ARTICLE CLASS OF EVIDENCE

$RCVS_2$ score and diagnostic approach for reversible cerebral vasoconstriction syndrome

Eva A. Rocha, MD, M. Akif Topcuoglu, MD, Gisele S. Silva, MD, PhD, and Aneesh B. Singhal, MD

Neurology® 2019;92:e639-e647. doi:10.1212/WNL.0000000000006917

Correspondence
Dr. Singhal
asinghal@partners.org

Abstract

Objective

To develop a method to distinguish reversible cerebral vasoconstriction syndrome (RCVS) from other large/medium-vessel intracranial arteriopathies.

Methods

We identified consecutive patients from our institutional databases admitted in 2013–2017 with newly diagnosed RCVS (n = 30) or non-RCVS arteriopathy (n = 80). Admission clinical and imaging features were compared. Multivariate logistic regression modeling was used to develop a discriminatory score. Score validity was tested in a separate cohort of patients with RCVS and its closest mimic, primary angiitis of the CNS (PACNS). In addition, key variables were used to develop a bedside approach to distinguish RCVS from non-RCVS arteriopathies.

Results

The RCVS group had significantly more women, vasoconstrictive triggers, thunderclap headaches, normal brain imaging results, and better outcomes. Beta coefficients from the multivariate regression model yielding the best *c*-statistic (0.989) were used to develop the $RCVS_2$ score (range −2 to +10; recurrent/single thunderclap headache; carotid artery involvement; vasoconstrictive trigger; sex; subarachnoid hemorrhage). Score ≥5 had 99% specificity and 90% sensitivity for diagnosing RCVS, and score ≤2 had 100% specificity and 85% sensitivity for excluding RCVS. Scores 3–4 had 86% specificity and 10% sensitivity for diagnosing RCVS. The score showed similar performance to distinguish RCVS from PACNS in the validation cohort. A clinical approach based on recurrent thunderclap headaches, trigger and normal brain scans, or convexity subarachnoid hemorrhage correctly diagnosed 25 of 37 patients with $RCVS_2$ scores 3–4 across the derivation and validation cohorts.

Conclusion

RCVS can be accurately distinguished from other intracranial arteriopathies upon admission, using widely available clinical and imaging features.

Classification of evidence

This study provides Class II evidence that the $RCVS_2$ score accurately distinguishes patients with RCVS from those with other intracranial arteriopathies.

RELATED ARTICLE

Editorial
Intracranial arteriopathies and RCVS: A discriminatory clinical tool
Page 309

MORE ONLINE

→ **Class of Evidence**
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

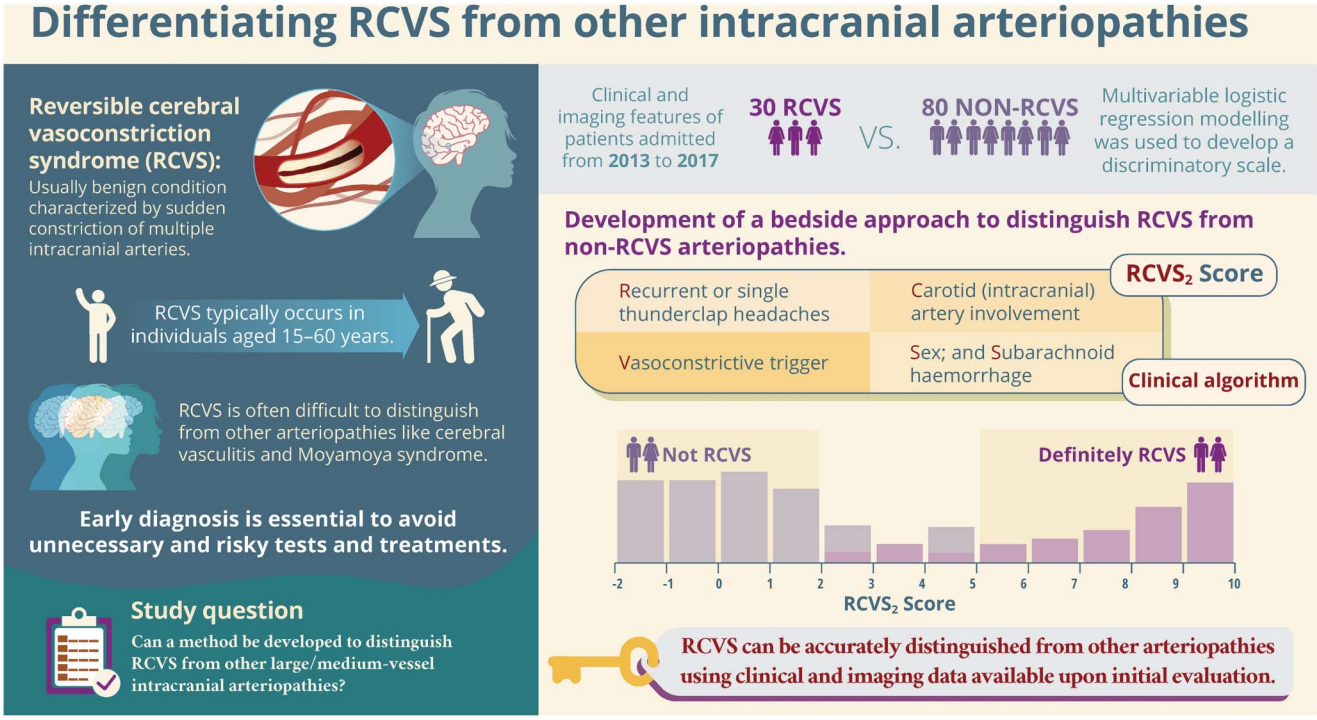
CME Course
NPub.org/cmelist

From the Department of Neurology (E.A.R., A.B.S.), Massachusetts General Hospital, Boston; Department of Neurology (E.A.R., G.S.S.), Universidade Federal de São Paulo, Brazil; Hospital Israelita Albert Einstein (G.S.S.), São Paulo, Brazil; and Department of Neurology (M.A.T.), Hacettepe University, Ankara, Turkey.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ICD-9 = International Classification of Diseases–9; **ICD-10** = International Classification of Diseases–10; **mRS** = modified Rankin Scale; **PACNS** = primary angiitis of the CNS; **PRES** = posterior reversible leukoencephalopathy syndrome; **RCVS** = reversible cerebral vasoconstriction syndrome; **SAH** = subarachnoid hemorrhage; **TCH** = thunderclap headache.



NPub.org/911040 doi: 10.1212/WNL.0000000000006917

Neurology

Over the last 2 decades, reversible cerebral vasoconstriction syndrome (RCVS) has become recognized as a group of conditions characterized by rapidly changing and reversible segmental cerebral artery narrowing and dilation, usually heralded by severe sudden-onset headaches.[1–10] Although one third to half the patients can develop stroke, over 90% have benign clinical outcome.[5,7] Historically, primary angiitis of the CNS (PACNS) has been an important mimic due to the presence of headaches, strokes, and angiographic abnormalities.[9,11] We recently published criteria to distinguish RCVS from PACNS upon admission, before documenting angiographic reversibility or brain biopsy.[9] Early distinction is particularly important since glucocorticoids, required to treat PACNS, can worsen clinical, imaging, and angiographic abnormalities in RCVS.[12]

RCVS usually affects individuals aged 15–60 years. Several other arteriopathies are common in this age range, including moyamoya disease, premature atherosclerosis, and vasculitis associated with rheumatologic disorders.[13] It can be difficult to distinguish RCVS from other arteriopathies since most lack a gold standard diagnostic test and are similarly associated with headache and stroke.[14,15] Early discrimination is important because of management differences: in RCVS, CSF examination and brain biopsy have little utility other than to exclude mimics. Unlike RCVS, other arteriopathies require specific therapies, e.g., steroids for rheumatic or radiation-induced arteriopathy, synangiosis procedures for moyamoya disease, or dual antiplatelet therapy for atherosclerosis. In this study, we developed and validated a score and developed a bedside approach to distinguish RCVS from undifferentiated intracranial arteriopathies during admission, i.e., before the final diagnosis was established based on pathology, infectious disease panels, or other laboratory tests.

Methods

The Massachusetts General Hospital's Research Patient Database Repository was queried for patients aged 18–55 years admitted between September 2013 and September 2017 who underwent head CT angiography and had an intracranial cerebral arteriopathy based on (1) ICD-9 or ICD-10 discharge codes for cerebral arteritis (437.4, 168.2, 168.7), atherosclerosis (437.0, 167.7), moyamoya disease (437.5, 167.5), granulomatous angiitis of the CNS (167.76), or cerebral vasospasm or cerebral vasoconstriction (167.84), and (2) discharge summaries containing the

search terms cerebral vasculitis, cerebral angiitis, cerebral arteriopathy, RCVS, or PACNS. Of the 202 patients retrieved, 110 had abnormal intracranial vascular imaging and a final diagnosis of an intracranial cerebral arteriopathy. The results of brain pathology, microbiology, and imaging studies obtained before or after the index hospitalization were used to confirm the diagnosis. For comparison and criteria development, patients were divided into 2 groups: RCVS and non-RCVS.

Clinical and imaging data

We extracted information on the following clinical variables: demographics, vasoconstrictive triggers, medical history, neurologic deficits, clinical outcome (discharge modified Rankin Scale [mRS] score), and laboratory test results.

We analyzed brain MRI, or if not available, head CT performed during hospitalization. Lesions were classified as infarction, hemorrhage (parenchymal or subarachnoid), or vasogenic edema (i.e., posterior reversible leukoencephalopathy syndrome [PRES], a condition that shares features with RCVS[16–18]). Subarachnoid hemorrhages (SAHs) were classified on their predominant location, convexity or nonconvexity. We documented the presence of fluid-attenuated inversion recovery sulcal hyperintensities (dot sign).[19,20]

Table 1 Clinical and laboratory features

	RCVS (n = 30)	Non-RCVS (n = 80)	OR (95% CI)	*p* Value
Age, y	41.1 ± 9.9	44.5 ± 10.9		0.14
Female	24 (80)	36 (45)	4.8 (1.6, 16.0)	0.002
White/Caucasian race	19 (63)	47 (59)	1.2, (0.5, 3.2)	0.83
Vasoconstrictive trigger	26 (87)	8 (10)	54.4 (14.4, 273)	<0.001
Vasoconstrictive drugs	17 (57)	6 (8)	16.1 (5.6, 52.3)	<0.001
Postpartum	7 (23)	1 (1)	23.2 (2.7, >999)	<0.001
Sexual orgasm	2 (7)	1 (1)	5.5 (0.27, 336)	0.37
Thunderclap headache at onset	28 (93)	3 (4)	359 (57, >999)	<0.001
Recurrent thunderclap headache	27 (90)	1 (1)	710 (71, >999)	<0.001
Gradual headache at onset	1 (3)	29 (36)	0.06 (0.008, 0.47)	0.001
No headache at onset	1 (3)	48 (60)	0.02 (0.001, 0.15)	<0.001
History of depression or anxiety	17 (57)	20 (25)	3.8 (1.5, 10.4)	0.004
History of migraine	8 (27)	9 (11)	2.8 (0.8, 9.4)	0.09
History of hypertension	5 (17)	32 (40)	0.3 (0.08, 0.9)	0.04
Admission BP >140/90 mm Hg	14 (48)	42 (57)	0.7 (0.3, 1.7)	0.57
Focal neurologic signs	9 (30)	66 (83)	0.1 (0.03, 0.3)	<0.001
Seizures	3 (10)	2 (3)	4.2 (0.4, 53.6)	0.24
Erythrocyte sedimentation rate, mm/h	17 ± 16	27 ± 30		0.14
Normal CSF examination results[a]	9/10 (90)	13/28 (46)	9.8 (1.1, 483)	0.04
Vasculitis on brain biopsy/autopsy	0/1 (0)	4/12 (33)	0.0 (0.0, 97.3)	1.0
Immunosuppressive therapy	5 (17)	21 (26)	0.4 (0.1, 1.4)	0.47
Calcium channel blocker therapy	19 (63)	1 (1)	55 (11, 546)	<0.001
Discharge mRS score	0 (0–0)	1 (0–3)		<0.001
0–2	28 (93)	55 (69)	3.8 (1.02, 21)	0.02
6	0 (0)	3 (4)	0.0 (0.0, 6.5)	0.68

Abbreviations: BP = blood pressure; CI = confidence interval; mRS = modified Rankin Scale; OR = odds ratio; RCVS = reversible cerebral vasoconstriction syndrome.
Values are mean ± SD, n (%), or median (interquartile range).
[a] CSF normal result ≤5 white cells and <40 mg/dL protein level.

Table 2 Imaging features

	RCVS (n = 30), n (%)	Non-RCVS (n = 80), n (%)	OR (95% CI)	*p* Value
Brain MRI performed	25 (83)	76 (95)	0.26 (0.06, 1.1)	0.11
Parenchymal lesion present	11 (37)	69 (86)	0.09 (0.03, 0.24)	<0.001
Infarct	4 (13)	57 (71)	0.06 (0.01, 0.2)	<0.001
Parenchymal hemorrhage	5 (17)	7 (9)	2.1 (0.6, 7.1)	0.40
Vasogenic edema (PRES)	3 (10)	1 (1)	5.6 (0.5, 65)	0.11
Serial inpatient scan performed	29 (97)	60 (76)	2.9 (1.1, 7.9)	0.03
New lesions	4 (14)	25 (42)	0.2 (0.07, 0.7)	0.02
SAH on initial examination	14 (47)	1 (1)	69 (8.5, 563)	<0.001
FLAIR dot sign	14 (52)	25 (39)	1.7 (0.7, 4.2)	0.37
Cerebral angiography type[a]				
DSA	4 (14)	13 (16)	1.8 (0.7, 6.2)	0.93
CTA	25 (83)	58 (72)	0.8 (0.2, 2.4)	0.35
MRA	1 (3)	9 (11)	0.3 (0.01, 1.5)	0.36
Artery involved				
Intracranial ICA	6 (20)	46 (58)	0.2 (0.07, 0.50)	<0.001
Middle cerebral artery	23 (77)	62 (78)	0.9 (0.36, 2.7)	1.0
Anterior cerebral artery	22 (73)	40 (50)	2.7 (1.1, 7.2)	0.047
Posterior cerebral artery	20 (67)	33 (41)	2.8 (1.2, 7.1)	0.03
Vertebral or basilar arteries	14 (47)	23 (29)	2.2 (0.9, 5.2)	0.12
AICA/PICA/SCA	12 (40)	6 (8)	8.2 (2.7, 24.9)	<0.001
Extracranial ICA or vertebral	2 (7)	10 (13)	0.5 (0.07, 2.0)	0.58
1st/2nd/3rd order intracerebral artery	22 (73)	30 (38)	4.6 (1.8, 11.5)	0.002
Angiographic narrowing >50%	23 (77)	66 (85)	0.6 (0.2, 1.7)	0.49

Abbreviations: AICA = anterior inferior cerebellar artery; CI = confidence interval; CTA = CT angiography; DSA = digital subtraction angiography; FLAIR = fluid-attenuated inversion recovery; ICA = internal carotid artery; MRA = magnetic resonance angiography; OR = odds ratio; PICA = posterior inferior cerebellar artery; PRES = posterior reversible encephalopathy syndrome; RCVS = reversible cerebral vasoconstriction syndrome; SAH = subarachnoid hemorrhage; SCA = superficial cerebellar artery.
[a] The modality used for analysis is depicted here; some patients had multiple imaging modalities.

Table 3 Logistic regression: Clinical and imaging predictors of RCVS

	β	Odds ratio	95% CI	*c*-Statistic
(Intercept)	−4.9			
Female sex	1.2	3.37	0.25, 88.91	
Acute TCH	5.4	226.32	23.79, >999	
Trigger	2.8	16.59	1.91, 361.15	0.989
SAH initial	1.4	4.03	0.04, 590.72	
Intracranial ICA involved	−2.1	0.12	0.003, 1.58	

Abbreviations: CI = confidence interval; ICA = internal carotid artery; RCVS = reversible cerebral vasoconstriction syndrome; SAH = subarachnoid hemorrhage; TCH = thunderclap headache.

Transfemoral, CT, and magnetic resonance angiography (in that order) were reviewed for the presence of arterial stenosis, classified as ≤50% or >50%. Note was made of the specific artery and segment (1st, 2nd, 3rd order branches) involved.

Statistical analysis

We used the Fisher exact test and Student *t* test as appropriate to compare RCVS and non-RCVS. Odds ratios and 95% confidence intervals were computed. A threshold of $p < 0.05$ was used for statistical significance. Exploratory forward stepwise logistic regression models with RCVS as the outcome measure were developed, using up to 6 variables per model to avoid overfitting. The model with the highest *c*-statistic was selected to develop a discriminatory score, based on the closest integer of the beta coefficient. Score

Table 4 $RCVS_2$ score

Criteria	Value
Recurrent or single TCH	
Present	5
Absent	0
Carotid artery (intracranial)	
Affected	−2
Not affected	0
Vasoconstrictive trigger	
Present	3
Absent	0
Sex	
Female	1
Male	0
Subarachnoid hemorrhage	
Present	1
Absent	0

Abbreviation: TCH = thunderclap headache.

thresholds to diagnose RCVS and non-RCVS were selected based on highest discriminatory performance. Score performance was assessed using specificity, sensitivity, and positive and negative predictive values. We then tested the ability of the score to distinguish RCVS from PACNS, using data from a published cohort.[9] Finally, we developed a simple bedside diagnostic approach using key variables identified from univariate analysis. The sensitivity, specificity, and positive and negative predictive values (with 95% confidence intervals) of key variables, or combinations, were computed. The RStudio statistical package (v. 1.1.383) was used for analysis.

Standard protocol approvals, registrations, and patient consents

This retrospective study was approved by our hospital's Human Research Committee.

Data availability statement

All data used for analysis are presented in the tables and figure in this article. Data will be shared after ethics approval if requested by other investigators for purposes of replicating the results.

Classification of evidence

Aiming to accurately distinguish RCVS from other intracranial arteriopathies, we developed the $RCVS_2$ score, which provides Class II evidence for the diagnosis of RCVS and exclusion of other large/medium-vessel arteriopathies.

Results

Of the 110 patients, 30 were diagnosed with RCVS and 80 non-RCVS including 13 PACNS, 24 moyamoya disease, 29 intracranial atherosclerosis, 4 radiation-induced arteriopathy, and 10 secondary vasculitis (3 associated with systemic lupus erythematosus, 2 with herpes virus, and 1 each with polyarteritis nodosa, Sjögren disease, HIV, and Hodgkin lymphoma).

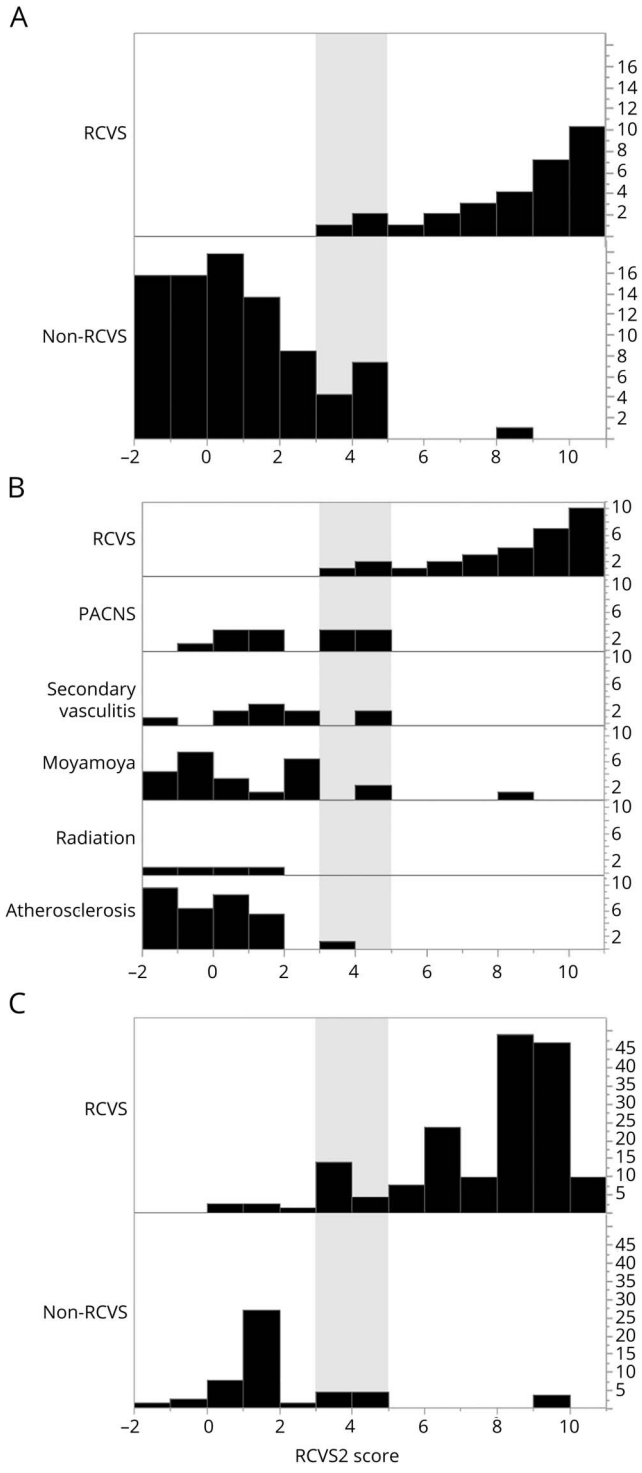
The following criteria were used for diagnosis. For RCVS, the diagnosis was confirmed on basis of angiographic reversibility or rapid arterial caliber change on serial imaging in 29 of 30 patients (median time from initial to follow-up angiography 3.5 days, interquartile range 1–10 days). One patient with RCVS did not undergo serial angiography but had classic postpartum angiopathy, which is included under RCVS.[4,8,16] For PACNS, 4

Table 5 $RCVS_2$ score performance

$RCVS_2$ score	Specificity	Sensitivity	PPV	NPV
Derivation cohort				
Score 5 or higher[a]	99 (93, 100)	90 (73, 98)	96 (82, 100)	96 (90, 99)
Score 3 or 4[a]	86 (77, 93)	10 (2, 27)	21 (5, 51)	72 (62, 80)
Score 2 or lower[b]	100 (88, 100)	85 (75, 92)	100 (95, 100)	71 (55, 84)
Validation cohort				
Score 5 or higher[a]	94 (82, 99)	86 (80, 91)	98 (94, 100)	67 (54, 78)
Score 3 or 4[a]	83 (69, 92)	11 (6, 17)	68 (46, 85)	22 (16, 28)
Score 2 or lower[b]	96 (92, 99)	77 (62, 88)	86 (71, 95)	93 (88, 97)

Abbreviations: NPV = negative predictive value; PPV = positive predictive value; RCVS = reversible cerebral vasoconstriction syndrome.
[a] Values for a RCVS diagnosis.
[b] Values for a non-RCVS diagnosis.

Figure Distribution of $RCVS_2$ scores



Histograms show the distribution of $RCVS_2$ scores in the derivation cohort (A, reversible cerebral vasoconstriction syndrome [RCVS] and non-RCVS; B, individual intracranial arteriopathies) and the validation cohort (C). The gray bars in A–C show patients with intermediate scores 3–4. PACNS = primary angiitis of the CNS.

patients were diagnosed by brain biopsy; the remaining 9 had inflammatory CSF results, abnormal cerebral angiography, and a progressive course consistent with PACNS, with no evidence for mimics on extensive laboratory tests; all met published diagnostic criteria for PACNS.[9,11,21] Patients with moyamoya disease had typical angiographic features[22] with nonreversibility on serial imaging. Intracranial atherosclerosis was diagnosed based on vascular risk factors with typical intracranial artery calcifications.[15] Patients with secondary vasculitis had systemic inflammatory blood biomarkers or evidence of CNS infection such as herpes zoster or HIV.[23] Radiation-induced arteriopathy was diagnosed if patients had a history of cerebral irradiation and no alternate cause.[24]

The overall mean age was 43.5 ± 10.7 years and 54.5% were women. Table 1 shows a comparison of the RCVS and non-RCVS groups. The RCVS group had significantly more women, triggers (vasoconstrictive drugs, postpartum state), thunderclap headache (TCH), and depression/anxiety. In comparison, the non-RCVS group more often presented without any headache and tended to have less migraine. Of note, postpartum onset was much more common in RCVS (23% vs 1%); the single non-RCVS postpartum patient developed transverse myelitis and vasculitic brain lesions 1 week after delivery and proved to have polyarteritis nodosa. TCH, the cardinal manifestation of RCVS, occurred in 93% of RCVS cases but also occurred in 4% of non-RCVS cases, all with moyamoya disease (3 patients; 2 with brain hemorrhage, and 1 diagnosed with moyamoya during investigation of primary TCH). Over half of the patients with RCVS had visual phenomena such as blurring or cortical visual loss; however, fewer than one third developed hemiparesis or aphasia. The discharge mRS score was significantly better in the RCVS group. Only 2 patients with RCVS, both with large brain hemorrhages, had discharge mRS score 5.

Brain and vascular imaging features are shown in table 2. The RCVS group had significantly more normal results on parenchymal brain imaging, and when abnormal, showed significantly fewer brain infarcts but a 10-fold higher frequency of PRES-like lesions. The non-RCVS group accumulated significantly more lesions on serial imaging. SAH was more common in RCVS and convexity (nonaneurysmal) SAHs were exclusively seen in RCVS. Arteriopathy was almost always diagnosed with transfemoral or CT angiography in either group. Sites of arterial involvement are depicted in table 2. The intracranial segment of the internal carotid artery was more often involved in non-RCVS, mostly due to moyamoya and intracranial atherosclerosis. The posterior circulation arteries were more often abnormal and the abnormalities more diffuse in RCVS.

Table 3 shows results of the multivariate logistic regression model that yielded the highest *c*-statistic (0.989) and accuracy (0.96) for diagnosing RCVS. Variables showing the highest odds ratios in the univariate analysis were included in this model. The closest integers of the beta coefficients were used to develop a diagnostic score (table 4). The score acronym $RCVS_2$ denotes the variables recurrent or single TCH; carotid (intracranial) artery involvement; vasoconstrictive trigger; sex; and SAH, with points for each as shown in table 4. The $RCVS_2$ score range is −2 to +10.

Table 6 Diagnostic algorithm: Key variables for RCVS

Variable	Specificity	Sensitivity	PPV	NPV
Recurrent TCH	99 (93, 100)	90 (73, 98)	96 (82, 100)	96 (90, 99)
Normal scan plus trigger	97 (91, 100)	60 (41, 77)	90 (68, 99)	87 (78, 93)
Convexity SAH	100 (95, 100)	47 (28, 66)	100 (77, 100)	83 (74, 90)

Abbreviations: NPV = negative predictive value; PPV = positive predictive value; RCVS = reversible cerebral vasoconstriction syndrome; SAH = subarachnoid hemorrhage; TCH = thunderclap headache.

As shown in table 5, score ≥5 had high sensitivity and specificity for diagnosing RCVS, and score ≤2 for excluding RCVS. Intermediate scores 3 and 4 had moderate specificity and low sensitivity for RCVS. The distribution of scores (figure, A) shows that the highest and lowest probabilities of RCVS and non-RCVS occur towards the extreme values of the $RCVS_2$ score. All RCVS patients scored 3 or more, and only one non-RCVS patient scored ≥5 points (score 8, the patient discussed above with primary TCH and moyamoya). The figure, B, shows the distribution of scores for each arteriopathy. Scores 3 and 4 comprised the main overlap between RCVS and every other arteriopathy, except for radiation arteriopathy, which always scored ≤1.

Next, the $RCVS_2$ score was validated against PACNS, using data from a recently published cohort of 206 patients (159 RCVS, 47 PACNS).[9] Only 8 RCVS and 5 PACNS cases were included in both cohorts. Again, $RCVS_2$ scores ≥5 and ≤2 had 94%–96% specificity for diagnosing and excluding RCVS, with high sensitivity (table 5). Excluding the overlapping patients (8 RCVS and 5 PACNS) from the validation cohort did not significantly alter our results (the specificity for diagnosing and excluding RCVS changed to 93% and 96%). The figure, C, provides a visual depiction of RCVS and PACNS across the range of scores. Only 3 patients with PACNS scored ≥5 (score 9; all had an RCVS-PACNS overlap syndrome, i.e., prolonged exposure to potent vasoconstrictive agents leading to vasoconstriction and secondary arterial inflammation).[25]

In both the derivation and the validation cohort, score 3–4 posed the biggest challenge when applying the $RCVS_2$ score (gray bars, figure, A–C). Given the lower discriminatory ability of score 3–4 and the inherent shortcomings of applying scoring systems to individual patients,[26] we additionally developed a clinical approach to distinguish RCVS from other arteriopathies using variables in tables 1 and 2 with the highest odds ratios (table 6). Recurrent TCH, in isolation, showed 99% specificity for the diagnosis of RCVS. The only non-RCVS patient with recurrent TCH was the patient referenced above with primary TCH whose evaluation revealed moyamoya. The combination of a trigger with normal brain imaging proved highly specific (97%) for RCVS, and can be useful in patients without onset headache, or when the onset history is non-obtainable (e.g., aphasia, somnolence). Finally, RCVS was the only arteriopathy associated with convexity SAH (100% specificity). The clinical approach correctly diagnosed 25 of 37 (68%) patients with $RCVS_2$ score 3–4 (the scores with the least accuracy) across the derivation and validation cohorts, showing the importance of using the score with the algorithm.

Discussion

Intracerebral arteriopathies are collectively the most frequent causes of ischemic stroke in young adults with an increasing frequency at younger ages.[14,27] Appropriate management depends on prompt diagnosis; however, at present most large and medium vessel arteriopathies lack validated diagnostic criteria. Their diagnosis is usually established only after invasive tests such as CSF examination or brain biopsy, or on basis of angiographic pattern and evolution. In this study, we found that our novel score and bedside diagnostic approach have excellent ability to distinguish RCVS from other arteriopathies, using variables widely available at the bedside soon after admission. Further, we showed that the $RCVS_2$ score accurately distinguishes RCVS from its closest mimic, PACNS. These results extend our previous study showing the utility of a bedside approach to distinguish RCVS from PACNS.[9] We anticipate that the $RCVS_2$ score will prove useful in clinical practice, and will be used in combination with the bedside approach, especially in patients with intermediate scores 3 or 4.

The distribution of scores (figure, A–C), and the fact that 88% of patients across both cohorts had scores ≥5 or ≤2, which provide 99%–100% specificity for diagnosis, provides assurance that most patients will be correctly diagnosed based on the $RCVS_2$ score. Another 10% were correctly diagnosed using the clinical approach. Of note, the clinical approach alone provides high specificity; however, not all patients with RCVS have recurrent TCH, and its sensitivity in patients with a trigger and normal scan is only 60%. We recommend a combined approach based on our results. Clinical judgment should be used when deciding if an identified trigger should be used in the score or approach, since vasoconstrictive potency can vary and a temporal relationship may be important. Finally, attention should be paid to nuances such as the infarct distribution (symmetric and watershed in RCVS), or presence of PRES-like lesions, or the smooth-tapered angiographic appearance of RCVS, which can aid diagnosis in exceptionally challenging cases.[9]

All patients had a newly diagnosed arteriopathy. The variables shown in tables 1 and 2 reflect the patient's first presentation and admission, therefore the score and approach are

applicable early during the disease course. We were careful to use stringent criteria for diagnosing arteriopathies. RCVS was diagnosed on the basis of angiographic reversibility or dynamic change, rather than clinical or imaging features such as TCH or convexity SAH, which could have led to bias. Nevertheless, the profile of RCVS proved consistent with prior reports, with female preponderance and a high frequency of TCH. Consecutive patients between ages 18 and 55 years (the typical age range of RCVS) retrieved from our institutional search were included for comparison. The upper age of 55 years is important when considering convexity SAH in the clinical approach, since such hemorrhages in older patients mostly result from cerebral amyloid angiopathy.[28,29] The relative proportions of individual arteriopathies may not reflect their true prevalence due to factors such as referral bias in this single-center study. Since not all arteriopathies (e.g., intracranial dissection, childhood arteriopathies) were studied, our results are only applicable to young adults with newly diagnosed angiographically evident cerebral arteriopathies included in our cohort.

The inclusion of consecutive and newly diagnosed cases, with careful patient selection, and the high rates of transfemoral and CT angiography, are major strengths of this study. The $RCVS_2$ score appears simple, feasible, and generalizable, given the reliance on common variables available soon after admission, enabling prompt and accurate diagnosis. We did not include CSF results in the score or the approach, since our preference was to utilize noninvasive and easily obtainable variables. Given the excellent discriminatory power of the score and clinical approach, follow-up tests (e.g., serial angiography) may not be required in patients with scores ≥5 to confirm the diagnosis of RCVS. Advanced 3T contrast-enhanced MRI[30] and biomarker levels (e.g., endothelin-1, circulating microparticles)[31,32] are unlikely to improve on the performance of the $RCVS_2$ score or approach overall, but could be useful in patients with intermediate scores. Invasive and potentially risky tests such as intra-arterial vasodilator therapy[33] and brain biopsy should be avoided for diagnosing RCVS, especially in arteriopathy patients with scores ≥5, given the usually benign outcome.

The main limitations of this study are its retrospective nature and conduct in a single academic center. In comparison to other published cohorts, our patients may have greater disease severity since they were inpatients in a stroke center, which may influence study generalizability. Patients described as having acute severe headache were coded as having TCH; however, we could not always confirm that they met the International Headache Society criteria for TCH.[34] As variables, vasoconstrictive trigger and TCH are dependent on accurate history-taking. The total number of patients with individual arteriopathies is relatively small, limiting the regression modeling; however, ours is one of the largest studies of undifferentiated cerebral arteriopathies. We validated the score against a single mimic, PACNS. External validation is still required, as is validation against childhood arteriopathies,[27] since RCVS can also affect children and teenagers.

The $RCVS_2$ score and diagnostic approach can be used to promptly diagnose and distinguish RCVS from mimics using easily available admission variables. We emphasize that the score and approach accurately predict the diagnosis of RCVS, and not reversibility of the syndrome, even though over 95% of patients with RCVS have a benign and self-limited course. Clinical discretion, and knowledge of RCVS subtypes[10] and predictors of clinical outcome,[12] should be used to determine whether admission and close observation is required.

Study funding

Dr. Rocha's visiting scholarship at Massachusetts General Hospital and Harvard Medical School, Boston, is sponsored by the Capes Foundation, Ministry of Education, Brazil (grant no. 88,881.133101/2016-01).

Disclosure

E. Rocha, M. Topcuoglu, and G. Silva report no disclosures relevant to the manuscript. A. Singhal has served as a medical expert witness and has received honoraria from the American Academy of Neurology, Medlink, Inc., and UpToDate. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* May 31, 2018. Accepted in final form December 14, 2018.

Appendix 1 Authors

Name	Location	Role	Contribution
Eva Rocha, MD	Federal University of Sao Paulo, Brazil Massachusetts General Hospital, Boston	Author	Collected the data, statistical analysis, drafted the manuscript
Mehmet Akif Topcuoglu, MD	Hacettepe University, Turkey	Author	Collected the data, revised the manuscript for intellectual content
Gisele Sampaio Silva, MD	Federal University of Sao Paulo, Brazil, Hospital Israelita Albert Einstein, São Paulo, Brazil	Author	Interpreted the data, revised the manuscript for intellectual content
Aneesh Singhal, MD	Massachusetts General Hospital, Boston	Author	Designed and conceptualized study, analyzed the data, interpreted the data, drafted the manuscript

References

1. Singhal AB, Caviness VS, Begleiter AF, Mark EJ, Rordorf G, Koroshetz WJ. Cerebral vasoconstriction and stroke after use of serotonergic drugs. Neurology 2002;58:130–133.
2. Hajj-Ali RA, Furlan A, Abou-Chebel A, Calabrese LH. Benign angiopathy of the central nervous system: cohort of 16 patients with clinical course and long-term followup. Arthritis Rheum 2002;47:662–669.
3. Singhal AB. Cerebral vasoconstriction syndromes. Top Stroke Rehabil 2004;11:1–6.
4. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative review: reversible cerebral vasoconstriction syndromes. Ann Intern Med 2007;146:34–44.
5. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome: a prospective series of 67 patients. Brain 2007;130:3091–3101.

6. Chen SP, Fuh JL, Wang SJ, et al. Magnetic resonance angiography in reversible cerebral vasoconstriction syndromes. Ann Neurol 2010;67:648–656.
7. Singhal AB, Hajj-Ali RA, Topcuoglu MA, et al. Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. Arch Neurol 2011;68:1005–1012.
8. Ducros A. Reversible cerebral vasoconstriction syndrome. Lancet Neurol 2012;11: 906–917.
9. Singhal AB, Topcuoglu MA, Fok JW, et al. Reversible cerebral vasoconstriction syndromes and primary angiitis of the central nervous system: clinical, imaging, and angiographic comparison. Ann Neurol 2016;79:882–894.
10. Topcuoglu MA, Singhal AB. Hemorrhagic reversible cerebral vasoconstriction syndrome: features and mechanisms. Stroke 2016;47:1742–1747.
11. Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angiitis of the CNS. Lancet Neurol 2011;10:561–572.
12. Singhal AB, Topcuoglu MA. Glucocorticoid-associated worsening in reversible cerebral vasoconstriction syndrome. Neurology 2017;88:228–236.
13. Camargo ECS, Singhal AB. Cerebral arteriopathies, venous thrombosis, and migraine. Semin Neurol 2017;37:339–350.
14. Singhal AB. Diagnostic challenges in RCVS, PACNS, and other cerebral arteriopathies. Cephalalgia 2011;31:1067–1070.
15. Wong LK. Global burden of intracranial atherosclerosis. Int J Stroke 2006;1: 158–159.
16. Singhal AB. Postpartum angiopathy with reversible posterior leukoencephalopathy. Arch Neurol 2004;61:411–416.
17. Bartynski WS, Boardman JF. Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol 2008;29:447–455.
18. Lee VH, Wijdicks EF, Manno EM, Rabinstein AA. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. Arch Neurol 2008;65:205–210.
19. Iancu-Gontard D, Oppenheim C, Touze E, et al. Evaluation of hyperintense vessels on FLAIR MRI for the diagnosis of multiple intracerebral arterial stenoses. Stroke 2003; 34:1886–1891.
20. Chen SP, Fuh JL, Lirng JF, Wang SJ. Hyperintense vessels on flair imaging in reversible cerebral vasoconstriction syndrome. Cephalalgia 2012;32:271–278.
21. Calabrese LH, Mallek JA. Primary angiitis of the central nervous system: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine 1988;67:20–39.
22. Hallemeier CL, Rich KM, Grubb RL Jr, et al Clinical features and outcome in North American adults with moyamoya phenomenon. Stroke 2006;37: 1490–1496.
23. Hajj-Ali RA, Calabrese LH. Diagnosis and classification of central nervous system vasculitis. J Autoimmun 2014;48-49:149–152.
24. Zou WX, Leung TW, Yu SC, et al. Angiographic features, collaterals, and infarct topography of symptomatic occlusive radiation vasculopathy: a case-referent study. Stroke 2013;44:401–406.
25. Topcuoglu MA, Jha RM, George J, Frosch MP, Singhal AB. Hemorrhagic primary CNS angiitis and vasoconstrictive drug exposure. Neurol Clin Pract 2017;7: 26–34.
26. Caplan LR. Scores of scores. JAMA Neurol 2013;70:252–253.
27. Wintermark M, Hills NK, deVeber GA, et al. Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the Vascular Effects of Infection in Pediatric Stroke Study. Stroke 2014;45:3597–3605.
28. Muehlschlegel S, Kursun O, Topcuoglu MA, Fok J, Singhal AB. Differentiating reversible cerebral vasoconstriction syndrome with subarachnoid hemorrhage from other causes of subarachnoid hemorrhage. JAMA Neurol 2013;70: 1254–1260.
29. Kumar S, Goddeau RP Jr, Selim MH, et al. Atraumatic convexal subarachnoid hemorrhage: clinical presentation, imaging patterns, and etiologies. Neurology 2010; 74:893–899.
30. Mandell DM, Matouk CC, Farb RI, et al. Vessel wall MRI to differentiate between reversible cerebral vasoconstriction syndrome and central nervous system vasculitis: preliminary results. Stroke 2012;43:860–862.
31. Erdbruegger U, Grossheim M, Hertel B, et al. Diagnostic role of endothelial microparticles in vasculitis. Rheumatology (Oxford) 2008;47:1820–1825.
32. Hajj-Ali RA, Major J, Langford C, et al. The interface of inflammation and subclinical atherosclerosis in granulomatosis with polyangiitis (Wegener's): a preliminary study. Transl Res 2015;166:366–374.
33. Kass-Hout T, Kass-Hout O, Sun CH, et al. A novel approach to diagnose reversible cerebral vasoconstriction syndrome: a case series. J Stroke Cerebrovasc Dis 2015;24: e31–37.
34. Headache Classification Committee of the International Headache Society. International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38: 1–211.

$RCVS_2$ score and diagnostic approach for reversible cerebral vasoconstriction syndrome

Eva A. Rocha, M. Akif Topcuoglu, Gisele S. Silva, et al.

Neurology 2019;92;e639-e647 Published Online before print January 11, 2019
DOI 10.1212/WNL.0000000000006917