in other types of ENT surgery such as to the head and neck. Although total laryngectomy completely removes vocal ability and produces high patient stress, and partial parotidectomy for a parotid benign tumor includes direct contact with the facial nerve outside of temporal bone, no DFP was observed after either procedure (total laryngectomy, 0 out of 629; partial parotidectomy, 0 out of 168: personal communication with Professor Hiroshi Miyahara, Department of Otolaryngology, Osaka Prefectural General Medical Center)[19]. Therefore, the actual surgical procedures themselves during temporal bone surgery may be more important than general surgery stress in the pathogenesis of DFP.

Two surgical procedures potentially important in the pathogenesis of DFP after otological and neurotological surgeries were previously described[2]; the 'mastoidectomy procedure' and 'facial nerve and/or chorda tympani nerve exposure'. During the mastoidectomy procedure, it was suggested that generation of heat and/or inflammation by drilling of the temporal bone might indirectly produce 'intratubal facial nerve edema'; when facial nerve edema is the main cause of DFP, this may account for the relatively early post-operative onset after operation[11,20]. By contrast, exposing the facial nerve and/or chorda tympani nerves in the operative field may induce herpes virus reactivation, which may account for a relatively late post-operative onset[21,22]. During the surgical procedures used for endolymphatic sac surgery in the present case, the facial-chorda tympani nerve was not exposed or touched directly, suggesting a role for the mastoidectomy procedure. However, the onset of DFP after sac surgery was relatively late in the present case (post-operative day 8), suggesting a role of reactivation of a virus; HSV and VZV serum tests were negative, ruling them out as candidates. Of note, although the nerves were not exposed in the surgical field during endolymphatic sac surgery in the present case, a high concentration of steroids around the endolymphatic sac might stimulate the chorda tympani nerve in the tympanic cavity, resulting in reactivation of some virus in the geniculate ganglion.

Conclusion

We reported the first case of DFP after endolymphatic sac surgery. As longer surgical times result in an increase in the DFP incident ratio from 0.001 to 0.1%, temporal bone surgeries should be performed rapidly without unnecessary procedures. Further basic and clinical studies are needed to elucidate the mechanisms of DFP onset.

Table 1. Incident ratio of delayed facial nerve paresis (DFP) after otological and neurotological surgeries.

Operation	Authors	The Number of Patients	DFP Ratio
Acoustic neurinoma surgery	Arriaga et al.,1993	468	14.5%
	Lalwani et al.,1995	129	29.5%
	Megerian et al.,1996	262	23.7%
	Yamada et al.,2002	94	9.6%
Vestibular neurectomy	Vrabec et al.,2003	70	11.4%
Tympanoplasty with mastoidectomy	Deka et al.,1988	235	8.5%
	Vrabec et al.,1999	486	1.4%
	Yamada et al.,2002	1182	0.3%
Cochlear implant	Cohen et al.,1988	459	1.7%
	Lalwani et al.,1998	41	4.9%
	Fayad et al.,2003	705	0.7%
Stapes surgery	Althaus et al.,1973	2307	0.2%
	Smith et al.,1990	1300	0.5%
	Shea et al.,2001	2152	0.5%
Endolymphatic sac surgery	Kamakura et al.,2010	150	0.7%

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Benign paroxysmal positional vertigo showing sequential translations of four types of nystagmus

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ABSTRACT

Objective: We report a case of benign paroxysmal positional vertigo (BPPV) showing sequential translation of four types of nystagmus and discuss its pathophysiology.
Methods: The case was 65-year-old female. We analyzed her nystagmus three-dimensionally.
Results: At the first visit, she showed vertical-torsio nystagmus of the posterior canal type of BPPV (P-BPPV) and subsequently showed recently reported geotropic nystagmus with a long time constant. Two weeks later, she showed apogeotropic nystagmus of the horizontal canal type of BPPV (AH-BPPV) and subsequently a geotropic nystagmus with a short time constant of the horizontal canal type of BPPV (GH-BPPV).
Conclusions: Three kind of nystagmus, namely P-BPPV, AH-BPPV and GH-BPPV can be explained by the otoconial debris hypothesis of the same ear. Finally, the recently reported geotropic nystagmus with a long time constant may be explained by a reversible lesion such as the denatured cupula or utricular imbalance of the same ear.

1. Introduction

Benign paroxysmal positional vertigo (BPPV) is caused by either canalolithiasis or cupulolithiasis [1] and can theoretically affect each of the three semicircular canals [1]. Torsio-vertical nystagmus in patients with the posterior semicircular canal (PSCC) type of BPPV (P-BPPV) is caused by canalolithiasis in PSCC [1]. Among the horizontal semicircular canal (HSCC) type of BPPV (H-BPPV), apogeotropic nystagmus in patients with H-BPPV (AH-BPPP) is caused by cupulolithiasis on the cupula of HSCC [1]. Geotropic nystagmus that is of limited duration with short time constant in patients with H-BPPV (GH-BPPV) is caused by canalolithiasis in HSCC [1]. Recently, another geotropic nystagmus that is persistent with long time constant was reported, suggesting that it is caused by the denatured cupula of less specific weight than the surrounding endolymph in HSCC [2].

Translation from P-BPPV to H-BPPV occurs when canalolithiasis moves from PSCC into HSCC [1]. Translation from AH-BPPV to GH-BPPV also occurs during the transition from cupulolithiasis to canalolithiasis in HSCC [3]. In this study, we report a case of BPPV that showed sequential translations of four types of nystagmus: torsio-vertical nystagmus of P-BPPV, the recently reported geotropic nystagmus with long time constant, apogeotropic nystagmus of AH-BPPV and geotropic nystagmus with short time constant of GH-BPPV. We analyzed each nystagmus three-dimensionally and discussed its pathophysiology.

2. Methods and subject

The case is 65-year-old female complaining of positioning vertigo. We recorded positional and positioning nystagmus at her first visit to our hospital and at her second visit two weeks later. She had no canal paresis in the caloric test with no other neurological signs. We did not perform canalith repositioning maneuver at any of her visit.

Positional and positioning nystagmus of her left eye was recorded on digital video (DV) with an infrared CCD camera (*RealEyes*, Micromedical Technologies). In the present study, eye movements were three-dimensionally described by rotation vectors [4]. The analysis method of the eye rotation vector and

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its accuracy has already been described elsewhere [3,5,6]. For the space coordinates, the *X* axis parallel to the naso-occipital axis (positive forward), *Y* axis parallel to the inter-aural axis (positive left), and *Z* axis normal to the *X*–*Y* plane (positive upwards) were defined. *X*, *Y*, and *Z* components mainly reflect roll, pitch, and yaw components, respectively. We used the unit degree that is given as $2\tan^{-1}$(magnitude of rotation vector) to represent the eye position as axis-angle representations [3]. Using $\mathbf{r}$ that is the rotation vector of eye position and with the following formula: $\omega = 2(d\mathbf{r}/dt + \mathbf{r} \times d\mathbf{r}/dt)/(1 + \mathbf{r}^2)$, we calculated the eye velocity ω around *X*, *Y*, and *Z* axes [4]. We then extracted the slow phase eye velocity (SPEV) of nystagmus by the method based on a fuzzy set approach [3]. Using the least squares method, SPEV against time was approximated exponentially. Finally, the time constant was calculated as the reciprocal of the coefficient of time [3].

3. Results

At the patient's first visit, she showed torsio-vertical nystagmus with clockwise and upward direction of its fast phase seen in patients with right P-BPPV [1], when she tilted her head backward in the sitting position (Fig. 1A). The maximum SPEV and time constant of the torsio-vertical nystagmus was 36.5°/s in *X* component and 2.4 s in *X* component, respectively (Fig. 3A ⓐ). The axis angles of SPEV of the nystagmus were plotted along the axis perpendicular to the plane of right PSCC (Rp) [7] on *XY*, *XZ* and *YZ* planes (Fig. 4A). She then showed the similar, but fatigued nystagmus with slower maximum SPEV (18.4°/s in *X* component) with the same short time constant (2.7 s) in right Dix-Hallpike maneuver (from sitting to right head hanging position) [1] (Fig. 3A ⓒ). Therefore, canalolithiasis was suggested in right PSCC.

But, in left Dix-Hallpike maneuver, she showed leftward horizontal nystagmus (Fig. 3A ⓓ). Thereafter, she showed the recently reported geotropic nystagmus with long time constant in supine position [2]. When her head was turned to right lateral position in supine, she showed rightward horizontal nystagmus with much longer time constant (183.3 s) (Figs. 1B and 3A ⓔ). When her head was turned to left lateral position in supine, she showed leftward horizontal nystagmus again with the same long time constant (1642.0 s) (Figs. 1C and 3A ⓕ).

Two weeks later, she visited our clinic again and showed leftward and rightward horizontal nystagmus, when she tilted her head forward and backward in the sitting position, respectively (Fig. 2A and B). Such nystagmus was seen in patients with AH-BPPV where cupulolithiasis induced apogeotropic nystagmus with long time constant in the supine position [8]. The time constant of the leftward and rightward horizontal nystagmus was as long as 20.1 and 25.9 s, respectively (Fig. 3B ⓖ and ⓐ). Actually, she showed leftward horizontal nystagmus with time constant of 13.9 s, when her head turned to right lateral position in supine (Figs. 2C and 3B first ⓔ). The axis angles of SPEV of the nystagmus were plotted along the axis perpendicular to the plane of left HSCC (Lh) [7] on *XY*, *XZ* and *YZ* planes (Fig. 4B). Because nystagmus induced by the ampullofugal inhibition of right HSCC rotates around the plane of left HSCC [9], cupulolithiasis was suggested in right HSCC.

Thereafter, she showed geotropic nystagmus seen in patients with GH-BPPV where canalolithiasis in HSCC induced geotropic nystagmus with short time constant in the supine position. When her head turned to left lateral position in supine, she showed leftward horizontal nystagmus with short time constant of 8.7 s (Figs. 2D and 3B ⓕ). When her head turned to right lateral position in supine, she showed rightward horizontal nystagmus with short time constant of 5.2 s (Figs. 2E and 3 second ⓔ). The maximum SPEV of the rightward horizontal nystagmus was 191.8°/s in *Z* component (Fig. 3B second ⓔ), which was greater than that of the leftward horizontal nystagmus (34.7°/s) (Fig. 3B ⓕ). Because

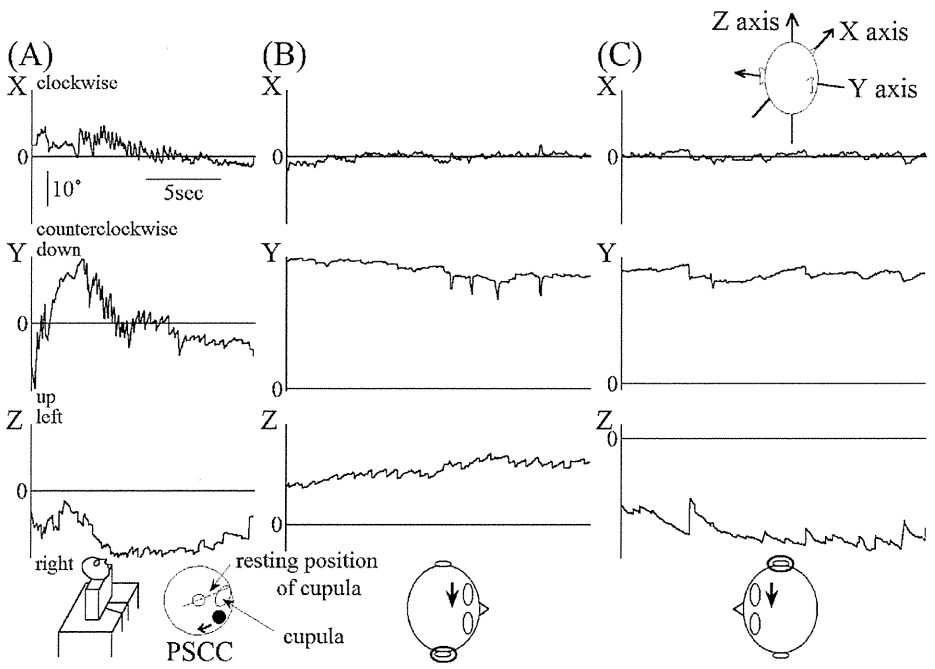

Fig. 1. Axis angles of the eye position in the patient at her first visit to our hospital. (A) When she tilted the head backward, she showed torsio-vertical nystagmus with clockwise and upward fast phase direction. (B) When she turned the head to right lateral position in supine, she showed horizontal nystagmu with a rightward fast phase direction. (C) When she turned to left lateral position in supine, she showed horizontal nystagmus with a leftward fast phase direction. Inserted figures show her head position and her right PSCC or HSCC with otocanial debris (•). The direction of the arrow near the eye of the inserted head figures shows the direction of her nystagmus.

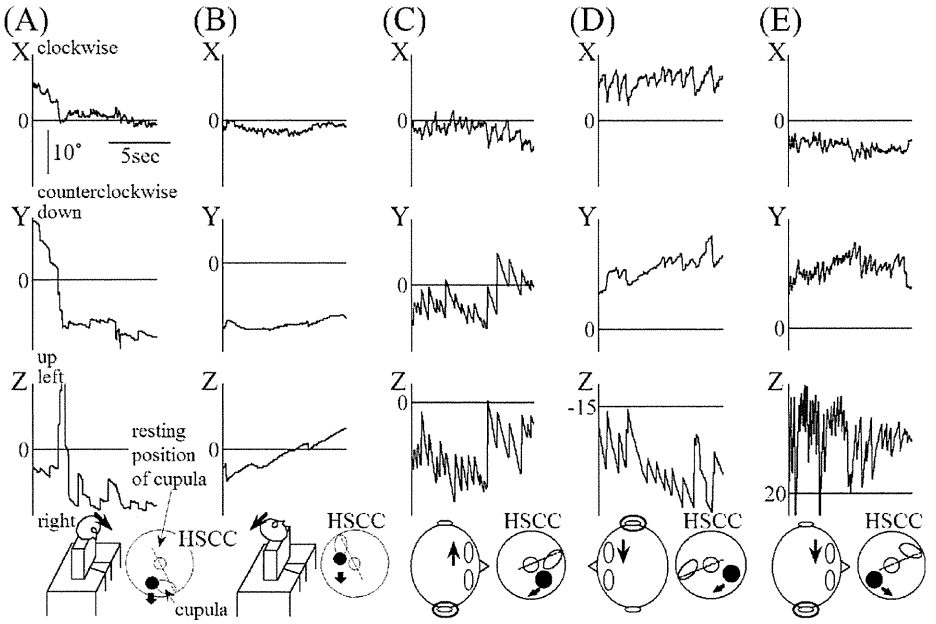

Fig. 2. Axis angles of the eye position of her nystagmus at her second visit to our hospital. (A) When she bowed the head, she showed horizontal nystagmus with a leftward fast phase direction. (B) When she tilted the head backward, she showed horizontal nystagmus with a rightward fast phase direction. (C) When she turned to right lateral position in supine at first time, she showed horizontal nystagmus with a leftward fast phase direction. (D) When she turned the head to left lateral position in supine, she showed horizontal nystagmus with a leftward fast phase direction. (E) When she turned the head to right lateral position in supine at second time, she showed horizontal nystagmus with a rightward fast phase direction.

geotropic nystagmus is stronger when the head turned to the side of the affected ear [8], canalolithiasis was suggested in right HSCC.

Three weeks after the first visit, her positional and positioning nystagmus had disappeared and she did not complain of any dizziness and/or vertigo, as this condition was generally realized as self limiting.

4. Discussion

At the first visit of the patient, she showed torsio-vertical positioning nystagmus and axis angles of its SPEV were plotted along the axis perpendicular to the plane of right PSCC. As demonstrated by Suzuki and Cohen the electrical stimulation of

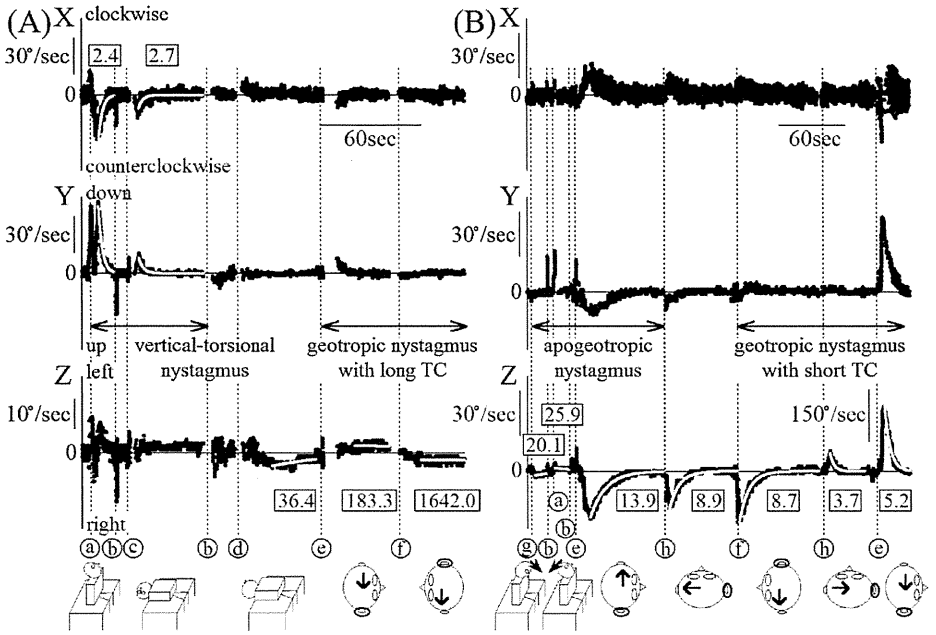

Fig. 3. Axis angles of SPEV of her nystagmus. (A) At her first visit to our hospital. (B) At her second visit to our hospital. After the point of second ⓔ, the scale of eye velocity in *Z* component was different from other part. The number enclosed by square represents the time constant. The unit was second. ⓐ Head backward in the sitting position, ⓑ head to the upright sitting position, ⓒ from sitting to right head hanging position, ⓓ left head hanging position, ⓔ head in right lateral position in supine, ⓕ head in left lateral position in supine, ⓖ head bowed in the sitting position, and ⓗ head in centered position in supine.

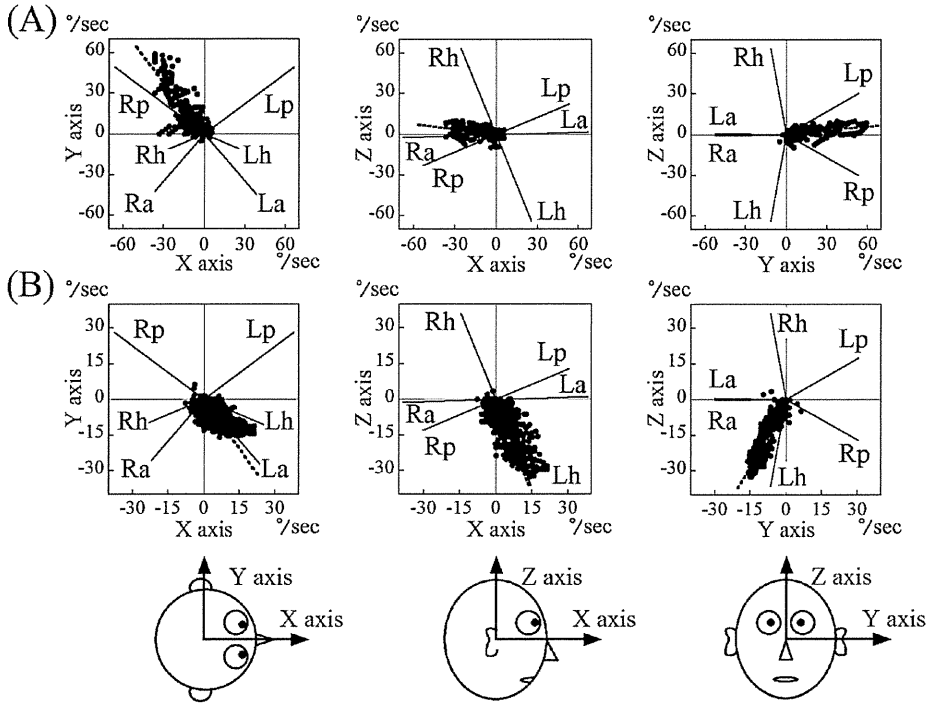

Fig. 4. The axis angles of SPEV are plotted in *XY*, *XZ*, and *YZ* planes. (A) Head backward at her first visit to our hospital. The axis angles of SPEV were plotted around the axis perpendicular to the plane of right PSCC (Rp). (B) Head in right lateral position in supine at her second visit to our hospital. The axis angles of SPEV were plotted around the axis perpendicular to the plane of left HSCC (Lh). Dotted line, the averaged rotation axis of SPEV. Ra, axis perpendicular to the plane of the right anterior semicircular canal; Rh, axis perpendicular to the plane of the right HSCC; Rp, axis perpendicular to the plane of the right PSCC; La, axis perpendicular to the plane of the left anterior semicircular canal; Lh, axis perpendicular to the plane of the left HSCC; Lp, axis perpendicular to the plane of the left PSCC [7].

single semicircular canal afferents induced eye movements around the plane of the canal in cats and monkeys [10,11], it is suggested that the torsio-vertical nystagmus originated from right PSCC. Taken together with the observations that the time constant of SPEV declination of the nystagmus was short (2.4 s) with SPEV fatigability after repeated positioning maneuver, these findings led to the diagnosis of right P-BPPV, suggesting canalolithiasis in PSCC of the right ear.

At her second visit, she showed apogeotropic positional nystagmus. Axis angles of SPEV of leftward horizontal nystagmus at right-side-down head position in supine were plotted along the axis perpendicular to the plane of left HSCC. Because nystagmus induced by the ampullofugal inhibition of right HSCC rotates around the plane of left HSCC [9], the leftward horizontal nystagmus was suggested to originate from right HSCC. Taken together with its time constant (13.9 s), these findings led to the diagnosis of right AH-BPPV, suggesting cupulolithiasis on the cupula of right HSCC. Translation from torsio-vertical nystagmus to apogeotropic nystagmus in the patient suggested that otoconial debris in the right PSCC as canalolithiasis moved into HSCC were attached on the cupula of the same ear. Translation from P-BPPV to H-BPPV in the same ear was reported previously [1].

Thereafter, she showed geotropic nystagmus in the supine position with short time constant and rightward horizontal nystagmus stronger than left one. These findings led to the diagnosis of right GH-BPPV, suggesting canalolithiasis in right HSCC. It is suggested that translation from apogeotropic nystagmus to geotropic nystagmus was due to displacement of otoconial debris from the cupula into the canal of the right HSCC. Such translation from AH-BPPV to GH-BPPV was reported previously [3].

In the present study, we analyzed patient's nystagmus three-dimensionally and found that she sequentially suffered from P-BPPV, AH-BPPV and GH-BPPV within 2 weeks. The pathophysiology was suggested as follows: otoconial debris dislodged from the otolith organ of the right ear dropped firstly into PSCC to be canalolithiasis of P-BPPV. Then, the otoconial debris moved into HSCC and was attached on its cupula to be cupulolithiasis of AH-BPPV. Thereafter, they were displaced from the cupula to the canal of HSCC of the right ear to be GH-BPPV.

The patient showed the recently reported geotropic nystagmus with long time constant after disappearance of torsio-vertical nystagmus of P-BPPV at her first visit [2]. The nystagmus may be explained by the denatured cupula of less specific weight than the surrounding endolymph in HSCC [2]. Geotropic nystagmus with long time constant might be explained by the otolith imbalance hypothesis. Accordingly, since otoconial debris is considered to be dislodged from the utricle [1,12], imbalance of utricular function reported in patients with BPPV [12] may induce geotropic nystagmus with long time constant [13]. The imbalance of utricular fuciton causes asymmetry of horizontal eye movement during otolith vestibulo-ocular reflex [14]. The suggested lesion such as the denatured cupula or utricular imbalance might have been of benign nature [15] because of disappearance of the nystagmus after three weeks at her first visit.

In conclusion, we showed a case of BPPV that showed sequential translations of four types of nystagmus: torsio-vertical nystagmus of P-BPPV, the recently reported geotropic nystagmus with long time constant, apogeotropic nystagmus of AH-BPPV and geotropic nystagmus with short time constant of GH-BPPV. Three kind of nystagmus except the recently reported geotropic nystagmus with long time constant can be explained by the otoconial debris hypothesis of the right ear. The recently reported

geotropic nystagmus with long time constant may be explained by reversible lesion such as the denatured cupula or utricular imbalance of the same ear.

Conflict of interest

None.

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3D analysis of spontaneous upbeat nystagmus in a patient with astrocytoma in cerebellum

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Abstract

Aims: We report the case of a 58-year-old female patient who consulted our Department complaining of positional vertigo and showing spontaneous upbeat nystagmus (UBN) in darkness.
Method: We analyzed her UBN three-dimensionally. The MRI scan revealed the astrocytoma in the left cerebellum involving the cerebellar vermis.
Result: Three-dimensional analysis showed a spontaneous UBN rotating around the intra-aural axis in the pitch plane.
Conclusion: Since the cerebellar vermis is known to plays an inhibitory role on the central vertical vestibule-ocular reflex (VOR), the present results suggest that the spontaneous UBN in darkness observed in this patient was induced by an imbalance of central vertical VOR tone.

Keywords: Upbeat nystagmus; Three-dimensional; Rotation vector; Cerebellar astrocytoma

1. Introduction

Upbeat nystagmus (UBN) consists of an upbeat gaze nystagmus due to the malfunction of vertical position integrator, or a spontaneous UBN due to the asymmetry of central vertical vestibule-ocular reflex (VOR) [1]. In the present study, we report the case of a patient with spontaneous UBN in darkness. Analyzing the UBN three-dimensionally, we show that the UBN was induced by an imbalance of central vertical VOR tone.

2. Case report

On September 11, 2007, a 58-year-old woman came on foot to our hospital complaining of a month history of positional vertigo when turning her head. She showed no hearing loss and had no other remarkable physical findings in both ears. On her follow-up visit on September 25, she had developed nausea a few days before. She could write her name clearly and smoothly and showed spontaneous UBN in darkness, but not gaze-evoked UBN or UBN in the primary position of gaze in light. The caloric test showed no canal paralysis with visual suppression of caloric nystagmus, but the eye tracking test recorded by electronystagmography (ENG) showed a saccadic pattern (Fig. 1A). There was dysmetria in

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finger-to-nose test. A brain MRI scan revealed a 2 cm diameter left cerebellar mass (Fig. 1B) located posterior to the forth ventricle. The mass showed low intensity on T1 weighted images with a surrounding edema (Fig. 1B(a)) and high intensity on T2 weighted images (Fig. 1B(b)). The peritumoral edema particularly affected the cerebellar vermis. On October 5, the patient underwent surgery to remove the cerebellar tumor by neurosurgeons and histological examination revealed an astrocytoma, grade 2–3 (Fig. 1C). After surgery, she was treated with radiation therapy from October 29 to December 7. On her post-operative follow-up visit she still showed spontaneous UBN in the darkness.

3. Method

Before operation on October 1, 2007, spontaneous UBN was recorded on videotape with an infrared CCD camera (RealEyes, Micromedical Technologies). The description of the eye movements in three dimensions was done using rotation vectors, which characterize the three dimensional eye position by a single rotation. The rotation vector was given by the axis of rotation, and its length was proportional to the size of the rotation. An eye position could be reached by rotating the eye from a reference position on a single axis. The reference position was defined as the position assumed by the eye when the subject was looking straight ahead with the head kept upright, while straight ahead was defined as looking at a target located horizontally in front of the eye [2]. The eye rotation vectors analysis method and its accuracy have already been described [3,4]. We converted the videotape images into 30 Hz digital images (720 × 480 dot) (PCV-R63K, SONY) and from these we reconstructed the space coordinates of the center of the pupil and an iris freckle. These coordinates (*X*, *Y*, *Z*) were defined so that the

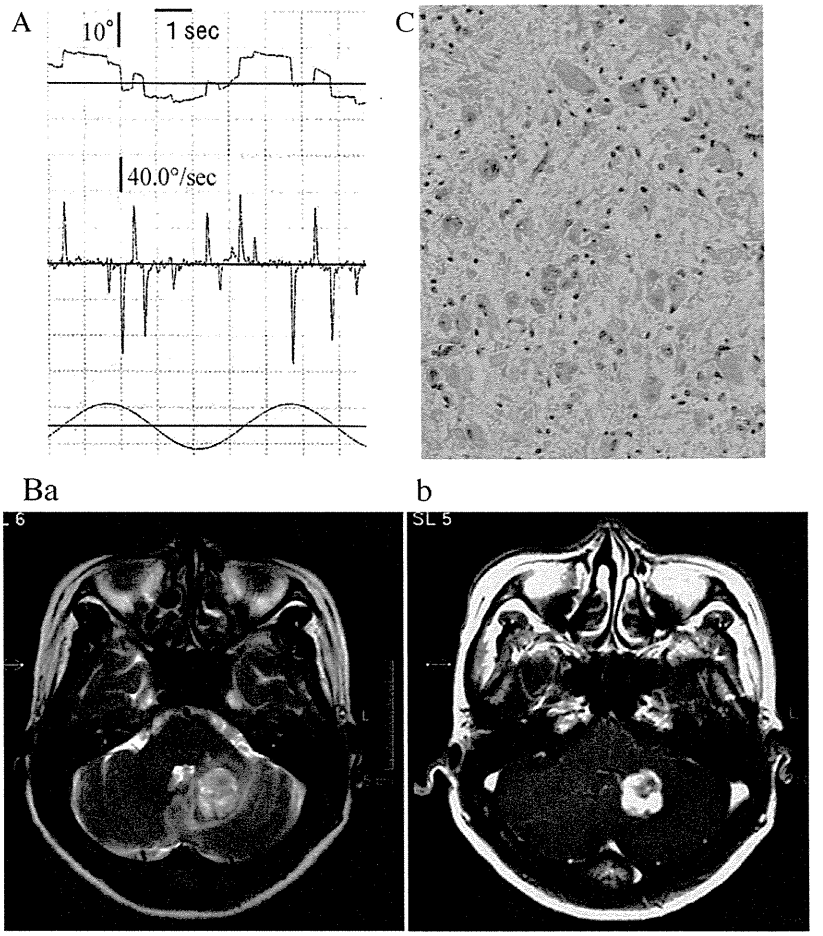

Fig. 1. (A) ENG during eye tracking test. From above, horizontal eye position, differential waveform of horizontal eye position, and horizontal target position. Her eye movement was saccadic. (B) The brain MRI imaging. (a) T1 weighted image, (b) T2 weighted image. There was a mass like lesion in left cerebellum which lies posterior to 4th ventricle and diameter of 2 cm. The mass was low intensity in T1 weighted image and high intensity in T2 weighted image. The mass was strongly enhanced. (C) The microscopic image of the cerebellar tumor, HE staining. Fibrillary and gemistocytic cell were mixed. Cells that have giant nucleus were seen.

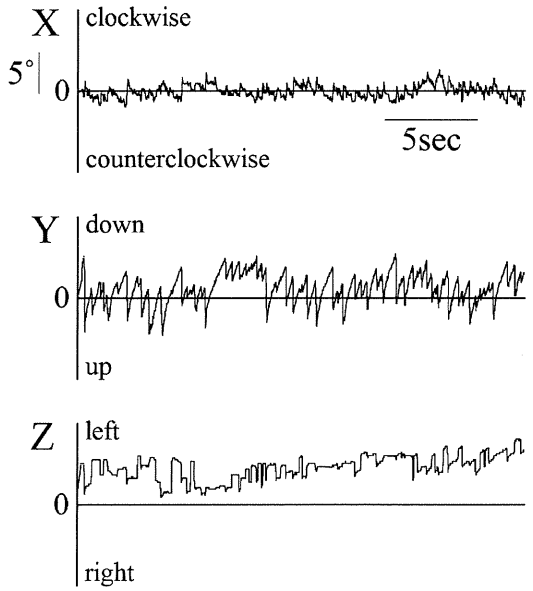

Fig. 2. Axis angle of eye position in *X*, *Y*, *Z* components of nystagmus when the patient was sitting in dark. UBN is clearly shown in *Y* component.

X-axis was parallel to the naso-occipital axis (positive forward), *Y*-axis parallel to the inter-aural axis (positive left), and *Z*-axis normal to the *X*–*Y* plane (positive upwards). *X*, *Y*, and *Z* components mainly reflect the roll, pitch, and yaw components, respectively. We used axis-angle representations [5]. The direction of rotation was represented as the subject's point of view. Using this method, we have already reported the three dimensional analysis of positional nystagmus in patients with benign paroxysmal positional vertigo [6,7]. In addition, we calculated the slow phase eye velocity (SPEV) ω around *X*, *Y*, and *Z* axes [2] and extracted the slow phase data from nystagmic eye movement data by using the method (patent applied for) based on a fuzzy set approach [8,9].

4. Results

The patient showed spontaneous UBN when sitting in darkness (Fig. 2), but not gaze-evoked UBN or UBN in the primary position of gaze in light. She also showed UBN in any head positions in supine. The SPEV of UBN was 5°/s when sitting and 10°/s in supine position (Fig. 3A). Three-dimensional analysis indicated that the spontaneous UBN

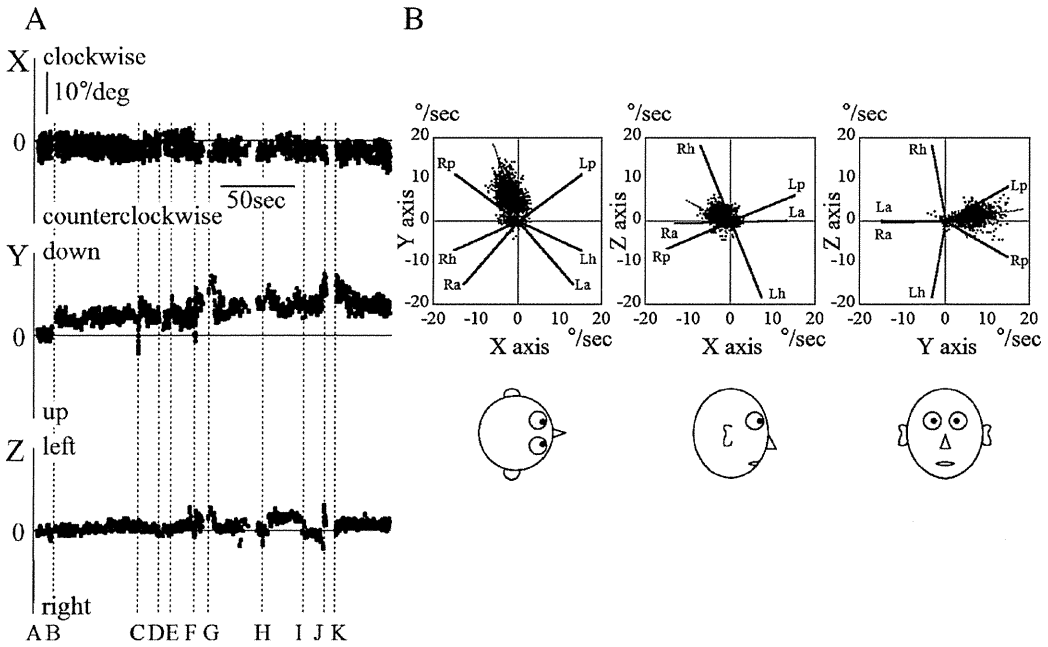

Fig. 3. (A) Axis angle of SPEV in *X*, *Y*, *Z* components of nystagmus. Her head position was changed in each dotted lines. A: Upright primary sitting position in light. B: Upright in dark. C: She bowed the head. D: Upright primary position. E: She leaned the head backward. F: Upright primary position. G: She changed her head from sitting to the head centered position in supine. H: She rotated her head to left in supine. I: She rotated her head to right in supine. J: Her head was the head centered position in supine. K: She changed her head from the head centered position to sitting. (B) Three-dimensional plotting of the axis angle of SPEV that is shown in (A). The axis angles were plotted around the axis that created pure vertical nystagmus. Ra, axis perpendicular to the plane of the right anterior semicircular canal (ASCC); Rh, axis perpendicular to the right horizontal semicircular canal (HSCC); Rp, axis perpendicular to the plane of the right posterior semicircular canal (PSCC); La, axis perpendicular to the plane of the left ASCC; Lh, axis perpendicular to the plane of the left HSCC; Lp, axis perpendicular to the plane of the left PSCC [10].

mainly consisted of Y component in the pitch plane (Fig. 2). Axis angles of SPEV of the UBN were plotted on *XY*, *XZ*, and *YZ* planes, demonstrating that the axes were almost parallel to the intra-aural axis (Fig. 3B).

5. Discussion

In the present study, the patient showed spontaneous UBN (Fig. 2), but not gaze-evoked UBN that is induced by the brainstem lesion involving the central integrator of vertical eye position. In addition, the patient showed spontaneous UBN in darkness, but not UBN in the primary position of gaze that is induced by an imbalance of central vertical VOR tone. However, the SPEV of spontaneous UBN of the patient was changed by the otolith input arising from head position (Fig. 3A). Since the SPEV of UBN in the primary position of gaze was also affected by the otolith modulation [11], it is suggested that spontaneous UBN in darkness as shown in this patient was of vestibular origin and was not induced by the brainstem lesion involving the central integrator of vertical eye position.

It was reported that the peripheral vestibular nystagmus induced by an imbalance of peripheral VOR tone rotates around the axis perpendicular to the plane of the affected canal [6,7], while the central vestibular nystagmus induced by an imbalance of central VOR tone rotates in pitch, yaw or roll planes [12]. In the present study, we analyzed spontaneous UBN in darkness of the patient three-dimensionally and demonstrated that her UBN rotated around the intra-aural axis in the pitch plane (Fig. 3B), suggesting it is of the central vestibular nystagmus type.

The central vertical VOR that involves central eye–head coordination in the pitch plane is mediated by pathways from the vertical semicircular canals and the otoliths, and received the inhibitory control of the cerebellar vermis. Since the MRI scan revealed the astrocytoma in the left cerebellum involving the cerebellar vermis (Fig. 1B), it is suggested that the spontaneous UBN in darkness in this patient was induced by an imbalance of central vertical VOR tone following the cerebellar vermis lesion.

The vestibular nystagmus could be suppressed by visual fixation in light [13]. Therefore, it is also suggested that the SPEV of spontaneous UBN in darkness was not enough to manifest as UBN in the primary position of gaze.

In conclusion, we report the case of a patient with spontaneous UBN in darkness due to a tumor involving the cerebellar vermis. The finding suggests that the patient's UBN was induced by an imbalance of the central vertical VOR tone.

Acknowledgements

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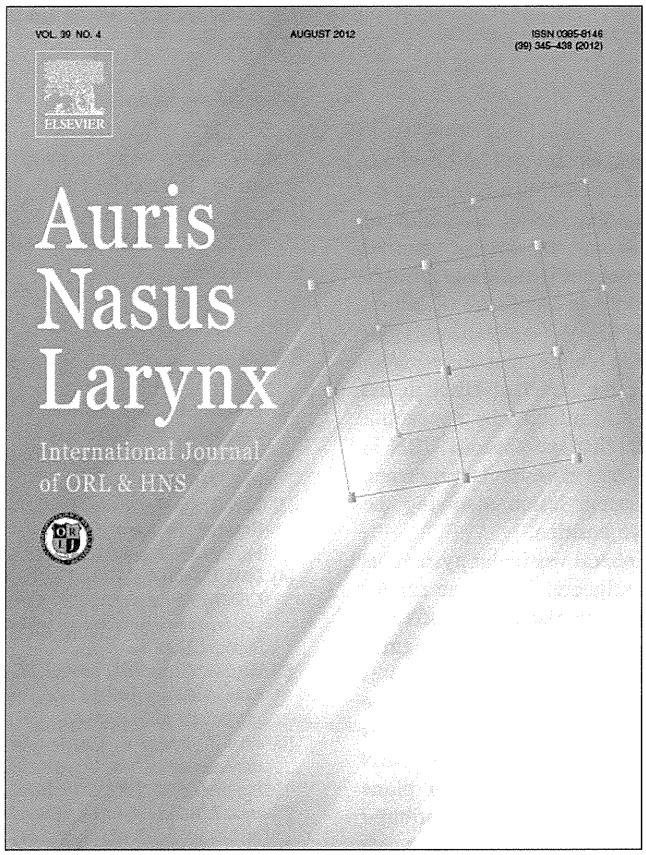

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Transient low-tone air-bone gaps during convalescence immediately after canal plugging surgery for BPPV

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ABSTRACT

Objectives: The aim of the present study was to elucidate the time course and frequency patterns of transient low-tone air-bone gaps (ABGs) after canal plugging for intractable BPPV.
Methods: We investigated eight patients with intractable BPPV who underwent canal plugging. Four were cases with posterior type (pBPPV) and the other four were those with horizontal type (hBPPV). Pure-tone audiometries (PTAs) were performed before and 7 days, 1 month and 6 months after surgery. ABGs (+) were defined as the three-tone-average ≥20 dB formulated by $(a + b + c)/3$, where a, b, and c are ABGs at 0.25, 0.5, and 1 kHz, respectively.
Results: The ratio of the number of patients with ABGs (+) at the post-operative 7th day and 1st month was 100.0% (8/8). The ratio at the post-operative 6th month was 0.0% (0/8). There were no significant differences in the time course or frequency patterns of the ABGs between pBPPV and hBPPV.
Conclusions: We clearly demonstrated eight cases with intractable BPPV showing transient low-tone ABGs during convalescence immediately after canal plugging. During that period, patients also complained of motion-evoked dizziness. All these findings suggest that, during such a convalescence period, the plugged area might not be fixed yet and could still induce the dizziness and low-tone ABGs, as enlarged vestibular aqueduct syndrome and superior semicircular canal deficiency syndrome exhibit low-tone ABGs due to the third mobile inner ear window. More than one month after surgery, both the ABGs and dizziness could disappear according to fixation of the plugged area.

1. Introduction

Benign paroxysmal positional vertigo (BPPV) is a disease firstly reported in 1952 [1]. Vertigo and dizziness of BPPV is thought to be due to the debris composed of small crystals of calcium from the utricle, which is stuck on the crista ampullaris [2] and/or floating in the canal [3]. BPPV has often been described as self-limiting, because symptoms often subside or disappear within one month of onset in posterior semicircular canal type of BPPV (pBPPV) and within two weeks of onset in horizontal semicircular canal type of BPPV (hBPPV) [4]. Various kinds of physical maneuvers and exercises called Epley maneuver [5] or Lempert method [6] have usually proved effective. Some of patients with BPPV are quite intractable against any kinds of conservative treatments and taken to the next step, canal plugging surgery.

Immediately after canal plugging surgery for intractable BPPV, we often experienced low-tone air-bone gaps (ABGs) during the convalescence. The ABGs were observed transiently within the post-operative 1st month but in all the cases who received canal plugging surgery. The total number of cases in the present study was limited ($n = 8$), because there were not so many intractable BPPV patients [4]. However, we would like to report the time course and frequency patterns of these ABGs after canal plugging and discuss the neuro-otological significance of these ABGs.

2. Materials and methods

The use of all the data in the present study was approved by the Ethics Committee of Osaka University, School of Medicine.

2.1. Patients

Patients were eligible for enrollment if they had received a clinical diagnosis of BPPV according to the criteria [7]. In brief,

Abbreviations: ABG, air-bone gap; pBPPV, posterior type of benign paroxysmal positional vertigo; hBPPV, horizontal type of benign paroxysmal positional vertigo; EVA, enlarged vestibular aqueduct syndrome; SSCD, superior semicircular canal deficiency syndrome.

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Table 1
Raw data for all the eight intractable BPPV cases.

Case	Type	Sex	Age	Laterality	Pre-aHL	Post-7d-aHL	Post-1m-aHL	Post-6m-aHL	Pre-ABG	Post-7d-ABG	Post-1m-ABG	Post-6m-ABG	Post-SDT	Post-7d-dizz	Post-1m-dizz	Post-6m-dizz
Case-1	P	M	30	R	10 10 10 100	30 20 20 15 15	25 20 20 20 20	10 10 10 10 10	0 0 10 −10 0	40 40 20 10 20	45 40 20 5 25	5 5 5 −5 0	100%/50 dB	+	+	−
Case-2	P	F	62	L	15 15 15 20 30	35 35 30 25 30	35 30 30 25 30	20 15 15 15 25	5 0 0 5 5	30 30 20 5 15	40 40 25 5 20	5 5 0 0 5	90%/100 dB	+	+	−
Case-3	P	F	58	R	20 15 20 35 35	35 30 35 30 35	35 35 35 30 30	20 20 25 35 35	5 5 0 −5 0	35 25 20 10 5	30 30 25 10 5	5 0 5 0 0	100%/ 70 dB	+	+	−
Case -4	P	M	51	L	20 15 15 20 35	25 20 20 20 35	25 25 20 20 35	20 20 15 25 35	5 0 −5 0 5	40 40 35 10 15	40 35 35 10 10	0 5 0 −5 5	100%/60 dB	+	+	−
Case -5	H	F	44	L	5 5 5 10 10	15 15 10 10 10	15 10 15 10 10	5 5 0 10 10	0 5 0 0 5	20 25 20 10 5	20 20 20 5 10	5 5 0 0 0	100%/60 dB	+	+	−
Case -6	H	M	62	L	25 20 15 20 20	30 25 20 20 25	30 20 20 25 25	20 20 15 20 25	15 10 0 5 0	30 25 20 10 10	25 25 20 5 0	15 5 0 0 0	95%/90 DB	+	+	−
Case -7	H	F	50	R	20 20 1520 20	25 25 20 15 20	20 15 15 20 20	2020 20 20 15	5 5 0 −5 0	25 20 25 5 10	20 25 20 5 10	10 10 10 −5 −5	100%/60 dB	|	|	−
Case -8	H	M	40	R	5 0 5 0 10	15 15 10 5 15	15 15 10	5 5 0 5 10	0 5 5 −5 0	20 20 20 10 10	25 20 25 10 5	5 5 0 −5 5	100%/50 dB	+	+	−

The raw data included type of BPPV (P/H), sex (M/F), age at surgery (age: years), laterality (L/R), pre- and post-operative 7th day, 1st month, 6th month air-conductive hearing level at 0.25–4 kHz (upper-lower) (aHL: dB), pre- and post-operative 7th day, 1st month, 6th month air-bone gaps at 0.25–4 kHz (upper-lower) (ABG: dB), post-operative 1st month speech discrimination test (SDT: %/dB), and post-operative 7th day, 1st month, 6th month motion-evoked dizziness feelings (+/−).

these criteria were as follows. Common history: rotatory vertigo, lasts <30 s and precipitated by head movements. Dix-Hallpike maneuver (pBPPV: brief latency (1–5 s), limited duration (<30 s), torsional nystagmus toward downmost ear, reversal of nystagmus upon sitting and fatiguability of the response. Lateral head turns (hBPPV): geotropic nystagmus and apogeotropic nystagmus. Exclusion of other causes: to exclude other disorders, a thorough history, and neurological, neurotological, and MRI examinations were performed. Intractable BPPV was designated in cases where various forms of medical treatments and otolith repositioning maneuvers [5,6] failed for at least six months.

We finally investigated eight patients with intractable BPPV who underwent canal plugging surgery between January 2004 and December 2010. The number of cases with definite and probable BPPV was 1546 during that period. The ratio of the number of patients with intractable BPPV was 0.52% (8/1546). Four out of eight were cases with pBPPV ($n = 4$) and the other four were those with hBPPV ($n = 4$). The pre-operative data for all the eight cases were shown in Table 1. There were no significant differences in patients' backgrounds between pBPPV and hBPPV.

2.2. Surgery

All the eight cases designated as having intractable BPPV received posterior or horizontal semicircular canal plugging surgery [8,9]. The canal plugging surgery procedure involved a simple mastoidectomy and exposing the compact bone of posterior or horizontal semicircular canal with the cutting burr. The canal was drilled carefully with the diamond burr until the membranous portion of the canal was exposed. Then, the space of canal was packed and sealed with bony paste, temporal muscle fascia and small pieces of bone tips to preventing the debris from floating. The packed and sealed area was covered with fibrin glue. The wound was closed with skin sutures.

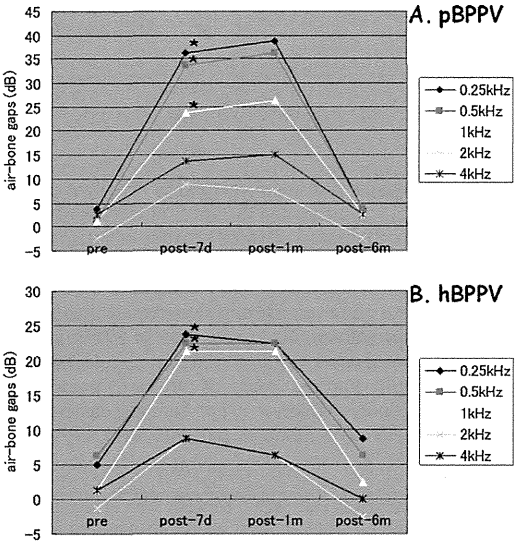

Fig. 1. Time course and frequency patterns of air-bone gaps (ABGs) before and after surgery.
Among frequencies ranging from 0.25 to 4 kHz, the size of ABGs at 0.25, 0.5 and 1 kHz significantly increased 7 days – 1 month after surgery both in patients with posterior type of BPPV (A: pBPPV; $^*p < 0.05$) and horizontal type of BPPV (B: hBPPV; $^*p < 0.05$) and returned to the pre-operative level until 6 months later. There were no significant differences in the time course or frequency patterns of the ABGs between pBPPV and hBPPV.

2.3. Evaluations

Pure-tone audiometries (PTAs) were performed before surgery and 7 days, 1 month and 6 months after surgery (Table 1). Hearing function was evaluated based on the 5-tone average of PTAs formulated by $(a + b + c + d + e)/5$, where a, b, c, d and e are hearing levels at 0.25, 0.5, 1, 2 and 4 kHz, respectively. More than 10 dB differences in hearing levels before and after treatment were

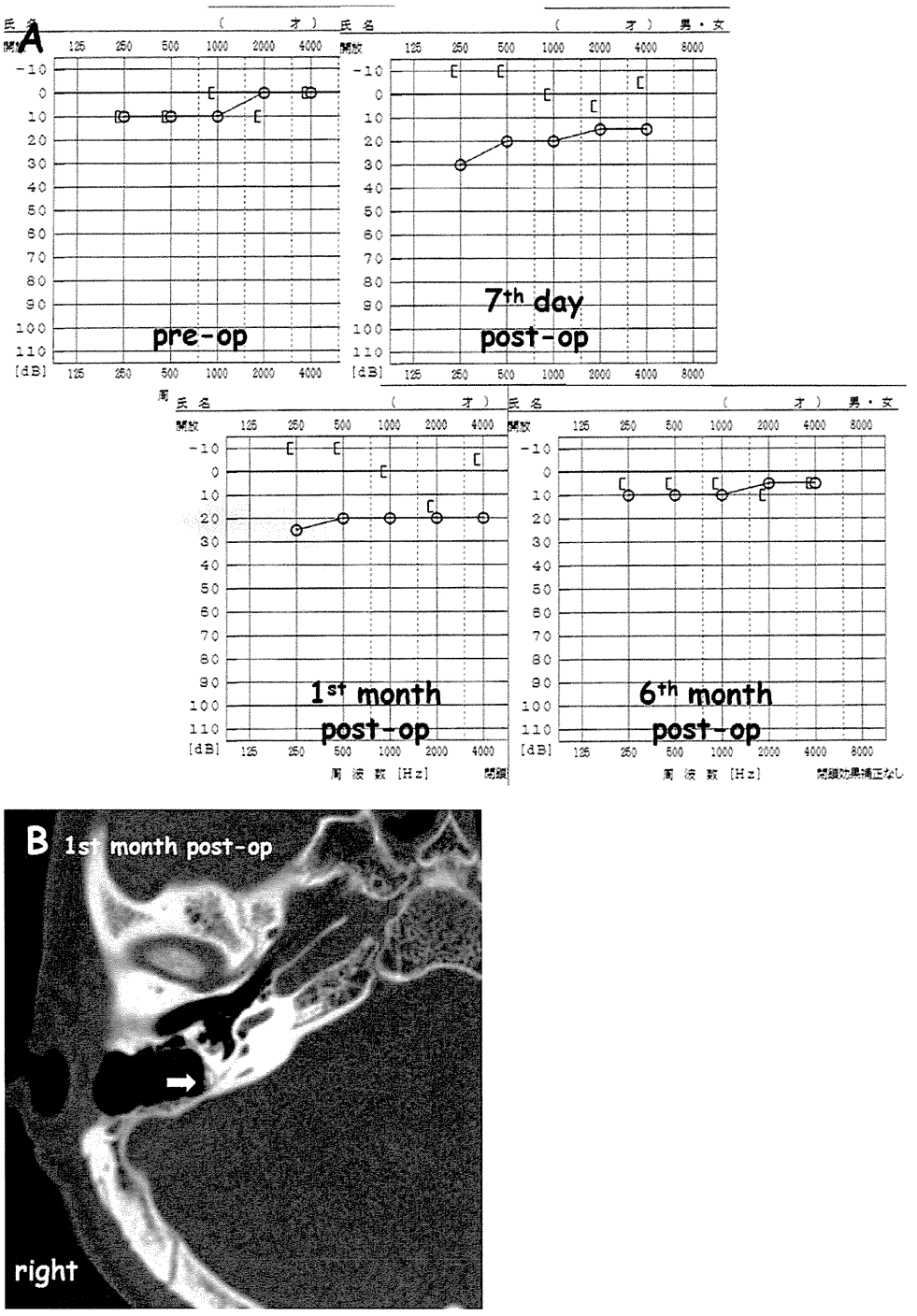

Fig. 2. A case with posterior type of BPPV (pBPPV) showing transient low-tone air-bone gaps (ABGs) after canal plugging surgery.
(A) A case with pBPPV had transient low-tone ABGs in the right ear before and after canal occlusion surgery (pre, post-op 7th day, post-op 1st month and post-op 6th month). There were no ABGs anymore 6 months after surgery. (B) CT scan showed no remarkable findings in the tympano-mastoid cavity around the posterior semicircular canal and fixed materials of connective tissues and bone tips there 6 months after surgery (post-op 6th month: an arrow). This case is Case-1 in Table 1.

regarded as "better", less than −10 dB differences as "worse" and the others as "no change".

ABGs were calculated by air-conductive hearing levels minus bone-conductive hearing levels at all the frequencies of 0.25, 0.5, 1, 2 and 4 kHz (Table 1). According to the previous paper, low-tone ABGs (+) were defined as the three-tone-average of ABGs ≥20 dB formulated by $(a + b + c)/3$, where a, b, and c are ABGs at 0.25, 0.5 and 1 kHz, respectively [10].

Speech discrimination test (SDT), tympanometry (TYMP) and stapedial reflex test (SRT) were used to determine whether ABGs

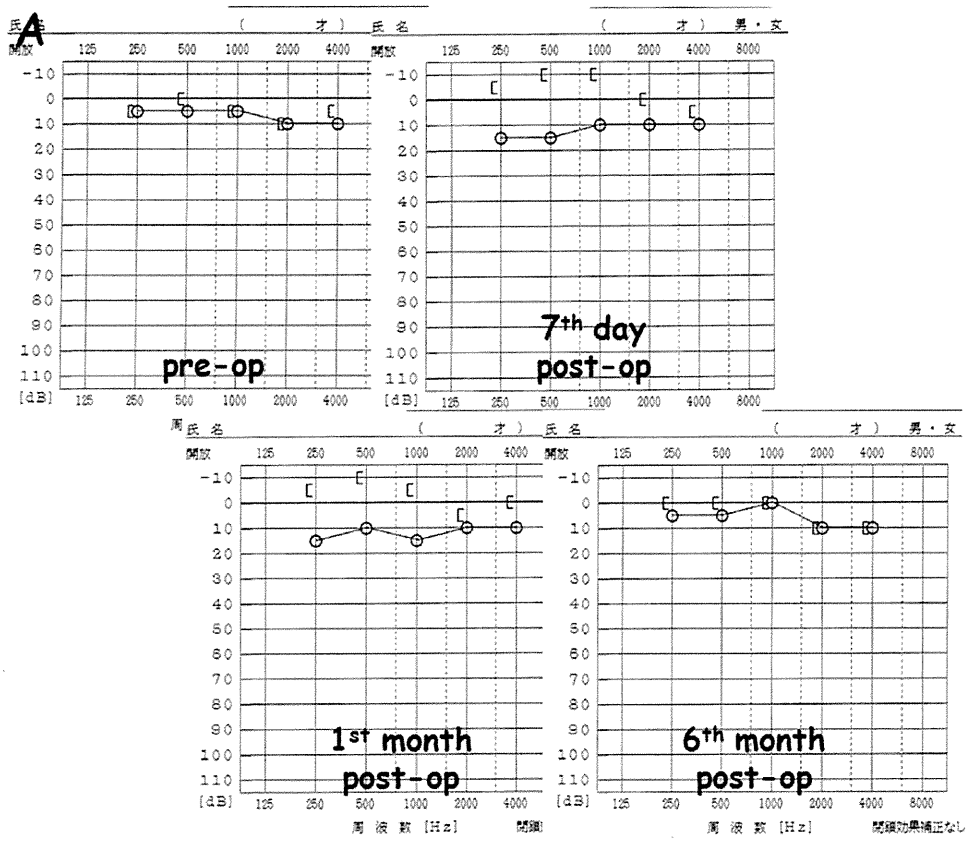

Fig. 3. A case with horizontal type of BPPV (hBPPV) showing transient low-tone air-bone gaps (ABGs) after canal plugging surgery.
(A) A case with hBPPV had transient low-tone ABGs in the right ear before and after canal occlusion surgery (pre, post-op 7th day, post-op 1st month and post-op 6th month). There were no ABGs anymore 6 months after surgery. (B) CT scan showed no remarkable findings in the tympano-mastoid cavity around the lateral semicircular canal and fixed materials of connective tissues and bone tips there 6 months after surgery (post-op 6th month: an arrow). This case is Case-5 in Table 1.

were conductive or sensorineural at the post-operative 1st month. Post-operative 1st month data of SDT (%/dB) were shown in Table 1. Post-operative motion-evoked dizziness feelings (+/−) were determined according to patients' subjective complaints (Table 1).

2.4. Statistical analysis

Statistical differences in patients' backgrounds including sex, age, pre-operative hearing level and ABGs between pBPPV and hBPPV groups were examined by Mann–Whitney *U*-test. Statistical differences in ABGs before and after surgery and those between pBPPV and hBPPV were examined by one way ANOVA and Mann–Whitney *U*-test. $p < 0.05$ was considered statistically significant. All the statistical analyses were performed with SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

3. Results

First of all, in all the eight cases, there were no significant changes in the air-conductive hearing levels between before and 6 months after canal plugging surgery (Table 1).

The ratio of the number of patients with low-tone ABGs (+) at the post-operative 7th day and 1st month was 100% both in patients with pBPPV and hBPPV (8/8). The ratio at the post-operative 6th month was 0% (0/8). There was no significant sensorineural hearing loss, middle ear lesion or stapes fixation at the post-operative 1st month according to the results from SDT, TYMP and SRT (data of TYMP or SRT not shown). Among frequencies ranging from 0.25 to 4 kHz, the size of ABGs at 0.25, 0.5 and 1 kHz significantly increased 7 days – 1 month after surgery both in patients with pBPPV and hBPPV and returned to the pre-operative level until 6 months later (Fig. 1) according to the decay profile of motion-evoked dizziness feelings (Table 1). There were no significant differences in the time course or frequency patterns of the ABGs between pBPPV and hBPPV.

Both the pre- and post-operative audiograms and the post-operative 6th month CT image in typical cases with pBPPV and hBBPV were demonstrated in Figs. 2 and 3.

4. Discussion

First of all, there were no significant changes in the air-conductive hearing levels between before and 6 months after canal plugging surgery. These results indicate that canal plugging could be a definitely safe surgical treatment for intractable BPPV as in the previous reports [8,9]. In the present study, transient low-tone ABGs were clearly observed in all the eight cases with intractable BPPV during convalescence immediately after canal plugging surgery. These ABGs were gradually diminished thereafter and disappeared by the post-operative 6th month according to the decay profile of motion-evoked dizziness. Therefore, we focused on these ABGs as a marker of conditions around the surgically plugged area.

Canal plugging is a surgery for intractable vertigo that firstly we open a hole at the semicircular canal bony wall, then pack and seal the space of canal with bony paste and connective tissues, and finally cover the plugged area with fibrin glue. Within around a month after surgery, patients usually complained motion-evoked dizziness. These findings suggest that, during such a convalescence period, the plugged area might not be completely fixed yet and could still induce the dizziness and ABGs, as enlarged vestibular aqueduct syndrome (EVA) [11,12] and superior semicircular canal deficiency syndrome (SSCD) [13,14] exhibit sound-evoked dizziness and low-tone ABGs due to the third mobile inner ear window. More than one month after surgery, both the dizziness and ABGs could disappear according to complete fixation of the plugged area.

The third mobile window theory of low-tone ABGs in patients with EVA [11,12] and SSCD [13,14] has been recently discussed. EVA and SSCD reduce the sound pressure coming through the oval window, and apparently cause impairment of air-conduction similar to a stiffness curve. By comparison, EVA and SSCD reduce the sound pressure at the scala vestibuli and widen the differences of sound compliance between the scala vestibuli and scala tympani, resulting in apparent bone-conduction improvement. Thus, impaired air-conduction and improved bone-conduction may cause the ABGs in patients with EVA and SSCD. In the present study, there were low-tone ABGs observed in all the eight patients with intractable BPPV but no significant differences in the time course or frequency patterns of the ABGs between pBPPV and hBPPV. These findings suggest that the site of the surgery-induced third mobile labyrinthine window might not make any influence on the time course or frequency patterns of the surgery-induced transient ABGs. Because of limitations of the total number of cases in the present study, further studies together with additional cases should be reported in later communications.

Conflict of interest

None.

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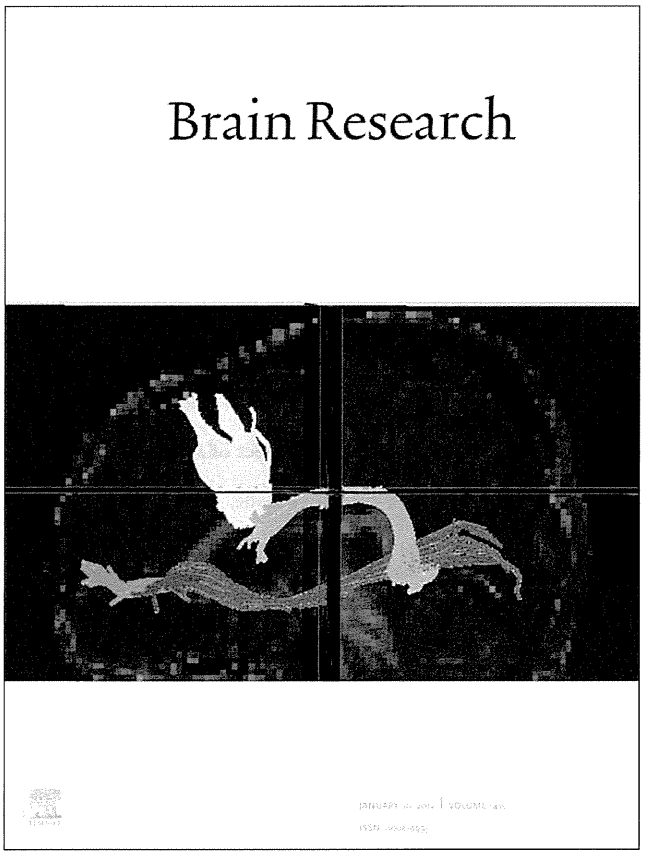

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Research Report

Implication of substance P neuronal system in the amygdala as a possible mechanism for hypergravity-induced motion sickness

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ABSTRACT

We previously reported that motion sickness was prevented in rats with amygdala lesion and that provocative motion stimuli increased the number of Fos-positive neurons in the amygdala, suggesting that the amygdala is one of the neural substrates involved in the development of motion sickness. NK-1 receptors in the brain stem and amygdala are thought to play an important role in emesis and affective disorders, respectively. In the present study, to elucidate a role of substance P neuronal system and NK-1 receptors in the brain stem and amygdala in the development of motion sickness, we measured changes in gene expression of NK-1 receptors and preprotachykinin, a precursor of substance P, using quantitative real-time PCR methods in solitary tract nucleus and amygdala in rats after provocative motion stimuli induced by 2G hypergravity load. Effects of systemic administration of CP-99,994, an antagonist for NK-1 receptors, on hypergravity-induced motion sickness were also examined using pica behavior, eating non-nutritive substances such as kaolin, as an index of motion sickness in rats. Hypergravity-induced motion sickness was inhibited by CP-99,994 with a dose-dependent and enantioselective manner. Preprotachykinin mRNA expression was increased in basolateral nucleus of amygdala and solitary tract nucleus after hypergravity load for 3 h, whereas NK-1 receptor mRNA expression was not changed by hypergravity in amygdala and solitary tract nucleus. Present results suggest that 2G hypergravity load activated the substance P neuronal system in amygdala as well as in the brain stem and this activation would be related to the development of motion sickness.

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Abbreviations: ANOVA, analysis of variance; CT, cycle of threshold; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; NK-1, neurokinin 1; PCR, polymerase chain reaction; VNC, vestibular nuclear complex

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1. Introduction

The most plausible theory of motion sickness is the neural mismatch (Reason, 1978). According to this theory, motion sickness is generated by an acute sensory mismatch between the expected sensory patterns and the new converging inputs from the labyrinths, eyes, and somatosensory receptors (Reason, 1978). Although the neural mismatch signals are probably neurally coded error signals, the anatomic location or neuronal system that generates them is still unknown. It is likely that the sensory information processing pathway, comparing the novel information to the stored sensory pattern, is responsible for the development of motion sickness.

Vestibular nuclear complex (VNC) and brain stem "emetic center" including the solitary tract nucleus, area postrema, and the dorsal motor nucleus of the vagus are known as the central neural substrates responsible for motion sickness (Brizzee, 1990; Miller et al., 1994). The former is the relay area of vestibular information to the central nervous system, and the "emetic center" is the final locus for the vomiting itself. However, the area responsible for convergence of sensory inputs and comparison with expected sensory patterns is still undetermined. On the other hand, the amygdala, one of the major components of the limbic system, receives various kinds of sensory information and evaluates its emotional significance, suggesting its crucial role in the development of autonomic signs and symptoms relating to emotional responses (Gallagher and Chiba, 1996; Ono et al., 1995). These assessments and responses to sensory information seem to suit with the neural mismatch theory of motion sickness. Furthermore, we reported that motion sickness was prevented in rats with amygdala lesion (Uno et al., 2000) and that provocative motion stimuli increased the number of Fos-positive neurons in the central nucleus of amygdala (Nakagawa et al., 2003), suggesting that the amygdala is one of the neural substrates involved in the development of motion sickness.

Substance P is a member of tachykinin family of peptides and is the most potent tachykinin at the neurokinin-1 (NK-1) receptor. Microinjection of substance P into the brain stem elicits an immediate emetic response (Gardner et al., 1994). Resinferatoxin, a compound that depletes substance P as well as the selective NK-1 receptor antagonist (CP-99,994 or maropitant) were shown to have anti-emetic properties (Andrews and Bhandari, 1993; Andrews et al., 2000; Hickman et al., 2008; Watson et al., 1995). These findings suggest that substance P and NK-1 receptors are involved in emetic response. Because previous reports demonstrated that NK-1 antagonists had broad anti-emetic properties against various emetic stimuli including nicotine, copper sulfate, and motion, NK-1 antagonists would block the final common emesis pathways such as the brain stem emetic center (Rudd et al., 1999; Rupniak and Kramer, 1999).

NK-1 receptors and substance P fibers are concentrated in the forebrain area including amygdala as well as brain stem emetic center (Inagaki et al., 1982; Mantyh et al., 1984; Sakanaka et al., 1982). Active sites of NK-1 antagonist on affective disorders were thought to be in the forebrain area such as amygdala, septum, hippocampus, hypothalamus, and periaqueductal gray (Rupniak and Kramer, 1999). In the present study, we hypothesized that substance P and NK-1 receptor-mediated pathways not only in the brain stem emetic center but also in amygdala would be crucial for the development of motion sickness. To elucidate the effects of substance P neuronal system and NK-1 receptors on the brain stem and amygdala and their role in the development of motion sickness, we used quantitative real-time PCR methods to measure the changes in gene expression of NK-1 receptors and preprotachykinin, a precursor of substance P, in the solitary tract nucleus and subnuclei of amygdala in rats after provocative motion stimuli induced by hypergravity load. Also, the effects of systemic administration of CP-99,994, an antagonist for NK-1 receptors, on motion sickness were examined in rats. Most mammals show vomiting in response to emetic stimuli including provocative motions. However, rats are a species that cannot vomit. Instead, they show a pica behavior, that is eating non-nutritive substances such as kaolin, as an illness response to a variety of emetic stimuli. Indeed, pica behavior in rats has been used as an animal model of emesis including motion sickness (Takeda et al., 1993).

2. Results

2.1. *Kaolin and food consumption*

Fig. 1 shows the effects of saline, CP-99,994 (30 mg/kg or 60 mg/kg) and its enantiomer CP-100,263 (60 mg/kg) on kaolin intake induced by hypergravity load. Drugs were administered at Day 3 and Day 4. Significant effects of groups ($F=7.91$) and time ($F=35.21$) were found. However, there was no group×time interaction ($F=1.54$, $p=0.13$). Kaolin intake was significantly decreased by CP-99,994 (60 mg/kg) compared with saline and CP-99,994 (30 mg/kg) ($p<0.01$). There was no difference between CP-99,994 (60 mg/kg) and enantiomer CP-100,263 (60 mg/kg). However, when the Day 3+4/Day 1+2

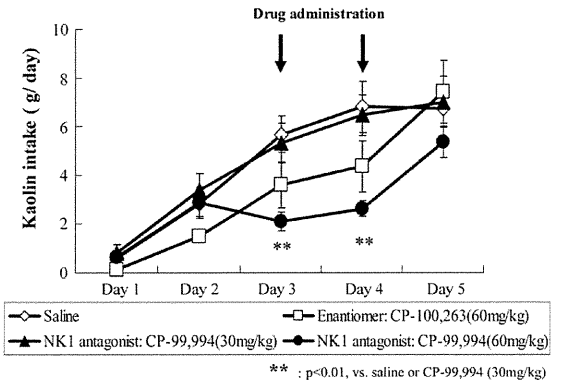

Fig. 1 – Effects of saline, CP-99,994 (30 mg/kg or 60 mg/kg) and its enantiomer CP-100,263 (60 mg/kg) on kaolin intake induced by hypergravity load. Drugs were administered at Day 3 and Day 4. Kaolin intake induced by hypergravity load was significantly decreased by CP-99,994 (60 mg/kg) compared with saline and CP-99,994 (30 mg/kg) ($p<0.01$).