Hyperventilation-induced nystagmus in peripheral vestibulopathy and cerebellopontine angle tumor

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ABSTRACT

Objective: To determine the incidence and characteristics of hyperventilation-induced nystagmus (HIN) in cerebellopontine angle (CPA) tumors and unilateral peripheral vestibulopathy (UPV), and to elucidate differential contribution of hyperventilation to bring out vestibular asymmetry between acute and chronic phases of UPV.

Methods: We recorded horizontal HIN in 33 patients with CPA tumors and 145 with UPV. The UPV included patients of either acute (7 days or less from symptom onset, n = 47) or chronic (more than 7 days from symptom onset, n = 98) phases.

Results: The incidence of HIN was higher in the CPA tumor than in the UPV group (82 vs 34%, $p < 0.01$) and was also higher in the acute than in the chronic UPV group (60 vs 21%, $p < 0.01$). Furthermore, HIN was more commonly ipsilesional (i-HIN) in the CPA tumor than in the UPV group (52 vs 8%, $p < 0.01$) and more commonly ipsilesional in the acute than in the chronic UPV group (21 vs 1%, $p < 0.01$). The patients with i-HIN and acoustic neuroma had a tendency to harbor smaller tumors and to have less severe caloric asymmetry.

Conclusions: The contribution of hyperventilation on vestibular nystagmus differs depending on the disease phase or underlying pathologies. Our study demonstrates that hyperventilation-induced nystagmus (HIN) beating to the side of reduced caloric response, hearing impairment, or abnormal auditory brainstem response responses may be a valuable sign for bedside detection of cerebellopontine angle (CPA) tumors. CPA tumor should be a prime suspicion in patients with acute vertigo and ipsilesional HIN, especially when the vertigo accompanies hearing impairments.

Neurology® 2007;69:1050–1059

Hyperventilation may elicit nystagmus by bring out vestibular asymmetry in central as well as peripheral vestibulopathies, including compensated peripheral vestibulopathies, perilymph fistula, acoustic neuroma, lesions at the craniocervical junction, and cerebellar degeneration.[1-7] Previous studies have described a higher incidence of ipsilesional horizontal hyperventilation-induced nystagmus (HIN) in acoustic neuroma, presumably due to an improvement of axonal conductance in partially demyelinated vestibular nerve fibers.[2,4,6] However, the characteristics and diagnostic value of HIN in detecting acoustic neuroma, compared with those in benign unilateral peripheral vestibulopathy (UPV), remain to be elucidated. Furthermore, to the best of our knowledge, no study has attempted to evaluate the effect of hyperventilation during the acute stage of peripheral vestibulopathies. Previously, only one study found higher incidence of HIN in acoustic neuroma (58%, 14/24) compared with those in end-organ pathology (18%, 7/38).[4] HIN was ipsilesional in 8 patients with acoustic neuroma (33%) and in 2 with end-organ pathology (5%). However, in the end-organ group, the authors mostly included patients with Ménière disease in which the direction of vestibular nystagmus can be variable according to the disease phase and involvement of the contralateral ear.

Supplemental data at www.neurology.org

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Disclosure: The authors report no conflicts of interest.

The aim of this investigation was to elucidate the differences in the incidence and characteristics of HIN between cerebellopontine angle (CPA) tumors and UPV, which may provide a bedside diagnostic clue for differentiating more devastating tumors from benign UPV. We also addressed differential contribution of hyperventilation to bring out vestibular asymmetry between acute and chronic phases of UPV.

METHODS **Subjects.** Thirty-three patients (11 men, age range 32 to 72 years, mean age 52.1 ± 12.4 years) with CPA tumors were recruited at the Dizziness Clinic of Seoul National University Bundang Hospital from November 2004 to December 2005. CPA tumors were confirmed with gadolinium-enhanced MRI (axial and coronal views) in all of the patients. The tumor size was determined by measuring the greatest absolute diameter of the tumor on gadolinium-enhanced axial or coronal magnetic resonance scans. Radiologic diagnosis of the CPA tumors included acoustic neuroma (n = 23), meningioma (n = 7), epidermoid cyst (n = 2), and jugular foramen schwannoma (n = 1). Sizes of acoustic neuroma varied from 0.2 to 3.5 cm (mean ± SD = 1.6 ± 1.0 cm), and 8 patients had acoustic neuroma less than 1.0 cm. Sizes of the meningioma varied from 2.0 to 5.0 cm (mean = 2.9 cm), and those of the epidermoid cyst in 2 patients were 5.0 and 6.0 cm. The jugular foramen schwannoma measured 3.5 cm. Pathologic confirmations were available in 9 patients with acoustic neuroma, 4 with meningioma, 2 with epidermoid cyst, and 1 with jugular foramen schwannoma. Patient 2 was reported previously.[3]

Of the 263 patients who showed unilateral canal paresis of 25% or more during bithermal caloric tests at the Dizziness Clinic of Seoul National University Bundang Hospital from November 2004 to December 2005, 145 with UPV were selected for analyses of HIN after excluding the patients with a diagnosis of Ménière disease (n = 63), the patients with CPA tumors (n = 21), and the patients with additional central lesions in the brainstem or cerebellum (n = 14) on brain MRI. Twenty patients who could not maintain adequate hyperventilation for 30 seconds were also excluded from the analyses. None of the UPV patients included had a previous history of neuro-otologic diseases or additional neurologic signs or symptoms. Of the 145 patients, 139 had a diagnosis of vestibular neuritis, and the remaining 6 had labyrinthitis. All of the patients except for the 6 with a diagnosis of labyrinthitis did not have hearing loss on audiometry. Retrocochlear pathologies and central lesions were also excluded with brain MRI in 45 patients including all 6 patients with labyrinthitis and 10 of the 11 patients with ipsilesional HIN (i-HIN). Between CPA tumors and UPV groups, there was no differences in age (52.1 ± 12.4 vs 56.5 ± 13.8 years, $p = 0.09$) and in the degree of canal paresis (50.9 ± 34.8 vs 60.9 ± 24.0%, $p = 0.14$) at examination (table 1).

The patients with UPV were divided into acute and chronic groups. The acute group comprised 47 patients with acute spontaneous vertigo (34 men, mean age 52 years, age range 19 to 75 years) who had a time interval of no more than 7 days from symptom onset to evaluation. The remaining 98 patients (49 men, mean age 59 years, age range 25 to 86 years) underwent evaluations of their vestibular function more than 7 days after symptom onset and were classified into the chronic group. Patients in the chronic group had a clear history of acute spontaneous vertigo. All of the patients received full neuro-otologic evaluations by the senior author (J.S.K.).

Table 1 Demographics and the characteristics of HIN in patients with CPA tumors and UPV

	CPA tumor (n = 33)	UPV (n = 145)	*p* Value
Age, y	52.1 ± 12.4	56.5 ± 13.8	0.090
Canal paresis, %	50.9 ± 34.8	60.7 ± 24.0	0.143
HIN			
Incidence, %	82	34	<0.01
Mean velocity, °/s	6.6 ± 8.0	13.2 ± 15.9	0.03
i-HIN			
Incidence, %	52	8	<0.01
Mean velocity, °/s	6.9 ± 3.7	29.9 ± 25.6	0.014

HIN = hyperventilation-induced nystagmus; CPA = cerebellopontine angle; UPV = unilateral peripheral vestibulopathy; i-HIN = ipsilesional HIN.

Oculographic study. Eye movements were recorded with video-oculography (SMI, Teltow, Germany). Spontaneous nystagmus was analyzed both with and without fixation while the subjects attempted to look straight ahead. Gaze-evoked nystagmus was induced with horizontal (±30 °) target displacements. Before hyperventilation, the maximum slow phase velocity (SPV) of spontaneous nystagmus was measured in the horizontal plane. SPV of the horizontal component while the eyes were deviated more than 5 ° from the gaze straight ahead and that with blinks were excluded from the analyses. Then participants hyperventilated for approximately 30 seconds while seated in the darkness, taking an average of one deep breath per second. From the end of hyperventilation, we measured the maximum SPV of the induced nystagmus for 1 minute.

Normative data of HIN were obtained from 41 healthy volunteers (21 men) with an age range from 22 to 77 years (mean ± SD = 42.0 ± 15.5 years). Because hyperventilation elicited weak transient horizontal nystagmus even in some of the normal controls, the presence of HIN was defined only when maximal SPV of the induced or augmented (maximal SPV of induced nystagmus − maximal SPV of spontaneous nystagmus) horizontal component by the hyperventilation exceeded 3 °/second (mean + 2 SD), which was obtained from the normal controls, and when the nystagmus lasted more than 5 seconds.

The video-oculography system used had a spatial resolution better than 0.01 ° (horizontal) and a sampling rate of 60 Hz.[8] The digitized eye position data were analyzed by using MATLAB software. All the experiments followed the tenets of the Declaration of Helsinki and the policies of our institutional review board. Informed consents were obtained after the nature and possible consequences of the study had been explained to the participants.

Laboratory evaluations. ***Auditory brainstem response.*** Auditory brainstem response (ABR) was elicited by broad-band clicks derived from 100-msec-duration rectangular pulses delivered through a TDH-49 earphone at a rate of 21.1 per second. Stimulus intensity ranged from 75 to 95 dB nHL according to the patients' hearing sensitivity within the 2.0- to 4.0-kHz pure tone range and ABR configuration. Every effort was made to obtain a response with clearly defined peaks I through V. The contralateral ear was masked with continuous broad-band noise (45 to 65 dB), determined by stimulus intensity. Neuroelectrical activities were recorded with surface electrodes on the scalp vertex and earlobes. Each tracing consisted of 10-msec sweeps average over 1,024 runs. All evoked potentials were replicated to ensure reliability. I through III, III through V, and I through V interpeak latencies were measured from the ipsilateral recording. The contralateral recording was used mainly to identify wave V. When response configuration did not allow the measurement of interpeak latencies, the absolute latency of wave V was measured instead, and its interaural latency difference (ILD-V) was evaluated, taking into consideration of the hearing sensitivity at 4.0 kHz. Interpeak latencies exceeding the following values are considered abnormal: I through III, >2.37 msec; III through V, >2.14 msec; I through V, >4.38 msec. These values include 1 SD above the mean for normal hearing individuals in our laboratory. Complete absence of identifiable waves in the presence of adequate pure tone average, absence of waves beyond wave I, and an ILD-V of greater than 0.4 msec were also considered abnormal.

Bithermal caloric tests. Bithermal caloric tests were performed in 31 patients. The caloric stimuli comprised alternate irrigation for 25 seconds with 50 mL of cold (30 °C) and hot (44 °C) water. Vestibular nystagmus was recorded binocularly using video-oculography (ICS Medical, IL). Asymmetry of vestibular function was calculated using the Jongkees formula, and caloric paresis was defined by the response difference of 25% or more between the ears.

Pure tone audiometry and speech discrimination. Patients also underwent pure tone audiometry (PTA) and speech discrimination test. PTA was performed by using air and bone conducted signals in an acoustic booth. The pure tone average was obtained by averaging hearing thresholds at 0.5, 1.0, and 2.0 kHz. A pure tone average of more than 20 dB was regarded as indicative of hearing loss. Mild, moderate, and profound hearing losses were defined as 21 to 40, 41 to 70, and more than 70 dB of pure tone average.

Brain imaging. MRI was performed with a 1.5-T unit (Intera, Philips Medical Systems, Best, The Netherlands) using the following imaging protocol (axial turbo spin-echo T2-weighted imaging, axial and sagittal spin-echo T1-weighted imaging, axial gradient-echo imaging, three-dimensional balanced fast field echo imaging, and axial enhanced spin-echo T1-weighted imaging). The imaging parameters were 4,800/100 (repetition time [msec]/echo time [msec]) for T2-weighted imaging, 500/11 for T1-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 to 220 mm. Three-dimensional balanced fast field echo imaging was performed to cover the entire brainstem with a following sequence: 8/4 (repetition time [msec]/echo time [msec]), flip angle of 50 °, section thickness of 1.4 mm, matrix of 512 × 512, and field of view of 150 mm.

Statistical analyses. Chi-square tests were used to compare the incidence of HIN and ipsilesional HIN (i-HIN) between CPA tumors and UPV groups and between the acute and chronic UPV groups. The *t* test was used when the severity of caloric asymmetry, and the maximal SPV of HIN and i-HIN were compared between the groups. In acute UPV, the *t* test was also used to compare the severity of canal paresis, the age, and the interval from symptom onset to evaluation between the i-HIN and contralesional HIN (c-HIN) groups. The Fisher exact test was used when the number of cells was small. All of the tests were performed by using SPSS (version 12.0, Chicago, IL), and p values < 0.05 were considered significant.

RESULTS

Clinical presentation of CPA tumors. Of the 33 patients with CPA tumors, 11 (33%) developed vertigo (recurrent in 7, chronic persistent in 2, and acute in 2) and 15 (46%) presented with auditory symptoms; there was hearing loss in 11 (progressive in 9 and acute in 2), tinnitus in 7, and ear fullness in 1 (table 2). Twelve patients (36%) experienced nonspecific dizziness, and 8 (24%) also reported headache. Five patients (15%) had ipsilesional facial hypesthesia, and 2 (6%) showed dysmetria of the ipsilesional limbs. Patient 27, with a large epidermoid cyst, presented with isolated diplopia. In Patient 22, CPA meningioma was found incidentally during the evaluation of sudden left hemiparesis due to right corona radiata infarction. Ipsilesional head thrust test was positive in 17 (52%) of 33 patients with CPA tumors.

Laboratory findings of CPA tumors. Ipsilesional caloric paresis was documented in 21 (68%) of the 31 patients who underwent bithermal caloric tests (table 2). Hearing impairments were found on audiometry in 16 (50%) of the 32 patients tested. The hearing impairments preferentially involved the high-frequency range, and speech discrimination was reduced in accordance with increase in pure tone thresholds in all the patients. We performed the ABR test in 30 patients, and analyzed the results in 25 who had adequate hearing thresholds, after excluding the 5 without ABR responses due to profound hearing loss (>70 dB) between 2.0 and 4.0 kHz. Sixteen (64%) of the 25 patients with adequate hearing for ABR testing showed abnormal responses (increased I through III or I through V interpeak latencies in 9 and no wave formation beyond wave I in 7).

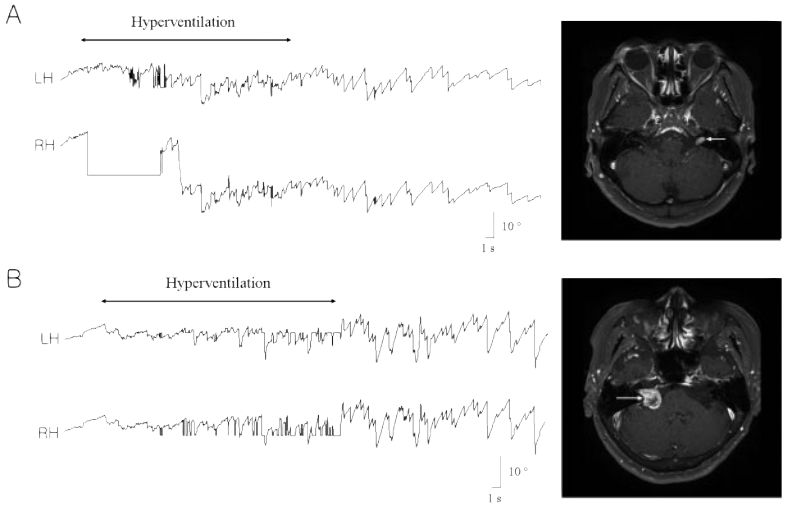
Between acoustic neuroma and other CPA tumors, there was no difference in the incidence of caloric paresis (70 vs 63%, $p = 1.00$) and abnormal ABR (71 vs 50%, $p = 0.39$). However, the incidence of hearing loss on audiometry was more frequent in the acoustic neuroma group than in other CPA tumor groups (68 vs 10%, $p = 0.01$).

Table 2 Clinical features and the results of laboratory evaluations of 33 patients with cerebellopontine angle tumors

Patient	Sex/age, y	Lesion side/tumor size, cm	Clinical symptoms	Spontaneous nystagmus, °/s	GEN	Head thrust test	HIN, °/s	ABR	CP, %	Audiogram
Patients with acoustic neuroma										
1	M/46	Lt/2	Ear fullness, acute vertigo	—	–	–	L7	N	N	HFHL (4 kH dip, 55 dB)
2	F/66	Lt/1	Recurrent vertigo	—	–	+	L6	NR	42	SNHL (50 dB), HFHL (70 dB)
3	F/44	Lt/1.3	Tinnitus, recurrent vertigo	—	–	–	L9	Increased I–III, I–V	N	N
4	M/37	Lt/3.5	Dizziness, headache	R3	+	+	L15	Increased I–III, I–V	69	N
5	F/66	Lt/2	Acute vertigo	—	–	+	R5	NR	100	SNHL (58 dB), HFHL (70 dB)
6	F/61	Lt/0.8	Chronic persistent vertigo	R2	–	–	L3	N	N	SNHL (40 dB)*
7	F/36	Rt/1	Hearing loss, tinnitus	—	–	+	R10	Increased I–III, I–V	84	SNHL (34 dB)
8	M/47	Lt/3	Tinnitus, dizziness, facial sensory loss	R1	+	+	R3	Wave I only	66	ND
9	M/53	Lt/0.2	Tinnitus, dizziness	L1	–	–	L2	Increased I–III, I–V	N	HFHL (4 kH dip, 65 dB)
10	F/64	Rt/0.2	Recurrent vertigo	—	–	–	R5	N	31	N
11	M/34	Lt/2.5	Hearing loss	R2	–	+	R6	Wave I only	76	SNHL (32 dB)
12	M/64	Lt/2.5	Hearing loss	R1	–	+	R6	NR	100	SNHL (68 dB), HFHL (70 dB)
13	M/71	Lt/0.8	Hearing loss, tinnitus, dizziness	—	–	+	L12	Increased I–III, I–V	65	SNHL (32 dB)
14	M/41	Lt/0.8	Hearing loss, chronic persistent vertigo	—	–	–	L4	Wave I only	38	SNHL (48 dB)
15	F/52	Lt/0.7	Headache	L3	–	–	L7	Increased I–III, I–V	N	N
16	M/57	Rt/2.5	Hearing loss, dizziness, facial sensory loss	L2	–	+	L7	ND	83	SNHL (70 dB)*
17	F/34	Lt/0.4	Headache	—	–	–	-	N	N	N
18	F/65	Rt/2	Acute hearing loss, headache	—	–	+	L9	Wave I only	95	SNHL (45 dB)
19	M/47	Rt/2.5	Hearing loss, tinnitus, facial sensory loss	L1	+	+	L5	Increased I–III, I–V	100	SNHL (66 dB), HFHL (53 dB)
20	F/62	Lt/3.5	Hearing loss, dizziness, facial sensory loss	R2	–	+	L5	NR	89	Complete hearing loss
21	F/39	Lt/1.2	Dizziness	L1	–	+	R45	Increased I–III, I–V	77	N
22	F/60	Lt/0.3	Dizziness, headache	R1	–	–	R5	N	N	N
23	F/71	Lt/1.3	Hearing loss, tinnitus, dizziness	L1	–	+	L2	NR	89	Complete hearing loss
Patients with other CPA tumors										
24	F/50	Rt JFS/3.5	Recurrent vertigo, dysmetria	L1	+	+	R5	Wave I only	54	N
25	M/72	Lt M/2	None	—	–	–	L4	N	N	N
26	F/32	Lt EC/6	Dizziness, dysmetria, facial sensory loss	R3	+	–	R3	ND	ND	SNHL (28 dB)
27	F/38	Rt M/4	Headache	—	–	–	R4	ND	ND	N
28	F/62	Rt M/2.5	Dizziness	—	–	–	R4	N	N	N
29	F/43	Rt EC/5	Diplopia	R1	–	–	L3	Increased I–III, I–V	30	N
30	F/49	Lt M/2.8	Acute hearing loss, recurrent vertigo	R4	–	+	R14	Wave I only	78	N
31	F/59	Rt M/2.5	Recurrent vertigo	—	–	–	—	N	N	N
32	F/37	Rt M/5	Dizziness, headache	—	–	+	R8	Wave I only	72	N
33	F/59	Rt M/1.8	Recurrent vertigo	R1	–	–	R5	N	49	N

* Patients 6 and 16 also had conductive hearing loss in the contralateral ear of tumor.
GEN = gaze-evoked nystagmus; HIN = hyperventilation-induced nystagmus; ABR = auditory brainstem response; CP = canal paresis; Lt = left side; Rt = right side; CPA = cerebellopontine angle; JFS = jugular foramen schwannoma; M = meningioma; EC = epidermoid cyst; L = left beating; R = right beating; N = normal; NR = no response; ND = not done; HFHL = high-frequency hearing loss; SNHL = sensorineural hearing loss; LFHL = low-frequency hearing loss.

Figure 1 Hyperventilation-induced nystagmus in two patients with acoustic neuroma



(A) Hyperventilation for 30 seconds induces ipsilesionally beating nystagmus in Patient 15 with small acoustic neuroma in the left side. The nystagmus has linear slow phases, a maximal frequency at 1.5 Hz, a maximal amplitude of 8°, and a peak slow phase velocity of 7°/second. (B) Hyperventilation induces contralesionally beating nystagmus in Patient 18 with large acoustic neuroma in the right side. Slow phases of the nystagmus are linear and maximal frequency, amplitude, and slow phase velocity of the nystagmus are 2 Hz, 14°, and 9°/second. Upward deflection in each tracing in this and following figures indicates rightward movements of the eyes. LH = horizontal position of the left eye; RH = horizontal position of the right eye.

Hyperventilation-induced nystagmus. ***Spontaneous nystagmus in CPA tumors and UPV.*** Without fixation, spontaneous nystagmus was found in 18 (55%) of 33 patients with CPA tumors, 43 (91%) of 47 with acute UPV, and 29 (30%) of 98 with chronic UPV (table 2). The fast phase of spontaneous nystagmus beat toward the intact side in 12 patients with CPA tumors, 42 with acute UPV, and 21 with chronic UPV. Spontaneous nystagmus was markedly suppressed with fixation in all the patients. Five patients (Patients 4, 8, 19, 24, and 26) with CPA tumors also showed gaze-evoked nystagmus.

HIN in CPA tumors. HIN was observed in 27 (82%) of the 33 patients with CPA tumors, 19 (83%) of the 23 patients with acoustic neuroma, and 8 (80%) of the 10 with other CPA tumors (table 2). The fast phase of HIN beat toward the tumor side (i.e., ipsilesional) in 17 (52%) of the 33 patients, 11 with acoustic neuroma (48%) and 6 with other CPA tumors (60%) (figure 1A), whereas it beat toward the healthy side (i.e., contralesional) in 10 (30%) (figure 1B). The mean maximal SPVs of HIN and i-HIN (after subtracting the spontaneous nystagmus component) were 6.6 ± 8.0 and 6.9 ± 3.7°/second. There was no difference in the incidence of HIN and i-HIN between the acoustic neuroma group and other CPA tumor groups (78 vs 80%, $p = 1.00$ and 48 vs 60%, $p = 0.71$). In patients with i-HIN, maximal frequency and amplitude of the nystagmus ranged from 1 to 3 Hz and 2 to 8°, whereas those in patients with c-HIN ranged from 1.5 to 2 Hz and 1 to 14°. Slow phases of HIN were linear, and HIN was markedly suppressed with visual fixation in all of the patients (figure 1).

Of the 17 patients with i-HIN, 14 (82%) showed ipsilesional abnormalities in at least one of the laboratory evaluations (11 with acoustic neuroma and 3 with other CPA tumors). Two patients with CPA tumors other than acoustic neuroma (Patients 25 and 28) did not reveal any abnormalities in the laboratory evaluations. Patient 28 had nonspecific dizziness, and Patient 25 did not report any symptoms. In the remaining 1 patient (Patient 27) with headache and meningioma, we performed pure tone audiometry only, which was normal. i-HIN was observed even in 10 patients with normal hearing on audiometry and in 6 with normal ABR.

Patients with acoustic neuroma and c-HIN had a tendency to harbor larger tumors and to have more severe caloric asymmetry. Seven of 8 patients with c-HIN had tumors larger than 1.0 cm, whereas 7 of 11 with i-HIN showed tumors less than 1.0 cm. Also, 7 of 8 patients with c-HIN had severe caloric asymmetry (>50%), whereas 7 of 11 with i-HIN had normal or mild caloric asymmetry (<50%). In patients with CPA tumors other than acoustic neuroma, we could not determine a correlation among the direction of HIN, tumor size, and the severity of caloric asymmetry because all patients had tumors larger than 1.0 cm and the sample size was too small.

HIN in UPV. In 28 (60%) of 47 patients with acute UPV, hyperventilation induced nystagmus or affected the horizontal component of the spontaneous nystagmus (table 3). HIN was ipsilesional in 10 patients (21%) (figure 2A and video [on the *Neurology* Web site at www.neurology.org]) and contralesional in 18 (38%) (figure 2B). In the remaining 19 patients, hyperventilation neither induced the nystagmus nor affected the spontaneous nystagmus.

The mean maximal SPVs of HIN and i-HIN were 18.9 ± 19.2 and 32.3 ± 25.7°/second. In acute UPV, no differences were noted between the i-HIN and c-HIN groups in terms of age (55.2 ± 15.1 vs 51.7 ± 15.2, $p = 0.63$), interval from symptom onset to evaluation (1.7 ± 1.3 vs 1.8 ± 1.6 days, $p = 0.82$), and the severity of canal paresis (65 ± 28 vs 69 ± 25%, $p = 0.66$). HIN had linear slow phases and showed marked suppression with visual fixation. The frequency and am-

Table 3 HIN in patients with CPA tumors, acute and chronic UPV

	CPA tumor (n = 33)	Acute UPV (n = 47)	Chronic UPV (n = 98)
HIN			
Incidence, %	82	60	21
Mean velocity, °/s	6.6 ± 8.0	18.9 ± 19.2	5.7 ± 2.0
i-HIN			
Incidence, %	52	21	1
Mean velocity, °/s	6.9 ± 3.7	32.3 ± 25.7	6

HIN = hyperventilation-induced nystagmus; CPA = cerebellopontine angle; UPV = unilateral peripheral vestibulopathy; i-HIN = ipsilesional HIN.

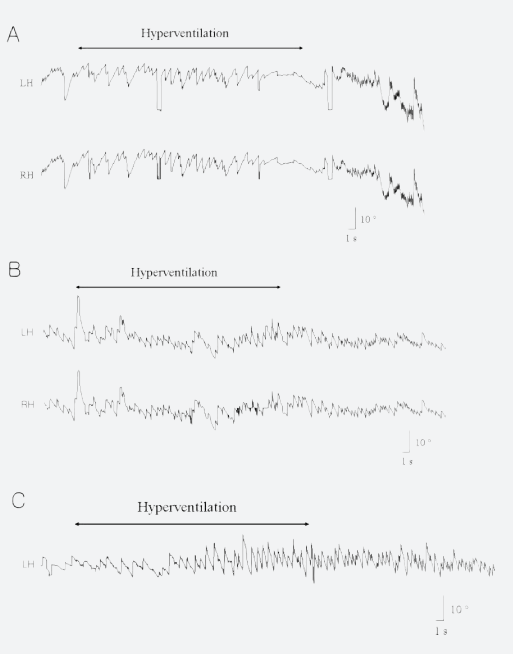
plitude of HIN ranged from 1 to 4 Hz and 2 to 16° (figure 2).

In contrast, hyperventilation induced nystagmus or affected the spontaneous nystagmus in only 21 (21%) of 98 patients with chronic UPV. The HIN was contralesional in 20 (20%) (figure 2C) and ipsilesional in only 1 patient (1%). In the chronic UPV group, the incidences of HIN and i-HIN were lower than those in acute UPV group (21 vs 60%, $p < 0.01$ and 1 vs 21%, $p < 0.01$). Also, the maximal SPV of HIN was lower in chronic UPV group than that in acute group (5.7 ± 2.0 vs 18.9 ± 19.2°/second, $p < 0.01$). In patients with c-HIN, maximal frequency and amplitude of the nystagmus ranged from 1 to 2 Hz and 2 to 10°. Maximal frequency, amplitude, and SPV of i-HIN in a patient were 2 Hz, 5°, and 10°/second. Slow phases of HIN were linear and HIN was markedly suppressed with fixation in all of the patients.

In view of higher incidence of i-HIN in CPA tumors, we performed brain MRI in 10 of 11 UPV patients with i-HIN, which did not show any retrocochlear pathologies.

Comparison of HIN between CPA tumors and UPV. The incidence of HIN in the CPA tumor group was higher than that in the UPV (82 vs 34%, $p < 0.01$), acute UPV (82 vs 60, $p = 0.04$), and chronic UPV groups (82 vs 21%, $p < 0.01$) (table 3). Furthermore, the incidence of i-HIN in the CPA tumor group was higher than that in the UPV (52 vs 8%, $p < 0.01$), acute UPV (52 vs 21%, $p = 0.01$), and chronic UPV groups (52 vs 1%, $p < 0.01$). The maximal SPVs of HIN and i-HIN were lower in the CPA tumor group than in the UPV (6.6 ± 8.0 vs 13.2 ± 15.9°/second, $p = 0.03$ and 6.9 ± 3.7 vs 29.9 ± 25.6°/second, $p = 0.01$) and acute UPV groups (6.6 ± 8.0 vs 18.9 ± 19.2°/second, $p < 0.01$ and 6.9 ± 3.7 vs 32.3 ± 25.7°/second, $p = 0.01$). Between the CPA tumor and chronic UPV groups, the maximal SPV of HIN did not differ (6.6 ± 8.0 vs 5.7 ± 2.0°/second, $p = 0.61$).

Figure 2 Hyperventilation-induced nystagmus in patients with unilateral peripheral vestibulopathy



(A) After hyperventilation, contralesionally beating spontaneous nystagmus reverses its direction in a patient with acute right vestibular neuritis. (B) Hyperventilation augments spontaneous right beating nystagmus in a patient with acute left vestibular neuritis. (C) In a patient with chronic left peripheral vestibulopathy, hyperventilation markedly enhances contralesionally beating spontaneous nystagmus. LH = horizontal position of the left eye; RH = horizontal position of the right eye.

Evolution of HIN during follow-up in patients with acute UPV. Twelve patients with HIN during the acute phase (5 with ipsilesional and 7 with contralesional) were followed up 1 to 11 months from symptom onset (table 4). Three of 5 patients with initial i-HIN (Patients 1 through 3) showed marked decrease in the intensity (Patient 1) or resolution (Patients 2 and 3) of nystagmus during follow-up at 1 to 8 months after symptom onset. Initial caloric asymmetry persisted in Patient 2 and recovered completely in Patients 1 and 3. In the remaining 2 patients (Patients 4 and 5), i- HIN changed into c-HIN 1 to 2 months after symptom onset in spite of persistent caloric asymmetry.

All 7 patients with c-HIN showed decreased intensity or resolution of nystagmus during the follow-up for 1 to 11 months after symptom onset. No direction reversal of the nystagmus was noted in these patients. Initial caloric

Table 4 Evolution of spontaneous and hyperventilation-induced nystagmus in 12 patients with acute UPV on follow-up recordings

	Initial recordings			Follow-up recordings			
Patients/lesion	CP, %	Spontaneous nystagmus, °/s	Hyperventilation-induced nystagmus, °/s	CP, %	Interval from the events, mo	Spontaneous nystagmus, °/s	Hyperventilation-induced nystagmus, °/s
Patients with i-HIN (n = 5)							
1/Rt	50	L6	R45	14	6	R1	R10
2/Lt	78	R9	L5	100	1	—	—
3/Rt	26	L2	R6	2	8	R1	R2
4/Rt	66	L6	R30	58	2	—	L4
5/Lt	95	R18	L5	92	1	R4	R9
Patients with c-HIN (n = 7)							
6/Rt	65	L13	L21	100	1	L4	L14
7/Lt	100	R20	R62	24	3	R1	R2
8/Lt	33	R7	R12	38	1	—	R2
9/Lt	54	R3	R12	100	3	R2	R6
10/Rt	56	L11	L22	100	11	R1	L5
11/Lt	56	R14	R24	17	1	R1	R3
12/Lt	85	R3	R13	89	2	R1	R7

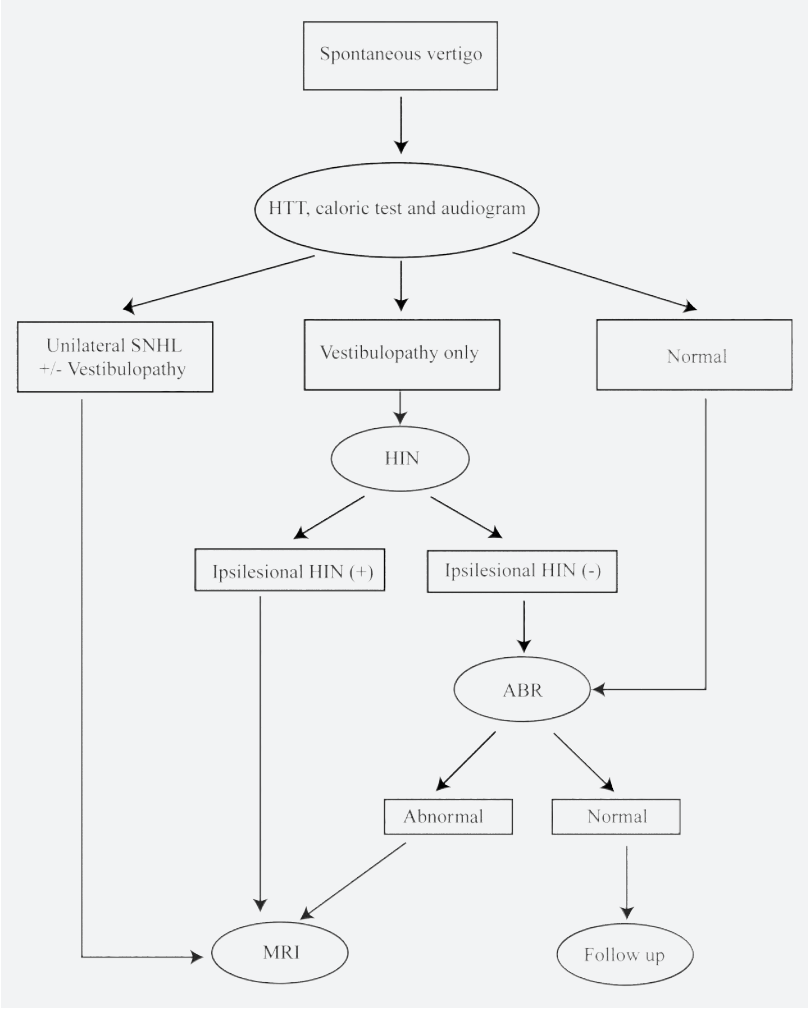
UPV = unilateral peripheral vestibulopathy; CP = canal paresis; i-HIN = ipsilesional hyperventilation-induced nystagmus; c-HIN = contralesional hyperventilation-induced nystagmus; Rt = right side; Lt = left side; R = right beating; L = left beating.

asymmetry persisted in 5 patients and resolved in the remaining 2.

DISCUSSION Although progressive unilateral hearing loss with dizziness or disequilibrium provides a high suspicion index of acoustic neuroma, our study showed that the incidence of vertigo or auditory symptoms and of abnormal audiometry or ABR are not high enough in CPA tumors. Only 33% and 46% of patients with CPA tumor reported vertigo or auditory symptoms at presentation. Hearing impairments were found in 50% on audiometry, and abnormal ABR was obtained in 64% after excluding the patients with profound hearing loss. Furthermore, only 10% of the patients with other CPA tumors showed hearing impairments on audiometry. The prevalence of acute vertigo or hearing loss is considerably low in CPA tumors (6 and 6%), which is similar to that of previous investigations with acoustic neuroma (4 to 7 and 3 to 23%).[9-15] These results indicate that additional clinical or laboratory markers are required for clinical suspicion of CPA tumors.

Regarding the incidence and characteristics of HIN in CPA tumors and UPV, our study involving a large number of patients replicates and extends the results of previous studies. Several studies have reported the incidence of HIN and i-HIN as 58 to 82% and 33 to 39% in acoustic neuroma, and as 18% and 5% in long-standing end-organ pathologies.[4,6] Other investigators have described either i-HIN (n = 2) or c-HIN (n = 4) in 6 patients with long-standing unilateral vestibular loss.[7] Unlike previous studies, we addressed a differential contribution of hyperventilation to bring out vestibular asymmetry between acute and chronic phases of UPV. We found that the incidences of HIN and i-HIN in CPA tumors were significantly higher than those in UPV regardless of the phase of illness, and the incidences in the acute UPV group were much higher than those in the chronic group. Most of the patients with i-HIN and CPA tumors had abnormality in at least one of the laboratory evaluations in the tumor side, and patients with i-HIN and acoustic neuroma had a tendency to harbor smaller tumors and to have less severe caloric asymmetry. Furthermore, we found i-HIN even in 10 patients with CPA tumor and normal hearing on audiometry, and in 6 with CPA tumor and normal ABR. In view of the low incidence (5%) of i-HIN in the chronic UPV group, HIN beating to the side of reduced caloric response, hearing impairments, or abnormal ABR may be a valuable sign for bedside detection of CPA tumor, even in patients with normal hearing or normal ABR (figure 3). However, visual fixation markedly suppressed HIN in

Figure 3 Algorithm for bedside and laboratory evaluation for cerebellopontine angle tumor in patients with spontaneous vertigo



ABR = auditory brainstem response; HIN = hyperventilation-induced nystagmus; HTT = head thrust test; SNHL = sensorineural hearing loss.

all of our patients. This profound suppression of HIN with visual fixation necessitates removal of visual fixation (e.g., Frenzel goggles or occlusive ophthalmoscopy[16]) for proper observation of HIN.

Even though acute vertigo and i-HIN are mostly encountered in the acute UPV group, CPA tumor should be considered in patients with acute vertigo and i-HIN, especially when the vertigo accompanies hearing impairments, as in our 2 patients (Patients 1 and 5).

In acoustic neuroma, previous investigators ascribed i-HIN to transient improvement of axonal conduction in the partially demyelinated vestibular nerve due to compression by tumors.[2-4,6] The improved axonal conduction may come from the reduction of extracellular Ca^{2+} due to decline in arterial P_{CO_2} by hyperventilation. Animal nerve preparations have shown that reduced ionized calcium increases nerve excitability,[17] in which conduction block attributable to nerve injury can be reversed by lowering the calcium content of the bathing medium.[18] In the setting of central compensation, hyperventilation-induced improvement of vestibular axonal conduction and resultant correction of the peripheral defect would result in transient central up-regulation and "excitatory (ipsilesional)" nystagmus.

On the contrary, c-HIN may result from axonal damage of the vestibular nerve and disrupted central compensatory mechanisms due to ischemia induced by hyperventilation. Hyperventilation may reduce cerebral blood flow by as much as 50%,[19] and tissue oxygenation is further reduced from the left displacement of the hemoglobin oxygen dissociation curve from the resulting alkalosis. This relative ischemia may alter vestibular compensatory mechanisms. These mechanisms are widespread in the CNS[20] and might therefore be susceptible to ischemia or metabolic changes brought about by hyperventilation.[21,22] These hypotheses could be supported by a tendency for smaller tumors to have i-HIN and less severe caloric asymmetry on the affected side, and for larger tumors to have c-HIN and complete loss of caloric responses. Earlier observation that hyperventilation induced contralesional nystagmus in all patients with surgical resection of acoustic neuroma is also in favor of this assumption. In agreement with the previous reports, we also found a trend that acoustic neuroma of larger size and more severe caloric paresis tended to be associated with c-HIN, whereas tumors of smaller size and mild caloric paresis are commonly associated with i-HIN.

In a study of HIN in 6 patients with longstanding unilateral vestibular loss, HIN was ipsilesional in 4 with either nerve section (n = 3) or total unilateral deafness (n = 1).[7] In the remaining 2 patients with presumed subtotal labyrinthine damage, the nystagmus was toward the side of canal paresis. The authors suggested that hyperventilation may help to reveal differences in the way that the CNS compensates for total or subtotal vestibular lesions. Alternatively, in the presence of subtotal labyrinthine lesions, the metabolic changes brought about by hyperventilation might stimulate partly damaged hair cells, or nerve endings, and provoke nystagmus by direct excitation of the abnormal side. Reduced P_{CO_2} and H^+ levels induced by hyperventilation result in increased neuronal excitability,[23] and reduced free calcium levels due to alkalosis also increase neuronal excitability.[24] The present study demonstrates differential contribution of hyper-

ventilation on vestibular nystagmus depending on the disease phase or underlying pathologies. The incidences of HIN and i-HIN were significantly higher in acute than in chronic UPV. We presume that i-HIN, mostly seen in acute UPV, may be caused by enhanced conduction in the demyelinated portion of the vestibular nerve due to viral infection or labyrinthine ischemia, likewise in acoustic neuroma. Direct excitation of the partially damaged hair cells or nerve endings due to increased neuronal or hair cell excitability after electrolyte, carbon dioxide, or acid–base changes induced by hyperventilation may be another possibility. Increased CSF protein in patients with vestibular neuritis, which begins approximately 2 weeks after onset, may support the demyelinating process in vestibular neuritis and can explain the higher incidence of i-HIN in acute UPV.[25,26] Some of our patients with initial i-HIN showed resolution of HIN or evolution of i-HIN to c-HIN during the follow-up even in the presence of persistent severe caloric asymmetry. These may be attributed to the evolution of initial demyelination into axonal degeneration along with disruption of the central compensatory mechanisms by hyperventilation. Evolution of initial demyelination into axonal degeneration also occurs in some patients with demyelinating peripheral polyneuropathy.[27] Differences in the incidence and direction of HIN between acute and chronic UPV may depend on the underlying pathology and degree of central compensation.

In our study, MRI was not performed in all patients with UPV. According to previous studies,[9-15] the incidence of acute isolated vertigo is very low in CPA tumors. Furthermore, because we excluded retrocochlear pathologies with MRI in patients with hearing loss (labyrinthitis) and in 10 of the 11 patients with i-HIN, we believe that the possibility of CPA tumor was extremely low in our UPV patients. Indeed, none of our patients with CPA tumor exhibited c-HIN in the presence of caloric paresis without hearing loss.

Received November 29, 2006. Accepted in final form April 6, 2007.

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