3. Healthy subjects have almost identical n10 responses to stimuli at Fz or a point diametrically opposite Fz (the inion) in which case one would expect very different, even opposite, semicircular canal stimulation (Iwasaki et al., 2008a) and so very different, even opposite, n10 responses.

4.4. Bone-conducted vibration vs air-conducted sound

High intensity air-conducted sound produces oVEMPs (Chihara et al., 2007) and that result appears to suggest that saccular receptors and the inferior vestibular nerve may have a major role in generating oVEMPs (Chihara et al., 2007). That expectation is not in accord with the results here where saccular and inferior nerve function is intact, but the oVEMPs are not present. How can these results be reconciled? In our recent physiological experiments on guinea pigs (Curthoys et al., 2008, unpublished evidence), we have found that some irregular otolithic neurons in the dorsal superior vestibular nerve (and so likely utricular) respond to BCV and also to ACS at high intensity (around 70 dB above ABR threshold). Such neurons could mediate oVEMPs to BCV and ACS stimuli. That result implies that patients with SVN should have absent or markedly reduced oVEMPs to air conducted sound stimulation of the affected ear, just as we have shown they have markedly reduced responses to BCV.

5. Conclusion

We conclude that the otolithic receptors and afferents in the superior division of the vestibular nerve which were probably affected by the superior vestibular neuritis (predominantly from the utricular receptors) are responsible for the generation of the n10 component of the oVEMP response to BCV. We suggest that cVEMPs and oVEMPs give complementary information about peripheral vestibular function: cVEMPs to ACS probably test primarily saccular and inferior vestibular nerve function whereas oVEMPs to BCV at Fz probably test primarily utricular and superior vestibular nerve function.

Acknowledgements

This work was supported by grants from the National Health and Medical Research Council of Australia and Garnett Passe and Rodney Williams Memorial Foundation.

References

Aw ST, Fetter M, Cremer PD, Karlberg M, Halmagyi GM. Individual semicircular canal function in superior and inferior vestibular neuritis. Neurology 2001;57:768–74.

Chihara Y, Iwasaki S, Ushio M, Murofushi T. Vestibular-evoked extraocular potentials by air-conducted sound: another clinical test for vestibular function. Clin Neurophysiol 2007;118:2745–51.

Colebatch JG, Halmagyi GM, Skuse NF. Myogenic potentials generated by a click-evoked vestibulocollic reflex. J Neurol Neurosurg Psychiatry 1994;57:190–7.

Curthoys IS, Kim J, McPhedran SK, Camp AJ. Bone conducted vibration selectively activates irregular primary otolithic vestibular neurons in the guinea pig. Exp Brain Res 2006;175:256–67.

de Burlet HM. Zur Innervation der Macula sacculi bei Säugetieren. Anat Anzeig 1924;58:26–32.

de Burlet H. Zur vergleichenden Anatomie der Labyrinthinnervation. J Comp Neurol 1929;47:155–69.

Fetter M, Dichgans J. Vestibular neuritis spares the inferior division of the vestibular nerve. Brain 1996;119:755–63.

Gianoli G, Goebel J, Mowry S, Poomipannit T. Anatomic differences in the lateral vestibular nerve channels and their implications in vestibular neuritis. Otol Neurotol 2005;26:489–94.

Goebel JA, O'Mara W, Gianoli G. Anatomic considerations in vestibular neuritis. Otol Neurotol 2001;22:512–8.

Halmagyi GM, Curthoys IS. A clinical sign of canal paresis. Arch Neurol 1988;45:737–9.

Iwasaki S, McGarvie LA, Halmagyi GM, Burgess AM, Kim J, Colebatch JG, et al. Head taps evoke a crossed vestibulo-ocular reflex. Neurology 2007;68:1227–9.

Iwasaki S, Smulders YE, Burgess AM, McGarvie LA, MacDougall HG, Halmagyi GM, et al. Ocular vestibular evoked myogenic potentials to bone conducted vibration of the midline forehead at Fz in healthy subjects. Clin Neurophysiol 2008a;119:2135–47.

Iwasaki S, Smulders YE, Burgess AM, McGarvie LA, MacDougall HG, Halmagyi GM, et al. Ocular vestibular evoked myogenic potentials in response to bone conducted vibration of the midline forehead at Fz—a new indicator of unilateral otolithic loss. Audiol Neurotol 2008b;13:396–404.

Jombik P, Bahyl V. Short latency responses in the averaged electro-oculogram elicited by vibrational impulse stimuli applied to the skull: could they reflect vestibulo-ocular reflex function? J Neurol Neurosurg Psychiatry 2005;76:222–8.

McCue MP, Guinan Jr JJ. Acoustically responsive fibers in the vestibular nerve of the cat. J Neurosci 1994;14:6058–70.

McCue MP, Guinan Jr JJ. Sound evoked activity in primary afferent neurons of a mammalian vestibular system. Am J Otol 1997;18:355–60.

Murofushi T, Curthoys IS, Topple AN, Colebatch JG, Halmagyi GM. Responses of guinea pig primary vestibular neurons to clicks. Exp Brain Res 1995;103:174–8.

Murofushi T, Halmagyi GM, Yavor RA, Colebatch JG. Absent vestibular evoked myogenic potentials in vestibular neurolabyrinthitis. An indicator of inferior vestibular nerve involvement? Arch Otolaryngol Head Neck Surg 1996;122:845–8.

Murofushi T, Curthoys IS. Physiological and anatomical study of click-sensitive primary vestibular afferents in the guinea pig. Acta Otolaryngol 1997;117:66–72.

Nadol JB. Vestibular Neuritis. Otolaryngol Head Neck Surg 1995;112:162–72.

Oostenveld R, Praamstra P. The five percent electrode system for high-resolution EEG and ERP measurements. Clin Neurophysiol 2001;112:713–9.

Rosengren SM, Todd NPM, Colebatch JG. Vestibular-evoked extraocular potentials produced by stimulation with bone-conducted sound. Clin Neurophysiol 2005;116:1938–48.

Suzuki JI, Tokumasu K, Goto K. Eye movements from single utricular nerve stimulation in the cat. Acta Otolaryngol 1969;68:350–62.

Todd NPM, Rosengren SM, Aw ST, Colebatch JG. Ocular vestibular evoked myogenic potentials (OVEMPs) produced by air- and bone-conducted sound. Clin Neurophysiol 2007;118:381–90.

Tsubota M, Shojaku H, Hori E, Fujisaka M, Hayashi N, Kurimoto M, et al. Effects of vestibular nerve section on sound-evoked myogenic potentials in the sternocleidomastoid muscle of monkeys. Clin Neurophysiol 2007;118:1488–93.

Welgampola MS. Evoked potential testing in neuro-otology. Curr Opin Neurol 2008;21:29–35.

Welgampola MS, Colebatch JG. Characteristics and clinical applications of vestibular-evoked myogenic potentials. Neurology 2005;64:1682–8.

Winer BJ, Brown DR, Michels KM. Statistical principles in experimental design. New York: McGraw Hill; 1991.

Clinical Neurophysiology 120 (2009) 581–587

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Ocular vestibular-evoked myogenic potentials (oVEMPs) require extraocular muscles but not facial or cochlear nerve activity

Yasuhiro Chihara [a,*], Shinichi Iwasaki [a], Munetaka Ushio [a], Chisato Fujimoto [a], Akinori Kashio [a], Kenji Kondo [a], Ken Ito [a], Takahiro Asakage [a], Tatsuya Yamasoba [a], Kimitaka Kaga [b], Toshihisa Murofushi [a,c]

[a] Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine, University of Tokyo, Hongo 7-3-1, Bunkyo-ku, 113-8655 Tokyo, Japan
[b] National Institute of Sensory Organs, Tokyo, Japan
[c] Department of Otolaryngology, Teikyo University, Mizonokuchi, Japan

See Editorial, pages 451–452

ARTICLE INFO

Article history:
Accepted 6 December 2008
Available online 10 February 2009

Keywords:
VEMP
oVEMP
Facial palsy
Hearing loss
Otolith
Saccule
Utricule
Vestibulo-ocular reflex

ABSTRACT

Objectives: Cervical vestibular evoked myogenic potentials (cVEMPs) have been found to be useful for clinical testing of vestibular function. Recently, investigators showed that short-latency, initially negative surface EMG potentials can be recorded around the extraocular muscles (oVEMPs) in response to air-conducted sound (ACS), bone-conducted vibration (BCV), and head taps. Although these evoked potentials, which are located around the eyes, most likely originate primarily from the otolith-ocular pathway, the possibility of contamination by other nerve activities cannot be completely eliminated. The purpose of the present study was to clarify the origin of oVEMPs by examining these possibilities using clinical findings.
Methods: Twelve healthy subjects and 15 patients were enrolled. Of the 15 patients, 3 patients had undergone exenteration of the unilateral intraorbital contents, one had undergone exenteration of the right eyeball with preservation of extraocular muscles, 5 had facial palsy, and 6 had profound hearing loss. ACS and/or BCV were used in these subjects.
Results: Exenteration of the unilateral intraorbital contents resulted in absence of myogenic potentials on the affected side. On the other hand, exenteration of the eyeball with preservation of extraocular muscles did not have a major impact on the responses. There were no significant differences in the waveforms between healthy subjects and patients with facial palsy or profound hearing loss.
Conclusions: The results suggested that short-latency, initially negative evoked potentials recorded below the eyes are not affected by cochlear or facial nerve activities and are dependent on the presence of extraocular muscles.
Significance: This study provides the evidence that oVEMPs originate from exraocular muscles activated through the vestibulo-ocular pathway.

1. Introduction

Cervical vestibular evoked myogenic potentials (cVEMPs) have been clinically used for testing vestibular function, especially of the saccule and the inferior vestibular nerve, since the first report of surface potentials from the sternocleidomastoid muscles (SCMs) in response to loud clicks in 1992 (Colebatch and Halmagyi, 1992; Colebatch et al., 1994; Murofushi et al., 1996; Welgampola and Colebatch, 2005).

Recent studies have shown that short-latency, initially negative surface EMG potentials can be recorded from around the eyes in response to air-conducted sound (ACS) and bone-conducted vibration (BCV) (Rosengren et al., 2005; Todd et al., 2004). It was assumed that these potentials could represent vestibular function mediated by crossed otolith-ocular pathway because these potentials were present in patients without hearing and absent on the contralateral side in those with unilateral vestibular loss (Chihara et al., 2007; Iwasaki et al., 2007). Investigators now use the term (extra)ocular vestibular evoked myogenic potentials (oVEMP or OVEMP) to refer to these responses. The oVEMPs are likely to be produced by synchronous activities in the extraocular muscles based on the following circumstantial evidence: (1) the largest

* Corresponding author. Tel.: +81 3 5800 8665; fax: +81 3 3814 9486.
E-mail address: y-chihara@umin.ac.jp (Y. Chihara).

1388-2457/$36.00
doi:10.1016/j.clinph.2008.12.030

oVEMPs are obtained from the electrodes placed inferior to the eyes with upgaze; (2) oVEMPs are inconsistent with the electro-oculography montage; and (3) oVEMPs occur before the eyes start to move (Rosengren et al., 2005; Todd et al., 2007).

An advantage of oVEMPs is that subjects do not have to contract the SCMs during recording, so that oVEMPs can be easily recorded from the elderly, children, and patients with cervical spondylosis (Chihara et al., 2007; Iwasaki et al., 2007). In addition, the neural pathway of oVEMPs apparently includes an ascending path from the vestibular nucleus, whereas that of cVEMPs includes a descending path to the SCMs (Welgampola and Colebatch, 2005). These different pathways between cVEMPs and oVEMPs may complement each other clinically.

However, it is possible that oVEMPs are contaminated by other factors, especially eye movements (electro-oculograms), facial nerve activities (blink reflexes), and cochlear nerve activities, given the properties of the stimulation (intense sound or vibration) and recording sites (close to the eyeballs and the orbicularis oculi muscles). The purpose of the present study was to clarify the origin of oVEMPs by examining these possibilities using clinical findings.

2. Materials and methods

2.1. Subjects

Twelve healthy subjects (10 men, 2 women; age range 26–40 years, mean age 30 years) were enrolled in the study with the approval of the University of Tokyo Human Ethics Committee. Each subject received oVEMP testing in response to both ACS and BCV stimuli. The subjects had no history of vertigo, hearing loss, or visual problems, except for standard refractive errors.

Fifteen patients with known lesions were also enrolled. Of these, 3 had undergone exenteration of the unilateral intraorbital contents due to malignant tumors, 1 had undergone exenteration of the left eyeball due to an injury, 5 had severe unilateral peripheral facial palsy, and 6 had bilateral profound sensorineural hearing loss with preserved vestibular function. In the 3 patients who had undergone exenteration of the unilateral intraorbital contents (Patients 1–3), the dead space had been grafted with free flaps obtained from the rectus abdominis muscles with pedicles. A patient (Patient 4) who had undergone exenteration of the left eyeball due to an injury had his left extraocular muscles kept intact and, thus, he could move his artificial eye (Table 1).

In 5 patients with facial palsy, 4 were due to Bell's palsy and 1 had a hemangioma in the left temporal bone (Table 1). The patients with Bell's palsy presented with acute facial weakness over a period of 24–48 h and had complete or nearly complete facial palsy within 1 week of the onset. The severity of the facial weakness in each patient was House–Brackmann grade V or VI (House and Brackmann, 1985).

In 6 patients with profound hearing loss, 1 had bilateral enlarged vestibular aqueducts, 2 had Connexin 26 gene abnormalities, 1 had familial hearing loss, and 2 had idiopathic bilateral hearing loss (Table 1). The cVEMP testing was not performed in subjects who could not maintain adequate SCM tension (Patients 11, 14, and 15). All patients showed preserved vestibular function based on caloric testing using cold water.

2.2. Air-conducted sound (ACS) and bone-conducted vibration (BCV) testing

ACS and BCV with 500 Hz short tone bursts (STBs) (rise/fall time = 1 ms, plateau time = 2 ms) were used (Chihara et al., 2007; Iwasaki et al., 2007).

ACS was presented through a calibrated headphone (type DR-531, Elega Acoustics Co., Ltd., Tokyo, Japan). The stimulus intensity was controlled by a Neuropack Sigma (Nihon Kohden, Tokyo, Japan) and set at 135 dB peSPL (peak equivalent sound pressure level). The stimulation rate was 5 Hz.

BCV was delivered through a bone vibrator, a Bruel and Kjaer (Naerum, Denmark) "Mini-shaker" 4810 fitted with a short rod that terminated in a 1-cm-diameter Bakelite cap (Iwasaki et al., 2007). The Mini-shaker was hand-held and contacted the subject's forehead at Fz (midline of the head at the hair line). The stimulus intensity was controlled by the same device used to produce ACS

Table 1
Data for patients.

Patient No.	Age (year)/sex	Disease		ACS–cVEMP Affected side/ unaffected side	ACS–oVEMP Affected side/ unaffected side	BCV–oVEMP Affected side/ unaffected side
1	51/M	rt. orbital tumor	extraocular m. ⊖	N/N	−/−	−/+
2	77/M	lt. maxillary tumor		N/N	−/+	−/+
3	65/F	lt. maxillary tumor		N/N	N/N	−/+
4	66/M	lt. eyeball injury	extraocular m. ⊕	N/N	+/+	+/+
5	27/F	rt. Bell's palsy		+/+	+/+	+/+
6	56/M	rt. Bell's palsy		+/+	+/+	+/+
7	60/M	lt. Bell's palsy		+/N	N/+	+/+
8	55/F	lt. Bell's palsy		+/+	−/−	+/+
9	61/M	lt. temporal bone hemangioma		N/+	+/N	+/+
				Left/right	Left/right	Left/right
10	4/F	bil. enlarged vestibular aqueduct		+/+	+/+	+/+
11	2/M	Connexin 26 gene abnormality		N/N	+/+	N/N
12	2/F	Connexin 26 gene abnormality		+/+	+/+	N/N
13	23/F	Familial hearing loss		+/+	+/+	+/+
14	70/F	Idiopathic hearing loss		N/N	N/N	+/+
15	63/F	Idiopathic hearing loss		N/N	N/N	+/+

lt: left, rt: right, bil: bilateral.
extraocular m.: extraocular muscles, ACS: air conducted sound, BCV: bone conducted vibration, cVEMP: cervical VEMP, oVEMP: ocular VEMP.
+: clear response, −: no response, N: no data.
When a patient had a conductive hearing loss, ACS assessment was skipped (N: no data). Likewise, if a patient had undergone neck surgery, such as neck dissection for malignant tumor, cVEMP assessment was skipped.

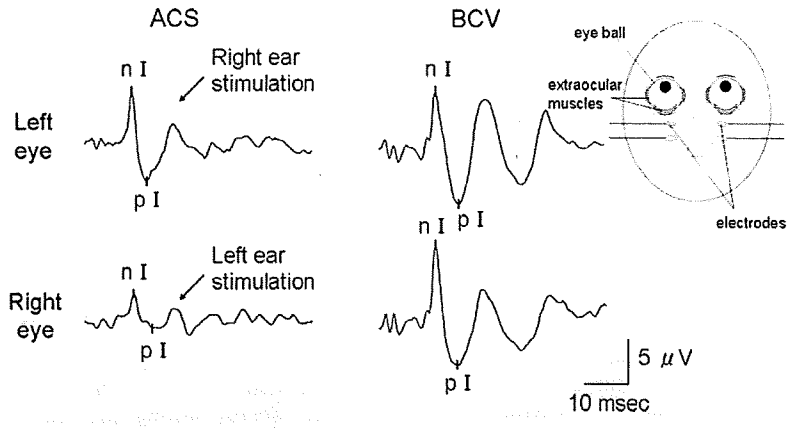

Fig. 1. An example of a 29-year-old healthy male who was tested using ACS and BCV. This subject was instructed to gaze upwards during stimulation. In the present study, the initial negative–positive biphasic potentials (nI and pI) were assessed. When ACS was delivered, the oVEMPs were, as stated in Section 2, predominantly obtained from the electrodes located beneath the eye contralateral to the stimulation (thus, when using ACS, ipsilateral eye responses to the stimulated ear are not shown in the figure). ACS: air conducted sound, BCV: bone conducted vibration, nI: the first negative peak, pI: the following positive peak.

(Neuropack Sigma). The stimulus intensity in the direction of the long axis of the rod was set at 120 dB FL (force level), which was calibrated using a Bruel and Kjaer (model BMK 4930) artificial mastoid.

For ACS, 0 dB SPL is referenced to 20 μP of air pressure, whereas for BCV, 0 dB FL is referenced to 1 μN of force on the head.

2.3. oVEMPs

The method used to record oVEMPs has been previously described (Chihara et al., 2007; Iwasaki et al., 2007; Todd et al., 2007). Briefly, the subjects were placed in the supine position, and surface electromyographic (EMG) activity was recorded from active electrodes placed on the face just inferior to each eye, with the reference electrodes placed 1–2 cm below. EMG signals were amplified and band-filtered between 5 and 500 Hz. The analysis time for each stimulation was 50 ms. Responses for up to 100 stimuli were averaged using the Neuropack Sigma. The subjects were instructed to look upward during recording to optimize the oVEMP responses (Chihara et al., 2007; Iwasaki et al., 2007; Rosengren et al., 2005). The initial negative peak (nI) with short latencies around 10 ms and the following positive peak (pI) were analyzed. When using ACS, the responses were predominantly obtained from the electrodes located beneath the eye contralateral to the stimulation (Chihara et al., 2007); thus, the contralateral eye responses were used for assessment when using ACS in the present study. When using BCV, the responses from both eyes were assessed, since BCV elicits bilateral eye responses simultaneously (Iwasaki et al., 2007).

2.4. Statistical analysis

One-way ANOVA was used to assess the overall difference in the latencies and amplitude between the groups using the statistical software package Statcel (Version 2, OMS Inc., Tokyo, Japan). The difference between the affected side and the unaffected side of facial palsy patients was also assessed using Student's *t*-test. Differences with a $p < 0.05$ were considered significant.

3. Results

3.1. oVEMPs in healthy subjects

Of the 12 healthy subjects, 11 showed oVEMP responses to ACS stimuli, and all showed oVEMP responses to BCV. The typical waveforms of the oVEMPs elicited by ACS and BCV are shown in Fig. 1. The average initial negative peak latency (nI), the subsequent positive peak latency (pI), and the amplitude between nI and pI of the healthy subjects are summarized in Table 2, and plotted in Fig. 2. The oVEMP responses showed substantial differences in amplitude among subjects whereas their latencies showed almost normal distributions. Especially, one normal control subject showed a very

Table 2
Latency and amplitude of healthy subjects and patients (means ± SD).

	Healthy subjects (n = 22 eyes for ACS, n = 24 eyes for BCV)	Unaffected side of patients with facial palsy (n = 3 eyes for ACS, n = 5 eyes for BCV)	Affected side of patients with facial palsy (n = 3 eyes for ACS, n = 5 eyes for BCV)	Patients with bilateral profound hearing loss (n = 8 eyes for ACS, n = 8 eyes for BCV)
ACS				
nI latency (ms)	11.0 ± 0.8	11.6 ± 0.8	11.2 ± 0.4	10.5 ± 0.3
pI latency (ms)	16.0 ± 1.3	16.9 ± 2.1	15.3 ± 1.5	15.1 ± 1.5
Amplitude between nI and pI (μV)	7.7 ± 7.5	4.1 ± 2.9	5.5 ± 3.6	3.5 ± 1.9
BCV				
nI latency (ms)	11.7 ± 1.2	10.5 ± 1.4	10.8 ± 1.8	10.9 ± 0.9
pI latency (ms)	16.7 ± 1.4	15.8 ± 2.3	15.4 ± 2.6	15.8 ± 1.3
Amplitude between nI and pI (μV)	13.1 ± 7.6	14.1 ± 8.1	14.6 ± 7.4	14.7 ± 7.2

ACS: air conducted sound, BCV: bone conducted vibration, nI: the first negative peak, pI: the following positive peak.

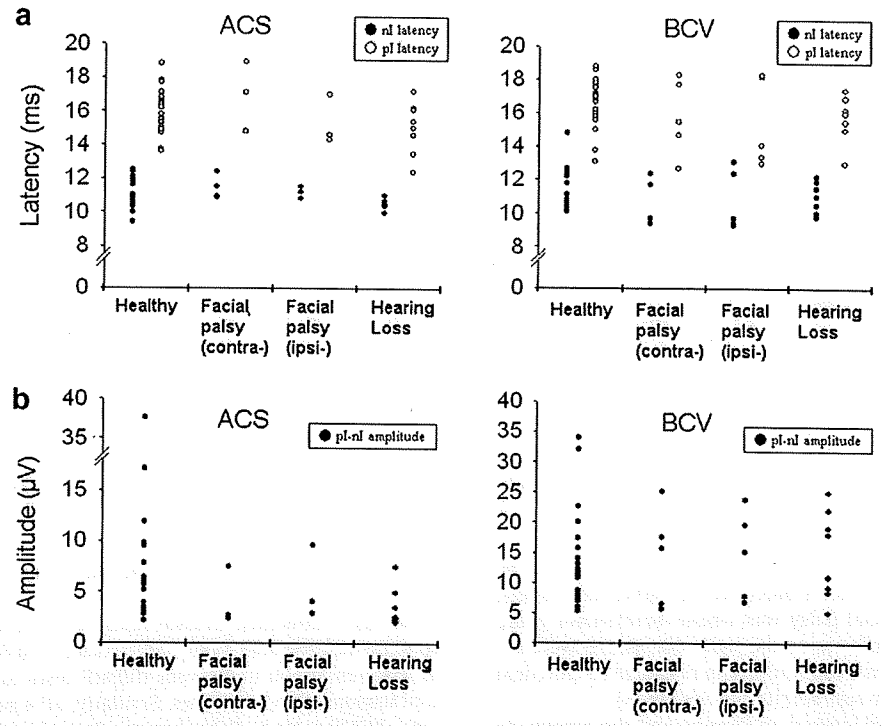

Fig. 2. Dotted charts of the nI and pI latencies and the amplitude between nI and pI. (a) Black and white circles show the nI and pI latencies, respectively. Both nI and pI latencies were not significantly different between the groups ($p > 0.05$, one-way ANOVA). (b) The black circles show the amplitude (μV) between nI and pI of each subject or patient. The amplitude did not differ between the groups ($p > 0.05$, one-way ANOVA). Healthy: healthy subjects ($n = 22$ eyes for ACS, $n = 24$ eyes for BCV), Facial palsy (contra-): unaffected side of patients with facial palsy ($n = 3$ eyes for ACS, $n = 5$ eyes for BCV), Facial palsy (ipsi-): affected side of patients with facial palsy ($n = 3$ eyes for ACS, $n = 5$ eyes for BCV), Hearing loss: patients with profound hearing loss ($n = 8$ eyes for ACS, $n = 8$ eyes for BCV).

large amplitude of oVEMPs to ACS (37.6 μV) in his left eye (Fig. 2b), but the subject did not have any symptoms suggesting otologic diseases including superior canal dehiscence syndrome (Minor et al., 1998; Rosengren et al., 2008; Welgampola et al., 2008).

3.2. Patients without unilateral intraorbital contents or without a unilateral eyeball

All patients who had undergone exenteration of unilateral intraorbital contents (Patients 1–3) showed the absence of oVEMPs on the affected (eye) side to either ACS or BCV stimuli (Table 1). Fig. 3 demonstrates the oVEMPs of a patient who underwent left orbital exenteration for maxillary carcinoma. He did not show oVEMPs on the left eye to right-ACS and Fz-BCV, whereas clear oVEMPs were recorded on the right eye to left-ACS and Fz-BCV (Fig. 3). On the other hand, a patient (Patient 4), who underwent left eyeball exenteration leaving the extraocular muscles intact showed oVEMPs on both sides in response to both ACS and BCV stimuli (Fig. 4). These results suggest that the extraocular muscles play critical roles in the generation of oVEMP responses.

3.3. Patients with unilateral facial palsy

All 5 patients with unilateral facial palsy showed clear BCV–oVEMPs both on the unaffected side and on the affected side, whereas 3 of the 4 recorded patients showed clear ACS–oVEMPs

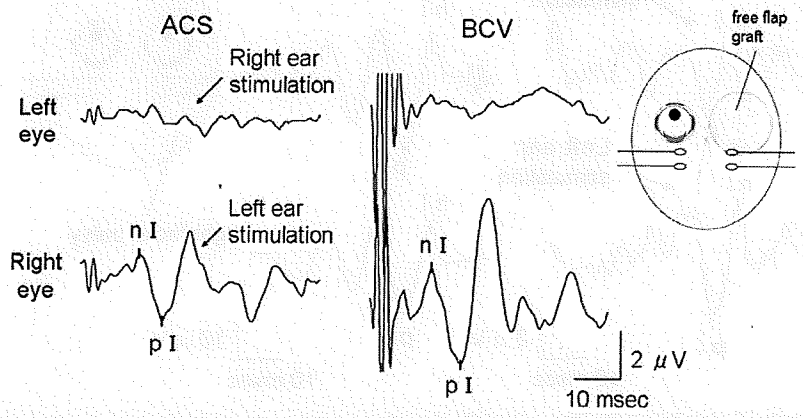

Fig. 3. An example of a 77-year-old male without left intraorbital contents (Patient 2). He showed no oVEMPs on the affected side.

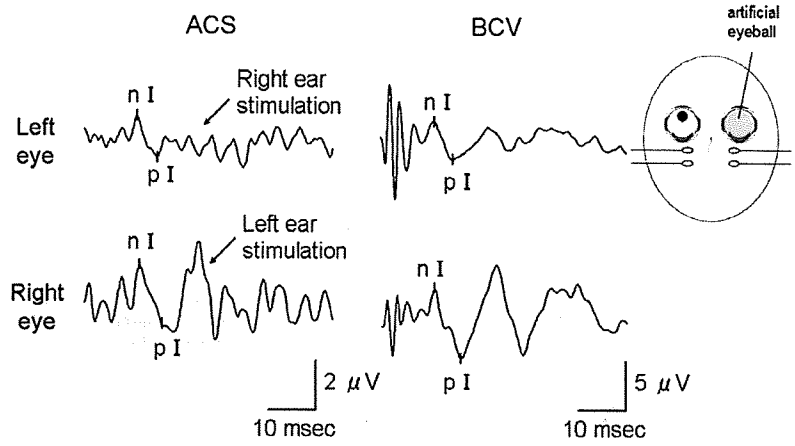

Fig. 4. An example of a 66-year-old male without the left eyeball but with intact left extraocular muscles (Patient 4). He showed clear oVEMPs on both sides.

on the affected side. Fig. 5 demonstrates oVEMP responses recorded from a patient with Bell's palsy on the right side (Patient 5). The severity of her facial palsy was House–Brackmann grade VI. She showed no blink reflexes on the right side, which were recorded from the orbicularis oculi muscles in response to electrical stimulation (18 mA) of the supraorbital nerve (Fig. 5).

The average values of nI latency, pI latency, and the amplitude between nI and pI of the 5 patients are shown in Table 2.

3.4. Patients with bilateral sensorineural profound hearing loss

We also performed oVEMP tests on 6 patients with bilateral profound hearing loss who had normal caloric responses. All of the 4 patients who underwent oVEMP tests to ACS showed clear nI–pI responses on both sides. Similarly, all 4 patients who underwent oVEMP tests to BCV showed clear nI–pI responses on both sides. Fig. 6 demonstrates the oVEMP responses in a patient with

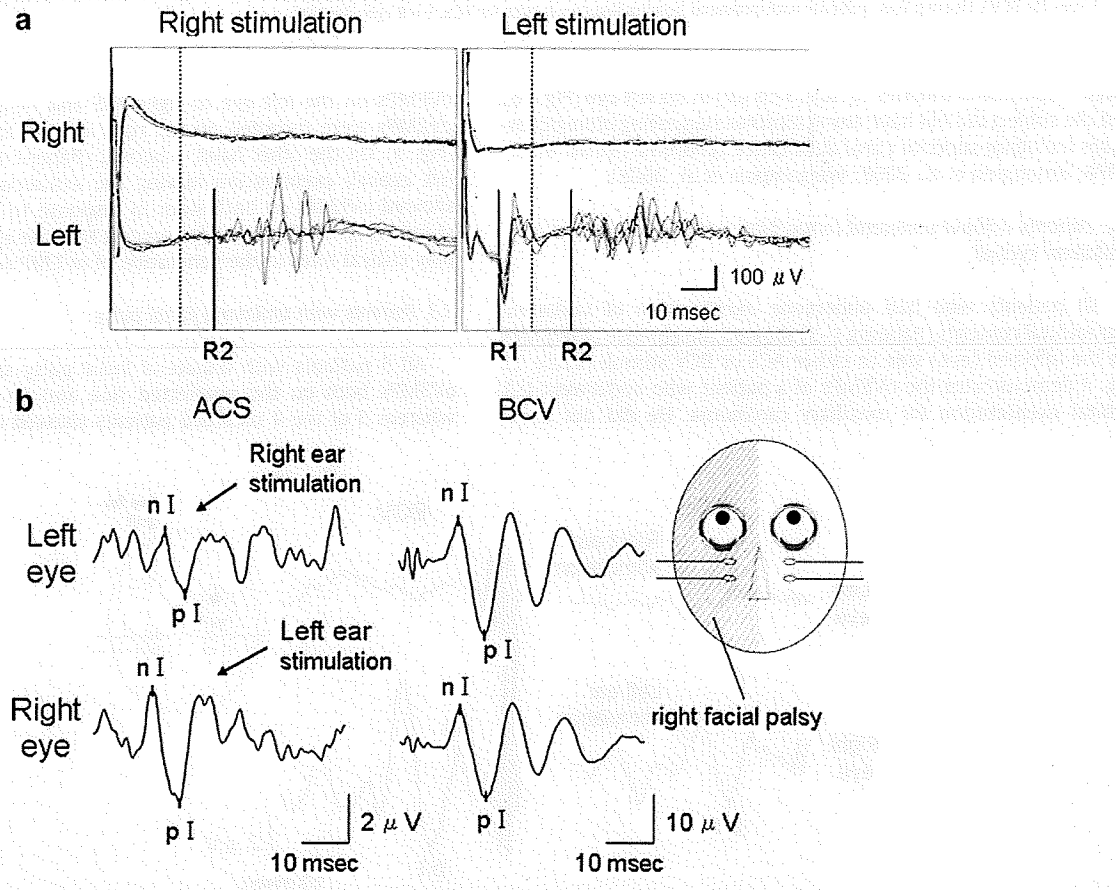

Fig. 5. An example of a 27-year-old female with right Bell's palsy (Patient 5). (a) She showed no response to the blink reflex test using 18 mA electrical stimulation on the affected side, whereas she showed good responses on unaffected side. (b) On the other hand, she showed clear oVEMPs on both sides.

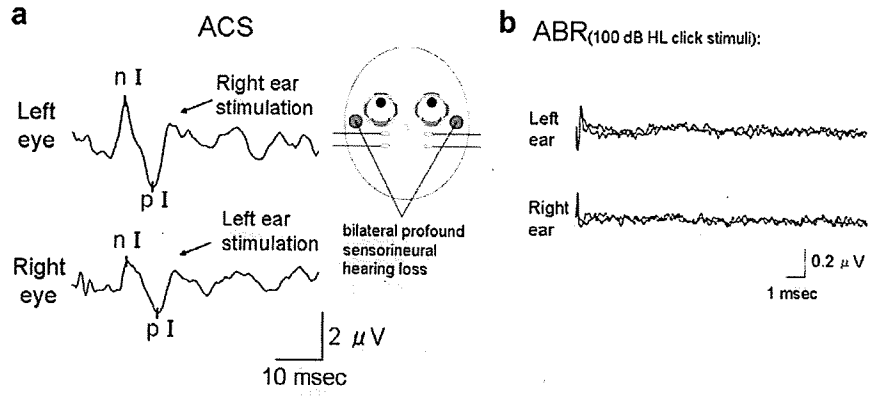

Fig. 6. An example of a 2-year-old girl with bilateral profound sensorineural hearing loss due to a Connexin 26 gene abnormality (Patient 12). (a) The patient showed clear oVEMPs on both sides in response to ACS stimuli. (b) She showed no response on ABR testing. ABR: auditory brainstem responses.

a Connexin 26 gene abnormality (Patient 12). She showed absent auditory brainstem responses (ABRs) to 100 dB nHL AC clicks, but normal responses on caloric testing and cVEMP tests. She showed normal oVEMP responses on ACS testing on both sides (Fig. 6).

The average values of nI latency, pI latency, and the amplitude between nI and pIof the patients with bilateral profound hearing loss are shown in Table 2.

The nI and pI latency and the amplitude between nI and pI of each healthy subject and patients with facial palsy and profound hearing loss are summarized in Fig. 2. No significant differences were observed in the latencies and amplitude of oVEMPs between the groups ($p > 0.05$, one-way ANOVA). There were also no significant differences between the affected side and the unaffected side of facial palsy patients ($p > 0.05$, Student's t-test).

4. Discussion

Previous studies have suggested that oVEMPs are generated by a crossed vestibulo-ocular reflex activated by ACS or BCV (Chihara et al., 2007; Iwasaki et al., 2007; Rosengren et al., 2005; Todd et al., 2004). However, a possibility remained that both ACS and BCV might excite nerves other than the vestibular nerves, thereby affecting the oVEMPs. In particular, blink reflexes elicited by tapping one side of the forehead (Overend, 1896) or electrically stimulating the supraorbital nerve (Kugelberg, 1952) (inputs = the trigeminal nerve, outputs = the facial nerve) and auditory brainstem responses (ABRs) evoked by AC clicks (Jewett et al., 1970; Sohmer and Feinmesser, 1970) (inputs = the cochlear nerve) may contaminate the early negative component of the oVEMPs, since the stimuli used to evoke these responses are similar to the BCV and ACS used to evoke oVEMPs. To clarify whether oVEMPs were affected by cochlear and/or facial nerve activities, oVEMPs were recorded from patients with facial palsy or profound hearing loss in the present study. Furthermore, in order to test the hypothesis that the responses are derived not from eyeballs or eye movements but from activities of the extraocular muscles, oVEMPs were recorded from patients without unilateral intraorbital contents or without an eyeball.

4.1. The contribution of unilateral intraorbital contents or unilateral eyeball to oVEMPs

All 3 patients without unilateral intraorbital contents (Nos. 1–3) showed no oVEMP responses on the affected side in response to both ACS and BCV (Table 1, Fig. 3), suggesting that intraorbital contents are indispensable for the generation of ipsilateral oVEMPs. This result is consistent with a previous study reported by Todd et al. (2007) but different from that reported by Rosengren et al. (2005). These two studies recorded oVEMPs from the same patient who had undergone right craniofacial resection and exenteration of the right eye and extraocular muscles. Rosengren et al. (2005) reported that short latency, negative potentials could be recorded from both of the patient's eyes, whereas Todd et al. (2007) reported that oVEMPs were present around the intact eye in response to AC and BC stimulation, but not present around the empty eye socket, as in the present study. The difference between these two studies was probably due to differences in the recording method, since Rosengren et al. (2005) placed active electrodes around the eyes with reference electrodes on the earlobe, whereas Todd et al. (2007) used a bipolar montage of electrode pairs placed around the eyes, which was similar to the method used in the present study. It is probable that the spread of excitation from the intact side to the empty side was avoided by the differential recording method using closely spaced electrodes for recording oVEMPs adopted by Todd et al. (2007) and the present study.

A patient without a left eyeball but with preserved extraocular muscles (Patient 4) was also assessed in the present study. This patient showed clear oVEMP responses in both eyes (Fig. 4), suggesting that the eyeball is not essential for the responses. This result, combined with the results obtained from patients without unilateral intraorbital contents, supports the hypothesis that oVEMPs represent electromyogenic activities of the extraocular muscles.

4.2. The influence of facial nerve activity on oVEMPs

All 5 patients with unilateral facial palsy (Nos. 5–9) showed almost symmetrical oVEMPs (Table 1, Fig. 5), and there were no significant differences in the latencies and amplitudes of the oVEMP responses evoked by ACS and BCV between these patients and healthy subjects, suggesting that facial nerve activity had little effect on the oVEMP waveform.

It is still possible that the BCV used in the present study might evoke a blink reflex as a modification of the "glabella tap reflex". The blink reflex response to a glabella tap is known to consist of an early (latencies around 12.5–15 ms) and a late (latencies around 30.5–32 ms) component bilaterally, the well-known R1 and R2 responses (Snow and Frith, 1989; Sunohara et al., 1985). The afferent limb of the reflex is mediated by the ophthalmic division of the trigeminal nerve, and the efferent limb is mediated by the facial nerve (Aramideh and Ongerboer de Visser, 2002; Kimura, 2001; May and Schaitkin, 2000). Our results suggest that the R1 and R2 responses do not have a significant effect on the oVEMP waveform in response to BCV. When recording the blink reflex, each stimulus

is applied in a random time sequence to avoid habituation (Esteban, 1999; Snow and Frith, 1989; Sunohara et al., 1985). On the other hand, when recording oVEMPs, stimuli with regular intervals are applied at Fz, causing habituation of the blink reflexes. When recording orbicularis oculi potentials to detect a blink reflex, the active electrodes are placed on the outer aspect of the lower lids, the reference electrodes are placed on the lateral surface of the nose, and the bandpass filters are set at about 32 Hz to 16 kHz (Kimura, 2001; Snow and Frith, 1989; Sunohara et al., 1985). These differences in the recording techniques may explain the lack of effect of blink reflexes on the oVEMPs. Rosengren et al. reported that voluntary forceful eye closure during recording had no effect on oVEMPs (Rosengren et al., 2005), which is consistent with the present result.

The ACS used in the present study might also evoke an "acoustic blink reflex", which is a response of the orbicularis oculi muscle that is part of the generalized auditory startle reaction (Aramideh and Ongerboer de Visser, 2002; Esteban, 1999; Kimura, 2001). Since the latency of the orbicularis oculi response to sound is usually between 40 and 60 ms (Aramideh and Ongerboer de Visser, 2002), it is plausible that the short latency oVEMPs that peaked at about 10 ms on ACS testing were not affected by the acoustic blink reflex.

4.3. The influence of cochlear nerve activities on oVEMPs

All 6 patients with bilateral profound sensorineural hearing loss (Nos. 10–15) showed clear oVEMP responses in the present study (Table 1, Fig. 6), and no significant differences were observed in the waveforms of the oVEMPs between these patients and the healthy subjects. It is known that both ACS and BCV evoke neural activities in the cochlear nerve and the brainstem, which can be recorded as ABR and middle latency responses (MLRs) (Burkard et al., 2007; Hall, 2007). Rosengren et al. and Iwasaki et al. also conducted oVEMP testing in a single patient with bilateral profound hearing loss and reported normal oVEMP responses on both sides in each patient (Iwasaki et al., 2007; Rosengren et al., 2005). Our results complement these previous findings that cochlear nerve activity, as well as facial nerve activity, does not affect extraocular potentials significantly. There are three possible reasons for this. Firstly, the peak amplitudes of ABR (wave V) and MLR (less than 1 μV) are much smaller than those of the oVEMPs. Secondly, the latencies of ABR (about 5–8 ms in wave V when 500 Hz STBs are used) and MLR (about 30 ms in wave Pa) do not overlap wave nI–pI of the oVEMPs. Thirdly, the ABR and MLR recording techniques are different from those for recording oVEMPs with respect to the point of electrode placement, stimulus repetition rates, and bandpass filter settings (Burkard et al., 2007; Hall, 2007).

4.4. The origin of oVEMPs

Findings in the present study provided information concerning the origin of the oVEMP responses and the influence of facial and cochlear nerve activities on these responses. Our results can be briefly summarized as follow. Exenteration of the unilateral intraorbital contents abolished the ipsilateral oVEMP response, while exenteration of only the eyeball did not have a major impact on the responses. Short-latency, initially negative evoked potentials of the oVEMPs were not influenced by cochlear nerve or facial nerve activities. Our results indicate that oVEMPs evoked by ACS and BCV are generated by activity in extraocular muscles. Given the evidence that the responses depend upon vestibular function, the effects are probably mediated through vestibulo-ocular reflex pathways.

Acknowledgments

This work was supported by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (C-20791181).

References

Aramideh M, Ongerboer de Visser BW. Brainstem reflexes: electrodiagnostic techniques, physiology, normative data, and clinical applications. Muscle Nerve 2002;26:14–30.
Burkard R, Eggermont J, Don M. Auditory evoked potentials: basic principles and clinical application. Philadelphia (PA)/Baltimore (MD): Lippincott/Williams & Wilkins; 2007.
Chihara Y, Iwasaki S, Ushio M, Murofushi T. Vestibular-evoked extraocular potentials by air-conducted sound: another clinical test for vestibular function. Clin Neurophysiol 2007;118:2745–51.
Colebatch JG, Halmagyi GM. Vestibular evoked potentials in human neck muscles before and after unilateral vestibular deafferentation. Neurology 1992;42:1635–6.
Colebatch JG, Halmagyi GM, Skuse NF. Myogenic potentials generated by a click-evoked vestibulocollic reflex. J Neurol Neurosurg Psychiatry 1994;57:190–7.
Esteban A. A neurophysiological approach to brainstem reflexes. Blink reflex. Neurophysiol Clin 1999;29:7–38.
Hall JWIII. New handbook of auditory evoked responses. Pearson Edu. Inc.; 2007.
House JW, Brackmann DE. Facial nerve grading system. Otolaryngol Head Neck Surg 1985;93:146–7.
Iwasaki S, McGarvie LA, Halmagyi GM, Burgess AM, Kim J, Colebatch JG, et al. Head taps evoke a crossed vestibulo-ocular reflex. Neurology 2007;68:1227–9.
Jewett DL, Romano MN, Williston JS. Human auditory evoked potentials: possible brain stem components detected on the scalp. Science 1970;167:1517–8.
Kimura J. Electrodiagnosis in diseases of nerve and muscle: principles and practice. New York: Oxford University Press; 2001.
Kugelberg E. Facial reflexes. Brain 1952;75:385–96.
May M, Schaitkin BM. The facial nerve. New York: Thieme; 2000.
Minor LB, Solomon D, Zinreich JS, Zee DS. Sound- and/or pressure-induced vertigo due to bone dehiscence of the superior semicircular canal. Arch Otolaryngol Head Neck Surg 1998;124:249–58.
Murofushi T, Halmagyi GM, Yavor RA, Colebatch JG. Absent vestibular evoked myogenic potentials in vestibular neurolabyrinthitis. An indicator of inferior vestibular nerve involvement? Arch Otolaryngol Head Neck Surg 1996;122:845–8.
Overend W. Preliminary note on a new cranial reflex. Lancet 1896;1:619.
Rosengren SM, McAngus Todd NP, Colebatch JG. Vestibular-evoked extraocular potentials produced by stimulation with bone-conducted sound. Clin Neurophysiol 2005;116:1938–48.
Rosengren SM, Aw ST, Halmagyi GM, Todd NP, Colebatch JG. Ocular vestibular evoked myogenic potentials in superior canal dehiscence. J Neurol Neurosurg Psychiatry 2008;79:559–68.
Snow BJ, Frith RW. The relationship of eyelid movement to the blink reflex. J Neurol Sci 1989;91:179–89.
Sohmer H, Feinmesser M. Cochlear and cortical audiometry conveniently recorded in the same subject. Isr J Med Sci 1970;6:219–23.
Sunohara N, Tomi H, Satoyoshi E, Tachibana S. Glabella tap sign. Is it due to a lack of R2-habituation? J Neurol Sci 1985;70:257–67.
Todd NP, Curthoys IS, Aw ST, Todd MJ, Rosengren SM, McGarvie LA, et al. Vestibular evoked ocular responses to air- (AC) and bone-conducted (BC) sound I: eye movements and timing in relation to vestibular evoked peri-ocular potentials (VEPP). J Vestib Res 2004;14:123–4.
Todd NP, Rosengren SM, Aw ST, Colebatch JG. Ocular vestibular evoked myogenic potentials (OVEMPs) produced by air- and bone-conducted sound. Clin Neurophysiol 2007;118:381–90.
Welgampola MS, Colebatch JG. Characteristics and clinical applications of vestibular-evoked myogenic potentials. Neurology 2005;64:1682–8.
Welgampola MS, Myrie OA, Minor LB, Carey JP. Vestibular-evoked myogenic potential thresholds normalize on plugging superior canal dehiscence. Neurology 2008;70:464–72.

Acta Oto-Laryngologica, 2009; 129: 1095–1100

informa
healthcare

ORIGINAL ARTICLE

Is the nerve origin of the vestibular schwannoma correlated with vestibular evoked myogenic potential, caloric test, and auditory brainstem response?

MUNETAKA USHIO[1], SHINICHI IWASAKI[1], YASUHIRO CHIHARA[1], NOBUTAKA KAWAHARA[2], AKIO MORITA[3], NOBUHITO SAITO[4] & TOSHIHISA MUROFUSHI[5]

[1]*Department of Otolaryngology, Graduate School of Medicine, University of Tokyo, Tokyo,* [2]*Department of Neurosurgery, Faculty of Medicine, Yokohama City University, Kanagawa,* [3]*Department of Neurosurgery, Kanto Medical Center NTT EC, Tokyo,* [4]*Department of Neurosurgery, Graduate School of Medicine, University of Tokyo, Tokyo and* [5]*Department of Otolaryngology, Teikyo University School of Medicine Mizonokuchi Hospital, Kawasaki, Japan*

Abstract

Conclusions. The results of the caloric test, vestibular evoked myogenic potential (VEMP), and auditory brainstem response (ABR) in patients with vestibular schwannoma (VS) did not show clear correlation with the nerve origin of the tumor but with tumor size. When we focused on patients with VS within the internal acoustic canal (IAC), neither the nerve origin of the tumor nor the tumor size showed clear correlation with the results of these tests. *Objectives.* This study examined the correlation of the nerve origin of VS, superior or inferior vestibular nerve, with the results of function tests. *Subjects and methods.* Subjects comprised 109 consecutive patients diagnosed as having unilateral VS. Each test was performed before surgery. Tumor size was measured with preoperative MRI. *Results.* The nerve origin of the tumor was identified in 63 of the 109 patients. The percentage of patients showing abnormal responses in each test was not different between 37 patients with superior VS and 26 patients with inferior VS. Also, no difference was observed for patients with VS within the IAC. Mean tumor size in patients showing abnormal responses was larger than that in patients showing normal responses on each test. However, this tendency was not observed for patients with VS within the IAC.

Keywords: *Vestibular schwannoma, vestibular nerve, caloric test, vestibular evoked myogenic potential (VEMP), auditory brainstem response (ABR)*

Introduction

Vestibular schwannoma (VS) is a benign tumor mainly arising from the superior vestibular nerve (SVN) or inferior vestibular nerve (IVN). The SVN innervates the lateral semicircular canal and anterior semicircular canal, utricle, and part of the saccule [1]. As the caloric test mainly reflects lateral semicircular canal functions, it is used to evaluate SVN functions. On the other hand, the IVN innervates the posterior semicircular canal as well as most of the saccule [1]. As vestibular evoked myogenic potential (VEMP) is considered to reflect the sacculo-collic reflex [2–4], it is used to evaluate IVN functions. Patients with VS show various extents of vestibular dysfunction including abnormal caloric test, abnormal VEMP, and abnormal auditory brainstem response (ABR). If the results of these vestibular and auditory function tests correlate with the nerve origin of the tumor, these tests may become useful to predict the nerve origin of the tumor before surgery. Moreover, such preoperative information on the tumor localization may be useful for the choice of an appropriate surgical approach.

Some authors reported the correlation of the nerve origin of the tumor with the results of vestibular tests. However, the correlation is still controversial. As regards the caloric test, Furuta et al. reported that abnormal caloric responses were seen in 1 of 2 patients with VS arising from SVN (superior VS)

Correspondence: Munetaka Ushio MD, Department of Otolaryngology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Tel: +81 3 5800 8665. Fax: +81 3 3814 9486. E-mail: IZT01356@nifty.ne.jp

(Received 19 August 2008; accepted 13 October 2008)

ISSN 0001-6489 print/ISSN 1651-2251 online
DOI: 10.1080/00016480802552543

and all of 12 patients with VS arising from IVN (inferior VS) [5]. Okada et al. reported that 5 of 6 patients with superior VS and 6 of 16 patients with inferior VS showed abnormal caloric responses [6]. These reports showed negative results for prediction of the nerve origin of the tumor using the caloric test. As regards the VEMP, Tsutsumi et al. reported that prediction of the nerve origin of the tumor was possible only in certain restricted cases [7]. In contrast, Chen et al. reported that VEMP could be used to predict the nerve origin of the tumor [8].

Based on these backgrounds, this study examined the correlation of the nerve origin of the tumor in patients with VS and the results of caloric test, VEMP, and ABR.

Subjects and methods

Patients

The study group comprised 109 consecutive patients diagnosed as having unilateral VS from January 1997 to December 2006. Diagnoses were confirmed surgically and histopathologically. The patients underwent vestibular and cochlear function tests before surgery in the Department of Otolaryngology at the University of Tokyo Hospital, and underwent removal of VS (left, $n=43$; right, $n=66$) in the Department of Neurosurgery. Mean $\pm$ standard deviation (SD) of age was 49.0 ± 12.1 years (range 21–75 years) at the time of examination.

Vestibular and cochlear function tests

The caloric test was performed using cold water. Percent canal paresis (CP) was calculated with the following formula using the maximum slow-phase eye velocity of induced nystagmus.

$$\text{percent canal paresis} = 100 \mid (\text{MSEVu} - \text{MSEVa}) \mid / (\text{MSEVu} + \text{MSEVa})$$

where MSEVu is maximum slow-phase eye velocity on the unaffected side irrigation and MSEVa is maximum slow-phase eye velocity on the affected side irrigation. Tests were performed using an electronystagmograph in the supine position (head up 30°) in a completely dark room. When CP was 20% or more, caloric response was regarded as abnormal.

VEMPs [9] were performed in response to clicks (0.1 ms, 95 dB normal hearing level (nHL); click-VEMP) and short tone bursts (500 Hz, rise/fall time 1 ms, plateau time 2 ms, 95 dBnHL; burst-VEMP) using Neuropack Σ (Nihon Kohden, Tokyo, Japan). Surface electromyographic activity (EMG) was recorded from symmetrical sites over the upper half of each sternocleidomastoid muscle (SCM), with reference electrodes on the lateral end of the upper sternum. The ground electrode was placed on the nasion. During the recording of both click- and burst-VEMP, patients were instructed to raise their heads to activate the SCM, and we monitored EMG of bilateral SCM. In all of the enrolled subjects, normal SCM activities were observed during recordings on both sides, indicating normal accessory nerve function. First, click-VEMP was performed. When click-VEMP showed no response on both sides, burst-VEMP was then performed. The responses of VEMP were regarded as abnormal when the responses on the affected side were absent or decreased in comparison with those on the unaffected side. For this comparison, the percent VEMP asymmetry [4] was calculated with the following formula using the amplitude of p13–n23 on the affected side (Aa) and that on the unaffected side (Au).

$$\text{percent VEMP asymmetry} = 100 \mid (\text{Au} - \text{Aa}) \mid / (\text{Au} + \text{Aa})$$

The upper limit of percent VEMP asymmetry was set as 34.1 according to the previous report [4].

ABR was also recorded using Neuropack Σ (Nihon Kohden, Tokyo, Japan). The electrodes were placed on the vertex and the mastoids. The ground electrode was placed on the nasion. Clicks (0.1 ms, 85 dBnHL) were presented through the headphone. The repetition rate of the stimulation was 10 Hz, and the time window for analysis was 10 ms. The responses to 1000 stimuli were averaged twice. ABR was considered abnormal or pathological if the result met one or more of the following conditions on the basis of normal range at our department and previous reports [10,11]. (1) The interpeak interval between waves I and V was more than 4.4 ms. (2) The interaural difference of the latency of wave V was more than 0.3 ms. (3) The interaural difference of interpeak interval between waves I and V was more than 0.2 ms. (4) No reproducible waves were recorded. (5) Absence of the later waves (wave III or V) was seen.

Evaluation of tumor size

Axial and coronal T1-weighted MRI with contrast medium (gadolinium DTPA) and axial T2-weighted MRI were performed using a fast spin echo program with 1.5 Tesla unit, 3.0 mm in thickness at intervals of 3.3 mm before surgery. Maximum diameter of VS was measured and employed as a tumor size.

Statistical analyses

Statistical analyses were performed using SPSS statistical software (SPSS, Chicago, IL, USA). The rate of patients showing abnormal results in each test

Table I. Nerve origin of the tumor and results of tests in 109 patients with VS.

Nerve of origin of tumor	*n*	Mean±SD tumor size	Number (%) of patients with abnormal response		
			Caloric test	VEMP	ABR
Identified	63	21.4±9.1			
Superior VS	37	21.7±9.4	32/37 (86.5)	24/31 (77.4)	35/37 (94.6)
Inferior VS	26	20.7±8.8	21/26 (80.8)	12/18 (66.7)	25/26 (96.2)
Not identified	46	27.4±12.9			

VS, vestibular schwannoma; VEMP, vestibular evoked myogenic potential; ABR, auditory brainstem response.

in patients with superior VS and those with inferior VS was compared using chi-squared test or Fisher's exact test. Mean tumor size in patients with superior VS and those with inferior VS, mean tumor size of abnormal and normal response in caloric test, VEMP and ABR, and mean canal paresis and mean percent VEMP asymmetry in patients with superior VS and those with inferior VS were compared using Student's *t* test. The percentage of patients showing abnormal results in each test in patients with VS limited within the internal acoustic canal (IAC) and those developing in the cerebellopontine angle (CPA) were compared using chi-squared test or Fisher's exact test. The data are presented using descriptive statistics: mean±SD. A difference of $p < 0.05$ was considered significant.

Results

Nerve origin of the tumor

Among the 109 patients with VS enrolled, the nerve origin of the tumor was identified in 63 patients by neurosurgeons. Among them, superior VSs were 58.7% (37/63), while inferior VSs were 41.3% (26/63) (Table I). Mean tumor size of superior VS (21.7±9.4 mm) and that of inferior VS (20.7±8.8 mm) were not significantly different ($p = 0.66$) (Table I).

Among the 26 patients with VS within the IAC, the nerve origin of the tumor was identified in nine patients by neurosurgeons. Among them, superior VSs were 44.4% (4/9), while inferior VSs were 55.6% (5/9) (Table II). Mean tumor size of superior VS (10.5±4.1 mm) and that of inferior VS (10.2±3.2 mm) were not significantly different ($p = 0.91$) (Table II).

Caloric test

Caloric test was performed in all the 63 patients. The abnormal caloric responses were seen in 86.5% (32/37) of patients with superior VS and in 80.8% (21/26) of patients with inferior VS (Table I). The percentage of patients with abnormal caloric responses showed no significant difference between patients with superior VS and those with inferior VS ($p = 0.54$). Mean canal paresis was not significantly different between patients with superior VS (61.6±36.2%) and those with inferior VS (62.4±35.7%) ($p = 0.93$). However, mean tumor size in patients showing abnormal caloric responses (22.4±8.6 mm) was significantly larger than that in patients showing normal responses (16.0±10.3 mm) ($p = 0.02$) (Figure 1).

In patients with VS within the IAC, the abnormal caloric responses were seen in 75.0% (3/4) of patients with superior VS and in 80.0% (4/5) of patients with inferior VS (Table II). The percentage of patients with abnormal caloric responses showed no significant difference between patients with superior VS and those with inferior VS ($p = 1.00$). Mean canal paresis was not significantly different between patients with superior VS (45.0±26.6%) and those with inferior VS (73.3±48.3%) ($p = 0.41$). Mean tumor size was not significantly different between patients showing abnormal caloric responses (10.5±4.1 mm) and those showing normal responses (9.8±2.0 mm) ($p = 0.85$) (Figure 2).

Table II. Nerve origin of the tumor and results of tests in 26 patients with VS limited within the IAC.

Nerve of origin of tumor	*n*	Mean±SD tumor size	Number (%) of patients with abnormal response		
			Caloric test	VEMP	ABR
Identified	9	10.3±3.4			
Superior VS	4	10.5±4.1	3/4 (75.0)	2/3 (66.7)	3/4 (75.0)
Inferior VS	5	10.2±3.2	4/5 (80.0)	3/5 (60.0)	5/5 (100)
Not identified	17	9.0±3.9			

VS, vestibular schwannoma; VEMP, vestibular evoked myogenic potential; ABR, auditory brainstem response; IAC, internal acoustic canal.

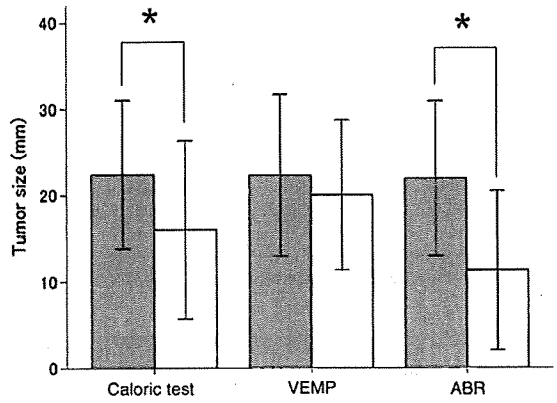

Figure 1. Difference of mean ± SD tumor size in patients with VS showing abnormal responses (gray bar) and that showing normal responses (white bar) on caloric test, VEMP, and ABR. Mean tumor size in patients showing abnormal caloric response was significantly larger than that in patients showing normal response ($p=0.02$). Mean tumor size in patients showing abnormal VEMP responses was slightly larger than that in patients showing normal responses. However, the difference was not significant ($p=0.35$). Mean tumor size in patients showing abnormal ABR was significantly larger than that in patients with normal response ($p=0.03$).

Seven of the nine patients whose VS remained only within the IAC (77.8%) showed abnormal caloric responses. In contrast, 47 of 54 patients with VS developing in the CPA (87.0%) showed abnormal caloric responses (29 of 33 patients with superior VS and 18 of 21 patients with inferior VS). The percentage of abnormal caloric responses in patients with VS developing into CPA was slightly larger than that in patients with VS within the IAC. However, the difference was not significant ($p=0.46$).

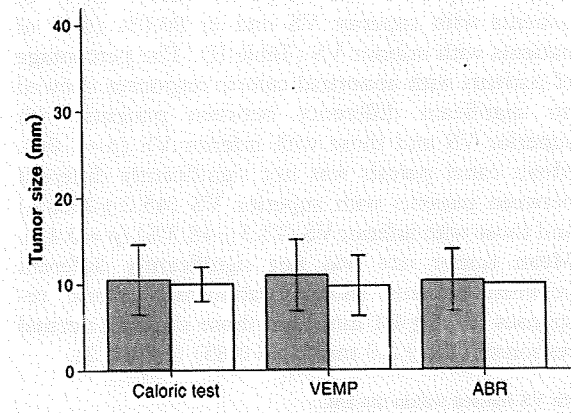

Figure 2. Difference of mean ± SD tumor size in patients with VS within internal auditory canal (IAC) showing abnormal responses (gray bar) and that showing normal responses (white bar) on caloric test, VEMP, and ABR. Mean tumor size in patients showing abnormal caloric response and that in patients showing normal response was not significantly different ($p=0.85$). Mean tumor size in patients showing abnormal VEMP responses and that in patients showing normal responses was not significantly different ($p=0.66$). Mean tumor size in patients showing abnormal ABR and that in patients showing normal response was not significantly different ($p=0.93$).

VEMP

VEMPs were recorded in 49 of 63 patients. In 14 patients, VEMP was not recorded because they had disease of the neck or were more than 70 years old. Abnormal VEMP responses were shown in 77.4% (24/31) of patients with superior VS and in 66.7% (12/18) of patients with inferior VS (Table I). The percentage of patients with abnormal VEMP responses showed no significant difference between patients with superior VS and those with inferior VS ($p=0.41$). Percent VEMP asymmetry was not significantly different between patients with superior VS (19.2 ± 37.5%) and those with inferior VS (17.6 ± 37.0%) ($p=0.71$). Mean tumor size in patients showing abnormal VEMP responses (22.2 ± 9.4 mm) was slightly larger than that in patients showing normal responses (20.0 ± 8.7 mm). However, the difference was not significant ($p=0.35$) (Figure 1).

In patients with VS within the IAC, the abnormal VEMP responses were seen in 66.7% (2/3) of patients with superior VS and in 60.0% (3/5) of patients with inferior VS (Table II). The percentage of patients with abnormal VEMP responses showed no significant difference between patients with superior VS and those with inferior VS ($p=1.00$). Percent VEMP asymmetry was not significantly different between patients with superior VS (32.5 ± 65.0%) and those with inferior VS (52.5 ± 61.8%) ($p=0.67$). Mean tumor size was not significantly different between patients showing abnormal VEMP responses (11.0 ± 4.2 mm) and those showing normal responses (9.8 ± 3.5 mm) ($p=0.66$) (Figure 2).

VEMP was performed in eight of nine patients with VS within the IAC. Among them, five patients (62.5%) showed abnormal VEMP responses. In contrast, in 54 patients with VS developing in the CPA, VEMP was performed in 41 patients. Among them, 33 patients (80.5%) showed abnormal VEMP responses (23 of 28 patients with superior VS and 10 of 13 patients with inferior VS). The percentage of abnormal VEMP responses in patients with VS developing into the CPA was slightly larger than that in patients with VS within the IAC. However, the difference was not significant ($p=0.36$).

ABR

ABR was performed in all 63 patients. Among them, abnormal ABR was shown in 94.6% (35/37) of

patients with superior VS and in 96.2% (25/26) of patients with inferior VS (Table I). The percentage of patients with abnormal ABR showed no significant difference between patients with superior VS and those with inferior VS ($p=1.00$). However, mean tumor size in patients showing abnormal ABR responses (21.9 ± 9.0 mm) was significantly larger than that in patients showing normal responses (11.3 ± 9.2 mm) ($p=0.03$) (Figure 1).

In patients with VS within the IAC, the abnormal caloric responses were seen in 75.0% (3/4) of patients with superior VS and in 100% (5/5) of patients with inferior VS (Table II). The percentage of patients with abnormal ABR responses showed no significant difference between patients with superior VS and those with inferior VS ($p=0.44$). Mean tumor size was not significantly different between patients showing abnormal ABR responses (10.4 ± 3.6 mm) and patients showing normal responses (10.0 mm) ($p=0.93$) (Figure 2).

Eight of the nine patients whose VS remained only within the IAC (88.9%) showed abnormal ABR responses. In contrast, 52 of 54 patients with VS developing in the CPA (96.3%) showed abnormal ABR responses (32 of 33 patients with superior VS and 20 of 21 patients with inferior VS). The percentage of abnormal ABR in patients with VS developing in the CPA was higher than that in patients with VS within the IAC. However, the difference was not significant ($p=0.38$).

Discussion

In this study, the percentage of abnormal responses on caloric test, VEMP, and ABR was not different between patients with superior VS and those with inferior VS. Also, no difference was observed in these tests for patients with VS within the IAC. This result suggests that there is no clear correlation between the results of each function test and the nerve origin of the tumor irrespective of the tumor size. Schwannoma is a benign tumor, extending not only inwardly but also outwardly. In addition, it could produce dysfunction of the nerve by compressing the nerve fiber and obstructing the blood supply to the nerve [7]. Thus, VS can affect all nerves in the IAC including the cochlear nerve. In fact, despite the high sensitivity of ABR for the diagnosis of acoustic neuroma [12–14], it rarely arises from the cochlear nerve. Also, although Shelton et al. and Ogawa et al. [15,16] reported that inferior VS tends to involve or compress the cochlear nerve more severely than superior VS due to the anatomic location, our results in ABR were not able to detect the above observations.

On the other hand, the tumor size in patients showing abnormal responses was larger than that in patients showing normal responses on each test. The difference was significant on caloric test and ABR, but was not significant on VEMP. In addition to the well-known fact that ABR has a high dependency on the tumor size [12–14], the caloric test may also serve as an indicator of tumor size. We suppose that a large VS affects functions of both the SVN and IVN irrespective of the nerve origin, because the space of the IAC is limited. On the other hand, there was no correlation between the tumor size and the proportion of abnormal responses for patients with VS within the IAC. The number of such patients was small in this study. However, our results suggest that the tumor size does not show clear correlation with the results of function tests in patients with small VS within the IAC. The percentage of abnormal responses in patients with VS developing into the CPA tended to be slightly larger than those within the IAC. However, this difference was not apparent.

In this study, 58.7% among the patients in whom the nerve origin was identified had superior VS whereas 41.3% had inferior VS. Some investigators reported that the percentage of superior VS and inferior VS is practically equal. Clemis et al. suggested that 50% of VS originated from the SVN [17]. Cohen et al. reported 70 superior VS and 58 inferior VS among 128 consecutive suboccipital/retrosigmoid approaches [18]. Slattery et al. reported 43.9% of superior VS and 48.3% of inferior VS among 151 consecutive middle fossa approaches [19]. On the contrary, other investigators reported that the percentage of superior VS and inferior VS is different. Okada et al. reported 147 VS cases who underwent a middle cranial fossa approach and the nerve origin was identified in 22 cases. Among them, 6 cases had superior VS whereas 16 cases had inferior VS [6]. Komatsuzaki et al. reported 271 VS cases who underwent the translabyrinthine approach and the nerve origin of the tumor was identified in 269 cases. Among them, 8.9% were superior VS whereas 84.8% were inferior VS [20]. The reason for such a difference concerning the proportions is unknown.

In conclusion, this study showed that the results of VEMP, caloric test, and ABR in patients with VS did not show clear correlation with the nerve origin of the tumor but with tumor size. In addition, when we focus on patients with VS within the IAC, neither the nerve origin of the tumor nor the tumor size showed clear correlation with the results of these tests.

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

References

[1] Sando I, Black FO, Hemenway WG. Spatial distribution of vestibular nerve in internal auditory canal. Ann Otol Rhinol Laryngol 1972;81:305–14.

[2] Murofushi T, Curthoys IS, Gilchrist DP. Response of guinea pig vestibular nucleus neurons to clicks. Exp Brain Res 1996; 111:149–52.

[3] Murofushi T, Curthoys IS. Physiological and anatomical study of click-sensitive primary vestibular afferents in the guinea pig. Acta Otolaryngol 1997;117:66–72.

[4] Murofushi T, Matsuzaki M, Mizuno M. Vestibular evoked myogenic potentials in patients with acoustic neuromas. Arch Otolaryngol Head Neck Surg 1998;124:509–12.

[5] Furuta S, Takahashi S, Higano S, Hashimoto S. Prediction of the origin of intracanalicular neoplasms with high-resolution MR imaging. Neuroradiology 2005;47:657–63.

[6] Okada Y, Takahashi M, Saito A, Kanzaki J. Electronystagmographic findings in 147 patients with acoustic neuroma. Acta Otolaryngol Suppl 1991;487:150–6.

[7] Tsutsumi T, Tsunoda A, Noguchi Y, Komatsuzaki A. Prediction of the nerves of origin of vestibular schwannomas with vestibular evoked myogenic potentials. Am J Otol 2000; 21:712–5.

[8] Chen CW, Young YH, Tseng HM. Preoperative versus postoperative role of vestibular-evoked myogenic potentials in cerebellopontine angle tumor. Laryngoscope 2002;112: 267–71.

[9] Colebatch JG, Halmagyi GM, Skuse NF. Myogenic potentials generated by a click-evoked vestibulocollic reflex. J Neurol Neurosurg Psychiatry 1994;57:190–7.

[10] Marangos N, Maier W, Merz R, Laszig R. Brainstem response in cerebellopontine angle tumors. Otol Neurotol 2001;22:95–9.

[11] Gordon ML, Cohen NL. Efficacy of auditory brainstem response as a screening test for small acoustic neuromas. Am J Otol 1995;16:136–9.

[12] Wilson DF, Hodgson RS, Gustafson MF, Hogue S, Mills L. The sensitivity of auditory brainstem response testing in small acoustic neuromas. Laryngoscope 1992;102:961–4.

[13] Godey B, Morandi X, Beust L, Brassier G, Bourdiniere J. Sensitivity of auditory brainstem response in acoustic neuroma screening. Acta Otolaryngol 1998;118:501–4.

[14] Schmidt RJ, Sataloff RT, Newman J, Spiegel JR, Myers DL. The sensitivity of auditory brainstem response testing for the diagnosis of acoustic neuromas. Arch Otolaryngol Head Neck Surg 2001;127:19–22.

[15] Shelton C, Brackmann DE, House WF, Hitselberger WE. Acoustic tumor surgery. Prognostic factors in hearing conversation. Arch Otolaryngol Head Neck Surg 1989; 115:1213–6.

[16] Ogawa K, Kanzaki J, Ogawa S, Tsuchihashi N, Ikeda S. Progression of hearing loss in acoustic neuromas. Acta Otolaryngol Suppl 1991;487:133–7.

[17] Clemis JD, Ballad WJ, Baggot PJ, Lyon ST. Relative frequency of inferior vestibular schwannoma. Arch Otolaryngol Head Neck Surg 1986;112:190–4.

[18] Cohen NL, Lewis WS, Ransohoff J. Hearing preservation in cerebellopontine angle tumor surgery: the NYU experience 1974–1991. Am J Otol 1993;14:423–33.

[19] Slattery WH 3rd, Brackmann DE, Hitselberger W. Middle fossa approach for hearing preservation with acoustic neuromas. Am J Otol 1997;18:596–601.

[20] Komatsuzaki A, Tsunoda A. Nerve origin of the acoustic neuroma. J Laryngol Otol 2001;115:376–9.

Testing Human Otolith Function Using Bone-Conducted Vibration

I.S. Curthoys,[a] A.M. Burgess,[a] H.G. MacDougall,[a] L.A. McGarvie,[b] G.M. Halmagyi,[b] Y.E. Smulders,[c] and S. Iwasaki[d]

[a]*School of Psychology, University of Sydney, Sydney, Australia*

[b]*Neurology Department, Royal Prince Alfred Hospital, Sydney, Australia*

[c]*Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands*

[d]*Department of Otolaryngology, University of Tokyo, Tokyo, Japan*

Bone-conducted vibration of the forehead, in the midline at the hairline (Fz) causes linear acceleration stimulation of both mastoids and results in an ocular vestibular-evoked myogenic potential (oVEMP), recorded by surface electromyogram (EMG) electrodes just beneath the eyes. The early n10 component of the oVEMP is symmetrical in healthy subjects, absent in patients with bilateral vestibular loss, and in patients after unilateral vestibular loss (uVL) n10 is small or absent on the side contralateral to the uVL, but of normal amplitude on the side contralateral to the healthy ear. The n10 component probably reflects mainly otolithic function, since in the guinea pig, primary otolith irregular neurons are selectively activated by bone-conducted vibration (BCV) at low intensities (0.1 *g*), whereas semicircular canal primary afferents are not activated even at high intensities (10 *g*).

Key words: **vestibular; labyrinth; otolith; vibration; bone conduction; unilateral otolithic loss; utricular macula; saccular macula; human**

The otolith–ocular response has been shown by electrical stimulation of the isolated utricular nerve in cats to produce a complex eye-movement response that includes activation of the contralateral inferior oblique and contralateral inferior rectus.[1] Five hundred hertz bone-conducted vibration (BCV) of the head causes a series of rapid changes in linear acceleration at the mastoids, which at low intensities (0.1 *g*) in the guinea pig selectively activates primary otolithic irregular neurons[2]—neurons that prefer changes in linear acceleration.[3] Semicircular-canal neurons are not activated by BCV, even at much higher intensity stimulation (10 *g*).[2] Using miniature linear accelerometers on the mastoids of human subjects we have shown that a BCV stimulus to the forehead in the midline at the hairline (the point called Fz) causes simultaneous linear acceleration stimulation of both mastoids. The BCV stimulus was a light tap from a tendon hammer, or a pulse, or a brief (6 ms) burst of 500 Hz by a Bruel and Kjaer 4810 minishaker. In healthy subjects this stimulus (repeated 20 or 50 times at 3/s) results in a surface electromyogram (EMG) potential around the eyes called an ocular vestibular-evoked myogenic potential (oVEMP).[4] If the subject lies supine and looks 20°–25° above straight ahead (Fig. 1A), then the early component of the oVEMP is a small (10 μV), short latency (10 ms to peak), negative (i.e., excitatory) EMG potential called n10.[5,6]

Healthy subjects show symmetrical, equal-amplitude n10 responses that are repeatable,

Address for correspondence: Dr. Ian S. Curthoys, School of Psychology, University of Sydney, Sydney, NSW 2006, Australia. ianc@psych.usyd.edu.au

Basic and Clinical Aspects of Vertigo and Dizziness: Ann. N.Y. Acad. Sci. 1164: 344–346 (2009).
doi: 10.1111/j.1749-6632.2008.03728.x

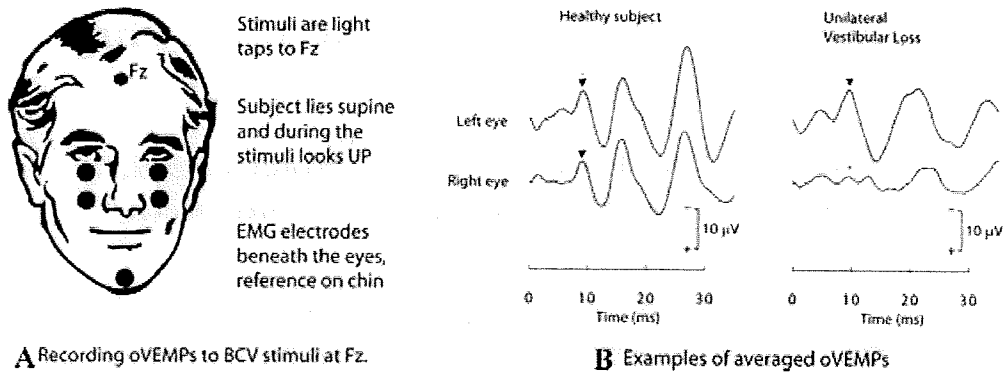

Figure 1. (**A**) Schematic figure of the stimulus location and the recording electrode locations for recording ocular vestibular-evoked myogenic potentials (oVEMPs). (**B**) Examples of the averaged n10 responses of a healthy subject and of a patient after unilateral vestibular loss to bone-conducted vibration (BCV) at the hairline (Fz).

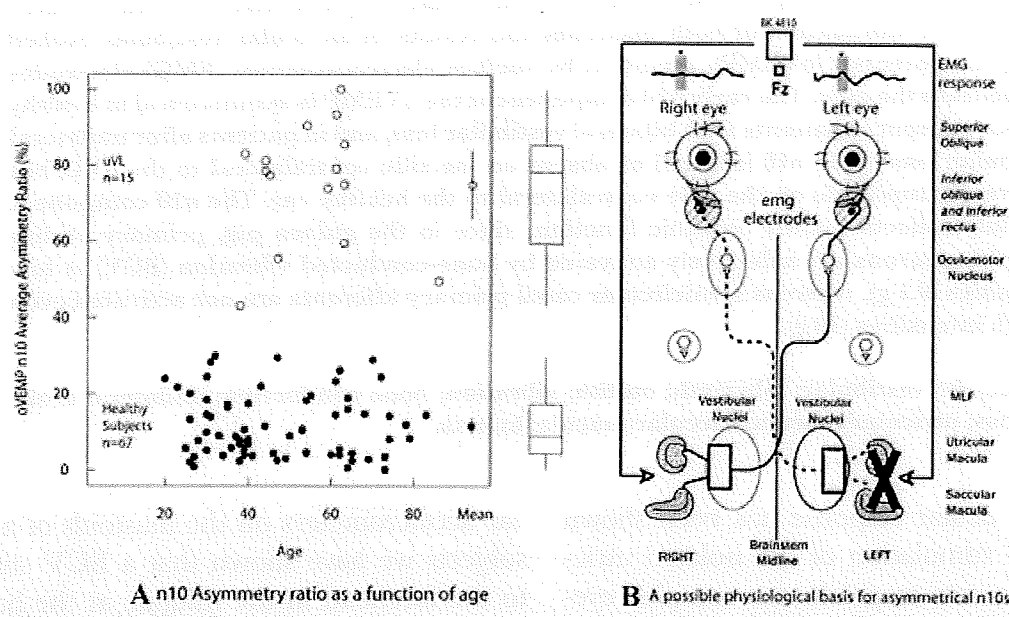

Figure 2. (**A**) The n10 asymmetry ratios to bone-conducted vibration (BCV) stimulation at the hairline (Fz) for 67 healthy subjects and 15 patients after unilateral vestibular loss. Every patient shows an asymmetry ratio (AR) larger than healthy subjects. Senior subjects can be tested without difficulty. (**B**) A schematic figure showing the possible pathways underlying the n10 response and its asymmetry after unilateral vestibular loss (uVL). Afferents from the saccular and utricular macula project to the vestibular nuclei, but the exact termination of the otolithic afferents that project to the oculomotor nucleus is not currently known, and the open square in the figure represents that uncertainty. The crossed projections of otolithic neurons to contralateral oculomotor nucleus are shown. Fz stimulation is indicated schematically, and the recording electrodes are shown close to the inferior obliques.

although there are large differences in amplitude between individuals.[5] Patients with bilateral vestibular loss, but with remaining hearing and facial functioning, do not have oVEMPs,[6] demonstrating that the n10 is vestibular and excluding the possibility that n10 is blink related. Patients after therapeutic surgical unilateral vestibular loss (uVL) show *asymmetrical* n10 responses—the n10 on the side opposite the healthy ear is normal amplitude, whereas the n10 on the side opposite the affected ear is small or absent.[5,7] To quantify the asymmetry we calculated the asymmetry ratio (AR), defined like canal paresis as ((larger n10 − smaller

n10)/(larger n10 + smaller n10)) × 100. The average AR for 67 unselected healthy subjects aged between 20 and 83 years was 11.73% ± 8.26 (SD), whereas the AR for 15 uVL patients was significantly higher at 75.03% ± 16.32 (see Fig. 2A).[5–7] Despite differences in technique similar ARs were obtained in Australian and Japanese uVL patients.

A schematic illustration of a pathway that may underlie the asymmetric n10 response to Fz BCV after uVL is shown in Figure 2B. It is based on known anatomical projections and the physiological results from Suzuki and colleagues.[1] The absence of the otolithic receptors on one side causes an absent n10 beneath the eye on the contralateral side, and thus will result in the asymmetrical n10 observed in uVL patients. This is a simple, fast, undemanding test of otolithic function that can be carried out even on senior patients and has a sound physiological basis.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Suzuki, J.I., K. Tokumasu & K. Goto. 1969. Eye movements from single utricular nerve stimulation in the cat. *Acta Otolaryngol.* **68:** 350–362.
2. Curthoys, I.S., J. Kim, S.K. McPhedran, *et al.* 2006. Bone conducted vibration selectively activates irregular primary otolithic vestibular neurons in the guinea pig. *Exp. Brain Res.* **175:** 256–267.
3. Goldberg, J.M. 2000. Afferent diversity and the organization of central vestibular pathways. *Exp. Brain Res.* **130:** 277–297.
4. Rosengren, S.M., N.P.M. Todd & J.G. Colebatch. 2005. Vestibular-evoked extraocular potentials produced by stimulation with bone-conducted sound. *Clin. Neurophysiol.* **116:** 1938–1948.
5. Iwasaki, S., L.A. McGarvie, G.M. Halmagyi, *et al.* 2007. Head taps evoke a crossed vestibulo-ocular reflex. *Neurology* **68:** 1227–1229.
6. Iwasaki, S., Y.E. Smulders, A.M. Burgess, *et al.* 2008. Ocular vestibular evoked myogenic potentials to bone conducted vibration of the midline forehead at Fz in healthy subjects. *Clin. Neurophysiol.* **119:** 2135–2147.
7. Iwasaki, S., Y.E. Smulders, A.M. Burgess, *et al.* 2008. Ocular vestibular evoked myogenic potentials in response to bone conducted vibration of the midline forehead at Fz. A new indicator of unilateral otolithic loss. *Audiol. Neurotol.* **13:** 396–404.

Clinical Neurophysiology 120 (2009) 1149–1153

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

The diagnostic value of vestibular-evoked myogenic potential in patients with vestibular schwannoma

Munetaka Ushio [a,*], Shinichi Iwasaki [a], Toshihisa Murofushi [b], Keiko Sugasawa [a], Yasuhiro Chihara [a], Chisato Fujimoto [a], Masako Nakamura [a], Takuhiro Yamaguchi [c], Tatsuya Yamasoba [a]

[a] Department of Otolaryngology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[b] Department of Otolaryngology, Teikyo University School of Medicine, Mizonokuchi Hospital, Kanagawa, Japan
[c] Department of Clinical Trial Data Management, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

ARTICLE INFO

Article history:
Accepted 28 January 2009
Available online 24 April 2009

Keywords:
Vestibular schwannoma
Vestibular-evoked myogenic potential (VEMP)
Caloric test
Sensitivity
Specificity

ABSTRACT

Objective: This study examined the diagnostic value of the vestibular-evoked myogenic potential (VEMP) in comparison with the caloric test in patients with vestibular schwannoma (VS).
Methods: Data were retrospectively collected from 803 consecutive patients who visited our vertigo clinic and underwent vestibular tests. Amongst them, 78 patients were diagnosed as having untreated unilateral VS. VEMP was performed using click and short-tone burst stimulation. The caloric test was performed using ice water. The sensitivity and specificity of each test were evaluated.
Results: Of the 78 patients with VS, 63 had abnormal VEMPs as well as abnormal caloric responses. Of the 725 patients without VS, 382 had normal VEMPs and 416 had normal caloric responses. The sensitivity and specificity of VEMP were 80.8% (95% CI: 72.0–89.5%) and 52.7% (95% CI: 49.1–56.3%), respectively; those of the caloric test were 80.8% (95% CI: 72.0–89.5%) and 57.4% (95% CI: 53.8–61.0%), respectively.
Conclusions: The sensitivity and specificity of VEMP and the caloric test showed no significant differences.
Significance: In patients with VS, although the specificity of VEMP was not very high, its sensitivity was high and comparable to that of the caloric test.

1. Introduction

Vestibular schwannoma (VS) is a benign tumour arising from the eighth cranial nerve. Almost all VSs arise from the superior or inferior vestibular nerve, and few arise from the cochlear nerve (Clemis et al., 1986; Cohen et al., 1993; Slattery et al., 1997; Komatsuzaki and Tsunoda, 2001). For diagnosing VS, the auditory brainstem response (Wilson et al., 1992; Gordon and Cohen, 1995; Godey et al., 1998; Marangos et al., 2001; Schmidt et al., 2001), the caloric test (Furuta et al., 2005; Hulshof et al., 1989; Okada et al., 1991) and magnetic resonance imaging (MRI) of the brain (Furuta et al., 2005; Robson et al., 1993) have been used, and the diagnostic efficiency of these tests has been reported (Thomsen et al., 1981).

Recently, vestibular-evoked myogenic potential (VEMP) has been used clinically as a part of the test battery to explore vestibular abnormalities (Murofushi et al., 1998; Takeichi et al., 2001; Patko et al., 2003). VEMP, which was first reported by Colebatch and Halmagyi in 1992 (Colebatch and Halmagyi, 1992), is a short-latency reflex recorded from the sternocleidomastoid muscle (SCM) in response to relatively intense auditory clicks delivered via headphones. As clinical and neurophysiological studies suggested that VEMPs originate from saccular afferents (Colebatch et al., 1994a; Murofushi et al., 1995, 1996a), it has been used as a clinical test of the saccule and the inferior vestibular nerve. Abnormal VEMPs have been reported in various diseases such as vestibular neuritis (Murofushi et al., 1996b), Meniere's disease (de Waele et al., 1999), VS (Murofushi et al., 1998; Takeichi et al., 2001; Patko et al., 2003), delayed endolymphatic hydrops (Ohki et al., 2002), idiopathic bilateral vestibulopathy (Matsuzaki and Murofushi, 2001) and sudden hearing loss with vertigo (Iwasaki et al., 2005a). However, to date, the clinical usefulness of VEMP has not been evaluated on the basis of the Standards for Reporting of Diagnostic Accuracy (STARD), which was recently established to improve the quality of reporting diagnostic accuracy studies (Bossuyt, 2003; Bossuyt et al., 2003a,b).

In the present study, we estimated the sensitivity and specificity of VEMP in patients with VS on the basis of the STARD and compared them with those of the caloric test.

* Corresponding author. Tel.: +81 3 5800 8665; fax: +81 3 3814 9486.
E-mail address: IZT01356@nifty.ne.jp (M. Ushio).

1388-2457/$36.00
doi:10.1016/j.clinph.2009.01.017

2. Materials and methods

2.1. Patients

From January 2002 to December 2006, data were retrospectively collected from 803 consecutive patients (376 men, 427 women; mean ± standard deviation [SD] age 49.1 ± 16.8 years, range 3–86 years) who visited our vertigo clinic and underwent vestibular tests, including VEMP and the caloric test. Amongst them, 78 patients (39 men, 39 women; mean ± SD age: 50.4 ± 12.8 years, range: 22–72 years) were diagnosed as having untreated unilateral VS based on a contrast-enhanced MRI of the brain. Amongst the VS patients, 53 patients underwent surgical resection and the tumours were neuropathologically confirmed to be VS. The present study included both patients who underwent the operation and those who did not, as exclusion of these patients may cause a strong bias in several factors such as the patient's age and the size and site of the tumour.

2.2. Methods

2.2.1. Evaluation of tumour size

Axial and coronal T1-weighted MRI before and after contrast (gadolinium diethylenetriaminepentaacetic acid (DTPA)) and axial T2-weighted MRI were performed using a fast spin-echo program with a 1.5-T unit (Signa; GE Medical Systems), 3.0 mm in thickness at intervals of 3.3 mm. Maximum diameters of VSs were measured and employed as tumour size.

2.2.2. Vestibular function tests

VEMP (Colebatch et al., 1994a) was recorded from the SCM in response to clicks (0.1 ms, 95 dB normal hearing level; click VEMP) and short-tone bursts (500 Hz, rise/fall time 1 ms, plateau time 2 ms, 95 dB normal hearing level; burst VEMP) using the Neuropack Σ (Nihon Kohden, Tokyo, Japan). Surface electromyographic activities were recorded from symmetrical sites over the upper half of each SCM, with reference electrodes on the side of the upper sternum. The ground electrode was placed on the nasion. During the recording of both click and burst VEMPs, patients were instructed to raise their heads to activate the SCM. Electromyograms of bilateral SCMs were monitored to confirm normal muscle activities, although the traces of the electromyograms were not rectified. First, click VEMP was recorded in all patients. When this showed no response on both sides, burst VEMP was then recorded because short-tone bursts of 500 Hz have been shown to be of value in detecting a residual function of the saccular nerve (McCue and Guinan, 1995; Murofushi et al., 1999; Walgampola and Colebatch, 2005). We analysed the first biphasic responses (p13–n23) on the ipsilateral SCM to the stimulated side (Colebatch et al., 1994b). The analysis time for each stimulus was 50 ms (0–50 ms after stimulus). The responses for up to 100 stimuli were averaged twice. When the VEMP responses on the affected side were decreased or absent, the patient was classified into a 'correctly identified by VEMP' group; when normal on both the sides, the patient was classified into an 'incorrectly identified by VEMP' group; and when absent, the patient was again classified into an 'incorrectly identified by VEMP' group because we cannot identify the affected side from the results of VEMP. For this comparison, the percent VEMP asymmetry was calculated with the following formula using the amplitude of p13–n23 on the affected side (*Aa*) and that on the unaffected side (*Au*):

$$\text{VEMP asymmetry } (\%) = 100(Au - Aa)/(Au + Aa).$$

The upper limit of percent VEMP asymmetry was set as 34.1 for click VEMP (Murofushi et al., 1998) and 34.0 for burst VEMP (Murofushi et al., 1999). The representative recordings of the patients with normal response on both sides and those of the patients with absent response on the affected side are shown in Fig. 1a and b, respectively.

The caloric test was performed using 4 °C cold water. Percent canal paresis (CP) was calculated with the following formula using the maximum slow-phase eye velocity of induced nystagmus responses on the affected side (*MSEVa*) and that on the unaffected side (*MSEVu*) using electronystagmograph in the supine position (head up 30°):

$$\text{CP } (\%) = 100(MSEVu - MSEVa)/(MSEVu + MSEVa).$$

A value of CP ⩽ 20% was considered normal, and the patient was classified into the 'incorrectly identified by the caloric test' group. A value of CP > 20% was considered abnormal (Iwasaki et al., 2005b), and the patient was classified into the 'correctly identified by the caloric test' group. When both the *MSEVa* and *MSEVu* were $<10^\circ\,s^{-1}$, it was regarded as a decreased response on both the sides.

2.2.3. Statistical analyses

Statistical analyses were performed using SPSS statistical software (Jandel; SPSS, Chicago, IL, USA). The data are presented as mean ± SD unless otherwise noted. The sensitivities and specificities of VEMP and the caloric test were compared using a chi-square test. The ages and tumour sizes of the patients were compared using Student's *t*-test (between two groups) or analysis of variance

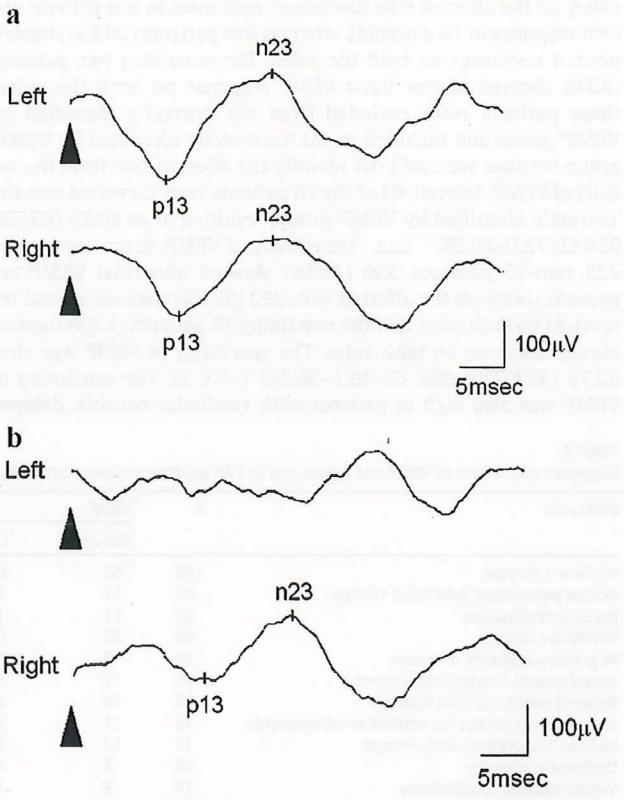

Fig. 1. Click-evoked vestibular-evoked myogenic potential (VEMP) records of representative patients with vestibular schwannoma (VS). (a) Click-VEMP responses for up to 100 stimuli averaged twice in patients with left VS. This patient showed normal responses on both sides. (b) Click-VEMP responses for up to 100 stimuli averaged twice in patient with left VS. This patient showed absent response on the left side and normal responses on the right side. The analysis time for each stimulus was 50 ms (0–50 ms after stimulus). Arrow heads indicate the time at which the stimuli were applied.

Table 1
Results of VEMP and caloric test in 78 patients with vestibular schwannoma.

	Results	Number of patients (%)	Sensitivity (%)	Mean ± SD tumour size
VEMP	Positive	63 (80.8)	80.8	23.3 ± 10.0
	Negative	15 (19.2)		18.4 ± 9.5
Caloric test	Positive	63 (80.8)	80.8	24.4 ± 9.6
	Negative	15 (19.2)		16.8 ± 8.5

(ANOVA) and Bonferroni-adjusted *t*-test (amongst multiple groups). A difference of $p < 0.05$ was considered significant.

3. Results

The results of VEMP and the caloric test in patients with VS are shown in Table 1 and those in patients without VS are shown in Table 2.

3.1. VEMP

Amongst the 78 patients with VS, 46 (59.0%) showed abnormal click VEMP solely on the affected side (decreased responses in seven patients; absent response in 39 patients), whereas eight (10.3%) showed normal responses on both sides. Twenty-four patients (30.8%) showed no click-VEMP response on both the sides; therefore, we recorded burst VEMP in these patients. Amongst them, 17 patients (70.8%) showed abnormal burst-VEMP responses solely on the affected side (decreased responses in one patient; absent response in 16 patients), whereas five patients (20.8%) showed normal responses on both the sides. The remaining two patients (8.3%) showed absent burst-VEMP response on both the sides; these patients were excluded from the 'correctly identified by VEMP' group and included in the 'incorrectly identified by VEMP' group because we could not identify the affected side from the results of VEMP. Overall, 63 of the 78 patients were classified into the 'correctly identified by VEMP' group, resulting in an 80.8% (63/78; 95% CI: 72.0–89.5%; Table 1) sensitivity of VEMP. In contrast, in the 725 non-VS patients, 330 (45.5%) showed abnormal VEMP responses solely on the affected side, 382 (52.7%) showed normal responses on both sides and the remaining 13 patients (1.8%) showed absent response on both sides. The specificity of VEMP was thus 52.7% (382/725; 95% CI: 49.1–56.3%; Table 2). The sensitivity of VEMP was also high in patients with vestibular neuritis, delayed endolymphatic hydrops, sudden hearing loss with vertigo and Ramsay Hunt syndrome, similar to the sensitivity in patients with VS (Table 2).

The ages of the VS patients in the 'correctly identified by VEMP' group (51.7 ± 12.3 years) and those of the patients in the 'incorrectly identified by VEMP' group (46.2 ± 15.4 years) were not significantly different ($p = 0.17$). The mean tumour size of the patients in the 'correctly identified by VEMP' group (23.3 ± 10.0 mm) was slightly larger than that in the 'incorrectly identified by VEMP' group (18.4 ± 9.5 mm); however, there was no significant difference between them ($p = 0.13$; Table 1). The tumours were located within the internal auditory meatus in 11 of the 78 patients (14.1%), whereas they extended to both the internal auditory meatus and cerebellopontine angle in the remaining 67 (85.9%).

Patients who showed absent click-VEMP response on both the sides were significantly older than those who did not (54.4 ± 9.5 years vs. 48.7 ± 13.8 years; $p = 0.04$). The tumour sizes in patients showing absent VEMP response on both sides (24.5 ± 9.9 mm) were not significantly different from those of the other patients (21.2 ± 9.7 mm; $p = 0.17$).

3.2. Caloric test

Amongst the 78 patients with VS, 63 (80.8%) showed decreased or no caloric responses and the remaining 15 (19.2%) showed normal caloric responses (mean CP, 7.6 ± 6.4). None of the VS patients showed decreased or absent responses on both the sides. The sensitivity of the caloric test was thus 80.8% (63/78; 95% CI: 72.0–89.5%; Table 1). In contrast, amongst the 725 non-VS patients, 289 (39.9%) showed decreased or absent caloric responses on the affected side, 416 patients (57.4%) showed normal responses on both sides and the remaining 20 patients (2.8%) showed decreased or absent response on both sides. The specificity of the caloric test was thus estimated to be 57.4% (416/725; 95% CI: 53.8–61.0%; Table 2). The sensitivity of the caloric test was also high in patients with vestibular neuritis, delayed endolymphatic hydrops, sudden hearing loss with vertigo and Ramsay Hunt syndrome, similar to the sensitivity in patients with VS (Table 2).

The mean tumour size of the patients in the 'correctly identified by the caloric test' group (24.4 ± 9.6 mm) was significantly larger than that in the 'incorrectly identified by the caloric test' group (16.8 ± 8.5 mm; $p = 0.04$; Table 1).

Table 2
Diagnoses and results of VEMP and caloric test in 725 patients without vestibular schwannoma.

Diagnoses	*n*	VEMP				Caloric test			
		Abnormal	*1	Normal	Sensitivity (%)	Abnormal	*2	Normal	Sensitivity (%)
Meniere's disease	105	52	0	53	49.5	50	4	51	47.6
Benign paroxysmal positional vertigo	64	12	2	50	18.8	12	0	52	18.8
Psychiatric dizziness	63	13	1	49	20.6	12	0	51	19
Vestibular neuritis	49	37	0	12	75.5	39	1	9	79.6
Migraine-associated dizziness	22	8	1	13	36.4	5	0	17	22.7
Sensorineural hearing impairment	19	12	0	7	63.2	9	0	10	47.4
Delayed endolymphatic hydrops	18	16	0	2	88.9	16	1	1	88.9
Brain tumour except for vestibular schwannoma	18	11	0	7	61.1	13	0	5	72.2
Sudden hearing loss with vertigo	17	13	0	4	76.5	13	0	4	76.5
Orthostatic disorder	16	3	1	12	18.8	3	0	13	18.8
Vertebrobasilar insufficiency	16	9	1	6	56.3	7	0	9	43.8
Ramsay Hunt syndrome	12	10	0	2	83.3	11	0	1	91.7
Cerebellar degeneration	7	3	1	3	42.9	3	1	3	42.9
Nonspecific vestibulopathy	250	112	4	134	44.8	87	8	155	34.8
Others	49	19	2	28	38.8	9	5	35	18.4
Total	725	330	13	382		289	20	416	

*1, absent VEMP response on both sides; *2, absent caloric response on both sides; although absent response on both sides may be pathological findings on VEMP or the caloric test in patients with bilateral diseases (e.g. bilateral Meniere's disease) or diseases that have no laterality (e.g. cerebellar degeneration), we regarded them as 'incorrectly identified' cases in this table.