HINTS to Diagnose Stroke in the Acute Vestibular Syndrome

Three-Step Bedside Oculomotor Examination More Sensitive Than Early MRI Diffusion-Weighted Imaging

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Background and Purpose—Acute vestibular syndrome (AVS) is often due to vestibular neuritis but can result from vertebrobasilar strokes. Misdiagnosis of posterior fossa infarcts in emergency care settings is frequent. Bedside oculomotor findings may reliably identify stroke in AVS, but prospective studies have been lacking.

Methods—The authors conducted a prospective, cross-sectional study at an academic hospital. Consecutive patients with AVS (vertigo, nystagmus, nausea/vomiting, head-motion intolerance, unsteady gait) with ≥ 1 stroke risk factor underwent structured examination, including horizontal head impulse test of vestibulo-ocular reflex function, observation of nystagmus in different gaze positions, and prism cross-cover test of ocular alignment. All underwent neuroimaging and admission (generally <72 hours after symptom onset). Strokes were diagnosed by MRI or CT. Peripheral lesions were diagnosed by normal MRI and clinical follow-up.

Results—One hundred one high-risk patients with AVS included 25 peripheral and 76 central lesions (69 ischemic strokes, 4 hemorrhages, 3 other). The presence of normal horizontal head impulse test, direction-changing nystagmus in eccentric gaze, or skew deviation (vertical ocular misalignment) was 100% sensitive and 96% specific for stroke. Skew was present in 17% and associated with brainstem lesions (4% peripheral, 4% pure cerebellar, 30% brainstem involvement; χ^2, $P=0.003$). Skew correctly predicted lateral pontine stroke in 2 of 3 cases in which an abnormal horizontal head impulse test erroneously suggested peripheral localization. Initial MRI diffusion-weighted imaging was falsely negative in 12% (all <48 hours after symptom onset).

Conclusions—Skew predicts brainstem involvement in AVS and can identify stroke when an abnormal horizontal head impulse test falsely suggests a peripheral lesion. A 3-step bedside oculomotor examination (HINTS: Head-Impulse—Nystagmus—Test-of-Skew) appears more sensitive for stroke than early MRI in AVS. (***Stroke***. 2009;40:3504-3510.)

Key Words: cerebrovascular accident ■ diagnosis ■ neurologic examination ■ sensitivity and specificity ■ vertigo

Acute vestibular syndrome (AVS) is characterized by the rapid onset (over seconds to hours) of vertigo, nausea/vomiting, and gait unsteadiness in association with head-motion intolerance and nystagmus lasting days to weeks. Patients often have a self-limited, presumed-viral cause for their symptoms known as vestibular neuritis or labyrinthitis, classified together as acute peripheral vestibulopathy (APV). Of the 2.6 million emergency department visits for dizziness or vertigo annually in the United States, APV is diagnosed in nearly 150 000.[1] However, some patients with AVS instead harbor dangerous brainstem or cerebellar strokes that mimic APV.[2–6] Small observational studies suggest perhaps $\geq 25\%$ of acute vestibular syndrome presentations to the emergency department represent posterior circulation infarctions.[3,6] CT scans have low sensitivity (approximately 16%) for acute infarction,[7] particularly in the posterior fossa,[8] and brain MRI is not always readily available. Studies also suggest that false-negative MRI can occur with acute vertebrobasilar strokes.[6,9,10] Consequently, bedside predictors are essential to identify patients with acute central vestibulopathies.

Although classical teaching suggests a focus on long-tract or frank cerebellar signs,[11,12] fewer than half of AVS presentations have limb ataxia, dysarthria, or other obvious neurological features.[6] Careful eye movement assessment may be

the only bedside method to identify vertebrobasilar stroke in these patients.[8] The most consistent bedside predictor of pseudolabyrinthine stroke in AVS appears to be the horizontal head impulse test (h-HIT) of vestibulo-ocular reflex (VOR) function[8] (Video 1a/b). This test was first described in 1988 by Halmagyi and Curthoys as a bedside test for peripheral vestibular disease.[13] Some authors have suggested the h-HIT be used as a definitive test to distinguish APV from stroke in patients with AVS.[4,14] Recent studies provide evidence that a normal VOR by h-HIT strongly indicates a central localization, but an abnormal VOR is a weaker predictor of a peripheral localization.[5,6] The sign's diagnostic usefulness is diluted principally by the fact that some patients with abnormal h-HIT (implying APV) actually harbor lateral pontine strokes.[6]

Another bedside predictor of central pathology in the acute vestibular syndrome is nystagmus, which changes direction on eccentric gaze.[5] AVS should generally be associated with a characteristic, dominantly horizontal nystagmus that beats only in one direction and increases in intensity when the patient looks in the direction of the nystagmus fast phase.[15,16] Vertical or torsional nystagmus in this clinical context is a clear sign of central pathology, but most strokes presenting an AVS picture have nystagmus with a predominantly horizontal vector that mimics APV.[6] What sometimes distinguishes the nystagmus typical of central AVS from APV is a change in direction on eccentric gaze[6] (Video 2a/b).

A third bedside predictor of central pathology is skew deviation. Skew deviation is vertical ocular misalignment that results from a right–left imbalance of vestibular tone (ie, neural firing), particularly otolithic inputs, to the oculomotor system.[17] It often occurs as part of the pathological ocular tilt reaction—the subtle clinical triad of skew deviation, head tilt, and ocular counterroll.[17] Skew is generally detected by alternate cover testing (Video 3) with or without a quantifiable prismatic correction. Although reported in patients with diseases of the vestibular periphery,[18] skew (with or without complete ocular tilt reaction) has principally been identified as a central sign in those with posterior fossa pathology.[17] It is most commonly seen with brainstem strokes[17] and has been reported as a herald manifestation of basilar occlusion.[19] A recent retrospective case–control study comparing oculomotor features in those with vestibular neuritis (ie, APV) with those with "vestibular pseudoneuritis" (mostly due to stroke) suggests skew deviation could be a specific sign of central disease in patients with AVS.[5]

We sought to assess the diagnostic accuracy of skew deviation for identifying stroke in AVS, including any added value beyond h-HIT. We hypothesized that the presence of skew would be insensitive but specific for stroke and that it would add probative diagnostic information to h-HIT results alone. We further sought to assess the overall sensitivity and specificity of a 3-step bedside oculomotor examination (Head-Impulse—Nystagmus—Test-of-Skew [HINTS]) for differentiating stroke from APV in AVS.

Materials and Methods

Data derive from an ongoing study of stroke in patients with AVS over the past 9 years. The study methods have been detailed previously in a report of h-HIT findings in 43 subjects[6] whose clinical data are also presented here in a larger series (101 subjects). Briefly, we present results of a prospective, cross-sectional study of patients presenting with AVS focusing on those at high risk for stroke. This Institutional Review Board-approved study was conducted at a single urban, academic hospital serving as a regional stroke referral center for 25 community hospitals. Patients with the core features of AVS (rapid onset of vertigo, nausea, vomiting, and unsteady gait with or without nystagmus) were identified primarily from the hospital emergency department. Additional patients were identified by review of stroke admissions for cerebellar infarction. Included were patients with at least one stroke risk factor (smoking, hypertension, diabetes, hyperlipidemia, atrial fibrillation, eclampsia, hypercoagulable state, recent cervical trauma, or prior stroke or myocardial infarction). Excluded were subjects with a history of recurrent vertigo with or without auditory symptoms.

For patients consenting to screening, the study neuro-ophthalmologist (J.C.K.) conducted a neurological and vestibular examination (including h-HIT, prism cross-cover test for ocular alignment, and observation of nystagmus in different gaze positions) according to a standard protocol.[6] A search for ocular counterroll by head-upright fundus photography to determine the presence of complete pathological ocular tilt reaction was performed in patients with either head tilt or vertical misalignment (suspected skew) without internuclear ophthalmoplegia. We defined severe truncal ataxia as the inability to sit upright unassisted without the use of arms to stabilize and included patients in whom lethargy may have contributed to their inability to sit.

All patients underwent neuroimaging, generally after bedside evaluation. If neuroimaging was performed before the study evaluation, the examiner was masked to these results at the time of clinical assessment. All patients (including patients with suspected APV) were admitted for observation and underwent serial daily examinations for evolution of clinical findings. The reference standard for a stroke diagnosis was confirmation of acute stroke by neuroimaging, generally MRI with diffusion-weighted imaging (DWI) on the day of the index visit. The reference standard for a diagnosis of APV was absence of acute stroke in the brainstem or cerebellum by MRI with DWI, lack of neurological signs on serial examination, and a characteristic clinical course. Most also underwent confirmatory caloric testing of vestibular function.

For predictive accuracy of skew deviation, we compared proportions with skew deviation in peripheral versus central cases and offer results stratified by h-HIT findings. Based on prior literature suggesting that 3 subtle oculomotor signs (normal h-HIT, direction-changing nystagmus, and skew deviation) might be, in aggregate, the best predictor of stroke in AVS,[8] we analyzed these 3 signs together. A priori, we defined the HINTS examination as either benign (abnormal h-HIT plus direction-fixed horizontal nystagmus plus absent skew) or dangerous (normal/untestable h-HIT or direction-changing horizontal nystagmus present/untestable or skew deviation present/untestable) and compared this test battery's sensitivity, specificity, and likelihood ratios for the presence of stroke relative to other neurological findings and early MRI with DWI. We calculate both positive likelihood ratios (the extent to which dangerous HINTS increase the odds of stroke or "rule in" the disease) and negative likelihood ratios (the extent to which benign HINTS decrease the odds of stroke or "rule out" the disease). Fisher exact and Pearson χ^2 were used for comparison of proportions with SAS 9.1 (SAS Institute Inc, Cary, NC). Likelihood ratios and CIs were calculated with MedCalc 9.6 (MedCalc Software, Mariakerke, Belgium). All P values were 2-sided with $P<0.05$ considered significant.

Results

We screened 121 patients with AVS and excluded 19 for a history of recurrent vertigo or dizziness (7 Menière syndrome, 5 vestibular migraine, 4 idiopathic recurrent vertigo, and 3 other disorders). One eligible subject refused enrollment. Of 101 patients reported here, 92 were identified by primary clinical screening and 9 through review of admitted

cerebellar infarcts. Fifty-nine presented initially to the emergency department, 4 were inpatients at symptom onset, one presented as an outpatient, and 37 were transferred to the neurology ward from other institutions (mostly from affiliate hospital emergency departments admitted directly to the stroke service).

The study population was 65% men with a mean age of 62 years (SD, 13 years; range, 26 to 92 years). The age range for patients with stroke was 26 to 92 with 15 patients aged <50 years, including 6 <40 years. In 30%, only one stroke risk factor was present; the others had at least 2 risk factors. Most were examined within 24 hours of symptom onset (75%). In 5 patients, the precise time of examination relative to symptom onset was unclear, because the precise time of symptom onset was unknown. Among the remaining 96 patients, the mean time to first examination was 26 hours (range, 1 hour to 9 days).

Most patients (97%) underwent stroke protocol MRI at the time of admission. One patient underwent CT followed by open MRI at another facility because of claustrophobia, and 3 underwent CT but no MRI (one was claustrophobic, one died before obtaining MRI, and one required ventriculoperitoneal shunt placement and was too ill for MRI). All 3 who did not have MRI had unequivocal cerebellar stroke by CT. Initial imaging occurred within 6 hours of study examination in most (70%). Among the 96 patients in whom time of symptom onset was known, imaging occurred within 72 hours of symptom onset in 97%; 2 patients were imaged at 4 days and one at 9 days after AVS onset. Eight with initial negative MRI underwent repeat MRI for unexplained signs (on initial or follow-up examination) suggesting brainstem localization. No patients had complications from diagnostic testing other than one claustrophobic reaction.

Of 101 high-risk patients with AVS, 25 had APV and 76 had a central lesion. Peripheral lesions were confirmed by caloric testing in 22 patients (19 with canal paresis, usually severe; 3 with only directional preponderance); 2 patients could not complete testing due to discomfort and one refused. Central lesions included 69 ischemic strokes, 4 hemorrhages (one dentate nucleus, 3 pontine [2 with pontine cavernoma]), 2 demyelinating disease (one presumed midbrain lesion, one medullary lesion), and one anticonvulsant toxicity (carbamazepine). Two patients did not have a demonstrable structural lesion on MRI that corresponded with the acute clinical syndrome (one patient with seesaw nystagmus and a presumed midbrain lesion who had demyelinating lesions elsewhere in the brain and the patient with anticonvulsant toxicity). Key clinical features suggesting a central localization (n=76) are presented in Table 1. These features are stratified by stroke location for ischemic lesions (n=69) in Table 2.

Acute auditory symptoms were infrequent but associated with strokes in the anterior inferior cerebellar artery territory and presumed secondary to labyrinthine infarction, cochlear nucleus involvement, or both. Craniocervical pain was more common among patients with central than peripheral lesions (38% versus 12%, $P=0.02$). All patients were unsteady (ie, broad-based gait or difficulty with tandem walking), but severe truncal ataxia (inability to sit without the use of arms

or assistance) was seen only among those with central lesions (34% versus 0%, $P<0.001$). As expected, lateral medullary (n=7), lateral pontine (n=5), and inferior cerebellar strokes (n=12) frequently mimicked APV (absent general neurological or obvious oculomotor signs), whereas medial brainstem cerebrovascular events did not (45% versus 5%, $P=0.001$). Another 36% of these lateral brainstem and cerebellar events (including one dentate hemorrhage) had severe truncal ataxia as their only obvious sign. Not surprisingly, medially located brainstem strokes and hemorrhages were associated with oculomotor paralysis, whereas lateral brainstem and cerebellar cerebrovascular events were not (80% versus 0%, $P<0.001$).

Skew deviation (mean, 9.9 prism diopters; range, 3 to 20 prism diopters) was present in 17% of our 101 subjects (case descriptions in Supplement; available at http://stroke.ahajournals.org) and untestable in 4% with central lesions due to seesaw nystagmus or oculomotor paralysis. Despite the large vertical ocular deviations, only 3 patients reported symptomatic diplopia at presentation, and 2 of these had comorbid internuclear ophthalmoplegia; several patients became aware of their diplopia during the crosscover test or developed symptomatic diplopia days or weeks after presentation as their oscillopsia abated. Skew was evident in 4% (n=1 of 25) with APV, 4% (n=1 of 24) with pure cerebellar lesions, and 30% (n=15 of 50) with demonstrated structural brain stem involvement (χ^2, $P=0.003$). A complete ocular tilt reaction was found in 6 subjects, all with brainstem strokes (2 lateral medullary, 2 lateral pontine, 2 interstitial nucleus of Cajal). Results of crosscover testing for skew deviation, stratified by h-HIT result, are compared with final diagnosis based on neuroimaging and clinical follow-up in Table 3. The majority (59%) of skews were associated with lateral medullary or lateral pontine strokes. Finding a skew correctly predicted the presence of a central lesion in 2 of 3 cases of lateral pontine stroke where a positive h-HIT incorrectly suggested benign APV and 7 of 8 cases with false-negative initial MRI. Taking skew together with h-HIT and direction-changing nystagmus as a 3-step bedside examination battery, a dangerous HINTS result was 100% sensitive and 96% specific for the presence of a central lesion, giving a positive likelihood ratio of 25 (95% CI, 3.66 to 170.59) and a negative likelihood ratio of 0.00 (95% CI, 0.00 to 0.11). Compared with traditional findings thought to indicate brainstem or cerebellar involvement in AVS, the HINTS battery was more sensitive than general neurological signs (100% versus 51%), obvious oculomotor signs (100% versus 32%), or both of these taken together (100% versus 67%; all $P<0.001$; Table 1). Diagnostic accuracy of bedside findings for identifying that subset of central AVS patients with ischemic stroke can be found in Table 4.

Neuroimaging by MRI with DWI was falsely negative in 8 patients with ischemic stroke (5 lateral medullary, one lateral pontomedullary, and 2 middle cerebellar peduncle infarctions). Negative scans were obtained 8 to 48 hours after symptom onset, including 4 that were negative at ≥24 hours. Follow-up MRI an average of 3 days later (range, 2 to 10 days) revealed the strokes. The sensitivity of early MRI with DWI for lateral medullary or pontine infarction was lower than that of the bedside examination (72% versus 100%,

Table 1. Key Clinical Features in Patients With Peripheral Versus Central AVS

Symptoms, Signs, and Imaging at Presentation	PAVS (n=25)	CAVS (n=76)	NLR Central (95% CI)
Associated symptoms	12%	41%	0.67 (0.53–0.85)*
Acute auditory symptoms	0%†	3%	0.97 (0.94–1.01)
Headache or neck pain	12%	38%	0.70 (0.56–0.88)*
General neurological signs (including truncal ataxia)	0%	51%	0.49 (0.39–0.61)*
Facial palsy	0%	1%	0.99 (0.96–1.01)
Hemisensory loss	0%	3%	0.97 (0.94–1.01)
Crossed sensory loss	0%	3%	0.97 (0.94–1.01)
Dysphagia/dysarthria	0%	3%	0.97 (0.94–1.01)
Limb ataxia	0%	5%	0.95 (0.90–1.00)
Mental status abnormality (lethargy)	0%	7%	0.93 (0.88–0.99)
Hemiparesis (including UMN facial weakness)	0%	11%	0.89 (0.83–0.97)
Severe truncal instability (cannot sit unassisted)	0%	34%	0.66 (0.56–0.77)*
Obvious oculomotor signs	0%	32%	0.68 (0.59–0.80)*
Dominantly vertical or torsional nystagmus	0%	12%	0.88 (0.81–0.96)
Oculomotor paralysis (3-4-6, INO, gaze palsy)	0%	21%	0.79 (0.70–0.89)*
Subtle oculomotor signs	4%	100%	0.00 (0.00–0.11)*
Direction-changing horizontal nystagmus	0%	20%	0.80 (0.72–0.90)*
Skew deviation present or untestable	4%‡	25%§	0.78 (0.67–0.91)*
h-HIT normal or untestable	0%	93%‖	0.07 (0.03–0.15)*
Initial imaging abnormal¶	92%	97%	0.33 (0.05–2.22)
Acute infarct or hemorrhage±chronic lesions	0%	86%	0.14 (0.08–0.25)*
Other acute pathology±chronic lesions	0%	1%	0.99 (0.96–1.01)
Only chronic lesions (leukoaraiosis)¶	92%	11%	11.18 (2.95–42.35)*

*P<0.05 for difference of proportion present in PAVS versus CAVS.

†Patients with recurrent peripheral audiovestibular disease were excluded from the study; therefore, the absence of auditory symptoms in PAVS may not represent an unbiased estimate.

‡Two patients with peripheral lesions developed skew deviation >1 week after symptom onset. These patients did not have skew at initial examination and are not counted here.

§Includes 3 patients with untestable skew deviation due to obvious oculomotor pathology.

‖Includes 4 patients with untestable h-HIT due to lethargy or obvious oculomotor pathology.

¶All subjects were required to have at least one stroke risk factor, so it is not surprising that imaging would often show evidence of leukoaraiosis even in those with peripheral diagnoses.

PAVS indicates peripheral AVS; CAVS, central AVS; NLR, negative likelihood ratio; UMN, upper motor neuron; INO, internuclear ophthalmoplegia.

P=0.004) with comparable specificity (100% versus 96%, P=1.0). MR angiography, performed in 33 of 69 with ischemic stroke, revealed unilateral vertebral or posterior inferior cerebellar artery occlusion in 15, bilateral vertebral stenosis in 3, and was normal in 15. Four were diagnosed radiographically with vertebral artery dissection, all young (ages 26, 35, 42, and 52 years).

Imaging evidence of mass effect was seen in the initial scan in 9 patients and in follow-up scan in one patient, all with cerebellar involvement. Among these 10 of 23 patients with cerebellar infarction, 3 were lethargic, but 7 had isolated, severe truncal ataxia without other obvious neurological signs at or near the time of imaging showing mass effect. In the majority of patients with APV (92%), MRI revealed nonspecific areas of periventricular high signal intensity on T2 or fluid-attenuated inversion recovery imaging but normal DWI compatible with chronic gliosis, presumed secondary to ischemic leukoencephalopathy in this population with ≥1 stroke risk factors.

Discussion

Our study demonstrates that skew deviation in AVS is strongly linked to the presence of brainstem lesions, most often ischemic strokes in the lateral medulla or pons. This study also proves that finding one of 3 dangerous, subtle oculomotor signs (normal h-HIT or horizontal nystagmus that changes direction in eccentric gaze or skew deviation) is more sensitive than the combined presence of all other traditional neurological signs for identifying stroke as a cause of AVS. The dangerous signs can be remembered using the acronym INFARCT (Impulse Normal, Fast-phase Alternating, Refixation on Cover Test). Perhaps most importantly, we have shown that a benign HINTS examination result at the bedside "rules out" stroke better than a negative MRI with DWI in the first 24 to 48 hours after symptom onset with acceptable specificity (96%).

The association between skew deviation and brainstem stroke is not surprising. Although cases of primary-position skew have been reported with peripheral vestibular disease,

Table 2. Key Clinical Features in Central AVS Caused by Ischemic Stroke by Lesion Location

Symptoms and Signs at Initial Presentation	LM±C (n)	LP or MCP±C (n)	MP or MM (n)	MB (n)	CO (N+) (n)	CO (N−) (n)	Total (n)
Associated symptoms	5	2	0	1	6	14	28
Acute auditory symptoms	0	2	0	0	0	0	2
Headache or neck pain	5	0	0	1	6	14	26
General neurological signs	10	7	2	3	2	9	33
Limb ataxia	0	0	0	1	0	0	1
Crossed sensory loss	2	0	0	0	0	0	2
Dysphagia/dysarthria	2	0	0	0	0	0	2
Mental status abnormality (lethargy)	0	0	0	0	0	3	3
Hemiparesis (including UMN facial weakness)	0	3	1	1	0	0	5
Severe truncal instability (cannot sit unassisted)	6	4	1	1	2	9	23
Oculomotor signs	17	12	11	6	8	15	69
Dominantly vertical or torsional nystagmus	3	1	1	1	0	0	6
Oculomotor paralysis (3-4-6, INO, gaze palsy)	0	0	9	5	0	0	14
Direction-changing horizontal nystagmus	7	4	0	0	1	3	15
Skew deviation present	6	4	2	3*	0	1	16*
h-HIT normal	17	8	11	5*	8	13*	62*
Total ischemic strokes	17	12	11	6	8	15	69

*Does not count untestable cases (2 skew, 2 h-HIT; see Table 3).

LM indicates lateral medulla; C, cerebellum; LP, lateral pons; MCP, middle cerebellar peduncle; MP, medial pons; MM, medial medulla; MB, midbrain; CO, cerebellum only; (N+), nodulus involved; (N−), nodulus not involved; UMN, upper motor neuron; INO, internuclear ophthalmoplegia.

and alternating skew deviation in lateral gaze is seen in some patients with bilateral cerebellopathy, lesions causing skew and the pathological ocular tilt reaction have most often been found in the brainstem.[17] Our prospective findings build on prior retrospective work suggesting a strong link between subtle oculomotor signs and stroke in patients with central AVS mimicking APV.[4,5] Although a normal h-HIT remains the single best bedside predictor of stroke[6] and its test properties are comparable to those of early MRI DWI, roughly one in 10 strokes will still be missed if other findings are not considered. We have identified 2 other subtle findings that should improve bedside detection of stroke without substantial loss of specificity.

Although physicians have become increasingly reliant on MRI DWI for acute stroke diagnosis, our study presents further evidence that care should be taken not to use DWI alone to rule out stroke in AVS in the first 24 to 48 hours after symptom onset. In our series, the sensitivity of DWI was 88% overall and 72% for lateral medullary and lateral pontine infarctions with these localizations very frequent among vertebrobasilar strokes mimicking APV closely. These estimates echo results from 2 prior studies of early DWI that reported on 206 vertebrobasilar strokes and found 77% sensitivity within 24 hours of symptom onset.[9,10]

Table 3. Skew Deviation Relative to Neuroimaging in AVS Stratified by h-HIT Results

	No Stroke by Final Imaging (n)	Stroke by Final Imaging (n)	Other CNS Diagnosis
Skew deviation absent	24	51	6
Normal h-HIT	0	47	4
Abnormal (untestable) h-HIT	24 (0)	3 (1*)	0 (2†)
Skew deviation present	1	16	0
Normal h-HIT	0	14	0
Abnormal (untestable) h-HIT	1 (0)	2 (0)	0 (0)
Skew deviation untestable	0	2†	1†
Normal h-HIT	0	1	1
Abnormal (untestable) h-HIT	0 (0)	0 (1†)	0 (0)
Total	25	69	7

*Untestable due to lethargy.

†Untestable due to oculomotor pathology (gaze palsy, bilateral third nerve palsy, seesaw nystagmus).

CNS indicates central nervous system.

Table 4. Bedside Signs and Initial MRI With DWI Test Properties for Ischemic Stroke in AVS

	Sensitivity (n=69)	Specificity (n=25)	NLR Stroke (95% CI)
General neurological signs*	19%	100%	0.81 (0.72–0.91)
Obvious oculomotor signs	28%	100%	0.72 (0.63–0.84)
Severe truncal ataxia	33%	100%	0.67 (0.56–0.79)
Any obvious signs	64%†	100%	0.36 (0.27–0.50)
Initial MRI with DWI	88%‡	100%	0.12 (0.06–0.22)
Dangerous bedside HINTS	100%	96%	0.00 (0.00–0.12)

*Excluding severe truncal ataxia (this Table only).

†Of 25 ischemic strokes without obvious signs, 12 were pure cerebellar, 7 were lateral medullary, 5 were lateral pontine or middle peduncle, and one was a medial brainstem infarct.

‡False-negative initial MRI with DWI occurred in 5 patients with lateral medullary infarctions, one with lateral pontomedullary infarction, and 2 with middle cerebellar peduncle infarction.

NLR indicates negative likelihood ratio.

Frontline misdiagnosis of posterior circulation strokes presenting with dizziness appears common, occurring in perhaps 35% of cases.[20] The high rate of misdiagnosis may not be surprising given that 58% of patients in our series either had no obvious signs or had only isolated, severe truncal ataxia. Inappropriate reliance on CT to exclude stroke likely exacerbates the problem.[21,22] The consequences of such misdiagnoses can be profound with one small series of missed cerebellar infarctions indicating adverse outcomes in 40%.[21] Misdiagnosis may be more likely in younger patients who are not generally considered to be at risk for stroke.[21] Vertebral artery dissections, the leading identifiable cause of posterior circulation stroke among young adults,[23] can present with an APV mimic.[24] We found 15 of our patients with stroke were age <50 years, and 3 of these were due to dissections.

Although the bedside techniques in the HINTS examination are not widely known among emergency physicians, internists, or even general neurologists, those without subspecialty training in neuro-otology can accurately interpret subtle oculomotor findings of this type,[25] suggesting that training in the use of these techniques may be possible. The 3 components of the HINTS (h-HIT of VOR function; observation for nystagmus in primary, right, and left gaze; alternate cover test for skew deviation) can be tested in approximately 1 minute at the bedside, whereas a more thorough, traditional neurological examination generally takes 5 to 10 minutes or more. An acute MRI brain with DWI takes at least 5 to 10 minutes of scan time plus a wait time of several hours to several days and typically costs >$1000. In an era in which efficiency and cost containment are at a premium, this bedside method may offer a quick, inexpensive alternative to current practice. Although additional confirmatory studies in a broader range of acute vestibular patients are needed, our data suggest that in time-pressured, frontline healthcare settings, this approach could potentially supplant complete neurological examination and neuroimaging without loss of diagnostic accuracy.

We identified several possible limitations to our study findings. Threats to internal validity include a partially unmasked examiner and selective MRI follow-up scans. As described previously,[6] the study examiner (J.C.K.), although masked to the results of imaging, was not masked to the patient's clinical history, general neurological examination, or obvious oculomotor findings when testing for subtler eye signs. Observer bias in the interpretation of subtle eye findings could have artificially inflated the sensitivity of these signs, but this seems unlikely for the 33% of cases in which obvious neurological findings were absent. MRI follow-up scans were obtained in only selected cases based on evolution of new neurological signs or atypical subtle oculomotor signs. This selective retesting could have led to some misclassification of strokes as APV, increasing the apparent sensitivity of the HINTS battery. However, all of these patients with APV were followed and evolved no neurological deficits acutely nor had strokes in clinical follow-up.

Threats to external validity include generalizability of examination technique and sampling from a high-risk subpopulation. Because patients were evaluated by a single examiner, it is unknown whether clinical findings could have

been replicated by other examiners. The growing literature on these subtle eye signs from multiple investigators suggests reproducibility, at least among subspecialists in the field.[4–6] We restricted our enrollment to high-risk patients with AVS with no history of prior recurrent vertigo and at least one stroke risk factor. We chose this approach because funds were not available to image all low-risk patients in whom MRI could not be justified clinically. This selection led to a highly enriched cerebrovascular cohort (76% central, 73% cerebrovascular, 69% ischemic stroke) and patients with APV who might be atypical (92% with leukoaraiosis). It is possible that a broader spectrum of patients with APV could have disclosed more with negative h-HIT results (including those with isolated inferior vestibular neuritis[26]) or the other 2 subtle signs, reducing the specificity of the "dangerous" HINTS result. However, a previous study of unselected patients with AVS suggests otherwise, estimating a 92% specificity when subtle eye signs were considered in a statistical prediction model.[5]

Summary

As has been shown previously, we found that lateral medullary, lateral pontine, and inferior cerebellar infarctions mimic APV very closely, and great caution must be exercised to avoid missing these posterior circulation strokes in patients with AVS. One in 5 strokes causing AVS affects a patient aged <50 years and one in 10 a patient aged <40 years. Typical neurological signs are absent in roughly half, and more than half of those with mass effect from large cerebellar infarctions have only severe truncal ataxia without other obvious neurological or oculomotor signs. Initial MRIs are falsely negative in 12% and can prove misleading out to 48 hours after symptom onset.

Skew deviation is an insensitive marker of central pathology but fairly specific predictor of brainstem involvement among patients with AVS. The presence of skew may help identify stroke when a positive h-HIT falsely suggests a peripheral lesion. Screening patients with AVS for one of 3 dangerous oculomotor signs (normal h-HIT, direction-changing nystagmus, skew deviation) appears to be more sensitive than MRI with DWI in detecting acute stroke in the first 24 to 48 hours after symptom onset. These "HINTS" to "INFARCT" could help reduce frontline misdiagnosis of patients with stroke in AVS and should be studied head-to-head for their comparative cost-effectiveness against neuroimaging by MRI DWI.

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Disclosures

None.

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