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ORIGINAL CONTRIBUTION

CME

Differentiating central from peripheral causes of acute vertigo in an emergency setting with the HINTS, STANDING, and ABCD2 tests: A diagnostic cohort study

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Abstract

Background: Diagnosing stroke in dizzy patients remains a challenge in emergency medicine. The accuracy of the neuroophthalmologic examination HINTS performed by emergency physicians (EPs) is unknown. Our objective was to determine the accuracy of the HINTS examination performed by trained EPs for diagnosing central cause of acute vertigo and unsteadiness and to compare it with another bedside clinical tool, STANDING, and with the history-based score ABCD2.

Methods: This was a prospective diagnostic cohort study among patients with isolated vertigo and unsteadiness seen in a single emergency department (ED). Trained EPs performed HINTS and STANDING tests blinded to attending physicians. ABCD2 ≥ 4 was used as the threshold and was calculated retrospectively. The criterion standard was diffusion-weighted brain magnetic resonance imaging (MRI). Peripheral diagnoses were established by a normal MRI, and etiologies were further refined by an otologic examination.

Results: We included 300 patients of whom 62 had a central lesion on neuroimaging including 49 strokes (79%). Of the 238 peripheral diagnoses, 159 were vestibulopathies, mainly benign paroxysmal positional vertigo (40%). HINTS and STANDING tests reached high sensitivities at 97% and 94% and NPVs at 99% and 98%, respectively. The ABCD2 score failed to predict half of central vertigo cases and had a sensitivity of 55% and a NPV of 87%. The STANDING test was more specific and had a better positive predictive value (PPV; 75% and 49%, respectively; positive likelihood ratio [LR+] = 3.71, negative likelihood ratio [LR−] = 0.09) than the HINTS test (67% and 44%, respectively; LR+ = 2.96, LR− = 0.04). The ABCD2 score was specific (82%, LR+ = 3.04, LR− = 0.56) but had a very low PPV (44%).

Conclusions: In the hands of EPs, HINTS and STANDING tests outperformed ABCD2 in identifying central causes of vertigo. For diagnosing peripheral disorders, the

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STANDING algorithm is more specific than the HINTS test. HINTS and STANDING could be useful tools saving both time and costs related to unnecessary neuroimaging use.

INTRODUCTION

Background

Vertigo, unsteadiness, and imbalance are common chief complaints in emergency departments (EDs).[1] Their incidence is increasing and reaches up to 4% of visits.[2,3] For emergency physicians (EPs), the challenge is generally to differentiate a benign vestibular disorder from a dangerous cerebral disease, particularly vertebrobasilar ischemia.[4,5] Acute vestibulopathy is the main cause of acute vestibular syndrome. Therefore, it is necessary that frontline providers recognize it efficiently for ruling out a cerebral disease.[6] However, in 20% of posterior circulation strokes, there is no obvious neurologic sign associated with vertigo or unsteadiness.[4,7] Indeed, stroke can mimic about 5% of benign paroxysmal positional vertigo (BPPV) cases and 25% of vestibular neuritis.[8-10] Thus, EPs should either manage these patients in the ambulatory setting if a vestibular disorder is suspected or urgently in the hospital if a cerebral disease is suspected. EPs commonly manage this diagnostic dilemma according to cardiovascular comorbidities.[11-13] This approach has raised concerns because it could also lead to overuse of neuroimaging, especially brain computed tomography (CT),[3,14,15] which has a detection rate for posterior fossa ischemia of only 16% to 42%.[14,16,17] Initial diffusion-weighted brain MRI is the criterion standard, but it is expensive, not available in many centers, and also imperfect.[18-21] These findings support the need of an objective clinical examination that can help control costs while achieving diagnostic accuracy.[3,22,23]

Importance

The HINTS test (head impulse, nystagmus, test of skew) can help differentiate causes of acute vestibular syndrome.[20,24-26] It has been validated by neuroophthalmologists to diagnose stroke in high-risk patients with a sensitivity of 100% and a specificity of 96%.[20,26] However, it is still misused or misunderstood by many EPs having no eye-examination skills.[27-32] A structured four-step bedside diagnostic algorithm named STANDING has been proposed for EPs (Figure S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14337/full).[33] Based on nystagmus assessment with Frenzel glasses, Head Impulse Test (HIT), gait evaluation, and positional tests, it promised being up to 95% sensitive and 96% specific to diagnose central causes of acute vertigo in the hands of trained EPs.[33,34] Finally, it may be attractive to use a stroke risk stratification tool that requires no clinical skills, like the ABCD2 score.[11] Findings of previous studies are conflicting about its relevance with ED dizzy patients.[11,26]

Goals

Our hypothesis was that EPs following training would be able to perform the HINTS test accurately, among dizzy patients having no frank focal neurologic sign. The objective of this study was to determine the accuracy of the HINTS test performed by trained EPs for diagnosing central causes of isolated acute vertigo and unsteadiness. We also sought to compare the HINTS test with the clinical tool STANDING and with the history-based score ABCD2.

METHODS

Design and settings

This was an investigator-initiated, single-center prospective assessment of the HINTS examination, the STANDING algorithm, and the ABCD2 score using diffusion-weighted brain MRI as the criterion standard. The trial was approved by an ethics committee (CPP EST 1, ID RCB 2019-A01585-52) and registered on clinicaltrials.org as NCT04118361. The oral consent of each participant was obtained and recorded in the patient's electronic record. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

Patients were recruited from October 2019 to January 2021 in the ED of a tertiary hospital, in Paris, France. The hospital was a thrombolysis center and had a stroke unit, a neurology department, and an otology department, with dedicated consultations. In the standard of care, brain CT with angiography of the Circle of Willis (CTA) was used in patients within 48 h of symptoms onset in those who have a stroke history or cardiovascular comorbidities. Diffusion-weighted brain MRI was used in line with current guidelines[35] and according with the neurologist if a stroke was highly suspected in high risk-patients within 24 h of symptoms onset. In patients having an otologic history, no urgent neuroimaging should be performed. Discharged patients received an MRI order and were referred to an otologist consultation in the ambulatory setting.

Patient's eligibility

Adults presenting with acute vertigo (spinning or nonspinning quality) or vestibulovisual symptoms (spinning, flowing, or oscillating quality) and postural symptoms (an unsteadiness or an imbalance), as defined by the classification of the Barany Society for at least 1 h and < 1 week were included in our 24/7 ED.[36] Patients having

no symptoms at the time of the examination, having frank localizing neurologic signs, or having another diagnosis on admission (hypotension, hypoglycemia, acute anemia, acute alcohol, or drug uses) and those who could not be assessed (severe dementia, oculomotor nerve palsy) were excluded. A patient could only be included once in the study. The absence of a brain MRI follow-up was considered as a protocol violation, and involved patients were excluded from the analysis.

Interventions

Index tests

One week before the study began, nine senior EPs received training led by two expert otologists. They had no specific skills in otology, neurology, or ophthalmology and had achieved their residency 1 to 3 years prior. The training comprised 4 h of individual lectures and 2 h of workshop, using a slide show with videos and demonstrations on normal volunteers. The objective was for EPs to be able to elicit and interpret a spontaneous nystagmus with Frenzel glasses, a positional nystagmus by Dix-Hallpike test (posterior canal test, most often involved), supine head roll test (horizontal canal test, i.e., Pagnini maneuver), vestibuloocular reflex (VOR) by HIT, and skew deviation by cover test and to perform treatment maneuvers (Semont and Epley). The training was repeated 7 months later. There was no supervised examination or knowledge assessment.

Investigators advertised the study to the ED team that contacted trained EPs when patients met inclusion criteria. Then patients underwent successively the HINTS examination and the STANDING algorithm by a trained EP blinded to the care of the attending EP. Outcomes and testing times were immediately reported on a dedicated data sheet. Attending EPs were blinded to results and performed initial neuroimaging in the standard of care.

Each component of the HINTS test was scored "central" or "peripheral" by a trained EP as defined by Kattah et al.[20]: (1) a positive HIT (i.e., an abnormal VOR) predicted peripheral vertigo, meaning that a HIT bilaterally normal predicted a central vertigo; (2) direction of nystagmus changing on eccentric gaze, vertical, or torsional nystagmus predicted a central AVS; (3) a skew deviation (i.e., vertical eye misalignment detected by alternate cover testing) was typical of a central vertigo. The presence of a central pattern was scored as "dangerous HINTS."[20] The components of the STANDING algorithm were immediately reported and scored by a trained EP: either "central" when the algorithm predicted a central disease or "peripheral" when it predicted an acute vestibulopathy or a BPPV (Figure S1). We used the algorithm as defined by Vanni et al.[34]: (1) spontaneous, positional, or absent nystagmus; (2) nystagmus direction observed with Frenzel glasses; (3) HIT assessment; (4) standing position and gait evaluation; and (5) when no spontaneous nystagmus was detected, a positional nystagmus was assessed by Dix-Hallpike and Pagnini maneuvers. The ABCD2 was calculated retrospectively to limit a potential interpretation bias. It was scored with seven possible ranges assigned for five elements (age, blood pressure, clinical features, duration of transient ischemic attack [TIA], and presence of diabetes). An ABCD2 score ≥ 4 was used as the threshold for central vertigo, as proposed by Navi et al[11] and Newman-Toker et al.[26]

Reference test

The criterion standard was the diffusion-weighted brain MRI, except for patients having a contraindication who underwent a brain CTA. Central diagnoses were defined as the presence of an acute brain process in posterior fossa detected either on ED neuroimaging or on a brain MRI used at least 48 h after symptoms onset, in the hospital or in the ambulatory setting. Hospitalized patients underwent MRI 48 to 72 h after symptoms onset, if it has not previously been performed in the ED. To ensure follow-up of discharged patients, an MRI appointment was arranged in the ambulatory setting, even if an initial CT/CTA has been previously performed. All peripheral diagnoses were established by the normality of the criterion standard. To further refine peripheral etiologies, an otologist examination was arranged for reappraisal of MRI result and performing video-nystagmography or video-HIT.

Outcomes

The primary outcome was the diagnostic accuracy (sensitivity and specificity) of the HINTS test performed by trained EPs to diagnose a central cause of isolated vertigo and unsteadiness.

The secondary outcomes were:

- The differences of accuracy between the HINTS examination, the STANDING algorithm, and the ABCD2 score.
- The perceptions of trained EPs on the use and the interpretation of HINTS and STANDING examinations.

Data collection

Results of each clinical component, testing time, and final outcomes of HINTS and STANDING tests were collected prospectively and immediately recorded on a data sheet by the trained EP. Two external investigators have verified the agreement between results of clinical components and the final outcome of HINTS and STANDING tests. Clinical key features and radiologic and organizational data were collected retrospectively from the computerized medical record.

Sample size

The prevalence of vertigo due to central diseases has been estimated at around 10% to 15% of acute vestibular syndromes.[4,9] From the literature, we anticipated a sensitivity of the HINTS test to diagnose central vertigo around 90% to 97% and a specificity for peripheral vertigo

around 80% to 90%.[20] According to an interrogation of our clinical database, 171 patients were recorded as vertigo of either central or peripheral cause from November 2018 to April 2019. After discussion with the EPs, the recruitment of a sample size of around 300 patients appeared feasible over 18 months. With a prevalence of 10%, around 30 patients are expected in the central cause group. With an expected sensitivity of 96.7% the precision of estimate (95% confidence interval [CI]) will be 82.8% to 99.0%. With an expected specificity of 90.0% the precision of estimate (95% CI) will be 86.4% to 93.6%. These precisions were considered as acceptable. The 95% CI was calculated with the exact binomial method.

Data analysis

The reporting followed the Standards for Reporting Diagnostic Accuracy Study (STARD) guidelines. Continuous variables were reported as mean (±standard deviation [SD]) or median (interquartile range [IQR]) and compared with Student's t-test or Wilcoxon test as appropriate. Qualitative variables were reported as number (%) and compared with the chi-square test or the Fisher's exact test as appropriate.

The diagnostic performance of the index tests will be summarized by calculating the sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), positive likelihood ratios (LR+), and negative likelihood ratios (LR–), with their 95% CI. For comparing sensitivity and specificity of the HINTS examination to that of the STANDING algorithm and the ABCD score, and calculating CIs, we used the method proposed by Roldán-Nofuentes.[37] Briefly, a global test was first performed to test a global difference in the test performance (on either sensitivity or specificity). If the test was significant a paired comparison was performed separately for sensitivity and specificity. The same analyses were performed in the prespecified subgroup of stroke comprised in central vertigo. The confidence of trained EPs about the use and the interpretation of clinical tests has been measured on a 5-point Likert scale (Table S1).

For analyzing how the index tests could have impacted the management of ED dizzy patients, we considered the summation of neuroimaging uses, requests to neurologist, and hospitalizations required for false-positive patients and then subtracted those that could have been avoided for true-negative patients, respectively, for the three tests.

All statistical tests were done with the R software (https://www.r-project.org/; version 4.0.4). All tests were two sided with a significance level set at a $p < 0.05$.

RESULTS

Characteristics of study subjects

We included 320 patients (Figure 1) among whom 192 (61%) underwent initial neuroimaging in the ED. Criterion standard imaging was immediately performed in 34 patients leading to eight central diagnoses. For 158 patients, a brain CT or a CTA had been performed, leading to 36 unequivocal central diagnoses. We analyzed 300 patients because 20 were unexpectedly lost at MRI follow-up. Almost all underwent an additional MRI according with the protocol ($n = 275$, 92%), with a median (IQR) delay of 4 (3–9) days after symptom onset, except for 12 with a contraindication and 13 with an unequivocal acute brain process on CT who were not reassessed by an MRI. Supplemental MRIs had found 18 misdiagnosed cases of central vertigo. Overall, criterion standard imaging diagnosed 62 cases of central vertigos and was normal in 238 patients, among whom 187 were evaluated by an otologist (79%). No otologist evaluation had suspected a central diagnosis or contested a normal MRI result.

The characteristics of the 300 patients are reported in Table 1. They had a mean age of 60±19 years and comprised 62.3% women. Among them, 41 had a history of stroke (13.7%). There were significantly more central vertigo cases in patients having at least one cardiovascular risk factor or a history of stroke, consuming alcohol, having fallen, or having an unsteady gait or systolic blood pressure of ≥160 mm Hg. Female sex, otologic history, otalgia, positive Romberg test, and vomiting were less frequent among patients with central vertigo than in those with peripheral vertigo. The 62 cerebral diseases were mainly strokes (42 infarctions [68%] and seven hemorrhages [11%]), followed by six cerebellar tumors (10%; Table 2). Among the 238 peripheral diagnoses, acute vestibulopathy was the leading cause ($n = 161$, 68%) including 92 cases of BPPV (40%) and 26 cases of vestibular neuritis (11%), followed by 30 cases of nonspecific vertigo (13%), 23 vestibular migraines (10%), and eight TIAs (3%; Table 3). Transient ischemic attacks were diagnosed by neurologists, based on clinical history, examination, MRI result, full resolution of symptoms within 24 h of onset, and exclusion of BPPV and orthostatic hypotension.[10] Despite extensive testing and otologic and neurologic input, nine patients (4%) had a normal MRI and no definite diagnosis (Table 3). Two patients died: one had an acute ischemic cerebellar stroke and experienced inhalation pneumonia and one had orthostatic hypotension and died because of COVID-19.

Main results

Based on the criterion standard, the HINTS test correctly identified 59 of 62 cases of central vertigo and 159 of 238 cases of peripheral vertigo (Tables 2 and 3). For three patients, examiners were unable to interpret the HINTS test. Two HIT were not performed because of a lack of neck mobility in patients having a BPPV. One cover test was not interpreted because the examiner was doubtful about skew deviation in a patient having an acute hydrocephalus with an obstruction of the ventriculoperitoneal shunt. The HINTS test had two false negatives involving multiple sclerosis lesions in the posterior fossa and an acute ischemic cerebellar stroke (Table 2). Both had continuous vertigo, significant imbalance without headache, neck pain, or hearing loss. They were discharged by the attending EP without initial neuroimaging. The 77 false-positive HINTS tests involved especially idiopathic BPPV (10%) and nonspecific vertigo (5%; Table 3).

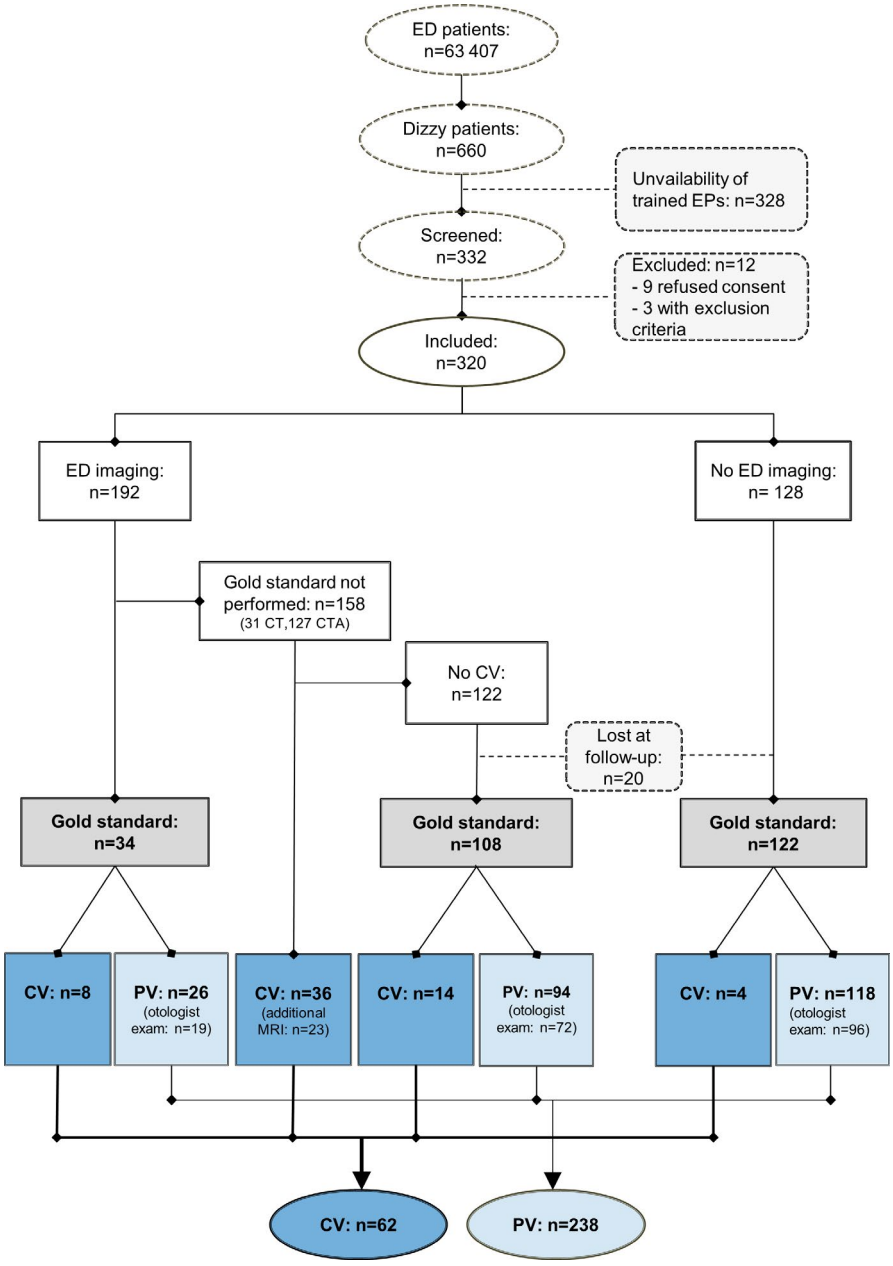

FIGURE 1 Study flow chart. Number of dizzy patients: estimated by review of the panel of visits in the ED during the study period. Criterion standard: diffusion-weighted brain MRI ($n = 275$) or CTA for patients with a MRI contraindication. MRI median (IQR) delay: 4 (3–9) days after symptom onset (3 [2–7] days for central diagnoses and 5 [3–10] days for peripheral diagnoses). CTA use for MRI contraindication: overall, $n = 12$ with 10 in the ED (two central vertigo), two in the ambulatory setting (no central vertigo). Exclusion criteria: two vertigo casess with a localizing neurologic sign and one acute alcohol intoxication. Lost at follow-up (protocol violations): no MRI performed (14 with ED imaging) and no data about clinical follow-up. Among the 62 CV cases, 36 were diagnosed on initial CT or CTA, of which 23 were reassessed by an additional MRI. CT, brain CT without contrast; CTA, brain CT with angiography of the Circle of Willis; CV, central vertigo; PV, peripheral vertigo

The HINTS test performed by trained EPs reached a sensitivity of 96.7%, a specificity of 67.4%, a PPV of 43.4%, and a NPV of 98.8% (LR+ = 3, LR− = 0.04; Table 4).

STANDING and ABCD2 correctly identified 58 and 34 cases of central vertigo and 178 and 195 cases of peripheral vertigo, respectively (Tables 2 and 3). None of the two false-negative HINTS tests was identified by the STANDING algorithm or by the ABCD2 score. The STANDING test had two additional false-negatives mimicking BPPV: one ischemic stroke with multiples basilar stenoses and one minor nontraumatic intracranial hemorrhage (Table 2). Half of the cases of BPPV undiagnosed by the HINTS test were diagnosed by the STANDING algorithm, through positional nystagmus testing (Table 3). The ABCD2 score failed to predict almost half of strokes, which were scored zero and involved six patients under the age of 60. Corresponding values of STANDING and ABCD2 diagnostic properties are summarized in Table 4. The sensitivity ($p = 0.62$) and the LR− ($p = 0.24$) of the HINTS test did not differ significantly from those of the STANDING test, whereas both specificity ($p < 0.001$) and LR+ ($p = 0.004$) were significantly better with the STANDING. Compared to the ABCD2 score, both sensitivity ($p < 0.001$) and specificity ($p < 0.001$) were better for the HINTS test as well as LR− ($p < 0.001$) but not LR+ ($p = 0.87$). Results were similar when considering only strokes.

The confidence of the trained EPs using HINTS and STANDING tests is summarized in Figure 2. Overall, they reported that the use of the HINTS examination was straightforward, but considerations about its reliability were more heterogeneous. They indicated that the test of skew was the easiest assessment whereas the evaluation of the nystagmus with Frenzel glasses was the most challenging. Overall, they reported high confidence in the two additional components of

TABLE 1 Baseline characteristics and medical management of enrolled patients, according to the cause of vertigo

	All patients, *n* = 300	Central vertigo, *n* = 62	Peripheral vertigo, *n* = 238	p-value
Demographic characteristics				
Age (years)	60.3 (±18.8)	71.8 (±14.9)	57.3 (±18.6)	<0.001
Sex, female	187 (62.3)	23 (37.1)	164 (68.9)	<0.001
Patient's history				
Cardiovascular risk factors	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.0 (0.0–2.0)	<0.001
Previous otologic disorder	64 (21.3)	5 (8.1)	59 (24.8)	0.004
Previous stroke or TIA	41 (13.7)	19 (30.6)	22 (9.2)	<0.001
Alcoholism	8 (2.7)	7 (11.3)	1 (0.4)	<0.001
Delay between symptoms onset and examination				
<4 h 30 min	46 (15.3)	12 (19.4)	34 (14.3)	0.12
4 h 30 min–24 h	115 (38.3)	17 (27.4)	99 (41.2)	
>24 h	139 (46.3)	33 (53.2)	106 (44.5)	
Medical context				
Fall	39 (13.0)	20 (32.3)	19 (8.0)	<0.001
Infection	37 (12.3)	3 (4.8)	34 (14.3)	0.04
Psychological stress	31 (10.3)	2 (3.2)	29 (12.2)	0.04
ABCD2 score	3.0 (2.0–4.0)	4.0 (3.0–4.0)	2.0 (2.0–3.0)	<0.001
Clinical observations				
Systolic blood pressure ≥160 mm Hg	127 (42.3)	38 (61.3)	89 (37.4)	<0.001
Continuous vertigo	254 (84.7)	43 (69.3)	211 (88.7)	<0.001
Unsteady gait	158 (52.7)	53 (85.5)	105 (44.1)	<0.001
Imbalance	209 (67.7)	48 (77.4)	161 (67.6)	0.13
Headache	97 (32.3)	24 (38.7)	73 (30.7)	0.23
Neck pain	34 (11.3)	11 (17.7)	23 (9.7)	0.07
Vomiting	191 (63.7)	19 (30.6)	172 (72.3)	<0.001
Positive Romberg test (*n* = 276)	100 (36.2)	5 (10.2)	95 (41.8)	<0.001
Acute auditory symptoms	18 (6.0)	1 (1.6)	17 (7.1)	0.14
Otalgia or abnormal otoscopy	29 (9.7)	2 (3.2)	27 (11.3)	0.05
Treatments				
Antithrombotic bolus	11 (3.7)	7 (11.5)	4 (1.7)	0.002
N-Acetyl-DL-leucine	103 (34.3)	2 (3.2)	101 (42.4)	<0.001
Initial neuroimaging				
CT	28 (9.3)	16 (25.8)	12 (5.0)	<0.001
CTA	126 (42.0)	36 (58.1)	90 (37.8)	
Diffusion-weighted MRI	24 (8.0)	6 (9.7)	18 (7.6)	
Request for a neurologist opinion	176 (59)	49 (79)	127 (53)	<0.001
Trained EP testing times (min)				
HINTS test		5.6 (±2.1)	5.7 (±3.0)	0.66
STANDING test		4.6 (±2.8)	5.55 (±3.2)	0.46
Outcomes				
ED length of stay (min)	280.0 (159.7–427.2)	392.0 (263.5–555.5)	248.5 (135.0–405.7)	<0.001
Hospitalization	95 (31.7)	48 (77.4)	47 (19.7)	<0.001
Hospital length of stay (days)	3.0 (2.0–6.0)	5.0 (2.0–7.0)	2.0 (2.0–4.0)	0.003

Note: Data are reported as number (%), means (±SD), or median (IQR). *p*-values were calculated with the chi-square test or Fisher's tests for dichotomous variables and the Wilcoxon or Student's *t* tests for continuous variables. Antithrombotic boluses were used for seven acute ischemic strokes and four TIAs (no thrombolysis and no thrombectomy). No attending physician had reported HINTS three-step rule in the clinical observation.

Abbreviations: Acute auditory symptoms, acute hearing loss or acute tinnitus; BPPV, benign paroxysmal positional vertigo; CT, noncontrast computerized tomography; CTA, CT with angiography of the Circle of Willis; MRI, magnetic resonance imaging; otologic history, antecedents of BPPV, hearing loss, cholesteatoma, or previous episodic vertigo with unknown etiology; TIA, transient ischemic attack.

TABLE 2 False-negative results according to the cause of central vertigo and the type of index test

Diagnosis	Total, *n* = 62	HINTS, *n* = 2	STANDING, *n* = 4	ABCD2, *n* = 28
Ischemic stroke	42 (67.7)	1 (1.6)	2 (3.2)	17 (61)
Hemorrhagic stroke	7 (11.3)	–	1 (1.6)	3 (4.8)
Cerebellar tumor	6 (9.6)	–	–	2 (3.2)
Cerebellar atrophy	3 (4.8)	–	–	2 (3.2)
Demyelinating disease	3 (4.8)	1 (1.6)	1 (1.6)	3 (4.8)
Acute obstructive hydrocephalus	1 (1.6)	–	–	1 (1.6)

Note: Data are reported as number (%). Ischemic stroke type: atherosclerotic, lacunar, embolic, vertebral dissection. Cerebellar atrophy included Wernicke encephalopathy and MELAS syndrome. Demyelinating disease included multiple sclerosis and progressive multifocal leukoencephalopathy. Missing value: for one patient the trained EP did not conclude with the HINTS test (no interpretation of the cover test for the patient having an acute hydrocephalus).

TABLE 3 False-positive results according to the cause of peripheral vertigo and the type of index test

Diagnosis	Total, *n* = 238	HINTS, *n* = 77	STANDING, *n* = 60	ABCD2, *n* = 43
Vestibular disorder	161 (67.6)	36 (15.1)	25 (10.5)	28 (11.8)
Idiopathic BPPV	90 (37.8)	24 (10.1)	12 (5.0)	14 (5.9)
Vestibular neuritis or labyrinthitis	26 (10.9)	4 (1.7)	5 (2.1)	9 (3.8)
Endolymphatic hydrops	24 (10.1)	4 (1.7)	3 (1.3)	3 (1.3)
Ototoxicity	8 (3.3)	4 (1.7)	4 (1.7)	2 (0.8)
Posttraumatic BPPV	6 (2.5)	–	–	–
Presbyvestibulopathy	4 (1.7)	1 (0.4)	1 (0.4)	2 (0.8)
Neurovascular conflict and schwannoma	3 (1.7)	1 (0.4)	1 (0.4)	1 (0.4)
Vestibular migraine	23 (9.6)	9 (3.8)	7 (2.9)	2 (0.8)
TIA	8 (3.3)	8 (3.4)	8 (3.4)	1 (0.4)
Peripheral neuropathy	6 (2.5)	6 (2.5)	6 (2.5)	1 (0.4)
Pseudo-vertigo	31 (13)	12 (5.0)	10 (4.2)	7 (2.9)
Undetermined	9 (3.8)	4 (1.7)	3 (1.3)	1 (0.4)

Note: Data are reported as number (%). Transient ischemic attacks (or vertebrobasilar insufficiencies) were suspected by neurologists based on clinical history, examination, MRI result, full resolution of symptoms within 24 h of onset, and exclusion of BPPV and orthostatic hypotension. Peripheral neuropathy included acute axonal and demyelinating neuropathies. Pseudo-vertigo included orthostatic hypotension, hypertensive crisis, cervicogenic dizziness, visual vertigo, vagal malaise, and anxiety disorder. Missing values: for two patients the trained EP did not conclude with the HINTS test, two Head Impulse Tests were not performed because of a lack of mobility in patients having a BPPV.

Abbreviations: BPPV, benign paroxysmal positional vertigo; TIA, transient ischemic attack.

the STANDING examination (positional maneuvers and gait evaluation). They were unanimous about the potential impact of clinical tools for decreasing requests to specialists and neuroimaging.

We also analyzed how HINTS and STANDING outcomes could have influenced the patient's pathway. Overall, the diagnostic yield of ED neuroimaging was 32% (MRI 60%, CT 57%, CTA 20%; Figure 1). Eighteen central diagnoses were established on MRI after the initial management (Figure 1). Among them, 13 were predicted by the HINTS test and 12 by the STANDING test. Considering respective LRs, the utilization of HINTS and STANDING examinations by trained EPs may have avoided 57 (33%) and 56 (32%) initial neuroimaging examinations, and 64 (36%) and 74 (42%) requests to the neurologist, respectively. HINTS and STANDING tests could have saved time as both were performed in 5 ± 3 min, a duration that did not differ between central and peripheral vertigo ($p = 0.66$ and $p = 0.46$, respectively; Table 1).

DISCUSSION

In the current literature, the effectiveness of the HINTS examination in emergency medicine have mainly been studied in

TABLE 4 Diagnostic accuracy of HINTS, STANDING, and ABCD2 index tests versus the reference test

	HINTS	STANDING	ABCD2
All central cause (95% CI)			
Sensitivity	96.7 (89.0–99.3)	93.4 (84.5–97.6)	55.7 (43.3–67.5)
Specificity	67.4 (61.2–73.0)	75.0 (69.1–80.1)	81.8 (76.4–86.2)
PPV	43.4 (35.3–51.8)	49.1 (40.2–58.1)	44.2 (33.1–55.2)
NPV	98.8 (95.7–99.7)	97.8 (94.5–99.2)	87.4 (83.1–91.8)
LR+	3.0 (2.4–3.6)	3.7 (2.9–4.7)	3.1 (2.1–4.3)
LR–	0.04 (0.01–0.17)	0.09 (0.03–0.21)	0.5 (0.4–0.7)
Stroke only (95% CI)			
Sensitivity	97.9 (89.6–99.8)	93.9 (83.7–98.1)	59.2 (45.3–71.8)
Specificity	64.5 (58.4–70.2)	71.8 (65.9–77.0)	80.6 (75.3–85.1)
PPV	35.3 (27.7–43.6)	39.6 (31.2–48.7)	40.3 (28.9–51.6)
NPV	99.4 (96.6–99.9)	98.3 (95.3–99.5)	90.7 (86.8–94.6)
LR+	2.8 (2.2–3.2)	3.3 (2.6–4.0)	3.1 (2.1–4.2)
LR–	0.03 (0.0–0.2)	0.1 (0.0–0.2)	0.5 (0.3–0.7)

Abbreviations: LR+, positive likelihood ratio; LR–, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

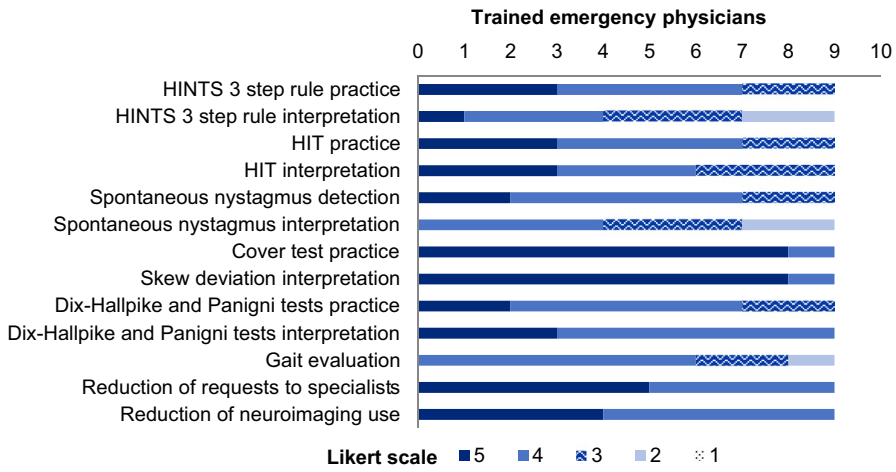

FIGURE 2 Confidence of trained EPs using clinical tests and perceptions about their impact in routine practice. The 5-point scale was defined by a minimum agreement of 1 (strongly disagree) and a maximum agreement of 5 (strongly agree). Number of HINTS and STANDING tests performed: >100 = one EP, >30 = one EP, 10–30 = two EPs, <10 = five EPs. HIT = Head Impulse Test

reviews.[27,32] A recent meta-analysis, using CT or MRI as reference tests, found that both sensitivity and specificity of the HINTS examination were better when it was performed by trained specialists (97% and 95%, respectively) rather than EPs (83% and 44%, respectively).[32] Moreover, Dmitriew et al.[27] claimed that the HINTS examination had a limited diagnostic value in EDs. First, we demonstrated that the two structured bedside clinical tools HINTS and STANDING can appropriately be used by trained EPs for identifying central causes of acute vertigo and unsteadiness. Especially, HINTS and STANDING were very good exclusion tests in the hands of trained EPs, by means of respective very low LR– (0.04 and 0.09, respectively). The sensitivity of the HINTS test was nearly as great as in the original study, in which it was performed by a neuroophthalmologist (97% vs. 100%).[20] However, the specificity remained lower than in neuroophthalmologists' studies to predict stroke (65% vs. 98%) or any central disease (67% vs. 84%).[20,26] Also, we noted that trained EPs performed the test more slowly than reported by specialists (5 min vs. 1 min).[20]

Several explanations could mitigate the lack of specificity. Excluding 20 patients lost at MRI follow-up may have resulted in the exclusion of patients who had a clinical suspicion of peripheral vertigo by the attending EP. It may have slightly decreased the specificity of the HINTS test. Moreover, if we had considered TIAs as part of central diagnoses, the specificity could have increased to 70% while maintaining same sensitivity and NPV. The generalization of HINTS test properties must also consider the population's characteristics. Previous cross-sectional studies enrolled highly selected patients: all having at least one cerebrovascular risk factor and 70% having at least two risk factors, whereas such patients were just one-half and one-quarter, respectively, in our cohort.[20,26] Moreover, in the original study, 45% of patients had a concomitant central localizing neurologic sign.[20] We limited this selection bias by excluding these patients. This clinical feature was highly critical, because ED patients having an isolated episode of vertigo may be improperly discharged if a central etiology is not suspected. Therefore, the rate of ED-misdiagnosed strokes (n = 18, 29%) was consistent with that

in the literature (10%–30%).[4,8,38,39] The specificity may then have turned out to be lower because of a low stroke prevalence (16% vs. 69%),[20] while enrolling 30% of BPPV cases. For these patients, the effective duration of spinning vertigo was probably more consistent with an episodic vestibular syndrome rather than an acute vestibular syndrome. A vague description of dizziness quality and confusing symptoms provided by patients is common.[40] Those likely had a triggered spinning vertigo episode at home and underwent a continuous false sense of motion and feeling of being unstable at the time of the examination.[36] They may have not met the criteria for receiving the HINTS test.[27] Therefore, it may have led to a misinterpretation of a normal HIT. These findings provide evidence of the usefulness positional nystagmus testing in an ED dizzy population. Thus, the STANDING algorithm was slightly more specific than the HINTS examination (75% vs. 67%). In addition, if we had considered TIAs as central diagnoses, the STANDING specificity could have increased at 77%, with sensitivity of 96% and NPV of 98%. Given the prevalence of nonspecific vertigo despite extensive neuroimaging and otologic testing (13%), it also emphasized the importance of timing, triggers, associated symptoms, and context in the initial diagnostic strategy.[6,31]

Compared to prior validation study, the STANDING specificity was lower (75% vs. 87%), whereas the sensitivity (94% vs. 95%), the NPV (98% vs. 99%), and the PPV (49% vs. 48%) were similar.[34] It could be explained by shortened trainings, conducted without supervised examinations because of availability reasons. We expect the specificity increase with clinical experience. Although well designed, the previous study was subject to an important verification bias, performing the criterion standard only when deemed appropriate. Of the 352 patients analyzed, 211 did not have neuroimaging (60%), of whom 116 had a final peripheral diagnosis (34% imaging and only 5% with a MRI).[34]

Finally, we also cautioned that the ABCD2 score was not appropriate for screening strokes or any cause of acute vertigo in an ED population. Our results were consistent with prior comparison study in high-risk patients.[26] It contradicted a previous single-center ED study that was limited by variable follow-up data and incomplete diagnoses evaluation.[11] Indeed, the ABCD2 score was not developed to predict cerebrovascular causes of acute vertigo, but to predict short-term stroke risk after TIA.[12] In routine practice, frontline providers do not use the ABCD2 score explicitly to guide the care pathway of individual dizzy patients. However, many EPs probably use a similar reasoning based on cardiovascular comorbidities and systolic blood pressure measurement and usually perform a neurologic examination omitting the eye-movement assessment.[27,30] Especially for predicting posterior strokes, the sensitivity was as low as reported by Newman-Toker et al.[26] (59% vs. 61%). Even if the specificity was higher than reported in high-risk cohorts (81% vs. 62%), the ABCD2 score should have missed a worrisome rate of ischemic strokes (35%).[26] It could have led EPs to manage strokes as peripheral disorders, particularly among young patients. Finally, even if we had considered TIAs as central diagnoses, the sensitivity and the NPV would have decreased to 49% and 84% respectively.

LIMITATIONS

Our study has several limitations. First, the order of the realization of the tests—HINTS, then STANDING—may have biased the interpretation of the STANDING examination by the examiner. We limited this bias by ensuring the independence of the examiner from care management. We were not able to assess interobserver reliability by performing each clinical test by two different examiners. To our knowledge, the STANDING validation study was the only one having evaluated this parameter in an ED. It showed a good overall reliability on 129 patients ($\kappa = 0.83$).[34] Also, we did not assess the baseline of knowledge following the training and individual diagnostic accuracies. However, our survey provided an interesting insight into trained EPs' perceptions on eye-movement assessments.

Second, by repeating MRIs, Kattah et al[20] and Newman-Toker et al[26] also demonstrated that early diffusion-weighted MRI could be falsely negative during the 48 h after symptom onset (12%–14%). We did not repeat MRI in patients who received it within 24 h from the symptom onset (8%), except for two patients because a stroke was highly suspected. Both were normal but repeated late at 5 and 19 days after symptoms onset. Therefore, we may have missed some small cerebellar strokes and considered them as peripheral diagnoses.

Third, it was a monocentric study. Based on sensitivities and low LR– for ruling out a central cause of vertigo, the study may advance the uptake of evidence-based eye-movement evaluation into emergency medicine. Only a few hospitals could guarantee MRIs and otologic examinations within short appointments to conduct a multicentric prospective study. Our findings could also suggest a great opportunity to save times and costs with a pathway foregoing CTA and neurologic referral when HINTS and STANDING outcomes are "peripheral."[3,22,23] Indeed, half of peripheral disorders have required extensive use of diagnostic resources in the attending care (neuroimaging plus request to the neurologist). Because it may be acceptable to miss multiple sclerosis lesions but not a posterior ischemic stroke, it will be necessary to conduct an unbiased randomized controlled trial validating HINTS or STANDING tests with even better sensitivities (96.3% and 93.4%, respectively) and smaller 95% CIs (89.0 to 99.3 and 84.5 to 97.6, respectively) than ours. Finally, the main limitation for future effective implementations of the eye-movement assessment in EDs may be physicians' motivation for continuous updating with suitable learning.[41] Nevertheless, it should be achievable in any hospital having an otology department. Frenzel's glasses are the only material required, which cost approximately €500. In our ED, this research allowed us to extend the training with most of the other seniors and residents.

CONCLUSION

In summary, trained emergency physicians can use the HINTS and STANDING tests as part of their workup to identify central acute vertigo with high sensitivity. With a reasonable training, these

structured clinical approaches showed a better accuracy than the traditional stroke risk stratification, ABCD2. Further research is still needed to implement clinical evidence and estimate their cost-effectiveness in EDs.

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CONFLICT OF INTEREST

The authors have no potential conflicts to disclose.

AUTHOR CONTRIBUTIONS

Camille Gerlier, Maëlle Hoarau, and Audrey Fels had full access to all data in the study and take responsibility for the integrity of data and accuracy of data analysis. Study concept and design: Camille Gerlier, Maëlle Hoarau, Carole Mousset, Hélène Vitaux, Wassim Farhat, Gilles Chatellier, Olivier Ganansia. Acquisition of data: Camille Gerlier, Maëlle Hoarau. Analysis and interpretation of data: Camille Gerlier, Maëlle Hoarau, Carole Mousset, Hélène Vitaux. Statistical expertise: Camille Gerlier, Audrey Fels, Gilles Chatellier. Draft manuscript: Camille Gerlier. Proofreading of the manuscript: Camille Gerlier, Maëlle Hoarau, Audrey Fels, Hélène Vitaux, Carole Mousset, Wassim Farhat, Marine Firmin, Victorine Pouyet, Audrey Paoli, Gilles Chatellier, Olivier Ganansia.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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