Systematic Review

Can "HINTS" aid the Diagnosis of Posterior Circulation Stroke among patients with Acute Vestibular Syndrome?

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[1,2] Conception of study
[1,2] Experimentation/Study conduction
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[1] Manuscript Writing
[4,5,6] Critical Review
[3] Facilitation and Material analysis

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Article Processing

Received: 02/09/2021
Accepted: 15/01/2022

Cite this Article: *Tahir, S., Tahir, N., Meraj, L., Zaka, N., Zaman, S., Malik, K. Can "HINTS" aid the Diagnosis of Posterior Circulation Stroke among patients with Acute Vestibular Syndrome? Journal of Rawalpindi Medical College. 31 Mar. 2022; 26(1): 146-154.*
DOI: https://doi.org/10.37939/jrmc.v26i1.1766

Conflict of Interest: *Nil*
Funding Source: *Nil*

Access Online:

Abstract

Introduction: Identifying posterior circulation stroke in patients with AVS without obvious focal neurological deficits poses a difficult diagnostic challenge. It is estimated that about 10% to 20% of emergency department patients have acute dizziness with AVS7. About 25% have brainstem or cerebellar strokes, rest of AVS patients presented with benign peripheral vestibular causes 7, 9-10. Rapid, accurate diagnosis of posterior stroke is important for early management as well as prevention of devastating complications. HINTS is a clinical three-step bedside oculomotor exam, that has been suggested of high diagnostic accuracy in identifying posterior circulation stroke in patients with isolated continuous vertigo.

Materials and Methods: A comprehensive systematic search of the literature was done using the NHS Evidence healthcare databases Medline, EMBASE, CLINIL, Google Scholar, and Cochrane.

Results: 10 relevant articles were identified, combining the results of all six prospective studies showing a total of 338 patients on which the Clinical HINTS exam was performed. The overall Hints exam sensitivity was 96.86% 95%CI (92.8-99), specificity 96.09% 95%CI (92.1-98.4) and negative predictive value was 0.03 95%CI (0.01-0.08). ROC analysis was done in which the area under the curve was found to be 0.965.

Conclusion: Delay in the diagnosis of posterior stroke can result in an 8-fold increase in mortality.[7] HINTS is a useful clinical bedside oculomotor exam, which if done appropriately by trained ED doctors, could aid in the early recognition of a subtly presenting posterior stroke with "acute isolated continuous vertigo". Hence, will improve the overall diagnostic evaluation of acute vestibular syndrome.

Keywords: AVS acute vestibular syndrome, HINTS head impulse, nystagmus, the test of skew, VOR vestibulo-ocular reflex, MRI magnetic resonance imaging, LR likelihood ratio.

Introduction

Dizziness is the commonly encountered chief presentation in Emergency departments. It accounts annually for about 4 million presented in the Emergency department and 160,000 to 240,000 (4% to 6%) have a cerebrovascular cause[1-6] in the United States. Dizziness is a broad term that encompasses vertigo, pre-syncope, unsteadiness, and other non-specific terms.[7] Roughly 250,000 to 500,000 US yearly attendances involve a high-risk-for-stroke clinically presented as an acute vestibular syndrome.[7] Acute vestibular syndrome is a syndrome of severe continuous vertigo or dizziness, nausea or vomiting, gait instability, head motion intolerance, and nystagmus lasting for days to weeks.[7-8] Although classical teaching suggests a focus on long-track or frank cerebellar signs, Acute vestibular syndrome has limb ataxia, dysarthria, or other associated neurological findings.[7,10-11]

Rapid, accurate diagnosis of stroke is important because a large cerebellar infarction later causes brain stem compression and increased intracranial pressure.[12] A small cerebellar stroke is usually caused by a cardiogenic embolism, the early detection and treatment can prevent life-threatening brainstem or cerebellar stroke.[12]

Our current practice to rule out posterior circulation stroke in suspected patients is based on neuroimaging (CT scan and/or MRI scanning). CT scan is the initial imaging for stroke evaluation and about 16% to 42% of early ischemic strokes[13-14] detection. Brain MRI is expensive and after posterior fossa, stroke may be falsely negative in up to 20%[7] in the first 24 hours. According to US statistics about one-third of vestibular strokes are missed despite spending hundreds of millions of dollars on brain imaging trying to 'rule out' dangerous central vestibular causes such as stroke.[1-2,15] Therefore, the need for a simple clinical bedside test with high sensitivity and specificity is imperative, which can not only reduce the misdiagnosis of posterior stroke, but also the cost of unnecessary neuroimaging. The HINTS (stands for Head Impulse, Nystagmus, and Test of Skew) oculomotor test has been suggested to be a test of high diagnostic accuracy. It is a three-part oculomotor test, that should only be performed on patients with "acute continuous vertigo". If any portion of the test indicates a central etiology, the test is considered positive and further evaluation for stroke is warranted. The three components of the exam are as follows:

Head impulse[16,17,31]

Peripheral vertigo has an abnormal (positive) head impulse test, whereas central vertigo has a normal (negative) head impulse test. Horizontal head impulse involves rapid head rotation with the subject's vision fixed on a nearby object. The VOR is impaired in peripheral vertigo; 'rapid rotation of the head toward the affected side will result in loss of fixation and movement of the eyes away from the target', followed by a corrective saccade looks back toward the target. The presence of corrective saccade is abnormal showing a positive test for peripheral vertigo. Patients with posterior stroke in the VOR remain intact and showed no corrective saccade. Patients have an abnormal head impulse test in combined stroke and inner ear infarction cases. The central nature of the lesion will be revealed by any one of three signs direction-changing nystagmus, skew deviation, or unilateral hearing loss.

Nystagmas[18]

Peripheral vertigo has unidirectional horizontal nystagmus, whereas central vertigo has a rotatory/vertical or direction-changing horizontal nystagmus. The change in direction of the fast phase of horizontal nystagmus indicates a central cause.

Test of SKEW[19]

Alternate eye cover testing may reveal skew deviation in patients with central vertigo and would be absent in peripheral vertigo. Patients with central vertigo will have a 'vertical misalignment' on the cover uncover test.

Materials and Methods

An extensive search of PUB MED, EMBASE, CINAHL, and Cochrane databases were done with keywords (Table 1). The Cochrane, the Google advance scholar, and Best BETs databases, including a hand search of the bibliography of the relevant papers, did not reveal any further articles (Figure 1). The last access date to the databases was 11th June 2015. All the systematic reviews, meta-analyses, prospective studies, retrospective studies, and case series on the application of the HINTS test were included. Excluded papers consisted of studies focusing only on one component of the HINTS or purely device-based articles, reviews on peripheral causes of vertigo, case reports, and paediatric studies. The articles published in other languages apart from English were also excluded in this practical review.

Table 1:

	Search terms
1	VERTIGO/
2	DIZZINESS/
3	(dizz* OR spinning OR "acute vestibular syndrome").ti,ab
4	1 OR 2 OR 3
5	HINTS.ti,ab
6	(head AND impulse AND nystagmus AND test AND of AND skew).ti,ab
7	"head impulse nystagmus test of skew".ti,ab
8	(oculomotor OR vestibulocular).ti,ab
9	(bedside OR bed-side OR "bedside").ti,ab
10	(acute AND diagnosis).ti,ab
11	9 AND 10
12	5 OR 6 OR 7 OR 8
13	11 OR 12
14	exp STROKE/
15	"posterior circulation".ti,ab
16	(cerebell* OR vertebrobasilar OR "posterior stroke").ti,ab
17	15 OR 16
18	14 OR 17
19	4 AND 13 AND 18
20	Limits applied Humans, English
21	Removal of duplicates

Results

Overall 173 articles were identified. 64 in MEDLINE, 97 in EMBASE, and 12 from CINAHL. No articles were found from Cochrane, best bets, or google scholar **(Figure 1).**

A hand search of the bibliography of articles did not yield any further studies. Based on title and abstract, after filtering for duplicates and applying limits 11 articles were found to be relevant. 10 articles were included in this review after reading the full text. One relevant article could not be accessed despite contacting the author as it was not published at the time. 6 out of 10 relevant studies were prospective and two sets of these studies were the continuation of each other. The individual studies have been appraised in **Table 2**. The first set consisted of a total of 190 patients on which HINTS and HINTS plus exam (assessment of acute hearing loss in AVS patients as a predictor of stroke) were performed by two neuro-ophthalmologists in a single US centre. It was considered to be the largest prospective study due to the merger of kattah et al[11] study into Newman-Toker et al.[20] The second set of prospective studies was Newman-Toker et al[22] and Mantokoudis et al[23] in which 26 patients were included. The fifth independent study by Chen et al[21] was carried out in a stroke unit at a tertiary hospital in Australia and included 24 patients on which the test was performed. The sixth prospective study enrolled 98 patients in an Italian Emergency department; the HINTS exam was done as a part of the STANDING algorithm (HINTS with gait testing) by five trained Emergency physicians **(Table 2).**

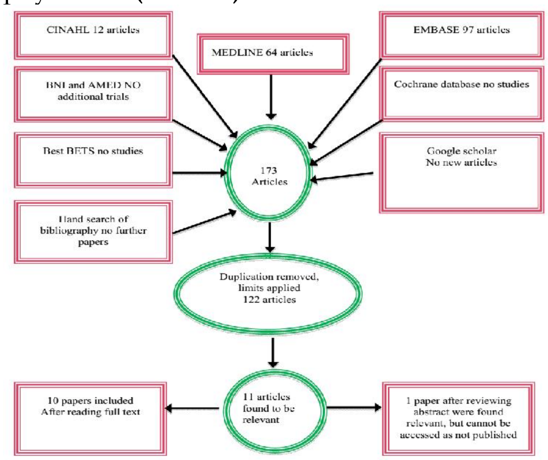

Figure 1: Flow-Chart for selection of articles

The results of individual studies were calculated by Medcalc[28] online to demonstrate the 95% confidence interval of sensitivity, specificity, positive negative predictive values, and stroke prevalence values **(Table 3, 4)**.

The overall sensitivity and specificity of the HINTS exam were calculated by combining the results of all the prospective studies **(Table 5)**. The total number of patients included was 338 and the sensitivity, specificity negative predictive values were calculated by Med Calc version 15.2. The results of the exam were as follows: sensitivity 96.86 with 95%CI (92.8-99), specificity 96.09% 95%CI (92.1-98.4), negative predictive value 0.03 with 95%CI (0.01-0.08). A ROC analysis[30] was done in which the area under the curve was found to be 0.965 **(Figure 2)**.

Table 2: Individual studies literature appraisal

Author, date, and country	*Patient group N*	*Study type (level of evidence)*	*Outcomes*	*Key results*
Newman-Toker *et al* [20] 2013 USA	n=190 AVS patients with at least one vascular risk factor, recruited from ED All patients had neuroimage.	Prospective single centre	Comparison of sensitivity and specificity of three clinical decision rules HINTS, HINTS plus (hearing loss) versus ABCD2 with cut-off value 4 or above	HINTS for central lesion had sensitivity of 96.8%(92.4-99), specificity of 98.5%(92.8-99.9), LR+ 63.9%(9.13-446.85), LR- 0.03%(0.00-0.09) HINTS PLUS sensitivity of 99.2%(96.1-100), specificity of 97 %(90.4-99.5),
	Strengths	Prospective, Consecutive sampling, Clear inclusion and exclusion, All patients received reference standard, All MRI negative patients had to follow up		
	Weaknesses	Patients were examined after admission from ED the clinical finding could have evolved Blinding of examiner was imperfect to clinical details of patients (20% having focal neurology)-observer bias Repeat MRI done selectively in patients with stroke suggestive HINTS Highly selective high-risk population for stroke-spectrum bias Trained neuro-ophthalmologist conducting the exam reducing external validity No inter-rater reliability was done for examiners performing HINTS It was not mentioned whether radiologists interpreting the MRI were masked to HINTS findings		
Chen *et al* [21] Australia, 2010	n=24 patients with AVS with vascular risk factors, All patients underwent MRI and MRA.	Prospective study single centre	Sensitivity and specificity of HINTS oculomotor test	100% sensitive 90% specific for stroke
	Strengths	Prospective All had reference standard Neurologists blinded to MRI results		
	Weaknesses	Unclear selection criteria Small sample size The neurologist conducting the oculomotor testing were not masked to clinical details High-risk AVS population No inter-observer reliability		
Mantokoudis *et al* [23] 2014 USA	n=26 patients with AVS, recruited from ED. Index test was device calculated quantitative Head impulse. All patients had clinical HINTS, MRI (DWI), and follow-up for 90 days in case of peripheral diagnosis.	Prospective 2 centre study	Diagnostic accuracy, sensitivity, and specificity of quantitative Head impulse by the device. The quantitative head impulse was calculated in the form of VOR gain alone to differentiate stroke from a peripheral disease	All 10 patients were correctly identified as stroke by clinical HINTS, 1 out of 16 peripheral syndrome patients was misdiagnosed as stroke by clinical HINTs as compared with device HINTS.
The study was included as it had clinical HINTS performed independently of Quantitative HINTS	*Strengths*	Prospective In 2 centres All had reference standards Blinding for experts using VOR Blinding of radiologists Kappa measured		
	Weaknesses	Small sample size Non-consecutive sampling selection bias highly trained experts dealing with device ICS device not tested against scleral coils Uninterpretable results of the head impulse device based test were excluded Difficult calibration The device did not quantify nystagmus and test skew No cost analysis done		

Tranutzer et al[7] 2011	10 studies of high or medium reference standards were included. n= 392 patients with AVS Reference standards to rule in or rule out stroke were MRI, repeat MRI, positive CT scan, follow up if negative neuroimaging	Systematic review	Pooled sensitivity, specificity Predictive values, likelihood ratios of each component of HINTS were calculated if they were applied in at least 2 studies	HINTS sensitivity 98%, specificity 85%, LR- 0.02
	Weaknesses	No formal test of heterogeneity was applied Only one study used a superior reference standard There was a variability of bedside tests as well as a small number of patients Evidence to support HINTS was limited to only 2 studies involving 184 patients Patients from high-quality studies had vascular risk factors limiting external validity		
Tehrani et al[24] 2014 USA Same study **Newman-Toker et al**[20]	n=105 AVS patients diagnosed with stroke were included. They were divided into 15 small strokes ≤ 10mm in diameter and 90 large strokes more than 10mm in diameter on MRI DWI. The gold standard was MRI (repeat MRI if HINTS suggestive of stroke), age range 41 -85	retrospective Single centre	Sensitivity of HINTS plus exam compared with the sensitivity of early MRI DWI (6-48hours) Percentage of false-negative early MRI in small and large strokes	HINTS plus sensitivity 100%, Early MRI-DWI 47% $p<0.001$ False-negative MRI is more common in small strokes than in large strokes 53% (8 of 15) vs 7.8% (7 of 90) $p<0.001$ 47% of small strokes had non-lacunar mechanism including 6 vertebral artery occlusions or dissections
	Weaknesses	Retrospective analysis Very small sample size Repeat MRI on selective patients Data dredging as the study analysis was done on the already conducted study thus chance of type one error Case capture imperfect		
Casani et al[12] Italy 2012	n=11 AVS patients with missed strokes diagnosed on MRI, 9 referred from ED, Age range 47- 80 without focal neurology	retrospective chart review	number of patients in which oculomotor tests suggested stroke	9 out of 10 patients had horizontal head impulse negative, 2 patients had central nystagmus, skew deviation was done in a few patients Although included all components of HINTS but did not use the term HINTS
	Weaknesses	Retrospective missed many cases Carried out by neuro-otologists The time frame from the onset of symptoms to MRI and HINTS exam was varied among patients Clinical and instrumental exams were not well explained or homogenous		
Cnyrim et al[25] Germany, 2007.	n=83 patients with AVS recruited from ED. All patients underwent MRI as well as electronystagmography with caloric irrigation. 43 patients had a central lesion (23 strokes, 12 multiple scleroses, 8 haemorrhages), 40 patients had vestibular neuritis	retrospective chart review	Sensitivity and specificity of bedside tests including HINTS	The overall sensitivity and specificity of 5 bedside signs gaze-evoked nystagmus, saccadic pursuit, Head thrust*, skew deviation, and subjective visual vertical 92% *Head thrust same as head impulse
	Weaknesses	Unclear selection criteria Small sample size The neurologist conducting the oculomotor testing were not masked to clinical details Trained neurologists reducing external validity High risk AVS population selection bias No inter-observer reliability done		
Vanni et al[26] Italy, 2015.	n=98 patients with AVS recruited from ED. 50% had one vascular risk factor. All patients had the HINTS exam as part of the STANDING* algorithm.	Prospective	Sensitivity and specificity of bedside tests including HINTS	HINTS sensitivity 92.9% Specificity 96.4%

	Reference standards included Local standards senior audiology evaluation, MRI in some patients *STANDING includes HINTS exam with gait testing	
	Strengths	Prospective Done by ED physicians Inter-observer reliability done Blinding of ED doctors and audiologists
	Weaknesses	Not all patients had Neuroimaging as reference standards Convenience sample No, follow up of patients not having MRI

Table 3: HINTS calculated values by Medcalc.net[28]
95% Confidence interval stated as CI

	Sensitivity	*Specificity*	*Negative predictive value*	*Positive predictive value*	*Negative likelihood ratio*	*Positive likelihood ratio*	*Prevalence*
Chen *et al*[21] 2010	100% CI 71.51-100	84.62% CI 54.55-98.08	100% CI 71.51-100	84.62% CI 54.55-98.08	0.00	6.50 CI 1.82-23.26	45.83% CI 25.55-67.18
Newman-Toker *et al*[20] 2013	96.77% CI 91.95-99.11	98.48% CI 91.84-99.96	94.20% CI 85.82-98.40	99.17% CI 95.46-99.86	0.03 CI 0.01-0.09	63.87 CI 9.13-446.85	65.26% CI 58.03-72.01
Mantokoudis *et al*[23] 2014	100% CI 69.15-100	93.75% CI 69.77-99.84	100% CI 78.20-100	90.91% CI 58.72-99.77	0.00	16.00 CI 2.40-106.74	38.46% CI 20.23-59.43
Vanni et al 2015	92.86% CI 66.13-99.82	96.43% CI 89.92%-99.26	98.78% CI 92.45-99.8	81.25% CI 58.5-93	0.07	26 CI 8.4-79	14.29% CI 8-22.81%

Table 4: HINTS PLUS TEST

Study	*Sensitivity*	*Specificity*	*Negative predictive value*	*Positive predictive value*	*Negative likelihood ratio*	*Positive likelihood ratio*	*Prevalence*
Newman- Toker *et al*[20] 2013	99.19% CI 95.59-99.98	96.97% CI 89.48-99.63	98.46% CI 91.72-99.96	98.40% CI 94.34-99.81	0.01 CI 0.00-0.06	32.73 CI 8.36-128.16	65.26% CI 58.03-72.01

Table 5: ROC curve:

Combining results of all prospective studies using MedCalc version15.2[30] [a] *Stroke = 1* [b] *Stroke = 0*

Variable	*HINTS*
Classification variable	Stroke
Sample size	338
Positive group [a]	159 (47.04%)
Negative group [b]	179 (52.96%)
Disease prevalence (%)	17

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	*0.965*
Standard Error[a]	0.0100
95% Confidence interval[b]	0.939 to 0.982
z statistic	46.249
Significance level P (Area=0.5)	<0.0001

[a] DeLong et al., 1988

Sensitivity	*95% CI*	*Specificity*	*95% CI*	*+LR*	*95% CI*	*-LR*	*95% CI*	*+PV*	*95% CI*	*-PV*	*95% CI*
96.86	92.8 - 99.0	96.09	92.1 - 98.	24.7	12.0 - 51	0.03	0.01 - 0.08	83.5	72.4 - 91	99.3	97.5 - 99.9

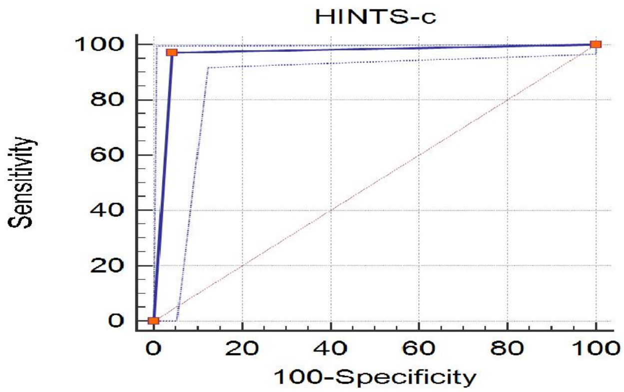

Figure 2: Receiver operating curve (ROC)

Discussion

This review aimed at providing Emergency physicians with the currently available evidence on the role of HINTS as a bedside oculomotor tool in aiding the evaluation of isolated 'acute continuous vertigo'. The two prospective studies, **Chen** ***et al***[21] and **Mantokoudis** ***et al***[23] showed 100% sensitivity for the HINTS exam. But looking closely, both of them had a wide confidence interval due to the small sample size **(Table 3)**. In the largest prospective study, **Newman-Toker** ***et al***[20] did a comparison of the HINTS exam with the ABCD score, although the comparison seemed unfair HINTS exam showed a sensitivity of 96.8% CI (91-99%) along with the specificity of 98.5% CI (91-99%). The addition of detection of new hearing loss (HINTS PLUS exam) boosted the sensitivity from 96% to 99.19%with a narrow confidence interval of 95-99% **(Table 4).** The study concluded that HINTS and HINTS PLUS exam sensitivity not only superseded the ABCD2 score but also the initial reference standard diffusion-weighted MRI up to 48 hours.

Mantokoudis ***et al***[23] included the cohort of **Newman-Toker** ***et al***[22] studies in which videooculography was done parallel to the clinical HINTS exam along with reference standard MRI. These studies were an attempt to reduce examiner error in conducting head impulse quantitatively to reduce observer bias. The patient sample was taken nonconsecutively and device calibration was an issue in addition to its handling by the experts. However, the clinical HINTS exam showed high sensitivity but a wide confidence interval **(Table 3)**.

Most of these studies had some common limitations like small sample size, no power calculation, no inter-observer reliability done of the examiners performing the clinical HINTS exam, partial masking of examiners to clinical details of patients reducing the internal validity. HINTS was performed by highly trained examiners, like neuro-ophthalmologists and neuro otologists thus reducing the external validity. This raised concerns about how well Emergency physicians will perform the HINTS exam. In Vanni et al[26] the HINTS exam was done by Emergency physicians after 6 hours of training and 10 practice assessments. The HINTS sensitivity was reduced to 92.9% with a wide confidence interval and specificity of 96.4% with a confidence interval of 93-98. In contrast to the other prospective studies, a selective MRI was done when considered appropriate by a senior audiologist and there was no follow-up of the patients who were considered to have peripheral vertigo. This could have led to the possibility of missed posterior strokes. Despite all these limitations, this study gave a rough idea about how well the HINTS exam will perform at the hands of no specialists. In **Chen** ***et al*** [21] the neurologists were trained for four hours and they performed the HINTS exam with reasonable accuracy as depicted by the results from their study but again with a wide confidence interval (Table 3). Most of the studies included patients with AVS who had at least one stroke risk factor on which the HINTS exam was applied, this leads to the possibility of spectrum bias and limits the generalizability of results. However, looking at this selected population, there was a large variability of risk factors, age ranges as well disease patterns which make it close to the general target population coming to an Emergency department.

Most of the studies had a high stroke prevalence up to 60%. However, the sensitivity and specificity of the test should not vary with prevalence. This theoretically answers the question regarding how HINTS would perform in AVS patients with no risk factors. Looking at Vanni et al[26] the stroke prevalence was calculated to be 14% with a sensitivity of 92% and specificity of 96%. A ROC analysis was done, with a 17% estimated prevalence[7] of stroke among AVS patients which showed a reasonable AUC value of 0.965 **(Table 5, Figure 2)**. Interestingly, some of the studies indicated that the HINTS exam when done by specialists, was more accurate than early MRI up to 48 hours to diagnose stroke in AVS patients.

Despite all these above-discussed limitations, the HINTS exam shows a promise in the assessment of patients with the acute vestibular syndrome. Though more studies are needed to accurately define how much training is required for the Emergency physicians' to be able to perform the exam well. At present, careful use of the HINTS exam should be encouraged among Emergency doctors due to its properties of being a non-invasive and practical bedside tool, especially in the current clinical scenario where there is no fixed or standard exam in ED to assess AVS patients. A pathway is suggested to differentiate posterior stroke from peripheral vertigo in which the HINTS exam can be utilized for the assessment of AVS patients in ED **(Figure 3).**

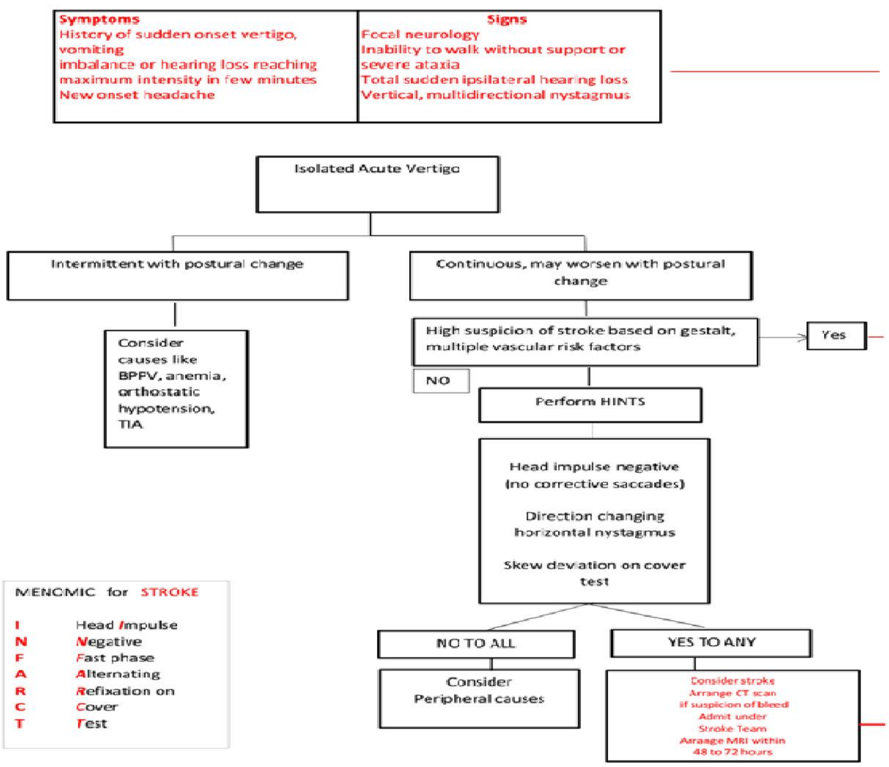

Figure 3: A suggested pathway to differentiate posterior stroke from peripheral vertigo in AVS patients in ED

Conclusion

Our current practice of suspecting or ruling out posterior circulation stroke in AVS patients without focal neurology relies solely on medical gestalt and thus misdiagnosis is frequent. The pooled analysis of the studies shows that the HINTS examination has a sensitivity of 96.86% with a 95% CI(92.81%-99.0%), a negative likelihood ratio of 0.03, and a specificity of 96.09 with 95% CI(92-98.4). Though the confidence intervals are relatively wide and the utility of the HINTS exam has not been widely tested by Emergency physicians in the ED, given appropriate training to perform the HINTS exam, we have a non-invasive clinical bedside test that can be a useful addition to our standard clinical assessment in patients with AVS. A positive HINTS exam in low-risk patients would suggest the need for further workup, whereas a negative HINTS exam in moderate-risk patients would reduce the need for unnecessary neuroimaging.

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