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Original Article

First Clinical Application of Octacalcium Phosphate Collagen Composite in Human Bone Defect

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We have previously demonstrated that octacalcium phosphate (OCP) collagen composite (OCP/collagen) promotes bone regeneration in a critical-sized bone defect of a rodent or canine model. This study was designed to investigate the bone regeneration of OCP/collagen in human bone defect as a first clinical trial. Two patients who had a radicular cyst or apical periodontitis consented to participate in our clinical study, and OCP/collagen was implanted into the defects after operation. Radiographic examination showed effective bone healing in each bone defect at 3 or 6 months. Likewise, computed tomography value significantly increased after implantation. Postoperative wound healing was uneventful, and neither infection nor allergic reaction against OCP/collagen was observed for the entire period. This study demonstrated that OCP/collagen would be safely used and enhanced bone regeneration in human bone defects. To reinforce the efficacy of OCP/collagen as a bone substitute material, it should be compared with other suitable comparators in the future.

Introduction

RECONSTRUCTION OF LARGE bone defects caused by extirpation of tumor and cyst is an important issue in the field of orthopedic and oral surgery.[1] Autologous bone includes osteoprogenitor cells, collagenous bone matrix, bone mineral, and growth factors, such as bone morphogenetic proteins.[2] This composition in autologous bone should promote the induction of new bone within bone defects if it is transplanted. However, there are problems associated with the use of autologous bone in terms of donor site pain, morbidity, infection, extra blood loss, and higher cost due to longer operation.[3]

Synthetic calcium phosphate has been widely used as a bone substitute of autologous bone, such as sintered ceramics of hydroxyaptite (HA), β-tricalcium phosphate (β-TCP), and calcium phosphate-based cements to form HA because it has no limitation in terms of availability, excellent osteoconductivity, and relatively uniform quality regardless of the production lot provided by manufacturers.[4–6] However, it is widely accepted that its bone regenerative properties are still inferior to those of autologous bone.[7]

Octacalcium phosphate (OCP) has been suggested to be a precursor of biological apatite, such as dentin, enamel, and bone. Indeed, the presence of OCP has been demonstrated in these types of biological apatite.[8–10] Our previous study indicated the superior osteoconductivity of synthetic OCP compared with that of amorphous calcium phosphate, dicalcium phosphate, Ca-deficient HA, and HA if implanted into the subperiosteal area of the calvaria of mice.[11] In addition, it has been confirmed that bone regeneration of synthetic OCP is higher than that of HA or β-TCP ceramic *in vivo*,[12] that synthetic OCP promotes osteoblastic cell differentiation while OCP is converted into HA *in vitro*,[13] and that the osteogenic effect is dependent on the amount of OCP.[14]

Although OCP possesses many desirable properties as a bone substitute, it cannot be molded using sintering processes because of its intrinsic crystal structure. To resolve the disadvantages, including the improvement of handling, OCP combined with atelocollagen (OCP/collagen) was prepared.[15] OCP/collagen significantly enhances bone regeneration more than OCP alone, collagen alone, and HA or β-TCP ceramic combined with collagen in rat calvarial bone defect,[15,16] and bone formation by OCP/collagen increases with the amount of OCP in the OCP/collagen.[17] Aiming at clinical application, bone regeneration by OCP/collagen was examined in canine models, and implantation of OCP/collagen significantly enhanced bone regeneration more than those of β-TCP, collagen, and untreated control at a critical-sized calvarial bone defect, a tooth extraction socket, or an alveolar cleft model.[18–21]

To the best of our knowledge, the present report is the first on the clinical evaluation of OCP/collagen. This new

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bone regenerative material was used for filling bone defects after cystectomy. The clinical evaluation of the two patients was conducted according to Japanese ethical guidelines and regulations. The first objective of this study was to investigate the safety of OCP/collagen for clinical use. The second objective was to investigate the efficacy of this material if implanted into a cyst cavity. Radiographic examination of the implanted sites was performed, and the findings were compared to those of the surrounding host bone up to 6 months after implantation.

Materials and Protocols of the Clinical Trial

Preparation of OCP/collagen

OCP was prepared by mixing calcium acetate hydrate solution and sodium phosphate monobasic solution as described previously,[11] and using sterile-filtered water during the whole preparation. The precipitates were washed several times with sterile-filtered water and then lyophilized. Sieved OCP granules (particle sizes 300–500 μm) obtained from the dried OCP were sterilized by heating at 120°C for 2 h in dry condition. Our previous study showed that such heating does not affect physical properties, such as the crystalline structure or specific surface area of OCP granules, although it was reported that increasing the temperature above 100°C induced collapse of the OCP structure because of dehydration.[22] Powder X-ray diffraction (XRD) patterns of the obtained OCP were recorded using step-scanning at 0.05-degree intervals from 3.00 to 60.00 degrees, with Cu Kα X-rays on a diffractometer (Mini Flex; Rigaku Electrical Co., Tokyo, Japan) at 30 kV and 15 mA. The range of 2θ included the primary peak (100) reflection of OCP around 4.7 degrees. Collagen was prepared from NMP collagen PS (Nippon Meat Packers, Tsukuba, Ibaraki, Japan), and a lyophilized powder of pepsin-digested atelocollagen was isolated from porcine dermis. NMP collagen PS was dissolved in sterile-filtered water and adjusted to a final concentration of 3% at pH 7.4. OCP/collagen was prepared from NMP collagen PS and OCP granules. OCP was added to the concentrated collagen and mixed.[15] The weight percentage of OCP in OCP/collagen was 77%. This OCP/collagen mixture was then lyophilized and disks were molded (9 mm diameter, 1 mm thick) (Fig. 1). The molded OCP/collagen underwent dehydrothermal treatment (150°C, 24 h) in a Vacuum Drying Oven, DP32 (Yamato Scientific, Tokyo, Japan). The clinical batches were prepared aseptically. Two pieces of the molded OCP/collagen were placed in a sterilized microcentrifuge tube (509-GRD-SC; Quality Scientific Plastics, San Diego, CA), and the OCP/collagen-containing tube was then packed with Fisherbrand® instant sealing sterilization pouch (9 × 13 cm; Fisher Scientific, Pittsburgh, PA). The packed OCP/collagen was subsequently sterilized using electron beam irradiation (5 kGy) to make it ready-to-use. After sterilization, the XRD pattern derived from OCP/collagen indicated a collapsed and reduced primary (100) peak with a shift from 4.7 to 5.3 degrees at 2θ, as previously reported.[15]

Design of the clinical trials

This study is a part of the clinical study of "Bone regenerative therapy by OCP collagen composites," which was registered as JPRN-UMIN000004655 in the University Hospital Medical Information Network in Japan (UMIN) and International Clinical Trials Registry Platform Search Portal of the World Health Organization. The protocol of the clinical trial was submitted and approved by the research ethics committee of the Tohoku University Graduate School of Dentistry under reference number 20–27. The principal investigator and promoter was Prof. Shinji Kamakura (DDS, PhD), and this trial was performed at the Department of Oral and Maxillofacial Surgery, Tohoku University Hospital, Sendai, Japan.

FIG. 1. A picture of OCP/collagen disks. OCP/collagen disk is 9 mm in diameter and 1 mm thick. OCP, octacalcium phosphate.

This clinical trial is a single-arm nonrandomized intervention study, and 10 cases of tooth extraction socket and cyst cavity were studied. All patients signed a formal consent form and were finally included in the study. The aim of the first clinical evaluation in this study was to demonstrate the safety, by clinical examination and recording of adverse events, of using OCP/collagen to fill these defects. The second clinical evaluation focused on bone regeneration in these defects by radiographic examination. This study reported two cases of cyst cavity after implantation of OCP/collagen.

Clinical, laboratory, and radiographic examination

Dental radiography and clinical examination were performed before cystectomy, and 1 and 7 days, and 1, 3, and 6 months after OCP/collagen implantation. A computed tomography (CT) was made before the cystectomy and 3 or 6 months after implantation. Then, the value of CT was measured at the center of the bone defect. The clinical examination involved the observation of general and local conditions, including inflammatory symptoms in the operative site. In addition, laboratory examination was carried out before cystectomy, and 1 day, and 1, 3, and 6 months

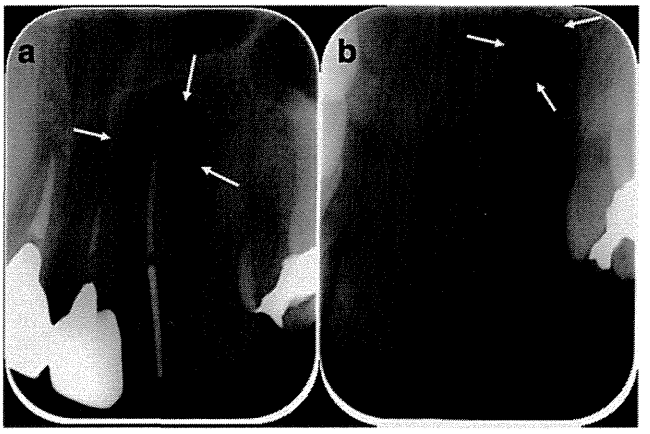

FIG. 2. X-ray pictures of patients. **(a)** Patient A: A radicular cyst at the apex of the left maxillary lateral incisor. **(b)** Patient B: A radicular cyst at the apex of the left maxillary central incisor. Arrows show the margin of the bone defect.

after implantation. This comprised factors such as peripheral blood figures, liver and kidney function, and urinalysis.

Case Reports

The first case (patient A) was a 37-year-old man and the second one (patient B) was a 23-year-old woman. Both patients consulted our hospital for the examination of radiolucent areas of anterior maxillary regions. Their medical histories contained nothing of relevance, and both patients were clinically diagnosed with radicular cyst of anterior maxilla by radiographic examination (Fig. 2a, b). The radiolucent figure of patient A was about 8 mm in diameter at the apical region of the left maxillary lateral incisor and that of patient B was about $5 \times 5 \times 10$ mm at the apical region of the left maxillary central incisor. Under local anesthesia, 2% lidocaine hydrochloride with 1:80,000 epinephrine was injected into anterior maxillary region, and both patients underwent cystectomy (Fig. 3a, b). After irrigation, OCP/collagen disks were implanted in the defect. Four or six disks of OCP/collagen were used in the defect of each patient (Fig. 3c, d). Then, ablated gingiva and periosteum were repositioned and sutured with absorbable suture (4-0 Coated Vicryl™; Ethicon, Inc., Irvine, CA). Both cases were diagnosed as radicular cyst by postoperative pathological examination.

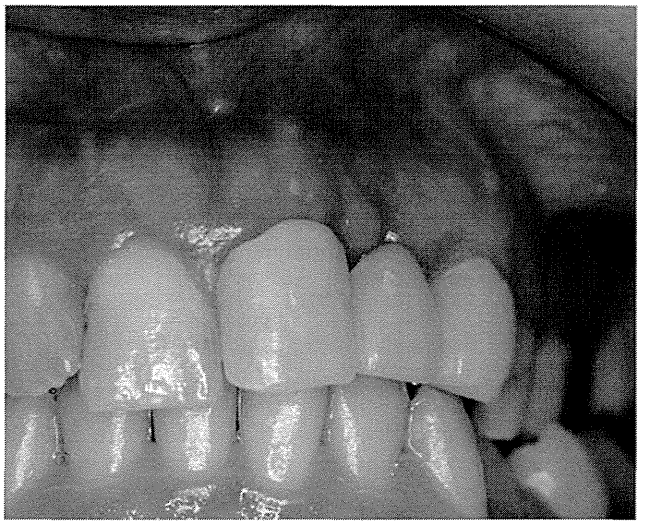

FIG. 4. Pictures of operative region in patient B at 6 months after OCP/collagen implantation. There was temporary crown restoration. Color images available online at www.liebertpub.com/tea

In both cases, postoperative wound healing was satisfactory, and there was no postoperative infection or allergic reaction at the operative site during the observation period. The height or width of alveolar bone was maintained until 6 months after OCP/collagen implantation (Fig. 4). Laboratory examination revealed no abnormal findings except that

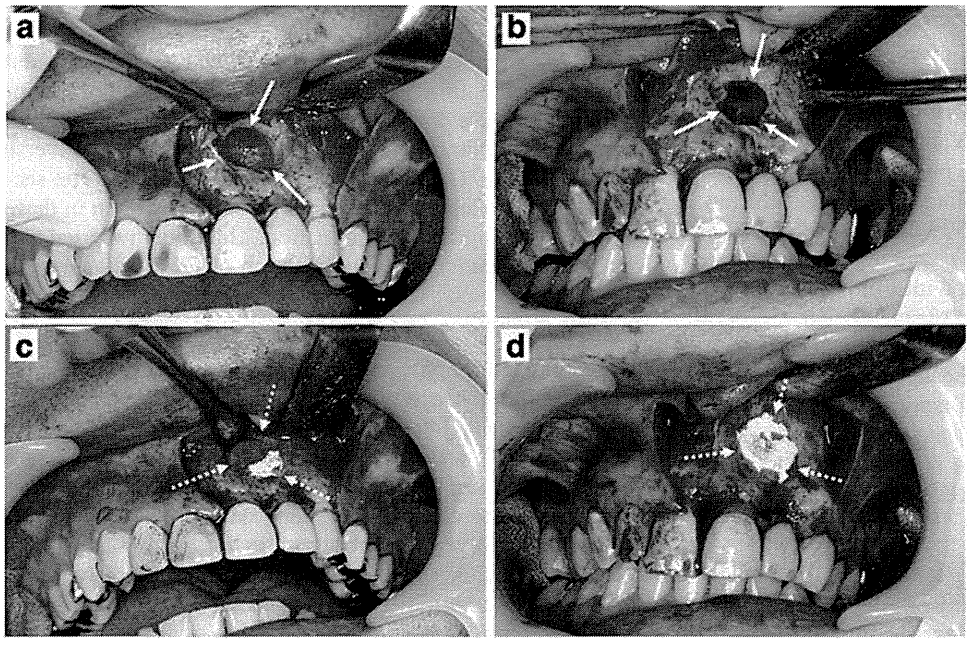

FIG. 3. Pictures of cystectomy and OCP/collagen disk implantation. Cystectomy of **(a)** patient A and **(b)** patient B. Arrows show the margins of these defects. Implantation of OCP/collagen disks at the defects of **(c)** patient A and **(d)** patient B. Dot arrows show OCP/collagen disks in these defects. Color images available online at www.liebertpub.com/tea

a slight increase of C-reactive protein was observed. In radiographic examination after the implantation of OCP/collagen, there was little radiopacity in the defect 1 day after the implantation (Fig. 5a, b). The radiopacity in the defect increased slightly at 3 months (Fig. 5c, d) and was further improved 6 months after the operation (Fig. 5e, f). Examination by CT scan showed that the defect of patient A or B was dotted with hard tissue-like bone at 3 months after implantation (Fig. 6c, d). At 6 months after OCP/collagen implantation, the density of the hard tissue was increased and the hard tissue spread in the defect (Fig. 6e, f). This hard tissue arose from the center of the defect as well as its margin.

The CT values of the radicular cysts before implantation were 21 Hounsfield units (HU) in patient A and 23 HU in patient B. The CT values of patient A were 327 and 527 HU at 3 and 6 months after OCP/collagen implantation, respectively. Similarly, those of patient B were 316 and 602 HU. The CT values increased significantly at 3 or 6 months compared with those before implantation (Table 1).

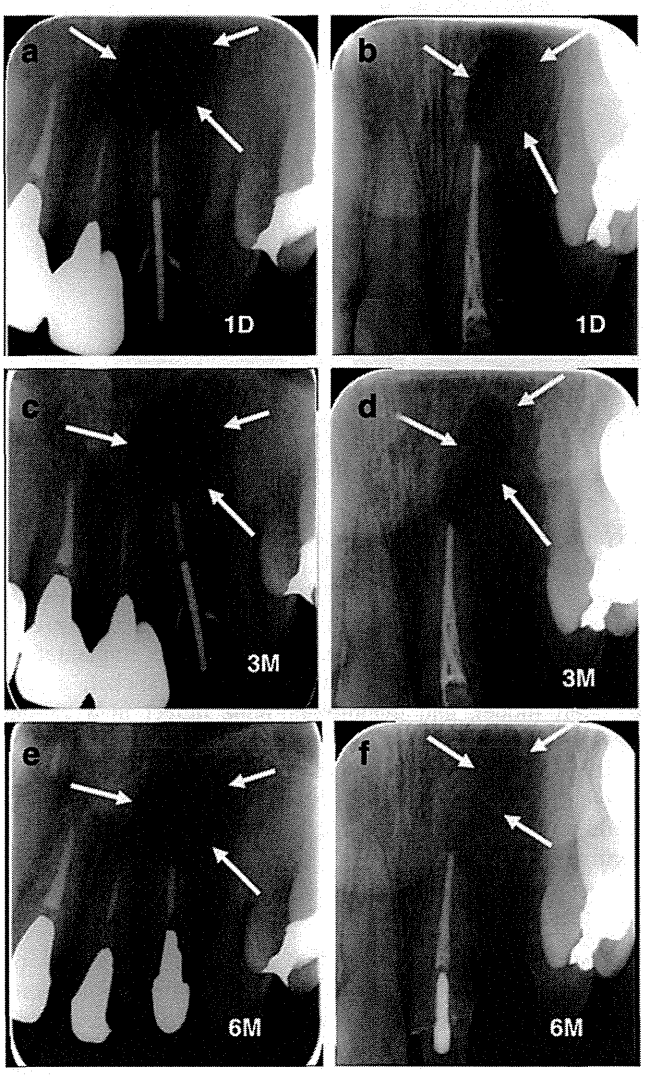

FIG. 5. X-ray pictures. **(a)** At 1 day after cystectomy in patient A and **(b)** patient B. **(c)** At 3 months after cystectomy in patient A and **(d)** patient B. **(e)** At 6 months after cystectomy in patient A and **(f)** patient B. Arrows show the margins of the bone defects.

Discussion

When OCP/collagen was implanted into bone defects after cystectomy, no postoperative infection or allergic symptom was observed for the entire period. In addition, no serious side effects were observed in this investigation. Laboratory examination showed no serious abnormal results in each patient, although C-reactive protein increased 1 day after OCP/collagen implantation as well as usual radicular cystectomy and recovered to its normal level at 7 days (data not shown). Although these patients complained of pain in the operative site for a few days, this symptom was controlled with a painkiller. In addition, postoperative wound swelling seemed to be limited compared with the operative stress. At 3 months after OCP/collagen implantation, the implanted site became hard on palpation. These results suggest that OCP/collagen would be safe to use if implanted into adult patients after cystectomy.

In radiographic examination, the radiopacity in the bone defect after OCP/collagen implantation increased with time. In addition, CT examination in the defect indicated dotted radiopacity at 3 months, which had increased and spread in the defect at 6 months. If OCP/collagen were implanted into a bone defect, the implanted OCP/collagen indicated radiopacity at several weeks after implantation, whereas OCP/collagen itself had little radiopacity.[14,15] Previous studies confirmed that the implanted OCP/collagen focuses and enhances bone regeneration and it is converted to apatite crystals as determined by XRD or Fourier transform infrared spectroscopy.[15,16] The increase of radiopacity in the bone defect originated from apatitic conversion from OCP and bone formation,[15] with most of it being dependent on bone formation.[14,16,21] Therefore, the increased radiopacity in these cases would be involved in new bone formation. This means that the implanted OCP/collagen would enhance bone formation in human bone defects.

The CT values in the defects of both patients were increased from 21 to 23 HU (before implantation) through 327–316 HU (3 months) to 527–602 HU (6 months). As CT value is proportional to bone mineral density, cancellous bone around the bone defect showed a change from ~200 to 600 HU, whereas cortical bone around it changed from ~600 to 1600 HU in the present cases. In addition, that of OCP or OCP/collagen changed from 130 to 140 HU. This suggests that new bone derived from OCP/collagen implantation was almost the same as cancellous bone at 6 months.

At 6 months after OCP/collagen implantation, dental radiography of patient B in the treated defect was more radiopaque than that of patient A, whereas the difference of radiopacity on CT or CT value at the center of the defect was less noticeable. The size of the defect or the amount of the implanted material might be related to the difference between the patients. Although this study remains obscure what would be elicited these difference, it should be examined in the future. Although this study indicated that the implantation of OCP/collagen would regenerate new bone in defects after cystectomy, no comparison of bone regeneration was performed between OCP/collagen-treated cases

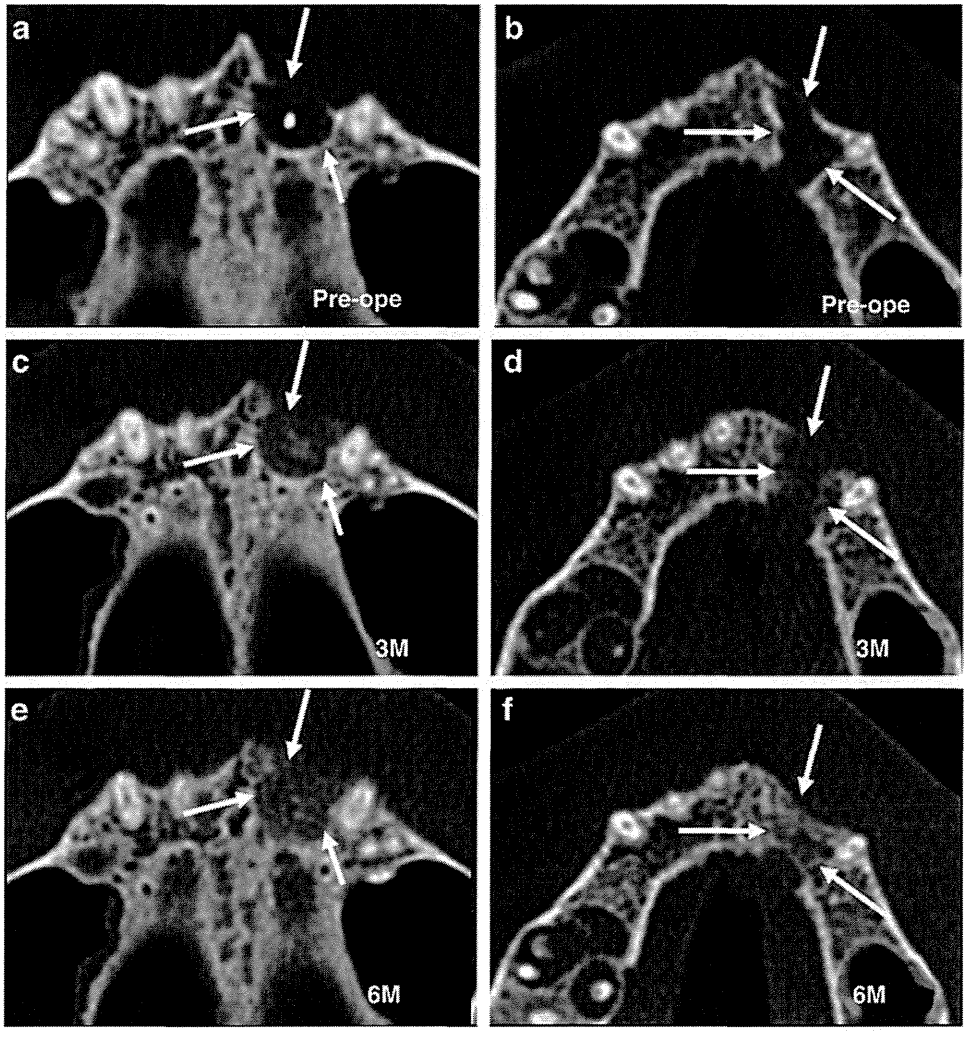

FIG. 6. Computed tomography pictures of horizontal plane. **(a)** Before cystectomy in patient A. The size was almost 8 mm in diameter. **(b)** Before cystectomy in patient B. The size was almost 5×5×10 mm. **(c)** At 3 months after cystectomy in patient A and **(d)** patient B. **(e)** At 6 months after cystectomy in patient A and **(f)** patient B.

and control cases treated with cystectomy but no implantation. This should be considered a limitation of this study, and there is a need for comparative study between OCP/collagen-treated cases and control cases to be performed to clarify the bone regenerative properties of OCP/collagen in the future.

In this study, we confirmed that OCP/collagen disk had good handling performance with softness like that of a sponge and styptic characterization by collagen. Because OCP/collagen itself has little radiopacity, it should be easy for clinicians to confirm bone regeneration in bone defects using X-ray examination. These properties convey some advantages to OCP/collagen in clinical use compared with other bone substitute materials.

In this clinical study, OCP/collagen was used in small bone defects created by cystectomy. However, our previous study demonstrated that OCP/collagen implantation enhanced bone healing at tooth extraction socket, alveolar cleft model, and mandibular bone defect in a canine model.[19–21,23] Therefore, OCP/collagen should be able to enhance bone regeneration in large bone defects. Studies to elucidate the bone regenerative properties of OCP/collagen in other bone defects or large bone defects should be performed in humans.

TABLE 1. COMPUTED TOMOGRAPHY VALUE AT BONE DEFECT

	Cyst (before cystectomy), HU	*3 months*	*6 months*
Patient A	21	327	527
Patient B	23	316	602

Computed tomography value was measured at the center of the defect.
HU, hounsfield unit.

Conclusion

This study demonstrated that OCP/collagen would be safely used and enhanced bone regeneration in human bone defects. To reinforce the efficacy of OCP/collagen as a bone substitute material, it should be compared with other suitable comparators in the future.

Acknowledgments

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Disclosure Statement

The authors (S.K. and O.S.) obtained a patent of OCP/Col in Japan (#5046511).

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Auditory evoked magnetic fields in patients with absent brainstem responses due to auditory neuropathy with optic atrophy

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HIGHLIGHTS

- Auditory evoked fields were measured in three patients with auditory neuropathy and optic atrophy showing absence of auditory brainstem responses.
- Bihemispherical AEF responses were clearly recorded in all patients for either left or right ear stimulus.
- Presence and abnormality of auditory cortical responses can be evaluated by AEFs in patients with auditory neuropathy even in the absence of ABRs.

ABSTRACT

Objective: To examine whether auditory evoked fields (AEFs) can be used to objectively evaluate hearing in patients with absent auditory brainstem responses (ABRs) due to auditory neuropathy.
Methods: Subjects were 3 patients with auditory neuropathy, 1 male aged 29 years and 2 females aged 18 and 27 years, with absence of click evoked ABRs for bilateral ear stimuli at a level of 105 dB nHL. All patients also had optic atrophy. AEFs were measured with a helmet-shaped magnetoencephalography system for 2.0 kHz tone bursts of 60 ms duration to the unilateral ear.
Results: Bihemispherical AEF responses were clearly recorded in all three patients for either left or right ear stimulus. Although the latencies of N100m were severely prolonged and amplitudes were considerably decreased compared to the normal range of N100m responses in our facilities, N100m latency of AEF was shorter in the contralateral hemisphere to the stimulated ear, as usually found in normal subjects, despite the abnormal delay in N100m latency in all conditions.
Conclusions: Presence and abnormality of auditory cortical responses can be evaluated by AEFs in patients with auditory neuropathy even under null responses in ABRs.
Significance: AEFs are useful to evaluate residual hearing in patients with auditory neuropathy.

1. Introduction

Auditory neuropathy is a type of sensorineural hearing loss which is characterized by absence or marked abnormalities of auditory brainstem responses (ABRs) beyond that expected for the degree of hearing loss, with preserved activity of the outer hair cells in the inner ear, including otoacoustic emissions (OAEs) and/or cochlear microphonics (CM) (Starr et al., 1996; Kaga et al., 1996). Psychophysically, word discrimination is impaired and disproportional to the pure-tone audiogram in these patients (Starr et al., 1996).

Auditory neuropathy includes many different etiologies causing absence of ABR with intact outer hair cell function (Doyle et al., 1998; Rance et al., 1999; Miyamoto et al., 1999; Bähr et al., 1999; Varga et al., 2003, 2006; Berg et al., 2005; Vlastarakos et al., 2008). The hearing loss caused by auditory neuropathy may be non-syndromic, in which the symptom is isolated, or syndromic, as a part of the symptoms associated with known hereditary neurological disorders, such as Charcot-Marie-Tooth disease, Friedrich's ataxia, mitochondrial disease, and autosomal dominant optic atrophy

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(ADOA), or secondary to general pathology such as hyperbilirubinemia, anoxia, and viral infection (Singh et al., 1989; Starr et al., 2000; Ceranić and Luxon, 2004; Amati-Bonneau et al., 2005; Brookes et al., 2008; Huang et al., 2009; Meyer et al., 2010; Mizutari et al., 2010; Cacace and Pinheiro, 2011).

The exact pathophysiology of auditory neuropathy remains unknown, but one key pathology type is thought to be synaptic dysfunction between the inner hair cells in the inner ear and the primary auditory neurons (Trussell, 1999; Khimich et al., 2005; Sterling and Matthews, 2005). However, the characteristic findings of auditory neuropathy such as absent ABR as well as poor speech perceptibility may result from desynchronized auditory nerve activity (Berlin et al., 2001, 2003). Therefore, auditory neuropathy has been described as auditory dys-synchrony.

Neural synchrony is important in recording auditory evoked responses, but the effects of dys-synchrony may vary with the different evoked responses; i.e., auditory N100 and P200 cortical sensory potentials to tones could be often obtained with delayed latency, despite the absence of ABR (Satya-Murti et al., 1983; Kraus et al., 1993; Starr et al., 1996, 2003, 2004; Rance et al., 2002; Michalewski et al., 2005). Differences in the degradation of such cortical responses may indicate variations in the dys-synchrony of the auditory nerve activity, so detailed assessment of the cortical response in auditory neuropathy may be important. Cortical responses in patients with auditory neuropathy have been examined by conventional electroencephalography (EEG) (Satya-Murti et al., 1983; Kraus et al., 1993; Starr et al., 1996, 2003, 2004; Rance et al., 2002; Michalewski et al., 2005) using minimal electrodes (Fz, Cz, Pz, etc.), so the recordings were not intended to analyze the right and left cortical responses separately. However, the effects of peripheral events on the auditory cortex may be different between the right and left hemispheres (Wienbruch et al., 2006; Morita et al., 2007; Hiraumi et al., 2008), so separate analysis of the bilateral cortical responses, which is possible by multichannel recording using EEG and/or magnetoencephalography (MEG), may provide additional information about the auditory cortical responses in patients with auditory neuropathy.

In the present study, the auditory N100m responses were measured by multichannel MEG in three patients with auditory neuropathy and optic atrophy (neuropathy) (Hari et al., 1980; Pantev et al., 1986; Näätänen and Picton, 1987; Reite et al., 1994; Pantev et al., 1995; Nakasato et al., 1995, 1997; Kanno et al., 1996; Kanno et al., 2000), to investigate the detailed abnormal cortical responses associated with sensorineural hearing loss caused by retrocochlear lesion, which is characterized by dys-synchrony.

2. Materials and methods

2.1. Subjects

This study included 3 patients, 1 male aged 29 years (Case 1) and 2 females aged 18 years (Case 2) and 27 years (Case 3), with auditory neuropathy diagnosed in the Department of Otolaryngology-Head and Neck Surgery, Tohoku University Hospital (indicated ages at N100m measurement). The diagnosis of auditory neuropathy was based on the following findings: absence or marked abnormalities of ABRs beyond that expected for the degree of hearing loss; and preserved outer hair cell activity including OAEs and/or CM. Clinical courses and background data of the participants are summarized in Table 1 and Fig. 1. All three subjects also had optic atrophy. Optic atrophies or optic neuropathies form a group of disorders that are characterized by visual loss due to retinal ganglion cell death (Meyer et al., 2010). Optic atrophy is often associated with auditory neuropathy in several genetic disorders, such as ADOA, Leber's hereditary optic atrophy, and deafness–dystonia–optic neuropathy syndrome (Singh et al., 1989; Ceranić and Luxon, 2004; Amati-Bonneau et al.,

Table 1
Clinical courses of three subjects.

Case	Hearing disturbance				Visual disturbance				Vestibular symptoms	Other neurological symptoms	Social activity (present)	Genetic examination	Communication method (present)	Family history
	Diagnosis	Onset (first noticed)	First visit to our oto-laryngology	Clinical course (see also Fig. 1)	Diagnosis	Onset (first noticed)	First visit to our ophthalmology	Clinical course (see also Fig. 1)						
1	AN	Around 15 y.o.	16 y.o. (7 y.o for screening)	Relatively stable after first visit	Optic atrophy	Around 5 y.o.	7 y.o.	Already considerably deteriorated at first visit	None (vestibular function test: not done)	None (no apparent abnormality indicated by pediatricians at 7 y.o.)	Office worker (using a computer for visual impaired)	Mitochondrial DNA (negative 3243 [A-G] 1555 [A-G] mutations)	Hearing aid + writing	Sister (Case 3) and father (hearing and visual disturbance)
2	AN	Around 10 y.o.	11 y.o.	Fluctuant	Optic atrophy	Around 6 y.o.	11 y.o.	Already considerably deteriorated at first visit	None (vestibular function test: not done)	None without Babinski (+) (examined in pediatric neurology including NCV*)	Clerical staff	Not done	Writing (hearing aid is not effective)	None
3	AN	Around 10 y.o.	18 y.o.	Relatively stable after first visit	Optic atrophy	Around 6 y.o.	11 y.o.	Already considerably deteriorated at first visit	None (vestibular function test: not done)	None	Massage therapist	Not done	Hearing aid + writing	Brother (Case 1) and father (hearing and visual disturbance)

AN: auditory neuropathy, y.o.: years old.
* NCV (nerve conduction velocity): motor nerve conduction velocity for median nerve and sensory conduction velocity for tibial nerve were examined in Case 2.

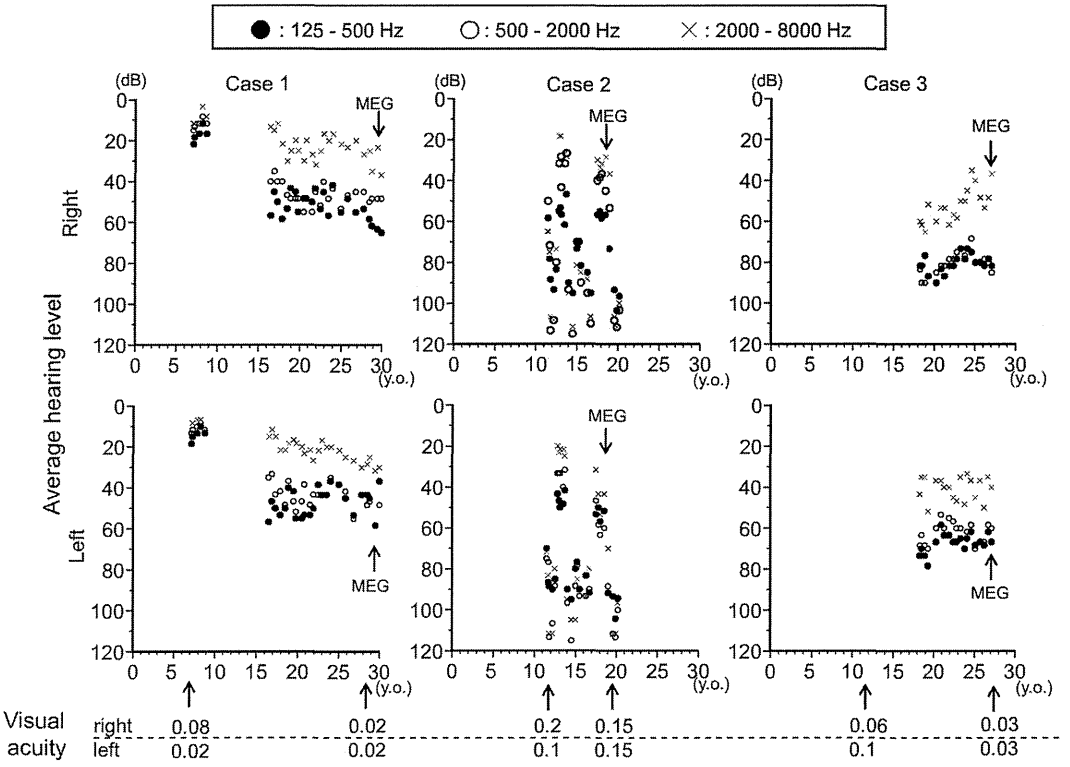

Fig. 1. Clinical course of hearing and visual acuity. Average hearing level for low (average threshold for 125, 250, and 500 Hz), mid (average threshold for 500, 1000, and 2000 Hz), high (average threshold for 2000, 4000, and 8000 Hz) frequency regions are plotted as a function of age of the patients. Visual acuities at first visit and at latest visit are also indicated at the bottom.

2005; Brookes et al., 2008; Huang et al., 2009; Mizutari et al., 2010; Cacace and Pinheiro, 2011), so genetic testing is usually recommended for abnormalities such as OPA1 gene and/or 11,778 mitochondrial DNA point mutation, which are known to cause the ADOA and Leber's hereditary optic atrophy, respectively (Singh et al., 1989; Amati-Bonneau et al., 2005; Huang et al., 2009; Mizutari et al., 2010; Cacace and Pinheiro, 2011). Unfortunately, our patients refused such genetic testing, so no genetic information was obtained except for the absence of mutation of mitochondrial DNA at 3243 and 1555 in Case 1, which was identified 11 years previously. At that time, available genetic testing was very limited in our laboratory and this genetic test was performed to screen for hearing loss due to genetic disorder. Cases 1 and 3 are siblings, with relatively stable hearing levels since the first visit to our department for hearing disturbance. In contrast, Case 2 had very fluctuant hearing. The exact reason for this hearing instability remains unknown. However, we suspected the possible presence of functional hearing loss, based on the discrepancy between the change in hearing level and subjective audibility. The present study was approved by the ethical committee of the Tohoku University Graduate School of Medicine. All parts of the present study were performed in accordance with the guidelines of the Declaration of Helsinki.

2.2. Otological examinations

The patients were interviewed to establish any history of hearing loss, followed by ear, nose, and throat examination, then pure-tone audiometry followed by measurements of distortion product OAEs, ABRs, and magnetic resonance (MR) imaging.

2.3. Measurement of auditory evoked fields (AEFs)

AEFs were recorded with a 160-channel whole-head type axial gradiometer system (MEGvision PQ1160c; Yokogawa Electric, Musashino, Tokyo, Japan) in a magnetically shielded room (Daido Steel Co., Ltd., Nagoya, Aichi, Japan) in the awake condition. The sensors of this system are configured as first-order axial gradiometers with a baseline of 50 mm; each coil of the gradiometers measures 15.5 mm in diameter. The sensors are arranged in a uniform array on a helmet-shaped surface at the bottom of the dewar and the mean distance between the centers of two adjacent coils is 25 mm. The stimulus to elicit the N100m response was a tone burst of 60 ms duration (rise and fall times of 10 ms, plateau time of 40 ms) at a frequency of 2 kHz and presented monaurally. The sound pressure level of the tone bursts was presented at 80 dB SPL at first. However, if no apparent N100m could be obtained at 80 dB SPL, then the sound level was increased in 10 dB steps up to 110 dB SPL until the N100m response was obtained. The minimum sound level to obtain the apparent N100m was defined as the detection threshold of N100m. Continuous masking noise (white noise) was applied to the contralateral ear. The level of masking noise was set at 30 dB below the stimulus level. Both ears were measured in all three patients. The signal and masking noises were presented to the subject through canal earphones (ER-3A; Etymotic Research, Elk Grove Village, IL). The mean interstimulus interval was 3.33 s (0.3 Hz) with 50% interstimulus variance. The AEFs were recorded only in the awake state as confirmed by real time monitoring of the occipital alpha rhythm by MEG. The MEG signal was band-pass filtered between 0.03 and 400 Hz, and sampled at 1250 Hz. The data from 100 ms before to 500 ms after the stimulus onset were averaged 50 times. The averaged data were digitally band-pass filtered from 2.0 to 20.0 Hz in the following off-line analysis.

The present study focused on the N100m response in adult patients with auditory neuropathy. The N100m response is the magnetic counterpart of the N1/N100 in EEG (Pantev et al., 1995). Peak latencies of the N100m responses were derived from the maximal root-mean-square value calculated on the basis of all

channels of all sessions. The location of each source was estimated at the N100m peak latency, using an equivalent current dipole (ECD) model with the best fit sphere for each subject's head. The source location was superimposed on the three-dimensional MR image of the individual subject using a MEG–MR image coordination integration system. The N100m response was identified as the first peak with latency longer than 80 ms based on the two criteria, the isofield map had the downward current orientation, and the estimated location of the current source by the ECD model was superimposed onto the auditory cortex on the three-dimensional MR image of the individual subject, which are known characteristics of the N100m in MEG (Hari et al., 1980; Pantev et al., 1986; Näätänen and Picton, 1987; Reite et al., 1994; Pantev et al., 1995; Nakasato et al., 1995, 1997; Kanno et al., 1996, 2000).

The amplitudes of the N100m responses in our subjects were often much smaller than those in normal subjects, sometimes nearly as low as noise level, and the N100m response was sometimes hard to identify based only on the conventional time-axis wave form, which is the usual way to identify N1/N100 in conventional EEG. However, even in such cases, the N100m could be clearly identified in MEG measurements by searching for the response peak fulfilling the above-mentioned N100m criteria, which is one of the advantages in using MEG to analyze the N100 response instead of the conventional EEG method.

Since the number of the patients examined in the present study was too small for statistical analysis, the abnormality of the N100m responses (at the maximum amplitude channel of each hemisphere) was determined based on the normal range of N100m responses at the maximum amplitude channel of each hemisphere in our facilities (Kohnan Hospital), which was defined for practical reasons as the mean ± 2 standard deviations of 37 normal subjects (31 males and 6 females, aged from 21 to 59 years [mean 31.0 years]).

3. Results

The findings of AEFs, audiograms, ABRs, and OAEs are shown in Figs. 2 and 3, and Table 2. The sound levels shown in Table 2 indicate the minimum sound level to obtain the apparent N100 m, that is the detection threshold. Measurement of auditory evoked magnetic fields to both ear stimuli in the contralateral hemispheres at the detection threshold levels are represented in Fig. 3, which shows the N100 m responses, isofield patterns, and the estimated ECDs of the contralateral ear stimuli. The degree of hearing loss in the audiogram varied with the patient, but the ABRs were absent and the distortion product OAEs were normal in all patients. Word discrimination scores were lower than expected from the degrees of hearing loss.

N100m responses in both the ipsilateral and contralateral hemispheres to the stimuli of either ear were compatible with the auditory response because of the ECD location in all patients (Table 2). The source of the N100m was localized in the primary auditory cortex along the superior temporal plane in each hemisphere for either ear stimuli. N100m responses were recorded in all cases, but the latencies were severely prolonged and the amplitudes were considerably decreased compared to the normal range of N100m responses in our facilities. However, despite the abnormal responses, the latencies of N100m were shorter for the contralateral than the ipsilateral stimuli as usually observed in normal subjects (Elberling et al., 1981, 1982; Reite et al., 1981; Pantev et al., 1986; Mäkelä et al., 1994; Nakasato et al., 1995). N100m responses observed in the contralateral hemispheres to the stimuli are shown as stacked waveforms in Fig. 3, in addition to the isofield patterns over the entire head and the estimated ECDs at the peak latency in the contralateral hemisphere, which are superimposed onto the individual horizontal and coronal MR images. Fig. 4 shows the relationships between average hearing level, speech intelligibility, and the detection threshold of N100m.

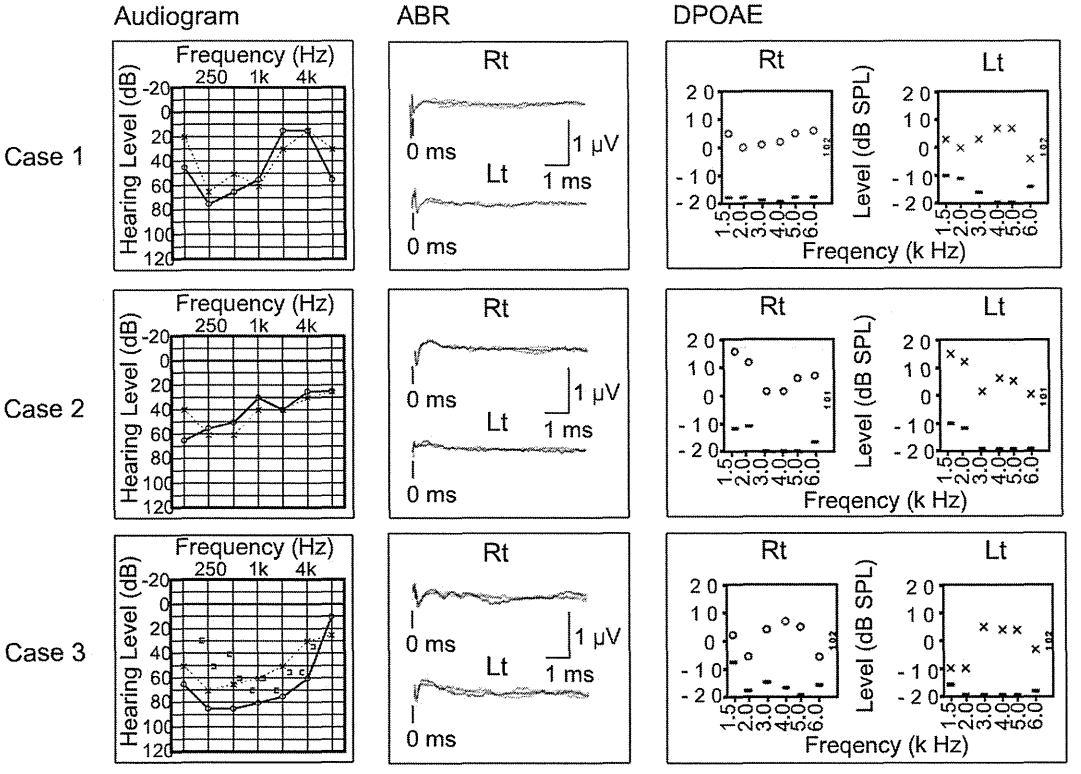

Fig. 2. Audiogram, ABR, and distortion product OAE (DPOAE) measured at the nearest point to the N100m measurements. ABRs to 105 dB nHL clicks were measured three times. All ears had absent ABRs, but hearing in audiograms was relatively preserved and DPOAEs were normal in each patient.

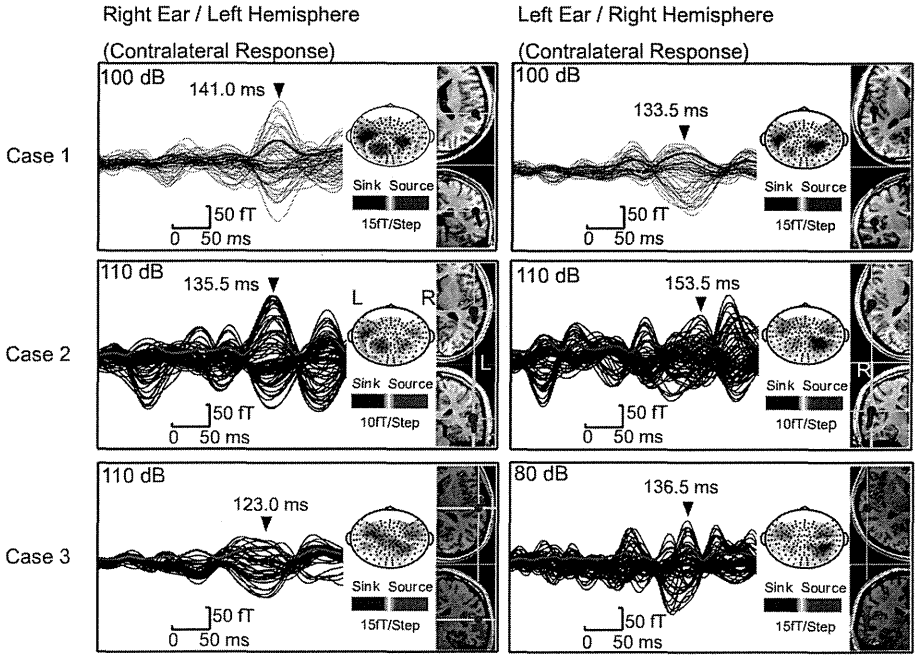

Fig. 3. Measurement of auditory evoked magnetic fields to both ear stimuli in the contralateral hemispheres. The N100m responses, isofield patterns, and estimated ECDs are indicated. Stacked waveforms show the N100m responses. The peak latencies of N100m (arrowhead) are derived from the maximum root-mean-square value (red line). Isofield patterns over the entire head, viewed from above, are shown above the waveforms: red contours (magnetic flux-out) and blue contours (magnetic flux-in) are shown with contour step of 15 fT in Case 1, 10 fT in Case 2, and 15 fT in Case 3 at the peak latency. Estimated ECDs superimposed onto the subject's MR images (panel right side, upper: horizontal and lower: coronal views). Note that the ECDs are located in the primary auditory cortices.

Table 2
Clinical characteristics of the patients with auditory neuropathy.

Case	Age (y) */Sex	Ear side	PTA (dB)	Word%	DPOAE	ABR	Normal range			
							N100m latency		N100m amplitude	
							Right hemisphere	Left hemisphere	Right hemisphere	Left hemisphere
							Right ear stimulation			
							77.8–116.6 ms	68.5–108.5 ms	350–461.6 fT	319.6–431.6 fT
							Left eat stimulation			
							66.4–101.2 ms	83.7–120.1 ms	427.6–541.2 fT	265.5–364.7 fT
1	29/M	Right	45	25% 90 dB	Normal	Absent	100 dB 148.5 ms	100 dB 141.0 ms	100 dB 85.2 fT	100 dB 145.3 fT
		Left	46.7	20% 80 dB	Normal	Absent	100 dB 133.5 ms	100 dB 151.0 ms	100 dB 95.1 fT	100 dB 133.8 fT
2	18/F	Right	40	30% 100 dB	Normal	Absent	110 dB 150.0 ms	110 dB 135.5 ms	110 dB 90.0 fT	110 dB 157.2 fT
		Left	46.7	20% 50 dB	Normal	Absent	110 dB 153.5 ms	110 dB 169.5 ms	110 dB 101.0 fT	110 dB 80.5 fT
3	27/F	Right	80	25% 100 dB	Normal	Abnormal**	110 dB 129.5 ms	110 dB 123.0 ms	110 dB 91.3 fT	110 dB 78.2 fT
		Left	58.3	40% 70 dB	Normal	Absent	80 dB 136.5 ms	80 dB 141.0 ms	80 dB 99.0 fT	80 dB 54.0 fT

PTA = pure tone average (threshold average for frequencies of 0.5, 1.0, and 2.0 kHz).
Word% = word discrimination score (word% correct).
DPOAE = distortion product otoacoustic emission.
ABR = auditory brainstem response.
N100m amplitude: N100m response at the maximum amplitude channel of each hemisphere. Normal range of N100m latency and N100m amplitude (for 2000 Hz tone bursts at a level of 80 dB SPL) in our facility are indicated in shaded area (average ± 2 standard deviation) (Kanno et al., 1996).
* Age: age at MEG measurement.
** Suspected cochlear microphonics were indicated.

4. Discussion

In the present study, N100m peaks in response to 2.0 kHz tone bursts were detected in the bilateral hemispheres of all three patients, despite the absence of click evoked ABRs (at 105 dB nHL). The latencies were severely prolonged and the amplitudes were considerably decreased compared to the normal range of N100m responses in our facilities, but shorter latencies were observed in the hemisphere contralateral to the stimulated ear compared with those in the hemisphere ipsilateral to the stimulated ear, as usually found in normal subjects. EEG has already suggested the presence of cortical responses in auditory neuropathy subjects with absent ABR (Starr et al., 1996; Michalewski et al., 2005). However, cortical responses were not analyzed for the separate hemispheres in these EEG studies. Such separate analysis of the bilateral cortical responses is worthwhile considering that the effects of peripheral events on the auditory cortex may be different between the right and left hemispheres (Wienbruch et al., 2006; Morita et al., 2007; Hiraumi et al., 2008). The assessment of cortical response by MEG would also be essential for further observing the effects of

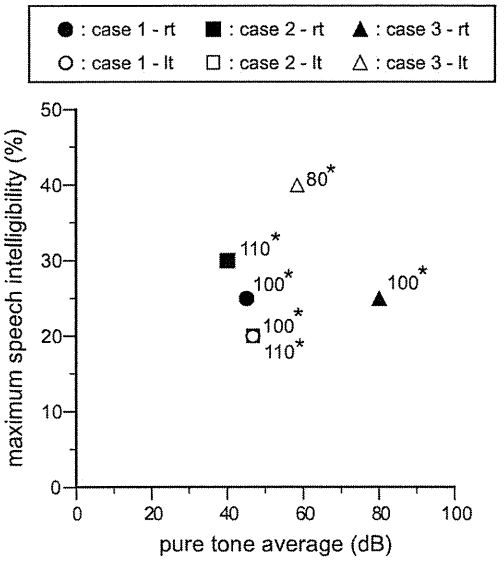

Fig. 4. Relationships between average hearing level, speech intelligibility, and the detection threshold of N100m. Maximum speech intelligibility is plotted as a function of pure tone average (500–2000 Hz) for each ear, and detection threshold level for each ear is shown for each symbol (marked with asterisks). N100m in response to 2 kHz tone-burst at a level of 80 dB SPL was only observed in the left ear of Case 3, in whom the best speech discrimination (40%) was obtained among the 6 ears of the 3 patients, although the hearing threshold at 2 kHz was worse than those of Cases 1 and 2, in whom stimuli at 100 dB or higher were needed to measure robust N100m response.

auditory dys-synchrony on other types of cortical response with hemispheric asymmetry, such as the auditory steady state response in response to amplitude modulation tone and cortical responses to speech stimuli.

MEG has evolved from a single-channel portable system to modern whole head systems providing an advanced and powerful method for direct and noninvasive brain function research (Bagic et al., 2009). The critical locations of AEFs can also be identified accurately with MEG (Romani et al., 1982; Alberstone et al., 2000; Nakasato and Yoshimoto, 2000; Godey et al., 2001). MEG is less prone to distortion than EEG, because the skull and other extracerebral tissues substantially affect electrical current fields in EEG, but are practically transparent to magnetic fields (Soeta and Nakagawa, 2009). Dipolar source analysis based on MEG can also effectively isolate the lateralized nature of auditory evoked potentials (Huang et al., 2003), which is an important advantage of MEG measurement in patients with pathology, since any delayed latency responses with deteriorated signal to noise ratio can be correlated with the auditory evoked N100m responses originating from the primary auditory cortices, based on the ECD locations with the best fit sphere for each subject's head (Hari et al., 1980; Pantev et al., 1986; Näätänen and Picton, 1987; Reite et al., 1994; Pantev et al., 1995; Nakasato et al., 1995; Kanno et al., 1996; Nakasato et al., 1997; Kanno et al., 2000).

The presence or absence of cortical responses and speech intelligibility may be related, as indicated in a previous study of young children with auditory neuropathy (Rance et al., 2002). The present study included too few cases to analyze the relationship between speech intelligibility and N100m response, but did appear to indicate similar trends. As shown in Table 2 and Fig. 4, the N100m in response to 2 kHz tone-burst at a level of 80 dB SPL was only observed in the left ear of Case 3, in whom the best speech discrimination (40%) was obtained among the 6 ears of the 3 patients, although the hearing threshold at 2 kHz was worse than those of Cases 1 and 2, in whom stimuli at 100 dB or higher were needed to measure robust N100m response. These results indicate that the measurement of cortical responses could be useful to assess the auditory pathophysiology in patients with auditory neuropathy. The relationship between the clinical characteristics and the parameters of the N100m response such as latency and amplitude also raises intriguing questions. These parameters were severely deteriorated in the present patients and would be expected to indicate some pathological conditions. However, these parameters are also affected by the hearing level and stimulation level, so further investigations using much more data are required to analyze these issues.

Auditory neuropathy includes many different etiologies causing absence of the ABR associated with intact outer hair cell function, such as synaptic dysfunction between the inner hair cells in the inner ear and the primary auditory neurons (Doyle et al., 1998; Rance et al., 1999; Miyamoto et al., 1999; Bähr et al., 1999; Trussell, 1999; Varga et al., 2003; Berg et al., 2005; Khimich et al., 2005; Sterling and Matthews, 2005; Varga et al., 2006; Vlastarakos et al., 2008). Therefore, analysis of the neurophysiological and psychophysical data based on the individual etiology would be preferable. Classification based on genetic disorders is a potentially useful way to categorize the etiology of auditory neuropathy. In our cases, the involvement of some specific genetic disorder is possible, since two of our patients were siblings, and all patients had similar clinical features including association with optic atrophy, age of onset of visual and hearing disturbances, and others. Unfortunately, we have no useful data on the genetic background relating to the etiology, so this aspect requires further study.

One mechanism which may explain the characteristic findings of auditory neuropathy is "desynchronized auditory nerve activity", which is caused by pathological dysfunction of the synapses between the inner hair cells and the auditory neurons or demyelinization of the auditory nerve (Starr et al., 1991; Berlin et al., 2001, 2003). The resultant de-synchronization of the spike timing between neurons deteriorates the wave formation of the ABR, which is the sum of the synchronized spike activities of the neurons evoked by sound stimuli. Investigation of the effects of de-synchronization on the ABR waveform with cats suggested that 1-ms jitter between the click stimuli and the averaging process can abolish the ABR waveforms (Starr et al., 1991). Therefore, dys-synchrony on the order of 1 ms could abolish the ABR wave even though the sound can be heard. On the other hand, the cortical auditory evoked response of N100m, which is also a synchronized response to tone, can be detected in patients with auditory neuropathy with absent ABR. The presence of the cortical auditory evoked response in patients with absent ABR may reflect different redundancies in temporal neural processing between the auditory cortex and brainstem or different susceptibility to "dys-synchrony" between the ABR and cortical response.

The different susceptibility of the ABR and the N100m may be partly explained by the different configurations of the response waves; i.e., comparison of the "duration" (duration between the onset and the endpoint of each wave) of the ABR and N100m response found that the duration of the ABR was much shorter (about 1/100) than that of the N100m response, based on data obtained in our facilities: average wave duration was 63.0 ± 11.3 ms (n = 20) for N100 m, 0.58 ± 0.1 ms (n = 20) for wave I of ABR, and 0.89 ± 0.2 ms (n = 20) for wave V. Therefore, the effects of "dys-synchrony" might be much larger on the ABR waveform than on the N100m. In fact, similar measurements concerning the effects of jitter between the onset of tone bursts and the averaging process on the N100m waveforms support this hypothesis; i.e., the amplitude of N100m waveform was little affected by jitter of 10–20 ms duration between the stimuli and averaging process, whereas jitter of longer duration was associated with reduced N100m amplitude, and jitter of 80 ms duration resulted in the N100m wave being almost completely abolished (unpublished data). Therefore, the

degree of abnormality observed in the N100m response may also reflect the dys-synchrony of the auditory fiber, so that more severe abnormality of the N100m indicates more severe pathophysiology of the auditory nerve. In this context, detailed measurements of the N100m responses including the response thresholds as well as response growth functions can be expected to provide more useful information concerning the pathophysiology of the patients with auditory neuropathy, although only the N100m responses to relatively high sound levels were examined in the present study.

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Research Article Open Access

Development of Clinicians' Communication Skills Influences the Satisfaction, Motivation, and Quality of Life of Patients with Stroke

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Abstract

Objective: To evaluate the influence of structuring the clinician's communication according to coaching theory on stroke patients' quality of life and satisfaction.

Methods: Prospective observational study was carried out at outpatient clinics for patients in the chronic post-stroke phase. Thirty-four clinicians involved in the management of patients with stroke and their105 patients in the chronic post-stroke phase. The clinicians enrolled in this study received training in communication skills based on coaching theory and utilized these skills when interviewing their patients with stroke. We assessed the main outcome measures and the clinicians' self-assessments of their communication skills before and after the training. The main outcomes were the patients' (1) satisfaction, (2) health-related quality of life, and (3) goal setting and action scores.

Results: The training significantly increased the patients' satisfaction with the clinicians' communication (46.8 before training vs. 48.6 after training, $p<0.001$), overall satisfaction (16.8 vs. 17.4, $p<0.001$), and goal setting/action (14.6 vs. 15.2, $p<0.05$) scores. Additionally, the training significantly increased the SF-36 subscale scores for bodily pain (56.6 vs. 65.0, $p<0.01$), general health (49.8 vs. 54.1, $p<0.05$), and social function (61.1 vs. 69.9, $p<0.05$).The patients whose satisfaction with the clinician's communication improved exhibited significantly greater improvements in their physical function scores and tended to exhibit greater improvements in their bodily pain and vitality scores than the no-improvement group. Furthermore, the patients whose goal setting and action improved tended to have greater improvements in their physical function, role limitation by physical problems, and mental health scores than the no-improvement group.

Conclusion: Training in coaching theory-based communication skills influenced stroke patients' satisfaction, goal setting and action, and HQOL. Clinicians should intentionally use structured communication to facilitate patients' active involvement in their rehabilitation.

Keywords: Stroke; Clinicians' communication; Patients' satisfaction; Health-related quality of life; Rehabilitation; Coaching; Outpatients

Introduction

Stroke is a disease with a high incidence and is one of the 3 major causes of death in Japan and the leading cause of need for long-term care, thus accounting for a high percentage of the total costs of medical care [1]. Residual disabilities after stroke include functional impairments, psychological problems, and loss of social adjustment, and the sequela of stroke hugely impact the quality of life (QOL) of both the patients and their family members for prolonged periods [2,3]. Clinicians involved in the management of stroke patients are required not only to deal with their patients' physical disorders but also to monitor such subjective aspects as the patients' and family members' adjustments to such disorders.

Patient/family education is a useful part of the holistic care of patients with stroke. Previous studies have shown the effectiveness of patient/family education [4]. Many researchers have considered what content should be included in the educational programs provided to the patient and family, but we should also consider the communication capabilities of the clinicians who are involved in advising and educating the patients. The objective of rehabilitation medicine is to help patients to improve their physical, psychological, social, occupational, and economic independence. Assistance from clinicians in setting goals and adopting spontaneous behaviors to minimize their disabilities is particularly important for stroke patients who have various residual disabilities that are anticipated to persist for prolonged periods. Therefore, providing clinicians with training in communication skills can be highly effective.

Coach training programs area based on coaching theory method for providing education in communication skills. The International Coach Federation defines coaching as partnering with clients in a thought-provoking and creative process that inspires them to maximize their personal and professional potential [5]. Coaching has been adopted not only in the field of business but also in the field of healthcare, where it has begun to attract close attention. In the health care field, coaching has been adopted for management of the lifestyles of patients with lifestyle-related diseases [6] such as diabetes mellitus [7-9], hypercholesterolemia [10], and heart diseases [11] and has yielded excellent results. Other studies have shown that coaching reduced pain [12] and improved patients' adherence to hospital/clinic visits [13], continuation of treatment [14], and medication use [15,16]. In addition, a few studies on telephone coaching for patients with spinocerebellar degeneration [17,18] demonstrated improvement in the patients' self-efficacy.

Coaching comprises the use of communication skills to facilitate spontaneous behaviors by the coached individuals and the setting of goals and facilitation of the coached individuals' acquisition of the knowledge and skills needed to achieve those goals [6]. Clinicians involved in rehabilitation might be able to improve their assistance

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of the rehabilitation efforts of stroke patients and their families by learning coaching theory and practicing intentional and structured communication with their patients.

The purpose of this study was to evaluate the influence of coaching theory-based structured communication by clinicians on the QOL and satisfaction of patients with chronic stroke. Therefore, we trained clinicians involved in the management of patients with stroke in coaching theory-based healthcare communication skills and assessed the efficacy of this training.

Methods

Participants

The participants in this study were clinicians involved in the management of patients with stroke and whose patients are in the chronic post-stroke phase.

The inclusion criteria for the clinicians were (1) 2 or more years of clinical experience, (2) responsibility for outpatients in the chronic post-stroke phase, and (3) the desire to participate in this training program. The inclusion criteria for the patients were (1) receipt of ambulatory care provided by one of the clinicians participating in this study, (2) age between 20 and 80 years, (3) onset of stroke at least 6 months prior, (4) retention of cognitive functions (score of 24 or higher on the Mini-Mental State Examination (MMSE) [19] or score of 21 or higher on the Revised Version of the Hasegawa Dementia Scale (HDS-R) [20]) and the ability to engage in daily conversation, and (5) absence of psychiatric diseases such as depression.

The clinicians were recruited through public announcements, such as advertisements in the Japanese Journal of Rehabilitation Medicine and on the study webpage. Each clinician participating in the study selected his or her patients who met the inclusion criteria. The protocol of this study was examined and authorized by the Institutional Review Board of Tohoku University Graduate School of Medicine.

Intervention

The clinicians received training in the use of coaching theory-based communication skills in clinical scenarios. This training consisted of 2 days of lectures and role-playing exercises about the principles and structure of coaching and the necessary communication skills (such as pacing, active listening, acknowledgement, questioning, suggestion, and assessment of the communication type) and was delivered by a certified master coach accredited by the International Coach Federation. The training was followed by a 3-month follow-up program. Each clinician received coaching-related tips by e-mail once a week. In addition, every other week each clinician reported the status of his or her practice of the skills in routine clinical practice. If the clinicians had any questions, they could ask their tutor and receive a reply.

Study design

This was a prospective observational study. Before and 1 month after the training, each clinician and patient completed a questionnaire. In addition, the patient's health-related QOL (HQOL, described later) was assessed 5 months after the training because we hypothesize that a patient's HQOL begins to change only after he/she sets some goals and begins engaging in the tasks needed to achieve those goals; therefore, 1 month is insufficient time for a valid evaluation of changes in the HQOL.

Outcome measures

The main outcomes were the patients' (1) satisfaction, (2) HQOL, and (3) goal setting and action. Each patient's satisfaction was evaluated using the Patient Satisfaction Questionnaire prepared by the American Board of Internal Medicine (ABIM-PSQ) [21,22]. The ABIM-PSQ was designed as a scale for assessing a patient's satisfaction with his or her communication with his or her clinicians. It includes 3 sub-scales comprising a total of 18 items. This study employed2 of these sub-scales: "satisfaction with the communication," consisting of 11 items (range of score: 11-55), and "overall satisfaction," consisting of 4 items (range of score: 4-20). The HQOL was assessed using the SF-36v2 (MOS 36-item Short Form Health Survey) [23,24]. The SF-36v2 is the most frequently used scale for general HQOL. It comprises 8 sub-scales: physical functioning, role limitation by physical problems (role physical), bodily pain, general health, vitality, social functioning, role limitation by emotional problems (role emotional), and mental health. The patient's "goal setting and action" was evaluated using 4 items (range of score: 4-20) adapted from the Coaching Skill Evaluation System prepared by the Japan Coach Association [25] and focused on evaluation of the patients' spontaneous behaviors (i.e., "I was able to take action towards achieving my goals after consulting with my doctors").

In addition, the clinicians' self-assessments of their communication skills were analyzed as a secondary outcome. The self-assessment consisted of evaluation of 12 items that were listed by the web program entitled "Coaching for medical interviews" as a coach-type clinician's competencies [26].

Statistical analysis

We calculated the mean and standard deviation or the frequency and percentage of the characteristics of the clinicians (sex, age, and length of career) and patients (sex, age, Barthel Index (BI), and time after onset of disease).

Before beginning the analysis of the outcomes, we verified the reliability and validity of the new scales used in this study. The factorial validity of each of the scales used for the assessment of "goal setting and action" and "clinician's self-assessment of communication skills" was analyzed by factor analysis (principal factor method and Varimax rotation), and the reliability was estimated using Cronbach's alpha coefficients [27].

The mean scores and standard deviations of the 4 outcome measures were calculated before and after the training, and paired t-tests were used to assess the levels of statistical significance of any differences in the mean values. Additionally, we calculated Cohen's effect size (Δ/baseline SD), for which a value of 0.2 is small, 0.5 is moderate, and 0.8 or greater is large [28].

Then, to test the associations of "patients' satisfaction" and "goal setting and action" with HQOL, we calculated the least mean square of the change after training of each SF-36 subscale score in2sets of 2 subgroups defined by their respective changes in "patients' satisfaction" and "goal setting and action" and adjusted for age. These subgroups were the "improvement" group, which included patients who exhibited numerically positive changes after training, and the "no-improvement" group, which included patients who exhibited no change or numerically negative changes after training.

The data were analyzed using SPSS version 15.0 for Windows (SPSS Inc., Chicago).

Results

Characteristics of the participants

Of the 34 clinicians enrolled in the study, 31 attended the training.

	Mean, SD or Frequency (%)	Range
Clinicians (n = 23)		
Age (years)	42.0, 8.2	27–57
Length of career (years)	15.6, 7.3	3–33
Gender, male, n (%)	17 (73.9%)	
Patients (n = 73)		
Age (years)	63.5, 10.2	36–85
Barthel index	85.1, 17.8	40–100
Time since onset (months)	60.4, 51.5	6–271
Gender, male, n (%)	57 (78.1%)	

Table 1: Characteristics of the participants.

	Factor			
Question items	**Attitude**	**Active listening**	**Acknowledgement**	**Suggestion**
Being able to assess an individual patient's type	**0.832**	0.028	-0.129	0.271
Practicing communication skills tailored to individual patients	**0.828**	-0.048	-0.049	0.409
Being mindful of my external appearance as a clinician (gaze, tone of voice, posture, distance from a patient, etc.)	**0.572**	0.371	0.245	0.058
Receivingfeedback from patients	**0.419**	0.403	0.221	0.105
Attaching importance to communication with patients	0.123	**0.699**	0.291	0.163
Asking questions of patients in a way that encourages them to answer freely and in a relaxed manner instead of demanding answers	0.374	**0.692**	0.357	0.200
Speaking and behaving in a manner that makes it easier for the patients to talk	0.118	**0.650**	-0.123	-0.009
Listening well to patients	-0.361	**0.644**	0.047	0.059
Respecting and admitting the patient's thoughts	0.140	0.018	**0.809**	-0.235
Informing patients in a way that makes it easy for them to accept	-0.190	0.197	**0.520**	0.251
Encouraging patients to become more independent and better able to receive treatment	0.204	0.121	0.094	**0.720**
Making requests and proposals in a that makes it easier for patients to accept	0.205	0.063	-0.091	**0.552**
Contribution ratio (%)	19.3	18.0	10.8	10.6

Table 2: Factor analysis of "clinicians' self-assessments of their communication skills".

The reasons for the inability of the remaining 3 clinicians to attend the training were change in the place of employment after registration and inability to recruit any suitable patients satisfying the inclusion criteria. Twenty-three clinicians completed the questionnaire before and after the training (collection rate, 74.2%). A total of 107 patients consented to participate, of who 105 participated in the study; the remaining 2 were unable to participate because of physical problems. Seventy-three patients completed the questionnaire before and after the training (collection rate, 69.5%). Table 1 summarizes the characteristics of the clinicians and the patients enrolled in the study.

Factorial validity and reliability of the new scales

Factor analysis of the 4 items measuring "goal setting and action" found the contribution of the primary factor to be 62.3% and the factor loading of each item on the primary factor to be 0.75-0.81, indicating that these 4 items were highly uni-dimensional and confirming their factorial validity. The Cronbach's alpha coefficient was 0.87.

Factor analysis of the 12 items measuring the clinicians' self-assessments of their communication skills resulted in the extraction of 4 factors (Table 2). The cumulative contribution of these 4 factors was 58.8%. The factors were designated "attitude" (4 items, range of score 4-20), "active listening" (4 items, 4-20), "acknowledgment" (2 items, 2-10) and "suggestion" (2 items, 2-10). The Cronbach's alpha coefficients were 0.79 for "attitude," 0.76 for "active listening," 0.49 for "acknowledgement," and 0.66 for "suggestion."

Effects of training in communication skills

Training significantly increased the patients' satisfaction with their clinicians' communication, overall satisfaction, and goal setting and action scores, but the effect sizes were small (Table 3). The subscale scores for the "bodily pain," "general health," and "social functioning" domains of the SF-36 increased significantly, but the effect sizes of these changes were also small. Furthermore, no part of the clinicians' self-assessments of their communication skills changed significantly after training.

The group whose "satisfaction with clinician's communication" improved after training (improvement group) exhibited significantly greater improvement in the physical functioning score and tended to exhibit greater improvements in the bodily pain and vitality score than the no-improvement group. The improvement group for "goal setting and action" tended to exhibit greater improvements in the physical functioning, role physical, and mental health scores than the no-improvement group (Table 4).

Discussion

The results of this study suggest the possibility that clinicians' intentional and structured use of communication skills during their treatment of patients with chronic stroke could increase the patients' satisfaction, levels of motivation for goal setting and action, and HQOL. Additionally, our study showed that increasing the patient's satisfaction and motivation to set goals and take action toward them might be able to improve HQOL in patients with stroke. In particular, the improvement inpatients' goal setting and action was a new finding not previously reported by any investigator. In addition, it is meaningful that chronically disabled patients, such as stroke survivors, whose conditions had largely stabilized in the long span of time since the onset

		Before training		After training		Paired t-test	Effect size
Outcome	**n**	**Mean**	**SD**	**Mean**	**SD**	**p value**	
Patients							
Satisfaction with the clinicians' communication	73	46.8	7.1	48.6	6.3	0.001	0.25
Overall satisfaction	71	16.8	2.6	17.4	2.3	0.001	0.23
Goal setting and action	69	14.6	2.3	15.2	3.1	0.034	0.26
HQOL(SF-36)							
Physical functioning	71	45.1	31.0	46.9	28.7	0.447	0.06
Role physical	70	46.1	35.1	47.8	31.9	0.650	0.05
Bodily pain	71	56.6	27.0	65.0	24.0	0.004	0.31
General health	70	49.8	22.4	54.1	18.4	0.018	0.19
Vitality	72	56.9	23.6	59.8	21.1	0.192	0.12
Social functioning	71	61.1	29.5	69.9	26.9	0.011	0.30
Role emotional	69	53.7	36.5	55.9	33.9	0.657	0.06
Mental health	72	63.3	22.3	63.0	19.3	0.904	-0.01
Clinicians							
Self-assessments of their communication skills							
Total score	23	43.4	4.3	44.7	5.8	0.165	0.09
Attitude	23	13.4	2.2	13.5	2.6	0.862	0.05
Active listening	23	15.5	2.1	16.0	1.9	0.260	0.24
Acknowledgement	23	7.7	0.9	8.0	1.1	0.259	0.33
Suggestion	23	6.8	1.2	7.4	1.3	0.069	0.50

Table 3: The outcomes of the patients and clinicians before and after the training.

	Satisfaction with clinician's communication					Goal setting and action				
	No improvement (N=40)		Improvement (N=25)			No improvement (N=39)		Improvement (N=26)		
	mean	SE	mean	SE	p-value	mean	SE	mean	SE	p-value
PF	-1.3	3.2	9.2	3.9	0.041	-0.7	3.5	8.7	3.7	0.073
RP					n.s.	-2.8	5.7	11.6	6.2	0.099
BP	3.3	4.0	15.5	4.9	0.060					n.s.
GH					n.s.					n.s.
VT	-1.8	3.3	7.6	3.9	0.071					n.s.
SF					n.s.					n.s.
RE					n.s.					n.s.
MH					n.s.	-3.9	3.4	6.0	3.7	0.056

SE: standard error of the mean, PF: physical functioning, RE: role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role emotional, MH: mental health, n.s.: not significant
The least mean square and standard error of the change after adjustment for age are shown. The SF-36 subscale score fields for which the differences between the 2 groups gave p values of <0.1 were left blank.

Table 4: Associations of improvements in "satisfaction with clinician's communication" and "goal setting and action" with improvement in health-related QOL.

of disease could be motivated to implement goal-oriented behaviors. Training the clinicians in communication skills was sufficient to produce these impressive changes.

Several previous reports have suggested that clinicians' communication skills can affect patients' satisfaction. Shilling et al. [29] reported that communication training improved "patient's satisfaction." Stewart [30] listed "improvement in patient satisfaction," "elevation in patient's motivation for treatment and increase in patient's knowledge and understanding," "improvement in adherence," "decrease in undesirable behaviors," and "improvement in clinician's satisfaction with patient management" as favorable effects of better communication with patients in clinical practice.

The improvements observed not only in the patients' satisfaction but also in their goal setting and action and HQOL were probably related to the basis of the communication skills practiced in coaching theory. Coaching aims to stimulate the client to alter his/her behaviors for achieving his or her goals. The clinicians who learned coaching theory not only conducted their conversations more carefully but also structured their use of the communication skills while remaining mindful of the need to assist patients to take action towards their goals. Furthermore, coaching is based on interactive communication. The conventional clinician-patient relationship is usually a 1-way dialogue in which the clinician "teaches" something to the patient. After learning coaching theory, our clinicians began to listen to their patients more carefully and practiced interactive communication, allowing the patient to feel free to ask questions. This approach likely modified the clinician-patient relationship to stimulate spontaneous behaviors and assist in self-made decisions.

Despite these promising results, the effect sizes for patients' satisfaction and HQOL in this study were small, indicating that the effect of this intervention was not large and was greatly variable overall. However, it is imperative to focus on the finding that HQOL was higher in the improvement group than in the no-improvement group. This suggests that a patient's satisfaction his or her clinicians' communication might actually improve his or her physical functioning, bodily pain, and vitality scores. Furthermore, patients who set goals

and act to achieve them may experience improvements in their physical functioning, role physical, and mental health scores.

Although the patients' satisfaction with their communications with their clinicians increased, the clinicians' self-assessments of their communication skills did not change significantly. This result could be interpreted as indicating a lack of improvement in the clinicians' communication skills following the training. However, the changes in the patients' outcomes make it unlikely that the clinicians' communication skills did not change. Instead, the finding of no change is more likely to reflect the influence of "response shift" (changes in the internal standards for self-assessment following intervention) [31]. The clinicians in the present study had been confident in their communications skills and gave high self-assessment scores before the training. It seems likely that these clinicians became aware of the inadequacy of their previous communication skills only after the training, resulting in a lack of any significant change in the assessment scores because of response shift.

Evaluation of the practice of communication skills by means of self-assessment is restricted by various factors, including response shift. The aforementioned study by Stewart et al. [30] adopted an objective method of evaluation in which clinical scenarios were video-recorded for subsequent assessment of the use of communication skills. This and similar methods are considered the best way to facilitate awareness of nonverbal communication [32]. Future analysis of the relationship between self-assessment and objective evaluation would be desirable.

One of the limitations of this study is that we did not use any quantitative variables to assess the extent to which the skills learned by the clinicians were actually utilized during clinical practice. Therefore, we did not analyze the relationships between the patient outcomes and the quantitative and qualitative aspects of the clinicians' uses of communication skills. However, the clinicians' reports on the statuses of their practice of the skills suggest that the clinicians consciously practiced coaching theory-based communication. For example, the clinicians reported, "When I attempted to talk to the family from my side, it was difficult to maintain a smooth dialogue, possibly because the family members did not have adequate time to think. When I attempted to talk to the family members so as to encourage them to think by themselves, the dialogue was smoother" and, "What I did first was to listen to what the patient/family had to say in order to create an atmosphere encouraging frank communication and express my sympathy. I was thus able to organize and confirm my knowledge about the feelings and expectations of individual patients and their family members. I experienced no trouble with the patient/family thereafter."

A randomized controlled trial (RCT) is required to reveal the effect of an intervention. However, the measurement of the effectiveness of an educational intervention is difficult because of the great differences among individuals. The effect sizes presented in this study will help to guide future RCTs in terms of the sample sizes required for this type of research protocol.

In this study, we selected patients with chronic stroke as our study participants. Stroke involves diverse disorders and the sequelae of stroke often persist for prolonged periods of time. When dealing with the rehabilitation of patients with diseases like stroke, it is essential to assist the patients in setting definite goals and motivate them to make proactive or voluntary attempts to minimize their disabilities. The coaching theory may be expected to be useful in the management of stroke with such features. However, we think that this training can be used on clinicians dealing with other kinds of patients with chronic disease. We expect that if clinicians learn the coaching theory and practice communication with patients in an intentional and structured manner, it may be possible to provide adequate assistance to the rehabilitation efforts of patients with chronic disease.

In conclusion, clinicians managing post-stroke outpatients learned intentional and structured use of communication skills in keeping with the principles of coaching theory-based communication skills training and used these during their interviews with community-dwelling post-stroke patients. This training improved the levels of satisfaction, the goal setting and implementation of proactive actions towards achieving those goals, and the HQOL of patients in the chronic post-stroke phase.

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