Final Progress Report

Title of Project:
Solutions for Vertigo Presentations in the Emergency Department (SOLVE) Project

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Abstract

Purpose: To determine the prevalence of stroke etiology in new-onset acute vestibular syndrome presentations and develop model-based decision support using a validated predictor of stroke and a bedside oculomotor examination.

Scope: A dangerous cause of new-onset dizziness is acute stroke, but lacking are prior studies to define the prevalence of stroke in this presentation. In addition, physicians have ranked decision support for identifying stroke in this situation as a top priority. Decision support to identify stroke etiology in this situation is also lacking.

Methods: Active and passive surveillances were used to identify new-onset dizziness patients with nystagmus or imbalance. Patients either received a clinical MRI or were offered a research MRI. Bedside information collected included history of stroke, components of the $ABCD^2$ score (a cardiovascular risk score including age, blood pressure, clinical features, duration, and diabetes), components of an oculomotor-based predictor of stroke (*HINTS*: head impulse, nystagmus pattern [central versus other or none], test of skew), and other central nervous system (CNS) features. Multivariable logistic regression was used to determine the association of the bedside information with acute stroke on MRI.

Results: The final population was 272 patients. The prevalence of acute stroke on MRI was 11% (30 of 272 subjects). Associations with stroke outcome were as follows: cardiovascular risk score (continuous) (odds ratio [OR] 1.81; 95% CI 1.26-2.62), prior stroke (OR 0.42, 95% CI 0.04-4.29), positive HINTS assessment (OR 2.87; 95% CI 0.96-8.58), and other CNS features (OR 2.84; 95% CI 1.20-6.70).

Key Words: Dizziness, vertigo, cerebrovascular disease, clinical decision support

Purpose

Uncertainty in the clinical management of dizziness presentations jeopardizes the value of healthcare by leading to overuse of expensive tests (i.e., head imaging) and adverse outcomes. The problem stems from the lack of estimates of the prevalence of stroke in dizziness presentations derived in an optimal way and the lack of valid methods for adjusting the probability of stroke in dizziness presentations based on history and examination components. As a result, clinicians rely on computerized tomography (CT) scans to discriminate stroke from non-stroke, but this approach not only is wasteful (unnecessary scans increase cost and length of stay in the emergency department (ED)) but also can be dangerous, because the test has a low sensitivity for stroke (26%).[1, 2] The need to address this problem is demonstrated by the ongoing rise in CT scan utilization in ED dizziness visits (169% increase from 1995 to 2004) and by ED physicians ranking the development of a clinical decision rule for dizziness presentations as the #1 priority for clinical problems in adults.[3, 4]

Developing clinical decision support for acute dizziness is a way to address uncertainty and improve healthcare value. Because dizziness presentations are heterogeneous, research to develop a clinical decision rule should begin with a focus on a common dizziness presentation presumed to have an important risk for stroke etiology: the acute vestibular syndrome (i.e., acute onset dizziness, nausea, nystagmus, and/or imbalance). In this R18 grant, we start by aiming to estimate the prevalence of stroke etiology in the acute vestibular syndrome. In addition, we aim to develop practical, model-based stroke risk decision support, which incorporates bedside information.

Scope

Dizziness presentations: Opportunity to Improve Value in Healthcare
Recent research on dizziness presentations demonstrates the following:

1) A fine line between presenting features of sinister and benign causes of dizziness.[5-8]
2) Alarming rates of misdiagnosis[9, 10] and the potential devastating effects of misdiagnosis.[9]
3) Variation in physician approaches to dizziness presentations.[11]
4) ED physicians ranked “identification of central or serious vertigo” as the #1 priority for clinical decision rule development in adults.[4]
5) Serious flaws in current strategies used by frontline physicians to discriminate causes in dizziness presentations.[11]
6) Dramatic increases in the use of CT scans in emergency department presentations for dizziness,[3] despite a low clinical value of CT scans.[1]

Frontline physicians have made a call for more research into dizziness presentations. In a recent survey, 94% (95% confidence interval [CI], 90%-97%) of emergency medicine physicians supported the development of a clinical decision rule for guiding the use of diagnostic testing in dizziness presentations.[11] In a separate study, a clinical decision rule for dizziness ranked as the #1 priority for adult clinical decision rule development.[4] Because dizziness presentations are so common – 7.5 million presentations per year in the United States[12] – the job of screening each patient for a sinister cause is a daunting task.

Frontline physicians must make critical decisions about which patients presenting with dizziness require only symptomatic care and which patients need a work-up for a sinister cause. Even after the physician decides to screen the patient for a sinister cause, the incorrect test could be ordered.[9] Though most causes of dizziness are benign,[13] some patients harbor a serious disorder, such as stroke.[5-9, 14]

Because “dizziness” is such a heterogeneous symptom, the initial steps to optimizing care should focus on the dizziness presentations with the most at stake. The dizziness presentation with the most at stake is the “acute vestibular syndrome,” because it carries an important risk of stroke and much uncertainty exists about how to discriminate a benign inner ear cause from stroke. If a stroke causing the acute vestibular syndrome is not identified early, herniation and death can ensue.[9] At the same time, rising rates of utilization of neuroimaging are a concern from a healthcare utilization perspective, because the most common cause of the acute vestibular syndrome is a benign inner ear disorder. Research focusing on the acute vestibular syndrome has the opportunity to improve quality and safety of patient care, foster appropriate use, and reduce unnecessary expenditures.

Prior studies have been performed to identify bedside methods to discriminate stroke from non-stroke etiology in acute dizziness presentations.[15-17] Methods used have included the ABCD^2 score (e.g., age, blood pressure, clinical features, duration, and diabetes) and the HINTS assessment (Head Impulse, Nystagmus pattern, Test of Skew). However, these prior studies are limited by a retrospective or referral-based case capture method and use of MRI based on routine care. In addition, the collective value of these previously developed methods has not been assessed.

Methods

Study Design and Setting
This was a prospective, single-center observational study that enrolled patients from November 21, 2009, to March 29, 2013. The study site is an urban, academic medical center. The main setting of recruitment was the level-1 trauma center emergency room. A minority of subjects were identified in the outpatient or inpatient settings. The study site institutional review board approved the study.

Study Population
Inclusion criteria were the presentation for the principal symptom of continuous dizziness *and* examination findings of either nystagmus (spontaneous or gaze-evoked) or new imbalance when walking that was both subjective from the patient’s perspective and objective based on the examination. The minimum requirement for objective imbalance was the inability to take 10 steps in tandem without a side step after up to two attempts. Dizziness symptoms were inclusive of vertigo (i.e., spinning or other illusory sensation of movement), lightheadedness, gait imbalance, or otherwise undifferentiated dizziness.

Excluded were persons <18 years of age, prisoners, and patients not fluent in English or not able to provide informed consent due to cognitive or psychiatric impairment. Patients were additionally excluded for chronic recurrent dizziness (defined as ≥5 episodes similar in quality, intensity, and duration to the current symptoms, with at least one episode more than a year ago and one within the past year); or dizziness thought to be the result of trauma, orthostatic hypotension, medication/drug intoxication, or a known medical disorder (e.g., hepatic encephalopathy, hydrocephalus). Subjects identified as having posterior canal benign paroxysmal positional vertigo (BPPV) (i.e., characteristic transient upbeat-torsional nystagmus on the Dix-Hallpike test) were excluded unless spontaneous or gaze-evoked nystagmus was also present. We did not exclude patients with horizontal positional nystagmus, because this pattern can be caused by central or peripheral disorders.[18, 19] Patients who had moderate to severe, new central nervous system (CNS) exam abnormalities were excluded (e.g., hemiparesis, hemisensory loss on examination, severe axial ataxia), but patients with possible or only very mild abnormalities (e.g., small deviations on coordination testing, mild dysarthria, or sensory symptoms) were not excluded.

Case Identification

To identify potentially eligible cases, we used several methods. An automated paging system was used for active surveillance. This system was programed to search the ED database and page study personnel regarding potentially eligible subjects. The search algorithm required updates and revisions during the study period for optimization and because the ED database changed during the course of the study. From study initiation to June 12, 2012, the program performed a search at 15-minute intervals for dizziness terms in the chief complaint or history of present illness (HPI) sections, which are completed by triage personnel. Search terms included dizziness, dizzy, vertigo, spinning, imbalance, ataxia, can't walk, nystagmus, unsteady gait, abnormal gait, or ataxic gait. Misspellings were also included. Triage personal recorded the chief complaint in this database by either selecting it from a menu or using free text. The HPI information was entered with free text. The ED database was changed to a different electronic medical record system on June 13, 2012. With the new database, the triage chief complaint could only be selected from a menu, and the free-text triage HPI was no longer searchable. With the new database, the following chief complaints triggered a page: "dizziness," "gait problem," and "cerebrovascular accident." There was no option for "vertigo" or other previously used terms. At later time periods, the algorithm to trigger a page was updated to include an order entry for meclizine during the visit or the recording of a dizziness or vestibular diagnosis (386.x, 388.5, 388.9, 780.2, 780.4, 994.6) in the electronic medical record. Additional active surveillance methods included study research assistants routinely reviewing the ED list of active patients and circulating in the ED. Passive surveillance methods included advertising the study (via emails, conference presentations, and posted signs) to ED, neurology, and otolaryngology healthcare providers, who were encouraged to contact study personal for potentially eligible patients. Subjects identified by our surveillance methods were screened in person (either by an investigator or a trained research assistant) for eligibility.

Baseline Measurements

Data collected from patients by study personnel

History of present illness information was obtained in a structured fashion by either a research assistant or investigator. Information collected included symptom onset date and time, type and severity of dizziness symptoms, other neurologic or neuro-otologic symptoms, and prior history of dizziness. The physical examination was performed in a structured fashion by a study investigator. The general neurologic examination included assessment of visual fields, cranial nerves, strength, sensation, coordination, and balance.

The oculomotor examination was performed, including a nystagmus assessment, assessment of skew deviation, and the head impulse test (HIT). For the purpose of exam reliability determination, the oculomotor examination was also video recorded. The nystagmus variable was scored from 0-4, with a 0 equal to no nystagmus and a 4 equal to positive nystagmus at a high velocity. Patients were classified as having bi-directional gaze-evoked nystagmus (GEN) when nystagmus was rated as a 2 or higher in one horizontal direction and a 1 or higher in the opposite direction. Patients were classified as having a central pattern of nystagmus if any of the following were observed: vertical nystagmus (i.e., up- or down-beat scored as 2 or higher) in primary position or gaze testing, or bi-directional GEN. The assessment of skew deviation was performed by the alternate cover test while the subject fixated on a straight-ahead target. Skew deviation was classified as present when alternating vertical re-fixations were observed. The head impulse test (HIT) was scored from a 0-4 for each side, with a 0 equal to no corrective saccade after the HIT and a 4 equal to a positive corrective saccade that was severely abnormal. A second examiner, when available, also performed an oculomotor exam so that the reliability of these components could be estimated.

Data collected from the medical record

From the medical record, we collected arrival date/time, first recorded blood pressure, and demographic information. From the physician's note, we abstracted past medical history and current medications.

Cardiovascular risk score

The $ABCD^2$ score was calculated for each subject by assigning points as follows: age 60 years or older = 1; systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 = 1; clinical features (symptoms or exam findings of unilateral weakness = 2, speech disturbance without weakness = 1); duration of symptoms (<10 minutes = 0, 10-59 minutes = 1, ≥ 60 minutes = 2); and diabetes (either past medical history or current use of an oral hypoglycemic medicine or insulin documented in physician's note) = 1.[20]

The HINTS Evaluation

The Head Impulse test, Nystagmus assessment, and Test of Skew (collectively referred to as "HINTS") was categorized as a 0, 1, or 2. Subjects were assigned to HINTS category 0 when there was no nystagmus (i.e., no nystagmus rated 2 or higher in any direction) or skew deviation on examination. The head impulse test was not considered in HINTS category 0 because, when nystagmus is not present, the value of the head impulse test in an acute presentation is uncertain.

Subjects were assigned to HINTS category 1 when a non-central pattern of nystagmus was present, the head impulse test was abnormal (i.e., HIT score of ≥2, suggesting a peripheral lesion), and skew deviation was not present. Subjects were assigned to HINTS category 2 (i.e., HINTS "positive" category) when a central pattern of nystagmus was present, the head impulse test was normal (i.e., HIT score of 0 or 1, suggesting a central lesion), *or* a skew deviation was present.

Other Central Nervous System (CNS) features
The variable other CNS features was scored as a "1" when there were sensory signs or symptoms, a visual field deficit, or dysmetria on the finger-nose-finger test.

Outcome Measure
The primary outcome was a cerebrovascular cause of dizziness, defined using MRI criteria of restricted diffusion or hemorrhage determined by a neuroradiologist. All enrolled subjects were offered a research MRI of the brain if an MRI was not performed as part of the clinical evaluation (determined by treating providers) or if a clinical care MRI was performed within 24 hours of symptom onset and was negative for a cerebrovascular cause. A repeat MRI was offered because studies have suggested potential for missed stroke when done under 24 hours.[21] MRIs were performed on either a 1.5T or 3T machine. The MRI protocol for clinical and research studies followed radiology department protocols, including the following sequences: T1-weighted images pre- and post-gadolinium in sagittal, axial, and coronal planes and T2-weighted images, fluid-attenuated inversion recovery (FLAIR) images, and diffusion-weighted images with apparent diffusion coefficient (ADC) maps in the axial plane. An abbreviated research MRI protocol was used if the subject already had a clinical MRI negative for a cerebrovascular cause and when subjects could not tolerate or declined the full MRI protocol. The abbreviated protocol included fluid-attenuated inversion recovery (FLAIR) images, diffusion-weighted images, and apparent diffusion coefficient (ADC) maps in the axial plane.

Statistical Analysis
Descriptive statistics were used to summarize demographic and clinical characteristics of the study subjects.

Reliability of HIT
Reliability of the head impulse test was calculated using intraclass correlation coefficients (ICC), separately for in-person second examinations and video-review second examinations. Both in-person and video-review second examinations were performed blinded to other clinical information. Methods to harmonize investigator exam scoring included discussion and review of the examination (after exam scores had been recorded) in 5-10 patients and 10 meetings to review videotaped oculomotor exams. ICC was calculated using multi-level models, with the exam score (0-4) as the dependent variable and exam scores nested in sides (i.e., right or left) and sides nested in patients.

Modeling associations with stroke outcome
Subjects were excluded from the analysis modeling outcomes if the patient had a history of multiple sclerosis or if an MRI was not performed within 14 days of onset. The sample was restricted to subjects having an MRI within 14 days of onset because of the reduced accuracy of MRI for new ischemia beyond this time period.[22-26] A multivariable logistic regression model was then constructed with acute ischemic stroke on MRI (0/1) as the dependent variable. The independent variables included $ABCD^2$ score (modeled continuously), HINTS, history of prior stroke (0/1), and other CNS features (0/1). Model discrimination was measured with the c-statistic, including 95% confidence intervals (CI). Statistical analysis was performed using Stata 12.0 (College Station, TX).

Results

Principal Findings
From November 21, 2009, to March 31, 2013, we performed in-person screening for eligibility in 3,296 visits. In an additional 73 visits, potential subjects declined to be screened by study personnel. Visits met eligibility criteria in 394 of the screenings, of which 341 were enrolled, 28 declined enrollment, and 25 were not enrolled because an investigator was not available to perform the examination.

One subject was enrolled twice (two different visits), because the outcome MRI test was not performed after the first enrollment. This patient's first visit was excluded from the current analysis. Additionally excluded from the current analysis were eight patients with contraindications for MRI, six patients with symptom onset more than 14 days from enrollment, five patients with a history of multiple sclerosis, and two patients with ophthalmoparesis.

Of these 319 enrolled subjects, 14.7% (47/319) did not receive a brain MRI within 14 days of symptom onset and thus were not included in the main analysis (exam data was included in the reliability analysis).

Of patients who received an MRI (272), the initial MRI was performed for clinical purposes in 158 (58%) and for research purposes in 114 (42%). Median age was 56.6 years (IQR, 48.7-67.1), and 51% were women. Race/ethnicity was follows: non-Hispanic White, 217 (80%); non-Hispanic Black, 34 (13%); Asian, 12 (4%); and Hispanic, 9 (3%). The median $ABCD^2$ score was 3 (IQR, 2-4). Twelve subjects had a history of stroke, 53 (19.5%) had a positive other CNS feature, and 119 (44%) had a central pattern of HINTS. Reliability of the head impulse test was moderate (ICC for in-person assessments, 0.51 [95% CI, 0.42-0.60] and for second video assessment, 0.55 [95% CI, 0.50-0.60]).

An acute stroke on MRI was identified in 30 of the 272 subjects (11.0%; 95% CI, 7.6%-15.4%) (n = 27 ischemic stroke, n = 3 intracerebral hemorrhage). The results of the logistic regression model are presented in the table. The model c-statistic was 0.77. Associations with acute stroke were significant for $ABCD^2$ score ($P<0.01$) and other CNS features ($P<0.05$), borderline significant for HINTS ($P=0.06$), and not significant for Prior Stroke ($P=0.47$).

Discussion
The findings of this study provide the most accurate estimates to date regarding the prevalence of acute stroke etiology in the acute vestibular syndrome presentation. We used rigorous surveillance methods, and all enrolled patients either had a clinical MRI or were offered a research MRI. The findings of the multivariable regression model indicate that the bedside information has the potential to meaningfully inform decision making regarding acute stroke etiology. However, future validation work is required before the use of this predictive information can be advocated for use in routine clinical practice.

Additional exploratory analyses are being performed, using a wider array of predictor variables and variable selection methods. We will also explore associations with longer-term functional outcomes.

Limitations
This was a single-center study at a tertiary medical center. Some factors could have impacted the patient's examination or our interpretation of it. MRI was performed prior to the clinical assessment in 15% of the subjects. Although investigators were blinded to the MRI results, it is still possible that subtle clues were conveyed. The oculomotor findings could have been affected by medication treatment. The use of MRI as the primary outcome measures could have resulted in some diagnostic misclassification.[16,27]

An important advantage of MRI as the outcome measure is its very high reliability for acute stroke classification.[2] We did not use a composite outcome measure of MRI plus clinician judgment, because the clinician would have used components of our index tests to classify the outcome (incorporation bias).[28] To reduce the possibility of MRI stroke misclassification,[16] we took efforts to have an MRI performed at least 24 hours after symptom onset and achieved this in 92% of the non-stroke group.

Implications
The prevalence estimated from this study provides important information for informing the pre-test probability of stroke on MRI in this presentation. If externally validated, the predictive information may be useful for triaging dizziness presentations to the ED.

Inclusion of AHRQ priority populations

In this project, women accounted for 51% of the subjects, and the median age was 56.6 years (IQR, 48.7-67.1). Race/ethnicity was follows: non-Hispanic White, 217 (80%); non-Hispanic Black, 34 (13%); Asian, 12 (4%); and Hispanic, 9 (3%).

List of Publications and Product

Manuscript submission is in progress.

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Table. Results of multivariable logistic regression model with dependent variable of acute stroke on MRI.

	Odds Ratio (95% CI) N=272
Primary Variables	
$ABCD^2$ (continuous) [a]	1.81 (1.26-2.62)
Prior Stroke	0.42 (0.04-4.29)
Other CNS Features [b]	2.84 (1.20-6.70)
Oculomotor Assessment	
HINTS [c]	
0	Ref
1	1.23 (0.32-4.78)
2	2.87 (0.96-8.58)
c-statistic	0.77 (0.69-0.85)

CNS = central nervous system

[a] ABCD2 (modeled continuously) assigns points based on the following: age 60 years or older = 1; systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 = 1; clinical features (symptoms or exam findings of unilateral weakness = 2, speech disturbance without weakness = 1); duration of symptoms (<10 minutes = 0, 10-59 minutes = 1, ≥ 60 minutes =2); and diabetes = 1.

[b] Other CNS features includes mild findings of any of the following: visual field deficit, dysmetria, or sensory symptoms or deficits. These are CNS features not included in the $ABCD^2$ score or HINTS assessment.

[c] HINTS (Head Impulse Test [HIT], Nystagmus [central pattern], Test of Skew) is scored as follows: No nystagmus on exam = 0; Positive nystagmus but peripheral HIT, no central nystagmus pattern, and no skew deviation = 1; and positive nystagmus but any of the following: normal HIT, central pattern of nystagmus, or skew deviation.