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Patterns of spontaneous and head-shaking nystagmus in cerebellar infarction: imaging correlations

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Horizontal head-shaking may induce nystagmus in peripheral as well as central vestibular lesions. While the patterns and mechanism of head-shaking nystagmus are well established in peripheral vestibulopathy, they require further exploration in central vestibular disorders. To define the characteristics and mechanism of head-shaking nystagmus in central vestibulopathies, we investigated spontaneous nystagmus and head-shaking nystagmus in 72 patients with isolated cerebellar infarction. Spontaneous nystagmus was observed in 28 (39%) patients, and was mostly ipsilesional when observed in unilateral infarction (15/18, 83%). Head-shaking nystagmus developed in 37 (51%) patients, and the horizontal component of head-shaking nystagmus was uniformly ipsilesional when induced in patients with unilateral infarction. Perverted head-shaking nystagmus occurred in 23 (23/37, 62%) patients and was mostly downbeat (22/23, 96%). Lesion subtraction analyses revealed that damage to the uvula, nodulus and inferior tonsil was mostly responsible for generation of head-shaking nystagmus in patients with unilateral posterior inferior cerebellar artery infarction. Ipsilesional head-shaking nystagmus in patients with unilateral cerebellar infarction may be explained by unilateral disruption of uvulonodular inhibition over the velocity storage. Perverted (downbeat) head-shaking nystagmus may be ascribed to impaired control over the spatial orientation of the angular vestibulo-ocular reflex due to uvulonodular lesions or a build-up of vertical vestibular asymmetry favouring upward bias due to lesions involving the inferior tonsil.

Keywords: vertigo; nystagmus; cerebellum; uvulonodulus; tonsil

Abbreviations: PICA = posterior inferior cerebellar artery; SCA = superior cerebellar artery

Introduction

Head-shaking at 2–3 Hz for ~20 s may induce nystagmus in patients with central as well as peripheral vestibular dysfunction (Takahashi *et al.*, 1990; Hain and Spindler, 1993; Perez *et al.*, 2004). In unilateral peripheral vestibular lesions, horizontal head-shaking typically induces contralesional nystagmus even during the compensated phase (Choi *et al.*, 2007*a*).

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Since excitatory vestibular inputs are more effective than inhibitory ones (Ewald's second law), asymmetric vestibular inputs would be generated during horizontal head-shaking in peripheral vestibulopathies. These asymmetric vestibular inputs are believed to be accumulated in the central vestibular structures (velocity storage) and be discharged as contralesional nystagmus after head-shaking (Hain *et al.,* 1987). The velocity storage is mediated by the medial vestibular nuclei and their commissural fibres, and is evidenced by prolonged vestibular responses even after cessation of the firing of the vestibular nerve (Katz *et al.,* 1991).

In contrast, the patterns of head-shaking nystagmus are various in central vestibular disorders (Demer, 1985; Hain and Spindler, 1993; Choi and Kim, 2009) and the mechanisms remain to be elucidated. However, only a few studies have investigated head-shaking nystagmus in central vestibulopathies (Walker and Zee, 1999; Minagar *et al.,* 2001; Kim *et al.,* 2005; Choi *et al.,* 2007*b*; Moon *et al.,* 2009).

Since the cerebellar nodulus and ventral uvula inhibit the velocity storage (Wearne *et al.,* 1996, 1998), lateralized cerebellar lesions may generate head-shaking nystagmus due to asymmetric or unilateral disinhibition of the velocity storage. Indeed, previous studies (Choi *et al.,* 2007*b*; Choi and Kim, 2009) suggested that asymmetric or unilateral loss of cerebellar inhibition over the velocity storage leads to ipsilesional head-shaking nystagmus in Wallenberg syndrome.

The vestibulocerebellum, which comprises the flocculus/paraflocculus, nodulus and ventral uvula, is also known to be important for ensuring that eye rotations occur in the same plane as head rotations. Therefore, cerebellar lesions may induce head-shaking nystagmus in the plane other than being stimulated during head-shaking (perverted head-shaking nystagmus), i.e. downbeat nystagmus after horizontal head-shaking (Schultheis and Robinson, 1981; Angelaki and Hess, 1995; Wearne *et al.,* 1998).

Thus, one can assume that cerebellar lesions would generate vertical as well as horizontal nystagmus after horizontal head-shaking. However, due to the lack of systematic clinical studies, there is still little knowledge about the patterns and mechanisms of head-shaking nystagmus in central vestibulopathies.

To define the characteristics and mechanisms of head-shaking nystagmus in circumscribed cerebellar lesions, we investigated head-shaking nystagmus in a large number of patients with isolated cerebellar infarction, mostly in the territory of posterior inferior cerebellar artery (PICA), which usually supplies the vestibulocerebellum. We also adopted a lesion subtraction analysis technique to determine the key structures responsible for head-shaking nystagmus (Rorden and Karnath, 2004).

Materials and methods

Patients

Initially, we recruited 144 consecutive patients with an isolated cerebellar infarction, who had been admitted to Seoul National University Bundang Hospital from 2004 to 2010. Finally, 72 patients [56 males, age range = 36–80 years, mean age ± standard deviation (SD) = 62.2 ± 12.2] were included in this study after excluding 72 patients. The excluded were 41 patients with infarction in the territory of the anterior inferior cerebellar artery, 17 with inadequate work-ups, seven admitted >2 weeks after symptom onset and seven with a history of peripheral vestibular disease or unilateral caloric paresis indicating a possible peripheral vestibular lesion. We excluded the patients with anterior inferior cerebellar artery infarction since it irrigates the inner ear in addition to the anterior inferior cerebellum, and the cerebellar patterns of head-shaking nystagmus could not be securely obtained in anterior inferior cerebellar artery infarction. Interval from symptom onset to evaluation ranged from 0 to 13 days (mean ± SD = 3.1 ± 2.7, median = 2.5).

The study included 51 patients with a unilateral PICA infarction, 10 with bilateral PICA infarctions, eight with a unilateral superior cerebellar artery (SCA) infarction, and three with an infarction involving both the PICA and SCA territories.

All patients underwent full neurological and neuro-otological evaluation by the senior author (J.S.K.). The presence of an isolated acute cerebellar infarction was confirmed by brain MRI. There was no evidence of additional infarction in the lateral medulla. Medication that could potentially affect the vestibular system was not allowed during the study.

All experiments complied with the tenets of the Declaration of Helsinki and the study protocol was also reviewed and approved by our institutional review board (B-0912-089-102).

Oculography

Eye movements were recorded binocularly at a sampling rate of 60 Hz using 3D video-oculography (SensoMotoric Instruments, Teltow, Germany). Digitized eye position data were analysed using MATLAB software.

While wearing the video-oculography goggles in a seated position, spontaneous nystagmus was recorded both with and without fixation in the primary position. The intensity of spontaneous nystagmus was determined by its mean slow-phase velocity (°/s) calculated on a 10-s recording.

Head-shaking nystagmus was assessed using a passive head-shaking manoeuvre. The examiner pitched the patient's head forward by ~30° to bring the horizontal semicircular canals into the plane of stimulation. The patient's head was then grasped firmly with both hands, and shaken horizontally in a sinusoidal fashion at a rate of 2.8 Hz with an approximate amplitude of ±10° for 15 s (Choi *et al.,* 2007*b*). The head shaking was paced to the sound of a periodic tone generated by a metronome, and the amplitude was controlled using online head motion monitoring.

The intensity of head-shaking nystagmus was calculated by subtracting the slow-phase velocity of spontaneous nystagmus from the maximal slow-phase velocity of the induced head-shaking nystagmus. Head-shaking nystagmus was defined to be present when it exceeded the values (mean + 2 SD) observed in normal controls (horizontal ⩾3°/s; vertical ⩾2°/s; torsional ⩾2°/s), and when the nystagmus lasted ⩾5 s. The normative data and detailed descriptions on the recording methods of head-shaking nystagmus have been previously published (Choi *et al.,* 2007*b*).

The head impulse test was performed manually with a rapid rotation of the head at an approximate amplitude of 20° in the yaw plane with high acceleration. Head impulse test was considered abnormal without recording if an obvious corrective saccade supplemented an inadequate slow phase (Halmagyi and Curthoys, 1988).

For bithermal caloric tests, each ear was irrigated alternately with 50 ml of cold (30°C) and hot (44°C) water for 25 s. Asymmetry of vestibular function was calculated using Jongkees' formula. Caloric

paresis was defined as a response difference of ⩾25% between the ears (Choi *et al.*, 2007*a*).

Magnetic resonance imaging

The MRI protocol included diffusion-, T_1-, and T_2-weighted gradient-echo axial imaging, and T_1-weighted sagittal imaging using a 1.5-T U (Intera; Philips Medical Systems). The imaging parameters were 4800/100 [repetition time (ms)/echo time (ms)] for T_2-weighted imaging, 500/11 for T_1-weighted imaging and 700/23 for gradient-echo imaging with a section thickness of 3 mm, a matrix size of 256×256 (interpolated to 512×512) and a field of view of 200–220 mm. Diffusion-weighted imaging was performed using the following parameters; $b = 1000$, 4119/89 (repetition time/echo time), a section thickness of 5 mm, a matrix of 128×128 (interpolated to 256×256) and a field of view of 220 mm. All patients underwent MRI within 2 weeks (mean ± SD = 7.5 ± 8.9 days, median = 4 days) after symptom onset.

Lesion analysis

To identify the structures involved in the generation of head-shaking nystagmus, we analysed the lesions in 51 patients with a unilateral PICA infarction. Patients with bilateral infarctions were excluded from the analysis since symmetrical damages to the structures responsible for head-shaking nystagmus would have cancelled out the lateralized effect of each structure. Patients with an SCA infarction were also excluded because only a few patients had an SCA infarction and no structures are shared between the PICA and SCA territories (Tatu *et al.*, 1996).

Using MRIcro software (www.mricro.com), diffusion-weighted MRI lesions of each patient were mapped onto slices of a T_1-weighted template MRI scan obtained from the Montreal Neurological Institute (MNI) (www.bic.mni.mcgill.ca/cgi/icbm_view), which is approximately oriented to match Talairach space (Talairach and Tournoux, 1988). All lesions were defined according to previously validated magnetic resonance anatomical templates (Tatu *et al.*, 1996). The nodulus and uvula, supposed to be the key structures of the vestibulocerebellum, were demarcated by the following methods: the nodulus is located near the midline just dorsal to the fourth ventricle at the section of the mid-pontine level on axial images; and the uvula, also located near the midline, is located dorsal to the nodulus at the mid-pontine level and just dorsal to the fourth ventricle at the lower pontine and upper medullary level. To facilitate lesion analysis, we flipped the regions of interest in patients with a left-sided infarction ($n = 19$), and finally arranged all regions of interest on the right side. Lesions were mapped onto slices corresponding to the Talairach *z*-coordinates −52, −48, −42, −38 and −32. To avoid information bias, all MRI lesions were checked and mapped by a neuroradiologist unaware of clinical information.

The patients with a unilateral PICA infarction were divided into two groups: those with head-shaking nystagmus and those without head-shaking nystagmus. Overlap images were then obtained for each group using lesion density plots. Subsequent subtraction of the overlapped lesions of patients without head-shaking nystagmus from those with head-shaking nystagmus yielded percentage overlay plots that indicated the relative frequencies of damage specific for head-shaking nystagmus in each region.

Statistical analysis

The χ^2- and Student's *t*-tests were used to compare the demographic and clinical variables of patients with and without head-shaking nystagmus. The χ^2-test was also used to determine the difference in the frequency of lesions involving the nodulus, uvula and tonsil between the patient groups with and without head-shaking nystagmus.

Results

Spontaneous nystagmus

Of the 51 patients with a unilateral PICA infarction, 16 (33%) patients showed spontaneous nystagmus. A horizontal component was observed in 14 patients, and was usually directed to the lesion side (11/14, 79%). An upward vertical component was observed in three and a downward in four patients. A torsional component beating ipsilesionally was observed in three patients (Fig. 1).

Spontaneous nystagmus was common in patients with bilateral PICA infarctions, and seven (70%) of ten patients showed spontaneous nystagmus, which was purely horizontal in three, purely upbeat in two, mixed torsional–horizontal in one and mixed vertical–horizontal in one. Half of the patients (four of eight) with SCA infarction had purely ipsilesional spontaneous nystagmus. Of the three patients with combined PICA and SCA infarctions, one with left PICA and right SCA infarction showed spontaneous nystagmus beating to the right with a small downbeat component.

Overall, 28 (39%) patients showed spontaneous nystagmus, which was mainly horizontal (purely horizontal in 16, purely vertical in four, mixed horizontal–vertical in four, mixed horizontal–vertical–torsional in three and mixed torsional–horizontal in one). In patients with a unilateral infarction, the horizontal component of spontaneous nystagmus usually beat to the lesion side when observed (15/18, 83%).

Oculographic data of all patients are provided in Supplementary Table 1.

Head-shaking nystagmus

Head-shaking nystagmus occurred in 23 (45%) of the 51 patients with a unilateral PICA infarction. Head-shaking nystagmus was purely vertical in 10, purely horizontal in six, mixed horizontal–vertical in six and mixed horizontal–vertical–torsional in one (Fig. 2). The horizontal component of head-shaking nystagmus was ipsilesional in all patients (Figs 2 and 3). In three patients with spontaneous contralesional nystagmus, horizontal head-shaking induced purely downbeat nystagmus in two with mixed horizontal–vertical spontaneous nystagmus (Patients 4 and 9), and did not induce head-shaking nystagmus in the remaining one with purely horizontal nystagmus (Patient 29). Perverted nystagmus was generated by horizontal head-shaking in 17 (74%) patients, and the vertical component was downbeat in all (Figs 2 and 4). Even in the patient with spontaneous upbeat nystagmus (Patient 1), horizontal head-shaking induced nystagmus beating downward.

Six of 10 patients with bilateral PICA infarctions showed head-shaking nystagmus; purely horizontal in three, purely vertical in two, and mixed horizontal-vertical in one. Of the seven patients

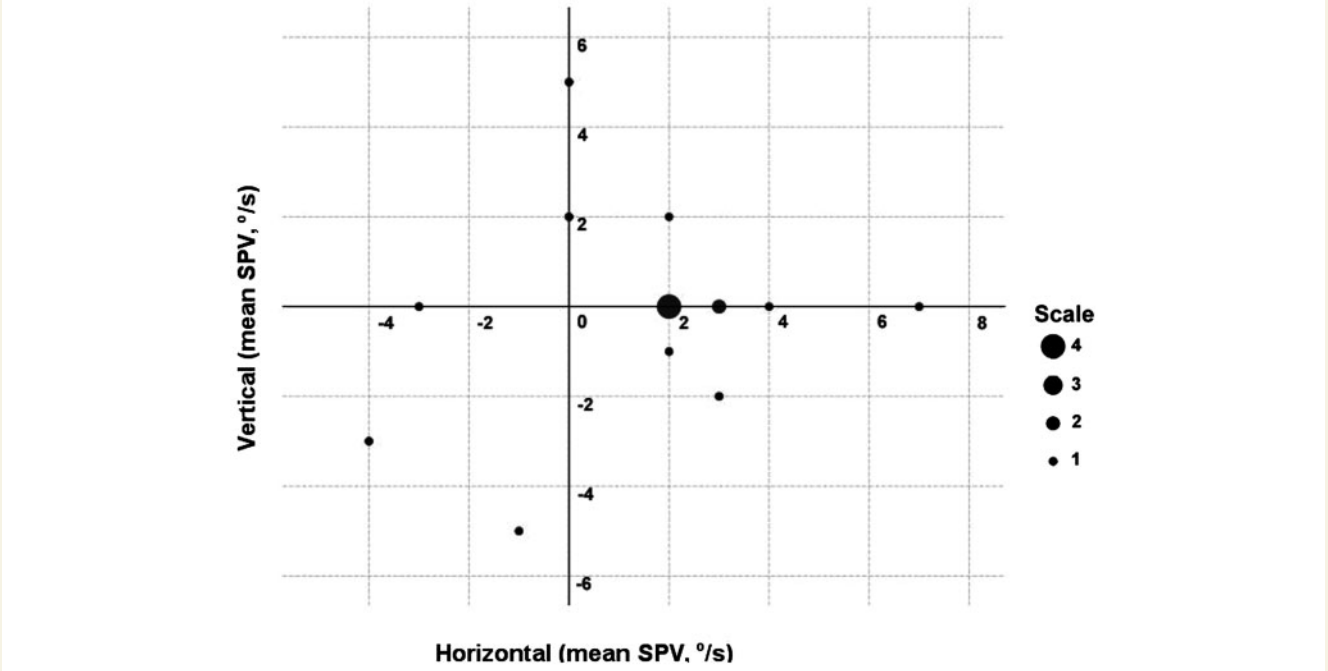

Figure 1 Patterns of spontaneous nystagmus in patients with unilateral posterior inferior cerebellar artery infarction. Horizontal and vertical mean slow-phase velocities (SPVs) of the spontaneous nystagmus in each patient are plotted in a two-dimensional plane. Positive values indicate slow-phase velocity in the contralesional and upward directions, i.e. ipsilesional and downbeat nystagmus.

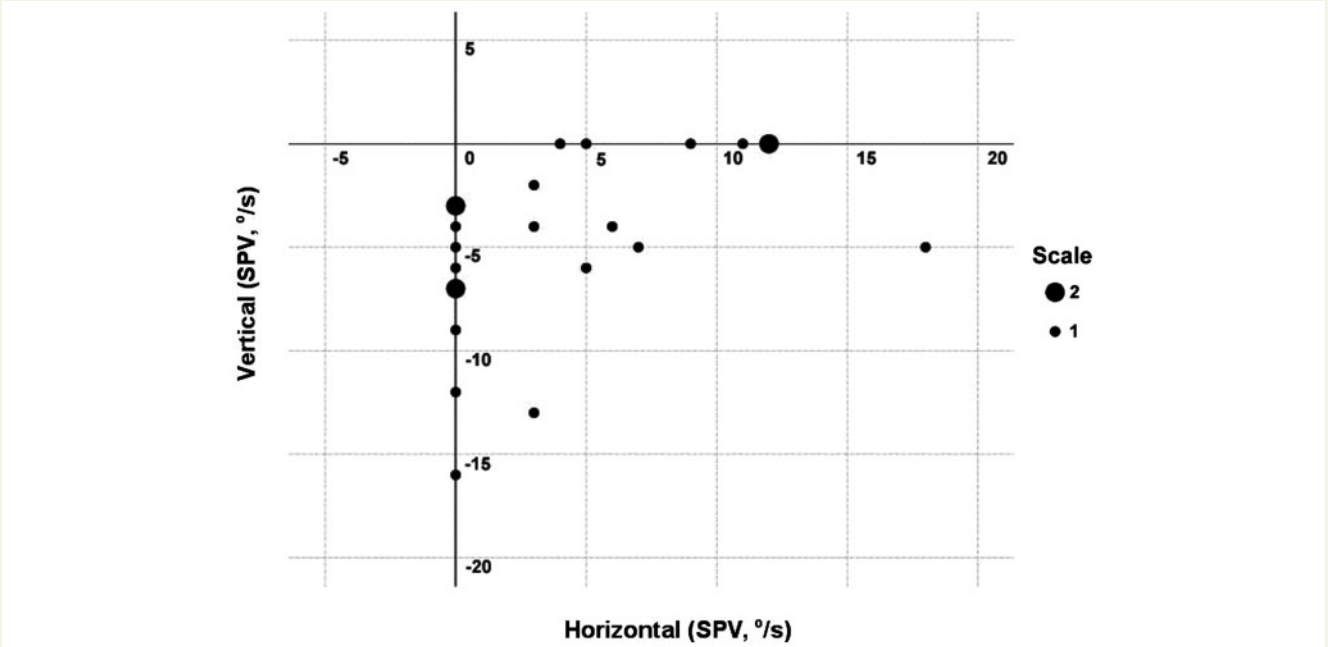

Figure 2 Patterns of head-shaking nystagmus in patients with unilateral posterior inferior cerebellar artery infarction. In each patient, horizontal and vertical components of head-shaking nystagmus are plotted in a two-dimensional plane. Positive values indicate slow-phase velocity (SPV) in the contralesional and upward directions, i.e. nystagmus beating ipsilesionally and downward.

with spontaneous nystagmus from bilateral PICA infarctions, five showed head-shaking nystagmus. In four of them, head-shaking nystagmus was in the opposite direction of spontaneous nystagmus for both vertical and horizontal components (Fig. 5). In the remaining patient (Patient 53), head-shaking augmented spontaneous upbeat nystagmus.

Head-shaking nystagmus was common in patients with SCA infarction. Six (6/8, 75%) of them showed head-shaking

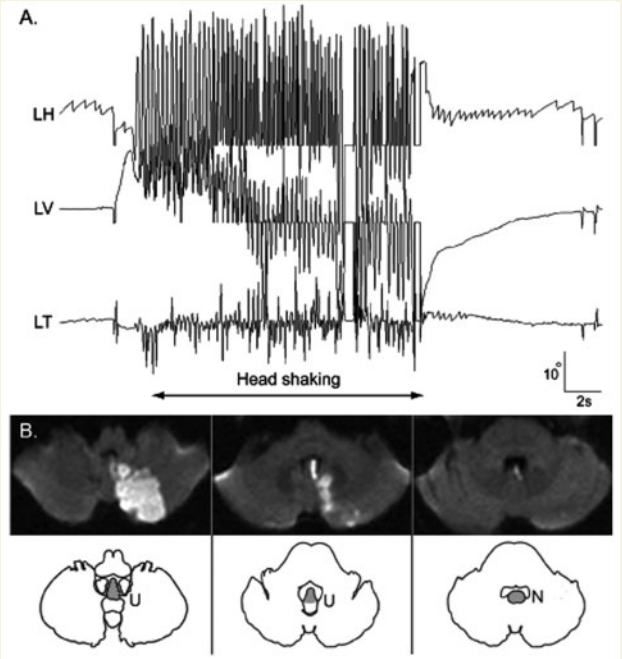

Figure 3 Augmentation of spontaneous nystagmus by horizontal head-shaking. Video-oculographic recording shows that horizontal head-shaking augments ipsilesional spontaneous nystagmus (**A**) in Patient 5 with left posterior inferior cerebellar artery infarction involving the uvulonodulus (**B**). Nodulus (N) and uvula (U) are demarcated in grey on the magnetic resonance templates (**B**). Upward deflection in each horizontal, vertical and torsional plane indicates rightward, upward and clockwise torsional eye motion, respectively, from the patient's view in this and the following figures. LH = horizontal position of the left eye; LT = torsional position of the left eye; LV = vertical position of the left eye.

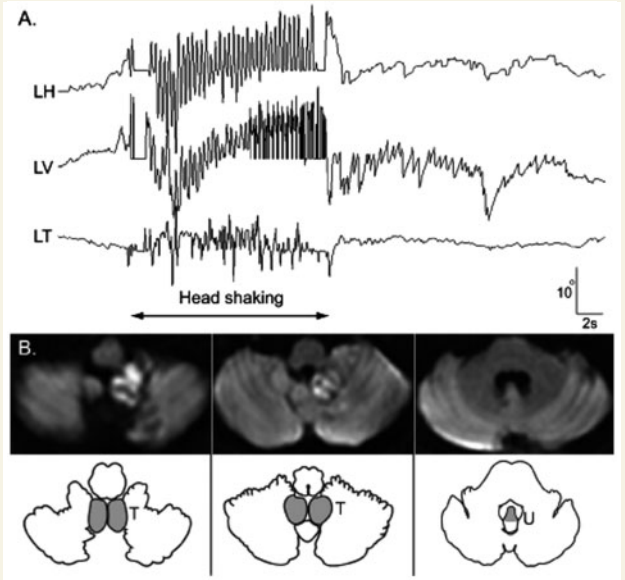

Figure 4 Perverted head-shaking nystagmus. Video-oculographic recording shows prominent downbeat nystagmus after horizontal head shaking (**A**) in Patient 22 with an infarction involving the left inferior tonsil on diffusion-weighted MRIs (**B**). Tonsil (T) and uvula (U) are demarcated in grey on magnetic resonance templates (**B**). LH = horizontal position of the left eye; LT = torsional position of the left eye; LV = vertical position of the left eye.

nystagmus, including purely horizontal in four, purely vertical in one and mixed horizontal-vertical in one. In three of four patients with spontaneous ipsilesional nystagmus, horizontal head-shaking augmented nystagmus in two and, in the remaining one, induced downbeat nystagmus additionally.

Two (67%) of the three patients with an infarction involving both the PICA and SCA territories showed head-shaking nystagmus. In one with left PICA and right SCA infarction, head-shaking nystagmus occurred in the opposite direction of spontaneous nystagmus for horizontal component, and in the other with left PICA and SCA infarction, purely downbeat nystagmus was induced by horizontal head-shaking.

Overall, head-shaking nystagmus was observed in 37 (51%) patients. Head-shaking nystagmus was purely vertical in 14, purely horizontal in 14, mixed horizontal–vertical in eight and mixed horizontal–vertical–torsional in one. Head-shaking nystagmus was perverted in 23 (23/37, 62%) patients and was mostly downbeat (22/23, 96%). Notably, all patients with a unilateral cerebellar infarction showed ipsilesional horizontal head-shaking nystagmus (18/18). Of the 28 patients with spontaneous nystagmus, 18 (18/28, 64%) exhibited head-shaking nystagmus and six of them (6/18, 33%) developed head-shaking nystagmus in the opposite direction of spontaneous nystagmus.

No difference was observed between the patients with and without head-shaking nystagmus in terms of age, sex, interval from symptom onset to evaluation or the prevalence of spontaneous nystagmus (Table 1).

Head impulse and bithermal caloric tests

Horizontal head impulse and bithermal caloric tests were normal in all patients.

Lesion analysis

The uvula, nodulus and inferior tonsil were found to be the structures primarily involved in the generation of head-shaking nystagmus (Fig. 6). Statistical analysis also confirmed that the nodulus, uvula and inferior tonsil were more frequently affected in patients with head-shaking nystagmus than in those without head-shaking nystagmus (Table 2).

Discussion

Our patients with acute isolated cerebellar infarction exhibited various patterns of head-shaking nystagmus, as previously described for head-shaking nystagmus in cases of central vestibulopathies (Walker and Zee, 1999; Minagar *et al.*, 2001; Kim *et al.*,

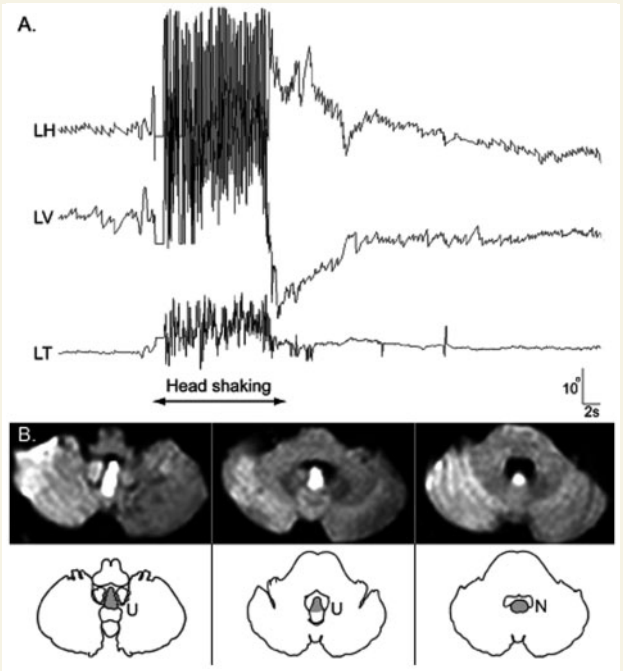

Figure 5 Head-shaking nystagmus developing in the opposite direction of spontaneous nystagmus. Video-oculographic recording shows that horizontal head-shaking induces horizontal nystagmus in the opposite direction of spontaneous nystagmus while downbeat component remains unchanged (**A**) in Patient 54 with isolated uvulonodular infarction (**B**). Nodulus (N) and uvula (U) are demarcated in grey on magnetic resonance templates (**B**). LH = horizontal position of the left eye; LT = torsional position of the left eye; LV = vertical position of the left eye.

Table 1 The demographic and clinical variables of patients with and without head-shaking nystagmus

Variables	Head-shaking nystagmus (*n* = 37)	No head-shaking nystagmus (*n* = 35)	*P*-value
Sex (male : female)	29 : 8	27 : 8	0.900[a]
Age (mean ± SD)	64.9 ± 11.1	59.4 ± 12.8	0.053[b]
Interval (mean ± SD) (day)	3.3 ± 2.4	3.0 ± 3.0	0.642[b]
Spontaneous nystagmus	18	10	0.081[a]
Vascular territory			0.366[a]
PICA, unilateral	23	28	
PICA, bilateral	6	4	
SCA	6	2	
PICA and SCA	2	1	

Statistical comparisons were performed using the a χ^2-test and the Student's b *t*-test.

2005; Choi *et al.*, 2007*b*; Moon *et al.*, 2009). However, despite this variety, the horizontal component of head-shaking nystagmus was uniformly ipsilesional in patients with a unilateral infarction. Furthermore, the vertical head-shaking nystagmus was predominantly downbeat. In addition, lesion analyses revealed that damage to the uvula, nodulus or inferior tonsil was primarily responsible for generation of head-shaking nystagmus in patients with unilateral PICA infarction.

Patterns and clinical implications of head-shaking nystagmus are well established in peripheral vestibular disorders. Typical pattern of head-shaking nystagmus in unilateral peripheral vestibulopathy consists of initially contralesional nystagmus that decays over 20 s and then goes through a weak reversal (Hain *et al.*, 1987). Although this may be accompanied by a vertical component, the slow-phase velocity of the vertical component is <20% of the horizontal component. Head-shaking nystagmus may serve as the most useful bedside test for identifying underlying vestibular imbalance even during the compensated phase in vestibular neuritis (Choi *et al.*, 2007*a*). Moreover, patterns of head-shaking nystagmus are known to reflect the degree of functional deficit in unilateral peripheral vestibulopathy (Perez *et al.*, 2004).

On the contrary, head-shaking nystagmus in central vestibular disorders is not as stereotyped as in peripheral vestibulopathies and its clinical implications are not yet clear. Unusually strong head-shaking nystagmus elicited by weak head-shaking, ipsilesional head-shaking nystagmus, strongly biphasic head-shaking nystagmus, intense head-shaking nystagmus in patients without caloric paresis and perverted head-shaking nystagmus have been regarded as features of central head-shaking nystagmus (Hain and Spindler, 1993; Minagar *et al.*, 2001; Kim *et al.*, 2005; Choi *et al.*, 2007*b*; Moon *et al.*, 2009).

Until now, only a few anecdotal reports have been available for head-shaking nystagmus after focal cerebellar lesions (Kim *et al.*, 2005; Moon *et al.*, 2009). A recent study reported ipsilesional head-shaking nystagmus in four of five patients with an isolated unilateral nodular infarction (Moon *et al.*, 2009). The ipsilesional head-shaking nystagmus in these patients was ascribed to asymmetric velocity storage due to unilateral or unequal disinhibition of the nodulus and ventral uvula over the vestibular nuclei (Waespe *et al.*, 1985; Solomon and Cohen, 1994). In another case report, cross-coupling of the vestibular responses due to vestibulocerebellar dysfunction was implicated in a patient with perverted downbeat head-shaking nystagmus after acute caudal cerebellar infarction (Kim *et al.*, 2005).

However, there have been no systematic studies concerning the pathomechanisms of head-shaking nystagmus in cerebellar lesions. Our study provided some answers to this issue by demonstrating patterns and responsible lesions of head-shaking nystagmus in cerebellar infarction.

We found that the nodulus and uvula were frequently involved in patients with head-shaking nystagmus due to unilateral PICA infarction. Nodulus and uvula can be the candidates for generation of head-shaking nystagmus in terms of modulating the velocity storage. The velocity storage, by holding the vestibular neuronal activity, extends the low-frequency characteristics of the angular vestibulo-ocular reflex and prolongs eye velocity responses even after the stimuli from the vestibular system have ceased (Cohen *et al.*, 1977; Raphan *et al.*, 1979). Velocity storage is also known to be responsible for spatial orientation of the angular vestibulo-ocular reflex (Raphan *et al.*, 1992; Wearne *et al.*, 1997). As a result, during angular vestibulo-ocular reflex, the axis of eye velocity tends to align with the gravito-inertial acceleration, a

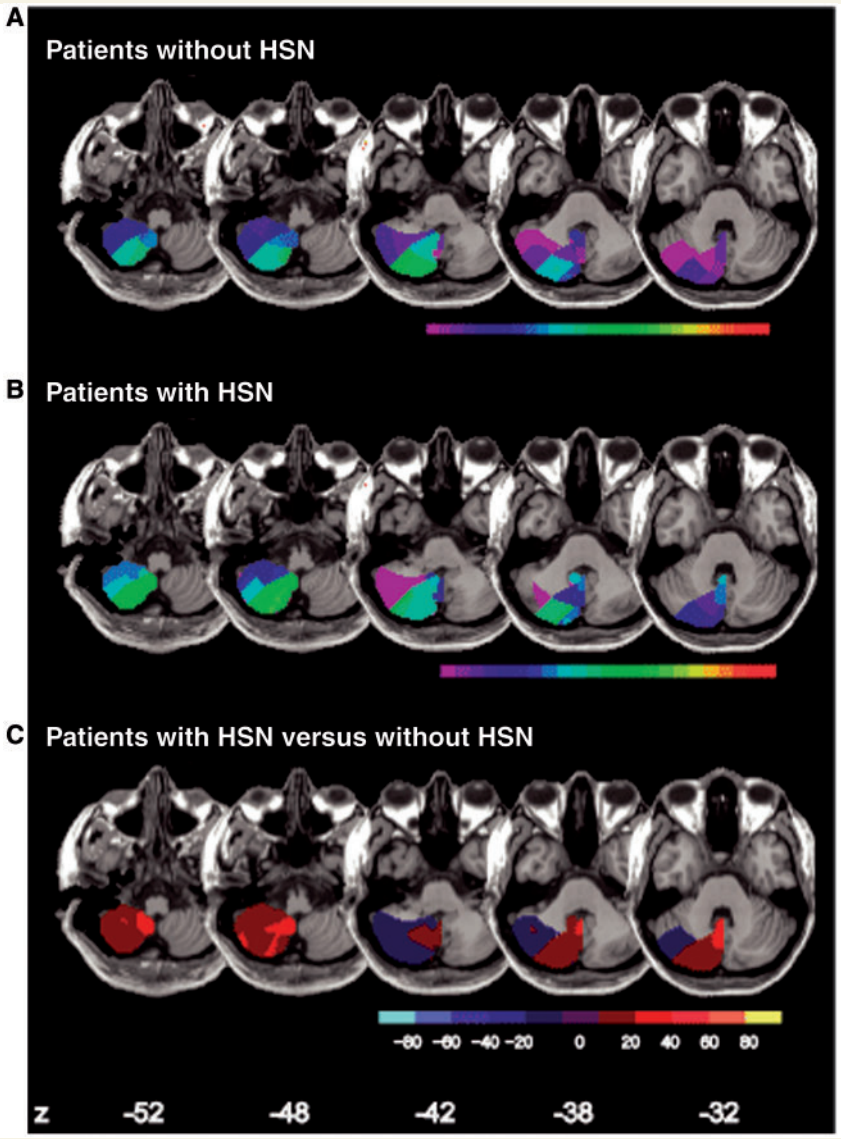

Figure 6 Lesion analyses in patients with unilateral posterior inferior cerebellar artery infarction. In 51 patients with a unilateral infarction in the territory of PICA, overlay plots of lesions (**A** and **B**) and subtraction images (**C**) show that the nodulus, uvula and inferior tonsil are primarily responsible for the head-shaking nystagmus (HSN). (**A** and **B**) Colours represent numbers of overlapping lesions with increasing frequency from violet ($n = 1$) to red ($n = 28$ for **A**, $n = 23$ for **B**). (**C**) Overlapped lesions in patients without head-shaking nystagmus (**A**) were subtracted from those of patients with head-shaking nystagmus (**B**). The percentages of overlapping lesions after subtraction are indicated by five different colours, where dark red represents differences from 1 to 20% and white-yellow represents differences from 81 to 100%. Colours represent increments of 20%. Regions coloured from dark blue (difference from −1 to −20%) to light blue (difference from −81 to −100%) indicate regions damaged more frequently in patients without head-shaking nystagmus. Talairach's *z*-coordinates for each transverse slice are provided.

Table 2 Proportions of patients with lesions involving each area in the territory of the posterior inferior cerebellar artery

Lesions	Head-shaking nystagmus ($n = 23$), *n* (%)	No head-shaking nystagmus ($n = 28$), *n* (%)	*P*-value
Nodulus ($n = 15$)	11 (73.3)	4 (30.8)	0.009
Uvula ($n = 16$)	12 (75.0)	4 (25.0)	0.004
Inferior tonsil ($n = 25$)	16 (64.0)	9 (36.0)	0.008

vector sum of gravitational and linear acceleration (Harris, 1987; Raphan and Cohen, 1988). These orientation properties of the angular vestibulo-ocular reflex are known to be modulated by inhibitory GABAergic Purkinje cells of the nodulus and ventral uvula (Wearne *et al.*, 1996, 1998). After ablating these structures, horizontal time constant becomes greater during rotation in head vertical posture and can no longer be shortened by tilting the gravito-inertial acceleration with regard to the head (Waespe *et al.*, 1985). Thus, unilateral uvulonodular damage can cause

horizontal head-shaking nystagmus by producing an asymmetry in horizontal velocity storage. Remarkably, the horizontal component of head-shaking nystagmus was uniformly ipsilesional when it occurred in our patients with unilateral PICA infarction. The nodulus and ventral uvula project their fibres exclusively to the ipsilateral vestibular complex (Wylie *et al.,* 1994; Barmack *et al.,* 2000). Accordingly, ipsilesional disinhibition of the velocity storage due to the unilateral uvulonodular damage may have produced a contralesional bias and ipsilesional nystagmus after horizontal head-shaking.

Nodulus and uvula can also be responsible for generating perverted head-shaking nystagmus as well as a horizontal one. In our study, 62% of our patients with head-shaking nystagmus showed perverted head-shaking nystagmus, which was mostly downbeat. As noted above, the nodulus and uvula play key roles in preserving spatial orientation of angular vestibulo-ocular reflex (Waespe *et al.,* 1985; Wearne *et al.,* 1996 1998). In macaque with an ablation of these structures, the axis of eye velocity remained fixed during angular vestibulo-ocular reflex regardless of the tilt of gravito-inertial acceleration (Waespe *et al.,* 1985), causing loss of spatial orientation of angular vestibulo-ocular reflex. Thus, lesions involving these areas may inappropriately transfer the activity of horizontal vestibulo-ocular reflex pathway elicited by horizontal head-shaking to the vertical vestibulo-ocular reflex pathway, resulting in generation of perverted head-shaking nystagmus. Indeed, in a previous report, patients with isolated nodular infarction showed perverted head-shaking nystagmus (Moon *et al.,* 2009).

In addition to the nodulus and uvula, the inferior tonsil (paraflocclulus) was also frequently involved in our patients with head-shaking nystagmus. Indeed, 13 of the 51 patients with a unilateral PICA infarction had isolated lesions in the inferior tonsil sparing the uvula or nodulus, and six (6/13, 46%) of them showed downbeat head-shaking nystagmus (purely downbeat in five). The flocculus and paraflocculus are also possible neural substrates for perverted head-shaking nystagmus. The flocculus and paraflocculus are known to send their inhibitory fibres to the floccular target neurons in the anterior canal vestibulo-ocular reflex pathway, with less involvement of the posterior canal vestibulo-ocular reflex pathway (Ito *et al.,* 1977; Sato and Kawasaki, 1990; Zhang *et al.,* 1995). Thus, lesions involving the flocculus/paraflocculus could disinhibit anterior canal projections and cause upward drift of the eyes. Accordingly, accumulation of vestibular asymmetry favouring upward bias during horizontal head-shaking may generate downbeat head-shaking nystagmus. According to a recent study (Walker and Zee, 2005), patients with cerebellar disease also showed upward deviation of the eyes during high-acceleration yaw impulse. The study also found a correlation between the upward eye velocity and excitation of the anterior canal. Moreover, the amount of upward eye velocity was well correlated with the gain asymmetry during head impulse in the pitch plane; higher gains during downward pitch. These findings all suggest that the upward bias of the eyes in cerebellar lesions is due to a selective disinhibition of anterior canal vestibulo-ocular reflex pathway from floccular and paraflocular dysfunction.

Head-shaking nystagmus was commonly observed in patients with infarctions involving the SCA territory, which was a rather unexpected finding. Since the SCA usually does not supply the structures involved in modulation of the velocity storage mechanism, it is unlikely that head-shaking nystagmus was generated by asymmetric velocity storage. Instead, the dentate nucleus, irrigated by the SCA, may be a candidate for generation of head-shaking nystagmus in SCA infarctions (Baier *et al.,* 2008). The dentate and fastigial nuclei as well as the vestibulo-cerebellum are connected to ipsilateral vestibular nuclei in rats (Delfini *et al.,* 2000). The dentate nucleus is also known to relay the vestibular signals in rabbits (Highstein, 1971). In humans, stimulation of unilateral dentate nucleus produced ipsiversive conjugate deviation of the eyes and contralateral nystagmus, whereas lesioning of the dentate nucleus gave rise to dizziness and contralateral eye deviation (Nashold *et al.,* 1969). Thus, one can assume that unilateral damage to the dentate nucleus leads to contralesional bias of eye motion due to disinhibition of the ipsilesional vestibular nuclei. This would result in ipsilesional head-shaking nystagmus. Indeed, the horizontal component of head-shaking nystagmus was uniformly ipsilesional in our patients with SCA infarction.

Although spontaneous nystagmus typically beat to the contralesional side in unilateral peripheral vestibulopathies, patterns of spontaneous nystagmus may vary in central vestibular disorders. However, the horizontal component of spontaneous nystagmus was mostly ipsilesional when observed in our patients with a unilateral PICA or SCA infarction. This is consistent with the results of a previous study (Lee *et al.,* 2006) that showed ipsilesional spontaneous nystagmus in 15 of 24 patients with medial PICA infarction. In addition, another study reported predominantly ipsilesional spontaneous nystagmus in approximately half of those with an SCA infarction (Kase *et al.,* 1993). Ipsilesional spontaneous nystagmus in patients with unilateral cerebellar infarction may be explained by damage to the vestibulocerebellum or its outflow tracts to the vestibular nuclei. The vestibulocerebellum receives a direct projection from the labyrinth and have strong connections with the vestibular nuclei. Since the Purkinje fibres from the vestibulocerebellum have an inhibitory effect usually on ipsilateral vestibular nuclei (Ito *et al.,* 1970; Langer *et al.,* 1985; Wylie *et al.,* 1994; Barmack *et al.,* 2000), damage to this area or its outflow tracts is likely to increase tonic activity of ipsilateral vestibular nuclei, causing ipsilesional nystagmus.

Notably, only 18 (64%) of the 28 patients with spontaneous nystagmus exhibited head-shaking nystagmus. Moreover, head-shaking nystagmus developed in the opposite direction of spontaneous nystagmus in six patients (6/18, 33%). These occasional dissociations in the generation and patterns of spontaneous nystagmus and head-shaking nystagmus in cerebellar infarctions suggest that the neural cells or fibres responsible for spontaneous nystagmus and head-shaking nystagmus are segregated in the caudal cerebellum. Otherwise, the velocity storage mechanism may have been suppressed during the acute stage of cerebellar infarction and thus failed to generate head-shaking nystagmus.

Our study has some limitations. First of all, the lesion overlapping study could not differentiate between dysfunction due to destruction of neuronal cell body and damage to fibres of passage originating from other areas. Furthermore, current structural MRI techniques do not permit the detection of an area functionally deranged due to hypoperfusion. Secondly, the role of the flocculus

in the generation of head-shaking nystagmus could not be assessed since we excluded the patients with infarctions in the territory of anterior inferior cerebellar artery that supplies the flocculus. Thirdly, the number of patients with isolated SCA infarction was insufficient for a lesion analysis since most patients with SCA infarction were excluded due to associated lesions in the brainstem or cerebral hemispheres. Fourthly, since recording of torsional eye movements are still unsatisfactory with the video-oculography system, the characteristics of torsional head-shaking nystagmus require further elucidation. Fifthly, we determined the abnormality of the head impulse test bedside without measurement. Bedside the head impulse test may be false-negative due to covert catch-up saccades (Weber *et al.,* 2008). Even though the sensitivity of the bedside head impulse test is acceptable (Jorns-Haderli *et al.,* 2007), complete sparing of the semicircular canals cannot be assured with the results of the bedside head impulse test alone. To detect corrective saccades more accurately, quantitative recording of the head impulse test may be required using a scleral search coil technique or video head impulse test system (MacDougall *et al.,* 2009).

In conclusion, about half of the patients with acute isolated cerebellar infarction developed head-shaking nystagmus, which was mostly ipsilesional or downbeat. Since the uvula, nodulus and inferior tonsil were preferentially damaged in those with head-shaking nystagmus, head-shaking nystagmus in cerebellar lesions may be ascribed to asymmetric disinhibition of the uvula/nodulus over the velocity storage. The downbeat head-shaking nystagmus may be explained by a build-up of vestibular asymmetry favouring upward bias due to disinhibition of the paraflocculus over the anterior canal vestibulo-ocular reflex pathway.

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Supplementary material

Supplementary material is available at *Brain* online.

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