observed, however, that in these patients the VEMPs recovered more rapidly than CP [13]. In the present study, 75% (6/8) of VN patients exhibited normal VEMPs in their affected side. Taken together, these results suggest that otolith function in the affected side was in the process of recovery and that sensitivity to sound had increased temporarily. This is plausible because more than one month (36.1 ± 40.7 days) had elapsed between VN onset and VEMP testing, allowing sufficient time for recovery to occur (Table 2). These findings are compatible with our hypothesis that cells involved in APRs mainly receive inputs from otolith organs, especially the saccule. These results also led us to hypothesize that in VN patients sound sensitivity of otolith organs may have increased to compensate for disequilibrium, and as a result, APRs also increased. Consistent with this hypothesis, is our finding that APRs in the affected side were significantly larger than those in the unaffected side. However, two patients exhibited normal APRs (nos. 1, 5) but abnormal VEMPs. One explanation for this result is that APRs receive input not only from the saccule but also from the cochlea or the other otolith organ, thus producing normal APRs in these patients.

In summary, our study provides evidence that assessing APRs may be useful for evaluating vestibulo-autonomic reflexes, especially otolith-autonomic reflexes. However, as they are affected by various factors, it is difficult to evaluate APRs correctly. To solve this problem, one clear next step might be to investigate APRs in vertiginous patients lacking CP but displaying abnormal VEMPs, as, for example, in patients with benign paroxysmal positional vertigo.

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Intermittent positional downbeat nystagmus of cervical origin

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ABSTRACT

Intermittent positional down beat nystagmus (p-DBN) is rare. We describe an unusual case of intermittent p-DBN which was induced by rotation, anteflexion, and lateral flexion of the neck. A 59-year-old man complained of loss of consciousness and lightheadedness. Positional testing revealed the p-DBN. The evoked p-DBN had latency and the patient had a feeling of passing out while the p-DBN was present. There were no abnormal findings in the vestibular functional examinations. Findings of the MRI were negative. MRA revealed no stenosis of the vertebral artery bilaterally, but there was an anatomical difference. The p-DBN characteristics were documented by electronystagmography during the positional test. The p-DBN lasted intermittently while maintaining the provoking position. It was found that p-DBN occurred with not only the rotation of the neck, but also in the anteflexion and lateral flexion of the neck. There was no stenosis of the vertebral artery (VA) on angiography, but we speculated that the cause of the p-DBN was the VA occlusion due to rotation, anteflexion, and lateral flexion of the neck.

1. Introduction

Positional down-beat nystagmus (p-DBN) is typically a clinical sign of central nervous system involvement. It occurs with lesions in the vestibulocerebellum or the craniocervical junction and with drug intoxication [1]. Experimental extirpation of the nodulus in the cat has been shown to cause postural DBN [2]. Occasionally, p-DBN is seen in patients without CNS involvement [1,3]. There is one report showing that canalithiasis of the anterior semicircular canal (ASC) causes p-DBN [4]. It is difficult to distinguish the origin of the p-DBN in the peripheral or central nervous system. Intermittent p-DBN is extremely rare.

We encountered a patient with p-DBN due to rotation and bending of the neck, which led us to suspect a cervical origin. In this report, we describe the features of neuro-otological findings, including nystagmus, and the clinical course.

2. Case report

A 59-year-old man complained of brief positional vertigo for 1 year and a feeling of passing out when he looked down to lift a piece of luggage. He also felt the vertigo when his head turned to the left while lying down. He visited our clinic in May 2011.

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There was no spontaneous or gaze nystagmus. The positional test revealed p-DBN in the left lateral position without head rotation (Fig. 1). The test also showed p-DBN with head rotation to the left (Figs. 1 and 2), but there was no nystagmus in the supine position or right ear down position. The p-DBN was also observed in the bending forward position. No nystagmus was evoked by changing position from the head hanging position to the sitting position. We carried out the examination in the sitting position, during neck torsion to the left, and p-DBN was not seen. However, during a strong twist of the neck to the left in the sitting position, the patient complained of a feeling of passing out. Therefore, vascular insufficiency was also thought to occur in the sitting position.

His hearing was normal bilaterally. There was no neuro-otological dysfunction and no cerebellar symptoms. Eye movement examinations, including the eye tracking test and the optokinetic nystagmus test, were normal. The caloric test with cold water at 10 °C and the visual suppression test were normal. Cervical and ocular vestibular evoked myogenic potentials were normal bilaterally. The subjective visual vertical test was normal. There were no abnormal findings in the brainstem, cerebellum, or inner ear on brain MRI. On MRA, the left vertebral artery (VA) was narrower than the right VA, but there was no stenosis in the VA bilaterally (Fig. 3). We presumed that the cause of the DBN was not from a central nervous system disorder, because the MRI, MRA, and electronystagmography were normal. We suspected cervical vertigo and performed the body rotation test without neck

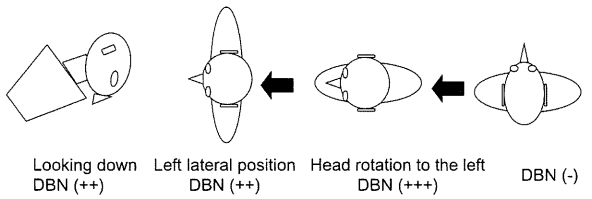

Fig. 1. Diagram representing the positions showing p-DBN. There was no nystagmus in the supine position. DBN was induced by head rotation to the left, the left lateral position without head rotation, and the looking down position.

rotation, which still showed DBN. We thought that the cause of the DBN was not exclusively of cervical origin, because the DBN was observed not only in the rotating head position, but also in the left lateral position, without rotating the head. Therefore, initially, we suspected that the cause of the nystagmus was due to the variants of anterior canal BPPV, or otolithic dysfunction. During the follow-ups in the outpatient clinic, the symptoms did not improve. After observing the nystagmus for several times at the clinic, we were able to rule out inner ear disease as a cause of the DBN. The nystagmus continued intermittently while maintaining the provoking position (Fig. 4). The p-DBN started with small increments and the amplitude became gradually larger and attenuated. The duration of a single p-DBN was approximately 20 s and restarted after an interval of 30–40 s. With regard to the left lateral position, the nystagmus, which started with small increments, was induced in the lateral position with lateral flexion (without pillow), but the DBN disappeared after placing a pillow in order to eliminate the lateral flexion of the neck (Fig. 5). We postulated the cause of the p-DBN to be VA occlusion due to compression by the cervical vertebrae. The patient was instructed to avoid the provoking position, and the frequency of the DBN and dizziness symptoms gradually decreased. For the convenience of the patient, angiography was performed only after the symptoms were alleviated. The angiography revealed no obstruction in the vertebral or basilar artery. The p-DBN disappeared 18 months later.

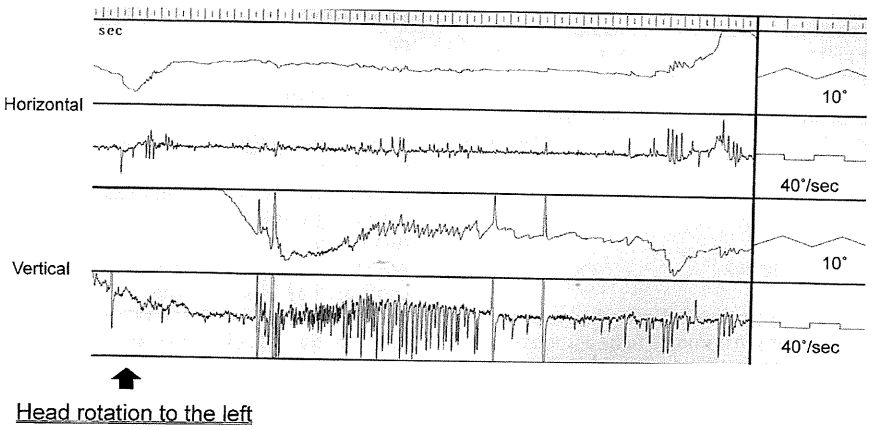

Fig. 2. Electronystagmograph of p-DBN in the present case during the positional test. The p-DBN was induced by head rotation to the left from the supine position. The evoked p-DBN had latency and was gradually reduced. The p-DBN was also observed at the left lateral position without head rotation.

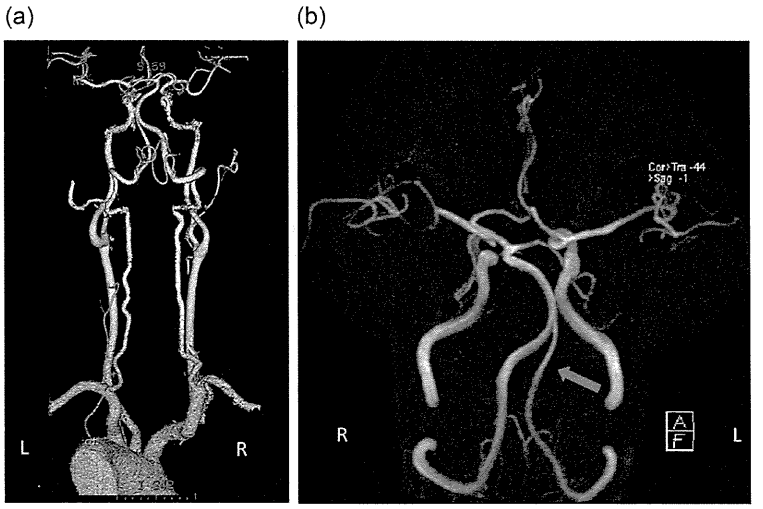

Fig. 3. (a) 3D-CT angiography (rear view) and (b) MRA (front view). There was no stenosis of the vertebral artery (VA) bilaterally. The left VA was narrower than the right VA (i.e., the right VA was dominant).

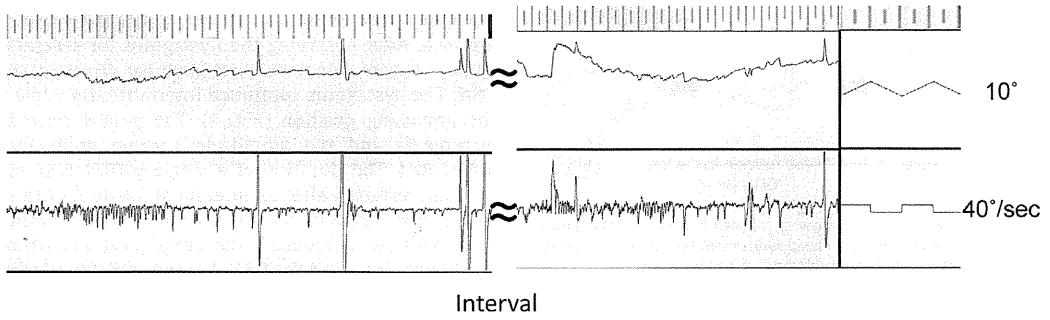

Fig. 4. Electronystagmograph of p-DBN in the present case during the positional test. The nystagmus continued intermittently while maintaining the left lateral position. The p-DBN started with small increments and the amplitude became gradually larger and then attenuated. The duration of a single p-DBN was approximately 20 s, the interval was about 40 s, and then the p-DBN re-appeared. The duration of the second p-DBN was approximately 10 s.

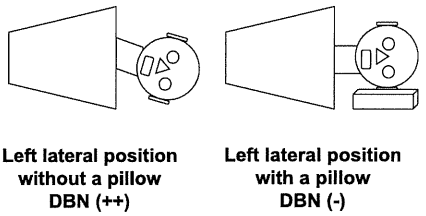

Fig. 5. Diagram representing the lateral positions showing p-DBN. Regarding the left lateral position, p-DBN was observed with flexion of the neck (i.e., without pillow). The p-DBN disappeared without flexion of the neck (i.e., with pillow).

3. Discussion

3.1. Positional down-beat nystagmus

DBN in primary gaze is a sign of central nervous system (CNS) dysfunction. The responsible lesion is known to be associated with the central part of the cerebellum, the cerebellum flocculus, and the inferior part of the brainstem, but the specific site is not yet confirmed. p-DBN is also known to occur in CNS disease, particularly lesions of the posterior fossa. It was reported that positional DBN is indicative of a vestibulocerebellar nodulus lesion [1]. Experimental extirpation of the nodulus in the cat causes postural DBN [2]. Katter et al. reported a case with a lower and posterior vermis hematoma that had developed p-DBN and intense vertigo upon lowering the head [5]. Physiologically, the nodulus may have an inhibitory effect on the gain of the vertical vestibulo-ocular reflex [6]. p-DBN may be caused by multiple sclerosis, ischemia, intoxication, cranio-cervical malformation, or cerebellar degeneration; however, sometimes there is no identifiable etiology in elderly patients [1].

Recently, there have been some reports that patients who have p-DBN without any obvious CNS dysfunction are considered to have ASC BPPV [4]. Initially, we suspected that the cause of the nystagmus was due to the variants of anterior canal BPPV, or otolithic dysfunction. The p-DBN continued intermittently while maintaining the left lateral position (without a pillow) in our present case. However, the nystagmus of the ASC BPPV does not continue intermittently while maintaining the lateral position. The p-DBN was also observed in the bending forward position in our case. If the patient has BPPV, the direction of the nystagmus should be reversed in the bending forward position. Based on the above observations, we ruled out the possibility of ASC BPPV.

3.2. Intermittent DBN

The reports describing cases of intermittent DBN [7–11] are shown in the table. From these previous reports, the etiologies of 2 in 5 cases were Arnold–Chiari malformation [8,9]. One case was a vermian arachnoid cyst [7]. The lesion site in these cases was the midline cerebellum. The etiology of another case was hypomagnesemia. In this case, swelling of the cerebellar nodulus was confirmed by MRI [10]. The cause of the remaining case was VA compression; the p-DBN in this case was induced by turning the head to the left side, like the present case. The angiography revealed the obstruction of blood flow by compression of the extra cranial left VA from an osteophyte [11]. From these reports, the responsible lesion for intermittent p-DBN appeared to be the cerebellar nodulus (see Table 1).

3.3. Suspected pathogenesis of p-DBN

Bow hunter's syndrome was described by Sorensen in 1978 from observation of a patient becoming symptomatic during archery [12]. It was defined as symptomatic, vertebrobasilar insufficiency caused by mechanical occlusion of the VA at the atlanto-axial level (C1-2) during head rotation. In our present case, angiography was performed only after the symptoms were alleviated. We were not able to document VA occlusion, but we speculated that the VA compression due to rotation, anteflexion, and lateral flexion of the neck caused the failure of blood flow to the nodulus, consequently, leading to intermittent p-DBN. Regarding VA obstruction, it was reported that the etiology of this obstruction is possibly related to the fact that when the head is

Table 1
Previous reports concerning intermittent down-beat nystagmus.

Age, gender	Inductive position(s)	Etiology	Author(s), year
27, M	Oblique head and neck extension	Vermian arachnoid cyst	Chan et al., 1991 [7]
32, F	Primary position Spine position	Arnold–Chiari malformation	Pedersen et al., 1980 [8]
36, F	Spine position	Arnold–Chiari malformation	Yee et al., 1983 [9]
59, M	No description	Hypomagnesemia swelling of the cerebellar nodulus	Sedenhizadeh, 2011 [10]
64, M	Neck rotation to the left	Obstruction of dominant VA	Rosengart et al., 1993 [11]
59, M	Neck rotation to the left looking down	Obstruction of VA?	Present case

rotated, the atlanto-axial joint on the side to which the head is turned is fixed, whereas the contralateral side of the atlas moves forward on the axis [13,14]. The segment of the VA between the atlas and the axis is stretched and narrowed in the process. Toole and Tucker [15] observed, in a study of 20 cadavers, that 75% of the cases demonstrated significantly compromised blood flow in one or both VAs with head rotation. In our patient, MRA and 3-D CT revealed that the left VA was narrower than the right VA. When the head was rotated to the left, mechanical occlusion of the dominant right VA occurred, thus inducing the insufficiency of the vertebrocerebellum, including the cerebellar nodulus.

The present case was followed up conservatively after instruction to avoid the provoking position. The frequency of the DBN and the dizziness gradually decreased. Kuether et al. [16] reported that nearly 50% of rotational VA obstruction treated conservatively eventually suffered from infarct or had residual neurological deficits. Careful follow-up is necessary in such cases.

Conflict of interest

The authors declare no conflicts of interest associated with this study.

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MAIN ARTICLE

Experimental study on the aetiology of benign paroxysmal positional vertigo due to canalolithiasis: comparison between normal and vestibular dysfunction models

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Abstract

Objectives: Using American bullfrog models under normal conditions and under vestibular dysfunction, we investigated whether mechanical vibration applied to the ear could induce otoconial dislodgement.

Methods: Vibration was applied to the labyrinth of the bullfrog using a surgical drill. The time required for the otoconia to dislodge from the utricular macula was measured. Vestibular dysfunction models were created and the dislodgement time was compared with the normal models. The morphology of the utricular macula was also investigated.

Results: In the normal models, the average time for otoconial dislodgement to occur was 7 min and 36 s; in the vestibular dysfunction models, it was 2 min and 11 s. Pathological investigation revealed that the sensory hairs of the utricle were reduced in number and that the sensory cells became atrophic in the vestibular dysfunction models.

Conclusion: The otoconia of the utricle were dislodged into the semicircular canal after applying vibration. The time to dislodgement was significantly shorter in the vestibular dysfunction models than in the normal models; the utricular macula sustained significant morphological damage.

Key words: Vertigo, Benign Paroxysmal Positional; BPPV; Vibration; Otoconia; Utricle; Trauma; Otologic Surgical Procedure; Bullfrog; *In Vitro*

Introduction

Benign paroxysmal positional vertigo (BPPV) occasionally develops after mechanical stimulation of the temporal bone, such as during ear or dental surgery and physical exercise using a vibration device. It is suspected that external vibration to the ear is one of the causes of BPPV. We investigated whether mechanical vibration applied to the ear could induce otoconial dislodgement using isolated labyrinthine models from the American bullfrog (*Rana catesbeiana*). Inner-ear disorders may also be predisposing factors for BPPV. We created vestibular dysfunction models and the time required for otoconial dislodgement to occur in these models was compared with the normal models. We also investigated the morphology of the utricular macula.

Materials and methods

We performed experiment 1 using the normal models and experiment 2 using the vestibular dysfunction models. All experiments were conducted according to the Tokyo Medical University's rules regarding animal experimentation.

Experiment 1 (normal models)

For the preparation of the experimental models, American bullfrogs weighing 110–220 g were selected. After the induction of deep anaesthesia with ether, they were decapitated and the bony labyrinth was removed, placed in a glass dish and 100 ml Ringer solution was added to the dish, according to the method described by Suzuki *et al.*[1] The caudal otic capsule was chiselled so that the entire posterior semicircular canal was exposed. The remaining membranous labyrinth was left enclosed in the bony capsule. The labyrinth preparation was held by forceps with the posterior semicircular canal in the undermost position. Mechanical vibration was applied to the upper surface of the bony otic capsule using a surgical drill (BL-F5A; Osada Electric Company, Tokyo, Japan) according to the method described by Otsuka *et al.* (Figure 1).[2] An end-cutting bur, with a tip measuring 5 mm in diameter,

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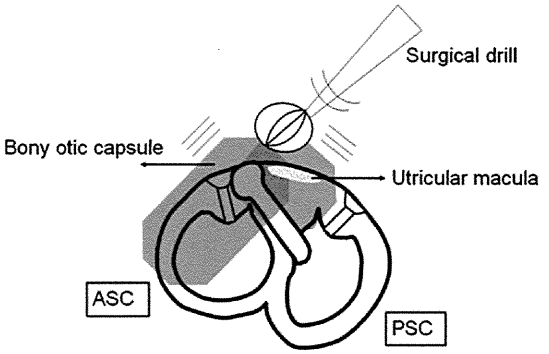

FIG. 1

Experimental model. Using a surgical drill, mechanical vibration was applied to the upper surface of the bony otic capsule of the labyrinth preparation. ASC = anterior semicircular canal; PSC = posterior semicircular canal

was used. The frequency of the vibration, as measured by a vibration analyser (VA-12; Rion, Tokyo, Japan), was 340 Hz. Care was taken not to rupture the membranous labyrinth. This allowed the otoconia to dislodge from the utricular macula and move into the posterior semicircular canal. The time required for otoconial dislodgement was measured. A dissection microscope (SZX12; Olympus, Tokyo, Japan) was used for observation.

Experiment 2 (vestibular dysfunction models)

The vestibular dysfunction models were created by injecting 300 μg (7.5 μl) of gentamicin into the perilymphatic space of the bullfrog labyrinth using a palatal approach.[3] The bullfrogs were kept alive for 7–14 days. Then, the same procedure as in experiment 1 was performed and the time required for otoconial dislodgement was measured. The dislodgement time was compared with that of the normal models. For statistical analysis, we used the Student's *t*-test. *P* values less than $p = 0.05$ were considered to be statistically significant. After the experiment, sections of the utricular macula were prepared for microscopic observation; they were fixed in formalin, embedded in paraffin, sectioned and stained with haematoxylin and eosin. The otoconia and the otolithic membrane were apparently lost during the staining process. We evaluated the condition of the sensory hairs and sensory cells accordingly.

Results

In all specimens, we observed that the otoconia had dislodged from the utricular macula and moved into the posterior semicircular canal when subjected to vibration (Figure 2).

Experiment 1 (normal models)

In the normal models ($n = 21$), the dislodgement times varied from 120 to 1000 s. The average dislodgement time was 456 s (2 standard deviations (SDs) = ± 248 s).

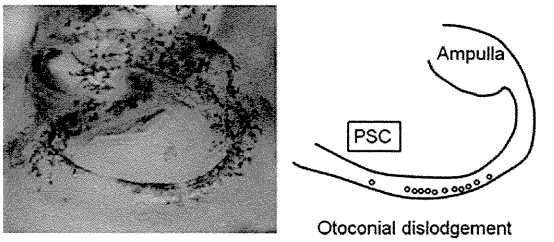

FIG. 2

Dissection microscopic image and model of otoconial dislodgement. The utricular otoconia dislodged from the macula and moved into the posterior semicircular canal (PSC) after vibration.

Experiment 2 (vestibular dysfunction models)

In the vestibular dysfunction models ($n = 14$), the dislodgement times varied from 45 to 300 s. The average dislodgement time was 131 s (2 SDs = ± 85 s), which was significantly shorter than in the normal models ($p = 0.0005$) (Figure 3).

The pathology of the utricular macula was investigated in nine of the vestibular dysfunction models. When compared with those of the normal model (Figure 4a), all of the sensory hairs of the vestibular dysfunction model (Figure 4b) were reduced in number. In three other vestibular dysfunction models, the otoconia were dislodged before applying vibration. In two of them, the morphological damage to the utricular macula was severe. In one specimen, the utricular sensory cells became atrophic (Figure 4c). In the other specimen, the sensory cells were missing altogether (Figure 4d).

Discussion

Ear surgery occasionally induces BPPV.[4–6] In our series of 48 tympanoplasty cases, 2 cases of direction-changing, horizontal positional nystagmus were observed after surgery.[7] In all cases, the positional nystagmus resolved in 14–27 days. The mechanical vibration effect of a surgical drill on the otolithic organ was considered responsible for the emergence of positional

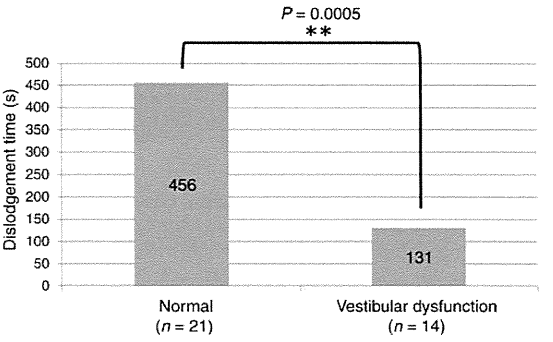

FIG. 3

Average time of otoconial dislodgement. The time to otoconial dislodgement was significantly shorter in the vestibular dysfunction models than in the normal models ($p = 0.0005$).

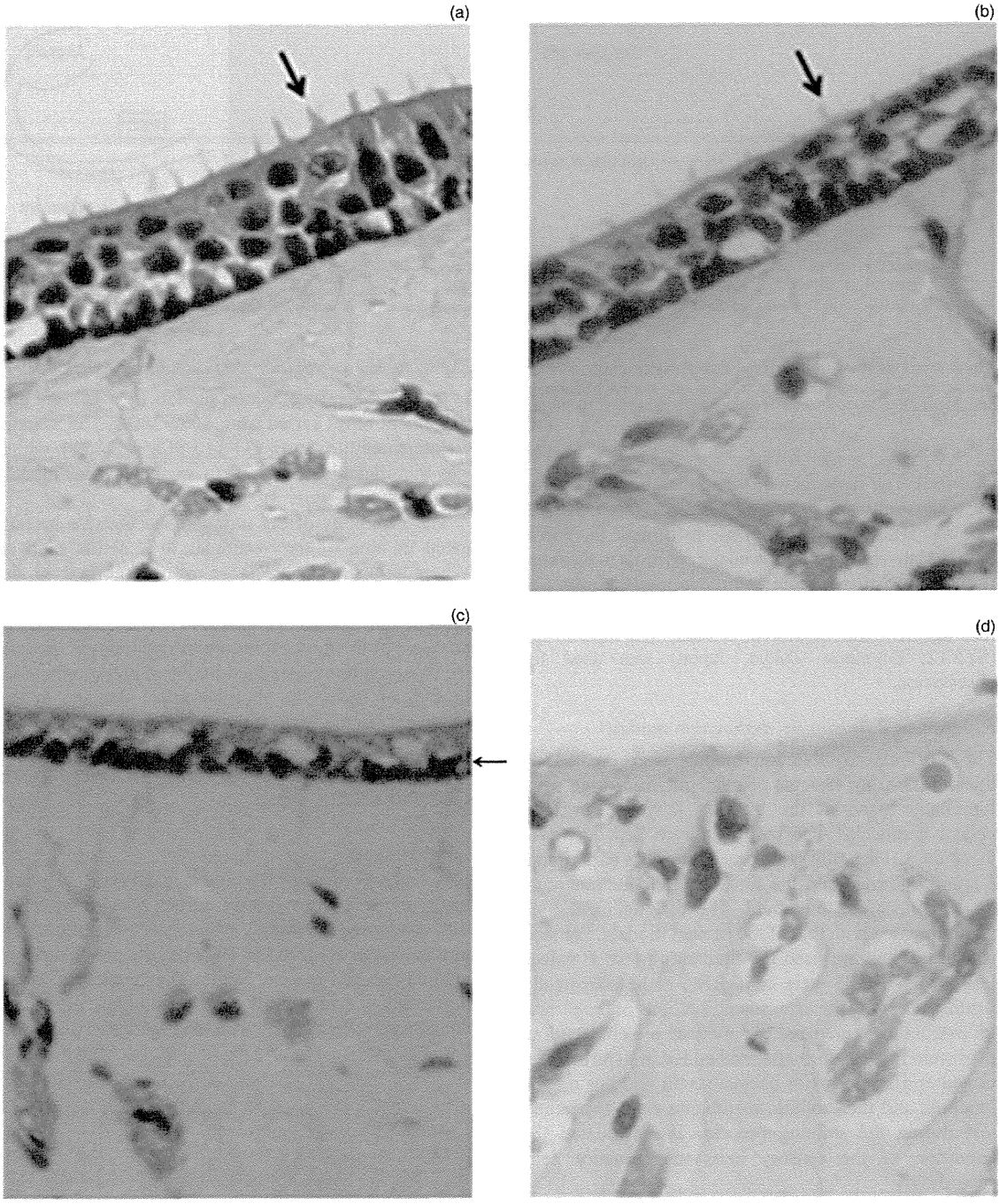

FIG. 4

Microscopic image of the utricular macula. When the normal model (a) was compared to the vestibular dysfunction model (b), there was a reduction in the number of sensory hairs (arrow) in the vestibular dysfunction model. In the utricular macula with dislodged otoconia before vibration, the morphological damage was severe; the sensory cells (arrow) became atrophic (c) or were missing altogether (d). (H&E; ×400)

nystagmus. There would have been no chemical effect on the endolymph since the inner ear was not disturbed during surgery.

Dental surgery also occasionally induces BPPV.[8–13] Chiarella *et al.*[14] reported that BPPV arose on the operation side within 7 days after dental surgery in 8 patients, in men aged under 45 and women aged under 40. Seven out of eight patients had BPPV of the posterior semicircular canal. One patient had lateral semicircular canal BPPV. It has been suggested

that vibrations are propagated throughout the bony structures reaching the labyrinth. At this level, mechanical energy would travel through the endolymphatic fluid or bone, eventually causing macular trauma. Amir *et al.*[15] reported that a 44-year-old woman developed BPPV following the use of a whole-body vibration training plate, a popular form of fitness equipment widely used in sports, rehabilitation and body workout treatments.

Whole-body vibration training can potentially generate displacement or dislocation of otoconia through vibration being transmitted to the inner ear. Dan-Goor and Samra[16] reported that a 44-year-old woman developed acute and severe positional vertigo on waking up, after continuously using noise-cancelling headphones for 12 h prior to going to sleep. They suspected that repeated mechanical disruption or vibration within the vestibular system could have dislodged otoconia into the posterior semicircular canal.

We investigated whether mechanical vibration could induce otoconial dislodgement using experimental models. Fine morphological studies have shown that the otoconia of the utricle are connected to each other by means of fine fibrils and are embedded in a gelatinous substance consisting of mucopolysaccharides.[17,18] The whole otoconial mass is covered by a supra-otoconial layer.[19] We expected that the otoconia would not be easily dislodged from the utricular macula by weak stimulation. We directly stimulated the inner ear with the vibration of a surgical drill. The otoconia were dislodged from the utricular macula and moved into the posterior semicircular canal within 20 min in all specimens. We were able to confirm that the utricular otoconia were dislodged after vibration. The intensity of the stimulus in this experiment was strong because the vibration was applied in close proximity to the labyrinth. Although a weaker stimulation may require a longer dislodgement time, the vibratory stimulus could be one of the causes of BPPV.

Benign paroxysmal positional vertigo is usually idiopathic, but in some cases, it arises after inner-ear disease. Karlberg *et al.*[20] reported that 81 out of 2847 BPPV patients (2.8 per cent) had definite BPPV of the posterior semicircular canal secondary to an ipsilateral inner-ear disease. Sixteen patients had Ménière's disease, 24 had acute unilateral peripheral vestibulopathy, 12 had chronic unilateral peripheral vestibulopathy, 21 had chronic bilateral peripheral vestibulopathy and 8 had unilateral sensorineural hearing loss. Katsarkas and Kirkham[21] found that 20 out of 255 BPPV patients (7.8 per cent) had secondary BPPV. Baloh *et al.*[22] found 80 (33.3 per cent) cases of secondary BPPV out of 240 BPPV patients. Hughes and Proctor[23] found 60 (39.7 per cent) cases of secondary BPPV out of 151 BPPV patients. The ratio of secondary BPPV thus varies widely. On the other hand, Inagaki *et al.*[24] analysed 123 cases of Ménière's disease, sudden deafness and vestibular neuronitis and found 14 cases (11.4 per cent) of secondary BPPV. Of 48 Ménière's disease cases, 4 (8.3 per cent) presented with BPPV. Three of 31 sudden deafness cases (9.7 per cent) and 7 of 44 vestibular neuronitis cases (15.9 per cent) presented with BPPV. Von Brevern *et al.*[25] screened 4869 participants in a cross-sectional, nationally representative, neurotological survey of the general adult population in Germany. The lifetime prevalence of BPPV was found to be 2.4 per cent. Patients with inner-ear disease develop BPPV more often than the general adult population.

We investigated whether inner-ear diseases can be predisposing factors for BPPV using an experimental approach. We performed experiments using vestibular dysfunction models created by injecting gentamicin into the perilymphatic space of the bullfrog labyrinth. The dislodgement time was significantly shorter in the vestibular dysfunction models than in the normal models, and the utricular macula sustained morphological damage, such as a reduction in the number of sensory hairs and sensory cell atrophy. The relationship between the short dislodgement time and the morphological damage of sensory cells is unknown.

- **Benign paroxysmal positional vertigo occasionally develops after vibration, such as during ear or dental surgery and physical exercise using a vibration device**
- **In this experimental study, utricular otoconia were dislodged into the posterior semicircular canal after vibration**
- **The time to dislodgement was significantly shorter in the vestibular dysfunction models than in the normal models**
- **Inner-ear diseases can be predisposing factors for benign paroxysmal positional vertigo**

A reduction in the number of sensory hairs possibly indicates an association with the changes in the otoconia and otolithic membrane. If this is true, the otoconia are easily dislodged by the damage. On the other hand, the sensory hairs protrude into the otolithic membrane and possibly support the membrane. A reduction in the number of the hair cells weakens the support, thus inducing dislodgement of the otoconia. Other insults, such as ischaemia, endolymphatic hydrops or ageing, potentially change the utricular macula, thus possibly leading to easy dislodgement of the otoconia from the macula.

Conclusions

In our study, the utricular otoconia were dislodged into the posterior semicircular canal after vibration. The time to dislodgement was significantly shorter in the vestibular dysfunction models than in the normal models; the utricular macula sustained morphological damage.

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ORIGINAL ARTICLE

Ocular vestibular evoked myogenic potentials induced by bone-conducted vibration in patients with unilateral inner ear disease

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Abstract

Conclusion: Patients with vestibular neuritis (VN) with complete canal paresis (CP) showed a higher rate of abnormal ocular vestibular evoked myogenic potential (oVEMP) than those with partial CP. From these results, it is speculated that the superior vestibular nerve function mainly affects oVEMP. Significant correlation was found between the grades of the hearing outcome and oVEMP in sudden sensorineural hearing loss (SSHL). *Objective:* We attempted to correlate the results of oVEMP with the results of cervical VEMP (cVEMP), results of subjective visual vertical (SVV), and clinical course in patients with various vestibular disorders. *Methods:* Twenty-two patients with VN, 65 with SSHL, and 22 with Meniere's disease (MD), were enrolled in this study. We compared the results of oVEMP with those of cVEMP, SVV, and the caloric test. Furthermore, the oVEMP results were compared with the initial hearing threshold, presence of vertigo, and hearing recovery in the patients with SSHL. *Results:* The patients with VN with complete CP showed a higher rate of abnormal oVEMP than those with partial CP. In the patients with SSHL, the hearing recovery rate was lower in the patients with abnormal oVEMP than in those with normal oVEMP.

Keywords: *sacculus, utriculus, otoliths, vestibular neuritis, canal paresis, sudden sensorineural hearing loss, Meniere's disease*

Introduction

Vestibular evoked myogenic potentials induced around the eyes are known as ocular vestibular evoked myogenic potentials (oVEMP) and are useful for the clinical examination of vestibular function. oVEMP is defined as a biphasic negative-positive myogenic response with a very short latency. The cervical evoked myogenic potential (cVEMP) has been used as a test of the vestibulo-collic reflex, particularly the sacculo-collic reflex. However, the origin of oVEMP remains unclear. Curthoys et al. and Govender et al. [1,2] showed that the superior vestibular nerve is the route along which the oVEMP response passes, and not the inferior vestibular nerve. It has been suggested that the primary negative potential of the oVEMP (nI) indicates crossed utricular function [1–3]. As regards examination of the utriculus, the subjective visual vertical (SVV) test has been recently discussed [4,6].

In the present study, we attempted to correlate the oVEMP results with results of cVEMP and SVV, and the clinical course in patients with representative diseases of the inner ear.

Material and methods

Subjects

From January 2010 to December 2012, oVEMP was measured in 109 cases of unilateral inner ear diseases. A detailed medical history was taken for all patients. The patients were also assessed by cVEMP, SVV, caloric test, and hearing test, evaluated for symptoms of vertigo, and assessed for hearing recovery rate. All the patients were accepted for treatment as inpatients.

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Examinations were performed as soon as possible after admission. A patient who described symptoms of vertigo at the onset or during the course of hospitalization was considered positive for vertigo.

Twenty-one healthy subjects including 7 men and 14 women (age range 24–62 years, mean age 32.8 years) from among the resident physicians and co-medical staff were enrolled as normal controls. None had a history of ear disease.

There were 22 patients with vestibular neuritis (VN) (5 women and 17 men; age range 34–68 years, mean age 53.0 years), 65 with sudden sensorineural hearing loss (SSHL) (30 women and 35 men; age range 17–82 years, mean age 48.9 years), and 22 with Meniere's disease (MD) (18 women and 4 men; age range 26–83, mean age 54.3 years).

The diagnostic criteria for VN were as follows: (1) a single attack of continuous vertigo lasting for at least several hours, (2) reduced lateral semicircular canal function (canal paresis (CP) > 20% on the affected side in the caloric test), (3) spontaneous nystagmus, and (4) no cochlear or other neurologic signs.

The diagnostic criteria for SSHL were as follows: (1) sudden unilateral sensorineural hearing loss of at least 30 dB over three frequencies developing within 72 h, (2) exclusion of hearing loss of greater than 30 dB on the pure-tone average of five frequencies (i. e. 0.25, 0.5, 1, 2, and 4 kHz), (3) no other neurological signs, (4) exclusion of acute low-tone sensorineural hearing loss, (5) no history of MD in either ear, (6) no previous otologic surgery, (7) treatment started within 8 days after onset.

The diagnostic criteria for MD were based on the guidelines proposed by the American Academy of Otolaryngology–Head and Neck Surgery in 1995 [6]: (1) two or more definitive spontaneous episodes of vertigo for 20 min or longer, (2) audiometrically documented hearing loss on at least one occasion, (3) tinnitus or aural fullness in the affected ear, and (4) other causes excluded. The affected ear was identified as the ear in which there was a low frequency hearing loss, and symptoms of fullness were reported.

We classified the pathology into VN as the vertigo-based labyrinthine disorders and SSHL and MD as the auditory-based disorders.

oVEMP measurement

oVEMP was measured using bone-conductive vibration (BCV). BCV was applied to the midline of the forehead at the hairline (a location called Fz). BCV was delivered using a hand-held mini-shaker (Bruel & Kjaer model 4810, Naerum, Denmark). The mini-shaker terminates in a bakelite cap 1.5 cm in diameter. The flat end of this cap was the contact point for the stimulator on the subject's Fz point. Surface electrodes were placed inferiorly to both eyes after the subject's skin beneath the eyes had been cleaned carefully with alcohol wipes. The active electrode was located over the inferior orbital margin and a reference electrode was placed 2 cm below the active electrode. The ground electrode was on the para-medial forehead.

The subjects were asked to lie in a supine position on the bed with their head supported by a pillow with the chin close to the chest, and to maintain a 30° upward gaze during recording. We placed the target at the point where the subject could examine the upper 30° field of view.

The signals were amplified and bandpass filtered between 20 and 2000 Hz. The stimulus intensity was 115 dB force level, 500 Hz with an analysis time of 40 ms, and 50 responses were averaged for each run. Two or three runs were performed to confirm the reproducibility of the results. In this study, the nI component was measured. The amplitude of nI was measured from baseline to peak.

The oVEMP asymmetry was calculated as follows: oVEMP signed asymmetry ratio (AR) = {(larger nI − smaller nI)/(larger nI + smaller nI)} × 100.

In this study, the average of normal subject's AR was 21.7 ± 14.0. The upper limit of the normal range of the percent oVEMP asymmetry was set by the normal subject's AR. The normal mean and range were set as 21.7 ± 2 SD. The upper limit of the normal range was set as 49.7 (mean ± 2 SD).

cVEMP measurement

cVEMP was recorded in the supine position. The skin over the upper half of the sternocleidomastoid (SCM) muscle was cleaned with alcohol wipes and surface electromyography electrode readings were recorded, with a reference electrode on the upper edge of the sternum and a ground electrode on the forehead. Rarefaction clicks (105 dB nHL, 0.5 ms) were delivered to each ear through a headphone with a stimulation rate of 5 per second. The patients were instructed to continuously raise their head to activate the SCM. The results were evaluated on the basis of comparative ratios between the first positive and first negative (p13-n23) amplitude on the lesion side and that on the healthy side. We defined a ratio of < 0.5 as an abnormal VEMP value [5].

SVV measurement

SVV was usually examined at 2 or 3 days after the patients were admitted. SVV was measured using a small rotatable luminous line in the upright body position in a completely darkened room. The patient

was seated in a chair and the head and chin were fixed on a forehead-chin rest in an upright position 50 cm away from the SVV device. The length of the luminous straight line on a computer screen was 15 cm. After the luminous line was randomly tilted automatically, the patient was asked to rotate the bar to the position they perceived as vertical using a hand controller. SVV measurement was performed 10 times for each patient, and the mean was regarded as the measured value.

Based on the results with normal subjects in our institute, the upper limit of the normal range of the SVV tilt was set as ± 2.0°, and SVV tilts outside the range of −2.0° to +2.0° were determined to be pathological.

Caloric test measurement

The caloric test was performed using electronystagmography. The CP level was calculated using the maximal slow phase eye velocity. A CP value of greater than 20% was defined as abnormal. We divided the patients into two groups according to CP severity: complete CP (absence of caloric response) and partial CP (reduced caloric response and a CP of > 20%).

Grades of hearing loss and hearing outcome in SSHL

We evaluated the hearing levels of the SSHL patients on the first visit. The hearing level was calculated using five frequencies (0.25, 0.5, 1, 2, and 4 kHz). The grade of hearing was based on the pure-tone average of the five frequencies. The criteria for the evaluation of the grade of hearing were as follows: grade 1, < 40 dB; grade 2, 40–60 dB; grade 3, 60–90 dB; grade 4, > 90 dB. We also evaluated hearing outcome 1 month after the onset as follows. Complete recovery was defined as recovery to a level similar to that of an intact ear or if all of the five frequencies of hearing level were less than 20 dB. Marked recovery was defined when the average of five frequencies was greater than 30 dB. Slight recovery was defined when the average of five frequencies was 10–29 dB. Unchanged was defined as being within a 10 dB improvement.

Stages of MD

The patients were classified by referring to the guidelines of the Committee on Hearing and Equilibrium in the USA [6]. Stage I included patients whose average pure-tone hearing thresholds (500, 1000, and 2000 Hz) were within 25 dB; stage II, 26–40 dB; stage III, 41–70 dB; and stage IV, > 70 dB.

Statistical analysis

The statistical add-in software for Microsoft Excel 2007 was used for statistical analysis. The Fischer test was employed to test the correlation between oVEMP abnormality and the severity of disease, presence of vertigo, cVEMP abnormality, and SVV abnormality. The Cochran-Armitage test was used to identify the relationships between oVEMP abnormality and hearing outcome. A p value of < 0.05 was considered to indicate a statistically significant difference.

Results

We compared the ratio of abnormal oVEMP in three inner ear diseases. We compared VN as the vertigo-based labyrinthine disorders, with SSHL and MD as the auditory-based disorders. The ratio of abnormal oVEMP was the greatest in VN (68.2%). It was 9.2% in SSHL and 9.1% in MD (Figure 1).

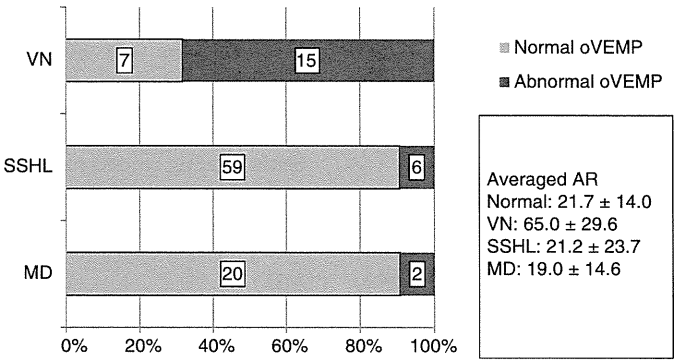

Figure 1. oVEMP results for each disease. In the comparisons of each disease, the ratio of abnormal oVEMP was greatest in vestibular neuritis (VN), followed by sudden sensorineural hearing loss (SSHL) and Meniere's disease (MD). AR, asymmetry ratio.

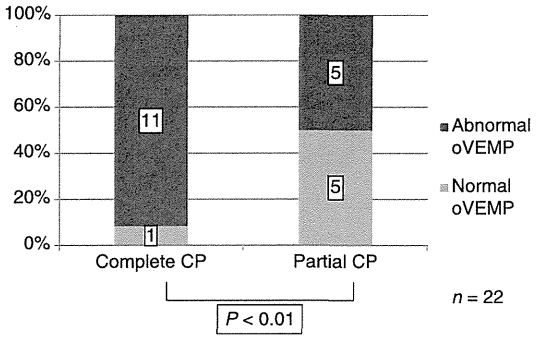

Figure 2. Magnitude of canal paresis (CP) in abnormal and normal oVEMP in patients with vestibular neuritis (VN). The patients with complete CP showed a higher rate of abnormal oVEMP than those with partial CP.

VN

Fifteen of 22 patients showed abnormal oVEMP, 7 of those showed normal oVEMP in VN (Figure 1). The average AR for oVEMP was 65.0 ± 29.6, which was significantly different from the normal AR.

We performed caloric tests in all VN patients, which revealed complete CP in 12 patients and partial CP in 10 patients. We analyzed whether or not changes in CP severity were related to the oVEMP. There was a significant difference in the rates of abnormal oVEMP between the partial and complete CP (Figure 2). The VN patients with complete CP showed a higher rate of abnormal oVEMP than those with partial CP.

Of 22 VN patients, 6 showed abnormal cVEMP and 16 showed normal cVEMP. We examined whether or not oVEMP results were related to cVEMP. Five of the six patients with abnormal cVEMP showed abnormal oVEMP and one showed normal oVEMP. Ten of the 16 patients with normal cVEMP showed abnormal oVEMP and 6 showed normal oVEMP. However, there was no significant correlation between oVEMP and cVEMP.

Seventeen of 22 patients showed an abnormal SVV. Twelve of 17 patients with an abnormal SVV showed abnormal oVEMP. Three of the five patients with a normal SVV showed abnormal oVEMP. There was no correlation between SVV and oVEMP in the VN patients.

SSHL

Of 65 patients, 6 showed abnormal oVEMP and 59 showed normal oVEMP (Figure 1). The average AR for oVEMP was 21.2 ± 23.7, which was not significantly different from normal AR.

We examined whether or not oVEMP results were related to cVEMP. Of 65 patients, 27 showed abnormal cVEMP and 38 showed normal cVEMP. Of the 27 patients with abnormal cVEMP, 4 showed abnormal oVEMP and 23 showed normal oVEMP. Of the 38 patients with normal cVEMP, 2 showed abnormal oVEMP and 36 showed normal oVEMP. There was no significant difference in the rates of abnormal oVEMP between the normal and abnormal cVEMP.

We examined whether or not oVEMP results were related to SVV. Of 65 SSHL patients, 20 showed an abnormal SVV, 39 showed a normal SVV, and 6 patients were not examined for SVV. There was no significant difference in the rates of abnormal oVEMP in those patients with normal and abnormal SVV.

Among the 65 SSHL patients, vertigo occurred in 25 patients. We compared the oVEMP in patients with and without vertigo. There was no significant difference in the rates of abnormal oVEMP in those patients with vertigo and those without vertigo.

SSHL patients were classified into the following four classes based on an initial measurement: grade 1 ($n = 3$), grade 2 ($n = 12$), grade 3 ($n = 23$), and grade 4 ($n = 25$). Abnormal oVEMP was noted in one patient in grade 1, one patient in grade 2, one patient in grade 3, and six patients in grade 4. Figure 3 shows the relationship between oVEMP and grade severity of initial hearing. The rates of abnormal oVEMP tended to be higher in the severe grade, but there was no significant correlation between abnormal oVEMP and grade severity of initial hearing. The SSHL patients with a high grade did not show a higher rate of abnormal oVEMP than those with low grade severity of initial hearing. We also classified SSHL patients into the following categories based on the hearing outcome: complete recovery ($n = 21$), marked recovery ($n = 19$), slight recovery ($n = 12$), and unchanged ($n = 13$). Figure 4 shows the correlations between oVEMP and hearing outcome. We found a significant correlation between hearing outcome and abnormal oVEMP. All patients with complete recovery and marked recovery had normal oVEMP. Abnormal oVEMP was noted in two patients in the slight recovery category and six patients in the unchanged group. The SSHL patients with better hearing recovery showed a lower rate of abnormal oVEMP ($p < 0.01$).

MD

Two of 22 patients with MD showed abnormal oVEMP and 20 showed normal oVEMP (Figure 1). The average AR for oVEMP was 19.0 ± 14.6, which was not significantly different from the normal AR.

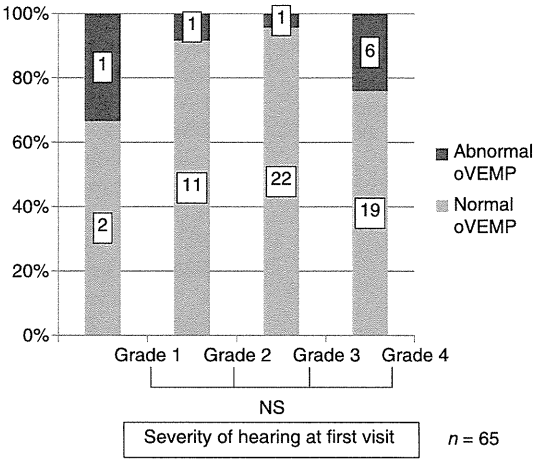

Figure 3. Relationship between oVEMP and severity of hearing at first visit in patients with sudden sensorineural hearing loss (SSHL). There was no significant correlation between abnormal oVEMP and degree of hearing loss at the first visit. The SSHL patients with a high grade at the first visit did not show a higher rate of abnormal oVEMP than those with a low grade of hearing loss. NS, not significant.

We examined whether or not oVEMP results were related to cVEMP. Of 22 patients with MD, 8 showed abnormal cVEMP. Of the 14 patients with normal cVEMP, 1 showed abnormal oVEMP and 13 showed normal oVEMP. Of the 8 with abnormal cVEMP, 1 showed abnormal oVEMP and 7 showed normal oVEMP. There was no significant difference in the rates of abnormal oVEMP in patients with normal and abnormal cVEMP.

We examined whether or not oVEMP results were related to SVV. Of 22 patients, 5 showed abnormal SVV. There was no significant difference in the rates of abnormal oVEMP between patients with normal and abnormal SVV. All of the 17 patients with normal SVV showed normal oVEMP. Of the five patients with abnormal SVV, two showed abnormal oVEMP. There was no significant difference in the rates of abnormal oVEMP between patients with normal and abnormal SVV.

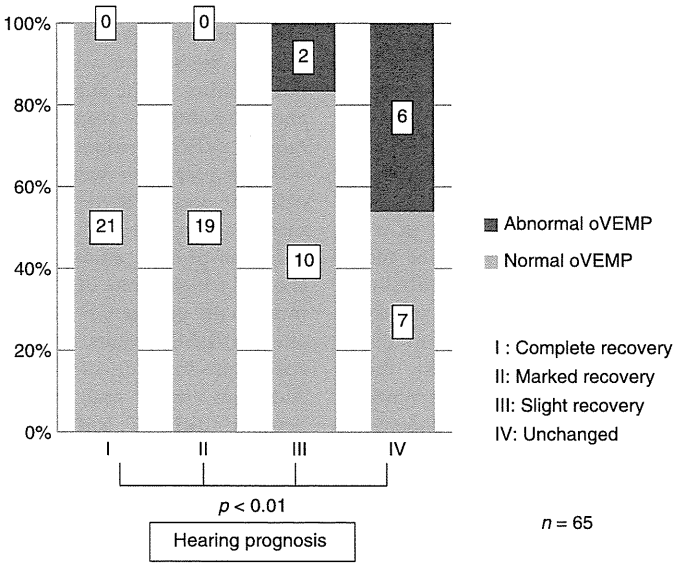

Figure 4. Relationship between oVEMP and hearing prognosis in sudden sensorineural hearing loss (SSHL). The hearing recovery rate was lower in the patients with abnormal oVEMP.

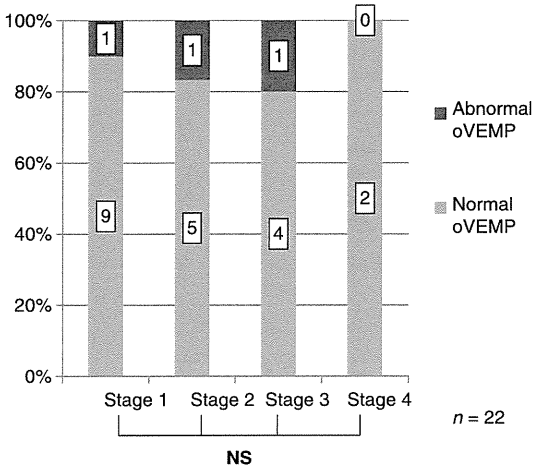

Figure 5. Relationship between oVEMP and stage of Meniere's disease (MD). There was no significant correlation between oVEMP and stage of MD. NS, not significant.

As regards MD, nine patients were classified as stage I, six as stage II, five as stage III, and two as stage IV. Among the six patients classified as stage II, one patient showed abnormal oVEMP. Among the five patients classified as stage III, one patient showed abnormal oVEMP. There was no significant relationship between stage and oVEMP (Figure 5).

Discussion

It is accepted that the ipsilateral p13-n23 of the air-conducted sound (ACS) cVEMP arises from saccular stimulation and measures inferior vestibular nerve function. In humans, oVEMP by BCV stimuli at Fz is suggested to reflect the function of the utriculus and superior vestibular nerve [7]. The oVEMP vestibular pathway appeared to be crossed and runs through the superior vestibular nerve. The vestibular origin of oVEMP is not yet fully understood. Iwasaki et al. showed that oVEMP in response to BCV of the midline forehead in patients with unilateral vestibular loss due to removal of the vestibular nerve was greatly reduced or absent on the side contralateral to the unilateral vestibular loss; the average AR for the patients was significantly higher than the average AR for healthy subjects [3]. Manzari et al. showed that oVEMP in unilateral vestibular loss due to removal of the eighth cranial nerve for treatment of vestibular schwannoma and neurectomy for treatment of MD reduced or eliminated n10 on the contralateral side [8]. oVEMP testing is acceptable even to senior patients because the procedure is quite easy. BCV is a modest stimulus that is not painful, is present for only a very brief time, and requires little effort on the part of the patient who is lying supine. However, few studies have been published about oVEMP in inner ear diseases. We have correlated oVEMP with cVEMP, SVV, the caloric test, and the clinical course in patients with vertigo-based labyrinthine disorders (VN) and auditory-based disorders (SSHL and MD).

We first consider the frequency of abnormal oVEMP in inner ear disease. Shin et al. reported that 73.2% of patients with VN had abnormal oVEMP [9]. Murofushi et al. reported that 100% of patients with VN had abnormal oVEMP, and 45% of patients with unilateral MD showed abnormal oVEMP [10]. In the present study, the ratio of abnormal oVEMP was the greatest in VN, followed by SSHL, and MD (Figure 1). These results indicate that oVEMP reflects the vestibular-evoked response rather than the auditory-evoked response and that superior vestibular function markedly affects oVEMP.

We investigated a vestibular-based labyrinthine disorder, VN. As regards AR, in previous studies [3,8], the AR of the patients with unilateral vestibular loss was significantly greater than the AR of the healthy subjects. In the present study, the results of AR in VN were similar to those of previous studies [2,3]. Most patients with VN had a higher AR than the average AR for healthy subjects; this result was significantly different.

Shin et al. found that oVEMP values were affected in superior VN while cVEMP values were apparently normal, while the opposite held for inferior VN [9]. They proposed that oVEMP responses were the result of utricular activation. Manzari et al. [11] reported that, in 59 patients with inferior vestibular neuritis, the function of the superior vestibular nerve (caloric and head-impulse responses) was within the normal range, cVEMP responses were asymmetrical, and oVEMP responses were normal. They showed that oVEMP and cVEMP differentiated utricular from saccular function [11].

In the present study, patients with complete CP showed a higher rate of abnormal oVEMP values than those with partial CP (Figure 2). CP severity may affect oVEMP results. In other words, oVEMP may reflect the function of the superior vestibular nerve. Although there was no significant relationship between cVEMP and oVEMP, VN patients with abnormal cVEMP tended to show abnormal oVEMP. These results suggest that the patients with both inferior and superior vestibular nerve disorder showed a higher rate of abnormal oVEMP than those with limited superior vestibular nerve disorder. The oVEMP abnormality depends on the severity of vestibular nerve disorder.

In particular, the caloric test is an index of superior vestibular nerve function. Although oVEMP is mainly affected by the superior vestibular nerve, it does not always match with the results of the caloric test. This result suggests that induction of oVEMP by BCV may reflect the vestibular function that is solely of the lateral semicircular canal, but rather that of the anterior semicircular canal and utriculus.

We also investigated auditory-based labyrinthine disorders, i.e. SSHL and MD. We first consider SSHL. In histopathologic findings of the cochlea, atrophic changes in the organ of Corti, stria vascularis, and tectorial membrane, as well as a significant decrease in the number of spiral ganglion cells and cochlear nerves have been reported [12]. The utriculus and semicircular canals might be normal or might have only mild lesions. Inagaki et al. [13] reported that the vestibular system changes in cases of sudden deafness with and without vertigo. One of the patients with vertigo had deposits in the utriculus. However, there was no remarkable difference in the density of vestibular hair cells in patients with vertigo and without vertigo [13]. Our finding that there was no significant difference in the rates of abnormal oVEMP in patients with and without vertigo was consistent with previous findings.

In the present study there was no significant correlation between abnormal oVEMP and degree of hearing loss at first visit. However, the hearing recovery rate was lower in the patients with abnormal oVEMP. This result suggests that oVEMP could be used for the prediction of prognosis in SSHL. Iwasaki et al. reported that the absence of cVEMP in 14 of 52 SSHL patients (26.9%) indicates a poor hearing recovery [14]. Our study showed a correlation between abnormal oVEMP and poor hearing recovery. In SSHL patients, abnormal oVEMP may indicate the greater spread of the lesion. The patients with abnormal oVEMP might have extensive vestibular disorders in addition to lesions in the organ of Corti, including stria vascularis and tectorial membrane.

Concerning the pathology of MD, it was reported that there is endolymphatic hydrops and saccular hydrops at the early stage [15]. At the later stages utricular hydrops, ruptures of the membranous labyrinth, fistulae of the membranous labyrinth, collapse of the membranous labyrinth, obstruction of longitudinal flow, and vestibular fibrosis develop. In addition, the level of hearing loss is generally correlated with the degree of hydrops in severe cases. Murofushi et al. showed that ACS oVEMP could be affected in the later stages of MD [10]. If hearing loss progresses, there should be high rates of abnormal oVEMP. Our results were not comparable to the previous studies [10,16]. Figure 5 shows that there was no difference between the degree of hearing loss and abnormal oVEMP. The small population of patients with MD in the present study may be responsible for the discrepancy in the results.

There was no correlation between SVV and oVEMP in the present study. In previous studies, it was reported that there was a correlation between oVEMP and SVV or SVH (subjective visual horizontal) in MD. Lin and Young showed that the rate of abnormal oVEMPs was 40% in MD, and that a significant correlation existed between SVH and oVEMP test results [16]. The utricular macula as well as the saccular macula is located close to the footplate of the stapes. BCV might stimulate not only utricular maculae, but also saccular maculae. The utricular condition is speculated to affect SVV more than the saccular condition [17]. oVEMP and SVV may share the same utricular reflex pathway, at least in part.

Conclusion

Patients with VN with complete CP showed a higher rate of abnormal oVEMP than those with partial CP. The superior vestibular nerve function mainly contributes to oVEMP. There were no significant differences in the incidence of abnormality between cVEMP and oVEMP in the patients with unilateral inner ear disease. There was no significant relationship between hearing level at first visit and oVEMP. Significant correlation was found between the grades of hearing outcome and abnormal oVEMP in patients with SSHL. oVEMP reflects the vestibular-evoked response rather than the auditory-evoked response and superior vestibular function markedly affects oVEMP.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Subsensory galvanic vestibular stimulation augments arterial pressure control upon head-up tilt in human subjects

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ABSTRACT

The vestibular system plays an important role in control of arterial pressure (AP) upon head-up tilt (HUT). To examine this role in human subjects, we previously compared changes in AP with and without high-amplitude galvanic vestibular stimulation (GVS), which is considered to obscure vestibular input. In contrast, regarding sensory function in skin and muscle, it has been documented that low-amplitude electrical stimulation improves both sensitivity and response. In the present study, we examined whether GVS of smaller amplitude improves AP control upon HUT. GVS was applied at the amplitude of the somatosensory threshold (0.3–0.8 mA), 0.1 mA over the threshold, and 0.1 and 0.2 mA below the threshold during HUT. AP decreased at the onset of HUT compared with that in the supine position in 15 of 25 subjects without GVS (-12 ± 2 mm Hg), but applying GVS at 0.1 mA below the somatosensory threshold diminished the decrease (0.3 ± 0.7 mm Hg). The APs of another 10 subjects were maintained or decreased by less than 5 mm Hg without GVS at the onset of HUT (4 ± 2 mm Hg), but applying GVS at the amplitude of 0.1 mA below the somatosensory threshold further increased the AP (12 ± 2 mm Hg). GVS at the other amplitudes did not result in AP changes in either group. Thus, subsensory weak GVS enhances AP control at the onset of HUT.

1. Introduction

The role of the vestibular system in the control of arterial pressure (AP) during postural change has been documented. In an animal study using cats, the magnitude of the fall in AP at the onset of 30° and 60° head-up tilt (HUT) was increased in the presence of vestibular lesions compared with that in intact cats (Doba and Reis, 1974). Previously, we clarified that galvanic vestibular stimulation (GVS) obscures the vestibulocardiovascular reflex in rats (Abe et al., 2008), and applied to the human subjects instead of vestibular lesions. Without GVS, AP is slightly increased in some subjects, but slightly decreased in the other at the onset of 60° HUT from the supine position. Thus, the averaged AP dropped only 4 mm Hg, compared to that during supine position. With applying GVS continuously, AP dropped by 16 mm Hg at the onset of 60° HUT from the supine position (Tanaka et al., 2009). Thus, the vestibular system also plays an important role in maintaining AP during postural change in human subjects.

To interrupt the vestibular-mediated cardiovascular response, we employed high amplitudes of 0.5 and 2.0 mA for rats and human subjects, respectively. At these amplitudes, head sway was observed in the rats (Abe et al., 2008), and human subjects experienced painless head sway (Tanaka et al., 2009). In contrast, some studies have shown that adding small-amplitude noise or subsensory electrical stimulation paradoxically improves the signal detection of receptors. Electric stimulation of the auditory nerve improved sound recognition of the auditory brainstem (Zeng et al., 2000). Subsensory electrical stimulation to the knee joint improved proprioception of the mechanoreceptors (Collins et al., 2010). As a result of this improvement, subsensory stimulation to the ankle muscles and ligaments reflexively improved postural stability (Ross et al., 2007). In the present study, we hypothesized that subsensory GVS improved or enhanced the vestibulocardiovascular reflex or AP control upon HUT. To examine the hypothesis, for both subjects whose AP is increased and decreased upon HUT, AP changes with and without GVS are measured in the present study.

2. Methods

23 healthy subjects and two otolaryngological outpatients of Gifu University Hospital comprising 15 males and 10 females (mean ± standard error (SE) of age, height, and weight were 28 ± 3 years, 164.9 ± 1.9 cm, and 60.2 ± 1.8 kg, respectively) were recruited for the study. For recruiting the subjects, otolaryngological outpatients were included, but the patients during treatment were excluded. Thus, subjects had no medication, and no past history of cardiovascular disease. This study was approved by the Institutional Review Board at Gifu University, and informed written consent was obtained from all subjects. The study was performed in accordance with the ethical standards laid down in 2008 version of Declaration of Helsinki.

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2.1. Vestibular function test

The vestibular function was examined to determine the relationship between the function and AP control upon HUT. 3 of 25 subjects had strong vertigo even after the end of the caloric test, and excluded from analysis of the relationship. Thus, 22 subjects were analyzed.

An air caloric test, which estimates unilateral canal paresis or relative reduction, was performed to test the semicircular canals and the related functions (Asai et al., 2009). Surface electrodes were placed beside the lateral angles of both eyes and frontal region of the head to detect eye movements using electronystagmography (Melvin et al., 2009). The signal was amplified, monitored, and recorded continuously at a rate of 120 Hz using an analog-to-digital converter with data acquisition and analysis software (CHARTR VNG/ENG, LCS Medical, Schaumburg, IL, USA). The electronystagmography data were passed through a low-pass filter with a high cut-off frequency of 30 Hz. The amplitude was calibrated with the angle of eye movement in advance. Subjects were shielded from light using goggles and positioned in supine with the head inclined 30° from the horizontal. The external auditory canals were alternately irrigated with warm air (50 °C) for 60 s and, after a recovery period, with cool air (24 °C) for 60 s using an air caloric stimulator (CHARTR NCA 200, LCS Medical, Schaumburg, IL, USA). The maximal slow-phase eye velocity of nystagmus was calculated following irrigation. Jongkees' formula was used to determine canal weakness (CW) or deviation of the responses as follows:

$$CW = [\{(RC + RW) - (LC + LW)\}/\{(RC + RW + LC + LW)\}] \times 100\ (\%)$$

where RC = right cool, LC = left cool, RW = right warm, and LW = left warm of the maximal slow-phase eye velocity of nystagmus (Enticott et al., 2003).

To test the otolith and the related functions, subjective visual vertical (SVV) testing was employed (Aoki et al., 2008). The subjects were seated upright and their heads were held in a vertical position by a chin rest. A 15-cm long and 5-mm wide rod with fluorescent tape was placed in front of each subject at a distance of 1 m. The rod was positioned at eye level in complete darkness, and randomly tilted in clockwise and counterclockwise directions. The subjects were required to adjust the rod to the subjective gravitational vertical position using a rotating handle wired to the rod. The degree of the rod, i.e., deviation from the real gravitational vertical was measured with precision digital angle-measuring equipment (NSL-150, Mutoh, Tokyo, Japan), which is connected to the rod. The degree can be measured to four places of decimals. Four trials in each direction were performed, and the difference in averaged degree between the directions was used for analysis.

2.2. Head-up tilt

AP was measured in the right middle finger with a continuous blood pressure monitor (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). During both supine position and HUT, the finger with the blood pressure cuff was placed at the heart level using an arm rest to avoid hydrostatic pressure difference between the heart and the measuring site throughout the measurement.

Data were monitored and recorded continuously using an analog-to-digital converter with data acquisition and analysis software (PowerLab, AD Instruments, Sydney, Australia) at the rate of 100 samples/s. For GVS, Ag/AgCl surface electrodes (area, 13.2 cm^2) were placed bilaterally over the mastoid processes. A biphasic current (0.1–0.9 mA, 200 ms duration, interphase delay changed randomly from 0 to 200 ms) was applied using an electric stimulator (NS-101; Unique Medical, Tokyo, Japan). Prior to measurement, the GVS amplitude was adjusted in 0.1-mA increments up to 0.9 mA, and the somatosensory threshold, which is the amplitude when starting to sense the stimulation, was determined. The procedure was performed for twice before measurement, and confirmed before each measurement with GVS again. Thus, the threshold was confirmed 6 times for each subject, and the threshold did not change throughout the measurements. For the measurements, the GVS was set at the following 4 amplitudes i.e., the somatosensory threshold, 0.1 mA over the threshold, and 0.1 and 0.2 mA below the threshold. 5 measurements i.e., measurements with GVS of 4 amplitudes and no stimulation (control) were numbered and a table of all order combination was made. The combination could be 5! = 120 arrangements, and the order for each subject was chosen from the table individually. Thus, no subject performed same order.

The subjects were positioned on a tilt table in the supine position, and the subjects' eyes were covered with an eye mask. The body was supported by a saddle to avoid contraction of the leg muscles (Tanaka et al., 2009). AP was stabilized in the supine position, and GVS was initiated. 1 min after the starting of GVS, the table was electrically tilted to 60° from the horizontal position. The target HUT angle was achieved in 3 s, and the volunteers were subjected to 2 min of 60° HUT. After 2 min of HUT, GVS was turned off, and the subjects were returned to supine position. The subjects were in the supine position at least 2 min, and AP was allowed to recover to the control level (Fig. 1). All subjects completed the experiments without any discomfort, including nausea and dizziness.

2.3. Analysis

The initial postural change was set at time zero. The mean AP values in the supine position for 30 s prior to HUT were considered to be the control values. The averaged value from 10 to 15 s, the largest change in AP, was used for analysis of its relationship with vestibular function and for comparison between GVS conditions. For analysis of the time course of AP changes, AP from 0 to 5, 5 to 10, 10 to 15, 15 to 20, 20 to 40, 40 to 60, and 60 to 120 s were averaged and compared with that in the supine position. To clearly observe the effect of GVS for change in AP, the subjects were divided in two groups according to the AP change. The averaged change in AP of all the subjects during 10 to 15 s was −4 mm Hg without GVS. To divide one subject of the just mean value, the border value was decided at −5 mm Hg in the present study. Thus, one comprised the subjects whose AP decreased by more than 5 mm Hg at the onset of HUT (DOWN, n = 15), and the other comprised the subjects whose AP increased or decreased by less than 5 mm Hg at the onset of HUT (UP, n = 10). Heart rate (HR) was calculated from peak to peak interval of the AP waveform. HR was also averaged and summarized in a similar way to AP.

The summarized data are represented as mean ± SE. To analyze the maximal changes in AP with and without GVS, one-way analysis of variance was employed. If statistically significant results were obtained, Scheffe's post-hoc test was employed for comparison between the conditions. To analyze the time course of AP changes, a repeated measure two-way analysis of variance was performed with time and conditions as factors. Statistical significance was set at $p<0.05$.

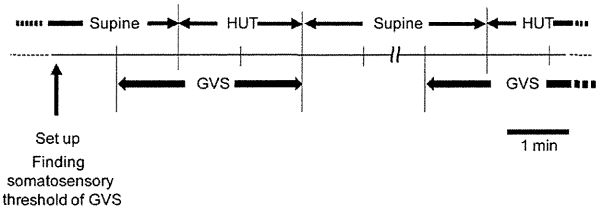

Fig. 1. Time course of head-up tilt (HUT) with galvanic vestibular stimulation (GVS). Prior to measurement, the somatosensory threshold was determined. GVS is started in supine position. 1 min after the starting of GVS, the subject was tilted to 60°. After 2 min of HUT, GVS was turned off, and the subject was returned to supine position at least 2 min. The procedure was repeated for 5 conditions.