Read [13], based on the vocal pedagogy of eighteenth century Italy. The Yuba theory is rooted in the belief that humans do not possess any vocal organ. Instead, humans utilize the larynx, which is part of the digestive and respiratory systems, to produce voice. From the practical perspective of vocal functional physiology, humans only have two registers – falsetto and natural. Intrinsic laryngeal muscles are skeletal muscles responsible for making these two registers. However, Toru Yuba considers intrinsic laryngeal muscles as being simultaneously both *semi-voluntary* and *semi-involuntary muscles*. This is because producing falsetto voice or, more importantly, coordinating two registers to eliminate *vocal register shock* cannot be easily controlled like any skeletal muscle, i.e. flexing the arm by the biceps or moving the fingers. Basically, the singing voice is developed by strengthening and coordinating the functions making the two registers – falsetto and natural voices. The frequency of the vibration of the vocal folds determines pitch. We can control and train the intrinsic laryngeal muscles by imitating a modeled voice and at the same time correct motor-related off-key singing. The method based on this theory has facilitated the voicing correction of many off-key singers.

In this treatment The YUBA Method mainly focuses on: producing the falsetto and natural voice; singing both registers independently; interchanging between both registers smoothly; and coordinating the singing of the two registers. The YUBA Method also develops basic abilities for singing by following these essential steps: teaching subjects how to sing a one octave scale, arpeggio, and jump.

The three ways of targeting the pitch adjustment in singing with The YUBA Method are as follows. (1) In the case of the pitch being too low, it is possible to raise the pitch by balancing via instruction with the falsetto voice and increasing air pressure. (2) In the case of the pitch being too high, it is possible to lower the pitch by balancing via instruction with the natural voice and decreasing air pressure. (3) In the case of being off-pitch due to the register shock, it is necessary to coordinate the natural and falsetto voice registers.

### *Treatment procedure*

First, we interviewed each patient to get their basic information: relevant medical and musical background, mental and physical health, and motivation for learning to sing.

In the singing diagnosis, we played the melody of the first two bars of 'Frog chorus' (song 1) as an introduction to each patient and then allowed them to sing the whole song from the first to the eighth bar a cappella (without accompaniment). The first four bars of 'Twinkle, twinkle little star' (song 2) were played as an introduction and the patients sang the complete song from the first to the twelfth bar a cappella. The last four bars of 'Sea' (song 3) were played as an introduction and the patients were asked to sing it from the first to the eighth bar a cappella. We diagnosed their singing acuity comparing their performance before and after each instruction. For one subject (case 2), we adjusted the key of song 1 and 2 to solve the problem of vocal range; the original key was too low for the subject to sing, therefore we raised the key for five semi-tones.

At the beginning of the instruction the instructor produced samples of both falsetto and natural voice several times, letting the subjects listen, while each time explaining to them about the difference in tone quality, i.e. 'This is the falsetto voice, that is the natural voice', to give them a clear concept of both voices. Secondly, for their falsetto voice instruction we made them imitate an owl call sounding like 'whoo', or a dog howling 'whoo', in a breathy high pitched voice. For their natural voice instruction, they produced 'ah—', in a less breathy, low pitched voice. These are vocal abilities necessary for elevating and lowering pitch. Third, we instructed them how to sing a one octave scale, a one octave arpeggio and a one octave jump in this order, until each sound pattern was sung nearly in tune. We instructed them to keep in tune by adjusting their generation of the falsetto voice and the natural voice, and adjusting their expiratory pressure according to the singing conditions of each subject. Lastly, we asked them to sing the same songs to compare their performance before and after instruction.

### *Method of measurement and analysis*

We used the data recorder to compare the fundamental frequencies of the subjects' singing voices with the frequencies of each reference MIDI sound by time series to examine the accuracy of their singing. In this study, we used the frequencies of MIDI signals as the correct reference frequencies. We statistically processed the sequential differences of the vocal frequencies of the subjects' singing before and after the singing voice instruction. We eliminated most of the recording noise, adjusted the volume range per data, and presented the frequencies of each musical note by MIDI for ease of computer processing. For their vocal frequencies, we selected and adopted the fundamental frequencies of their singing voices to the exclusion of overtones. We then calculated the differences between the fundamental frequencies of their singing and the frequencies of the MIDI signals per sample.

Here, we use the frequency measurement unit 'cent', to compare each example of sampling data over MIDI reference frequencies. The mean ($\bar{x}$) of fundamental frequencies in each subject's singing is calculated by dividing the sum of $x$ by the number of data ($x$) through singing and SD as a standard deviation with respect to $x$ in each subject's singing. In spectrum analysis of the data, we used sampling period 1/86(Sec.) and 4096 points for the frequency resolution.

Data were processed as follows. We did not accept as voice data that which did not correspond to MIDI data. Therefore, the obtained data are somewhat short compared with the actual time series. The statistic for data analysis in this situation is made only when the data for both groups correspond.

In statistical processing, we compared each mean ($\bar{x}$) of singing of all cases and their SDs before and after the singing voice instruction. The changes of mean pitch of each subject's singing were indicated by the former ($\bar{x}$) and the change of the width of sound deviation were indicated by the latter (SD). We determined whether or not the SD of the frequencies was improved through these statistical tests.

We evaluated means, SDs, and $p$ value (probability by Student's $t$ test) in every singing sample of each case in the following way. As an example, we explain the procedure for song 1 of case 1. We used the same procedure for other songs and other cases.

1. We collected all fundamental frequency data in a singing session that correspond to some MIDI note frequency (e.g. C note). As for song 1, its MIDI tone sequences are like C, D, E, F, E, D, C, …, where each tone is included multiplicatively. In this case, for example, we collected data of the first C and of the seventh C as same group data (e.g. C is included eight times in song 1). Then we evaluated the mean of a singing fundamental frequency in a song for C from the data with the 'cent' unit.
2. By the same process described above, we can evaluate all means of singing fundamental frequencies that should be equal to each reference MIDI tone frequency in the song. We calculated the mean for each voice corresponding to MIDI's six notes, from C to A, in song 1.
3. We applied this processing to song 1–B1 [singing data before instruction (first day)] and song 1–A4 [singing data after instruction (fourth, last day)]. Then we obtained the mean of all fundamental frequency data in a singing session as for before and after instruction.
4. Using data from (3), we tested the difference of mean of fundamental frequencies of a song between before and after instruction. Here we used Student's paired $t$ test, with $\alpha = 0.05$.
5. We also evaluated mean of SDs of a song with the same processing as described above using SDs that correspond to each MIDI tone frequency in a song. The value of each SD corresponds to scattering measure of each singing session in this study.
6. We applied the same procedure to song 1, song 2, and song 3 for every case (1, 2, and 3). As well as simple statistical analysis, we calculated quantitatively the variation between the results and the target MIDI frequencies.

## Results

Here we use following abbreviations. B1, before instruction [1st time]; A1, after instruction [1st time]; A2, after instruction [2nd time]; A3, after instruction [3rd time]; A4, after instruction [4th time]. Table II shows mean ($\bar{x}$), ±SD [unit: cent] and $p$ (T <t) before and after the singing voice instruction. $p$ (T <t) is probability by Student's $t$ test with $\alpha = 0.05$ to B1 and A4 pair and All. 'All' are evaluated by simple average of all cases or songs. A function of statistical data processing in MS-EXCEL was used.

Figure 1 shows means ($\bar{x}$) of fundamental frequency of voice of singing for three songs (1, 2, and 3) for each case. Figure 2 shows the absolute values of mean ($\bar{x}$) by gray bar and ±SDs by vertical bold line for every song for each case.

Table II. Mean ($\bar{x}$) ±standard deviation (SD) [cent] and $p$ (T <t).

| | | Case 1 | | | Case 2 | | | Case 3 | | | All |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Song | Parameter | B1 | A4 | $p$ | B1 | A4 | $p$ | B1 | A4 | $p$ | $p$ |
| Song 1 | $\bar{x}$ | −317.4 | −2.1 | 0.0058 | 609.4 | −19.3 | 0.0002 | −258.9 | −7.1 | 0.0005 | 0.0022 |
| | ±SD | 272 | 219.7 | 0.0588 | 264.4 | 211.5 | 0.0399 | 127.9 | 150.2 | 0.1307 | 0.0765 |
| Song 2 | $\bar{x}$ | −382 | −183.3 | 0.0266 | 447.1 | −204.2 | 0.0018 | −339.8 | −64.9 | 0.0008 | 0.0097 |
| | ±SD | 256.9 | 247.4 | 0.0008 | 305.2 | 207.1 | 0.9893 | 153.3 | 148.2 | 0.0108 | 0.3336 |
| Song 3 | $\bar{x}$ | −739.6 | −452.8 | 0.0026 | 178.1 | 128.9 | 0.3858 | −749.4 | −221.5 | 0.0027 | 0.1304 |
| | ±SD | 261.8 | 272.4 | 0.0469 | 289.8 | 270.7 | 0.7409 | 145.6 | 210.2 | 0.0014 | 0.2631 |

### *Average pitch after the singing voice instruction was improved*

As shown in Table II, we obtained a level of significance of 5% $p$ (T < =t) = {0.002 (song 1), 0.01 (song 2), 0.13 (song 3)} by $t$ test for $\bar{x}$ from averaging all cases. As a result, we could conclude that the average of frequencies of all subjects' singing was improved after instruction, because the average pitch after the instruction approached the best value (0). We found that the average of frequencies of all subjects' singing was improved remarkably by a few periods of instruction. Figures 1 and 2 show the same behaviors.

### *Scattering of pitch (SD) was improved slowly by instructions*

From the table, we found that the average pitch of singing of all cases was improved soon after each instruction, although the SDs of singing were improved slightly. Overall, the SD between fundamental frequencies of their singing and reference MIDI sounds became smaller by instruction, although the pace of the improvement of scattering of pitch was slow. We found that improvement for the scattering of pitch needs continuous instruction. This shows the difficulty in curing the scattering of pitch of singing. Figure 2 illustrates this statement.

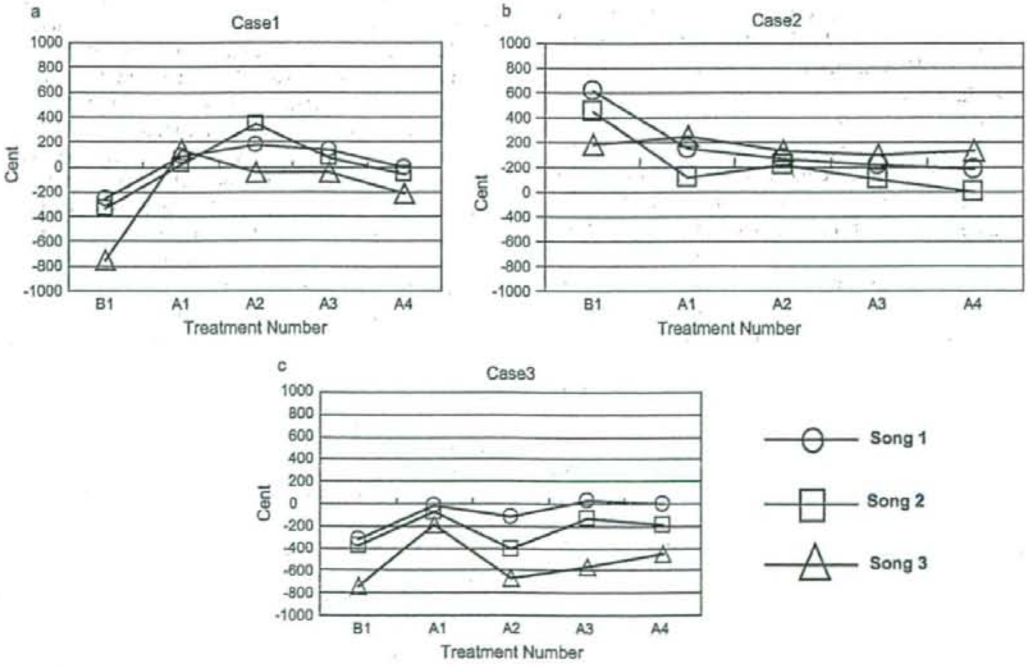

Figure 1. Means ($\bar{x}$) of singing in (a) case 1, (b) case 2, and (c) case 3 for every song (1, 2, and 3). B, before instruction; A, after instruction.

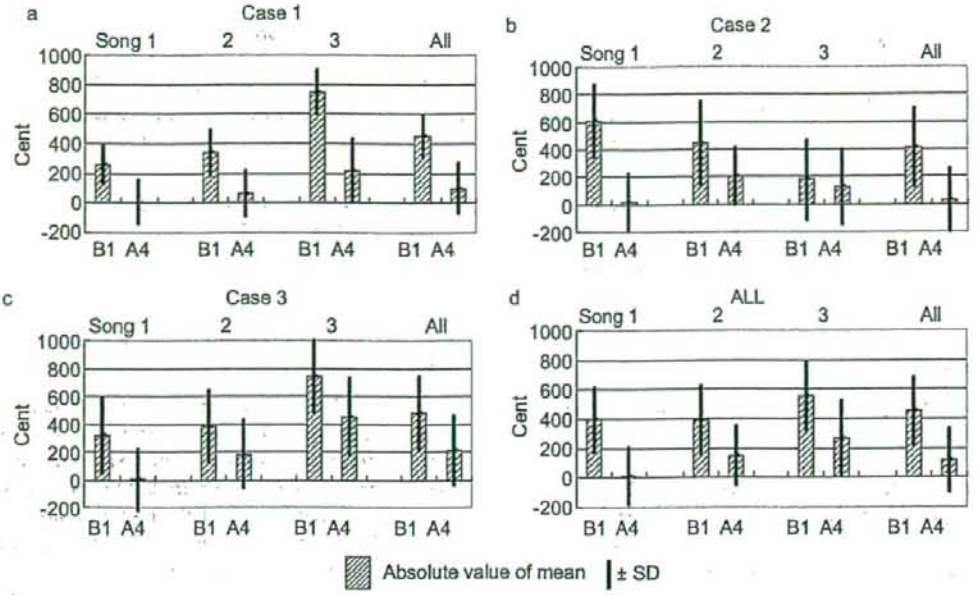

Figure 2. Means and SDs of singing for three songs (1, 2, and 3); (a) case 1, (b) case 2, (c) case 3, (d) all. B, before instruction; A, after instruction.

## Discussion

It is known that people with cochlear implants tend to sing off-key, monotonously, and flat. Former results have been the work of two separate research groups using The YUBA Method. One subject group in Hawaii tested 60 elementary students attending the normal level of hearing classes and found that the main effect of treatment was at the $P<0.0001$ significance level. In 2004 the latter group tested eight pediatric patients with cochlear implants and found a clear improvement in their singing ability and that the main effect of treatment was at the $p<0.02$ significance level.

This latest research method was improved to provide more of a wide spectrum of results with the patients. This time we conducted the research at a patient's individual level, with four exposures over 40 days as opposed to an individual exposure. We also had the patients sing three whole songs instead of four bars of one song, to provide a larger base of data to process for the results. The three sample songs were deliberately picked for varying levels of difficulty and singing patterns for the same reason. The songs were also chosen because they are well known, to maximize realism within the research. An instructor's voice and electric piano sound were used as reference sounds to clarify the pitch and melody for the patients.

Based on earlier research, we expected that the mean fundamental frequencies of their singing would approach the mean MIDI specified frequencies as references for this study. Also, we thought that the deviation between fundamental frequencies of their singing and reference MIDI sounds would decrease. We expected that these factors would remain constant despite the longer period of exposure and variation in level of difficulty.

Initial consultations with the three patients showed that they could almost distinguish between falsetto and natural voices. Building on this ability, the application of The YUBA Method allowed them to control their laryngeal muscular activities, as demonstrated in their improved ability to produce both the falsetto and natural voices; to sing a one octave scale, arpeggio, and jump guided by an electric piano; to sing the three songs a cappella; and to raise or lower pitch in the rendition of songs. After every instruction, the singing ability, particularly matching pitch, of each patient was diagnosed.

Before instruction, the first patient (case 1) sang monotonously and lower than the targeted pitch. After receiving instructions regarding the falsetto voice, the patient sang higher than the targeted pitch, resulting in off-key singing. Furthermore, she had vocal register shock when shifting from the natural to the falsetto voice and vice versa. When instructed to coordinate the two registers, the improvement in her singing pitch was apparent despite not being able to erase the vocal register shock completely.

The second patient (case 2) sang monotonously and higher than the targeted pitch at the outset, thereby exhibiting a narrow vocal range manifested in singing a higher key when asked to sing in a low note and vice versa. Based on this diagnosis, instructions were given regarding the two registers to expand his vocal range and to introduce the concept of high and low pitch. In addition, the key of songs 1 and 2 was changed from C to F to adapt to the patient's high-pitched male voice. Although the patient still found difficulty in producing definite falsetto and natural voices, he showed an expansion of his vocal range, with a tendency to produce the falsetto and natural voices when prompted.

Originally, the third patient (case 3) sang monotonously and lower than the targeted pitch. After receiving instructions, he was able to produce the falsetto voice. However, he could not produce the falsetto voice constantly until the end of the fourth instruction. Diagnosis revealed an improvement in his singing pitch but his pitch still registered below the target.

If the second and third patients (cases 2 and 3) produced two registers constantly, there would be a better improvement of matching pitch for their singing.

Science is relentlessly in pursuit of improving human quality of life through research. Science is finding that the human body, while fallible, may be repaired and updated through technology. As medical research technology allows us to repair our 'hardware' (the body) through surgery, prosthetic parts, pacemakers, cochlear implants, etc., we invariably have to update the 'software' (technological method) simultaneously. This unique technological method will serve to better the quality of life for the hearing disabled.

In this study, we were able to improve significantly the singing abilities of people with cochlear implants by The YUBA Method. This is an example of how technology developed by research has compensated for the inadequacy of the body's hardware.

In the case of acquired deafness it is known that hearing and speaking abilities can be regained quickly and certainly after implanting an artificial cochlea. This means that even if people lose their hearing ability through some disorders such as senile hearing loss, disease, or accidents, they can regain the pleasure of verbal communication.

We felt that the results of this research were encouraging; however, two uncontrollable factors contributed negatively to our work. First we were unable to use headphones during the experiment due to the subjects' medical condition. Consequently, our results were recorded with electric piano accompaniment and voice simultaneously, making it more difficult to analyze than in the case of normal-hearing subjects. Second, we believe that the various psychological profiles of the subjects detracted from our results and analysis. They were affected during the recording by the performance anxiety based on both prior teasing and having to sing in front of several adult persons in the laboratory. We believe that for these two reasons our results have been adversely affected and we wish to minimize these two factors as much as possible in future work.

This unique technological method can be used as an alternative method for speech therapy rehabilitation. Intonation is positively affected via this method over a larger vocal range than traditional speech therapy alone.

We conjecture that the patients might improve matching pitch better with accompaniment than unaccompanied.

## Conclusion

Although overall improvement was not so dramatic due to a lack of retention, session by session advancement of matching pitch for targeted MIDI sound was predominantly obvious. It was proved that The YUBA Method worked to improve matching pitch for the singing of patients with cochlear implants. At this research stage, we cannot conclude with absolute certainty that this technology will work with all people with cochlear implants. However, we are positively encouraged by the results of this, our second study. The same technological method used in an earlier study had similar results. Therefore we feel confident that this unique technological voice method works well.

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# Hearing profile and MRI myelination of auditory pathway in Pelizaeus–Merzbacher disease

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**Abstract**

*Conclusions.* This study showed that delayed auditory pathway myelination is common in Pelizaeus–Merzbacher disease (PMD), but this delay does not necessarily indicate poor hearing function. *Objective.* PMD is a rare recessively inherited X-linked leukodystrophy characterized by defective central nervous system myelination owing to a mutation in the proteolipid protein gene (*PLP*). The aims of this study were to evaluate the hearing function and auditory brain response (ABR) findings of patients with PMD and relate these findings to MRI-assessed myelination in the central auditory pathway. *Patients and methods.* We retrospectively studied eight male pediatric patients with PMD. Serial auditory examinations included audiometry, behavior audiometry, distortion product otoacoustic emission (DPOAE), and ABR. MRI-assessed myelination in the auditory pathway was evaluated in the PMD patients and in 23 normal young children as a control group. *Results.* Audiometry showed normal to moderate hearing impairment and the hearing threshold improved with age and became almost normal over time. DPOAEs positivity and only ABR wave I or waves I and II were found in all the patients. MRI showed delayed myelination in all the patients and the auditory pathway was myelinated up to the inferior colliculus in four cases and up to the medial geniculate body in four cases. Serial MRIs showed no progression in myelination. No clear relation was found between hearing threshold and MRI-assessed myelination in the auditory pathway.

**Keywords:** *ABR, DPOAE, progression, audiometry*

## Introduction

Pelizaeus–Merzbacher disease (PMD) is a recessively inherited X-linked leukodystrophy caused by a mutation in the proteolipid protein gene (*PLP*) on chromosome Xq 22. *PLP* mutations result in dysmyelination, i.e. a lack of properly formed myelin, and in this respect PMD is different from other leukodystrophies. The neuropathologic characteristics of PMD are (i) a low reduction in the number or absence of myelin sheaths in large areas of the white matter, predominantly in the periventricular regions; (ii) well-preserved neurons and axons; and (iii) relatively preserved islets of myelin giving the white matter a patchy 'tigroid' appearance without active demyelination. A strong relation between the degree of dysmyelination and clinical severity was found [1–3].

The classification suggested by Seitelberger [4,5] according to clinical and pathologic features is now divided into two subtypes, namely the classic and connatal forms. The onset of the classic form occurs in the first year of life with muscular hypotonia, nystagmus, and delayed motor development. Tigroid dysmyelination is observed on neuropathologic investigation. In contrast, patients with the rare and more malignant connatal form show little developmental progress. Severe neurologic symptoms include feeding problems, stridor, and marked spasticity resulting in multiple contractures. Pathologic examination shows a complete lack of myelination throughout the brain.

Cognitive delay in early childhood and a delay or difficulty in speaking are commonly observed in PMD patients. In the first case report by Pelizaeus,

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he noted that 'sight and hearing were undisturbed and the patient always understood spoken language' [1]. In the classic form of PMD, most patients acquire some degree of language skill, which may even approach normal levels; however, the speech is dysarthric and language output speed is usually slow. In addition, they also have some degree of cognitive disability. On the other hand, patients with the connatal form of PMD usually exhibit poor growth and develop very limited language skills [5]. Previous studies seldom addressed hearing function and the results from those that did showed variability. Some reports presented patients with severe to extremely severe sensorineural hearing disturbance [6,7], whereas some presented patients with good auditory perceptions [8–11].

Abnormal auditory brainstem responses (ABRs) presenting as the absence of later components after wave I or wave II are common neurophysiological characteristics in PMD patients [10–12]. It has been suggested that these abnormal ABR findings and hearing impairment can be attributed to the dysmyelination of the central auditory pathway. However, a systemic myelination study focusing on the central auditory pathway had seldom been carried out.

In this study, we applied magnetic resonance imaging (MRI) as a method for assessing the dysmyelination of the central auditory pathway in PMD. We aimed to (a) document the various aspects of hearing profiles and ABR findings in PMD patients, (b) evaluate the myelination of the central auditory pathway by MRI, and (c) determine the relation between the hearing function and ABR findings with myelination milestones in the central auditory pathway.

## Patients and methods

### *Patients*

We retrospectively studied eight male pediatric patients with PMD. Mean age ± SD at study entry was 4.75 ± 4.1 years. The diagnosis of PMD was confirmed on the basis of clinical symptoms, MRI features, ABRs, and a mutation analysis of the *PLP* gene; all the patients had the classic form of PMD. Some of the patients had already participated in previous studies with our group [11]. The patients' clinical data are shown in Table I.

### *Hearing assessment*

*Audiometry and speech test.* Conditioned orientation reflex (COR) audiometry or pure tone audiometry was conducted to evaluate hearing. Serial audiometry was found in three patients. Speech discrimination score was evaluated in one patient (patient 7) using monosyllables and three-syllable words. Other speech tests include a Japanese version of the Illinois Test of Psycholinguistic Abilities (ITPA) or the picture vocabulary test (PVT) was administered to four patients (patients 2, 3, 5, and 7).

*Distortion product otoacoustic emissions (DPOAEs).* DPOAEs were recorded and analyzed using an ILO-88 OAE dynamic analyzer system. Patients were tested inside an electrically shielded sound-attenuating room.

*Auditory brainstem response (ABR).* We tested all the patients in the supine position in an electrically shielded sound-attenuating room. Silver disk electrodes were placed on each patient's forehead referenced to the mastoid tip on the test side and connected to the ground on the opposite mastoid tip. We used click stimuli. Each click stimulus was presented for 1 cycle of a 3000 Hz sine wave. Monaural headphones (TDH-39) delivered 2000 clicks at a rate of 10 clicks/s. The stimulus intensity was 85 dB nHL. An on-line computer averaged, displayed, and recorded the data. The patients were sedated with trichloryl chloride during ABR recordings.

### *MRI assessment of auditory pathway*

Nine MRI scans of the eight patients were evaluated. Every patient underwent MRI at 1.5 T; in each case the T2-weighted images were obtained using spin-echo sequences. Sections were perpendicular to the long axis of the brain and were 5–7 mm thick. To distinguish the effect of age-related myelination changes in the MRI results, we also examined the auditory pathway by MRI in normal young children ($n = 23$, aged from 0 months to 2 years) who were determined to be clinically healthy on the basis of MRI results and the clinical course observed by pediatricians and used as control groups. T2-weighted images were selected for several reasons. T2-weighted images provided information on degrees of myelination [13,14], and yielded more reliable graded judgments of myelin [15]. It is generally agreed that T1-weighted images are more useful in the first 6–8 months of age to image myelin, and T2-weighted images are more useful after 6 months of age [16,17].

The images were examined for signs of myelination in the central auditory pathway both in gray matter (i.e. cochlear nucleus, superior olive, and medial geniculate body) and white matter (i.e.

Table I. Clinical characteristics of patients.

| Parameter | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 |
|---|---|---|---|---|---|---|---|---|
| Present age/sex | 20/male | 24/male | 9/male | 7/male | 21/male | 7/male | 23/male | 8/male |
| Age of symptom onset | 1 month | 2 weeks | 1 month | 7 months | 5 months | 1 month | 7 months | 3 months |
| First sign | Nystagmus, head shaking | Nystagmus, head shaking | Nystagmus, motor retardation | Nystagmus, head tremor | Nystagmus, motor retardation | Nystagmus, head tremor | Nystagmus, head tremor | Nystagmus, motor retardation |
| Nystagmus | Horizontal | Horizontal | Horizontal | Horizontal | Horizontal | Horizontal | Horizontal | Horizontal |
| Seizures | − | − | − | − | − | − | − | − |
| Stridor | − | − | − | − | − | − | − | − |
| Muscular hypotonia | + | + | + | + | − | − | + | + |
| Spasticity | + | + | + | + | + | + | + | + |

cochlear nerve, lateral lemniscus, inferior colliculus branchium, and auditory radiation). Myelination was considered to be present in white matter if the signal intensity was hypointense in unmyelinated white matter on T2-weighted spin-echo MR images. Myelination was considered to be present in gray matter structures if the signal intensity was hypointense in the cortex on T2-weighted spin-echo MR images, as described by Barkovich [18]. The identity of the structures was confirmed by consulting a neuroanatomy textbook [19] and a previous study on young children [18]. Moreover, the tigroid appearance of preserved myelin and cerebral and cerebellar atrophies were evaluated.

## Results

### *Hearing functions*

*Audiometry and speech test.* Figure 1 shows the audiometry results of the eight patients. Hearing threshold was essentially within the normal range for two of the eight cases (patients 4 and 7). The remaining six cases showed moderate hearing loss (Table II). The average hearing threshold was 29.1 dB ± 4 dB. The audiograms showed a flap-type hearing impairment in seven patients, and a steeply down-sloping configuration in patient 3. The serial audiograms showed improvements in the hearing threshold and showed normal hearing (patients 4 and 7) or mild hearing impairment (patient 1) over time.

The speech discrimination score (patient 7) showed a good result (90% on both sides at 30 dB). However, receptive language delays were found among patients 2, 3, 5, and 7. On the auditory subtests of the ITPA, the score of patient 2 fell within the 2–3 year age level at the age of 4 years; that of patient 3 fell within the 5 year age level at the age of 6 years; that of patient 7 fell within the 5–6 year age level at the age of 16 years. On the picture vocabulary test (PVT), the score of patient 5 fell within the 4–5 year age level at the age of 11 years.

*DPOAE.* DPOAEs were within normal range in all the patients. DP-grams showed that all DP levels were higher than the noise floor levels at all the frequencies, the range being 0–17 dB.

*ABRs.* Both wave I and wave II were well delineated but the subsequent components were absent in patients 1–4; only wave I was recorded and all the subsequent components were absent in patients 5–8 (Table II).

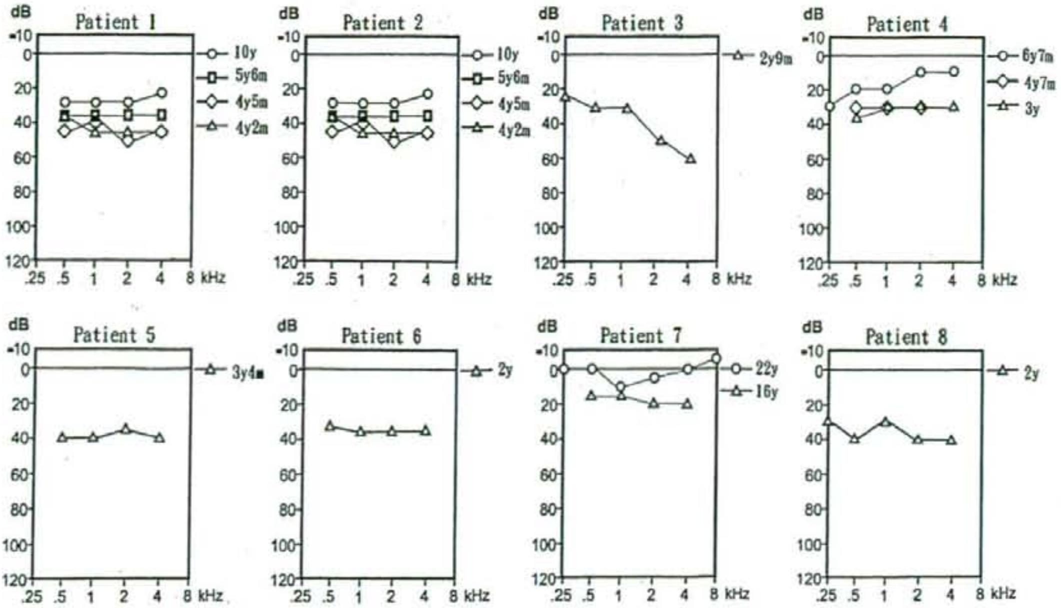

Figure 1. Audiograms of PMD patients. Serial audiograms showed improvements in hearing threshold and showed normal hearing (patients 4 and 7) or mild hearing impairment (patient 1) over time.

### *MRI assessment of auditory pathway*

MRI conducted at a median age of 2 revealed a delay in myelination in all the patients (Figure 2, Table III). Myelination process only reached the inferior colliculus brachium (patients 1, 2, 6, and 8) or medial geniculate body (patients 3, 4, 5, and 7); it was not found in the auditory radiation. The second MRI scan in patient 3 showed no improvement in myelination. Morphological abnormalities including cerebral or cerebellar atrophy were visualized in two patients (patients 4 and 5). Tigroid appearance was visualized in all the patients.

In the mature newborns control group, the cochlear nerve, cochlear nucleus, and superior olivary nucleus were myelinated. The lateral lemniscus, inferior colliculus brachium, and medial geniculate body were myelinated at approximately 3 months; the auditory radiation was myelinated at approximately 15 months.

## Discussion

This study revealed that patients with the classic form of PMD had normal to moderate hearing threshold impairment and receptive language delays were common among these patients. There was a tendency for hearing threshold to improve with age and become almost normal over time. This progression has never been reported. Some reports showed improvements in other clinical symptoms over time, particularly in female cases [20], but most of the neurological symptoms do not improve in male patients. Several authors have stated that the myelination of different tracts in the nervous system might express functional maturity [10,14], and that there seems to be a relation between delayed myelination and delayed hearing function development.

In all the patients, the DPOAEs showed positivity and ABR showed wave I only or waves I and II only; this may indicate functioning hair cells, spiral ganglion cells, and auditory nerves, with pathology affecting the central auditory pathway in the brainstem. The absence of waves III–V may denote desynchronized conduction, which may be associated with hearing loss.

Neuroradiological scanning offers a convenient diagnostic tool and yields results that correspond well to neuropathological findings. By MRI, normal postnatal myelin formation is monitored by an inversion of T1- and T2-weighted signals, which correspond to an increase in the levels of myelin lipid constituents with a concurrent decrease in tissue water content. MRI can also show a hypomyelination pattern, i.e. the reversal of white matter signal intensity on T1- and T2-weighted images. MRI thus allows an in vivo evaluation of myelination milestones [15–18]. For the first time, we applied MRI to investigate the myelination of the auditory pathway in PMD patients. Our results showed that irrespective