Hemorrhagic Reversible Cerebral Vasoconstriction Syndrome

Features and Mechanisms

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Background and Purpose—To compare hemorrhagic and nonhemorrhagic reversible cerebral vasoconstriction syndromes (RCVS) with a view to understand mechanisms.

Methods—This single-center retrospective study included 162 patients with RCVS. Clinical, brain imaging, and angiography data were analyzed.

Results—The mean age was 44±13 years, 78% women. Hemorrhages occurred in 43% including 21 patients with intracerebral hemorrhage (ICH) and 62 with convexal subarachnoid hemorrhage (cSAH). The frequency of triggers (eg, vasoconstrictive drugs) and risk factors (eg, migraine) were not significantly different between hemorrhagic and nonhemorrhagic RCVS or between subgroups (ICH versus non-ICH, isolated cSAH versus normal scan). Hemorrhagic lesions occurred within the first week, whereas infarcts and vasogenic edema accumulated during 2 to 3 weeks ($P<0.001$). Although all ICHs occurred before cSAH, their time course was not significantly different ($P=0.11$). ICH and cSAH occurred earlier than infarcts ($P\leq0.001$), and ICH earlier than vasogenic edema ($P=0.009$). Angiogram analysis showed more severe vasoconstriction in distal versus proximal segments in all lesion types (ICH, cSAH, infarction, vasogenic edema, and normal scan). The isolated infarction group had more severe proximal vasoconstriction, and those with normal imaging had significantly less vasoconstriction. Multivariable analysis failed to uncover independent predictors of hemorrhagic RCVS; however, female sex predicted ICH ($P=0.048$), and angiographic severity predicted infarction ($P=0.043$).

Conclusions—ICH and cSAH are common complications of RCVS. Triggers and risk factors do not predict lesion subtype but may alter central vasomotor control mechanisms resulting in centripetal angiographic evolution. Early distal vasoconstriction is associated with lobar ICH and cSAH, and delayed proximal vasoconstriction with infarction. **(*Stroke*. 2016;47:1742-1747. DOI: 10.1161/STROKEAHA.116.013136.)**

Key Words: cerebral arterial diseases ■ headache ■ stroke ■ subarachnoid hemorrhage ■ vasoconstriction

The reversible cerebral vasoconstriction syndrome (RCVS) is well characterized as a group of conditions typically heralded by severe thunderclap headaches (TCH) associated with reversible segmental multifocal cerebral artery vasoconstriction.[1–5] Approximately one third to half develop intracerebral hemorrhage (ICH), convexal subarachnoid hemorrhage (cSAH), ischemic stroke, and reversible brain edema (posterior reversible leukoencephalopathy syndrome or posterior reversible encephalopathy syndrome [PRES]), either alone or in combination.[6–9] The pathophysiology of this syndrome is not known. It is unclear why some patients develop hemorrhagic lesions and others ischemic or edematous lesions. In a previous study, we showed that there were no significant differences between RCVS subgroups as defined by presumed risk factors and triggers, such as previous migraine and vasoconstrictive drugs.[4] The aim of this study was to understand the mechanisms (the role of risk factors, triggers, and angiographic evolution) in hemorrhagic and nonhemorrhagic RCVS.

Materials and Methods

This retrospective study was approved by our Institutional Human Research Committee. We included 162 patients with RCVS encountered at Massachusetts General Hospital from 1998 to 2016. The clinical and brain-imaging features of the first 159 patients have been published.[1,4] We were careful to exclude patients with primary angiitis of the central nervous system, a close mimic of RCVS, based on published criteria.[1] Serial cerebral angiography confirmed reversibility in 128 patients, and 30 patients developed sudden, severe headaches, segmental arterial narrowing on cerebral angiography, and had a self-limited clinical course in the absence of immunosuppressive treatment and no recurrences during follow-up. The final 4 patients died; 2 patients showed normal cerebral arteries (no evidence of vasculitis) on autopsy and 2 showed immediate angiographic resolution

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with intra-arterial vasodilator infusion (considered a diagnostic test for RCVS by some[10,11]) before their demise. Hospital records were reviewed to extract information on demographics, triggers, medical history, neurological deficits, clinical course, and laboratory test results.

We analyzed the initial and follow-up imaging (brain magnetic resonance imaging [MRI] or, if not available, head computed tomography [CT]) performed during the first admission. We recorded the brain lesion type as infarction, hemorrhage (parenchymal, subarachnoid, or subdural), or vasogenic edema. Parenchymal hemorrhages were classified according to number, size, and location (lobar, deep, or cerebellar). cSAH were classified according to the number of sulci involved, location (frontal, parietal, occipital, and temporal), and whether there was involvement of the Sylvian fissures and basal cisterns. We documented the presence and number of deep sulcal T2-hyperintensities (hyperdense vessel or dot sign on fluid-attenuated inversion recovery), which reflects dilated cortical surface arteries in RCVS.[12,13] cSAH were distinguished from the fluid-attenuated inversion recovery hyperdense vessel sign on the basis of signal abnormalities on head CT or gradient-echo or susceptibility-weighted MRI.

We analyzed the first digital subtraction cerebral angiogram, CT angiogram, and magnetic resonance angiogram in order of preference to determine the site of arterial involvement. Arterial sites were classified as proximal (internal carotid artery; first segments of the anterior, middle, and posterior cerebral arteries; vertebral arteries; and basilar artery); middle (second segments of the anterior, middle, and posterior cerebral arteries and the superior, anterior–inferior, and posterior–inferior cerebellar arteries); and distal (distal branch arteries). In each arterial segment, we recorded the severity of narrowing (0=none, 1=mild, <50% reduction in caliber as compared with the nearest normal segment, and 2=definite, ≥50% caliber reduction). A mean intracranial vasoconstriction severity score was obtained for each patient.[1]

Categorical data were analyzed using the χ^2 test, Fisher exact test, Student *t* test, or Mann–Whitney *U* test, as appropriate. A time-to-event analysis using serial imaging data was performed for the 4 lesion subtypes (cSAH, ICH, PRES, and ischemic stroke). A value of $P<0.05$ was considered significant. Bonferroni correction was applied for multiple comparisons. Univariate and multivariate analyses were performed to identify predictors of various lesion types. SPSS v.21 was used for analyses.

Results

The overall mean age was 44±13 years, 78% women. Hemorrhages occurred in 43% of the cohort. Figure 1 shows representative images of hemorrhagic RCVS.

A total of 24 parenchymal hematomas were detected in 21 patients (13%). Five patients had isolated ICH, and the rest had concurrent lesions: 6 cSAH, 2 infarctions, 2 PRES, and 6 lesion combinations. Four patients with lobar ICH had adjacent subdural hemorrhage. The location of parenchymal ICH was lobar in 16 patients (multiple in 1), deep gray in 3 patients (all with ventricular extension), cerebellar in 1 patient, and in multiple locations in 1 patient. ICH volume was small (<10 mm^3; mean: 2.8±2.9 mm^3) in 11 patients, medium (10–30 mm^3; mean: 17.7±5.8 mm^3) in 5 patients, and large (>30 mm^3; mean: 66±22 mm^3) in 8 patients. Nineteen patients had ICH on initial imaging and 2 developed new ICH on follow-up. Five of 19 patients with ICH on initial imaging showed new brain lesions on follow-up, including 4 who developed recurrent ICH.

cSAH was detected in 62 patients (38%). In 36 patients, concurrent lesions were present: 6 ICH, 8 infarctions, 12 PRES, and 10 lesion combinations. Additional subdural hematomas were noted in 3 patients. cSAH was bilateral in 38% of patients. It was confined to one cortical sulcus in 36%, and involved 2 sulci in 26%, and ≥3 sulci in 38% of patients. Extension to the superior portion of the Sylvian fissure and ambient cistern was rare (3 cases). The frontal lobe sulci were involved in 79%, parietal in 32%, occipital in 23%, and temporal in 10%. Of the 62 patients with cSAH, 56 (90%) had cSAH on initial imaging and 6 developed cSAH on follow-up (of these, 4 had initially normal scans). Thirteen of 56 patients with cSAH on initial imaging showed new lesions on follow-up, including 8 who developed recurrent cSAH.

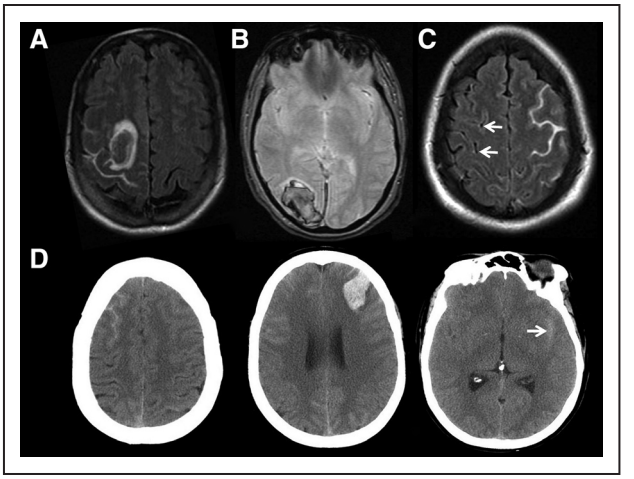

Figure 1. Brain hemorrhages in reversible cerebral vasoconstriction syndromes. **A**, Right frontal intracerebral hemorrhage (ICH) with adjacent convexal subarachnoid hemorrhage (cSAH) on axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). **B**, Right occipital ICH with adjacent subdural hemorrhage on axial gradient-echo MRI. **C**, Left frontal cSAH and multiple dot signs (arrows) in the right hemispheric sulci on axial FLAIR-MRI. **D**, Axial head computed tomography images from the same patient showing a right frontal cSAH and left frontal ICH with cSAH extending into the superior Sylvian fissure (arrow).

Table 1 shows a comparison of hemorrhagic and nonhemorrhagic groups. Patients with any form of hemorrhage (ICH or cSAH) were significantly older by an average of 4 years. There were no significant differences in sex, triggers, previous migraine or depression, or presenting signs and symptoms (hypertension, focal neurological deficits, and seizures). Systolic and diastolic blood pressures showed no significant differences between groups. Patients with any hemorrhage had fewer recurrent TCH, fewer concurrent infarctions, and a higher frequency of the fluid-attenuated inversion recovery hyperintense vessel sign. There were no significant differences in the length of stay or discharge clinical outcome.

Because the hemorrhagic RCVS group included both ICH and cSAH which have different phenotypes, we conducted further subgroup analyses. First, we compared patients with ICH to those without ICH. There were no significant differences in demographics, triggers, medical history, admission blood pressure, and neuroimaging features; however, the ICH group showed a trend for fewer TCH recurrences, significantly more focal neurological deficits, and a trend for worse discharge outcomes (Table 1). Of note, the blood pressure

Table 1. Subgroup Comparisons: Clinical and Imaging Features

Variable	Any Hem (n=71)	No Hem (n=91)	*P* Value	Any ICH (n=21)	No ICH (n=141)	*P* Value	Iso cSAH (n=26)	No Lesion (n=38)	*P* Value
Age, y (mean±SD)	46±12	42±13	0.04	43±13	44±13	0.67	47±11	39±15	0.02
Female, %	83	74	0.15	91	80	0.14	81	55	0.04
White race, %	81	85	0.26	69	86	0.28	83	90	0.67
Trigger									
Vasoconstrictive drugs, %	61	59	0.88	52	61	0.31	58	50	0.36
Physiological/idiopathic, %	31	29	0.74	24	31	0.37	42	45	0.85
Postpartum, %	9	11	0.59	19	9	0.13	4	5	0.79
Previous depression, %	44	40	0.60	38	42	0.75	43	34	0.35
Previous migraine, %	42	40	0.73	48	40	0.49	39	32	0.60
Previous hypertension, %	42	33	0.15	43	36	0.55	27	26	0.59
TCH present, %	93	87	0.30	91	90	0.62	100	97	0.59
Recurrence, %	69	78	0.13	62	76	0.14	85	90	0.42
Recurrence number	2.0±1.6	2.9±2.7	0.02	1.6±1.4	2.6±2.4	0.06	2.5±1.4	3.4±3.3	0.19
Admission BP >140/90, %	49	47	0.80	62	46	0.13	39	37	0.55
Hemiparesis/aphasia, %	28	29	0.80	62	23	<0.001	5	4	0.64
Visual symptoms, %	13	16	0.45	52	35	0.095	21	19	0.56
Generalized seizures, %	9	19	0.06	5	16	0.18	4	0	0.41
Infarction, %	23	42	0.01	19	36	0.11	0	0	…
Vasogenic edema (PRES), %	33	24	0.25	33	27	0.36	0	0	…
FLAIR dot sign, %	65	50	0.04	71	54	0.10	39	34	0.47
Length of stay, d	9±6	10±10	0.40	12±6	9±9	0.097	5±3	4±4	0.08
Discharge mRS 0–3, %	91	90	0.75	81	92	0.097	100	100	…
Discharge mRS 4–5, %	6	7	…	14	6	…	0	0	…
Discharge mRS 6, %	3	2	0.44	5	2	0.47	0	0	…

BP indicates blood pressure; FLAIR, fluid-attenuated inversion recovery; Hem, hemorrhage; ICH, intracerebral hemorrhage; iso cSAH, isolated convexal subarachnoid hemorrhage; mRS, modified Rankin Scale score; PRES, posterior reversible leukoencephalopathy syndrome; and TCH, thunderclap headache.

was not significantly different between patients with ICH and PRES (systolic, 154±35 versus 163±36; *P*=0.333 and diastolic, 85±17 versus 88±18; *P*=0.466).

A comparison of patients with cSAH to those without cSAH is not presented because of significant differences in the presence of concurrent lesions that affect phenotype (eg, the cSAH group had more concurrent ICH [19% versus 9%; *P*=0.049]). Instead, we compared patients with isolated cSAH to those with normal brain imaging (ie, both groups with no parenchymal lesions). The normal brain imaging group was younger by an average of 8 years and had a lower percentage of women, but there were no other significant differences (Table 1).

Time to Occurrence

Figure 2 shows the cumulative event rates and median time to the occurrence of different lesions. Time to occurrence was defined as the time from the first symptom (typically TCH) to the first imaging study showing the lesion. There was a significant difference between subtypes (ANOVA *P*<0.001). Nearly all hemorrhagic lesions occurred within the first week, whereas infarcts and PRES steadily accumulated during 2 to 3 weeks. Although all ICHs occurred earlier than cSAH, the time course was not significantly different (*P*=0.11). ICH and cSAH occurred earlier than infarcts (*P*≤0.001), and ICH occurred earlier than PRES (*P*=0.009). Given that CT and MRI have different sensitivities for hemorrhagic and nonhemorrhagic lesions, we repeated this analysis in patients with MRI data, but there was no significant change in the results (Figure 2, middle). Similarly, there was no significant change in the results when considering patients with isolated lesion types (Figure 2, bottom).

Vasoconstriction

To understand the effect of arterial vasoconstriction on lesion development, we compared angiographic involvement and the severity of vasoconstriction in proximal, middle, and distal cerebral artery segments among different lesion types (Table 2). Given the lower sensitivity of magnetic resonance angiogram for distal vasoconstriction, only digital subtraction cerebral angiogram or CT angiogram was used for this comparison.[7] Furthermore, because many patients had lesion

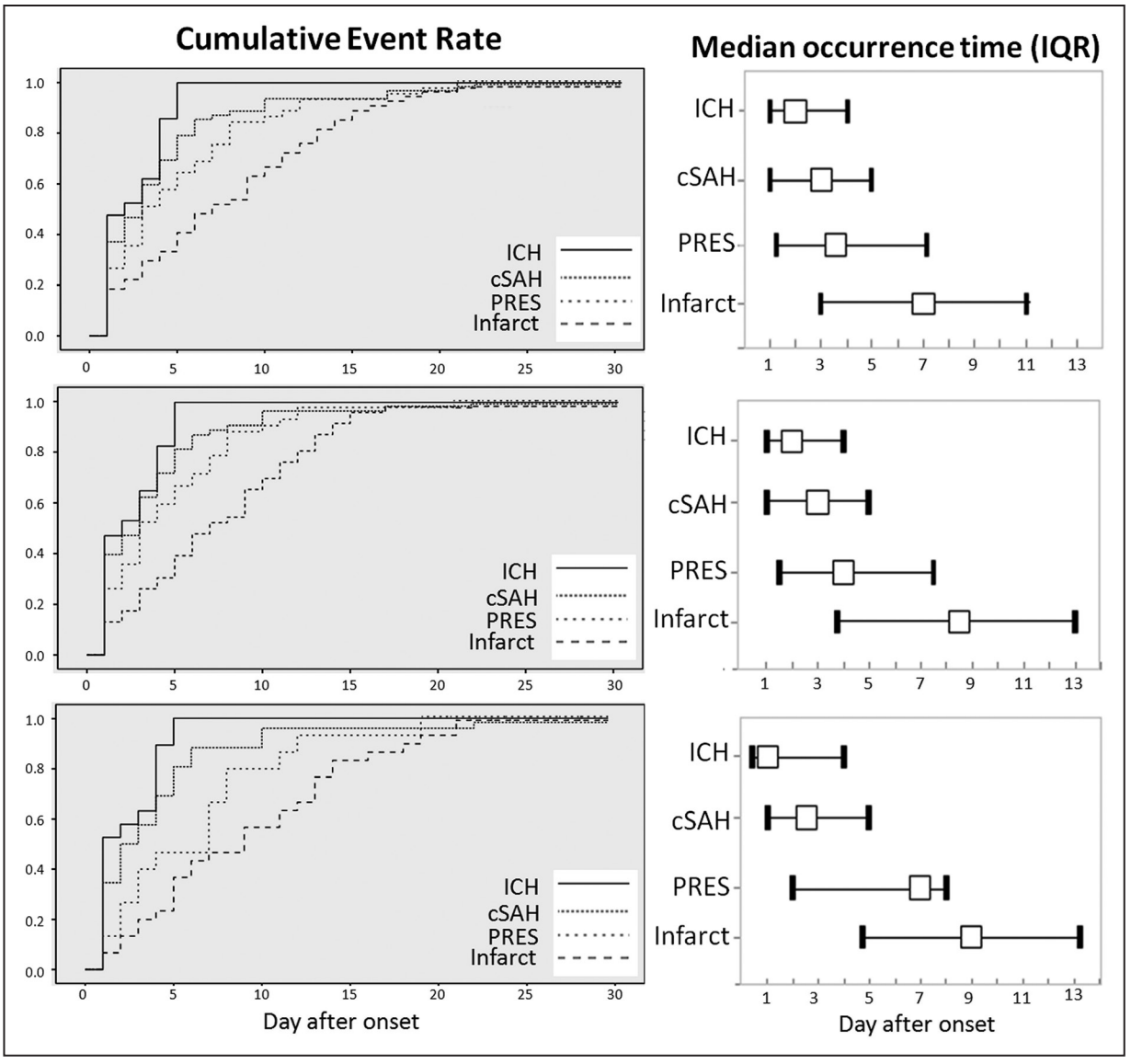

Figure 2. Temporal differences in reversible cerebral vasoconstriction syndrome (RCVS) subtypes. Cumulative event rates (**left**) and time to occurrence (**right**) among different RCVS lesion subtypes. **Top**: Lesions identified on either head computed tomography or brain magnetic resonance imaging (MRI). **Middle**: Subanalysis, lesions identified on brain MRI. **Bottom**: Subanalysis, isolated lesion subtypes (see text for details). cSAH indicates convexal subarachnoid hemorrhage; ICH, intracerebral hemorrhage; IQR, interquartile range; and PRES, posterior reversible leukoencephalopathy syndrome.

combinations, to avoid confounding, we restricted this analysis to patients with isolated cSAH, ICH without infarction, isolated infarction, isolated PRES, and normal brain imaging. Vasoconstriction was diffuse, affecting the proximal, middle, and distal segments, in all lesion types. However, the severity of vasoconstriction (the percentage of arteries with >50% caliber reduction and the mean severity score) was consistently higher in distal as compared with proximal arterial segments in all groups. The isolated infarction group had more severe proximal vasoconstriction as compared with the other groups. Conversely, patients with normal MRI had significantly less vasoconstriction in the middle and distal segments. There was no correlation between the number of recurrent TCH and angiographic severity scores (r=0.1; P=0.26).

Independent Predictors of Hemorrhage

Multivariable analysis adjusting for age, sex, drugs, systolic blood pressure, and angiographic severity score were performed to identify independent predictors of hemorrhagic and nonhemorrhagic lesion types. None of these variables predicted hemorrhagic RCVS; however, female sex predicted ICH (P=0.048), and angiographic severity score predicted ischemic stroke (P=0.043).

Discussion

In our large cohort of RCVS, brain hemorrhages were frequent (43%). Hemorrhagic and nonhemorrhagic groups showed no significant differences in risk factors such as migraine, or triggers such as medications, or clinical features or outcomes. The minor differences in demographics were driven largely

by the significantly younger age and female predominance of patients with cSAH, which was the most frequent subtype of hemorrhage. Established risk factors for ICH (previous hypertension and admission blood pressure) were not significantly different between groups. In a previous study, we found no major differences in RCVS subgroups defined by risk factors and triggers.[4] These data suggest that the phenotype of RCVS is relatively homogenous regardless of lesion type or precipitant.

Our results are consistent with a previous study showing older age and female preponderance in patients with hemorrhage and an earlier occurrence of hemorrhagic lesions in RCVS.[9] Unlike that study, we found that ICH occurred earlier than cSAH and that female sex and migraine were not independent predictors of hemorrhagic RCVS. These differences can be explained by the differences in sample size, recruitment (mainly inpatients versus emergency department patients), and the higher percentage of concurrent infarcts in our cohort. Our results are also consistent with a previous serial transcranial Doppler ultrasound study showing persistence of proximal vasoconstriction[14] and a previous magnetic resonance angiogram study showing that proximal vasoconstriction occurs later (mean 16.3 days) after symptom onset.[15]

A novel feature of this study is the comparison of hemorrhagic subtypes. Patients with cSAH seemed similar to those without any brain lesions, supporting the benign nature of cSAH. Patients with ICH had fewer recurrent TCH, presumably because of limited communication from their more severe deficits or perhaps because of interference of headache pain pathways by the hematoma itself. Patients with ICH had more focal deficits on admission, consistent with the earlier occurrence of ICH, and had tended to have less favorable outcome at discharge. The lack of significant differences in risk factors, triggers, blood pressure, and other variables in the subgroup analyses of ICH and cSAH (Table 1) suggests that these factors do not influence the lesion type.

Important observations include the differences in time course of lesion occurrence and the distinct vasoconstriction patterns across groups. Hemorrhagic lesions occurred earlier than ischemic or edematous lesions. In patients with hemorrhage, the distal vessels were more commonly and more severely affected, and correspondingly there was a higher frequency of the fluid-attenuated inversion recovery hyperdense vessel sign. The predominantly lobar and hemispheric surface location of hemorrhages implicates affliction of the distal arterial bed and fits with the more severe distal vasoconstriction in hemorrhagic RCVS. Conversely, infarcts were associated with proximal, severe vasoconstriction, and patients without any brain lesion had the mildest angiographic abnormalities. These data support the distal-to-proximal (centripetal) progression of angiographic abnormalities during a span of ≈2 weeks.[9,16] These observations further suggest that angiographic abnormalities are dynamic and support the hypothesis that rapid changes in arterial caliber may induce ischemia–reperfusion injury, culminating in hemorrhages.[17] The diffuse, severe proximal artery vasoconstriction correlates with the typical anterior–middle and middle–posterior cerebral artery watershed infarcts in RCVS.

Table 2. Subgroup Comparisons: Angiographic Abnormalities

	Isolated cSAH (n=24)	ICH Without Infarct (n=16)	Isolated Stroke (n=20)	Isolated PRES (n=10)	Normal MRI (n=28)
Onset to CT/MRI, d (mean±SD, median)	4±4 (2.5)	2±1.5 (1)	9±6 (9)	6±5 (7)	…
Onset to angio, d (mean±SD, median)	7±6 (5.5)	4±3 (3)	9±8 (6)	9±6 (9.5)	6±4 (5)
Any vasoconstriction present					
Proximal segment, %	63	69	95	70	82
Middle segment, %	96	88	95	90	79
Distal branches, %	96	82	80	80	71
Severe (>50%) vasoconstriction					
All arteries, %	23±28	25±19	47±30*	29±28	13±20*
Proximal segment, %	7±18	11±17	38±30*	15±21	8±17
Middle segment, %	27±37	25±19	51±33*	37±36	13±22*
Distal branches, %	42±41	52±42	58±41	42±42	22±29*
Mean vasoconstriction severity score					
All arteries	0.87±1.21	0.70±0.41	1.09±0.58	0.87±0.58	0.42±0.43*
Proximal segment	0.28±0.36	0.39±0.42	0.93±0.58*	0.56±0.53	0.26±0.34*
Middle segment	0.77±0.70	0.73±0.41	1.17±0.60	1.08±0.66	0.48±0.51*
Distal branches	1.12±0.69	1.21±0.76	1.28±0.75	1.12±0.78	0.68±0.65*

Angio indicates angiogram; cSAH, convexal subarachnoid hemorrhage; CT, computed tomography; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; and PRES, posterior reversible leukoencephalopathy syndrome.

*Bonferroni-corrected $P<0.01$ vs one or more of the other groups (see text for details).

Because lesion types correlate with the angiographic patterns but not risk factors or triggers, we speculate that risk factors/triggers activate or lower the threshold for a central mechanism underlying RCVS, and in turn, this central mechanism drives distal-to-proximal angiographic progression and culminates in different lesions during the ensuing days or weeks. Differences in the density and distribution of receptors that control arterial tone and the innervation of cerebral arteries from the adrenergic and serotonergic pathways emanating from the hypothalamus, locus coeruleus, raphe nuclei, first division of the trigeminal nerve, and dorsal root of C2 may form the anatomic basis for this central mechanism. The same central mechanism probably underlies the unusual TCH that characterize RCVS. Although there was no association between the number of recurrent TCH and angiographic severity scores, recurrences may still influence the temporal progression or the duration of angiographic abnormalities.

A major strength of our study is the detailed analysis of one of the largest cohorts of RCVS, enabling a comparison of isolated lesion subtypes. Furthermore, because CT is less sensitive for nonhemorrhagic lesions, we conducted additional analysis using only MRI data. The angiographic analysis was novel and restricted to digital subtraction cerebral angiogram and CT angiogram which are more reliable imaging modalities for distal vasoconstriction. Imaging analysis was completed, and angiographic severity scores were derived before initiating this study, so a blinded neuroimaging evaluation was deemed unnecessary. Limitations of our analysis include the inconsistent time of imaging (which was driven by clinical indications), and hence, the subacute findings may be biased toward symptomatic lesions such as new infarctions. Lesion development (especially infarction) may be influenced by iatrogenic factors, such as glucocorticoid therapy,[4] calcium-channel blocker or vasodilator treatment, or angiographic complications,[18] which were not considered in this study.

Aside from providing mechanistic insights, our results have important clinical implications. On the basis of our data and previous publications,[8] patients should be counseled about the risk of developing new brain lesions and clinical worsening, yet reassured that the eventual outcome is largely benign (Table 1). Infarcts and PRES can occur as late as 3 weeks after headache onset. However, it is not clear how lesions can be prevented or whether vasoconstriction monitoring has any use. Although some case series suggest benefit with nimodipine,[19] other studies have not shown therapeutic benefit with calcium-channel blocker therapy.[4,16] The risk of developing new brain lesions seems substantial (5 of 19 patients) in patients with ICH and relatively low (5 of 56 patients) in those with cSAH on initial imaging. Hence, patients with initial ICH should be monitored more closely. Although we did not find a significant association between risk factors/triggers and lesion subtype, these factors have been consistently associated with RCVS and should be avoided at least in the acute stages.

Disclosures

Dr Singhal has served as a medicolegal expert witness and received honoraria for contributing book chapters to Medlink, Inc and UptoDate, Inc. The other author reports no conflicts.

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