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REVIEW

Vascular vertigo: updates

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Abstract
Discriminating strokes in patients with acute dizziness/vertigo is challenging especially when other symptoms and signs of central nervous involvements are not evident. Despite the developments in imaging technology over the decades, a significant proportion of acute strokes may escape detection on imaging especially during the acute phase or when the lesions are small. Thus, small strokes causing isolated dizziness/vertigo would have a higher chance of misdiagnosis in the emergency department. Even though several diagnostic algorithms have been advanced for acute vascular vertigo, we still await more comprehensive and sophisticated ones that can also be applied to transient vestibular symptoms due to vascular compromise. In this respect, vascular and perfusion imaging would be informative. Application of artificial intelligence and teleconsultation may be future perspectives for real-time decision in acute dizziness and vertigo. Several new constellations of ocular motor and vestibular findings have been added to the strokes involving the brainstem and cerebellum. Defining these characteristics would help understanding the function of central vestibular structures and allow more accurate localization of the strokes involving these structures.

Keywords Stroke · Dizziness · Vertigo · Nystagmus · Vestibulo-ocular reflex

Approach to acute vascular vertigo

Even with introduction of the head impulse, nystagmus, and test of skew (HINTS) examination, which has been proved to be more effective in identifying strokes in acute vestibular syndrome (AVS) than MRIs [1, 2] misdiagnosis of posterior fossa infarcts remains considerable in emergency care settings [3–7]. Isolated dizziness and vertigo are the symptoms most tightly linked to missed strokes [3, 4, 6]. Since the diagnostic yield of any single test has been unsatisfactory for strokes causing acute dizziness and vertigo [8, 9] recent studies have attempted an integrated approach by incorporating the features of dizziness/vertigo, accompanied symptoms and signs, presence of vascular risk factors, and findings of ocular motor examination [8–16].

Diagnostic errors in acute strokes in emergency departments

A recent meta-analysis revealed that about 9% of cerebrovascular events are missed at initial presentation, and patients with mild transient nonspecific symptoms, such as dizziness, are at higher risk for misdiagnosis [5]. A population-based cohort study identified that the relative risk (RR) of 30-day stroke was 9.3 times higher than the matched renal colic controls after discharge from an Emergency Department (ED) with a diagnosis of peripheral vestibular disorders [17]. Of note, there was a 50-fold increased risk of hospitalization due to a stroke within 7 days after discharge. Plausible explanations for this frequent misdiagnosis in patients with acute dizziness/vertigo include a faulty diagnostic paradigm based on defining the type of dizziness, inadequate knowledge on bedside eye movement findings, over-reliance on vascular risk factors, and false reassurance by negative CT or MRIs [3]. Indeed, only a minority of ED providers adopts an eye movement-based diagnostic algorithm and even fewer are

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confident in these bedside skills [3]. In this regard, adoption of portable video-oculography devices and tele-consultation may be a future perspective for training of and feedback for the frontline clinicians dealing with acute dizziness and vertigo [2].

Acute transient vestibular syndrome

Acute transient vestibular syndrome (ATVS) is defined as resolution of acute vestibular symptoms and signs within 24 h [9], and may be a manifestation of a transient ischemic attack (TIA) involving the vertebrobasilar territory (VB-TIA). A single-center prospective study showed a high prevalence of stroke in ATVS (27%) [9]. In this instance, the diagnostic algorithm of HINTS or HINTS plus (HINTS plus acute hearing loss detected by finger rubbing) cannot be applicable and the findings of eye movement examination are mostly unrevealing since the symptoms and signs are mostly resolved by the time of assessment (73%). Instead, associated craniocervical pain and focal neurological symptoms/signs were the indicators of strokes in ATVS, and perfusion-weighted imaging (PWI) may help identifying strokes in ATVS of unknown causes (Fig. 1). Vertigo was the only symptom in the majority of patients with ATVS due to transient cerebellar hypoperfusion. Given that unilateral cerebellar hypoperfusion is associated with a stenosis or occlusion of the ipsilateral vertebral artery in about 80% of patients with ATVS, vascular imaging including MR or CT angiogram combined with PWI may be informative [9]. We also require "posterior circulation" stroke scale in acute transient or persistent dizziness/vertigo to define a specific case that will potentially have a benefit from thrombolysis or endovascular treatment [18].

A new diagnostic approach to acute vascular dizziness and vertigo

The traditional approach to acute dizziness emphasized defining the type of dizziness—vertigo (vestibular), presyncope (cardiovascular), disequilibrium (neurological), and nonspecific (psychiatric/metabolic). However, the data from a large national survey contradict this approach [19]. Even the patients with suspected peripheral vestibular disorders tend to report 3 different types of dizziness (spinning/vertigo, floating/tilt, and light-headedness), with vertigo as the primary type in only 25%. Thus, over-reliance on this traditional approach may lead to misdiagnosis of strokes in patients with acute dizziness [3, 19, 20]. Recently, an alternative diagnostic algorithm adopted classification of dizziness/vertigo into three types, acute, episodic, and chronic, according to the patterns of presentation [20]. VB-TIAs mostly present episodic spontaneous vertigo while completed strokes mostly present acute prolonged spontaneous vertigo. This new approach may be more practical than the

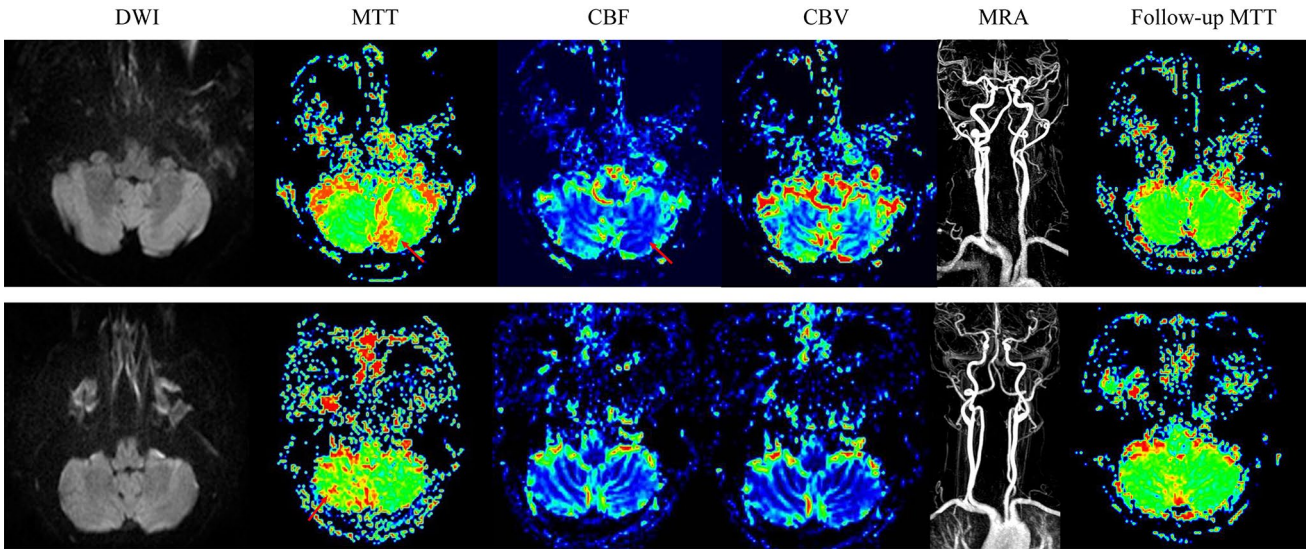

Fig. 1 Diffusion-weighted image (DWI, first panel), MR angiography (MRA, fifth panel), and initial (second, third, and fourth panels) and follow-up perfusion-weighted images (PWI, sixth panel) in 2 patients with acute transient vestibular syndrome due to cerebellar hypoperfusion. In the first patient, the initial PWIs reveal a prolonged mean transit time (MTT) and a reduced cerebral blood flow (CBF) in the left medial cerebellum without a diffusion restriction and cerebral blood volume (CBV) change. MRA shows a left vertebral artery (VA) hypoplasia. Follow-up PWI 3 days later discloses a normalized MTT in the left medial cerebellum. In the second patient, the initial PWI demonstrates a prolonged MTT in the right whole cerebellum without a diffusion restriction, CBF/CBV changes, and VA anomaly. Follow-up PWI 15 days later is normalized (adapted and modified from Ref. [9])

traditional quality-of-symptom-based approach in managing the patients with dizziness/vertigo.

Bedside versus quantitative head impulse tests in acute vestibular syndrome

Of the HINTS, negative head impulse test (HIT) is most sensitive for diagnosis of acute spontaneous vertigo due to strokes [1]. However, covert saccades that are generated while the head is still moving can hardly be perceived by the bare eyes and reduce the sensitivity of bedside HIT [21]. A prospective blind study on 150 patients showed that the overall sensitivity of bedside HIT was 34% with a specificity of 100% [22]. Complete vestibular loss was associated with the highest sensitivity of 87.5%. In contrast, quantitative HIT using a video-based equipment can differentiate posterior inferior cerebellar artery (PICA) strokes from vestibular neuritis (VN) with a sensitivity of 88% and specificity of 92% when the bilateral mean gains for the horizontal semicircular canals are 0.70 or more [23, 24]. However, anterior inferior cerebellar artery (AICA) strokes are at risk of being misclassified based on the VOR gain alone [25]. Quantitative analysis of corrective saccades may enhance the diagnostic accuracy [25]. Recently, the reliability of bedside and video HITs was assessed in 40 patients presenting with AVS to the emergency department of a tertiary-care center [26]. In that study, bedside HIT was abnormal in about 80% of the patients with VN, but normal in all with a stroke, which was similar to the findings obtained with analysis of the VOR gain during video HIT. These results indicate that video HIT does not add much for differential diagnosis of AVS, but future comparative studies incorporating analyses of corrective saccades are required in a larger number of patients with AVS.

Other diagnostic approaches and risk factors for strokes in acute dizziness and vertigo (Table 1)

Since the accuracy of HINTS for strokes was validated only in patients with acute spontaneous vertigo of more than 24 h, spontaneous nystagmus and one or more vascular risk factors, its diagnostic utility may not be generalized to other types of dizziness/vertigo. The STANDING algorithm (discrimination between **S**pon**TA**neous and positional nystagmus, evaluation of the **N**ystagmus **D**irection, head **I**mpulse test), and evaluation of equilibrium was explored in 352 patients with acute dizziness/vertigo by the emergency physicians [10]. The overall accuracy of this algorithm for central vertigo was 88%, with a high sensitivity (95%), specificity (87%), and negative predictive value (99%). The posterior circulation ischemia (PCI) score [high blood pressure (1′), diabetes mellitus (1′), ischemic stroke (1′), rotating and rocking (− 1′), difficulty in speech (5′), tinnitus (− 5′), limb and sensory deficit (5′), gait ataxia (1′), and limb ataxia (5′)] was reported to be more helpful than ABCD^2 and Essen scores for clinicians to differentiate PCI from other types of dizziness/vertigo [11]. Using a new diagnostic score (TriAGe + with eight variables: triggers, atrial fibrillation, male gender, blood pressure ≥ 140/ 90 mm Hg, brainstem

Table 1 Diagnostic algorithms proposed for acute vascular dizziness and vertigo

Indicators	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Areas under ROC curve
HINTS [1]	100	96	99	100	0.995
STANDING [10]	95	87	48	99	NC
PCI score[a] (ABCD^2 score[b]) [11]	NC	NC	NC	NC	0.82 (0.62)
TriAGe + score[c] [12]	NC	NC	NC	NC	0.82
NLR > 2.8 and the absence of horizontal nystagmus [14]	NC	NC	NC	NC	0.84
Abnormal VAECCS [13]	54	95	75	88	NC
Abnormal ultrasound [16]	41	100	100	84	NC

NC not calculated, *NLR* neutrophil-to-lymphocyte ratio, *NPV* negative predictive value, *PCI* posterior circulation ischemia, *PPV* positive predictive value, *ROC* receiver operating characteristic, *STANDING* spontaneous and positional nystagmus, the evaluation of the nystagmus direction, the head impulse test, and the evaluation of equilibrium (staNdinG), *VAECCS* vertebral artery extracranial color-coded duplex sonography;

[a]PCI score comprises high blood pressure, diabetes mellitus, ischemic stroke, rotating and rocking, difficulty in speech, tinnitus, limb and sensory deficit, gait ataxia, and limb ataxia

[b]ABCD^2 is composed of age, blood pressure, clinical features, duration of symptoms, and diabetes

[c]TriAGe+ score includes eight variables: triggers, atrial fibrillation, male gender, blood pressure ≥ 140/ 90 mm Hg, brainstem or cerebellar dysfunction, focal weakness or speech impairment, dizziness, and no history of dizziness/vertigo or labyrinth/vestibular disease

or cerebellar dysfunction, focal weakness or speech impairment, dizziness, and no history of dizziness/vertigo or labyrinthine/vestibular diseases) in 498 patients with acute dizziness, the prevalence of stroke rose significantly as the score increased: 5.9% for a score of 0–4; 9.1% for 5–7; 24.7% for 8–9; and 57.3% for 10–17 [12]. When the cutoff was set at 5, the score obtained a high sensitivity (96.6%) with a good negative likelihood ratio (0.15). This new score outperformed the $ABCD^2$ score for the prediction of stroke. Other risk factors for stroke in acute dizziness/vertigo included sudden hearing loss and vertigo in a close temporal proximity[13], a combination of neutrophil-to-lymphocyte ratio (NLR) > 2.8 and absence of horizontal nystagmus [14], and abnormal cerebral vasculature on extracranial color-coded duplex sonography [15] or ultrasound [16]. With all these advancements, however, we still await more comprehensive and sophisticated diagnostic algorithms for vascular dizziness/vertigo. Application of artificial intelligence would expedite the development of algorithms for real-time decision in acute dizziness and vertigo [8].

New vestibular and ocular motor findings in circumscribed brainstem or cerebellar strokes

Over the years, several distinct oculomotor and vestibular syndromes have been identified in strokes circumscribed to specific vestibular structures located in the brainstem or cerebellum [27–51]. These new findings allow defining the function of central vestibular structures in humans and a more accurate localization of lesions involving those structures in the brainstem and cerebellum in patients with acute dizziness and vertigo.

Brainstem strokes

Patients with lateral medullary infarction (LMI) frequently show spontaneous, gaze-evoked, and head-shaking nystagmus [27]. However, the patterns of positional nystagmus have rarely been described in LMI. A study reported positional geotropic nystagmus in approximately one-third of patients with acute or subacute LMI [28]. The prevalence and underlying mechanism of geotropic positional nystagmus requires further elucidation in brainstem and cerebellar strokes. LMI rarely presents unidirectional horizontal nystagmus and decreased VOR gain mimicking unilateral peripheral vestibulopathy [29] or pre-syncope due to orthostatic hypotension without vertigo or Horner's syndrome [30].

Patients with LMI may show various patterns of otolithic dysfunction. Almost all patients with LMI (42/45, 93%) show at least one component of the ocular tilt reaction (OTR) or subjective visual vertical (SVV) tilt that is invariably ipsiversive (Fig. 2) [31]. In contrast, ocular and cervical vestibular-evoked myogenic potentials (VEMPs) are abnormal in less than one-third of the patients [31]. Abnormal ocular VEMPs are more common in patients with the OTR than those without (38 vs. 6%), whereas abnormality of cVEMPs shows no correlation with the presence of OTR [31]. This discrepancy in impaired processing of otolithic signals suggests different anatomical substrates and/or dissimilar reciprocal modulation for processing of the signals from the utricle and saccule in central vestibular structures located in the dorsolateral medulla [31].

In 11 patients with isolated medullary hemorrhages, the presenting symptoms were mostly vertigo and headache [32]. All patients showed spontaneous nystagmus along with other neuro-otological findings that included central positional nystagmus, gaze-evoked nystagmus, ocular lateropulsion, skew deviation, or abnormal HITs. Thus, neuro-otologic examination would be essential in diagnosing medullary hemorrhage.

The nucleus prepositus hypoglossi (NPH) participates in integration of the velocity into position signals for horizontal eye movements so that the eyes can be held steady in eccentric positions in the orbit [33]. Brainstem infarctions involving the NPH show a distinct pattern of eye movement abnormalities: ipsilesional-beating spontaneous nystagmus; horizontal gaze-evoked nystagmus, more intense on looking toward the ipsilesional side; central patterns of head-shaking nystagmus (HSN); impaired smooth pursuit, greater ipsilesionally; and static contralateral ocular deviation. Of interest, head impulse VOR gains were decreased for the contralesional horizontal canal while the gains for both anterior canals were increased. These findings may be attributed to an imbalance in the loop connecting the NPH, inferior olive, flocculus, and vestibular nuclei [33].

Strokes involving the medial longitudinal fasciculus (MLF) cause diverse ocular motor and vestibular abnormalities in addition to internuclear ophthalmoplegia (INO) [34–36]. These include upbeat or jerky seesaw nystagmus, contraversive OTR and SVV tilt, impaired vertical VOR and smooth pursuit, and abnormal oVEMPs and cVEMPs [34–36]. Ten patients with INO due to strokes showed a prominent decrease in the VOR gain for the contralesional posterior canal (PC) during HITs [34]. This suggests that the MLF serves as a main passage for the high acceleration VOR from the contralateral PC. The associations and dissociations of the vestibular dysfunction in these patients indicate variable combinations of damage to the vestibular fibers ascending or descending in the MLF even in strokes causing isolated unilateral INO.

In midbrain lesions, rotational vertigo is rarely reported (14%) and mostly transient (< 1 day) even when present

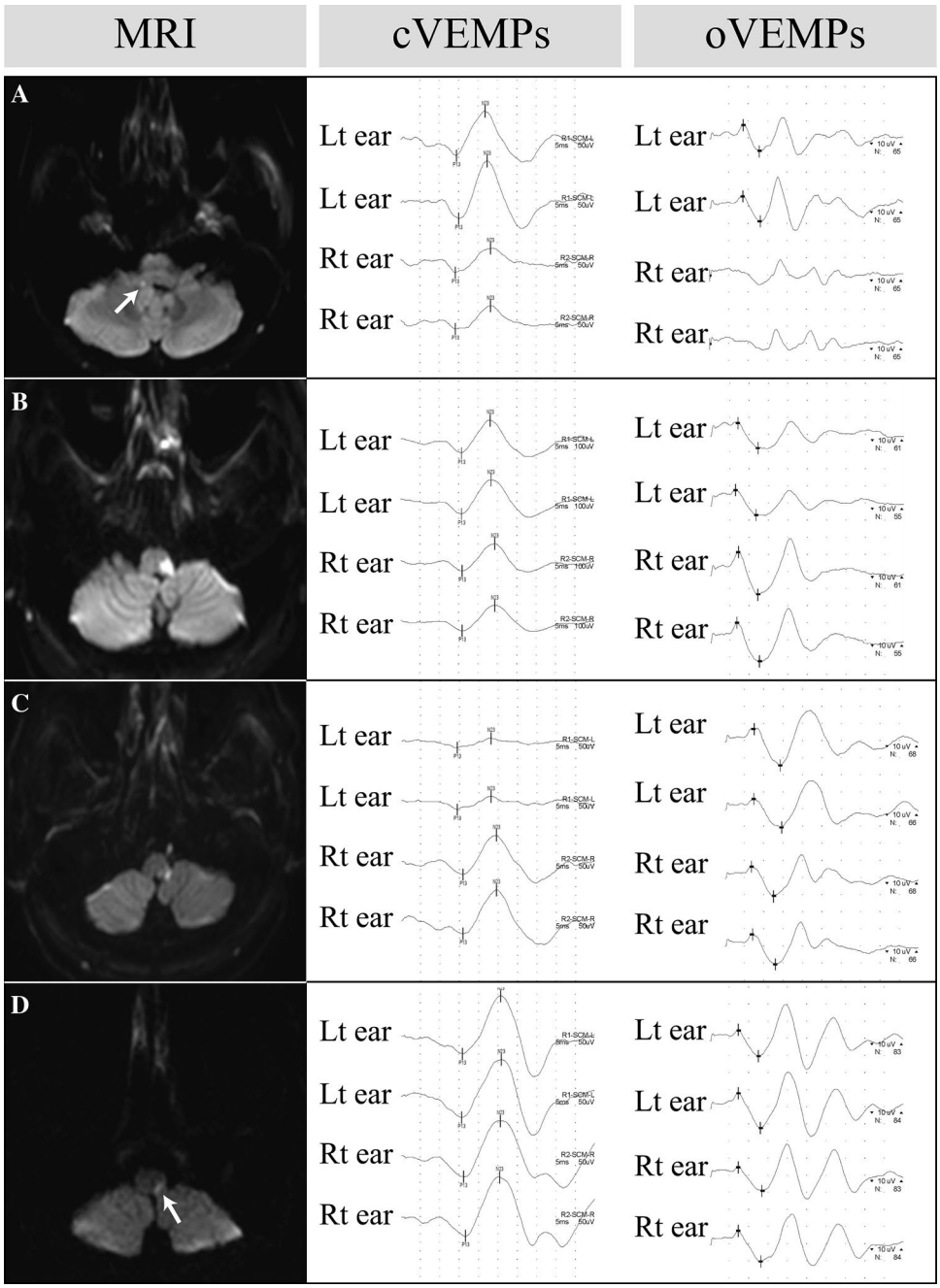

Fig. 2 Cervical and ocular vestibular-evoked myogenic potentials (VEMPs) from representative cases of lateral medullary infarction. **a** A patient with an infarction restricted to the medial vestibular nucleus shows a decreased amplitude of cervical VEMPs (cVEMPs) and absence of ocular VEMPs (oVEMPs) during stimulation of the ear on the lesion side. **b** A patient with an infarction in the middle medulla shows normal cVEMPs, but a decreased amplitude of oVEMPs (IADamp = 23.1%, normal range < 21.5%) during stimulation of the ear on the lesion side. **c** A patient with a caudal medullary infarction shows decreased amplitude of cVEMPs (IADamp = 47.0%, normal range < 22.5%) but normal oVEMPs during stimulation of the ipsilesional ear. **d** A patient with a caudal medullary infarction shows normal cVEMPs and oVEMPs (Adapted from Ref. [31])

[37]. In midbrain strokes, transient rotational vertigo is mostly associated with lesions involving the caudal tegmentum while swaying or unspecific dizziness is mostly described in lesions involving the rostral midbrain or meso-diencephalic junction [37]. Using a mathematical neural network model of the head direction cell system, it was postulated that unilateral dysfunction of the angular velocity cell system generates rotational vertigo while unilateral dysfunction of the head direction cell system leads to dizziness or unsteadiness [37].

Deviation of the perceived verticality in the roll plane may occur in acute unilateral lesions involving the pathways from the vertical semicircular canals or otolith organs via the vestibular nuclei and thalamus to the parieto-insular vestibular cortex [38–40]. Other signs in the roll plane include ocular torsion, skew deviation, and head tilt, which are termed as the OTR. While unilateral lesions from the labyrinth to the rostral midbrain tegmentum result in complete OTR or its ocular motor components, only perceptual tilts determined by SVV tilts occur in lesions affecting the centromedial or

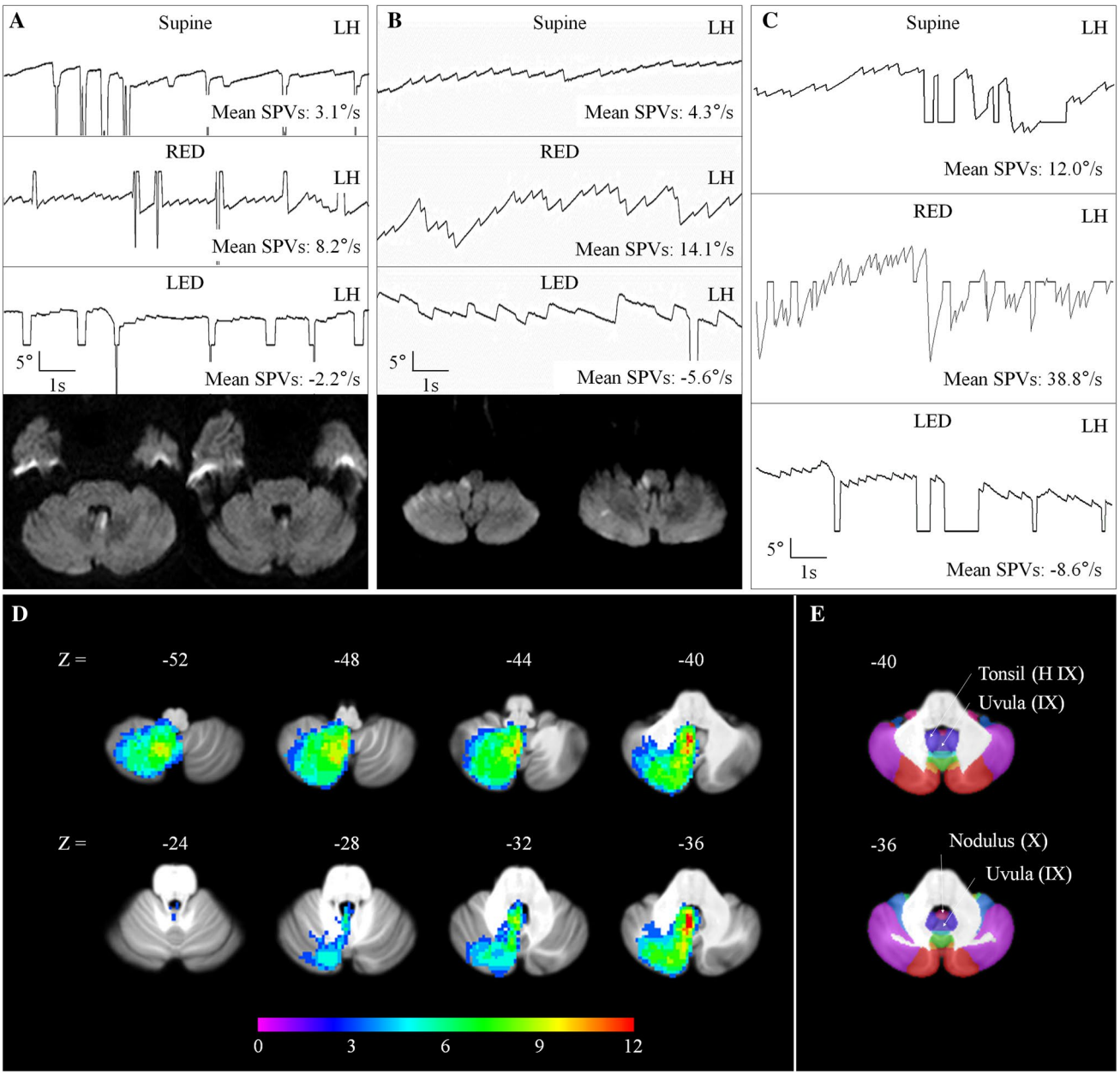

Fig. 3 Illustration of spontaneous and apogeotropic nystagmus in CPN group and overlay lesion plots in 22 patients with apogeotropic CPN from unilateral lesions. **a** A patient with a left-sided nodulus lesion shows ipsilesional left-beating nystagmus while supine and apogeotropic nystagmus in the ear-down position to either side with the ipsiversive left-beating positional nystagmus greater than the contraversive right-beating one. **b** Another patient with infarctions involving right lateral medulla and cerebellum shows contralesional left-beating nystagmus while supine and greater ipsiversive nystagmus in right ear-down position. In each recording, upward deflection indicated rightward eye motion. **c** A patient with apogeotropic BPPV involving the left horizontal semicircular canal shows ipsilesional left-beating nystagmus while supine and apogeotropic nystagmus during head turn to either side while supine. The ipsiversive left-beating nystagmus in the right ear-down position was stronger than the contraversive right-beating nystagmus in the left ear-down position. **d** The lesions are mostly overlapped (red color) in the nodulus (X), uvula (IX), and tonsil (H IX) on the spatially unbiased atlas template of the cerebellum and brainstem (SUIT, ver. 2.5.3). The numbers of overlapping lesions are illustrated by different colors from violet ($n=1$) to red ($n=12$). **e** Illustration of the areas corresponding to the nodulus, uvula, and tonsil in two representative templates of the SUIT (adapted from Ref. [41]). *LH* horizontal position of the left eye. *SPV* slow-phase velocity

posterolateral vestibulo-thalamic subnuclei or the parieto-insular vestibular cortex (PIVC), which are either ipsilateral or contralateral with a lesser degree compared to those observed in the brainstem lesions (thalamus: mean 3°–5°, cortex: mean 4°–6°, brainstem, mean 8°–14°) [40]. Traditionally, the effect of unilateral peripheral lesions on

perceived verticality has been attributed to a lesion-based bias of the otolith system [38, 39]. However, using a neural network model, it was proposed that perceived visual tilt after peripheral lesions is due to the effect of a torsional semicircular canal bias on the central gravity estimator [40].

Cerebellar strokes

The vestibulocerebellum, especially the nodulus and uvula, is involved in estimation of the gravity direction and in generation of the translational VOR using the convergent inputs from the semicircular canals and otoliths. Patients with cerebellar infarctions affecting the nodulus and uvula may show positional nystagmus (apogeotropic nystagmus in the ear-down position and downbeat nystagmus in straight head-hanging position) [41–44], transient downbeat nystagmus after horizontal head-shaking (perverted nystagmus) [45–47], and diminished tilt suppression of the post-rotatory nystagmus [46]. A recent study identified the characteristics, lesion locations, and mechanism of apogeotropic central positional nystagmus (CPN) compared to apogeotropic benign paroxysmal positional vertigo (BPPV) [41]. In CPN, the lesions mostly overlapped in the vestibulocerebellum (nodulus, uvula, and tonsil, Fig. 3). It was postulated that the estimate of gravity direction is erroneously biased away from the true vertical when the tilt-estimator circuit in the brain malfunctions due to lesions involving the vestibulocerebellum. If the bias is toward the nose, when the head is turned to the side while supine, there would be sustained apogeotropic type of CPN because of an inappropriate feedback signal indicating that the head is rotating when it is not [41].

Tilt suppression of post-rotatory nystagmus is impaired in about one-third of the patients with cerebellar infarctions mostly involving the nodulus and uvula [46]. Transient downbeat nystagmus is usually found after horizontal head-shaking (perverted nystagmus) in association with cerebellar dysfunction, probably due to an enhanced central processing of the signals from the ACs [48]. Along with positional downbeat nystagmus and impaired tilt suppression, this cross-coupled HSN appears to indicate midline cerebellar dysfunction [46].

In humans, isolated floccular infarction is rare because the flocculus is mostly supplied by a branch from the AICA and the AICA also irrigates the dorsolateral pons and inner ear [49, 50]. Acute unilateral flocculus syndrome due to an infarction included spontaneous nystagmus beating to the lesion side, impaired ipsilesional pursuit, contraversive OTR and tilt of SVV, and increased VOR gains during lower-frequency and decreased gains during higher-frequency stimulations [49]. A recent study on another patient with an isolated flocculus infarction showed similar findings, but initially ipsilesional caloric paresis, reduced head impulse VOR gain only for the contralesional horizontal canal, and a complete contraversive OTR [50]. The caloric responses became normalized within a few weeks, but the abnormal HIT persisted for months in that patient [50].

Unilateral strokes involving the middle cerebellar peduncle (MCP) may produce acute vertigo and imbalance with distinct ocular motor abnormalities that include spontaneous horizontal/torsional nystagmus, gaze-evoked nystagmus, OTR, abnormal head impulse responses, and bilaterally impaired horizontal smooth pursuit [51].

Compliance with ethical standards

Conflicts of interest We have no disclosure of any competing interest.

Ethical approval for research involving human participants and/or animals All experiments followed the tenets of the declaration of Helsinki, and this study was approved by the Institutional Review Board.

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