Use of HINTS in the acute vestibular syndrome. An Overview

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ABSTRACT
Following the initial description of HINTS to diagnose acute vestibular syndrome (HAVS) in 2009, there has been significant interest in the systematic evaluation of HINTS to diagnose stroke and other lesions common causes of AVS in several studies ranged from the mid-50s to early 60s. This is an age group typically affected with multiple stroke risk factors, with high ABCD2 scores, and although VN is the most common cause of continuous vertigo and will also focus on vascular vertigo, which a common VN mimics (pseudoneuritis or pseudo-VN). The average age of affected patients in several studies ranged from the mid-50s to early 60s. This is an age group typically affected with multiple stroke risk factors, with high ABCD2 scores, and although VN is the presumable result of an acute viral infection of the superior vestibular nerve (VN) or autoimmune disorder, stroke involving the cerebellum or brainstem must be a consideration in the differential diagnosis.

INTRODUCTION
The AVS is the result of an acute unilateral peripheral or central vestibular lesion that causes a sudden asymmetry of the normal vestibular nuclei neuronal firing rate. Patients with an AVS experience vertigo, nausea and vomiting and head movement intolerance. By and large, the sudden onset of an AVS is associated with severe anxiety, largely due to the continuous and frequently intense illusion of rotation and the associated vasovagal response. The examiner looks for static (head still) and dynamic (head moving) ocular motor findings, related to alterations of the angular vestibulo-ocular reflex (VOR): nystagmus and head impulse test (HIT) gain, alterations of the vestibulo-spinal reflex: postural unsteadiness and gait imbalance are additional findings. The purpose of this chapter is to discuss the use of ‘HINTS’ on the diagnosis, triage and management of patients with AVS.

DEFINITION AND EPIDEMIOLOGY
The acute vestibular syndrome (AVS) is defined as the sudden onset of acute, ‘continuous’ vertigo (lasting longer than 24hours), associated with nausea, vomiting and head motion intolerance. The term was initially introduced by Hotson and Baloh in 1998. Vestibular neuritis (VN), the most common cause of an AVS, has an estimated annual incidence of 3.5 per 100 000 populations. It is also estimated that 10%–20% of dizzy patients visiting emergency departments (ED) have an AVS which corresponds to 25 000 to 500 000 annual ED visits in the USA alone. The second most common cause of an AVS is an ischaemic stroke involving the cerebellum or the brainstem (probably 5%–10% of all patients with AVS). Vertigo and nystagmus ranked as the most common symptom/sign in patients with posterior circulation stroke in The New England Posterior Circulation Registry. Pertinent to the subject of this chapter, I will focus on the AVS with VN as the first published as 10.1136/svn-2018-000160 on 23 June 2018. Downloaded from http://svn.bmj.com on April 4, 2024 by guest. Protected by copyright.

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study the function of the horizontal semicircular canal; further studies thereafter defined the quantitative parameters of caloric-induced horizontal nystagmus that are widely used to date; however, this diagnostic technique could not be easily performed at bedside. Additional bedside vestibular diagnostic manoeuvres to perform in comatose patients developed. Alfred Bielschowsky in 1939 introduced the ‘horizontal and vertical doll’s eyes manoeuvre’ intended to determine the anatomic and physiological integrity of the brainstem. Ice water caloric testing used for decades in brain death assessment protocols (2010 AAN Guideline) has no additional practical use at present time. However, the contribution from neuropathological developments, subsequently, highlighted the urgent need for more precise and expeditious diagnostic testing strategies to detect VN mimics such as cerebellar infarcts associated with malignant oedema and risk of death. To address these needs, clinicians developed new techniques based on the nystagmus characteristics. Thus, unidirectional horizontal nystagmus that follows Alexander’s law and increases with fixation block was the anticipated finding with benign peripheral vestibular lesions. However, this nystagmus pattern is frequent in central lesions and thus is not a localisation finding. On the other hand, horizontal gaze direction changing nystagmus is a specific sign of a central lesion. In addition, the presence of vertical or purely torsional nystagmus is the result of central lesions as well. Central nystagmus signs when present have high specificity but unfortunately are infrequent. Moreover, not infrequently, patients with central lesions have unidirectional nystagmus characteristics identical to those seen with peripheral lesions; therefore there was need to investigate additional signs or a test combination that would yield higher specificity. Nystagmus analysis alone provided evidence of central localisation in a small series of initially false-negative-stroke MRI patients.

In 1988, Halmagyi and Curthoys described the HIT of the angular VOR. Loss of the VOR in the AVS is associated with a positive horizontal head impulse test (h-HIT) which has been found consistently as a reliable sign of a peripheral vestibulopathy. Studies of patients with AVS with high stroke risk factors soon followed and used the horizontal HIT (h-HIT) as a possible sensitive and specific test to provide specific AVS lesion localisation. In an investigator-blinded study, the hypothetical central versus peripheral AVS diagnostic value of h-HIT was tested. Patients with AVS routinely underwent h-HIT testing, prior to imaging or if imaging was performed prior to the h-HIT, the results were concealed to the study investigator. Central AVS lesions were associated with a normal h-HIT, and this was the rule in strokes located in the m-PICA territory, involving either the cerebellum, the medulla or both. The clinical value of a normal h-HIT in patients with AVS with a false-negative stroke MRI was compelling enough to warrant repeat imaging which consistently demonstrated the stroke missed in the first MRI.

AICA territory strokes, however, continue to be a diagnostic challenge, as lesions affecting the vestibular root entry, fasciculus or nucleus may potentially be associated with a positive (abnormal h-HIT). To address the potential localisation dilemma, patients with AVS with large-slew deviation (>than 3-prism dioptres), favours central localisation; this finding in my experience is an excellent discriminator. Skew deviation is a sign of an abnormal otolith-ocular reflex (OOR); thus large amplitude skew deviation and the ocular tilt reaction (OTR) are more common with central lesions. While these two signs may be seen rarely with VN, other peripheral vestibulopathies such as postsurgical cases and severe bacterial inner ear otitis may be an exception to the rule. Gufoni integrated both nystagmus direction and skew deviation in a prospective study of patients with predominantly horizontal nystagmus, the fast phase either can be away from the hypertropic eye (called ‘downhill’) or towards the hypertropic eye (called ‘uphill’). Dr Gufoni proposed downhill nystagmus as a central marker and uphill nystagmus as a peripheral marker. However, when we retrospectively applied this concept to our previously published cohort, the uphill pattern was present in 18 central patients confirmed by imaging. A downhill pattern, on the other hand, was associated with central lesions.

The triad of h-HIT, horizontal, direction changing nystagmus and skew deviation compared with the results of MRI performed within 48 hours after symptom onset revealed that the combined value of the three ocular motor tests; provided greater sensitivity (100%) and specificity (96%). In the first submission, the title of the manuscript was ‘Subtle Eye Signs in AVS differentiate central from peripheral vestibular lesions’, however, one manuscript reviewer suggested a change in the title, and David Newman-Toker, M.D., PhD then coined the acronym: ‘HINTS’, widely used since then. The acronym refers to HI: Head Impulse, N: Nystagmus direction and TS: Testing Skew. In addition, a second acronym and mnemonic: INFARCT summarises the application of HINTS: IN: Impulse normal, FA: Fast Alternates (referring to the nystagmus fast phase) and RCT: Refixation on cover test (skew deviation).

Since the introduction of HINTS, there have been several papers using the diagnostic triad (table 1). HINTS has been more sensitive that DWI MRI in several reports, particularly in lacunar strokes. I intend to discuss the results of these studies. Will review in addition, the possibility of additional signs pointing to a central localisation.
under the family of HINTS PLUS signs.\(^{15,19}\) Importantly, graphic recording of h-HIT has been possible for the last few years, using Video head impulse goggles (vHIT). There are several advantages of these recordings which provide VOR gain values for all six semicircular canals, vHIT records both overt and covert saccades,\(^{iii}\) in addition, it records the number of corrective saccades, their latency and the detection of artefacts that may lead to equivocal clinical responses.\(^{25}\) We will discuss these new techniques and their potential application. The pilot phase of a clinical trial (AVERT Acute Video-Oculography for Vertigo in Emergency Rooms for Rapid Triage) to analyse the diagnostic and triaging impact of a vHIT protocol guided management of patient with AVS began in January 2016. David Newman Toker, M.D., PhD is the PI in the study with a three-site recruiting locations.

We will proceed with the description of each of the HINTS triad components as it is routinely performed in the evaluation of patients with AVS.

| Reference            | Year Location | Number of study patients | VN positive h-HIT | Stroke negative h-HIT | Stroke positive h-HIT | Stroke positive stroke MRI | False negative stroke MRI | Skew OTR | Direction changing h-nystagmus |
|----------------------|---------------|--------------------------|-------------------|-----------------------|-----------------------|---------------------------|--------------------------|-----------|-------------------------------|
| Newman-Toker et al   | 2008 USA      | 42                       | 8                 | 31                    | 3 (9%)                | 3                         | Exclusion criteria         | 9         | 14                            |
| Kattah et al         | 2009 USA      | 101                      | 25                | 62                    | 5                     | 8                         | 15 Stroke 1 VN             | 14        |                               |
| Choi et al           | 2014 Korea    | 34                       | Not Reported      | 33                    | 1                     | 6                         | 2                        | 4         |                               |
| Batuecas et al       | 2014 Spain    | 91                       | 83                | 7                     | 1                     | 0                         | 1                        | 4         |                               |
| Chen et al\(\ast\)   | 2014 Australia| 24                       | 14                | 8                     | 2                     | 0                         | 6                        | 1 VN      |                               |
| Kerber et al         | 2015 USA      | 272                      | 78                | 20                    | 4                     | 1                         | Included in HINTS Positive 12/79 | Included in HINTS Positive 17 |           |
| Carmona et al        | 2016 Argentina, Spain, Portugal, Israel | 114 | 72 | 32 | 7 (All AICA) | 0 | 27/114 4 VN | 24/42 |           |

Table 1 HIT positive: in favour of stroke diagnosis with either normal gain, vertical or purely torsional nystagmus or with horizontal, direction changing nystagmus with horizontal gaze positions

HIT, head impulse test; OTR, ocular tilt reaction; VN, vestibular neuritis.

and vertical nystagmus in patients with AVS with stroke risk factors.

Primary position spontaneous horizontal nystagmus that increases with fixation removal and follows Alexander’s law\(^{iv}\) is the rubric of VN and other peripheral vestibulopathies. The clinical examination of patients with AVS should begin therefore by analysing the direction of the nystagmus in all cardinal positions of gaze, followed by testing the effect of fixation block in each gaze position. Direct ophthalmoscopy and monocular occlusion introduced by David Zee, M.D. is very effective,\(^{26}\) the penlight test, described by Newman-Toker et al is also a helpful bedside technique to test the effect of fixation block. The patient covers one eye while the examiner shines a penlight in the fellow eye. The retinal bleach effect from sustained light exposure blocks fixation of the uncovered eye and enhances a latent vestibular nystagmus.\(^{27}\) Frenzel’s goggles and other recently designed portable goggles are additional options.\(^{28}\) Typically, peripheral vestibular lesions are associated with unidirectional nystagmus that increases in the gaze direction of the fast phase (Alexander’s law). This nystagmus pattern, however, may be seen with cerebellar or brainstem lesions.\(^{14,16,19}\) Clinicians must be alert to detect ‘pseudo-neuritis’ presentations due to stroke and other acute neurological syndromes. In the majority of the studies using the h-HIT, VN is associated

\(\ast\)These visual triggered saccades occur when the angular VOR is decreased as a result of primary vestibular dysfunction (periphery, root entry or vestibular nucleus). Overt Saccade: Catch-up saccade noted after a head impulse test. Covert saccade: Corrective saccade occurs during the head impulse test and cannot be detected without vHIT recording.

\(\ast\)The amplitude of the nystagmus increases in the gaze-direction of the primary position nystagmus fast phase.
with a positive HIT, unidirectional horizontal nystagmus that follows Alexander’s law, a negative MRI and a typical benign clinical course.

Of note, the possibility of ‘pseudo-spontaneous nystagmus in the primary position of gaze’, due to horizontal canal paroxysmal positional vertigo becomes evident with a horizontal nystagmus fast phase direction change prompted by a forward head pitch. This nystagmus direction switch is typical for horizontal canal (hc) benign paroxysmal positional vertigo (BPPV).

To confirm hc BPPV, I observe the nystagmus elicited by head roll1 in the supine position. Two horizontal nystagmus patterns may occur: the first type and most common, is a rather robust, fast velocity nystagmus in the direction of the head roll (geotropic); the second type involves a fast nystagmus phase beating away from the direction of the head roll (apogeotropic). Both types should be treated with canal repositioning manoeuvres and do not require additional testing. An apogeotropic nystagmus type may be seen with central lesions32 and less commonly with geotropic variants31.

As mentioned before, Hotson and Baloh identified horizontal nystagmus with fast phase direction change as a specific central sign.1 This finding, coupled with a normal h-HIT, is compelling enough to repeat imaging when a false negative MRI study. Peripheral lesions do not cause this nystagmus pattern.14 16 To explain the gaze induced direction change,3 impairment of gaze-holding pathways (neural integrator) in the cerebellum, the brainstem or their connecting fibres in the cerebellar peduncles must be compromised.14 15 Clinicians may rely with confidence on horizontal, direction changing nystagmus as a central localisation sign.

Rebound horizontal nystagmus7 was not common in the ischaemic lesions series summarised in table 1,14 16 it may be seen with cerebellar or extra-axial brainstem lesions and is always a central sign.32 Clinicians should also be aware of the fact that demyelination, infectious and nutritional/toxic aetiologies may be responsible for a central AVS.33 34 Imaging, clinical examination and laboratory testing will identify most of these possibilities. Head shaking for a few seconds usually increases the amplitude of the primary nystagmus; however, variations such as posthead shaking horizontal nystagmus direction change or its conversion to vertical nystagmus (perverted nystagmus) are central signs. This nystagmus elicitation technique was the only central localisation in one patient from a previous AVS, AICA stroke series.35 Positional testing (Dix Hallpike or lateral head roll in the supine position) does not change the h-primary gaze nystagmus direction. Furthermore, any direction change will also point to central localisation.36 Finally, primary gaze vertical or purely torsional nystagmus point to central localisation15 and was relatively uncommon in most AVS series summarised in table 1.

The h-HIT test in patients with AVS
Clinicians use the h-HIT extensively since its inception in both unilateral and bilateral vestibulopathy.10 12 The normal response to a rapid, passive eye movement as a subject fixates on a central target is an equal and opposite eye movement of the same magnitude (Gain: ratio of head velocity/eye velocity is 1.0). The head thrusts may be performed with the head moving towards or away from centre position, the VOR gain does not change.37 In the event of a peripheral vestibular lesion involving the primary VOR pathway, the acceleration signal to move the eyes is impaired, resulting in gain loss (less than 1.0), consequently the eyes cannot stay on target and once the head stops a refixation saccade is thus required. Typically the vHIT performed in acute peripheral AVS shows a significant right versus left asymmetry and a conspicuous unidirectional corrective saccade.38

Choi et al from Korea reported in 2014 their experience with HINTS in 34 patients with isolated vestibular syndromes due to lacunar stroke (table 1). They found central ocular motor signs in 33 patients and had 6 patients with initially false negative DWI MRI studies.23 Batuecas et al from Spain in 2014 also used the HINTS diagnostic triad in 91 patients with AVS, 8 of them had a stroke and 7 had central HINTS. No false negative MRI studies were reported.39 The majority of the remaining patients with peripheral lesions had peripheral HINTS results; a small number of peripheral lesions had a normal h-HIT, suggesting peripheral vestibular diagnoses other than VN. Chen et al from Australia in 2011 and later in 2014 studied patients with AVS, recording the h-HIT using magnetic search coils, which is the gold standard for ocular motor recording accuracy. All their patients with stroke had positive MRIs. Their contribution outlined the value added by v-HIT recordings to the analysis of the h-HIT. Significant gain asymmetry occurs in peripheral lesions (in particular VN). In addition, such asymmetry occurs in AICA strokes with a peripheral vestibular h-HIT pattern, although of lesser magnitude. Other patterns occur in AICA strokes with a central pattern and PICA strokes. Lateral medullary lesions were not part of the analysis.40 41 In 2015 Kerber et al22 reported their experience with HINTS in a large cohort from the University of Michigan in Ann Arbor. They found a central HINTS pattern in 20 out of 29 patients who had stroke. Of note, seven of their patients did not have spontaneous nystagmus, which may be a special diagnostic category in which the HINTS triad needs additional investigation.
Figure 1  Axial DWI MRI. The top three panels represent serial images obtained when the patient was asymptomatic. The lower three panels obtained while symptomatic, about 10 hours later with primary gaze upbeat nystagmus and a right internuclear ophthalmoplegia. The red arrow points to the mid-basilar stenosis and occlusion of the lumen of a paramedian penetrator artery. The yellow arrow points to the midline pontine tegmentum/basis pontis.
AVS. It is therefore, important to add the cross-cover test routinely in the AVS examination protocol even in patients without diplopia.

Ocular motor examination of the OOR begins by asking the patient to fixate on a central target and observing the vertical position of the eyes. Occasionally, large amplitude skew is obvious by simple observation. More commonly, however, skew manifests when the examiner tests fixation with the alternate cross-cover. Whereas patients with normal ocular alignment do not have a refixation movement, patients with an impaired OOR have disconjugate vertical refixating saccades to stay on target (skew). An impaired OOR results in conjugate ocular torsion but disconjugate vertical alignment. Accordingly, one eye is lower: hypotropic and the fellow eye is higher: hypertropic. This is the most common OOR abnormality found in patients with ischaemic stroke. This technique identifies skew even in patients with intense nystagmus. In addition, analysis of the head position at rest should be observed; as sustained head tilt may be seen in association with skew. The cross-cover technique described in our study measured the degree of skew deviation (average amplitude of 9.9 prism-dioptres, with a range from 3 to 20 prism-dioptres). Finally, digital fundus photography if available may provide evidence of conjugate ocular torsion, the third OTR component. VN affects more frequently the superior vestibular nerve, which provides most of the innervation to the utricle; thus, low amplitude skew deviation is infrequent in VN, and when present is generally of low amplitude. Keane in 1975 defined the lateralisation value of skew deviation. Whereas the hypotropic eye is ipsilesional in peripheral vestibular and midbrain lesions, it is generally contralesional in pontine and midbrain lesions.

The vHIT measures all HINTS triad components. The recording performed at bedside is very sensitive in detecting and quantitating skew deviation. HINTS tracings will provide an objective measure of canal and otolith function and set a baseline for further follow-up. It may also be useful in understanding the process of vestibular compensation in peripheral and central vestibular lesions.

HINTS PLUS

In 2013, HINTS PLUS hearing loss due to cochlear or brainstem ischaemia was introduced as a new sign that could potentially increase diagnostic accuracy. The vascular supply to the inner ear, the fourth-nerve complex (cochlear, superior and inferior vestibular and facial nerves) in the cerebellopontine angle, the cochlear nerve root entry and the cochlear nucleus derives frequently from AICA (~80% of cases), the basilar artery (~15%–20%) and only rarely via PICA. Hearing loss/deafness in patients with AVS is infrequent in acute stroke. A thorough neurological evaluation should follow the HINTS examination. Severe truncal ataxia adds sensitivity to HINTS PLUS. In general, entertain the possibility of a central lesion in patients who are acutely unable to stand and walk independently.

Transient ischaemic attacks: TIA

The evaluation of the patient with ‘continuous vertigo’ in general leads to a precise diagnosis. The challenge is the evaluation of episodic vascular vertigo. Dizziness was the most common symptom of posterior circulation compromise in the New England Posterior Circulation Registry. A recent case highlights this challenge. A 61-year-old woman with an ABCD2 score of ‘4’ presented with a 24-hours history of three, recurrent vertigo episodes that lasted ~30 min each, associated with imbalance, nausea and vomiting (figure 1). Her examination was normal and the initial MRI, including DWI was unremarkable, she did not have an MRA; she was able to walk out of the hospital without assistance. On awakening the next morning, she had severe ataxia, oscillopsia and diplopia. On examination, she had primary gaze upbeat nystagmus and a right internuclear ophthalmoplegia. MRI showed a pontine stroke, due to occlusion of the lumen of a penetrator branch of the basilar artery. The lesson learnt is the need to include vascular imaging in these high-risk patients, either CT angiography or MRA.

CONCLUSION

The potential diagnostic impact of vHIT by objectively analysing HINTS which has been described as an ECG of the eye will enable in future years development of updated management guidelines which combine improved diagnostic accuracy and patient safety with effective, low-cost management.

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