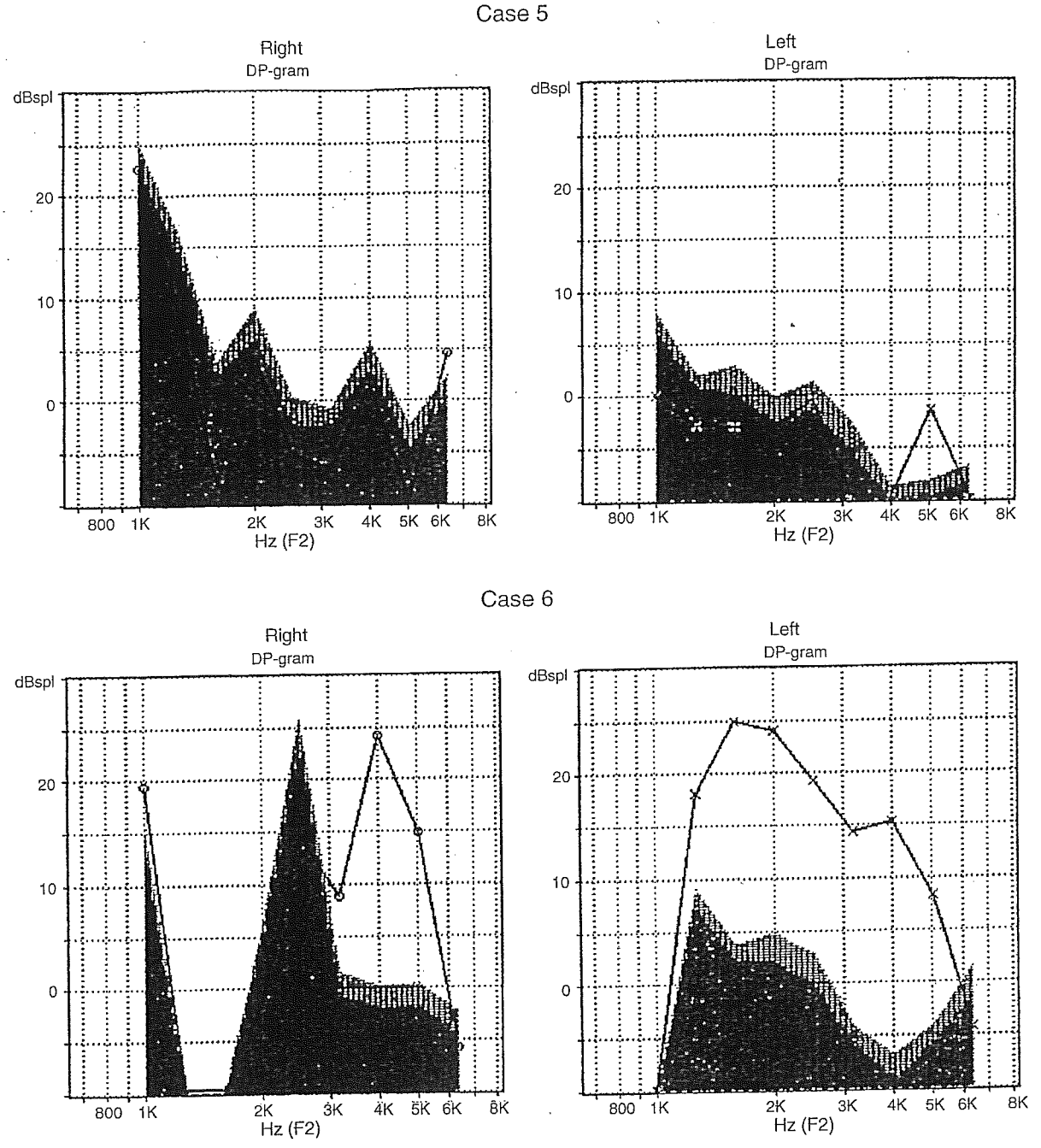

Fig. 1. (*Continued*).

patients have been neglected without auditory training or aural habilitation. However, in 1979, Kaga et al. [8] and Sohmer and co-workers [9] reported the peripheral lesion theory using the results of ABR studies. Although ABR showed peripheral hearing loss patterns in both reports, Kaga insisted that the lesion was located in the cochlea, while Sohmer was convinced the site was in the cochlear nerve. Until now, this problem has remained unsolved, as no reliable and objective means of evaluating cochlear function has been available.

The recent introduction of DPOAE has provided a useful tool for evaluating cochlear function, allowing us to undertake the present study. In our study, behavioral audiometry showed threshold elevation of 50–75 dB in all patients. ABR showed no response in any case at 95-dBHL stimulus. Brainstem lesion patterns [14] (normal wave/with abnormal later comportnents) were not observed. These ABR findings suggest that these patients are likely to have peripheral auditory lesions, particularly at the cochlea or cochlear nerve [8]. DPOAE were totally

Table 2 Theories of lesion location

I	Basal ganglia	Goodhill (1950) Gerrard (1952) Carhart (1967) Suga (1974)
II	Cochlea nerve	Sohmer (1979)
III	Cochlea	Kelemen (1956) Flottorp (1957) Markle (1963) Schuknecht (1974) Hervei (1977) Kaga (1979)

absent in five patients, and present to the normal extent in one patient. DPOAE are considered to reflect function of the outer hair cells [1,2]. Our findings thus indicate that cerebral palsy patients who suffer from hearing loss predominantly display outer hair cell dysfunction [14]. In one case with normal DPOAE, the presence of auditory nerve disease appears likely [15].

In newborn infants, the blood labyrinth barrier is immature, as is the blood brain barrier. Ototoxic drugs and hyperbilirubin are thus easily transferred to the inner ear, and hearing disorders readily occur [16]. In addition, cochlear outer hair cells are susceptible to hypoxia, so infants who experience asphyxia may be likely to undergo damage to the outer hair cells following prolonged hypoxia [16].

Our results suggest that hearing disorders in patients with cerebral palsy due to asphyxia or neonatal hyperbilirubinemia are potentially localized in the cochlea, and hearing aids may prove effective. Emphasis is needed on the fact that early detection of hearing disorders and early aural habilitation using hearing aids will enable optimal development of auditory function.

6. Conclusion

Lesions causing hearing impairment in our six patients with cerebral palsy due to asphyxia or neonatal hyperbilirubinemia potentially include the cochlea particularly the outer hair cells, and cochlear nerve.

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Vestibular-Evoked Myogenic Potentials in Infancy and Early Childhood

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Objective: **Hearing impairment and the often concurrent loss of vestibular function, which is rarely assessed in infants, can both impair sensory integration critical to the development of normal motor coordination. This study demonstrates, for the first time, that vestibular function in infants can be noninvasively assessed using vestibular-evoked myogenic potentials (VEMPs). Our intentions were to demonstrate that VEMPs can be reliably recorded from neonates and to compare neonatal VEMPs with those obtained from normal adults.** ***Study Design:*** **Prospective cohort study.** ***Methods:*** **Myogenic evoked potentials induced by air- and bone-conducted auditory stimuli were recorded from the sternocleidomastoid muscles of 12 normal neonates and 12 neonates with various clinical findings. These included infants with bilateral atresia of the external auditory canals, Treacher-Collins syndrome, and neonates who failed universal neonatal screening.** ***Results:*** **With the exception of one patient with hearing loss, reproducible biphasic VEMPs were recorded from the sternocleidomastoid muscle of all the infants using loud, short tone-burst sounds.** ***Conclusions:*** **The VEMP has characteristics that differentiate it from the postauricular response and the Jaw reflex. The VEMPs were dominant on the side ipsilateral to the stimulated ear. The overall morphology of the neonatal VEMP is quite similar to that of adults. The major neonatal differences are a shorter latency of the n23 peak and higher amplitude variability. Our results suggest that recording of the VEMP in neonates with various audio-vestibular problems provides useful information about vestibular function in this population and may provide information that leads to better care and rehabilitation for neonates at risk of developmental and motor system delay.** ***Key Words:*** **Vestibular-evoked myogenic potentials, VEMP, childhood hearing loss.**

Laryngoscope, **115:1440–1444, 2005**

INTRODUCTION

In humans, intense sound and vibration can produce vestibular reflexes and illusions of movement. In 1958, Geisler and Rosenblith[1] and later Bickford and Cody[2] recorded short latency responses to clicks at the inion in normal subjects and in patients with known lesions of the audiovestibular system. In recent years, it has been demonstrated that loud clicks generate short latency vestibular-evoked myogenic potentials (VEMPs).[3] Pathologic human models have also been used to provide further evidence of vestibular (saccular) origin of the potentials. Colebatch et al.[3] showed that VEMPs were still evident in patients who had a profound sensorineural hearing loss (HL). Yet, VEMPs were abolished in all of their patients who had unilateral vestibular neurectomy. They also reported that VEMPs were abolished in some but not all patients who had unilateral loss of caloric response after vestibular neuritis. They hypothesized that the VEMP is of vestibular origin and that the saccule was probably the acoustically sensitive organ. Murofushi et al.[4] demonstrated a close relationship between the presence of VEMP in patients with acoustic neuromas or vestibular neurolabyrinthitis and the functional integrity of the inferior vestibular nerve. Later, Sheykholeslami and Kaga[5] were able to induce an inion response from patients with labyrinthine defects secondary to streptomycin sulfate toxicity. Finally, Sheykholeslami et al.[5,6] recently confirmed a saccular origin of this short-latency acoustic response, verifying that a saccular acoustic response persists in the human ear and has well-defined frequency tuning curve. Currently, recorded VEMPs are provoked by using a variety of stimuli including clicks,[3] tone bursts,[5] electrical stimulation,[7] bone-conduction sound,[8] and head tapping.[9] VEMPs are gaining more attention as a diagnostic and prognostic test for otologic and neurotologic disorders as well as other general medical disorders such as multiple sclerosis, patients with various neuropathies, and brainstem lesions. However, there have been no re-

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ports addressing the feasibility of recording the VEMP in the difficult to test population of infants and small children, much less addressing the characteristics of this response in neonates.

A great deal of literature exists regarding the causes, pathophysiology, and natural history of acquired and congenital HL. However, despite the intimate relationship between the cochlea and the vestibular system with respect to embryology, physiology, and anatomy, very little can be known about the status of the balance system in infants and very young children with or without deafness. The purpose of this study was to evaluate the feasibility of recording the VEMP in neonates and to introduce it as a rapid, convenient, and noninvasive technique to investigate vestibular system integrity in this age group.

METHODS

Twenty-four subjects consisted of 12 healthy infants and children and 12 patients (5 with atresia of the external auditory canal [EAC], 2 with Treacher-Collins syndrome, and 5 who failed universal and/or follow up neonatal hearing screening tests) who participated in this study. Their ages ranged from 1 month to 12 months (18 boys and 6 girls; average age of 2.3 months). This study was approved by the Institutional Review Board of the Tokyo University Hospital (Tokyo, Japan) and was conducted in accordance with the Principles expressed in the Declaration of Helsinki.

Auditory Physiologic Tests

Full battery auditory tests including behavioral observation audiometry (BOA), conditioned oriented response (COR), distortion product otoacoustic emissions (DPOAE), and auditory-evoked brainstem responses (ABR) were administered to all the subjects.

Vestibular-Evoked Myogenic Potentials

VEMPs were recorded from all subjects. Typical VEMP recording procedures were used with some modifications. Surface electromyography (EMG) activity was recorded using Neuropack Sigma (Nihon, Koden, Japan) by means of Ag/AgCl electrodes. Recording was conducted in a sound-proof room. Averaging techniques were used to record the VEMP from the body of the sternocleidomastoid (SCM) in subjects with the reference (+) electrode placed at the insertion point of the SCM to the sternum. The active electrode was placed over the middle portion of the ipsilateral SCM muscle body. Auditory stimuli consisted of air- or bone-conducted short tone bursts (500 Hz, 95 dB nHL, rise/fall time = 1 ms, plateau = 2 ms) presented to the ears or mastoid processes ipsilateral to the contracted SCM muscle by way of a supra-aural headphone (DR-531, Elega Acous, Japan) or a standard bone-conduction vibrator (BR-41, Rion, Japan). EMG responses from each side were amplified, bandpass-filtered (20 Hz to 2 kHz), and averaged. Analysis time was 100 ms. In normal subjects, the mean peak latency (in ms) and the mean amplitude (in mV) of the two early peaks (p13 and n23) were measured. Subjects were tested in the supine position on a parent's lap with their heads rotated as far as possible to the side contralateral to the stimulated ear. SCM muscles were kept contracted by using the routing reflex in the younger subjects. In older subjects, the contraction was maintained by hanging their head down and turned to contralateral side while we tried to attract their attention by audiovisual stimulations or by parents calling their infant from the opposite direction. Those maneuvers activated the ipsilateral SCM muscles. EMG activity was set as the reference level of the tonic contraction (usually 100-400 mV), and one of the technicians was controlling the subjects to achieve and maintain the contraction at this level throughout the test. The test was halted when the subject's electromyogenic potentials level dropped below 100 mV and restarted after achieving the desired level. Subjects were allowed to relax between recording runs. When the procedure was completed for one side, subjects were given a rest, after which the entire procedure was repeated for the contralateral SCM muscle.

RESULTS

Auditory Assessment Results

All normal subjects passed the screening tests. They were considered normal only if they had DPOAE amplitude of at least 5 dB above the noise level, ABR threshold of 30 dB nHL or better and behavioral tests threshold at 30 dB or better were obtained for all tested frequencies. The test results were compared with the center's age specific normative data. Patients with unilateral atresia had normal hearing in the normal ear as evaluated by DPOAE, ABR, and behavioral tests. Table I shows the auditory and vestibular tests results for all patients.

VEMPs Results

Healthy subjects. In all of the 12 normal subjects, air-conducted sound-evoked biphasic responses (p13 and n23 peaks) were larger in amplitude on the side of the stimulated ear. Figure 1 shows typical response configurations (nonrectified electromyogram) in a 4-month-old

TABLE I.
Results of Auditory and Vestibular Tests used in Study.

	ABR	OAE	BOA	COR	A-VEMP	B-VEMP
Normal ears of patients with Atresia of the EAC (5)	Nor	Nor	Nor	Nor	Nor	NA
Atretic ears of patients with atresia of the EAC (5)	NA	NA	NA	NA	NA	Nor
Patients who failed the universal neonatal hearing screening (10)	Neg	Neg	Neg	Neg	Nor (8 ears)	NA
Patients with Treacher-Collins Syndrome (2)	Neg	Neg	Neg	NA	Nor	NA

Note that the results of the normal subjects are not included in the table. Numbers in the parenthesis represents the number of ears tested.

Nor = normal; NA = not applied; Neg = negative; EAC = external auditory canal; VEMP = vestibular-evoked myogenic potential; A-VEMP = air-conducted VEMP; B-VEMP = bone-conducted-VEMP.

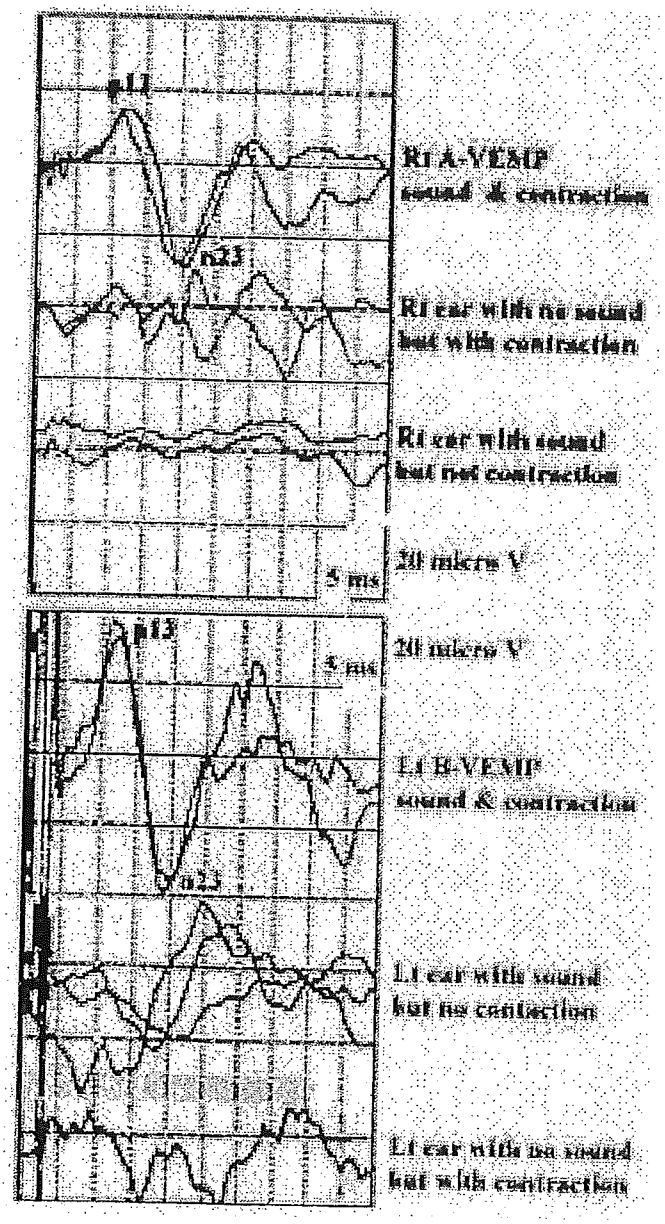

Fig. 1. Vestibular-evoked myogenic potentials (VEMPs) recorded on the sternocleidomastoid (SCM) muscles ipsilateral to the stimulation sides in a 4-month-old boy with normal hearing. Lt indicates electromyographic responses of the left SCM muscle to the left ear stimulation; Rt, electromyographic of the right SCM to the right ear stimulation. Two responses have been superimposed for each condition to demonstrate reproducibility of VEMP in each individual recording. Different traces are demonstrated to exclude the possibility of artifact recordings including trace with sound on and SCM contracted, sound off and contracted muscle, and sound on without SCM contraction.

boy. The amplitude of the first positive-negative response showing a relatively large intersubject difference because the subjects' tonic EMG activities were controlled only in each subject (not all subjects). As described for adults, the latency of the first peak was relatively constant across the subjects with more variation for peak n23. The latency of the peak of n23 was shorter in all neonates compared with adulthood waveform peak latencies. Figure 1 shows different waveforms recorded in different conditions: in the presence of sound without SCM muscle contraction, no sound with SCM muscle contraction, no sound and contractions, and with sound in presence of constant SCM contraction.

Patients

Patients with unilateral atresia of the external auditory canal. Figure 2 shows the bone-conducted VEMPs recorded from the ipsilateral SCM muscle to stimulated mastoid process by way of a bone vibrator. It has been recently shown that loud bone-conduction sounds can produce VEMPs dominantly in the ipsilateral SCM muscle in controls subjects with normal hearing and in patients with various cochleovestibular diseases.[10] These evoked potentials also appear to be generated by a vestibulocollic reflex.[10]

Patients who failed primary or follow-up universal neonatal hearing screening tests. Figure 3 shows air-conducted VEMPs from a patient who failed the universal and follow-up hearing screening tests. We examined five patients in this category that showed no ABR, DPOAE, and BOA responses. Four of the five patients displayed normal VEMPs that consisted of first positive peak (p13) followed by a second negative wave (n23), and only one patient had no VEMPs.

Patient with Treacher-Collins syndrome. Figure 4 represents B-VEMP responses recorded from a 2-month-

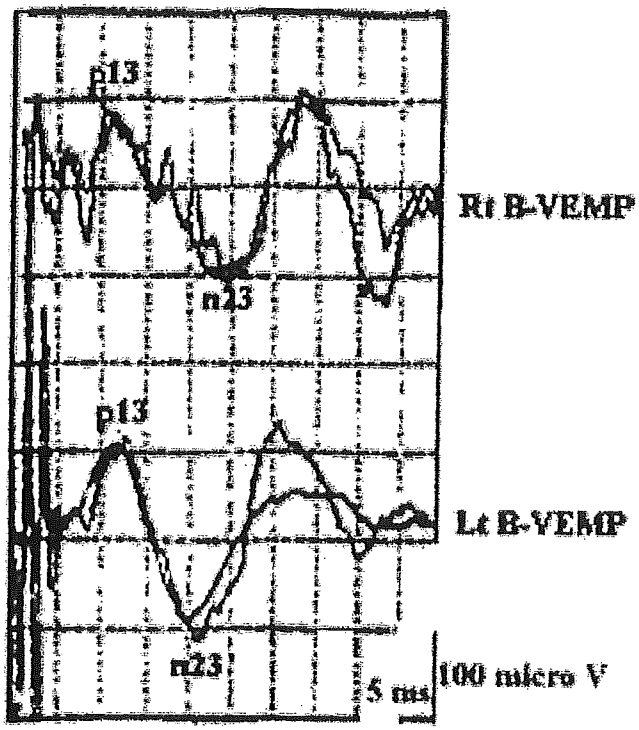

Fig. 2. Bone-conducted evoked myogenic potentials recorded from a 2-month-old patient with bilateral atresia of the external auditory canal (EAC). Traces Lt and Rt correspond to the stimulated sides by way of a bone-conduction vibrator on the mastoid processes. Two recordings have been superimposed for each trace to illustrate reproducibility of responses. Traces consisted of P13 and N23 potentials.

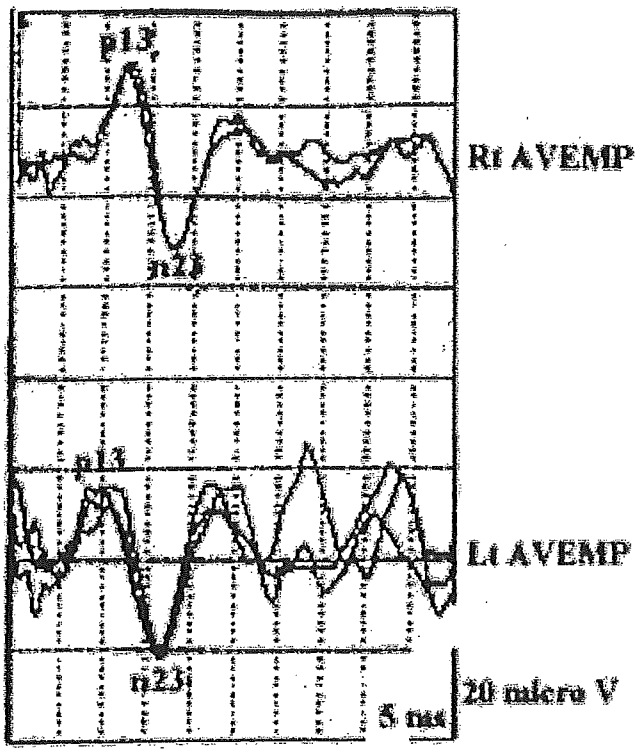

Fig. 3. Air-conducted vestibular-evoked myogenic potentials (A-VEMPs) recorded from a 3-month-old patient who failed primary and secondary hearing screenings. Lt, electromyographic responses of the left sternocleidomastoid (SCM) muscle to left ear; Rt, electromyographic responses of the right SCM to right ear stimulation.

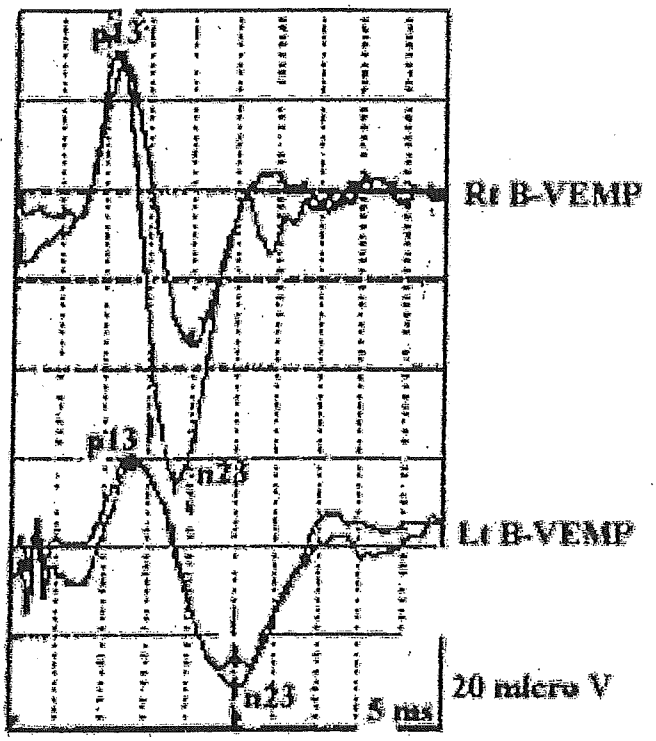

Fig. 4. Bone-conducted vestibular-evoked myogenic potentials (B-VEMPs) recorded from a 2-month-old patient with Treacher-Collins syndrome. Patient suffered from bilateral atresia of external auditory canal (EAC) in addition to other facial anomalies. Traces Lt and Rt correspond to the stimulated sides by way of a bone conduction vibrator on the mastoid processes. Two recordings have been superimposed for each trace to illustrate reproducibility of responses.

old female infant with Treacher-Collins syndrome manifested, in part, by bilateral atresia of the EAC. The VEMPs latency and amplitude were the same in comparison with earlier reports.[8,10]

DISCUSSION

In this study, we have shown that brief, intense sound stimuli can evoke reproducible, short-latency alternations in EMG activity in the SCM muscle, the VEMP, in infants and very young children regardless of their hearing status. All normal subjects, the normal ear of patients with atresia of the EAC, and 8 of the 10 ears with no ABR, OAE, and BOA or COR responses showed normal biphasic VEMP waveforms to loud air-conducted sound stimuli. Ears with atresia of the EAC showed the same biphasic response to bone-conducted sound stimuli, which has been shown to be of vestibular origin.[10] Neonatal VEMP responses were variable in amplitude, with consistent timing for peak p13 but shorter peak n23 latencies in comparison with adult VEMP peaks latencies.

Evoked VEMPs have characteristics that differentiate them from the postauricular responses and the Jaw reflex. Both of those reflexes appear to depend on cochlear afferents and are evoked bilaterally after stimulation of one ear. Although bone-conducted sound stimulates both ears acoustically, B-VEMP could be record dominantly on the ipsilateral SCM muscle to the stimulated ear.[8,10] The VEMP is also a separate phenomenon from the physiologic startle reflex to sound, which has a rapid habituation, a prolonged refractory period, and a much longer latency. In contrast with the discussed reflexes, the VEMP and its amplitude are dependent on the level of tonic ipsilateral SCM muscle activation. As shown in Results (Fig. 1), we were unable to evoke any reproducible myogenic potential without sufficient SCM muscle contraction, even in the presence of loud sound stimuli. This also was true for subjects who contract their SCM muscles in the absence of sound stimuli. We assumed that these responses are of vestibular origin similar to adult responses and that they are not artifactual or a part of the discussed reflexes.

Difficulties that we experienced during VEMPs recording in this study were 1) difficulty of maintaining EMG activity levels at a desired level for the period of data acquisition, which required several interruptions of the recording session and restarting data collection after achieving the same level of muscle contraction, 2) recording sessions that were much longer for infants partly because of the difficulty described above and partly because of the time necessary to educate parents and have their help during the test period, and 3) and the necessity of having a technician in the room for positioning and controlling the muscle contraction level.

The anatomic contiguity of the vestibular labyrinth, the cochlea, and related structures often puts vestibular function at risk for compromise by the same etiologies and insults known to impair cochlear function. Hearing im-

pairment is frequently accompanied by a disruption in balance and orientation functions, but this latter function is only rarely assessed in infants and young children. Since the 1950s, many studies have been performed with the aim of establishing the incidence of vestibular pathology in the hearing-impaired or deaf population. Approximately 20% to 40% of deaf children manifest significant hypo- or areflexia of a horizontal semicircular canal (HSSC).[11–13] These studies have used various methods to test the HSSCs function. They measured reflexive horizontal eye movements in response to rotation of the child's head or caloric irrigation. Such tests do not evaluate other semicircular canals or the otolithic organs, which may have more influence on the development of postural control than the horizontal canals.

Unlike adults, the most common presentation of peripheral vestibular loss in young children is delayed motor development and loss of postural control.[12] Vestibular loss can impair the process of integration of sensory stimuli critical to the normal development of motor coordination and locomotion.[14] The vestibular system is also responsible for maintenance of visual acuity during active head movements. Vestibulospinal influences contribute both to the posture adopted by an individual and maintenance of that posture despite postural perturbations. Vestibular function loss puts children at risk of significant vestibuloocular interaction impairment during normal activity and maintaining equilibrium in dark environments. Therefore, recording the VEMP to assess the function of the otolithic organs in these age groups gives the clinician information about vestibulocollic function. VEMP testing will complement caloric testing and tests of AVOR and gives a more complete picture of infants' vestibular and motor functions.

Hearing and vestibular assessments of infants and very young children are a challenging and often frustrating experience for clinicians and audiologists. Infants and young children have little or no attention span and limited ability for oral communication. Standard vestibular testing and the assessment of spontaneous nystagmus, headshaking nystagmus, and some other vestibular tests can be performed with older children if the testing environment is adapted to the special needs of those children. These tests are not feasible in infants or very young children because of the lack of the child's attention and focus. Some of the vestibular tests require parents or a technician to be present to hold the child during the entire test session. As a result, some technical issues arise when the child is held by another person during tests. For example, in rotational testing, the axis of rotation must be carefully monitored, and in some circumstances a magnetic coil or an IR-video system may be used for monitoring of the head rotation relative to chair rotation. In this study, we demonstrated that VEMPs could be evoked in the neonatal population. The test is feasible and relatively easy to perform without any necessity to alter overall test recording methodology or data acquisition settings.

We conclude that the VEMP can be used as an objective test in infants and very young children to explore the vestibular system and sacculocollic pathways.

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Ebselen prevents noise-induced excitotoxicity and temporary threshold shift

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Abstract

This investigation tested the hypothesis that a noise-induced temporary threshold shift (TTS) can be attenuated by a peroxynitrite scavenger, ebselen (2-phenyl-1,2-benzisoselenazol-3(2H)-one). Guinea pigs received an oral dose of the vehicle or 10 mg/kg ebselen 1 h before exposure to 115 dB SPL 4-kHz octave band noise for 3 h. In controls, auditory brainstem response (ABR) thresholds increased by 25–45 dB immediately after noise and returned to pre-exposure baseline thresholds 7 days later. Ebselen eliminated this ABR threshold shift following noise exposure. In controls, swelling of the afferent dendrites beneath the inner hair cells was evident immediately after noise, whereas ebselen significantly reduced this pathology. These findings suggest that scavenging peroxynitrite can attenuate noise-induced excitotoxicity and, thereby, TTS.

Keywords: Guinea pig; Noise-induced hearing loss; Nitric oxide; Peroxynitrite

After exposure to intense sound, auditory thresholds can be elevated permanently, or temporarily for minutes, hours or days, depending on the parameters of acoustic overstimulation. These two phenomena, permanent (PTS) and temporary threshold shift (TTS), are dependent on mechanisms not fully understood [1,9,18]. At least two different mechanisms have been proposed for PTS: a direct mechanical trauma and a metabolic overstimulation of the cellular elements of the organ of Corti (OC). Direct mechanical trauma may damage the delicate stereocilia of the sensory hair cells or, with higher stimulation intensity, the structural integrity of the OC and basilar membrane. Intense noise exposure may also overdrive the pathways that are responsible for maintaining OC homeostasis, thus leading to metabolic changes that compromise the system. Metabolic overstimulation may be associated with biochemical traumatic processes, most notably the generation of reactive oxygen species (ROS), which may serve as triggers for necrosis or apoptosis [4,10].

Several mechanisms proposed for TTS include synaptic fatigue, metabolic fatigue of either stria vascularis or the hair cells, and changes in cochlear blood flow. Histopathological changes reported in TTS include disarrayed, splayed, fused, collapsed, or floppy stereocilia of the hair cells, buckling of the pillar bodies, and swelling of the afferent nerve terminals [9,16,17]. Postsynaptic damage in the afferent dendrites beneath the inner hair cells (IHCs) is an important component of noise-induced hearing loss [15–17], and synaptic repair mechanisms are thought to be involved in restoring function after acoustic trauma [15,17].

It has been shown that the IHCs release glutamate as a neurotransmitter activating the afferent dendrites [11] and that excess release of glutamate due to intense noise exposure causes excitotoxicity in the afferent dendrites [14]. Excess synthesis of nitric oxide (NO), which can react with $O_2^{\bullet -}$ to form highly aggressive peroxynitrite ($ONOO^-$) radicals, is known to play an important role in glutamate excitotoxicity [3,6]. Glutamate and NO can act independently or sequentially to cause excitotoxicity. NO may induce glutamate release by neurons, which then stimulates NMDA receptors and triggers excitotoxicity [8]. Conversely, when NMDA receptors are activated, Ca^{2+} influx stimulates NO production through calcium- and calmodulin-dependent neuronal nitric oxide synthase, potentially leading to neuronal death [3]. The

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toxic effects originally attributed to NO are now considered to be mediated mostly by the compound peroxynitrite [2]. Thus, in the present study, we tested the hypothesis that ebselen, a glutathione peroxidase mimic and a scavenger of peroxynitrite, attenuates noise-induced excitotoxicity and TTS.

Twenty-four male albino guinea pigs (250–350 g), with normal auditory brainstem response (ABR) thresholds at 2, 4, 8 and 16 kHz, were randomly divided into vehicle-treated ($n = 14$) and ebselen-treated experimental groups ($n = 10$). These animals received an oral dose of 0.25 ml of 99% chloroform solution alone (vehicle) or containing 10 mg/kg ebselen one hour before exposure to noise. Ten mg/kg of ebselen was selected because this dose most effectively attenuates PTS in guinea pigs [13]. The animals were subjected to a 3-h noise exposure (115 dB SPL, 4-kHz octave band noise) generated within a single-walled, sound-deadened chamber. Two separately caged animals were tested at one time and allowed to move freely during exposure. The sound chamber was fitted with speakers driven by a noise generator and power amplifier. A 0.5-in. Bruel and Kjaer condenser microphone and a fast Fourier transform analyzer were used to measure and calibrate the sound level at various locations within the chamber to ensure stimulus uniformity within ±1 dB.

Five animals in each group underwent ABR measurements immediately and 1, 3, 7, and 14 days after noise exposure to assess the effect of ebselen on TTS. The method of ABR measurement has been described previously [13]. In brief, animals were anesthetized with a mixture of xylazine hydrochloride (10 mg/kg, i.m.) and ketamine hydrochloride (40 mg/kg, i.m.), and needle electrodes were placed subcutaneously at the vertex (active electrode), beneath the pinna of the measured ear (reference electrode), and beneath the opposite ear (ground). The stimulus duration was 15 ms; the presentation rate, 11/s; and the rise/fall time, 1 ms. Responses of 1024 sweeps were averaged at each intensity level (5 dB steps) to assess threshold. Threshold was defined as the lowest intensity level at which a clear reproducible waveform was visible in the trace.

Four animals given vehicle alone were euthanized under deep anesthesia with xylazine hydrochloride and ketamine hydrochloride 7 days after noise exposure to assess hair cell damage. Two animals unexposed to noise served as controls. The cochleae were perfused intrascalarly with 4% paraformaldehyde and immersed in the same fixative overnight. The surface of the organ of Corti was stained with rhodamine phalloidin and each turn of the cochlea was observed under fluorescent microscope as previously described [13]. The influence of ebselen on noise-induced morphological changes in the cochlea was examined in the remaining animals ($n = 5$ in each group). These animals were deeply anesthetized with a mixture of xylazine hydrochloride and ketamine hydrochloride immediately after the termination of noise exposure. The left bulla was then exposed and the perilymphatic spaces perfused for 10 min with 2% paraformaldehyde in 2.5% glutaraldehyde. The animals were then sacrificed and the left cochlea quickly removed, immersed in the same fixative for 24 h, and decalcified in 10% ethylenediaminetetraacetic acid for 14 days. The specimens were post-fixed in 1% osmium tetroxide for 2 h, dehydrated in a graded series of ethanol, and embedded in epoxy resin. Ultra-thin sections were obtained from the very upper part of the basal turn corresponding to the region most responsive to frequencies in the range of 4–6 kHz and observed under transmission electron microscope (TEM). We focused on the histological changes in the stria vascularis, the hair cells and supporting cells, and the afferent dendrites beneath the IHCs. Because the extent of swelling of the afferent dendrites was obviously different between vehicle- and ebselen-treated animals, we compared the area (μm^2) of the swollen dendrites in the two groups. In each animal, a total of 10 sections that contained the nucleus of different IHC were collected. From these, five sections were chosen randomly for measuring and statistical analysis by a blinded technician who did not know the aim of the current study. The images of these sections were captured using a scanner, the area of the swollen dendrites measured using Adobe Photoshop image analysis software, and the mean of the areas calculated. Student's t-test was used for statistical analysis.

The experimental protocol was approved by the University Committee for the Use and Care of Animals at the University of Tokyo and conforms to the National Institute of Health Guide for the Care and Use of Laboratory Animals.

ABR thresholds before noise exposure were essentially equivalent among all animals. In vehicle-treated controls, ABR thresholds were moderately increased immediately after noise; the threshold shifts were approximately 25 dB at 2 kHz and 45 dB at 4, 8, and 16 kHz. The ABR thresholds then showed gradual recovery, returning to pre-exposure baseline thresholds 7 days later, indicating that the noise exposure induced a TTS. In contrast, ebselen-treated animals showed virtually no ABR threshold shifts after noise (Fig. 1). The ABR thresholds shifts immediately after noise were significantly different ($p < 0.001$) at all frequencies measured between control and ebselen-treated animals. The IHCs and outer hair cells (OHCs) were well preserved in both vehicle-treated noise-exposed animals and unexposed controls; the number of missing OHCs in the lower two turns was 6.4 ± 2.5 in the former and 4.9 ± 4.4 in the latter, suggestive that the noise used did not cause hair cell death.

In controls that were euthanized immediately after noise, the OC in the upper basal turn showed numerous swollen dendrites beneath the IHCs. In contrast, pathological changes were quite limited in ebselen-treated animals (Fig. 2). The mean area of swollen dendrites was significantly smaller ($p < 0.01$) in ebselen-treated animals compared to controls. In neither controls or ebselen-treated animals sacrificed immediately after noise exposure was there obvious evidence of other pathological changes reported to be correlated to TTS, such as edema or vasoconstriction in the stria vascularis, buckling of the pillar bodies, or fusion or loss of stereocilia.

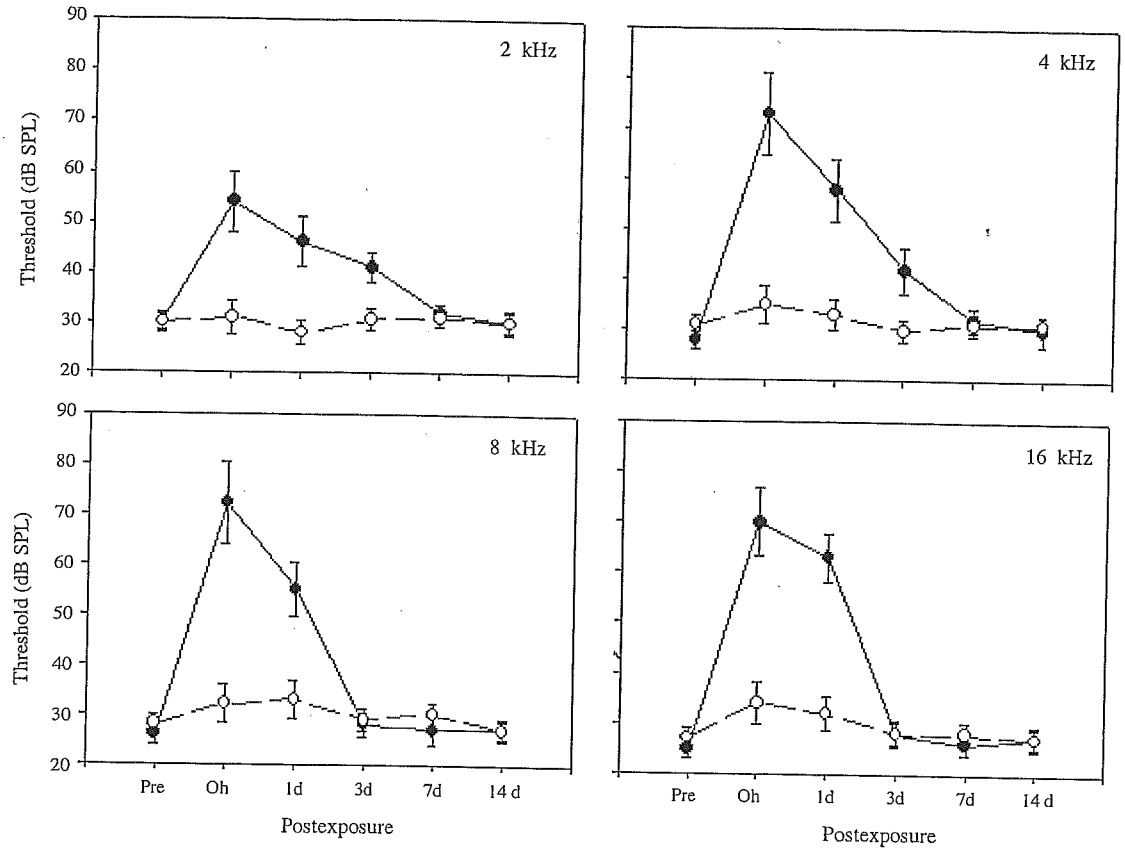

Fig. 1. Thresholds of auditory brainstem response (mean ± S.D.) measured before and immediately and 1, 3, 7, and 14 days following noise exposure in vehicle-treated controls (●) and ebselen-treated animals (○).

The current study shows that ebselen virtually prevents noise-induced TTS under conditions where vehicle-treated controls developed a TTS of approximately 25–45 dB. TEM observation revealed that immediately after noise, the afferent dendrites beneath the IHCs were severely swollen in control animals, whereas such pathological changes were significantly reduced in ebselen-treated animals. Other pathological changes were not evident in either controls or ebselen-treated animals. Because we did not examine otoacoustic emissions or use scanning electron microscopy, it is possible that functional and/or subtle anatomical changes in the regions other than the afferent dendrite, especially the OHCs, were missed. However, the above findings indicate that ebselen can attenuate noise-induced changes at least in the afferent dendrites beneath the IHCs and thereby TTS.

Using fluorescent dye 4,5-diaminofluorescein diacetate, it has been shown that in the normal guinea pig cochlea, NO is present in the afferent nerves and their putative endings near the IHCs, putative efferent nerve endings near the OHCs, the IHCs and OHCs, and blood vessels [20], and that inducible NO synthase (iNOS) is expressed in cochlear nerve fibers, as well as in hair cell stereocilia, Hensen's cells, and the stria vascularis [19]. It has also been reported that, when exposed to broadband noise (3 h/day at 110 or 120 dB SPL) for three consecutive days, NO concentration is increased in the perilymph, NO fluorescence becomes more intense in the IHCs and OHCs [21], and iNOS fluorescence signals becomes more intense in cochlear tissues compared to unexposed controls [19]. In addition, it has been reported that cochlear perfusion with kainic acid (KA), a conformationally restricted analog of glutamate known to have excitotoxic effects on spiral ganglion cells, causes significant elevation of thresholds of the cochlear nerve compound action potential and that this threshold shift is significantly reduced by pretreatment with nitroindazole, a competitive inhibitor of neuronal NOS [6]. The toxic effects originally attributed to NO are now regarded to be mediated mostly by the compound peroxynitrite [2]. Considering these findings, it is likely that ebselen attenuated noise-induced excitotoxicity and thereby TTS, by scavenging peroxynitrite formed by the reaction between noise-induced $O_2^{\bullet -}$ and NO.

It may also be possible that ebselen attenuated TTS because of its antioxidant property. It has been shown, however, that topical application of R-PIA, which increases endogenous antioxidant levels, to the chinchilla cochlea facilitates the recovery of hearing function 4 days after noise exposure but does not attenuate initial noise-induced threshold shifts [5]. Ohinata et al. [10] have shown that lipid peroxidation (8-isoprostane formation) in the OC induced by intense noise is significantly attenuated by *N*-methyl-D-aspartate (NMDA) receptor antagonists and anti-oxidant *N*-acetylcysteine, but not by NOS inhibitor, L-*N* (omega)-nitroarginine methyl

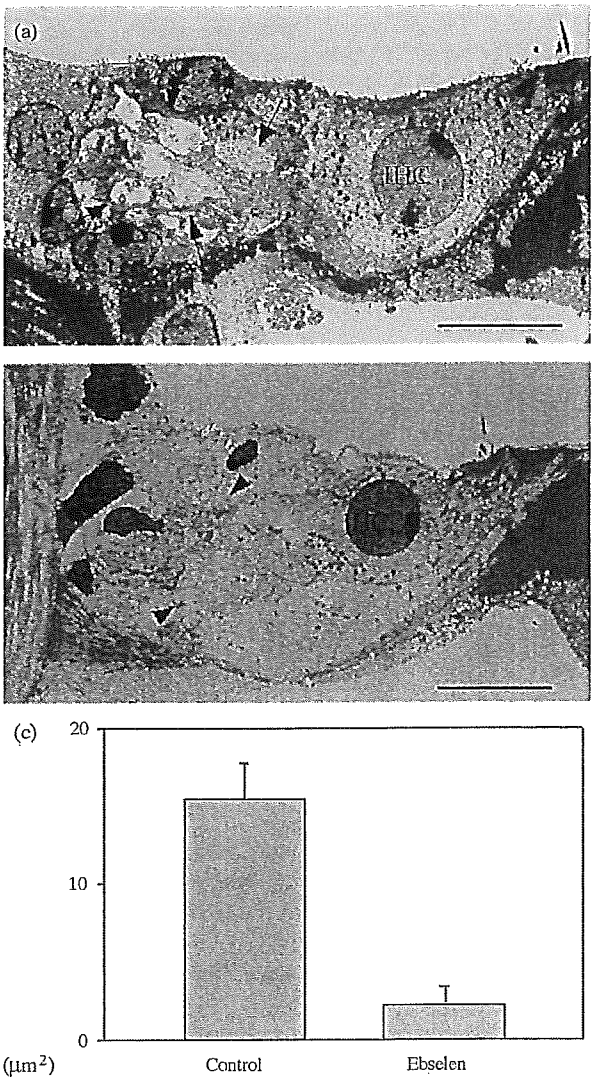

Fig. 2. Typical transmission electron microscopic findings in the medial side of the organ of Corti immediately following noise exposure in vehicle-treated controls (a) and ebselen-treated animals (b). The afferent dendrites are markedly swollen in vehicle-treated controls (arrows) but relatively normal in ebselen-treated animals (arrowheads). The bar indicates 10 μm; IHC: inner hair cell. (c) The mean ± S.D. of areas (μm^2) of the swollen afferent dendrites in the vehicle-treated control and ebselen-treated animals.

ester. Therefore, it is unlikely that ebselen's protective effect against TTS is provided chiefly by scavenging ROS or reducing ROS formation in the OC.

In conclusion, the current study shows that ebselen can prevent noise-induced excitotoxicity and thereby TTS. This prevention likely reflects ebselen's scavenging of peroxynitrite, thus supporting the view that peroxynitrite, at least in part, mediates excitotoxicity induced by intense noise. It has previously been shown that ebselen can also attenuate PTS in guinea pigs [13] and rats [7]. Since ebselen has already been used in humans clinically to treat ischemic stroke with few or no side effects [12], our findings reinforce the potential clinical utility of ebselen to prevent and/or treat noise-induced hearing loss in humans.

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新生児聴覚スクリーニングで難聴が疑われた乳児の聴覚評価

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要旨：新生児聴覚スクリーニングで両耳 refer となり，ABR で両側難聴と診断を受けた15症例に対し聴覚閾値の推移の把握を目的に BOA および COR を行い，周波数毎の閾値の変化とそれに影響をおよぼすと考えられる要因を検討した。

重度，高度および中等度難聴すべての聴力程度で聴力閾値の改善がみられたが，中等度難聴で改善傾向が顕著であり，補聴器の選択・適合等の初期介入には十分な配慮が必要と考えられた。また，重度難聴で ABR 無反応あっても BOA，COR で反応が得られる場合がほとんどであるため聴覚評価を繰り返しカウンセリングには十分時間をかけることが必要と考えられる。

今回，難聴児であっても聴覚の発達にともなう閾値の改善が認められ，同時に検査閾値は検査月齢に依存していることが示唆された。したがって，聴覚評価は聴覚の発達および身体発達を考慮し慎重に行うことが重要である。

－キーワード－
新生児，聴覚スクリーニング，BOA，COR，聴覚発達

1．はじめに

新生児聴覚スクリーニングが欧米のみならず本邦でも導入され，新生児期に発見される難聴児は今後着実に増加することが予想される。スクリーニング検査の効果は，refer 後の対応が確実かつ円滑に実施されるかどうかにおおきく左右されるのは言うまでもない。

新生児聴覚スクリーニングで難聴を疑われた児の精密検査は，難聴の診断のみならず補聴器の選択・適合，療育プログラムの作成および保護者へのカウンセリングといった初期介入にとって重要である。乳児期の精密検査には，聴性脳幹反応(auditory brainstem response，以下 ABR)が主に使用されるが，現在でも周波数情報を得るには聴性行動反応聴力検査(behavioral observation audiometry，以下 BOA)および条件詮索反応聴力検査（conditioned orientation response audiometry，以下 COR）は乳児期の聴覚評価にとって重要な位置を占める。

乳児期の聴覚評価には，聴覚の発達による閾値の改善を考慮する必要があることは健聴児では報告されている。一方難聴児では，療育の観点から閾値変化を乳児期に把握する意義は大きいと考えられるが，難聴児の出現率や発見時期の関係から発達にともなう閾値変化の経過を観察することは容易でなく，1歳児以降の BOA の報告[1)]はあっても乳児期ではほとんどないと言ってよい。今回，新生児聴覚スクリーニングで両耳 refer となり，ABR 検査で両側難聴と診断を受けた症例の聴覚閾値の年齢による変化の把握を目的に，BOA および COR の閾値を周波数毎に比較検討した。

2．対象と方法

自動 ABR による新生児聴覚スクリーニングで両耳 refer となり，診断用 ABR 検査で難聴が疑われ岡山かなりや学園に来園した症例のうち，発達に遅れが

認められなかった15例を対象とした。BOAは3カ月以内に防音室内でスピーカを通した音場の定量的BOAおよび楽器音による定性的BOAを，CORは6カ月以降に防音室内でスピーカを通して言語聴覚士が行った。閾値の音圧は騒音計リオンNL-06で測定した。

3．結　果

初診時年齢は全例生後3カ月以内で，聴力程度はABR検査の結果により分類した。両側無反応の7例を重度難聴とし，以下高度難聴2例，中等度難聴6例で男8例，女7例であった。15例中難聴のリスク因子を持つものは3例で家族性の因子を持つ重度難聴2例，母体の子宮内感染症による聴器毒性薬剤使用歴のある中等度難聴の1例であった（表1）。

重度難聴では7例中4例で定量的および定性的BOAのいずれでも反応が認められなかったが，他の3例では250Hz，500Hz，1000Hzで反応があり，楽器音に対しても眼瞼反応がみられた。2000Hzで反応が得

表1　症例の概略

症例	聴力程度	初診年齢	ABR		リスク因子
			右	左	
1	重度	1ヶ月	90—	90—	＋
2		3ヶ月	100—	100—	—
3		0ヶ月	90—	90—	—
4		1ヶ月	115—	115—	—
5		3ヶ月	115—	115—	—
6		2ヶ月	110—	110—	—
7		2ヶ月	95—	95—	＋
8	高度	0ヶ月	90—	80＋	—
9		0ヶ月	80＋	80＋	—
10	中等度	1ヶ月	70＋	60＋	＋
11		2ヶ月	70＋	70＋	—
12		1ヶ月	80＋	70＋	—
13		0ヶ月	60＋	60＋	—
14		0ヶ月	60＋	60＋	—
15		1ヶ月	80＋	70＋	—

ABR
＋：反応あり
—：反応なし

表2　定性的BOAの反応と様式

症例	聴力程度	楽器			聴性反応の様式
		タイコ	シンバル	スズ	
1	重度	—	—	—	
2		＋	＋		目が動く
3		＋	＋	—	まばたきをする
4		—	—	—	
5		＋	＋		目を開ける
6		—	—	—	
7		—	—		
8	高度	＋	＋	＋	まばたきをする
9		＋	＋	＋	目が開く、動きが止まる、ビクッとする
10	中等度		＋		目が動く、ビクッとする
11		＋	＋		目が動く、ビクッとする
12		＋		＋	目を開く
13		＋	＋	＋	目が動く、体の動きが止まる
14		＋	＋	＋	目が動く、ビクッとする
15		＋	＋	＋	まばたき、赤くなる、ビクッとする

＋：反応あり
—：反応なし

表3　重度難聴児のBOAとCOR

症例	検査年齢	BOA(dBSPL)					検査年齢	COR(dBSPL)				
		250	500	1000	2000	4000		250	500	1000	2000	4000
1	2ヶ月	102—	112—	108—	101—	96—	9ヶ月	92	98	105	100–	90–
2	3ヶ月	93	95	104	91–	90–	6ヶ月	99	97	99	101–	93–
3	1ヶ月	102	108	110	101	92—	8ヶ月	108	103	100	100	100–
4	1ヶ月	104–	102–	100–	91–	90–	7ヶ月	106	103	105–	91–	90–
5	3ヶ月	91	105	106	97–	92–	6ヶ月	100	107	100	100–	94–
6	2ヶ月	104–	110–	110–	107–	103–	9ヶ月	109–	108–	100–	100–	100–
7	3ヶ月	106–	102–	104–	93–	85–	7ヶ月	108	108	105	100–	100–

—:反応なし

表4　高度難聴児のBOAとCOR

症例	検査年齢	BOA(dBSPL)					検査年齢	COR(dBSPL)				
		250	500	1000	2000	4000		250	500	1000	2000	4000
8	1ヶ月	98	80	80	70	80	8ヶ月	89	88	80	73	72
9	1ヶ月	88	81	81	72	63	6ヶ月	80	79	65	67	55

表5　高度難聴児の閾値の変化量

症例	周波数毎の変化量(dBSPL)					変化量の平均
	250	500	1000	2000	4000	
8	9	−8	0	−3	8	1.2
9	8	2	16	5	8	7.8

られたのは症例3のみで4000Hzでは7例全例無反応であった。しかし，CORではBOAで反応が得られなかった症例1，4，7の3例に反応が認められ，CORでも反応が得られなかったのは症例6のみであった。6例全例で反応が得られた周波数は250Hz, 500Hzで，1000Hzで反応が得られたのは5例であった。しかし，2000Hzで反応が認められたのは1例のみで，4000HzではBOAと同じく全症例に反応が得られな

表6　中等度難聴児のBOAとCOR

症例	検査年齢	BOA(dBSPL)					検査年齢	COR(dBSPL)				
		250	500	1000	2000	4000		250	500	1000	2000	4000
10	1ヶ月	96	94	82	71	67	7ヶ月	66	56	60	54	54
11	2ヶ月	89	104	90	91	89	7ヶ月	73	69	65	63	62
12	1ヶ月			90	72	64	8ヶ月	80	58	55	53	46
13	3ヶ月	74	62	53	52	49	8ヶ月	64	56	52	51	43
14	2ヶ月	87	80	82	79	72	9ヶ月	72	60	64	54	51
15	3ヶ月	65	66	66	68	63	6ヶ月	67	65	56	58	56

表7　中等度難聴児の閾値の変化量

症例	周波数毎の変化量(dBSPL)					変化量の平均	
	250	500	1000	2000	4000		
10	30	38	22	17	13	24	*
11	16	35	25	28	27	26.2	*
12			35	19	18	24	*
13	10	6	1	1	6	4.8	
14	15	20	18	25	21	19.8	*
15	−2	1	10	10	7	5.2	
平均	13.8	20	18.5	16.7	15.3		
著変例平均	20.3	31	25	22.3	19.8	*著変例	

かった（表2，表3）。

高度難聴では2例とも，定量的および定性的BOA，CORですべての周波数で反応が得られ，1例でCORでは閾値の改善傾向がみられた。ABRで一側に重度難聴が疑われる症例では，閾値の改善がほとんどみられなかった（表4，表5）。

中等度難聴の6例ではBOA，CORともにすべての周波数で反応が得られ約14dB－20dBの閾値改善が認められた。6例中4例はBOAで高度難聴が疑われたが，CORではすべての周波数で約20dB－30dBの顕著な閾値改善がみられた。改善した閾値の周波数別の平均値を値の大きい順に示すと，6例では500Hzで20.3dB，以下1000Hz18.5dB，2000Hz16.7dB，4000Hz15.3dB，250Hz13.8dBであった。著変例4例の平均値でも改善した周波数の順はほぼ同じであった。BOAで良好な反応が得られた症例13，15ではCORの閾値は大きな改善がみられなかった（表6，表7）。症例13，15のBOAの初回検査月齢は3カ月であり，

顕著に改善が見られた他の4例は月齢が1ないし2カ月であった。

4．考　察

乳幼児の聴覚スクリーニングは歴史的にいろいろな方法が検討されてきたが[2]，近年自動ABRやOAEというスクリーナーの開発により新生児期でのスクリーニングが可能になり，スクリーニング後の精密検査が重要な意味を持ってきた。

乳児期の聴覚評価にはABRの出現以前から発達年齢に合わせた聴覚検査法が開発されてきた[3]。特に，BOAおよびCORという行動観察による検査は周波数特異性が乏しいABR検査と異なり周波数毎の閾値の測定が可能であるため，療育効果の評価にとっても有用である。しかし，検査閾値の判断は，検査時の諸条件にもよるが，それ以上に発達年齢による影響が避けられず，閾値の比較評価には慎重さが要求される[4,5]。特に，新生児期とその後の3カ月は，モロー反射，耳性眼瞼反射，また音がすると泣く，泣き止む，静まる，顔をしかめるなどの驚愕反射が指標となるため，閾値の推定は容易ではなく[6,7]，閾値より最小反応値という用語の検討もされている[8]。

聴力正常児の聴覚の発達による閾値の改善については，Northernら[3]により刺激音による反応レベルに違いがあるが，ノイズメーカを音源とした場合4カ月までは50－60dBSPL，4カ月から7カ月は40－50dBSPL，7カ月から9カ月は30－40dBSPL，9カ月から13カ月は25－35dBSPLと年齢毎の乳幼児期の基準値が報告されている。本邦でも加我ら[9]は，月齢1－3カ月ではBOA，4カ月－2歳ではCORを実施し，1000Hzと2000Hzの平均値では生後1カ月で90dB，6カ月で45dB，12カ月で30dBと聴覚閾値が変化し，特に，2カ月から3カ月にかけて急激な閾値の改善がみられると報告している。同様に，鈴木ら[4]も新生児の反応閾値は反応にばらつきが大きく，はっきりとした反応を観察するには80－90dBHLの刺激音が必要としている。

我々の報告でも中等度難聴児で検査月齢に差はあるものの，発達に伴い，6例中4例に20dBから30dBの閾値の改善がみられ，難聴児であっても中等度より軽い難聴であれば発達に合わせて顕著な閾値の改善が認められた。検査月齢が1ないし2カ月の症例の閾値改善が顕著であったことから判断して，難聴児であっても加我らが示した2カ月以降に閾値が改善することが示唆され，療育上重要な指標となると考えられる。また，今回は250Hzから4000Hzまでのすべての周波数で変化の幅には差が見られたものの閾値の改善が認められた。したがって，諸検査で中等度難聴と推定される場合は，初期介入時に閾値が改善することを考慮したカウンセリングおよび補聴器の選択・調整を行うことが妥当である。

周波数毎の改善傾向では，著変例で500Hzが4000Hzに比し10dB以上良かった。Wilsonら[10]は500Hz，1000Hz，4000Hzのワーブルトーン使用した音場検査で6－7カ月児の平均値はそれぞれ17.5dBSPL，17.5dBSPL，16.3dBSPLまた10－90パーセンタイルの範囲でもそれぞれ10dBと差がみられなかったとしているが，難聴児の場合，高音漸傾型が多く，高音の閾値上昇で反応が得られにくいことから今回の結果は十分予想されることである。

今回，高度難聴と重度難聴でも閾値の改善傾向がみられたものの，聴力程度を考慮すれば中等度難聴のような改善が期待できないのは当然であろう。Karikoskiら[1]も高度から重度難聴の評価にはBOAの有効性は限定されると述べているが，ABRが無反応であった重度難聴児でも音場検査の250Hz，500Hz，1000Hzおよび楽器によるBOAで反応が得られる場合があり，またCORが可能となった時点でほとんどのケースで1kHz以下に反応が認められたことを考慮すればABRと合わせてBOA，CORによる検査を実施することの意義はスクリーニング後の聴覚の評価では大きいと考えられる[11]。それ以上にBOAあるいはCORで得られた周波数毎の閾値は精密検査後の補聴および療育目標の設定に貴重な情報をもたらす。また，難聴ということに大きな不安を抱いている保護者に対し，BOAおよびCORで音に対する反応を見せることで，聴覚活用の可能性を示すことにより，保護者を安心させ難聴の理解および障害の受け入れのきっかけになることは臨床上よく経験することでありその価値は少なくない[12,13]。

閾値の改善には聴覚伝導路の発達が関わるとされるが，今回の結果からも難聴児でも同じ現象が起こると考えられる。また条件付けによらないBOAと条件付けによるCORでは反応の再現性や閾値のばらつ

きに大きな差が認められ[10]，発達に合わせた検査法への適応能力が影響しているのも大きな要因と考えられるため，聴覚評価には聴覚および身体発達を考慮し十分時間をかけるという慎重さが求められると同時に，検査結果の説明は保護者の心理面および聴覚障害児の将来の発達を考慮しカウンセリングの中で丁寧に繰り返し実施することが重要である。

ま と め

1．難聴の程度に関わらず閾値の改善がみられた。特に中等度難聴はCORでの閾値改善傾向が顕著であるため補聴器の選択・適合および保護者へのカウンセリングにおいて十分な配慮が必要である。

2．重度難聴でABRが無反応であった症例でも音場および楽器によるBOAで反応が得られる場合があるため，ABR検査と併せてBOAを実施することの意義はスクリーニング後の聴覚評価において大きいと考えられた。

3．重度難聴でもCORが可能となった時点でほぼ全例で1000Hz以下に反応が認められており，聴覚評価には聴覚および身体発達を考慮し十分時間をかける慎重さが求められた。

4．難聴児であっても生後2カ月以降に聴覚の発達にともなう閾値の改善が認められることが示唆された。

稿を終えるに臨み，松本耳鼻咽喉科・松本憲明先生のご校閲に深謝する。

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Hearing evaluation of infants suspected of having hearing loss with a newborn hearing screening program

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Behavioral Observation Audiometry (BOA) and Conditioned Orientation Response Audiometry (COR) were used in 15 children whose hearing loss had been identified with a newborn hearing screening program. The cases with moderate hearing impairment especially demonstrated greater improvements than those with severe and profound deafness, although improvements in the COR threshold, compared to the BOA threshold, could in some degree be observed in most cases regardless of their severity of deafness. Thus, interventional procedures including hearing assessments, amplification using hearing aids and counseling families with hearing impaired children must be conducted carefully and appropriate revision should repeatedly be required. It has already been reported that normal hearing infants demonstrated improvements in hearing thresholds during their first year of life, and similar improvement can be observed among children with hearing impairment as regards their auditory development.

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原　著

軽度難聴児の言語発達に与える高次脳機能 —神経心理学的評価に基づく認知特性の検討

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Evaluations of Higher Brain Functions that Affect Language Development of Children with Mild Hearing Impairment —Cognitive Preference Evaluated by Neuropsychological Tests

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Learning disability is the single most frequent complication of hearing impairment, occurring in up to 15% of all school-aged deaf children. Neuropsychological evaluations of these cases may contribute to further diagnosis of the additional handicaps and the identification of a suitable procedure for better intervention. A nine-year-old boy with mild hearing impairment was referred to our hospital because of his poor language development. His average pure tone audiometry was 35 dBnHL in the right ear and 65 dBnHL in the left ear and audiological interventions with a hearing aid had already been started before the referral to our clinic. Although mild mental retardation was suggested by WISC-III, as FIQ65 (VIQ 65, VIQ71, and PIQ65), non-verbal intelligence examined by RCPM corresponded to the normal range. Verbal and non-verbal semantic disorder was considered by the results from ScTaw and SLTA. He was later diagnosed as having Asperger syndrome and his semantic problem concomitant with Asperger syndrome could be another cause of his additional language delay.

キーワード：軽度難聴　意味理解障害　広汎性発達障害

目　的

難聴診断の低年齢化が進む中，療育方針の決定には客観的根拠に基づいた言語発達の予後予測が必須である。難聴児の言語発達の様相は多様であり，聴能訓練が順調に推移した症例が必ずしも良好な言語発達の経過をたどるとは限らない[1]。特に学齢前に言語発達が一定の段階に達していない児は，何らかの認知神経心理学的課題を抱えている。この傾向は高度感音難聴に限らない。軽度難聴児にも同様に存在し，その様相が多岐にわたる。今回，純音性の感音性難