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Risk of Stroke Following the ICD-9 Discharge Code Diagnosis of Hypertensive Encephalopathy

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Abstract

Background and Purpose—Although chronic hypertension is a well-established risk factor for stroke, little is known about stroke risk after hypertensive encephalopathy (HE), when neurologic sequelae of hypertension become evident. Therefore, we evaluated the risk of stroke following a diagnosis of HE.

Methods—We identified all patients discharged from California, New York, and Florida emergency departments and acute care hospitals between 2005 and 2012 with a primary *International Classification of Diseases, 9th Edition, Clinical Modification* discharge diagnosis of HE (437.2). Patients discharged with a primary diagnosis of seizure (345.x) served as negative controls, while patients with a primary diagnosis of transient ischemic attack (TIA) (435.x) were positive controls. Our primary outcome was the composite of subsequent ischemic stroke or intracerebral hemorrhage (ICH). Kaplan-Meier survival statistics were used to calculate cumulative outcome rates, and Cox proportional hazard analysis was used to examine the association between index disease types and outcomes while adjusting for vascular risk factors.

Results—We identified 8,233 patients with HE, 191,091 with seizure, and 308,680 with TIA. The 1-year cumulative rate of ischemic stroke or ICH after HE was 4.90% (95% confidence interval [CI], 4.45–5.40), as compared to 0.92% (95% CI, 0.88–0.97) following seizure and 4.49% (95% CI, 4.42–4.57) following TIA. The risk of ICH was significantly elevated in those with HE (HR, 2.0; 95% CI, 1.7–2.5) but not TIA (HR, 1.0; 95% CI, 0.9–1.1), when compared to seizure patients.

Conclusions—Patients discharged with a diagnosis of HE face a high risk of future cerebrovascular events, particularly ICH.

Keywords

stroke; hypertensive encephalopathy; ischemic stroke; hemorrhagic stroke; intracerebral hemorrhage; risk factor; hypertension; epidemiology

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Conflicts of Interests/Dislosures

None

Approximately 1–2% of patients with chronic hypertension at some point develop hypertensive emergency,^{1–3} where blood pressure rises substantially and causes end-organ dysfunction.^{4, 5} In up to 16% of these hypertensive emergencies, end-organ dysfunction involves the brain and is termed hypertensive encephalopathy (HE).^{2, 4–6} Current teaching describes HE as a rapidly evolving syndrome of severe hypertension (or sharp relative rise in blood pressure) associated with seizures, focal neurological signs, or symptoms of cerebral edema such as headache, nausea, or depressed consciousness.⁷ The mechanisms by which blood pressure elevations result in encephalopathy are uncertain but are postulated to involve arteriolar dilatation beyond auto-regulatory capacity, which subsequently disrupts the blood-brain barrier and leads to extravasation of plasma.^{5, 8–11} Because they share similar pathophysiology, HE often manifests as reversible posterior leukoencephalopathy syndrome (RPLS), accounting for 61% of RPLS cases.^{5, 12}

Although chronic hypertension is a well-established risk factor for stroke,¹³ HE may represent a separate entity that further increases stroke risk. There is a paucity of literature evaluating the subsequent risk of cerebrovascular events following a diagnosis of RPLS or HE.⁹ However, eclampsia, a disease with similar pathophysiology as HE, is associated with increased long-term stroke risk,^{14, 15} which raises the question whether episodes of HE may also serve as additive risk factors for stroke. Therefore, we performed a retrospective cohort study to determine the association between a diagnosis of HE and the risk of subsequent stroke.

Materials and Methods

Design

We retrospectively evaluated the risk of stroke after a discharge diagnosis of HE using administrative data from three states: the California Office of Statewide Health Planning and Development, the New York State Department of Health, and the Florida Agency for Health Care Administration. These organizations collect standardized discharge data from all nonfederal emergency department (ED) visits and hospitalizations within the state, and report these data in a de-identified format to the Agency for Healthcare Research and Quality for its Healthcare Cost and Utilization Project.¹⁶ Patients are assigned a de-identified personal linkage number that allows them to be followed across ED encounters and hospitalizations over multiple years.¹⁷ Up to 25 discharge diagnoses are coded at each encounter using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* system. The institutional review board at Weill Cornell Medical College approved this study.

Validation of the HE Diagnosis Code

To our knowledge, the *ICD-9-CM* code for HE (437.2) has never been validated in the literature. Therefore, we performed a retrospective chart review at our hospital to determine the test properties of the diagnosis code. We identified all admissions to our institution with HE as the primary discharge diagnosis code from 2009 through 2013 (n=22). Additionally, we identified 22 discharges with other primary cerebrovascular diagnosis codes (e.g., transient ischemic attack or ischemic stroke) and no HE code. A board-certified neurologist

(M.P.L.) reviewed all available medical records from these 44 encounters and adjudicated a final diagnosis while remaining blinded to the diagnosis code. HE was diagnosed if systolic blood pressure was greater than 180 mm Hg or diastolic blood pressure was greater than 120 mm Hg and there were (1) seizures, visual changes, confusion, altered consciousness, or focal neurological deficits that resolved with blood pressure control, or (2) brain imaging demonstrating cerebral edema without accompanying hemorrhage or ischemia (any acute infarction on brain imaging resulted in a different cerebrovascular diagnosis such as intracerebral hemorrhage [ICH] or ischemic stroke). We specifically excluded patients with headache as the sole complaint, as there would be no objective clinical findings in these cases, and this would narrow the spectrum of patient presentations in our diagnosis of HE. Using this diagnostic schema as the gold standard, we calculated the sensitivity and specificity of the *ICD-9-CM* code 437.2 for the diagnosis of HE. Validation of the *ICD-9-CM* code for HE (437.2) at our institution showed that the code has 93% sensitivity and 71% specificity.

Patients

Using *ICD-9-CM* code 437.2 in the primary discharge diagnosis position, we identified consecutive patients 18 years or older with the diagnosis of HE between 2005–2011 in California, 2006–2011 in New York, and 2005–2012 in Florida. These observation periods were chosen in order to have at least one year of follow-up data for all study patients. Patients coded as having HE on multiple encounters were identified at the time of their first-ever recorded ED visit or hospital admission with HE. To minimize ascertainment bias, we excluded patients with documented cerebrovascular disease (*ICD-9-CM* codes 430–438 in any discharge diagnosis position) prior to, or during, the index hospitalization for HE. We excluded non-residents of California, New York, or Florida in order to maximize patient follow-up.

As control groups, we identified all patients discharged from nonfederal California, New York, or Florida EDs or hospitals between 2005 and 2012 with a primary discharge diagnosis of seizure or transient ischemic attack (TIA). We selected seizure (345.x) as a negative control because it is a paroxysmal neurological event that does not considerably increase stroke risk.¹⁸ This code has up to a 99% positive predictive value, a 97% negative predictive value, and sensitivities between 70–99%.^{19, 20} Conversely, we selected TIA (435.x) as a positive control because it is a well-established risk factor for subsequent stroke.^{18, 21}

Measurements

Patients with HE were followed for at least 1 year from their index visit for a primary composite outcome of ischemic stroke or ICH. Ischemic stroke was defined as a hospitalization with *ICD-9-CM* codes 433.x1, 434.x1, or 436 in any discharge diagnosis position without a primary discharge code for rehabilitation (V57) or an accompanying diagnosis of trauma (*ICD-9-CM* 800–804 or 850–854) or ICH (*ICD-9-CM* 431) or subarachnoid hemorrhage (*ICD-9-CM* 430) in any diagnostic position.²² ICH was defined using *ICD-9-CM* code 431 in any discharge position without concomitant codes for rehabilitation (V57) in the primary diagnosis position or trauma (*ICD-9-CM* 800–804 or

850–854) in any position. These administrative codes for ischemic and hemorrhagic stroke have been previously validated as having a sensitivity and specificity of 85% or higher.²² Patients entered observation immediately after discharge from the index encounter with HE diagnosis and were followed until death, the occurrence of the primary outcome, or the end of follow-up. In secondary analyses, ischemic and hemorrhagic strokes were considered separately.

In order to account for potential confounding from demographic characteristics and vascular risk factors, we collected data on the following patient variables: age, sex, race, insurance status; and diagnoses of hypertension, diabetes, atrial fibrillation, coronary artery disease, congestive heart failure, peripheral vascular disease, chronic kidney disease, and chronic obstructive pulmonary disease.

Statistical analysis

Descriptive statistics were used to calculate crude rates and Kaplan-Meier survival statistics were used to evaluate cumulative rates. Patients entered observation at the first visit that resulted in a discharge diagnosis of HE, seizure, TIA, or hypertension, and were censored at the time of in-hospital death or last available follow-up data. Multivariable Cox proportional hazard analysis was used to examine the association between index disease type and subsequent stroke while accounting for the potential confounders listed above, using seizure as the reference in our model. We performed sensitivity analyses using inverse probability weighting to account for imbalances in sample size between diagnosis groups. As our goal was to isolate the relationship between our exposures and outcome, all covariates were left in place regardless of statistical significance. Significance was two-sided and defined using an alpha of 0.05. All analyses were performed using STATA version 13 (StataCorp, College Station, TX).

Results

We identified 8,233 patients with a diagnosis of HE, 191,091 patients with seizure, and 308,680 patients with TIA. Compared to the other diagnostic cohorts, those with HE were more likely to be female, black, and have more vascular risk factors (Table 1). Within the HE cohort, patients were mostly white women with a high proportion of traditional vascular risk factors. Most patients (89.7%) diagnosed with HE were hospitalized from the ED.

There were 27,642 strokes over the course of follow-up, of which 24,780 (89.6%) were ischemic and 2,862 (10.4%) were hemorrhagic (Table 2). The 1-year cumulative rate of our combined primary endpoint of ischemic stroke or ICH was 4.90% (95% confidence interval [CI], 4.45–5.40) following a diagnosis of HE, as compared to 4.49% (95% CI, 4.42–4.57) following TIA and 0.92% (95% CI, 0.88–0.97) following seizure. Similar findings were observed when considering only ischemic strokes: the 1-year cumulative rate of ischemic stroke was 4.12% (95% CI, 3.70–4.59), 4.15% (95% CI, 4.08–4.22), and 0.75% (95% CI, 0.71–0.79) for HE, TIA and seizure diagnoses, respectively. In contrast, first-year rates of ICH were substantially higher in patients diagnosed with HE (0.81%; 95% CI, 0.63–1.04), as compared to TIA patients (0.36%; 95% CI, 0.34–0.38) and seizure patients (0.18%; 95% CI, 0.16–0.20).

After adjusting for patient demographics and vascular risk factors, ischemic stroke risk was elevated in patients with diagnoses of HE (hazard ratio [HR], 1.9; 95% CI, 1.7–2.0) and TIA (HR, 2.2; 95% CI, 2.1–2.3) when compared to those with seizures. ICH risk was significantly increased in patients with HE (HR, 2.0; 95% CI, 1.7–2.5) but not in those with TIA (HR, 1.0; 95% CI, 0.9–1.1). Our findings were unchanged in sensitivity analyses weighted to account for imbalances in sample size between groups.

Discussion

Using administrative claims data from a large, multi-state cohort, we found that patients diagnosed with HE are at high risk for stroke over the ensuing year. Specifically, patients diagnosed with HE have comparable annual rates of ischemic stroke and significantly higher rates of ICH when compared to patients diagnosed with TIA.

Few data exist on the risk of stroke following a HE diagnosis,⁹ as most reports focused on the increased risk of stroke at presentation with HE.^{8, 23, 24} We found that stroke risk remains increased long after the resolution of an episode of HE. This evidence suggests that patients with uncontrolled hypertension, particularly when their disease results in neurological manifestations, may need improved long-term observation and blood pressure management.

Our study has several notable limitations. First, by relying on administrative claims and diagnosis codes, we have no means to confirm the assigned diagnoses through review of imaging studies, and some of these cases of HE may have represented diagnoses of stroke. Since the rate of misdiagnosis is bidirectional (i.e., strokes are misclassified as HE,²⁵ and HE is misclassified as stroke²⁶), such misclassification would have unknown effects on our findings. However, the rate of misdiagnosis of hypertensive emergency for ischemic stroke has been notably small (8%) in a previous report.²⁵ Furthermore, review of medical records indicated that the diagnosis code for HE faithfully captures the clinical diagnosis at the time of care. This suggests that regardless of any misclassification in regards to the true diagnosis, the current clinical label of HE represents a vulnerable population of adults who face a high risk of subsequent cerebrovascular events. However, we lacked data on the specialty of the providers who cared for these patients, and therefore could not account for potential differences in diagnosis depending on the physician's specialty. Second, we were unable to differentiate between patients who did or did not have signs of visible cerebral edema on magnetic resonance imaging studies, as we did not have access to these imaging records and there is no specific *ICD-9-CM* code for RPLS (i.e., those patients who would have positive imaging for cerebral edema⁸). This distinction may be clinically significant as patients with RPLS often present with ICH^{23, 24} and therefore may have higher rates of recurrent hemorrhage. Future studies using the *ICD-10-CM* classification system, which does have a diagnosis code for RPLS, may be helpful to further differentiate HE and RPLS, which are likely two disease entities with overlapping features on the same spectrum.^{5, 8}

Conclusions

We found that patients discharged from acute care hospitals with the diagnosis of HE face an increased risk of stroke, particularly ICH, long after their index event has resolved. These findings suggest that patients with HE may benefit from improved risk factor modification and closer follow-up.

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Table 1

Baseline Patient Characteristics

Characteristic ^a	HE (N = 8,233)	TIA (N = 308,680)	Seizure (N= 191,091)
Male	3,026 (36.8)	130,527 (42.3)	99,011 (51.8)
Race ^b			
White	3,998 (49.8)	211,758 (70.3)	107,376 (57.7)
Black	2,312 (28.8)	34,110 (11.3)	37,046 (19.9)
Hispanic	1,092 (13.6)	39,144 (13)	30,386 (16.3)
Asian	361 (4.5)	8,252 (2.7)	3,580 (1.9)
Other	269 (3.4)	7,804 (2.6)	7,787 (4.2)
Payment source ^b			
Medicare	4,584 (55.7)	198,760 (64.4)	56,249 (29.5)
Medicaid	985 (12)	17,827 (5.8)	42,427 (22.2)
Private	1,729 (21)	71,814 (23.3)	50,274 (26.3)
Self-pay	635 (7.7)	11,577 (3.8)	30,425 (15.9)
Other	300 (3.6)	8,631 (2.8)	11,637 (6.1)
Hypertension	8,233 (100)	206,207 (66.8)	44,719 (23.4)
Diabetes	2,822 (34.3)	78,515 (25.4)	20,124 (10.5)
Coronary heart disease	1,740 (21.13)	68,262 (22.1)	10,624 (5.6)
Congestive heart failure	899 (10.9)	19,686 (6.4)	4,244 (2.2)
Peripheral vascular disease	527 (6.4)	13,690 (4.4)	1,875 (1.0)
Chronic obstructive pulmonary disease	657 (8.0)	24,138 (7.8)	6,839 (3.6)
Chronic kidney disease	1,979 (24)	17,776 (5.8)	5,437 (2.9)

Abbreviations: HE, hypertensive encephalopathy; TIA, transient ischemic attack.

^aData are presented as number (%) unless otherwise specified.

^bPercentages reflect all patients for whom racial and insurance data were available.

Table 2

First-year Stroke Risk in Patients Diagnosed with HE, TIA and Seizure, Stratified by Stroke Subtype.

Outcome by Stroke Subtype	HE (N = 8,233)	TIA (N = 308,680)	Seizure (N= 191,091)
Cumulative stroke rate ^a			
Ischemic	4.12% (3.70–4.59)	4.15% (4.08–4.22)	0.75% (0.71–0.79)
ICH	0.81% (0.63–1.04)	0.36% (0.34–0.38)	0.18% (0.16–0.20)
Combined stroke ^b	4.9% (4.45–5.40)	4.49% (4.42–4.57)	0.92% (0.88–0.97)
Hazard ratio ^a			
Ischemic	1.9 (1.7–2.0)	2.2 (2.1–2.3)	Ref
ICH	2 (1.7–2.5)	1 (0.9–1.1)	Ref
Combined stroke ^a	1.9 (1.7–2.0)	2 (1.9–2.1)	Ref

Abbreviations: HE, hypertensive encephalopathy; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; Ref, reference

^aData are presented as outcome measure followed by 95 % confidence intervals in parentheses.^bPrimary outcome of combined ischemic and hemorrhagic events