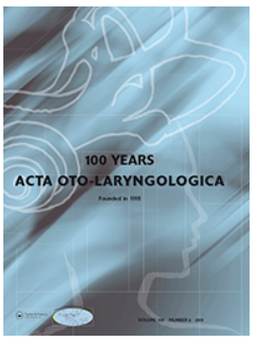

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RESEARCH ARTICLE

Acute vestibular asymmetry disorder: a new disease entity in acute vestibular syndrome?

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ABSTRACT

Background: Acute vestibular syndrome (AVS) is characterized by the rapid onset of vertigo, nausea, vomiting and gait unsteadiness, which lasts for days.

Aims/objectives: We report cases as acute vestibular asymmetry disorder (AVAD), with presentations that mimic vestibular neuritis (VN) but without central lesions.

Materials and methods: We retrospectively reviewed records of patients presenting with acute spontaneous vertigo lasting more than 24 h from January 2011 to June 2016. Among 341 patients, five showed different findings that did not indicate either VN or stroke. We analyzed the clinical features and vestibular assessments of these patients.

Results: All five patients showed spontaneous nystagmus continuing for several days. However, head impulse tests (HITs) did not reveal a corrective saccade. Brain magnetic resonance imaging showed no abnormal lesions. The bithermal caloric test revealed directional preponderance without canal paresis. Finally, the slow harmonic test of the rotatory chair revealed unilateral high gain and phase within the normal range, but a significantly asymmetric response was observed. No patients showed recurrence during follow-up.

Conclusions and significance: Our study suggests that a normal HIT in AVS is not always a dangerous sign indicating an acute stroke. From our observations, we propose that AVAD would be a new disease entity within AVS.

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KEYWORDS
Acute vestibular syndrome; magnetic resonance imaging; vertigo

Introduction

Acute vestibular syndrome (AVS) is characterized by the rapid onset of vertigo, nausea/vomiting, and gait unsteadiness and is associated with head motion intolerance and nystagmus lasting days to weeks [1]. AVS is usually attributed to vestibular neuritis (VN) or, if acute hearing loss occurs, neurolabyrinthitis [2]. However, some patients with AVS exhibit dangerous brainstem or cerebellar stroke that mimics VN [3].

The head impulse test (HIT) to evaluate the vestibulo-ocular reflex (VOR) in AVS is an important test for differentiation [4]. Newman-Toker et al. [5] reported that a normal HIT differentiates acute cerebellar strokes from VN. Moreover, they suggested that a normal horizontal HIT is the single best predictor of stroke in patients with AVS without definite neurologic symptoms or signs. However, we questioned whether AVS with a normal HIT always indicates a stroke.

We observed patients with acute spontaneous vertigo lasting several days and showing a normal HIT and caloric test without other accompanying neurologic or audiologic symptoms or signs. We propose to define this clinical entity as acute vestibular asymmetry disorder (AVAD). The purpose of our report is to describe the clinical features of AVAD and to provide possible mechanisms underlying the condition.

Materials and methods

Patients

We retrospectively reviewed our database of all consecutive patients with AVS admitted to our dizziness clinic from January 2011 to June 2016. Among them, we excluded those with definite neurologic symptoms or signs and hearing loss. All patients with AVS underwent vestibular function tests, including bithermal caloric test, rotatory chair test and bedside or video HIT and magnetic resonance imaging (MRI) with a brainstem thin section to confirm the absence of a central lesion. This study was approved by the Institutional Review Board of Soonchunhyang University.

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Neurotological examinations

The bedside neurotological examination included evaluations of spontaneous nystagmus with and without visual fixation, gaze-evoked nystagmus, head-shaking nystagmus, positional nystagmus without fixation, ocular misalignment including skew deviation, head tilt, and eye movements including smooth pursuit, saccades, and the VOR as measured with HIT. Eye movements were also quantitatively assessed with video-oculography (SLVNG®; SLMED, Seoul, Korea). Spontaneous nystagmus was recorded with and without visual fixation while sitting. Spontaneous nystagmus was considered abnormal when it was present even during visual fixation or when the slow-phase velocity of spontaneous nystagmus exceeded the values observed in healthy controls ($\geq$1.1°/s) without fixation.

Bithermal caloric tests were considered abnormal when there was a response difference of 25% or more between the ears. For the rotatory chair test, we used System 2000 (Micromedical Technologies Inc., Chatham, IL, USA). In the complete darkness field, we were able to maintain a waking state by asking patients to complete simple operations such as subtracting 7 from 100 with eyes open. The gain, asymmetry, and phase of the VOR were obtained by applying a sinusoidal rotation stimulus at a maximum angular velocity of 60°/s at 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, and 0.64 Hz (Micromedical Spectrum software). We also performed video HIT (cases 5 and 6) using a system for acquisition and analysis of eyeball and head movements (ICS impulse 1 version 1.0; GN Otometrics, Taastrup, Denmark).

Results

The diagnoses of all 341 patients with AVS were as follows: VN, $n = 331$; cerebellar stroke, $n = 4$; brainstem stroke, $n = 1$; and other, $n = 5$ (Table 1). The group of five patients diagnosed as 'other' was subsequently defined as having AVAD. Those patients exhibited similar findings to one another, including (1) acute spontaneous vertigo lasting more than 24 h with unidirectional spontaneous nystagmus (mostly horizontal–torsional); (2) no auditory symptoms including tinnitus, ear fullness, or hearing impairment, and no hearing loss documented with pure-tone audiometry; (3) no caloric paresis, normal HIT and normal gain on rotatory chair tests; and (4) exclusion of central lesions with brain MRI, including brainstem thin section and neurological examinations (Table 2).

All patients with AVAD had negative findings in the position changing tests, including the Dix–Hallpike test and supine head roll test. All patients had negative findings on the horizontal HIT. Moreover, there were no abnormal observations in video-oculography and only directional preponderance was observed in the caloric test. Cervical vestibular evoked myogenic potentials (cVEMP) were also normal in these patients. In the rotatory chair test, patients with AVAD showed asymmetry, normal to high gain, and no phase lead in the slow harmonic acceleration test. Brain MRI was completely normal, and all patients underwent MRI within 48 h of vertigo onset.

All patients were hospitalized and no new neurologic symptoms or signs appeared during admission. Furthermore, during the follow-up of 28–92 months (median = 70) from symptom onset, none developed migrainous headaches, Meniere's syndrome, or cerebellar stroke.

Representative case

A 59-year-old woman (case 4) presented with vertigo and imbalance for 5 days. She had no previous significant medical or surgical history. She denied any diplopia, tinnitus, aural fullness, or hearing impairments. Bedside neurotologic examination showed spontaneous right-beating nystagmus. HITs were normal in both horizontal directions. She did not show gaze-evoked nystagmus, head tilt, or skew deviation.

Video HIT was performed 2 days after symptom onset and was observed to be normal (Figure 1(A)). Bithermal caloric tests revealed no canal paresis with a rightward directional preponderance (Figure 1(B)). In the rotatory chair test, gain from sinusoidal harmonic acceleration was normal with leftward directional preponderance and normal phase (Figure 1(C)). Pure-tone audiometry was normal. Because the patient presented with acute spontaneous vertigo with normal HIT and caloric tests, brain MRI including a brainstem thin section was performed and no abnormal findings were observed. The patient had no recurrence of vertigo for 2 years.

Discussion

AVS can be categorized according to peripheral and central causes [1,6]. VN, which is the most common cause of AVS, is characterized by acute spontaneous vertigo accompanied by nausea, vomiting, and imbalance that last more than 24 h [3]. Unilateral vestibular hypofunction can cause unidirectional nystagmus, ocular tilt reaction, and canal paresis in

Table 1. Differential diagnosis of our cases ($n = 341$) with acute vestibular syndrome.

		Laboratory testing		
Cause	Physical examination	Audiography	Caloric test	Brain imaging
Vestibular neuritis ($n = 331$)	SN; positive HIT	Normal	Unilateral canal paresis	Normal
Brainstem and cerebellar infarct ($n = 5$)	SN; normal HIT	Normal	Normal	MRI showed infarction in medulla ($n = 1$) or cerebellum ($n = 4$)
Acute vestibular asymmetry disorder ($n = 5$)	SN; normal HIT	Normal	Normal	Normal

SN: spontaneous nystagmus; HIT: head impulse test; MRI: magnetic resonance imaging.

Table 2. Demographics and neurotological findings from patients with acute vestibular asymmetry disorder.

Case	Sex/Age	Duration of vertigo (days)	SN	GEN	Horizontal HIT	Caloric test CP (%)	Rotatory chair test			cVEMP	PTA	Follow-up (months)
							Gain	Asymmetry	Phase			
1	M/41	4	L	–	Negative	24	WNL	R	WNL	WNL	WNL	73
2	M/29	3	L	–	Negative	14	WNL	R	WNL	WNL	WNL	70
3	F/43	1	R	–	Negative	3	WNL	L	WNL	WNL	WNL	92
4	F/59	5	R	–	Negative	10	WNL	L	WNL	WNL	WNL	28
5	M/69	7	R→L	–	Negative	13	WNL	R	WNL	WNL	WNL	48

M: male; F: female; SN: spontaneous nystagmus; L: left; R: right; GEN: gaze-evoked nystagmus; HIT: head impulse test; CP: caloric paresis; WNL: within normal limits; cVEMP: cervical vestibular evoked myogenic potentials; PTA: pure-tone audiometry.

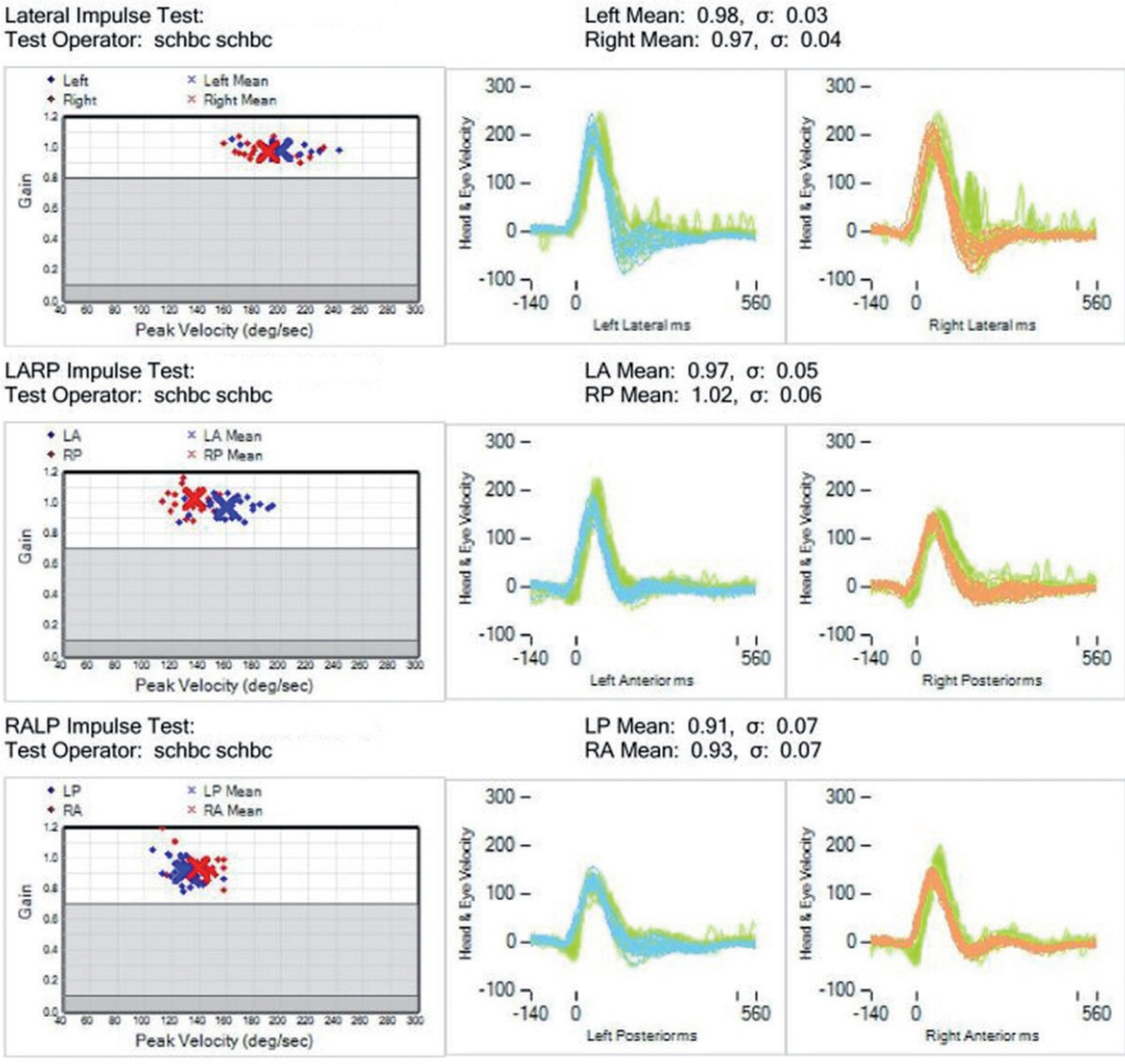

Figure 1. Neurotological findings in case 4. (A) Normal head impulse test. (B) Normal caloric response (canal paresis: 9.9%, directional preponderance: 49.9%). (C) Initial rotatory chair revealed normal vestibulo-ocular reflex gains and deviation to the left side without phase lead on sinusoidal rotation. LARP: left-anterior-right-posterior; RALP: right-anterior-left-posterior.

patients with VN. The characteristic feature of VN is the presence of horizontal–torsional nystagmus toward the healthy side and abnormal bedside HIT or caloric paresis on the lesion side. Decreased VOR gain with asymmetry and phase lead in rotatory chair tests can be observed in patients with VN [7].

If patients with acute spontaneous vertigo have spontaneous nystagmus but bedside HIT is normal, central vestibulopathy, especially ischemic infarction of the posterior fossa, should be strongly suspected [5,8]. While there were 331 patients with VN during the study period, only five patients had central vestibulopathy. Among those with central vestibulopathy, four had posterior inferior cerebellar artery infarction and one had brainstem (lateral medullary) infarction. All patients with central vestibulopathy mimicking VN and without other accompanying neurologic or audiologic symptoms or signs showed normal HITs at the initial visit.

It can be questioned whether patients with AVS showing normal HIT always have an acute stroke. Our study demonstrates that the five patients with acute spontaneous vertigo

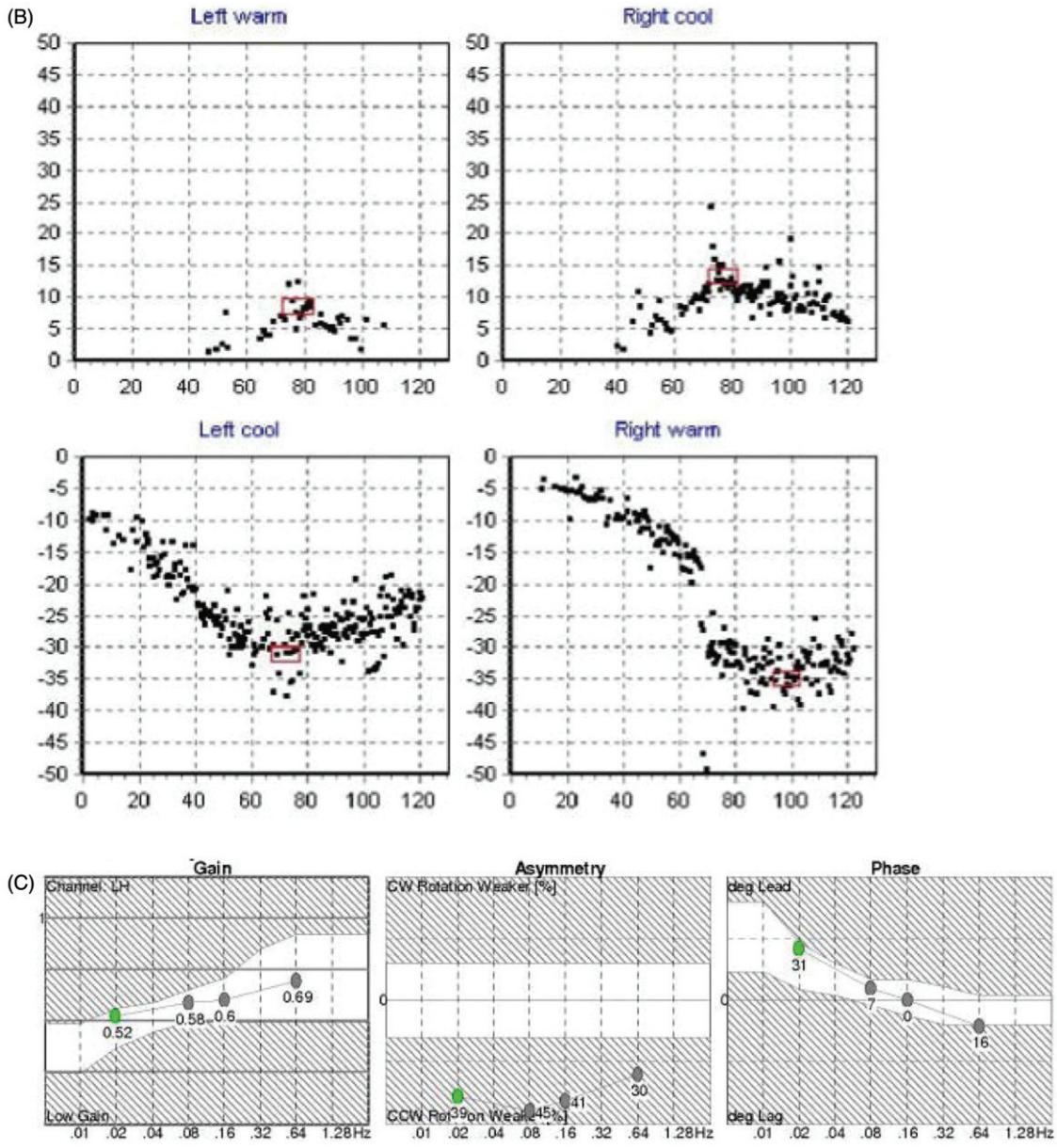

Figure 1. Continued.

and normal HIT and caloric tests had normal brain MRI. Although initial diffusion-weighted MRI misses 12% of strokes [9]. All five patients underwent MRI 48 h after symptom onset. Moreover, during the follow-up, none developed posterior fossa stroke. Currently, there is no accepted disease or syndrome explaining our five cases. Therefore, our report offers a new disease entity within AVS, which we have named AVAD. If this is a valid disease entity, what do we know about the pathophysiology of AVAD?

Normal vestibular end organs generate an equal resting-firing rate, which is the same on both sides [10]. This continuous excitation is transmitted to the vestibular nuclei via vestibular nerves. Pathologic processes affecting an end organ or vestibular nerve alter its firing frequency, thereby creating a vestibular tone imbalance. This causes a spontaneous nystagmus with the slow-phase (the pathologic component of the nystagmus) of the eye movements in the direction of the impaired labyrinth. This imbalance is also the cause of other manifestations such as rotatory vertigo, postural imbalance, nausea, and vomiting [3]. We speculate that AVAD shows vestibular asymmetry due to unilateral vestibular hyperexcitability or disinhibition rather than

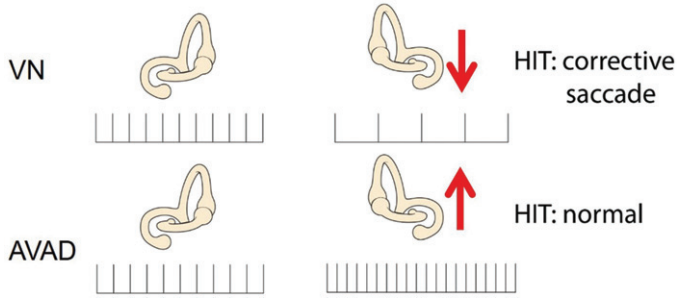

Figure 2. Proposed mechanism for acute vestibular asymmetry disorder (AVAD) compared with vestibular neuritis (VN). HIT: head impulse test.

unilateral hypofunction according to the raw data of rotatory chair test that corrected for spontaneous nystagmus. Therefore, an increasing firing rate of the pathologic side in AVAD caused spontaneous nystagmus while maintaining normal HIT (Figure 2).

Aside from cerebellar strokes, there are several known diseases that cause spontaneous nystagmus due to unilateral hyperfunction. First, in the case of Meniere's disease, nystagmus may beat towards the affected ear and HIT may be normal [11]. Leakage of the potassium-rich endolymph into the perilymph leads to excitation of the first-order afferent nerve, which is known to be the mechanism underlying vestibular asymmetry in the Meniere's disease acute phase [12]. However, the duration of nystagmus in our cases of AVAD was much longer than is usually observed in Meniere's disease, and there was no recurrence during follow-up periods. Second, the acute transient vestibular syndrome is another cause of spontaneous nystagmus [13]. If perfusion of the cerebellum, especially the posterior inferior cerebellar artery territory, decreases without evidence of acute stroke in diffusion-weighted imaging, hyperactivation of the ipsilateral vestibular nucleus due to disinhibition may occur, resulting in the asymmetric firing of central vestibular neurons. However, acute transient vestibular syndrome includes only cases showing resolution of vestibular symptoms and signs within 24 h after onset. Moreover, if cerebellar perfusion decreases over 24 h as in our cases, the stroke will inevitably occur. Third, paroxysmal disorders such as vestibular migraine, episodic ataxia, and recurrent spontaneous vertigo with interictal head-shaking nystagmus can also be considered [14–16]. There is also a possibility that a hyperactive and asymmetric velocity-storage is the underlying mechanism of spontaneous vertigo and nystagmus of our patients However, the duration of our patients' vertigo persisted for several days, unlike these disorders. In addition, no central sign such as gaze-evoked nystagmus or vigorous head-shaking nystagmus during vertigo attack was observed, and no recurrence despite the relatively long duration of follow-up (up to 92 months) was not compatible with these diseases.

Ahn et al. [17] reported that 'mild unilateral vestibular deficit' was the most common final diagnosis among patients who did meet the diagnostic criteria of VN. However, they gave an arbitrary diagnosis based on the only caloric test without HIT and rotatory chair test. Halmagyi et al. [18] presented cases of acute vertigo with a normal caloric response, identified as selective inferior VN. While horizontal HIT also evaluates lateral canal function via the nerve fibers of the superior vestibular nerve, the cVEMP test assesses inferior vestibular nerve function via the sacculocolic reflex. We performed cVEMP and all AVAD patients showed normal responses on both sides. In addition to these disorders, spontaneous nystagmus can result from microvascular compression [19] or viral neuritis, although this is very rare [20]. Nonetheless, the exact mechanisms underlying vestibular nerve hyperexcitability on one side remain unknown.

The strength of this study was a relatively long period of follow-up and comprehensive neuro-otological examination including rotational chair tests, video HIT, and cVEMP. Although this study was limited to single-institution studies with small sample size, our observation suggests that unilateral vestibular hyperactivity or disinhibition may be responsible for acute vertigo and nystagmus in a subgroup of patients with AVS of unknown etiology.

Conclusions

Our study showed that normal HIT in AVS is not always a dangerous sign indicating an acute stroke. Our report suggests a new disease entity within AVS, which we call AVAD. Further research is required to investigate patients with AVAD.

Disclosure statement

No potential conflict of interest was reported by the authors.

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