



Predictors and outcomes of ischemic stroke in reversible cerebral vasoconstriction syndrome

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Abstract

Introduction The clinical factors predisposing to ischemic stroke in reversible cerebral vasoconstriction syndrome (RCVS) are unclear. In this observational cross-sectional study, we aimed to evaluate the risk factors and clinical outcomes associated with the development of ischemic stroke in patients with RCVS.

Methods We utilized the Nationwide Readmissions Database 2016–2017 to identify all hospitalizations with RCVS, with or without acute ischemic stroke. Independent predictors of and clinical outcomes associated with ischemic stroke were analyzed using logistic regression.

Results Among 1065 hospitalizations for RCVS (mean \pm SD age 49.0 ± 16.7 years, female 69.7%), 267 (25.1%) had ischemic stroke. Patients with ischemic stroke were more likely to have hypertension (OR 2.33, 95% CI 1.51–3.60), diabetes (OR 1.81, 95% CI 1.11–2.98), and tobacco use (OR 1.64, 95% CI 1.16–2.33) and were less likely to have a history of migraine (OR 0.56, 95% CI 0.35–0.90). Ischemic stroke was associated with higher odds of cerebral edema (OR 3.15, 95% CI 1.31–7.57) and respiratory failure (OR 2.39, 95% CI 1.28–4.44). Patients with ischemic stroke also had longer hospital stay by a mean duration of 6.7 days, $P < 0.001$, higher hospital charges by a mean of \$72,961, $P < 0.001$, and a higher likelihood of not being discharged to home (OR 3.57, 95% CI 2.39–5.33). They had higher in-hospital mortality rate; however, the difference was not statistically significant.

Conclusion Ischemic stroke affects nearly 25% of patients with RCVS and is associated with adverse clinical outcomes. RCVS patients with cerebrovascular risk factors might have a higher predisposition for developing ischemic lesions during the disease process.

Keywords RCVS · Hypertension · Tobacco · Diabetes · Cerebral edema · Disposition

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by diffuse, segmental cerebral artery vasoconstriction, usually heralded by severe thunderclap headaches, spontaneously resolving within 3 months [1, 2]. While most patients have a benign clinical course, a significant minority

can develop stroke, which is the cause for major morbidity and mortality in this syndrome [3–5]. There is increasing evidence to suggest that ischemic stroke in RCVS is associated with proximal vasoconstriction [6]. However, it is still unclear what factors predispose some patients to develop the ischemic lesions. We aimed to evaluate the risk factors and outcomes associated with ischemic stroke in RCVS.

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Methods

Study population

Data were obtained from the Nationwide Readmissions Database 2016–2017, developed by the Agency for Healthcare Research and Quality for the Healthcare Cost and Utilization Project [7]. The Nationwide Readmissions Database

is an all-payer (Medicare, Medicaid, private insurance, and self-pay) inpatient care database with approximately 36 million discharges per year from short-term hospitals in 22 states in the U.S., representing about 50% of total national hospitalizations. The number of discharges is weighted to estimate the nationally representative statistics. All analyses in this study complied with the Healthcare Cost and Utilization Project data use agreement and the study was exempt from the Institutional Review Board as the Nationwide Readmissions Database is a publicly available database containing deidentified data.

The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) code I67.841 was used to identify the hospitalizations with the discharge diagnosis of RCVS. Acute ischemic stroke was identified using the ICD-10 codes I63.x, I67.81, I67.82, and I67.89. Only the first RCVS hospitalization of the year for each patient was included and hospitalizations with the diagnosis of hemorrhagic stroke were excluded.

Patient characteristics, covariates, and outcomes

Baseline patient characteristics including age, sex, median household income; hospital characteristics including bed size, ownership/control, location and teaching status; and other hospitalization variables such as the expected primary payer, length of stay, total charges, and discharge disposition were extracted from the data. The ICD-10 diagnosis and procedure codes were used to identify the comorbidities, complications, and interventions performed during the hospital stay. Secondary clinical outcomes included length of stay, hospital charges, discharge disposition, and in-hospital mortality. Disposition at the time of discharge included home, transfer to a short-term hospital, skilled nursing facility, intermediate care or other type of facility, home health care, and against medical advice. Disposition outcomes other than to home were combined and assessed as a clinical outcome.

Statistical analysis

We used the survey design methods to account for data clustering and stratification to generate national estimates. Continuous variables were represented as mean [(standard deviation (SD))] and categorical variables as proportions. Predictors of ischemic stroke were screened using univariate logistic regression with results expressed as odds ratio (OR) and 95% confidence interval (CI). Multivariable analysis was performed using a stepwise backward elimination method starting with all variables from univariate analysis with $P < 0.05$. Multivariable model was checked for multicollinearity using a variance correlation matrix. Logistic and linear regressions were used to identify the association between ischemic stroke and the clinical outcomes. There

were no missing values for variables, except for hospital charge, primary payer, and median household income, which were missing in $< 1.5\%$ of the cases. All reported P values were two-sided with $P < 0.05$ considered significant. All analyses were performed using Stata, version 15.0 (Stata-Corp, College Station, TX).

Results

Population characteristics

Among 71,451,419 weighted discharges during the study period, 1,938 had a discharge diagnosis of RCVS. Based on the inclusion criteria, 1065 discharges for RCVS were included for further analysis. The baseline characteristics of all patients are shown in Table 1. The mean (SD) age was 49.0 (16.7) years and 69.7% were female. Common comorbidities included hypertension (55.6%), hyperlipidemia (31.9%), migraine (25.1%), depression (23.7%), and diabetes (21.5%). Lumbar puncture (36.4%) and cerebral angiography (25.0%) were the most frequently performed inpatient procedures. Most patients had private insurance (43.6%) and a majority of the hospitalizations were at the large (73.9%), teaching hospitals (88.2%). The mean (SD) length of stay was 7.1 (10.3) days and approximately 26% of patients had discharge disposition other than home.

Predictors of ischemic stroke

Among the total 1065 patients, 267 (25.1%) had occurrence of ischemic stroke at presentation or during the initial hospitalization. Table 2 shows the comparison of baseline characteristics between patients with and without ischemic stroke. After multivariable adjustment, patients with ischemic stroke were more likely to have history of hypertension (OR 2.33, 95% CI 1.51–3.60), diabetes (OR 1.81, 95% CI 1.11–2.98), and tobacco use (OR 1.64, 95% CI 1.16–2.33) and less likely to have a history of migraine (OR 0.56, 95% CI 0.35–0.90).

Clinical outcomes

Table 3 shows different clinical outcomes in patients with ischemic stroke in reference to those without any ischemic stroke. Ischemic stroke was associated with higher odds of cerebral edema (OR 3.15, 95% CI 1.31–7.57) and respiratory failure requiring mechanical ventilation (OR 2.39, 95% CI 1.28–4.44). Patients with ischemic stroke also had longer hospital stay by a mean duration of 6.7 days, $P < 0.001$, higher hospital charges by a mean of \$72,961, $P < 0.001$, and a higher likelihood of being discharged other than to home (OR 3.57, 95% CI 2.39–5.33). They had higher in-hospital

Table 1 Baseline characteristics of patients admitted due to RCVS (*N* = 1065)

Demographics	
Age, years	49.0 (16.7)
Women	742 (69.7)
Comorbidities	
Hypertension	592 (55.6)
Hyperlipidemia	340 (31.9)
Diabetes	229 (21.5)
Coronary artery disease	119 (11.2)
Head and neck vessel atherosclerosis	82 (7.7)
Migraine	267 (25.1)
Anxiety	222 (20.8)
Depression	252 (23.7)
Unruptured cerebral aneurysm	57 (5.3)
Atrial fibrillation	58 (5.4)
Heart failure	70 (6.6)
Obesity	172 (16.1)
Obstructive sleep apnea	76 (7.1)
Pre-eclampsia/eclampsia	32 (3.0)
Alcohol	41 (3.9)
Tobacco	449 (42.2)
Cocaine or other stimulant use	51 (4.8)
Cannabinoid use	103 (9.7)
Opioid use	42 (4.0)
Work-up	
Cerebral angiography	267 (25.0)
Lumbar puncture	388 (36.4)
Interventions	
Tissue plasminogen activator	27 (2.5)
Prolonged intubation	64 (6.0)
Hospital characteristics	
Primary payer	
Medicare	286 (26.9)
Medicaid	238 (22.4)
Private insurance	463 (43.6)
Self	41 (3.8)
Other	34 (3.2)
Bed-size	
Small	92 (8.6)
Medium	186 (17.5)
Large	787 (73.9)
Location/teaching status	
Nonmetropolitan	13 (1.2)
Metropolitan non-teaching	113 (10.6)
Metropolitan teaching	939 (88.2)
Control	
Government, nonfederal	131 (12.3)
Private, nonprofit	865 (81.2)
Private, invest own	70 (6.5)
Hospital complications	
Cerebral edema	44 (4.1)

Table 1 (continued)

Demographics	
New onset seizure	38 (3.6)
Mechanical ventilation	70 (6.6)
Sepsis	44 (4.1)
Tracheostomy	17 (1.6)
PEG tube placement	20 (1.9)
Outcomes	
Acute ischemic stroke	267 (25.1)
Length of stay, days	7.1 (10.3)
Hospital charges, USD	95,416 (130,362)
In-hospital mortality	14 (1.3)
Not discharged to home	276 (25.9)

Values are represented as number (percentage of the column) or mean (standard deviation)

mortality rate, the difference, however, was not statistically significant.

Discussion

This study describes the rate, risk factors, and clinical outcomes of ischemic stroke in one of the largest cohorts of hospitalized patients with RCVS to date. One in four patients in our study had the diagnosis of acute ischemic stroke. The incidence of ischemic stroke in RCVS has been reported to range from 4 to 6% in the studies recruiting patients with acute headaches (and angiographic abnormalities) from the headache clinics or emergency rooms [8, 9] to as high as 39% in a study from tertiary care referral centers based on the inpatient setting [3]. This variation in the rate of ischemic stroke is likely reflective of recruitment bias with a higher disease severity among the hospitalized patients.

Ischemic strokes in RCVS are typically seen in the anterior-middle and middle-posterior cerebral artery watershed territories [6]. Ischemic lesions could be caused by severe vasospasm of medium- and large-sized arteries or could result from cerebral edema in some patients [2]. The only study comparing patients with RCVS with and without ischemic stroke found that the angiographic severity score predicted the occurrence of ischemic infarcts [6]. Although we did not have access to the imaging data, ours is the first study to give a detailed description of the clinical characteristics associated with ischemic stroke in RCVS. We found that hypertension, diabetes, and tobacco use were independently associated with the occurrence of ischemic stroke. These are all major risk factors for intracranial atherosclerosis [10]. We speculate that intracranial atherosclerosis along with the right shift of the cerebral blood flow autoregulation curve in chronic hypertension [11], might be associated with

Table 2 Predictors of ischemic stroke in RCVS ($N=1065$)

Variables	RCVS, no stroke ($N=798$)	RCVS with ischemic stroke ($N=267$)	OR/difference in means (95% CI)	P value
Age, years	48.7 (17.1)	49.9 (15.6)	1.2 (–1.9–4.3)	0.436
Women	564 (70.6)	178 (66.9)	0.84 (0.57–1.23)	0.369
Hypertension	396 (49.6)	196 (73.4)	2.80 (1.82–4.32)	<0.001
Hyperlipidemia	232 (29.0)	108 (40.6)	1.67 (1.09–2.56)	0.018
Diabetes	139 (17.5)	89 (3.4)	2.39 (1.48–3.85)	<0.001
CAD	84 (10.5)	35 (13.3)	1.31 (0.70–2.45)	0.398
Head/neck vessel atherosclerosis	49 (6.1)	33 (12.3)	2.15 (1.09–4.22)	0.026
Migraine	220 (27.6)	47 (17.6)	0.56 (0.36–0.86)	0.008
Anxiety	166 (20.8)	56 (21.0)	1.01 (0.66–1.55)	0.962
Depression	171 (21.5)	81 (30.4)	1.60 (1.00–2.55)	0.049
Atrial fibrillation	40 (5.1)	17 (6.4)	1.28 (0.54–3.04)	0.577
Heart failure	51 (6.4)	20 (7.4)	1.17 (0.53–2.61)	0.699
Obesity	120 (15.0)	52 (19.4)	1.36 (0.89–2.09)	0.156
OSA	53 (6.7)	23 (8.4)	1.29 (0.63–2.66)	0.486
Tobacco	308 (38.6)	141 (52.7)	1.77 (1.26–2.50)	0.001
Cocaine or other stimulant use	30 (3.8)	21 (7.7)	2.12 (1.11–4.06)	0.023
Cannabinoid use	82 (10.3)	21 (7.9)	0.75 (0.37–1.54)	0.434
Opioid use	31 (3.9)	11 (4.1)	1.05 (0.31–3.60)	0.934
Payer, other than private insurance	407 (51.0)	194 (72.9)	2.58 (1.76–3.78)	<0.001
Bed-size small/medium	218 (27.3)	60 (22.6)	0.78 (0.54–1.12)	0.179
Non-teaching hospitals	81 (10.2)	45 (16.7)	1.78 (1.13–2.79)	0.012

Values in second and third columns represent mean (standard deviation) or number (percentage of the column). Odds ratio/difference in means is in comparison to RCVS with no ischemic stroke

OR odds ratio, CI confidence interval, CAD coronary artery disease, OSA obstructive sleep apnea

Table 3 Outcomes of ischemic stroke in RCVS ($N=1065$)

Variables	RCVS, no stroke ($N=798$)	RCVS with ischemic stroke ($N=267$)	OR/ β coefficient (95% CI)	P value
Cerebral edema	22 (2.8)	22 (8.2)	3.15 (1.31–7.57)	0.010
New onset seizure	22 (2.8)	17 (6.3)	2.42 (0.90–6.51)	0.080
Mechanical ventilation	40 (5.1)	30 (11.3)	2.39 (1.28–4.44)	0.006
Sepsis	30 (3.8)	14 (5.3)	1.43 (0.56–3.62)	0.449
Tracheostomy	–	–	3.76 (0.82–17.18)	0.088
PEG tube placement	12 (1.5)	–	2.04 (0.52–8.11)	0.308
Length of stay, days	5.3 (7.6)	12.0 (14.6)	6.81 (4.54–9.09)	<0.001
Hospital charges, USD	76,743 (109,156)	149,704 (167,189)	65,693 (40,759–90,627)	<0.001
Not discharged to home	154 (19.3)	123 (46.0)	3.57 (2.39–5.33)	<0.001
In-hospital mortality	–	–	9.18 (0.97–86.59)	0.053

Values in second and third columns represent number (percentage of the column) or mean (standard deviation). Values <10 have not been reported

OR odds ratio, CI confidence interval

a higher susceptibility to developing ischemic lesions from proximal vasoconstriction in patients with these risk factors. Interestingly, we found that history of migraine was associated with a lower risk of developing ischemic stroke. While the exact reason for this finding is unclear, but the changes in

cerebrovascular reactivity and the putative epiphenomenon of vasodilation underlying migraine [12], might potentially be associated with a protective effect against the uncontrolled vasoconstriction associated with ischemic stroke in RCVS.

Stroke is the most severe manifestation of RCVS that can lead to permanent neurologic deficits and even death [9], and is hence the major determinant of the long-term prognosis in RCVS [2]. In this study, we found that patients with ischemic stroke were significantly more likely to develop cerebral edema and respiratory failure requiring mechanical ventilation. They had a longer hospital stay, higher total hospital charges, and were less likely to be discharged home. Patients with ischemic stroke also had a higher all-cause in-hospital mortality; however, the association was not statistically significant because of small number of patients who died.

RCVS is a relatively rare and a heterogenous disorder and most of the previous studies are limited to single-center or regional cohorts. So, one of the major strengths of our study includes the utilization of large, nationally representative database, increasing the generalizability of our findings. However, the results of this study should be interpreted in the context of potential limitations. First, we did not have data about the clinical presentation, triggers/precipitants, or radiographic studies, and with the inclusion of cases solely based on the use of ICD-10 codes, the possibility of misdiagnosis of RCVS cannot be completely ruled out. Specifically, intracranial atherosclerosis is a close radiological mimic of RCVS that can potentially confound the association between ischemic stroke and the risk factors analyzed in this study. However, we used a validated ICD-10 diagnostic code for RCVS that was recently shown to have 100% sensitivity and 90% specificity in an administrative claims database [13]. To further enhance the diagnostic specificity of RCVS and eliminate the potential confounding effect of intracranial atherosclerosis, we carried out sensitivity analysis and identified the predictors of ischemic stroke after excluding patients with a concomitant diagnosis of intracranial atherosclerosis either during the initial RCVS hospitalization or during any of the follow-up readmissions in the same calendar year. We found that 28 (2.6%) patients had a secondary diagnosis of intracranial atherosclerosis and we identified similar predictors of ischemic stroke even after excluding these patients. Second, in the general clinical practice, RCVS patients can be seen in the headache clinics, emergency room, or inpatient stroke units. However, the present study was based on the inpatient setting only, which might have led to an overestimation of the neurologic complications. Despite these limitations, this study provides relevant benchmark data on ischemic stroke in RCVS.

Conclusion

In conclusion, we found that ischemic strokes affect nearly 25% of patients with RCVS and is associated with increased rate of other neurologic complications and worse functional

outcomes. Patients with traditional cerebrovascular risk factors might have a higher predisposition for developing ischemic lesions.

Author contributions All authors were involved in the conception of the study design. Statistical analysis was performed by AG. The first draft of the manuscript was written by AG and SO-G. All authors were involved in the critical revision of the manuscript. All authors read and approved the final version of the manuscript.

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Data availability The Nationwide Readmissions Database is a publicly available dataset that can be obtained after completion of the HCUP data use agreement.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethics approval The study was exempt from the Institutional Review Board as we used a publicly available database with deidentified information.

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