Recent advances in central acute vestibular syndrome of a vascular cause

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Abstract

Acute vestibular syndrome (AVS) is characterized by acute onset of spontaneous prolonged vertigo (lasting days), spontaneous nystagmus, postural instability, and autonomic symptoms. Peripheral AVS commonly presents as vestibular neuritis, but may also include other disorders such as Meniere's disease. Vertigo in central AVS due to vertebrobasilar ischemic stroke is usually accompanied by other neurological dysfunction. However, it can occur in isolation and mimicking peripheral AVS, particularly with cerebellar strokes. Recent large prospective studies have demonstrated that approximately 11% of patients with isolated cerebellar infarction presented with isolated vertigo mimicking peripheral AVS, and the bedside head impulse test is the most useful tool for differentiating central from peripheral AVS. Herein we review the keys to the diagnosis of central AVS of a vascular cause presenting with isolated vertigo or audiovestibular loss.

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1. Introduction

Acute vestibular syndrome (AVS) is characterized by acute onset of spontaneous prolonged vertigo (lasting days), spontaneous nystagmus, postural instability, and autonomic symptoms [1,2]. AVS can be divided into peripheral (i.e., inner and vestibular nerve) and central (i.e., brainstem and cerebellum) causes. The peripheral causes of AVS included acute vestibular neuritis (VN), Meniere's disease, and migraine. Vertebrobasilar ischemic stroke (VBIS) can also cause isolated prolonged vertigo mimicking peripheral AVS [3–5]. Recent studies have shown that cerebellar infarction mimicking central AVS is more common than previously thought and the bedside head impulse test (HIT) is the most useful tool for differentiating central AVS from more benign disorders involving the inner ear [4,5]. Clinically, it is important to differentiate central AVS of a vascular cause from
central AVS of a vascular cause

Vertigo is resulted from imbalance of tonic discharge of the vestibular systems arising from the inner ears on both sides. The origin of vertigo may be peripheral or central. When the vertigo occurs as a symptom of VBIS, it is usually associated with other neurological symptoms or signs [6]. Three possible structures responsible for central AVS of a vascular cause are the nodulus, root entry zone of the eighth nerve in the pontomedullary junction, and vestibular nucleus (Fig. 1). Theoretically, a small infarct localized to these structures can cause vertigo with no accompanying other neurological symptoms or signs since all of these structures receive afferent vestibular inputs from the inner ear (Fig. 2). Because none of these structures are known to be more sensitive to ischemia than other surrounding structures, the incidence of central isolated vertigo associated with ischemic stroke is low. Rarely, lesions involving the flocculus lobe or dorsal insular cortex can also cause isolated vertigo (Fig. 2) [7–9]. Vertigo due to a lesion involving the dorsal insular cortex is usually not associated with nystagmus and a flocculus lesion is commonly associated with other central signs with gaze-evoked nystagmus and asymmetrical oculomotor dysfunc-

tion [7,9]. Therefore, in such cases, clinicians may conclude that vertigo is caused by damage to the central vestibular structure.

3. Classification of central AVS

3.1. Cerebellar ischemic stroke

3.1.1. Frequency, pattern of involved vascular territory, and associated vestibular dysfunction

Vertigo is one of the commonest symptoms in patients with cerebellar stroke syndrome. Among cerebellar stroke syndrome, cerebellar ischemic stroke probably ranks first as central AVS of a vascular cause. A small retrospective study showed that as many as 25% of patients with vascular risk factors who presented to an emergency medical setting with isolated severe vertigo, nystagmus, and postural instability have a cerebellar infarction in the territory of the medial branch of the PICA (mPICA) [10]. A recent large prospective study on clinical findings of 240 patients with isolated cerebellar infarction also demonstrated similar results. In this study, about 11% (25/240) with isolated cerebellar infarction had isolated vertigo only and most (24/25: 96%) patients with isolated vertigo had an infarct in the territory of the mPICA including the nodulus [5]. Another more recent study using diffusion-weighted imaging found that 75% of patients with at least one vascular risk factor who presented with acute isolated vertigo had acute stroke, mostly involving the caudal cerebellum in the mPICA territory [4]. In PICA territory cerebellar infarction, the key structure responsible for vertigo is the nodulus. The nodulus is strongly connected to the ipsilateral vestibular nucleus and receives direct projections from the labyrinth [11,12]. Functionally, nodulovestibular Purkinje fibers have an inhibitory effect on the ipsilateral vestibular nucleus [11,12]. A predominant involvement of mPICA territory cerebellar infarction associated with central AVS may be explained in several ways. First, the mPICA usually supplies the nodulus, a part of the vestibulocerebellum [13]. Thus, infarction in the territory of the medial PICA can cause severe vertigo. Second, dysmetria, a major finding of the cerebellar lesion, may be minimal or absent after a cerebellar infarction in the territory of the mPICA if the size of an infarct is not large [5,14,15]. Third, gaze-evoked asymmetrical nystagmus, which commonly occurred in central vestibulopathy of cerebellar origin, is sometimes absent in the PICA territory cerebellar lesion [5,14–18]. Finally, hearing loss that is generally considered a peripheral sign commonly accompanies anterior inferior cerebellar artery (AICA) stroke, not PICA stroke [19]. Since the superior cerebellum supplied by the superior cerebellar artery (SCA) does not have significant vestibular connections, cerebellar infarction in the SCA territory rarely causes vertigo [20,21]. The vestibulo-ocular portion of the cerebellum is located primarily in the flocculonodular lobes, which are supplied by branches of the AICA and PICA. The low incidence of vertigo in SCA distribution may be a useful clinical distinction from PICA or AICA cerebellar infarction in patients with acute vertigo and limb ataxia [20,21].

In PICA territory cerebellar infarction, the direction of nystagmus and degree of postural instability were variable. The prominent cerebellar signs, particularly severe axial instability and direction changing gaze-evoked nystagmus (occurring in 71% and 54%, respectively, in the aforementioned series [5]), can help in the differential, but these findings are less reliable. Similarly, perverted head shaking (mostly downbeating) and positional downbeating nystagmus as important signs of central vestibular dysfunctions are found in only half of the cases with cerebellar infarction [22]. In contrast, the vestibular dysfunction in some patients with PICA territory cerebellar infarction is similar to that in those with VN. For example, spontaneous unidirectional, ipsilesional nystagmus and mild postural instability with standing or walking independently could be seen in cases with PICA territory cerebellar infarction (occurring in 17% and 29%, respectively, in the aforementioned series [5]). The mechanism of spontaneous unidirectional, ipsilesional nystagmus may have
involved an increased tonic activity of ipsilesional medial and superior vestibular nucleus neurons, caused by disconnection of inhibitory nodulovestibular Purkinje fibers from neurons in the vestibular nuclei [16–18]. The nystagmus in PICA territory cerebellar infarction involving the nodulus may be contrasted with that of a unilateral VN, in which the tonic resting firing rate of semicircular canal afferents is decreased and contralesional nystagmus is due to unopposed activity of the intact vestibular nucleus. Overall, although the severity of imbalance and the appearance of nystagmus in PICA territory cerebellar infarction can help in differentiating central AVS from VN, these findings are less reliable for differentiating two conditions. PICA territory cerebellar infarction should be considered in the differential diagnosis of central AVS, even if the nystagmus and imbalance are more typical of VN.

3.1.2. Clinical implication of central AVS due to cerebellar ischemic stroke from the standpoint of mechanism of stroke

Isolated vertigo associated with cerebellar infarction (mainly in the distribution of the PICA) may give clinicians two important messages. First, although small PICA territory cerebellar infarction causing vertigo generally has a benign prognosis, isolated PICA territory cerebellar infarction usually results from emboli originating from the heart or great vessels [23], and recurrent emboli should need to be treated. Second, patients with cerebellar infarction may have isolated vertigo with no other cerebellar signs, even though there is a relatively large size of a lesion on brain MRI because the threshold of damage to the central nervous system for producing neurological symptoms or signs appears to be different in individuals and other areas of the cerebellum may be able to compensate for the mPICA territory damage. These situations have been previously reported in the literature [5,24]. Cerebellar infarction may develop a mass effect in 10% to 25% of cases and PICA territory infarcts are more likely to produce a mass effect than SCA territory infarcts [25,26]. Large PICA territory cerebellar infarction can cause brainstem compression, hydrocephalus, cardiorespiratory complications, coma, and death [27–29]. Thus, in view of the different therapeutic strategies and potentially grave prognosis of the strokes involving the vertebrobasilar artery territory, it is of great importance to differentiate central AVS of a vascular cause from more benign disorders involving the inner ear.

3.2. Central AVS associated with brainstem ischemia

As noted above, the central vestibular system located in the brainstem is not more vulnerable to ischemia than other surrounding structures. Thus, mono-symptomatic attacks of vertigo and nystagmus without any other brainstem symptoms and signs would be unusual in brainstem ischemia. Selective damage to the vestibular nucleus and root entry zone of the eighth nerve in the pontomedullary junction can cause isolated vertigo [30–34]. Because the root entry zone of the eighth cranial nerve has a rich network of anastomotic vessels arising from the lateral medullary artery, anterior inferior cerebellar artery, inferior lateral pontine artery, and arteries supplying adjacent dura matter and petrous bone [35,36], the possibility of focal infarction in that area is extremely low in a clinical practice. There were case reports of central AVS due to a demyelinating lesion localized to the root entry zone of the eighth nerve [30,31], but isolated vertigo due to focal infarction in the root entry zone of the vestibular nerve was not available in the literature. Focal ischemia in the vestibular nucleus can cause isolated vertigo and nystagmus mimicking acute VN [32–34]. Recently there was one case report [32] of a patient with an isolated vestibular nucleus infarction who presented with isolated prolonged vertigo, spontaneous horizontal nystagmus with a torsional component, a positive head impulse test result, and unilateral canal paresis to caloric stimulation. All of these findings are consistent with VN. This report emphasized that isolated vestibular nucleus infarction should be considered in the differential diagnosis of central vascular vertigo syndrome, especially when the patient has unilateral canal paresis, but other neurologic symptoms or signs are absent. Vertigo in the lateral medullary infarction is usually associated with other neurological symptoms or signs, but tiny infarct in the lateral medulla can present with vertigo without other localizing symptoms [37]. In this case, the HIT might be positive, if medial vestibular nucleus is involved.

4. Which of the neurological examinations at the bed side is most useful for differentiating central AVS from more benign disorders involving the inner ear?

If a patient showed signs of central vestibular dysfunction such as vertical nystagmus in the primary position, direction changing gaze-
evoked nystagmus, perverted head shaking nystagmus, asymmetrical oculomotor dysfunction, or severe postural instability with falling during the attack of vertigo, clinician can easily discern that vertigo is originated from the central vestibular dysfunctions. However, as mentioned above, these central signs do not always appear in each patient with central vertigo. It is generally considered that the bedside HIT and caloric test are useful tools for differentiating central AVS from a more benign disorder involving the inner ear. Normal HIT and caloric test results are regarded as reliable signs for an intact peripheral vestibular function, thus suggesting a central lesion. The major advantage of the HIT, in addition to the convenience factor (i.e., bedside HIT with no special equipment required) is the fact that it rarely causes vomiting whereas caloric test is potnet at this. Further, in the presence of significant spontaneous nystagmus, caloric testing is unreliable. More recently, video HIT has been validated in selected vestibular disorders [38] and it has the advantage over bedside HIT in distinguishing spontaneous nystagmus from the vestibulo-ocular reflex (VOR) slow phase response. Finally, HIT reflects the functional status of the vestibulo-ocular reflex (VOR) needed in locomotion (i.e., high frequencies of VOR) whereas caloric test assesses the low-frequency range of VOR [39]. Because about 17% of patients with PICA territory cerebellar infarction present with pseudo-VN [5], stroke patients should be evaluated with the HIT. The significance of HIT for differentiating stroke from VN has been confirmed by another recent paper [4] that showed that a negative HIT result (i.e., normal vestibulo-ocular reflex) is strongly suggestive of a central lesion with a pseudo-VN presentation. However, bedside HIT has several limitations, in which the covert saccade during the head rotation (instead of overt saccade after head rotation) is almost impossible to detect by simple visual observation at the bedside [40], and spontaneous nystagmus during the acute period also interferes with assessment of bedside HIT. Accuracy of the bedside HIT is also influenced by examiner’s experience [41]. It is well known that experienced examiners are more conservative, whilst novices tend to overcall. Furthermore, lateral pontine lesion encompassing the root entry zone of the eighth nerve can cause a positive HIT result, causing a peripheral lesion to be mistakingly suspected. Because of the limitations of bedside HIT, 9% to 30% of positive bedside HIT results have been reported in patients with cerebellar or brainstem strokes [4,42]. Diagnostic accuracy of bedside HIT for differentiating central AVS from VN may be enhanced if other central signs are included for differentiating two isolated vertigo syndromes. A refined bedside examination protocol that combined HIT with search for direction-changing nystagmus in eccentric gaze or skew deviation was 100% sensitive and 96% specific for identification of stroke, whereas the initial diffusion weighted MRI missed 12% of them [4]. Another recent report also showed similar findings that sensitivity and specificity for identification of stroke was 100% and 90%, respectively if one of the following signs suggestive of a central lesion was present: normal bedside HIT, central type nystagmus, skew deviation, or abnormal vertical smooth pursuit [43]. Since mild degree of skew deviation usually goes unnoticed during the bedside examination and gaze-evoked nystagmus is also sometimes absent in the central AVS, HIT at the bedside can be the best tool for differentiating central AVS from a more benign disorder involving the inner ear although bedside HIT has some limitations. The normal caloric test is also considered a reliable sign of an intact peripheral vestibular function. Overall, the most consistent bedside predictor of central AVS of a vascular cause appears to be the HIT and normal HIT result usually guarantees an absence of peripheral pathology [4,5,43-45]. Differential diagnostic points for central and peripheral AVS are summarized in Table 1.

5. Why infarction in the territory of the anterior inferior cerebellar artery (AICA) seldom serves as a common cause of central AVS of a vascular cause presenting with isolated vertigo?

Like mPICA cerebellar infarction, AICA territory infarction usually gives rise to acute prolonged vertigo. However, AICA territory ischemic stroke seldom leads to the central AVS of a vascular cause presenting with isolated vertigo because there is nearly always associated unilateral hearing loss (due to mostly cochlear ischemia) and most patients will have multiple brain stem signs such as facial palsy, Horner syndrome, or crossed sensory loss [19,46,47]. Furthermore, in the AICA syndrome, the patients usually showed severe imbalance with falling and direction-changing, gaze-evoked, asymmetrical nystagmus (Bruns’ nystagmus), whereas patients with peripheral AVS always can stand or walk without support and have direction fixed, gaze-evoked nystagmus beating toward the intact side [1,6]. A recent report showed that only 5% of patients with AICA territory ischemic stroke presented with acute prolonged vertigo and canal paresis to caloric stimulation without hearing loss, mimicking peripheral AVS [48]. Indeed, AICA territory infarction usually leads to acute audiovestibular loss with severe vertigo and hearing loss (i.e., acute labyrinthine infarction) rather than isolated vestibular loss.

Table 1

<table>
<thead>
<tr>
<th>Common causes</th>
<th>PICA-Caudal cerebellum including nodulus, lateral medulla</th>
<th>AICA-pons/Root entry zone/ labyrinth</th>
<th>Vestibular nucleus</th>
<th>Vestibular neuritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated vertigo</td>
<td>Possible, common</td>
<td>Possible, uncommon</td>
<td>Possible, uncommon</td>
<td>Almost always</td>
</tr>
<tr>
<td>Caloric canal paresis</td>
<td>None</td>
<td>Normal</td>
<td>Abnormal, if medial subnucleus involved</td>
<td>Abnormal, if superior or complete vestibular nerve involved</td>
</tr>
<tr>
<td>Bedside head impulse test</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Abnormal, if medial subnucleus involved</td>
<td>Abnormal, if superior or complete vestibular nerve involved</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Ipsilesional (cerebellum), ipsilesional or contralateral (lateral medulla)</td>
<td>Common</td>
<td>Ipsilesional or contralateral</td>
<td>Rarely</td>
</tr>
<tr>
<td>Spontaneous nystagmus</td>
<td>Direction-changing (Brun’s)</td>
<td>Unidirectional</td>
<td>Variable</td>
<td>Unidirectional</td>
</tr>
<tr>
<td>Effect of gaze on nystagmus</td>
<td>Unidirectional</td>
<td>Unidirectional</td>
<td>Variable</td>
<td>Unidirectional</td>
</tr>
<tr>
<td>Skew deviation</td>
<td>Variable, typically Direction-changing</td>
<td>Variable</td>
<td>Variable</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Side of truncal deviation</td>
<td>Unilateral</td>
<td>Unilateral</td>
<td>Unilateral</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Postural instability</td>
<td>Ischemic</td>
<td>Ischemic, demyelination</td>
<td>Ischemic</td>
<td>Viral, idiopathic</td>
</tr>
<tr>
<td>Common causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Direction-fixed unidirectional gaze-evoked nystagmus beating toward the healthy side.
* Direction-changed bidirectional gaze-evoked nystagmus that the intensity was maximal when gaze to the lesion side.
6. Prolonged vertigo and hearing loss as the presenting symptoms of VBIS may be misdiagnosed as Meniere’s disease

Recent papers have shown that 8–30% of patients with posterior circulation ischemic stroke (mainly AICA territory) had acute audiovestibular loss with vertigo, fluctuating hearing loss and/or tinnitus before more widespread infarction and at this stage, patient may be misdiagnosed as having peripheral pathology with Meniere’s disease [47–49]. Selective ischemia to the inner ear can explain isolated prodromal audiovestibular disturbance because the inner ear requires high-energy metabolism and has little collateral circulation [50–52]. Although there are as yet no systematic data on what a high-risk factor suggesting impending stroke is or what interventions might be beneficial at the stage of isolated audiovestibular loss, patients with prodromal audiovestibular disturbance were more likely to have focal or diffuse stenosis of the basilar artery presumably close to the origin of the AICA than patients without audiovestibular disturbance [19,47,53]. This finding highlighted that AICA infarction should be considered, particularly in elderly patients with vascular risk factors and acute audiovestibular loss, even when MRI does not demonstrate acute infarction in the brain. At this stage, clinician should consider a further investigation and a proper management to prevent progression of acute audiovestibular loss into a more widespread posterior circulation stroke, mainly in the territory of the AICA. Because current diagnostic methods (including MRI) cannot confirm labyrinthine infarction among the acute audiovestibular loss syndrome, clinicians should consider all the clinical evidences when attempting to determine the etiology of acute audiovestibular loss rather than emphasizing that MRI is the best way to distinguish other pathology from vascular etiology. Illustrative case with recurrent vertigo and fluctuating hearing loss mimicking Meniere’s disease as initial symptoms of impending AICA territory cerebellar infarction is shown Fig. 3.

7. When does the patient with isolated vertigo need an urgent brain scan?

For patients with spontaneous prolonged vertigo, in addition to the obvious cases of associated neurological symptoms or signs, an urgent brain scan to rule out central vascular vertigo syndrome should be considered in 1) older patients presenting with isolated spontaneous prolonged vertigo, in 2) any patient with vascular risk factors and isolated spontaneous prolonged vertigo who had a normal NIH stroke, in 3) any patient with isolated spontaneous prolonged vertigo who had directional changing gaze-evoked nystagmus or severe gait ataxia with falling at upright posture, in 4) any patient presenting with acute spontaneous vertigo and new onset headache, especially occipital, and in 5) any patient with vascular risk factors and acute onset of vertigo and hearing loss without Meniere’s history [5,43]. Since brain CT is known to have less accuracy in detecting an acute ischemic lesion within the posterior fossa [29], brain MRI with diffusion image is considered the golden standard for diagnosis of isolated vertigo due to ischemic stroke.

Conflict of interest

All authors have reported no conflicts of interest.

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