Vertigo in brainstem and cerebellar strokes

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Purpose of review
The aim of this study is to review the recent findings on the prevalence, clinical features, and diagnosis of vertigo from brainstem and cerebellar strokes.

Recent findings
Patients with isolated vertigo are at higher risk for stroke than the general population. Strokes involving the brainstem and cerebellum may manifest as acute vestibular syndrome, and acute isolated audiovestibular loss may herald impending infarction in the territory of the anterior inferior cerebellar artery. Appropriate bedside evaluation is superior to MRI for detecting central vestibular syndromes. Recording of vestibular-evoked myogenic potentials is useful for evaluation of the central otolithic pathways in brainstem and cerebellar strokes.

Summary
Accurate identification of isolated vascular vertigo is very important since misdiagnosis of acute stroke may result in significant morbidity and mortality, whereas overdiagnosis of vascular vertigo would lead to unnecessary costly work-ups and medication.

Keywords
brainstem, cerebellum, dizziness, stroke, vertigo

INTRODUCTION
Approximately 20% of ischemic events are known to involve the neural structures supplied by the posterior (vertebrobasilar) circulation, and dizziness/vertigo is one of the most common symptoms of vertebrobasilar diseases [1]. In cerebrovascular disorders, the dizziness/vertigo usually accompanies other neurological symptoms and signs. Indeed, medical adage had taught us that isolated vertigo mostly comes from peripheral vestibular diseases. However, isolated vascular vertigo might have been underestimated. With recent developments in clinical neurotology and neuroimaging, diagnosis of isolated vertigo from brainstem and cerebellar strokes has increased markedly (Fig. 1). Furthermore, transient isolated vertigo is the common manifestation of vertebrobasilar insufficiency [2].

It is important to differentiate isolated vertigo of a vascular cause from more benign disorders involving the inner ear since therapeutic strategy and prognosis differ in these two conditions. Misdiagnosis of acute stroke may result in significant morbidity and mortality, whereas overdiagnosis of vascular vertigo would lead to unnecessary costly work-ups and medication.

THE ACUTE VESTIBULAR SYNDROME AND STROKE
Acute vestibular syndrome (AVS) is characterized by rapid onset of vertigo, nausea/vomiting, and gait unsteadiness in association with head motion intolerance and nystagmus lasting days to weeks [3,4]. Most patients with AVS have acute peripheral vestibulopathy, but some may harbor brainstem or cerebellar strokes.
Prevalence of stroke in acute vestibular syndrome

In previous studies, dizziness and vertigo accounted for 3.3% of visits to an emergency department (ED) [5], and stroke was responsible for 3.2–4.0% of them [5,6]. A study also reported that only 0.93% of patients discharged home with a diagnosis of dizziness/vertigo at ED developed a major vascular event during a follow-up of 180 days [7]. However, another study found that those patients had two-fold [95% confidence interval (CI) 1.35–2.96, \( P < 0.001 \)] higher risk of stroke or cardiovascular events than the patients without dizziness/vertigo during a follow-up of 3 years [8]. The authors also demonstrated that the patients hospitalized with isolated vertigo have a 3.01 times (95% CI 2.20–4.11, \( P < 0.001 \)) higher risk for stroke than the general population during the 4-year follow-up [9**]. Particularly, the vertigo patients with three or more risk factors have a 5.51-fold higher risk for stroke (95% CI 3.10–9.79, \( P < 0.001 \)) than those without risk factors [9**].

Another study adopted the ABCD² score [10], a clinical prediction tool to assess the risk of stroke after a transient ischemic attack, to predict cerebrovascular events in ED patients with dizziness [11*]. The authors found that only 1.0% of patients with a score of 3 or less had a cerebrovascular event compared to 8.1% of the patients with a score of 4 or more [11*]. Especially, 27.0% of the patients with a score of 6 or 7 suffered from cerebrovascular episodes [11*]. Thus, the ABCD² score may predict cerebrovascular attacks in patients with transient vertigo.

Bedside diagnosis of stroke in acute vestibular syndrome

It is not always easy to differentiate isolated vascular vertigo from acute peripheral vestibulopathy at the bedside. However, a previous study showed that a three-step bedside oculomotor examination for HINTS [normal horizontal head impulse test (HIT), direction-changing nystagmus, and skew deviation) is more sensitive for stroke than early MRI whilst maintaining a high specificity [4,12**]. Indeed, initial diffusion-weighted MRI may be false-negative in 12–20% of stroke patients within the first 48 h [4,12**]. A recent study also confirmed diagnostic utility of the signs including normal horizontal HIT, skew deviation, abnormal vertical smooth pursuit, and central type nystagmus at the bedside: they found a 100% sensitivity and 90% specificity for stroke if one of those signs was present in AVS [13]. Since mild degree of skew deviation usually goes unnoticed during the bedside examination and gaze-evoked nystagmus (GEN) is also sometimes absent in cerebellar stroke, bedside HIT may be the best tool for differentiating isolated vertigo due to cerebellar stroke from acute peripheral vestibulopathy. However, bedside HIT has some limitations, and may be positive in patients with cerebellar or brainstem strokes [14–16].

Lesion sites of stroke in acute vestibular syndrome

In AVS due to stroke, the lesions are mostly found in the cerebellum, usually in the territory of the posterior inferior cerebellar artery (PICA) [17]. A patient with recurrent asystole due to sick sinus syndrome showed downbeat nystagmus during the presyncopal attack with vertigo [18], which suggests that the inferior cerebellum is vulnerable to hypoperfusion. In the brainstem, small infarction restricted to the vestibular nuclei may mimic acute
period peripheral vestibulopathy [19,20]. Accordingly, the clinical examination in AVS should be detailed enough to detect subtle central signs such as impaired fixation suppression of the nystagmus, skew deviation, and normal HIT in addition to normal calorics [19–21]. Conventional angiography or perfusion imaging may help diagnosis of AVS due to vascular compromise [22,23,24*]. Occasionally, serial evaluation is required to confirm stroke in AVS since MRI cannot detect isolated labyrinthine infarction that may progress and involve the portions of the brainstem and cerebellum supplied by the anterior inferior cerebellar artery (AICA) [21,25].

VESTIBULAR DYSFUNCTION IN BRAINSTEM STROKE

Since the brainstem contains the neural structures involved in the integration and conveyance of the vestibular signals, brainstem lesions gives rise to various vestibular symptoms and signs. Of them, nystagmus is the most important finding, and several reports have recently described characteristics of various forms of nystagmus from brainstem lesions. Also, several studies have explored vestibular-evoked myogenic potentials in brainstem lesions.

Nystagmus in brainstem stroke

Upbeat nystagmus mostly occurs in brainstem lesions, but exact mechanisms remain to be elucidated [26]. In view of exponentially decreasing slow phases and disobedience to Alexander’s law, upbeat nystagmus was ascribed to unstable as well as leaky neural integrator for vertical gaze [27,28]. Upbeat nystagmus may occur in extrinsic lesions compressing the medulla [27], or in intrinsic pathologies involving the medulla [29]. In the medulla, upbeat nystagmus has been ascribed to damage of the nucleus intercalatus and nucleus of Roller, or the cell groups of the paramedian tract (PMT). In another patient with bilateral internuclear ophthalmoplegia (INO) from dorsal pontine infarction, interruption of the projections from the interstitial nucleus of Cajal to PMT or to the nucleus intercalatus and nucleus of Roller has been invoked [28].

Acquired pendular nystagmus is commonly encountered in multiple sclerosis and in brainstem stroke as the syndrome of oculopatalatal tremor [30]. In contrast to acquired pendular nystagmus in multiple sclerosis, the nystagmus in oculopatalatal tremor has a larger amplitude, higher peak velocity, lower frequency, and larger asymmetry and irregularity of the ocular oscillations [31**].

Seesaw nystagmus indicates conjugate torsional nystagmus with dissociated vertical components. The pendular form of seesaw nystagmus is mostly observed in association with chiasmal anomaly or visual loss, whereas jerky seesaw nystagmus has been reported in lesions involving the brainstem from the medulla to upper midbrain. A recent study explored three distinctive patterns and mechanisms of jerky seesaw nystagmus in INO mostly from brainstem infarction [32**]. Of the 33 patients, 11 (33%) showed ipsiversive torsional nystagmus in both eyes with the vertical components in the opposite directions, whereas 18 (55%) had ipsiversive torsional nystagmus with a larger upbeat component in the contralesional eye, and 4 (12%) exhibited ipsiversive torsional nystagmus with a greater downbeat component in the ipsilesional eye. These patterns of jerk seesaw nystagmus in INO suggest a disruption of neural pathways from the contralateral vertical semicircular canals with or without concomitant damage to the fibers from the contralateral utricle.

Several case reports have described various patterns of induced nystagmus in brainstem strokes. Perverted head-shaking nystagmus (HSN) refers to nystagmus that develops in a plane other than that being stimulated by the head-shaking, and usually indicates cerebellar lesion. However, perverted HSN (downbeat nystagmus after horizontal head-shaking) may occur in focal tegmental pontine infarction [33]. Paroxysmal positional upbeat nystagmus may be observed in a small pontine infarction restricted to the area of ventral tegmental tract [34], and apogeotropic nystagmus in infarction involving the dorsolateral medulla where the nucleus prepositus hypoglossi is located [35].

Otolithic dysfunction in brainstem stroke

Vestibular-evoked myogenic potentials (VEMPs) have become important diagnostic tools to assess central otolithic pathways in brainstem and cerebellar lesions. Cervical VEMP (cVEMP), inhibitory potential recorded in the contracting sternocleidomastoid muscles, may be abnormal in patients with lateral medullary infarction (Wallenberg syndrome) in either the ipsilesional or contralesional side [36,37]. However, the abnormality of cVEMP did not correlate with the presence of ocular tilt reaction/tilt of the subjective visual vertical, spontaneous nystagmus, or HSN [36]. The abnormal cVEMP in Wallenberg syndrome indicates a direct damage to the sacculocollic reflex pathway or disruption of commissural modulation between the vestibular nuclei [36]. Ipsilesional cVEMP was also abnormal in half of the patients with medial
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Vertigo in cerebellar stroke

Cerebellar stroke is one of the most common causes of central AVS of a vascular cause. Dizziness/vertigo is the most common symptom of cerebellar stroke, and may be isolated, especially when the lesions are restricted to the territory of the medial PICA [17]. Indeed, about 17% of patients with PICA territory infarction simulated acute peripheral vestibulopathy [17]. Anterior inferior cerebellar artery infarction is characterized by acute audiovestibular loss with or without other neurological symptoms and signs from brainstem or cerebellar involvement [46]. In a previous study, eight subtypes of AICA infarction was proposed according to the pattern of neurotological presentations, and combined loss of auditory and vestibular function was the most common type [46]. Since isolated labyrinthine damage may precede ponto-cerebellar involvement in AICA infarction, audiovestibular loss may serve as a window to prevent the progression into more widespread infarction involving the posterior circulation, mainly in the AICA territory [46,47]. Clinicians should keep it in mind that acute audiovestibular loss may herald impending AICA territory infarction, especially when patients had basilar artery occlusive disease close to the AICA origin, even though other central signs are absent and MRI does not demonstrate acute infarction [46,47].

Nystagmus in cerebellar stroke

Gaze-evoked nystagmus is an invaluable sign indicating central vestibular dysfunction. In a recent study on horizontal GEN in 21 patients with acute unilateral cerebellar stroke, unidirectional GEN was found in 33% of the patients and the nystagmus was directed either toward or away from the lesion side [48]. The structures responsible for unidirectional GEN included the pyramid, uvula, tonsil, and parts of the biventer and inferior semilunar lobules [48]. GEN may be a sign indicating damage to the midline and lower cerebellar structures. Of interest, however, none of the patients showed spontaneous nystagmus and none of the patients with GEN had a lesion in the flocculus, which is known to have a major role in the gaze-holding mechanism [48].

Another study found HSN in 51% (37/72) of patients with acute isolated cerebellar infarction mainly in the PICA territory [49]. The horizontal component of HSN constantly beat to the lesion side. Perverted HSN occurred in 23 (23/37, 62%) patients and was mostly downbeat (22/23, 96%). Lesion subtraction analyses revealed that damage to the uvula, nodulus, and inferior tonsil was mostly responsible for generation of HSN in patients with unilateral PICA territory infarction. The authors ascribed the ipsilesional HSN to unilateral disruption of uvulonodular inhibition over the velocity storage. In contrast, perverted HSN was explained by impaired control over the spatial orientation of the angular vestibulo-ocular reflex due to uvulonodular lesions or a build-up of vertical

medullary infarction, especially when the lesions extended to the dorsal tegmentum where the medial longitudinal fasciculus (MLF) locates [38]. These findings supports that cVEMP is mediated by the inhibitory medial vestibulospinal tract that descends within the MLF [38], cVEMP may be abnormal in pontine infarction above the level of the vestibular nuclei, which suggest 'supravestibular' modulation of cVEMP responses [37].

Ocular VEMPs (oVEMPs), the crossed excitatory otolith-ocular responses, may be abnormal in more than half of the patients with mostly acute brainstem infarction [39]. The main lesion sites responsible for abnormal oVEMPs corresponded to the MLF, the crossed ventral tegmental tracts, and the oculomotor nucleus [39]. Complementary to cVEMP, oVEMP may be adopted to assess the ascending otolith-ocular reflex pathways in brainstem strokes.

In patients with skew deviation caused by brainstem or cerebellar lesions including strokes, the significant reduction in the gain of ocular counter-roll indicates a disruption of the utriculo-ocular pathway as the mechanism of skew deviation [40].

VESTIBULAR DYSFUNCTION IN CEREBELLAR STROKE

The proportion of cerebellar infarction in larger series of stroke patients is approximately 1.5% with an average age of the patients at about 60 years [41,42]. Cerebellar hemorrhage represents approximately 10% of all cerebellar strokes [42]. Correct identification of cerebellar stoke is important for proper management and better prognosis, especially during the acute phase. Patients with cerebellar infarction should undergo evaluation for embolism from the heart or great vessels to prevent recurrences [43]. Cerebellar infarction may develop a mass effect in 10–25% of cases and PICA territory infarcts are more likely to produce a mass effect than infarctions in the territory of the superior cerebellar artery (SCA) [41,44]. Large cerebellar infarction can cause brainstem compression, leading to hydrocephalus, cardio-respiratory complications, coma, and death [45].

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vestibular asymmetry favoring upward bias due to lesions involving the inferior tonsil [49**]. In AICA infarction, HSN is also common with both peripheral and central patterns. Careful evaluation of HSN may provide clues for AICA infarction in patients with acute audiovestibular loss [50]. To understand full characteristics of cerebellar HSN, however, further studies are required in patients with infarctions involving the SCA territory.

**Vestibular function tests in cerebellar stroke**

Little has been known on long-term outcome of vestibular loss associated with cerebellar infarction. A recent study found that caloric responses became normal in about 70% (20/30) of the patients with caloric paresis associated with posterior circulation ischemic stroke when followed up for at least 1 year [27,51]. Moreover, all the patients with a follow-up more than 5 years after stroke onset showed normalization of the caloric responses although the mechanism underlying this recovery is unclear [51].

Vestibular-evoked myogenic potentials were also explored in cerebellar strokes. In AICA infarction, a half of the patients showed abnormal cVEMPs in response to click sounds in the lesion side [52]. Patients with abnormal cVEMPs are more likely to have caloric paresis or sensorineural hearing loss, compared with those with normal cVEMPs. These findings suggest that peripheral vestibular structure plays a crucial role in producing abnormal cVEMPs in AICA infarction [52]. Abnormal cVEMPs may indicate adjacent brainstem involvement in patients with cerebellar stroke [53].

**CONCLUSION**

Patients with isolated vertigo are at higher risk for stroke than the general population. Strokes involving the brainstem and cerebellum may manifest as AVS. Isolated acute audiovestibular loss may herald impending AICA territory infarction. Detailed bedside examination is superior to MRI for detecting central vestibular syndromes. Recording of vestibular-evoked myogenic potentials is useful for evaluation of the central otolithic pathways in brainstem and cerebellar strokes.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 107).

9. Lee CC, Su YC, Ho HC, et al. Risk of stroke in patients hospitalized for isolated vertigo: a four-year follow-up study. Stroke 2011; 42:48–52. This study demonstrated that patients hospitalized with isolated vertigo have higher risk for stroke than the general population, and the vertigo patients with three or more risk factors have a higher risk for stroke than those without risk factors.
24. Noh Y, Kwon OK, Kim HJ, et al. Rotational vertebral artery syndrome due to compression of nondominant vertebral artery terminating in posterior inferior cerebellar artery. J Neurol 2011; 258:1775–1780. The patient described in this study clearly showed that isolated vertigo and nystagmus may occur due to transient ischemia of the inferior cerebellum or lateral medulla.