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Chasing dizzy chimera: Diagnosis of combined peripheral and central vestibulopathy

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ABSTRACT

Diagnosis of combined peripheral and central vestibulopathy remains a challenge since the findings from peripheral vestibular involvements may overshadow those from central vestibular disorders or vice versa. The aim of this study was to enhance detection of these intriguing disorders by characterizing the clinical features and underlying etiologies. We had recruited 55 patients with combined peripheral and central vestibulopathy at the Dizziness Clinic of Seoul National University Bundang Hospital from 2003 to 2013. Peripheral vestibular involvement was determined by decreased caloric responses in either ear, and central vestibulopathy was diagnosed with obvious central vestibular signs or the lesions documented on MRIs to involve the central vestibular structures. Combined peripheral and central vestibulopathy could be classified into four types according to the patterns of vestibular presentation. Infarctions were the most common cause of acute unilateral cases while cerebellopontine angle tumors were mostly found in chronic unilateral ones. Wernicke encephalopathy and degenerative disorders were common in acute and chronic bilateral disorders. Twenty five (45.5%) patients showed only vestibular findings with or without auditory involvements, but association with gaze-evoked nystagmus, impaired smooth pursuit or central types of head shaking nystagmus indicated a central vestibular involvement in most of them (23/25, 92.0%). Given the requirements for urgent treatments and potentially grave prognosis of combined vestibulopathy, central signs should be sought even in patients with clinical or laboratory features of peripheral vestibulopathy. Scrutinized bedside evaluation, however, secured the diagnosis in almost all the patients with combined vestibulopathy.

1. Introduction

Due to potentially grave prognosis of central vestibular disorders, differentiation of central from peripheral causes has always been the prime goal in the diagnostic approaching of the vestibular symptoms such as dizziness, vertigo, and unsteadiness [1]. Recent progress in clinical neurotology and neuroimaging, however, markedly improved diagnosis of isolated peripheral or central vestibular disorders [2]. Especially, the introduction of head impulse tests (HITs) and HINTS (negative HIT, direction-changing nystagmus, and skew deviation) has greatly enhanced bedside differentiation of central from peripheral vestibular disorders [3,4].

Several disorders may involve both peripheral and central vestibular structures, and failure to identify central signs in these chimeric disorders may lead to disastrous outcome since the prognosis is mostly dependent upon central vestibular involvements. However, combined peripheral and central vestibulopathy frequently poses a diagnostic difficulty since the peripheral vestibular signs may overshadow the central ones or vice versa [5]. For example, the HINTS may not be enough to detect central disorders such as anterior inferior cerebellar artery (AICA) infarction that mostly presents acute prolonged vertigo from lesions involving the brainstem and cerebellum as well as the inner ear [6]. Furthermore, recent studies described positive HITs in various lesions involving the brainstem or cerebellum, making the distinction between the central and peripheral vestibular lesions more difficult [7–9]. The aim of this study was to enhance detection of these intriguing disorders by characterizing the clinical features and underlying etiologies.

2. Methods

At the referral-based Dizziness Clinic of Seoul National University Bundang Hospital, 55 patients (27 men, mean age = 63.0, age range = 31–86) had a diagnosis of combined peripheral and central vestibulopathy from 2003 to 2013. Peripheral vestibular involvements were determined when the patients showed caloric paresis (CP) in either ear.

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Central vestibulopathy was defined by obvious central neurotologic signs including HINTS, head-shaking nystagmus (HSN) with central patterns, or by lesions involving the central vestibular structures, as was documented on MRIs. The ocular motor findings other than HIT and skew deviation were based on the results of oculography. According to the chronologic patterns of neurotologic presentation and the lesion side, the combined vestibulopathy was classified into four types; acute unilateral, acute bilateral, chronic unilateral, and chronic bilateral.

Acute vestibular syndrome was defined as sudden onset of vestibular symptoms and signs with their peak within days and gradual improvements thereafter while the chronic syndrome was defined as persistence or worsening of vestibular symptoms and signs for more than three months. Some patients have been described previously [6,8,10].

The patients had bedside evaluation of the ocular alignment using cover and alternate cover tests, spontaneous and evoked nystagmus, saccades, smooth pursuit (SP), visually enhanced vestibulo-ocular reflex (VVOR), in addition to routine neurological examination [11]. The nystagmus was also evoked by horizontal head-shaking, and positional maneuvers that included head bending, and leaning, lying down, head turning to either side while supine, and straight head-hanging. Spontaneous nystagmus (SN) was observed both with and without fixation, and the evoked nystagmus was evaluated only without fixation using video Frenzel goggles (SLMED, Seoul, Korea). Bedside HITs were performed manually with a rapid rotation of the head of ~20° amplitude in the planes of all semicircular canals (SCCs). The HIT was considered abnormal if a corrective saccade consistently supplemented the inadequate slow phase in the plane of the SCCs stimulated [12].

Nystagmus was recorded binocularly at a sampling rate of 60 Hz using a video-oculography (SensoMotoric Instruments, Teltow, Germany) [13]. Detailed methods have been described previously [13,14]. GEN was defined by the direction-changing nystagmus that beat in the direction of gaze in the both horizontal (±30°) planes. Central patterns of HSN included HSN beating to the lesion side, HSN in the opposite direction of SN, and perverted HSN (mainly downbeat nystagmus developing in response to horizontal head-shaking) [6,15–17].

HITs were measured in 14 patients. To quantify HITs, the head and eye movements were recorded using a magnetic search coil technique in a 70 cm cubic search coil frame (Skalar, Delft, The Netherlands) [10]. Detailed description on the methods and normative data is available elsewhere [10]. Patients also had evaluation of bithermal caloric tests, ocular torsion using fundus photography, and tilt of the subjective visual vertical [13]. CP was determined when the summated peak slow phase velocities of the induced nystagmus in response to cold and warm water did not exceed 10°/s in either ear.

MRIs were obtained with a 3.0 T or 1.5 T unit (Intera, Philips Medical Systems, Best, The Netherlands) with a section thickness of 3 or 5 mm [18]. The arterial territories were determined according to the previously validated anatomical templates [19].

3. Results

3.1. Etiology

Overall, the etiologies of combined peripheral and central vestibular disorders included infarctions ($n = 23$, 41.8%), tumors ($n = 17$, 30.9%), degenerative disorders ($n = 7$, 12.7%), Wernicke encephalopathy (WE, $n = 5$, 9.1%), cerebral superficial siderosis (n = 2, 3.6%), and infection (n = 1, 1.8%) (Table 1). All the infarctions involved the brainstem or cerebellum. The tumors were invariably located in or around the cerebellopontine angle (CPA). The radiological diagnosis of extra-axial tumors ($n = 12$) was uniformly vestibular schwannoma including the one with neurofibromatosis type 2. Radiologic or pathologic diagnosis of the intra-axial tumors included anaplastic astrocytoma ($n = 2$) and lymphoma ($n = 3$). Patients with degenerative disorders had the diagnosis of cerebellar ataxia and bilateral vestibulopathy (CABV, $n = 5$) [20] or cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome (CANVAS, $n = 2$) [21]. Five patients had WE due to chronic alcoholism (n = 2) or long-term total parenteral nutrition ($n = 3$). The superficial siderosis was idiopathic in one and due to repeated hemorrhages from spinal cord chordoma in the other.

Table 1
Etiologies of combined peripheral and central vestibulopathy.

Etiologies	No.	Percentage (%)
Infarction	**23**	**41.8**
AICA	*13*	*23.6*
AICA + PICA	*8*	*14.5*
PICA	*1*	*1.8*
Venous	*1*	*1.8*
CPA tumor	**17**	**30.9**
Extra-axial	*12*	*21.8*
Intra-axial	*5*	*9.1*
Degenerative disorder	**7**	**12.7**
CABA	*5*	*9.1*
CANVAS	*2*	*3.6*
Wernicke encephalopathy	**5**	**9.1**
Superficial siderosis	**2**	**3.6**
Infection	**1**	**1.8**
Total	**55**	**100.0**

AICA, anterior inferior cerebellar infarction; CABV, cerebellar ataxia and bilateral vestibulopathy; CANVAS, cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome; CPA, cerebellopontine angle; PICA, posterior inferior cerebellar artery.

3.2. Clinical characteristics

All patients experienced dizziness ($n = 9$, 16.4%), vertigo ($n = 27$, 49.1%), or unsteadiness ($n = 19$, 34.5%). Other common findings included hearing loss ($n = 25$, 45.5%), limb ataxia, ($n = 17$, 30.9%), headache ($n = 14$, 25.5%), facial palsy ($n = 13$, 23.6%), and diplopia ($n = 10$, 18.2%). Twenty five (45.5%) patients showed only vestibular findings with or without auditory involvements. In these patients, associated GEN, impaired SP, and the central types of HSN allowed determination of central vestibular involvements in almost all the patients (23/25, 92%) (Table 2).

The combined vestibulopathy was classified into four types; acute unilateral ($n = 21$, 38.2%), acute bilateral ($n = 8$, 14.5%), chronic unilateral ($n = 15$, 29.1%), and chronic bilateral ($n = 11$, 20.0%).

3.3. Acute unilateral combined vestibulopathy

Except one with Ramsay Hunt syndrome, all patients (21/22, 95.5%) in this group had acute cerebellar or brainstem infarction (Fig. 1). The infarctions involved the territories of AICA or posterior inferior cerebellar artery. One patient had a venous infarction involving the middle cerebellar peduncle.

All had acute spontaneous vertigo along with nausea/vomiting (15/22, 68.2%), hearing loss (12/22, 54.5%), limb ataxia (11/22, 50.0%), facial palsy (5/22, 22.7%), or diplopia (4/22, 18.2%). Vertigo or imbalance was the only clinical finding in five patients (22.7%).

GEN occurred in 16 (16/22, 72.7%) and skew deviation in four patients (5/22, 22.7%). Bedside HITs were positive during head turning to the side of CP in 20 (90.9%) patients. Central types of HSN were observed in nine (4.1%) patients. Six (27.3%) patients exhibited CPN, downbeat ($n = 3$), upbeat ($n = 1$) or apogeotropic ($n = 2$). Impaired SP (15/22, 68.2%) was also common. The patient with Ramsay Hunt syndrome showed GEN although brain MRIs were normal. Overall, the HINTS was negative in five patients (5/22, 22.7%), and three of them showed central types of HSN, and another had CPN and impaired SP. The remaining patient (patient 8) had no central signs, but the ocular motor evaluation was incomplete (Table 2).

Table 2
Summary of the clinical features.

No.	Age/sex	Etiology	Lesion side	CP	HIT	Hearing loss	Limb ataxia	Facial palsy	Diplopia	GEN	SN	Central HSN	Impaired SP	Dysmetric saccades	CPN	OTR/SVV tilt
Acute unilateral combined vestibulopathy																
1	34/M	Infarction, PICA	R	R	B	−	−	−	−	+	L	−	−	−	−	−
2	67/M	Infarction, AICA	R	R	B	−	−	−	−	+	L	−	−	+	Down	R(OT, SVV tilt)
3	67/M	Infarction, AICA	L	L	L	L	L	L	SD	+	−	Perverted, ipsilesional	+	−	−	L(HT, SD, OT)
4	68/F	Infarction, AICA	R	R	R	R	−	−	SD	−	L	−	+	−	ND	R(HT, SD, SVV tilt)
5	36/F	Infarction, AICA	L	L	L	N	−	−	−	+	R	−	+	+	Down	L(OT)
6	70/M	Infarction, AICA	R	R	R	R	−	−	−	+	R	−	+	−	−	R(OT,SVV tilt)
7	68/M	Infarction, AICA	L	L	L	L	L	−	−	+	R	Perverted	ND	ND	−	L(OT, SVV tilt)
8	69/F	Infarction, AICA	R	R	R	−	−	−	−	ND	L	−	ND	ND	−	−
9	81/F	Infarction, AICA	R	R	R	−	−	−	U	−	R	Perverted, opposite direction to SN	ND	ND	ND	−
10	73/F	Infarction, AICA	L	L	L	−	L	−	−	−	R	Perverted	+	−	−	L(OT, SVV tilt)
11	86/F	Infarction, AICA	L	L	L	L	L	L	−	−	R	Ipsilesional, opposite direction to SN	+	+	−	L(HT, OT, SVV tilt)
12	63/F	Infarction, AICA	R	R	R	−	−	−	−	+	L	−	+	−	−	R(OT,SVV tilt)
13	65/F	Infarction, AICA	L	L	L	L	−	−	−	+	−	−	+	slow	Up	−
14	65/M	Infarction, AICA	L	L	L	L	L	−	SD	+	R	Ipsilesional	+	+	Apo	L(SD, OT, SVV tilt)
15	63/M	Infarction, AICA + PICA	L	L	L	L	L	−	−	+	R	−	+	+	−	L(HT, OT, SVV tilt)
16	76/M	Infarction, AICA + PICA	R	R	R	−	L	−	−	−	L	−	+	−	Apo	L(SVV tilt)
17	75/M	Infarction, AICA + PICA	L	L	L	−	L	−	−	+	R	−	−	+	ND	L(HT, OT, SVV tilt)
18	72/M	Infarction, AICA + PICA	B	L	ND	−	L	L	−	+	R	Perverted	+	+	Down	L(HT, SD, OT, SVV tilt)
19	62/M	Infarction, AICA + PICA	L	L	L	L	L	L	−	+	−	Ipsilesional	+	+	ND	L(HT, SD, OT, SVV tilt)
20	65/M	Infarction, AICA + PICA	R	R	ND	R	R	R	U	+	R	Perverted	+	+	ND	R(HT, SVV tilt)
21	64/F	Infarction, venous	L	L	L	L	−	−	−	+	R	−	+	+	−	−
22	69/F	Infection, Ramsay-Hunt	L	L	L	L	−	L	−	+	R	−	−	−	−	−
Acute bilateral combined vestibulopathy																
23	74/M	Infarction, , AICA + PICA	R	B	B	−	−	R	−	+	−	−	+	−	−	R(HT, OT, SVV tilt)
24	73/F	Infarction, AICA + PICA	L	B	L	L	L	L	−	+	R	ND	+	−	ND	L(SD, OT, SVV tilt)
25	53/M	Wernicke's encephalopathy	B	B	B	−	B	−	−	+	Up	−	+	+	ND	−
26	64/M	Wernicke's encephalopathy	B	B	B	−	−	−	O	+	Up	−	+	+	Down	−
27	63/F	Wernicke's encephalopathy	B	B	B	−	B	−	O	+	−	−	+	slow	−	−
28	45/F	Wernicke's encephalopathy	B	B	B	−	−	R	O	V	−	−	ND	ND	−	−
29	62/M	Wernicke's encephalopathy	B	B	Normal	−	−	−	−	+	−	−	−	+	−	−
Chronic unilateral combined vestibulopathy																
30	45/M	Vestibular schwannoma	R	R	R	R	−	−	INO	Brun	−	−	+	−	Apo	−
31	52/F	Vestibular schwannoma	R	R	R	R	−	−	−	−	−	−	ND	ND	ND	R(SVV tilt)
32	75/M	Vestibular schwannoma	L	L	ND	L	−	−	−	Brun	R	−	+	+	−	L(OT)
33	45/M	Vestibular schwannoma	L	L	ND	L	−	−	−	+	L	−	ND	ND	−	−
34	35/M	Vestibular schwannoma	L	L	L	−	−	L	−	+	R	−	ND	ND	−	R(SVV tilt)
35	62/F	Vestibular schwannoma	R	R	B	R	−	−	−	+	L	−	+	+	−	−
36	56/F	Vestibular schwannoma	L	L	ND	−	−	−	−	−	R	Perverted	−	−	−	−

(continued on next page)

Table 2 (*continued*)

No.	Age/sex	Etiology	Lesion side	CP	HIT	Hearing loss	Limb ataxia	Facial palsy	Diplopia	GEN	SN	Central HSN	Impaired SP	Dysmetric saccades	CPN	OTR/SVV tilt
37	63/F	Vestibular schwannoma	L	L	L	L	−	−	−	−	−	Perverted	ND	ND	−	L(SVV tilt)
38	53/F	Vestibular schwannoma	R	R	R	R	−	−	−	+	L	−	ND	ND	−	R(SVV tilt)
39	31/M	Vestibular schwannoma	L	L	ND	−	−	L	−	Brun	L	Perverted, Ipsilesional	ND	ND	Up	L(OT)
40	76/M	Cerebellar anaplastic astrocytoma	L	L	L	−	L	−	U	Brun	L	−	+	+	Apo	L(HT)
41	52/M	MCP anaplastic astrocytoma	R	R	R	R	R	−	−	Brun	L	−	−	−	−	R(HT, OT, SVV tilt)
42	65/M	Lymphoma	L	L	L	−	−	L	−	+	R	−	+	+	ND	R(HT)
43	65/M	Lymphoma	R	R	R	−	−	−	−	+	−	−	ND	ND	−	L(SVV tilt)
44	68/M	Lymphoma	B	R	Normal	−	−	−	−	−	R	−	ND	ND	−	L(SVV tilt)
Chronic bilateral combined vestibulopathy																
45	36/F	Neurofibromatosis type 2	B	B	R	B	B	−	−	+	−	ND	ND	ND	ND	ND
46	47/F	Vestibular schwannoma	R	B	B	R	−	R	U	+	R	Perverted	ND	ND	−	L(OT, SVV tilt)
47	73/F	Cerebral superficial siderosis	B	B	B	−	−	−	−	+	R	−	+	+	−	−
48	42/F	Cerebral superficial siderosis	B	B	B	B	−	−	−	+	−	−	+	+	−	−
49	81/F	CANVAS	B	B	B	−	−	−	−	+	R	−	+	−	Apo	L(SVV tilt)
50	78/F	CANVAS	B	B	B	−	−	−	−	−	Down	Perverted	+	+	−	−
51	79/F	CABV	B	L	B	B	−	−	−	+	−	−	+	−	ND	−
52	76/F	CABV	B	B	B	−	−	−	−	+	Down	−	+	−	Apo	R(SVV tilt)
53	64/M	CABV	B	B	L	−	−	−	−	+	R	−	+	−	−	L(SVV tilt)
54	85/F	CABV	B	B	B	−	−	−	−	+	−	−	+	+	ND	L(SVV tilt)
55	72/F	CABV	B	B	B	−	−	−	−	+	−	−	+	+	−	−

AICA, anterior inferior cerebellar artery; Apo, Apogeotropic; B, Bilateral; CABV, cerebellar ataxia and bilateral vestibulopathy; CANVAS, cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome ; CP, caloric paresis; CPA, cerebellopontine angle; CPN, central positional nystagmus; GEN, gaze evoked nystagmus; HIT, head impulse test; HSN, head-shaking nystagmus; L, left; ND, not done; OTR, ocular tilt reaction; PICA, posterior inferior cerebellar artery; R, right; SD, skew deviation; SN, spontaneous nystagmus; SP, smooth pursuit; SVV, subjective visual vertical; U, diplopia of unknown causes; INO, diplopia due to internuclear ophthalmoplegia; SD, skew deviation; O, diplopia due to ophthalmoplegia.

3.4. Acute bilateral combined vestibulopathy

The etiologies of this group included WE in five (5/7, 71.4%) and infarctions in two patients (2/7, 28.6%). All the patients with WE showed symptoms and signs suggestive of central lesions in addition to dizziness/vertigo and imbalance, which included mental status changes ($n = 3$), diplopia (n = 3), limb ataxia ($n = 2$), and facial palsy ($n = 1$). Furthermore, all the patients showed central patterns of neurotologic findings such as spontaneous upbeat (n = 2), GEN ($n = 4$), slow or dysmetric saccades (n = 4), impaired SP (n = 3), and vertical GEN (n = 1, Fig. 2).

3.5. Chronic unilateral combined vestibulopathy

All the patients ($n = 15$) with chronic unilateral combined vestibulopathy had tumors in and around the CPA. The patients with vestibular schwannoma usually presented progressive ipsilesional hearing loss (7/10, 70.0%), but only one (1/5, 20%) of the patients with intra-axial tumor reported hearing loss. Patients usually suffered from unsteadiness during gait (11/15, 73.3%).

Nine patients showed positive HITs only to the lesion side while one (patient 35) exhibited positive HITs in both directions. GEN was observed in 11 patients and was of Bruns' type in five of them. Central types of HSN were found only in three. CPN was observed in 3 patients, and was apogeotropic in 2 and upbeat while lying down in one. Horizontal SP was impaired in five.

3.6. Chronic bilateral combined vestibulopathy

The underlying disorders included CABV ($n = 5$) or CANVAS ($n = 2$) in 7, CPA tumors in 2, and cerebral superficial siderosis in the remaining two patients. One of the two patients with CPA tumors showed bilateral CP from unilateral vestibular schwannoma confirmed on MRIs.

Patients in this group typically presented with chronic unsteadiness with or without vertigo ($n = 11$, 100.0%). All the patients with a CPA tumor and cerebral superficial siderosis had bilateral or unilateral hearing loss.

Examination showed GEN ($n = 10$, 90.9%), positive HIT in one or both horizontal directions (n = 10, 90.9%), impaired SP (n = 10, 90.9%), and CPN ($n = 2$, 18.2%). Perverted HSN was observed in one with a CPA tumor and another with CANVAS. The patient with bilateral vestibular schwannoma from neurofibromatosis type 2 showed unilaterally positive HIT in the presence of bilateral CP. One patient with CABV had unilateral CP, but showed bilaterally positive HITs. They also showed GEN and impaired SP, and one patient had apogeotropic CPN.

4. Discussion

This study analyzed the etiologies and clinical features of combined central and peripheral vestibulopathy according to their patterns of presentation to aid in diagnosis of these intriguing vestibular disorders. Especially, we focused on the clinical characteristics and examinations that may help detecting additional central lesions in the presence of peripheral vestibulopathy. Of interest, isolated audiovestibulopathy, which has been considered a typical feature of peripheral vestibulopathy, was common (45.5%) in our patients with combined vestibulopathies. However, associated central signs, such as GEN, the central types of HSN, or CPN indicated central vestibular involvements in almost all patients.

In this study, involvement of the peripheral vestibular organs was based on the CP. The results of caloric tests and bedside or quantitative HITs coincided well in most patients (40/49, 81.6%). Of interest, two patients with an isolated unilateral vestibular nuclear infarction showed

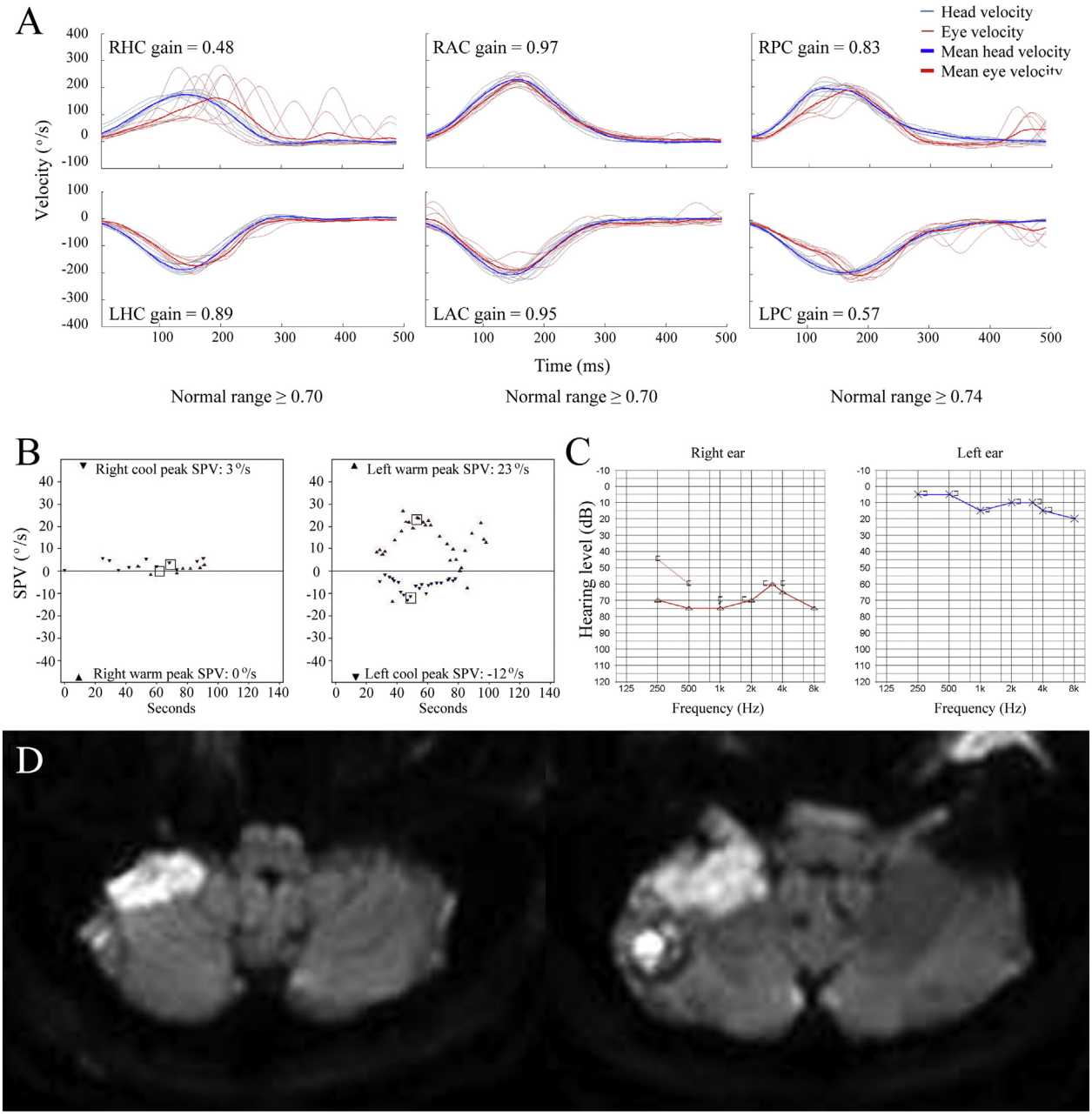

Fig. 1. Findings in a patient with acute unilateral combined vestibulopathy. A 70-year-old man (patient 6) with isolated audiovestibulopathy for 10 days shows a decreased gain with covert and overt saccades during head impulse tests for right horizontal semicircular canal (A), right caloric paresis (B), and right sensorineural hearing loss (C). Diffusion-weighted MRIs show acute hemorrhagic infarction involving the right anterior cerebellum, mainly in the territory of the anterior inferior cerebellar artery (D).

ipsilesional CP, but bilaterally positive HITs [8]. Since the medial vestibular nucleus (MVN) is the immediate recipient of peripheral vestibular projections, and is involved in the central processing of these vestibular signals through the connections with the flocculus [7], combination of peripheral and central vestibular findings strongly suggests a lesion involving the MVN in patients [8]. In chronic combined vestibulopathy, these dissociative patterns of the VOR were more conspicuous. One patient (patient 35) with progressive imbalance for several years showed bilaterally positive HITs but only ipsilesional CP from unilateral vestibular schwannoma compressing the cerebellum (Fig. 3). Since the HITs were bilaterally impaired in the presence of normal caloric responses in a patient with isolated unilateral floccular infarction [7], the impaired HIT in the contralesional direction may be explained by dysfunction of the flocculus, which appears to facilitate high-frequency VOR [7]. The associated GEN also supports floccular dysfunction in this patient. The dissociation between CP and abnormal HITs were also observed in one patient with CABV (patient 51). In a previous study of 31 patients with CANVAS, five showed only unilateral CP, and nine exhibited normal caloric responses in the presence of bilaterally positive HITs. The authors supposed a selective impairment of high-frequency VOR, probably due to preferential involvements of the irregular vestibular afferent fibers or floccular dysfunction [22]. On the contrary, normal or unilaterally impaired HITs were found in the presence of bilateral CP in some patients with acute combined vestibulopathy; one with infarction and the other with WE. One with WE (patient 29) showed normal bedside HITs in the presence of bilateral CP from symmetrical lesions involving the dorsal medulla including the vestibular nuclei. In a previous study, two patients with WE showed bilateral CP and impaired VOR during HITs for both HCs, and the vestibular paresis was explained by vulnerability of the MVN to thiamine deficiency [10]. In chronic combined vestibulopathy, the patients with CABV and neurofibromatosis type 2 showed bilateral CP,

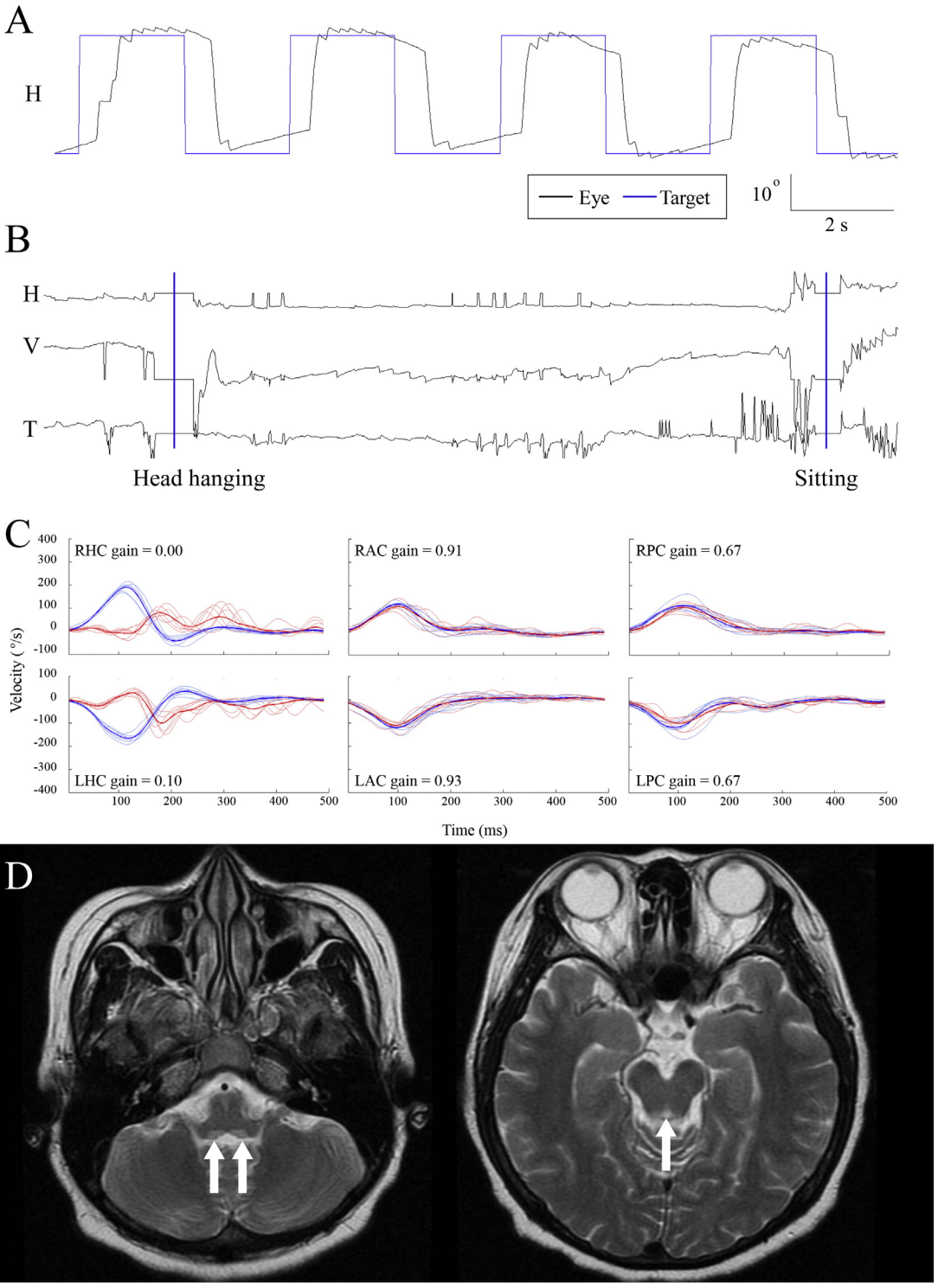

Fig. 2. Findings in a patient with acute bilateral combined vestibulopathy. A 64-year-old man (patient 26) with dizziness and horizontal diplopia for five days shows bilaterally hypometric horizontal saccades with a mild slowing and increased latency, and downbeat nystagmus in the head-hanging position (B). The head impulse tests were abnormal for bilateral horizontal semicircular canals (C). T2-weighted MRIs show symmetric lesions of high signal intensity in the bilateral dorsal medulla and midbrain tegmentum (D).

but only unilaterally impaired HITs. Owing to the slowly progressive nature of these disorders, central adaptation may have affected the VOR, especially during high-frequency stimulations associated with flocculus. The bedside HITs are less sensitive especially when the vestibular deficits are partial. Furthermore, the early covert saccades during bedside HITs can conceal loss of the VOR [23]. Nevertheless, the dissociations in the performance of the VOR according to stimulation frequency can be a clue for central lesions in combined vestibulopathy.

Patients with acute unilateral combined vestibulopathy commonly showed the well-known clinical findings of cerebellar or brainstem infarction, which included diplopia, facial palsy, and limb ataxia. When acute vestibulopathy is associated with these findings, stroke should be the prime suspicion. However, determining the etiology of isolated

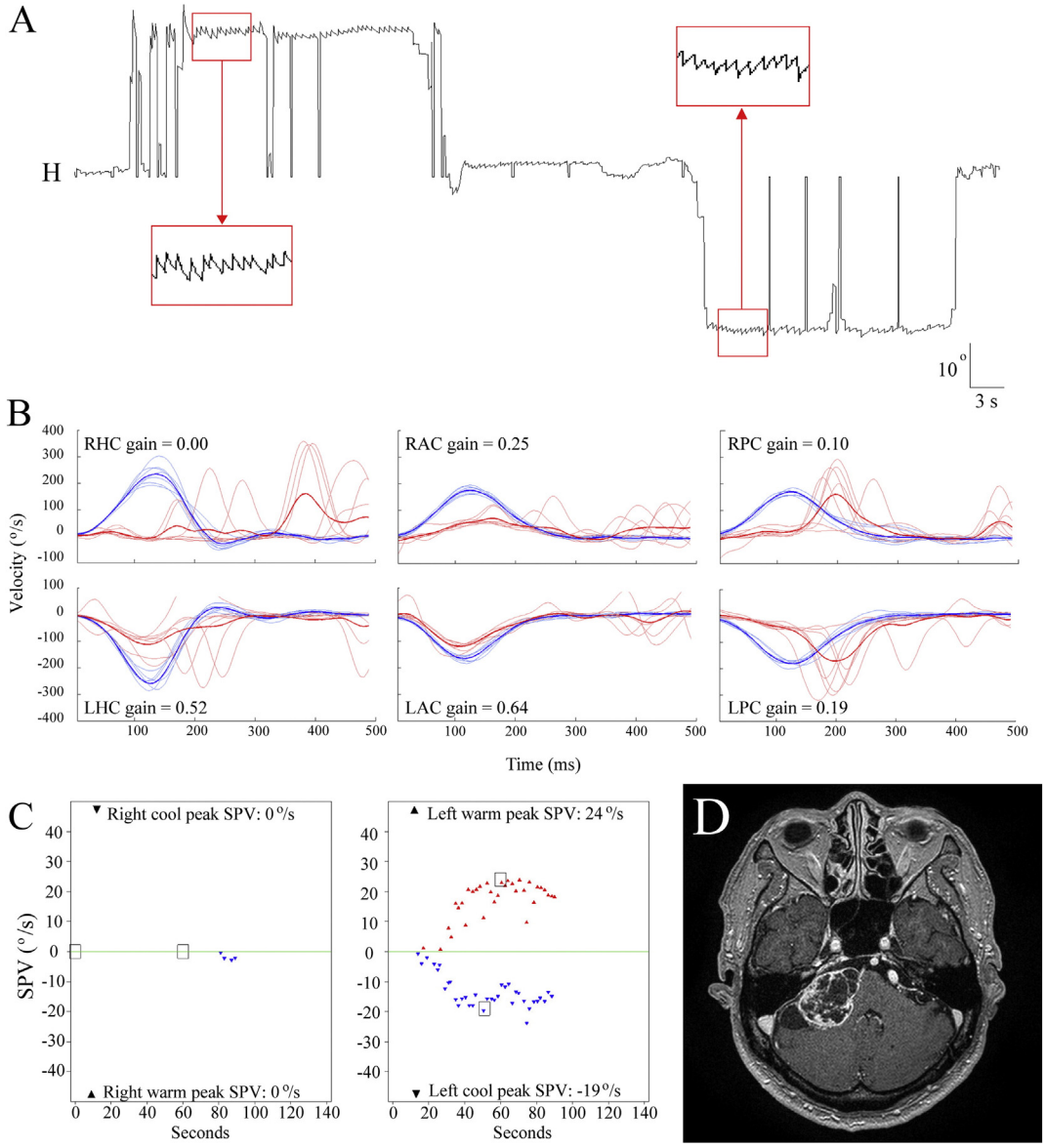

Fig. 3. Findings in a patient with chronic unilateral combined vestibulopathy. A 62-year-old woman (patient 35) with progressive imbalance and right hearing loss for several years shows gaze-evoked nystagmus during lateral gazes (A), bilaterally decreased head impulse gains of the vestibulo-ocular reflex for all six semicircular canals (B), and right caloric paresis (C). MRIs disclosed a large vestibular schwannoma compressing the brainstem and cerebellum on the right side (D).

acute vestibular syndrome requires more detailed neuro-otologic examination, like the HINTS [4]. However, since the HIT is mostly positive in combined vestibulopathy, the HINTS may not be sufficiently robust to detect central lesions in patients with combined peripheral and central vestibulopathy. Indeed, HINTS was false negative in 17.2% of acute combined vestibulopathy. This is consistent with our previous finding on negative HINTS in five (29.4%) of the 17 patients with AICA infarction [15]. Therefore, detection of central lesions may require additional tests such as horizontal head shaking that additionally detected central patterns of HSN in three of the five with negative HINTS [5]. Especially, since the AICA supplies both the peripheral labyrinth and central vestibular structures [24], the combined vestibulopathy with hearing loss may be the main features in AICA infarctions [25]. GEN is the most common central sign in this group as well as in other types of combined vestibulopathies. It is due to defective horizontal neural integration subserved by the nucleus prepositus hypoglossi (NPH), MVN, and flocculus. Impaired SP was the second most common central sign in this group of patients. Overall, central involvements were inferred from GEN and impaired SP in almost all the patients in this group (20/22).

WE was the most common cause of acute bilateral combined vestibulopathy. Distinct from acute unilateral group, the associated neurological symptoms and signs due to thiamine deficiency [26] allowed the diagnosis of central involvements without a difficulty. In WE, the vestibular nucleus and NPH are frequently involved, giving rise to vestibular paresis and GEN [27,28]. Due to symmetrical lesions involving the vestibular structures, signs of vestibular imbalances in the yaw and roll planes were not evident in this group of patients. Instead, vertical nystagmus was common. Of interest, two patients with unilateral infarction and the clinical features of acute audiovestibulopathy showed bilateral CP and were assigned to this group. The reason for CP in the contralesional side is unknown. In a previous study, stenosis of basilar artery near the origin of both AICAs can cause bilateral hearing loss with vertigo [29]. Otherwise, the contralesional CP may be an adaptive response to acute unilateral vestibular paresis [23].

Patients with chronic unilateral combined vestibulopathy presented chronic imbalance and hearing loss with or without unilateral cerebellar dysfunction. The cardinal etiology was intra- or extra-axial tumors involving the CPA [30,31]. Vestibular schwannoma, the majority of

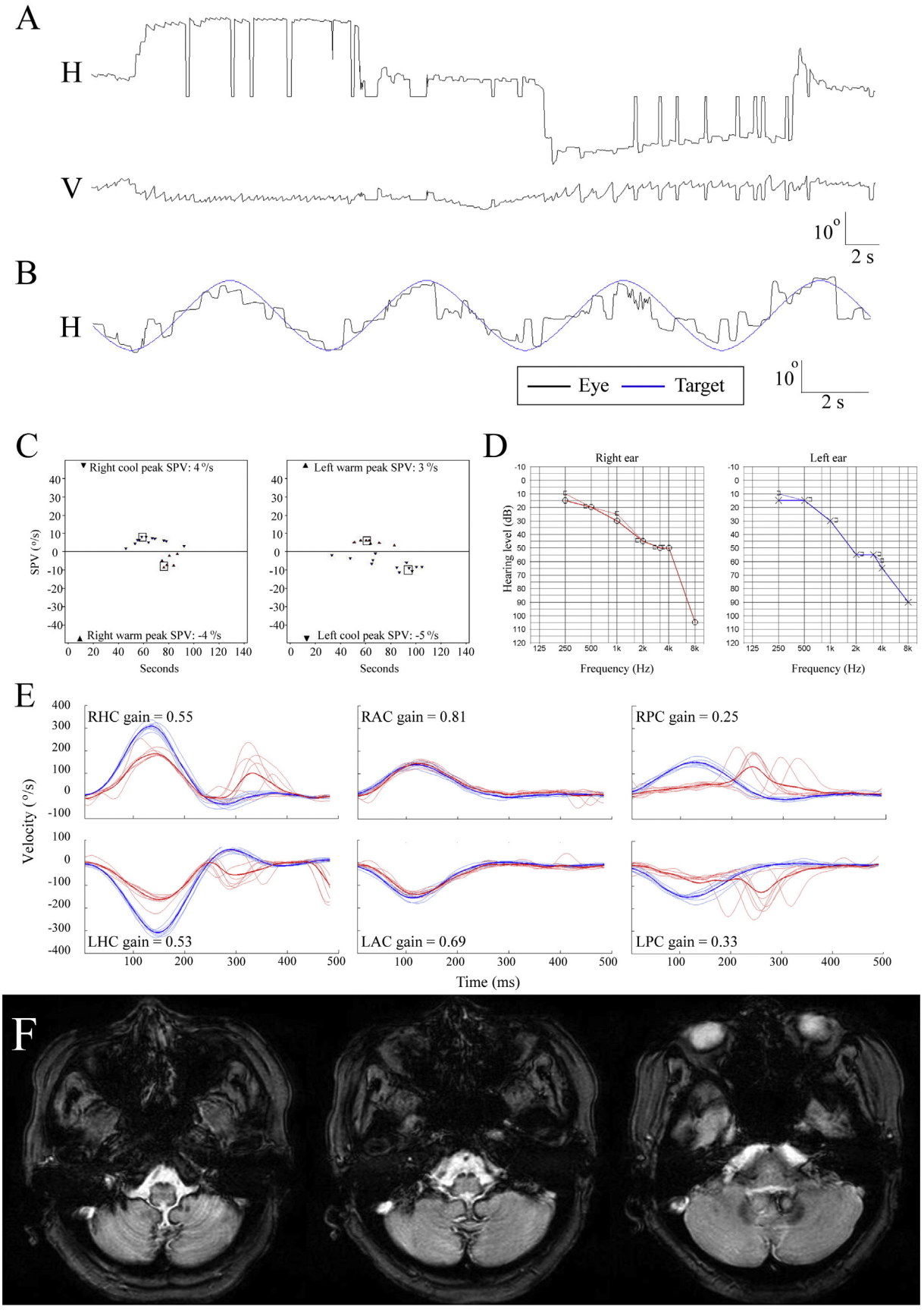

Fig. 4. Findings in a patient with chronic bilateral combined vestibulopathy from superficial siderosis. A 47-year-old woman (patient 47) with progressive unsteadiness for one year showed gaze-evoked nystagmus during lateral gazes (A), severely impaired horizontal smooth pursuit (B), bilateral caloric paresis (C), and high-frequency hearing loss in both ears (D). The head impulse VOR gains are reduced for the horizontal and posterior semicircular canals on both sides (E). Gradient-echo MRIs show superficial cerebral hemosiderosis involving the whole cerebellum, brainstem, and vestibular nerve (F).

CPA tumors, originates from the vestibular nerve and causes central as well as peripheral vestibulopathy by compressing the nearby cerebellum and brainstem [9,30]. The intra-axial tumors in this area also caused combined vestibulopathy by involving the vestibular root entry zone and vestibular nuclei in the pons, as in our patients with astrocytoma and lymphoma. GEN in the presence of chronic unsteadiness and unilateral hearing loss was the typical feature observed in most patients (86.7%), and addition of horizontal head shaking and positional tests revealed central signs in the remaining patients.

In chronic bilateral combined vestibulopathy, conspicuous cerebellar dysfunction masqueraded peripheral vestibular involvements. Patients with neurofibromatosis type 2 and superficial siderosis had prominent hearing loss while those with CABV and CANVAS had normal hearing [21,22]. Thus, the detection of peripheral vestibular involvements is the key to determine the underlying pathology in this group. Cerebral superficial siderosis is characterized by progressive neurological deficits due to chronic subarachnoid bleeding from deposition of hemosiderin into the brainstem, cerebellar convolutions and cranial nerves [32]. Due to its longer glial segment, the vestibulocochelar nerve is the most vulnerable to hemosiderin deposition, and audiovestibular dysfunction is common in this disorder (Fig. 4) [33,34]. CABV and CANVAS are characterized by cerebellar ataxia and bilateral vestibulopathy with or without peripheral neuropathy [20,21,35,36], In a previous study, 31 patients with CANVAS showed bilaterally positive HITs and impaired SP in all, and GEN in more than 90% [21]. Since SP and the VOR are simultaneously impaired in these patients, impaired VVOR is a typical sign indicating combined vestibulopathy during bedside evaluation [20]. Degenerative diseases involving the cerebellum, such as spinocerebellar ataxia type 6, may mimic chronic bilateral combined vestibulopathy, by showing positive HITs in addition to cerebellar signs [37]. However, normal caloric responses are the differential point.

In this study, peripheral vestibular involvement was defined by caloric paresis. Since caloric paresis may be observed in brainstem lesions involving the vestibular fascicle or nuclei [8,9,38], the presence of caloric paresis does not necessarily indicate a peripheral vestibular involvement. This is especially true for the patients with Wernicke encephalopathy or AICA/PICA infarctions, especially when there is no hearing loss. However, we adopted caloric paresis as a marker of peripheral vestibular involvement since it is the most well-known feature of peripheral vestibulopathy, and is rarely, if any, found in central vestibulopathy.

5. Conclusion

In summary, AICA infarction is the most common cause of acute unilateral combined vestibulopathy while CPA tumors should be a prime suspicion in chronic cases. In acute bilateral cases, WE should be considered. Hemosiderosis, CABV and CANVAS are the most common causes of chronic bilateral combined vestibulopathy. Dissociated performance of the VOR according to stimulation frequency may be a feature of combined vestibulopathy. The HINTS may not be enough to detect central lesions in combined peripheral and central vestibular disorders. Thus, the central neurologic signs, especially GEN, central types of HSN, and impaired SP, should be sought carefully even in patients with obvious clinical or laboratory features of peripheral vestibulopathy.

Conflict of interest statement

No conflicting relationship exists for the authors.

Author contributions

Dr. Choi conducted the experiments, analyzed and interpreted the data, and wrote the manuscript.

Ms. H.J. Kim conducted the experiments, and analyzed and interpreted the data.

Dr. J.S. Kim conducted the design and conceptualization of the study, interpretation of the data, and revised the manuscript.

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