ONLINE FIRST

Reversible Cerebral Vasoconstriction Syndromes

Analysis of 139 Cases

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Objectives: To compare the clinical, laboratory, and imaging features of patients with reversible cerebral vasoconstriction syndromes evaluated at 2 academic centers, compare subgroups, and investigate treatment effects.

Design: Retrospective analysis.

Setting: Massachusetts General Hospital (n=84) or Cleveland Clinic (n=55).

Patients: One hundred thirty-nine patients with reversible cerebral vasoconstriction syndromes.

Main Outcome Measures: Clinical, laboratory, and imaging features; treatment; and outcomes.

Results: The mean age was 42.5 years, and 81% were women. Onset with thunderclap headache was documented in 85% and 43% developed neurological deficits. Prior migraine was documented in 40%, vasoconstrictive drug exposure in 42%, and recent pregnancy in 9%. Admission computed tomography or magnetic resonance imaging was normal in 55%; however, 81% ultimately developed brain lesions including infarcts (39%), convexity subarachnoid hemorrhage (34%), lobar hemorrhage (20%), and brain edema (38%). Cerebral angiographic abnormalities typically normalized within 2 months. Nearly 90% had good clinical outcome; 9% developed severe deficits; and 2% died. In the combined cohort, calcium channel blocker therapy and symptomatic therapy alone showed no significant effect on outcome; however, glucocorticoid therapy showed a trend for poor outcome ($P=.08$). Subgroup comparisons based on prior headache status and identified triggers (vasoconstrictive drugs, pregnancy, other) showed no major differences.

Conclusion: Patients with reversible cerebral vasoconstriction syndromes have a unique set of clinical imaging features, with no significant differences between subgroups. Prospective studies are warranted to determine the effects of empirical treatment with calcium channel blockers and glucocorticoids.

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THE MEDICAL LITERATURE spanning the last 50 years contains numerous examples of patients with reversible cerebral arterial narrowing, frequently associated with severe headaches and stroke. Published reports have used variable nomenclature, eg, Call-Fleming syndrome,[1] migraine angiitis, postpartum angiopathy, and drug-induced vasospasm. Because of certain overlapping

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features (headache, stroke, angiographic abnormalities) with primary angiitis of the central nervous system (PACNS), some cases have been reported as "benign angiopathy of the central nervous system"[2] and others, as a self-limited vasculitis. Only recently has it become apparent that these patients have similar clinical imaging features.[3-6] In 2007, we tentatively proposed the term *reversible cerebral vasoconstriction syndrome* (RCVS) and elucidated its key features to increase recognition and facilitate accurate diagnosis.[7] Prospective case series and review articles adopting this contemporary term have helped to further characterize RCVS.[8-11]

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At present, the pathophysiology of RCVS remains unknown, and there is uncertainty about including potentially distinct entities under a single syndrome.[12] Despite significant advances in characterizing RCVS[7-11] and PACNS,[13,14] physicians remain fearful of delaying immuno-

Table 1. Summary of Critical Elements for the Diagnosis of RCVS[a]

Elements
1. Transfemoral angiography or indirect (CT or MRI) angiography documenting segmental cerebral artery vasoconstriction
2. No evidence for aneurysmal subarachnoid hemorrhage
3. Normal or near-normal cerebrospinal fluid analysis (protein level <80 mg/dL, white blood cell count <10/μL, normal glucose level)
4. Severe, acute headache, with or without additional neurological signs or symptoms
5. The diagnosis cannot be confirmed until reversibility of the angiographic abnormalities is documented within 12 wk after onset, or if death occurs before the follow-up studies are completed, autopsy rules out conditions such as vasculitis, intracranial atherosclerosis, and aneurysmal subarachnoid hemorrhage, which can also manifest with headache and stroke.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; RCVS, reversible cerebral vasoconstriction syndromes.
[a]From Calabrese et al.[7]

suppressive therapy in patients who may ultimately prove to have PACNS. Hence, patients who truly have RCVS are frequently administered immunosuppressive agents or subjected to the risks of brain biopsy. To our knowledge, the effects of calcium channel blockers, such as nimodipine,[15,16] and empirical glucocorticoids have not been studied. This 2-center study was initiated to further characterize RCVS and address these questions.

METHODS

We retrospectively analyzed 139 consecutive patients with RCVS personally encountered at Massachusetts General Hospital (MGH) (n=84, 1998-2009) or Cleveland Clinic (CC) (n=55, 1993-2009). In the absence of validated diagnostic criteria, inclusion was based on experience-based guidelines (**Table 1**) for the diagnosis of RCVS.[7] Patients with "probable" RCVS (without follow-up vascular imaging) were included, and their data were compared with patients with angiographic reversal on follow-up imaging. Patients without thunderclap headaches (TCHs) were included if there was evidence for reversible angiographic abnormalities and no evidence for PACNS. To determine short-term clinical outcome, modified Rankin Scale (mRS) scores were calculated from clinical notes documented closest to follow-up imaging (2-4 months) or hospital discharge.

To investigate the relationship between migraine and RCVS, and to address whether RCVS is one syndrome or many,[12] we compared subgroups based on prior headache status and presumed risk factors. From medical record reviews, we could not confirm whether prior headaches met the definition of migraine.[17] If not recorded, prior headache was considered absent. Cases were classified on the basis of the identified trigger or associated risk factor as "post partum" (delivery until 6 weeks post partum), "drugs" (exposure to vasoconstrictive agents), or "other" (no identifiable trigger or associated with head trauma or procedures like carotid endarterectomy and colonoscopy). Cases with multiple potential triggers were classified into the presumed higher-risk category.

Statistical analysis used the Fisher exact test, *t* test, or Cochran-Mantel-Haenszel test, with a significance level of .05. Logistic regression models were used to estimate the likelihood of poor outcome. This study was approved by human research committees at both institutions.

RESULTS

Table 2 shows clinical, laboratory, and imaging features; treatment; and outcomes of the entire cohort and a comparison between centers.

CLINICAL FEATURES

The mean age was 42.5 years (range, 13-69 years), with only 3 patients (2 boys, 1 girl) younger than 18 years and 9 women older than 60 years. Women composed 81% of the cohort and were significantly older than men (mean [SD] age, 44.2 [11] vs 34.9 [12] years; $P<.001$). All races were affected in a distribution consistent with the racial profile of our referral base. There were no significant differences in demographic features. As compared with CC, MGH patients had a significantly higher frequency of vasoconstrictive drug exposure, recent pregnancy, and prior headaches. The spectrum of vasoconstrictive drugs was wide: prescription medications including sumatriptan succinate and selective serotonin or serotonin-norepinephrine reuptake inhibitors; nonprescription medications such as pseudoephedrine in cough suppressants; over-the-counter or nonpharmaceutical agents such as diet pills and exercise stimulants containing amphetamines; and illicit drugs such as ecstasy, cocaine, and marijuana. Nearly all patients reported headache at onset and 85% described "explosive-onset, worst-ever" headaches, consistent with TCH.[17] The severity of headache usually prompted an emergency department visit within hours. Most patients experienced recurrent TCHs over 3 to 12 days. Activities such as coughing precipitated recurrent TCHs. The frequency and intensity of TCHs diminished over time. Some developed transient hypertension around the time of headache exacerbation. In general, the systemic examination was normal. Generalized tonic-clonic seizures occurred in 17%. Focal neurological deficits were recorded in 43%, including aphasia, hemiparesis, or ataxia (35%) and visual deficits (29%, often elements of Balint syndrome). Brisk tendon reflexes were a common acute finding. There were no significant between-center differences in presenting symptoms or neurological deficits.

LABORATORY TESTS

Extensive tests were performed to exclude mimics such as PACNS and aneurysmal subarachnoid hemorrhage. There were no significant between-center differences in the frequency of abnormal test results. Erythrocyte sedimentation rate and C-reactive protein level were normal in 90%, and serological test results excluded rheumatologic disorders. Cerebrospinal fluid examination was performed in 78% (Table 2) and results were entirely normal (protein <60

mg/dL, white blood cell count <5/μL) in 78%; the rest had minor abnormalities attributed to underlying stroke or coexisting diseases like Guillain-Barré syndrome; none had xanthochromia. Brain tissue (open brain biopsy or full autopsy in 2 patients) was available in 17% and subjected to extensive histological studies, including electron microscopy in 1 published case.[18] There was no evidence for arterial inflammation or infection.

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

While all patients had cerebral vasoconstriction, 55% showed no lesion on initial head computed tomography (CT) or magnetic resonance imaging (MRI) (Table 2). Follow-up brain and vascular imaging were routinely obtained to determine angiographic reversal or evaluate new symptoms. Ultimately, 81% developed brain lesions (**Figure**) including ischemic stroke (39%), convexity subarachnoid hemorrhage (cSAH) (34%), lobar intracerebral hemorrhage (ICH) (20%), and brain edema (38%). There were no significant differences in neuroimaging results. Isolated ischemic stroke was the most common lesion (37 patients, 27%), followed by isolated cSAH (22 patients, 16%), and isolated ICH (9 patients, 6%). Ten patients had both ICH and cSAH, 9 had cSAH and ischemic strokes, 2 had ICH and ischemic strokes, and 6 patients had a combination of infarcts, ICH, and cSAH. Brain infarcts and hemorrhages were typically located in "watershed" regions and edematous lesions, usually in posterior regions in a pattern consistent with the posterior reversible leukoencephalopathy syndrome (PRES).[19] The cSAH was minor, occupying 1 to 3 sulcal spaces. Infarcts were usually bilateral and symmetric, and some patients had multiple ICHs. The presence of SAH often raised concern for a ruptured aneurysm or arteriovenous malformation, leading to repeated imaging.

VASCULAR IMAGING

The diagnosis of RCVS was based on CT angiography, MRI angiography, or transfemoral angiography in all patients, except one who underwent serial transcranial Doppler ultrasonography (case 3).[20] Most patients were subjected to 2 vascular imaging modalities. Transfemoral angiography was performed in nearly all patients at CC, while MGH patients more frequently underwent CT angiography and MRI angiography (Table 2). Typical angiographic findings included multiple areas of smooth or tapered arterial narrowing followed by segments of normal-caliber or distended arteries (Figure). The abnormalities were usually multiple and bilateral, often resulting in severe narrowing, and affected all intracerebral arteries and their branches. The extracranial segments of the internal carotid or vertebral arteries were rarely affected; arterial constriction typically started at the level of the dural penetration.

Follow-up vascular imaging to confirm RCVS was performed in 78%. Arterial abnormalities reversed completely in 74% and partially in 24%. The median time from onset to final vascular imaging was 66 days at CC and 56 days at MGH. The few patients without confirmatory follow-up tests, and 2 patients without angiographic reversal on follow-up, were still included since they had typical clinical imaging features and a consistent clinical course (ie, probable RCVS).[7] There were no significant differences (data

Table 2. Clinical, Laboratory, and Neuroimaging Features[a]

Characteristic	% All Patients (N=139)	% CC (n=55)	% MGH (n=84)	*P* Value
Age, y, mean (SD)	42.5 (12)	43 (11)	42 (12)	.65[b]
Male	34.9 (12)	39 (9)	32 (13)	.16[b]
Female	44.2 (11)	44 (11)	44 (11)	.91[b]
Female	81	80	82	.75
Race				
White	80	76	82	
African American	5	9	2	.16[c]
Other	13	9	16	
Associated trigger				
Vasoconstrictive drugs	42	36	58	.009
Post partum	9	4	12	.08
Other	50	60	30	<.001
Prior headache disorder	40	24	50	.002
Onset with any headache	95	95	95	.99
Onset with TCH	85	84	86	.74
Recurrent TCH	82	74	88	.06
Medical evaluation on day 1	60	35	85	<.001
Neurological deficits	43	38	46	.34
Seizures at onset	17	16	18	.82
CSF				
CSF analysis performed	78	80	77	.71
Normal protein level	84	86	83	.72
WBC count <5/μL	85	85	85	
WBC count 5-10/μL	12	13	11	.96[c]
WBC count >10/μL	3	3	3	
Brain pathology study	17	22	13	.18
Initial CT or MRI normal	55	57	55	.83
Any CT or MRI abnormal	81	79	82	.68
Brain lesion type				
Infarction	39	38	40	.75
Brain edema	NA	NA	38	NA
Convexity SAH	34	23	42	.02
Lobar hemorrhage	20	23	18	.49
Cerebral angiographic studies				
CT angiography	53	11	80	<.001
MRI angiography	61	46	71	.002
Transfemoral angiography	70	93	55	<.001
Follow-up vascular imaging				
Performed	78	76	79	.76
Direct/indirect angiography	66	60	70	.21
Transcranial Doppler	32	35	30	.55
Treatment				
Calcium channel blockers	63	87	46	<.001
Glucocorticoids	53	93	27	<.001
Both	44	87	15	<.001
Neither	27	7	40	<.001
Modified Rankin Scale score				
0-3	89	95	86	.08
4-6	11	5	14	

Abbreviations: CC, Cleveland Clinic Foundation; CSF, cerebrospinal fluid; CT, computed tomography of the head; MGH, Massachusetts General Hospital; MRI, magnetic resonance imaging of the brain; NA, not applicable; SAH, subarachnoid hemorrhage; TCH, thunderclap headache; WBC, white blood cell.

[a] Statistical analysis used χ^2 or Fisher exact tests, unless otherwise specified.

[b] *t* Test.

[c] Cochran-Mantel-Haenszel test.

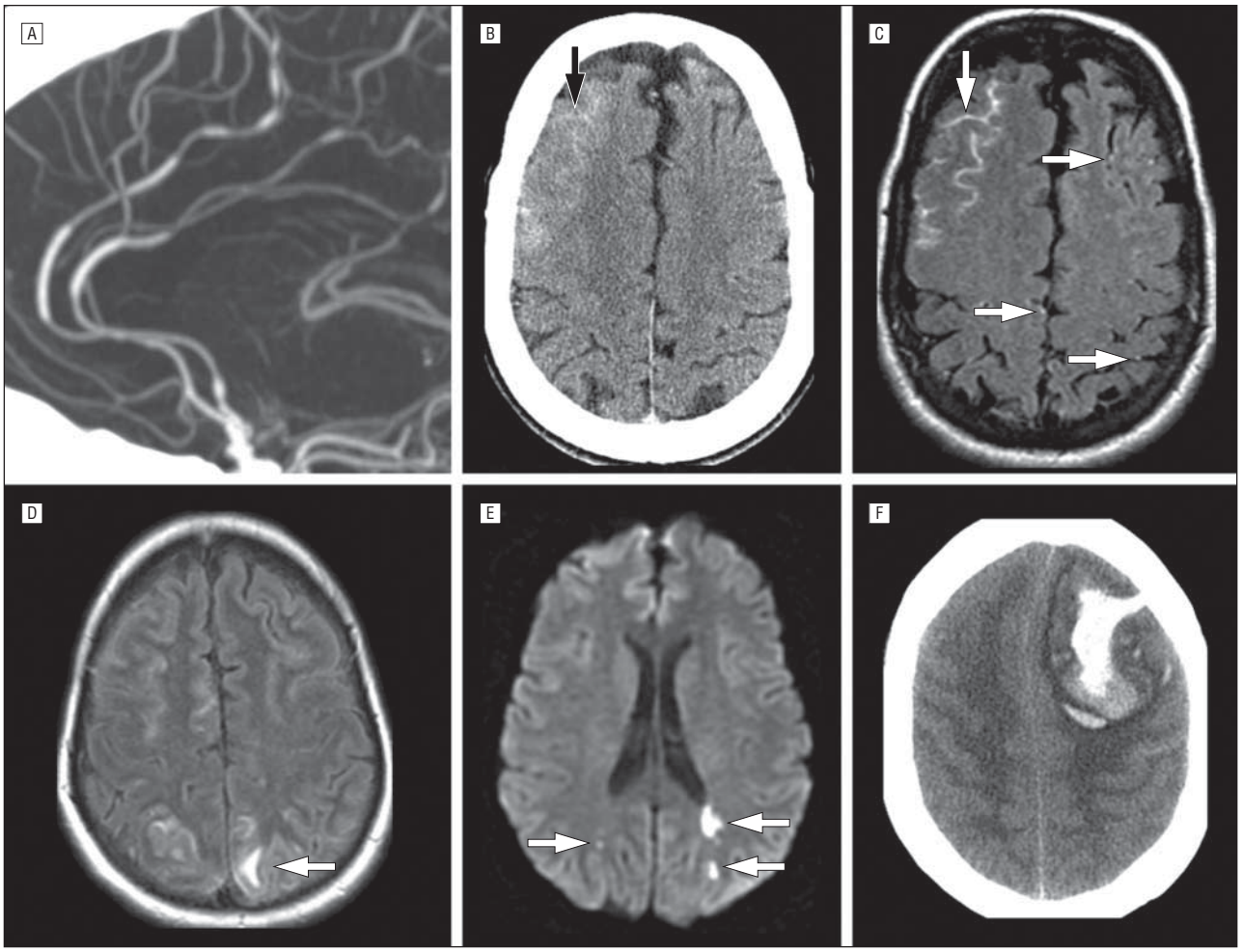

Figure. Typical neuroimaging features of reversible cerebral vasoconstriction syndrome. A, Head computed tomography angiogram, sagittal maximum-intensity projection image, showing the classic "sausage on a string" appearance of both anterior cerebral arteries. B, Head computed tomography, axial image, showing subarachnoid hemorrhage overlying the right frontal lobe (vertical arrow). C, Brain magnetic resonance imaging, axial fluid-attenuated inversion recovery image, in the same patient, showing the right frontal subarachnoid hemorrhage (vertical arrow) as well as multiple dot-shaped hyperintensities (horizontal arrows) within the sulci of both hemispheres, suggesting the presence of dilated cortical surface arteries. D, Brain magnetic resonance imaging, axial fluid-attenuated inversion recovery image, showing the posterior-predominant crescentic hyperintense signal in the cortical-subcortical regions (arrow). Corresponding diffusion-weighted and susceptibility-weighted images (not shown) were normal. These findings suggest the presence of brain edema as described in the posterior reversible leukoencephalopathy syndrome. E, Brain magnetic resonance imaging, axial diffusion-weighted image, showing ischemic lesions (arrows) in the bilateral "watershed" regions of the middle and posterior cerebral arteries. F, Head computed tomography scan, axial image, showing a left frontal parenchymal hemorrhage.

not shown) in the clinical features, frequency of laboratory abnormalities, CT/MRI findings, treatment, and clinical outcome between the 78% of patients who underwent follow-up vascular imaging (angiography or transcranial Doppler ultrasonography) vs 22% who did not and between the 66% who underwent follow-up direct or indirect angiography vs 34% without serial angiography.

TREATMENT

There were 3 main treatment strategies (Table 2) with significant differences between centers: (1) 63% received oral calcium channel blockers, such as nimodipine or verapamil hydrochloride, for days to weeks, (2) 53% received short courses of glucocorticoids (intravenous methylprednisolone or oral prednisone), and (3) 27% received neither calcium channel blockers nor glucocorticoids. There was no apparent reason for selecting a particular strategy. Overall, steroids were given to 57% with focal deficits vs 51% without focal deficits ($P=.50$); at MGH, calcium channel blockers were given to 50% with brain infarcts vs 44% without infarcts ($P=.66$). The "neither treatment" strategy was predominantly followed at MGH, whereas 87% of CC patients received both calcium channel blockers and glucocorticoids. Symptomatic treatment comprising analgesics and laxatives was routinely administered.

SHORT-TERM OUTCOME

Excellent clinical outcome (mRS score 0-1) was documented in 78%; an mRS score of 2 or 3, in 11%; severe deficits (mRS score 4-5), in 9%; and 3 patients (2%) died of progressive vasoconstriction despite receiving calcium channel blockers, glucocorticoids, and neurointerventional therapy.[18] Brain infarction ($P<.001$) but not hemorrhage ($P=.15$) was associated with poor outcome (mRS score 4-6).

SUBGROUP COMPARISONS

Table 3 and **Table 4** show subgroup comparisons based on prior headache status and identified risk factors. No significant differences were observed between patients with or without prior headaches. Prior headache status did not affect the incidence of headache at onset, recurrent TCHs, or angiographic reversibility. Subgroups based on risk factors had similar features, although patients with "other" risk factors were older and postpartum patients had a higher incidence of seizures (postpartum eclampsia), normal cerebrospinal fluid testing results, and a lower rate of ICH. Brain edema, assessed only at MGH, was more frequent with vasoconstrictive drugs ($P=.04$). There were no significant subgroup differences in angiographic reversibility or clinical outcome.

EFFECT OF TREATMENT ON SHORT-TERM CLINICAL OUTCOME

Table 5 shows the effect of treatment on clinical outcome. Calcium channel blockers and the "neither treatment" strategy had no significant effect. Glucocorticoids were associated with a trend for poor outcome ($P=.08$; odds ratio [OR], 2.7; 95% confidence interval [CI], 0.8-8.8). Since nearly 90% of CC patients received both calcium channel blockers and glucocorticoids, this association was essentially driven by MGH patients ($P=.002$; OR, 7.6; 95% CI, 2.0-28.7). At MGH, 23 patients received glucocorticoids; 11 (48%) had further disease progression within 2 to 6 days after starting therapy. Logistic regression analysis adjusting for focal neurological deficits showed that the presence of focal deficits ($P=.02$; OR, 13.7; 95% CI, 1.6-116) and glucocorticoid use ($P=.02$; OR, 5.7; 95% CI, 1.4-23.6) were independent predictors of poor outcome. Finally, we analyzed the effects of each treatment given alone. Calcium channel blocker montherapy (29 patients, all at MGH) was associated with good outcome ($P=.13$ combined cohort; $P=.03$ MGH cohort). Among 13 patients who received glucocorticoid montherapy, 3 had a poor outcome as compared with 12 of 126 who did not receive glucocorticoids (23% vs 9%; $P=.15$).

Table 3. Comparison of RCVS Subgroups Based on Prior Headache Status[a]

Characteristic	% No Prior Headache (n=55)	% Prior Headache (n=84)	*P* Value
Age, y, mean (SD)	44 (12)	41 (12)	.11[b]
Female	78	86	.31
Race			
White	77	84	.44[c]
African American	7	2	
Other	13	13	
Associated trigger			
Vasoconstrictive drugs	46	58	.18
Post partum	10	7	.76
Other	35	36	.82
Onset with any headache	94	96	.70
Onset with TCH	85	86	.88
Recurrent TCH	80	85	.50
Medical evaluation on day 1	62	69	.39
Neurological deficits	38	51	.14
Onset with seizures	17	18	.82
CSF			
CSF analysis performed	82	73	.19
Normal protein level	83	86	.72
WBC count <5/μL	85	89	.68[c]
WBC count 5-10/μL	14	8	
WBC count >10/μL	3	3	
Brain pathology	17	16	.96
Initial CT or MRI normal	54	58	.60
Any CT or MRI abnormal	63	51	.15
Brain lesion type			
Infarction	42	36	.68
Brain edema (MGH cases)	33	43	.25
Convexity SAH	33	36	.68
Lobar hemorrhage	17	24	.34
Cerebral angiographic studies			
CT angiography	44	66	.01
MRI angiography	55	71	.06
Transfemoral angiography	76	60	.04
Follow-up vascular imaging			
Performed	75	82	.35
Direct/indirect angiography	62	73	.19
Transcranial Doppler	29	36	.33
Reversal of arterial narrowing			
Complete	75	73	.44[c]
Partial	22	27	
None	4	0	
Modified Rankin Scale score			
0-3	90	87	.37
4-6	10	13	

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography of the head; MGH, Massachusetts General Hospital; MRI, magnetic resonance imaging of the brain; RCVS, reversible cerebral vasoconstriction syndromes; SAH, subarachnoid hemorrhage; TCH, thunderclap headache; WBC, white blood cell.

[a] Statistical analysis used χ^2 or Fisher exact tests, unless otherwise specified.

[b] *t* Test.

[c] Cochran-Mantel-Haenszel test.

COMMENT

This 2-center study provides key information on the clinical and imaging characteristics of RCVS and its subgroups and our hypothesis about the effects of treatment. There was internal consistency between the MGH and CC cohorts, and our results are remarkably consistent with the prospective studies by Ducros et al[10] in France and Chen et al[8,9] in Taiwan. We did observe some differences that are likely due to study design; for example, we encountered referrals and inpatients who were more likely to harbor brain lesions, while the French and Taiwanese groups mainly recruited patients with TCHs and angiographic abnormalities from the emergency department. Collectively, these studies show that the profile of RCVS is nearly identical both within the United States and around the world.

The relatively large number of patients accumulated in the absence of a concerted effort suggests that RCVS is fairly common. Our patients had a high rate of transfemoral and CT angiography, which are more sensitive and specific than MRI angiography in identifying cerebral vasoconstriction.[21] Many patients underwent mul-

Table 4. Comparison of RCVS Subgroups Based on Triggers/Risk Factors[a]

Characteristic	% Drugs (n=69)	% Post Partum (n=12)	% Other (n=58)	*P* Value
Age, y, mean (SD)	40 (12)	32 (6)	47 (10)	<.001
Female	74	100	86	.04
Onset with TCH	84	75	88	.46
Onset with seizures	16	33	15	.33
CSF				
Protein level ≤60 mg	92	100	73	.05
WBC count <5/μL	89	100	80	.36
Convexity SAH	38	25	32	.59
Ischemic stroke	44	33	35	.55
Lobar hemorrhage	20	8	25	.37
Reversal of arterial narrowing				
Complete	73	70	76	.37
Partial	27	20	22	
None	0	8	2	
Modified Rankin Scale score				
0-3	88	83	91	.66
4-6	12	17	9	

Abbreviations: CSF, cerebrospinal fluid; RCVS, reversible cerebral vasoconstriction syndromes; SAH, subarachnoid hemorrhage; TCH, thunderclap headache; WBC, white blood cell.

[a] Statistical analysis was performed using the Fisher exact test except for age (*t* test).

Table 5. Effect of Treatment on Clinical Outcome

Treatment	Exposed	No. (%)	% mRS 0-3	% mRS 4-6	*P* Value
Calcium channel blockers	Yes	87 (63)	90	10	.52
	No	52 (37)	88	12	
Glucocorticoids	Yes	74 (53)	85	15	.08
	No	65 (47)	94	6	
Neither	Yes	38 (27)	92	8	.37
	No	101 (73)	88	12	

Abbreviation: mRS, modified Rankin Scale score.

tiple imaging modalities. Arterial narrowing was severe, even in the absence of brain lesions. These data raise confidence that we included bonafide cases and not questionable cases with subtle angiographic findings. Follow-up studies were performed in nearly 80% to confirm the diagnosis of RCVS. Patients with and without follow-up angiography had similar clinical presentations, neuroimaging results, and clinical outcomes, suggesting that a diagnosis of probable RCVS in the acute setting (without waiting for confirmatory follow-up imaging) is accurate and could be used to make management decisions. Our data suggest that RCVS can be easily distinguished from PACNS by considering the dramatic onset with recurrent TCHs, clinical setting, type and location of brain lesions, and normal cerebrospinal fluid results. Patients exhibiting these features should no longer be subjected to brain biopsy or empirical immunosuppressive therapy.

In both centers, RCVS predominantly affected women (ratio 4:1) and individuals of all races in the third through sixth decades of life. Children were also affected, as reported by others.[22,23] Our results emphasize that the clinical presentation of RCVS is typically dramatic, with nearly 90% developing abrupt-onset, worst-ever headaches (TCHs) that prompt emergent medical evaluation. The differential diagnosis of TCH includes aneurysmal SAH, pituitary apoplexy, and cerebral venous sinus thrombosis.[24] Immediate brain imaging is warranted to exclude these ominous conditions. However, approximately 80% of our patients developed recurrent TCHs, which is exceptional in the other conditions associated with TCH, and 55% had no lesion on the initial CT or MRI. This suggests that the combination of recurrent TCHs with normal CT/MRI results has high predictive value in uncovering cerebral vasoconstriction and diagnosing RCVS. Indeed, 1 study showed that 39% of patients with idiopathic recurrent TCHs have underlying cerebral vasoconstriction.[25] Our data support the notion that idiopathic TCHs and RCVS belong to the same spectrum of disorders. Further, more than one-third of patients had reversible brain edema and clinical features of PRES (headache, seizures, visual symptoms), supporting the hypothesis that RCVS and PRES have a shared pathophysiology.[26]

As compared with CC, the MGH cohort had a higher frequency of vasoconstrictive drug exposure and prior headaches. These differences are probably explained by the retrospective, nonstandardized method of data collection and differences in the proportion of inpatients and community referrals between centers. We identified a high rate of exposure to a variety of vasoconstrictive drugs,[5,10] and some patients were taking multiple vasoconstrictive agents belonging to different classes.[20] While our observations are consistent with Ducros et al,[10] and while the temporal relationship and mechanistic effects of these drugs are tantalizing, we emphasize that large-scale epidemiological and prospective case-control studies are required before these drugs can be definitively implicated.

Historically, authors have attributed the sudden, prolonged arterial narrowing of RCVS to vasoconstrictive drug use, pregnancy, migraine, neurosurgical procedures, hypercalcemia, and even unruptured cerebral aneurysms. The seemingly unrelated and diverse range of presumed triggers highlights the uncertainties regarding pathophysiology. We did not find any significant differences between subgroups based on risk factors or prior headache status. Postpartum women tended to have less brain hemorrhage, but there were only 12 postpartum cases. With regard to migraine, the numerous differences from RCVS have been previously elaborated.[27] Our results emphasize that RCVS is not simply a severe attack of migraine with the fortuitous demonstration of angiographic narrowing and validate the International Headache Society classification that distinguishes these conditions.[17] We acknowledge that the subgroup definitions were somewhat arbitrary, with a broad range of settings included under "other," and there might be subtle differences between the individual conditions. However, the remarkable similarity between these subgroups justifies their inclusion under the contemporary term *RCVS*.

More than one-third of our patients developed minor cSAH, similar to published RCVS cases.[28-30] Several features distinguish RCVS-SAH from vasospasm associated with SAH due to ruptured cerebral aneurysms and "angiography-negative" SAH: patients with RCVS typically have recurrent TCHs and small-volume SAH overlying the hemispheric convexities; often have coexisting ICH or PRES; develop watershed rather than territorial infarcts; have distinct angiographic features (early-onset, prolonged, multifocal, usually bilateral, segmental vasoconstriction and vasodilatation); and by definition show no evidence for a ruptured aneurysm. The cSAH in RCVS probably results from minor leaks or rupture of surface vessels and is unlikely to account for the diffuse cerebral vasoconstriction and dilatation. The proportion of cSAH was higher at MGH, where 95% of patients underwent MRI with fluid-attenuated inversion recovery (FLAIR) sequences that are sensitive for detecting subarachnoid hemorrhage.[31] Most patients also had CT scans and gradient-echo MRI sequences that confirmed that FLAIR subarachnoid hyperintensities were indeed due to hemorrhage. We applied caution in distinguishing hemorrhage from dilated segments of cortical surface arteries, which can result in linear or dot-shaped hyperintensities (dot sign) within the deep sulcal spaces on FLAIR imaging, particularly in patients with RCVS.[32] In the MGH cohort, 70% of patients had the FLAIR sulcal dot sign, suggesting potential utility of this indirect sign to identify patients with RCVS.

Despite the presence of severe vasoconstriction, ischemic stroke (39%), and lobar hemorrhage (20%), the clinical outcome was largely benign. However, some patients did have disabling strokes or progressive vasoconstriction leading to fatal outcome.[18] The use of the term *reversible* is still justified because it denotes reversibility, or the dynamic nature of arterial constriction. Partial angiographic reversibility (24% in our series) occurring within days after onset in patients with otherwise typical features of RCVS reflects this dynamic process and virtually rules out mimics such as PACNS or atherosclerosis.

Although ours is by far the largest series of RCVS, we found no evidence that calcium channel blockers improved outcome or were superior to symptomatic treatment alone. Their effects may be confounded by coadministration of glucocorticoids in particularly ill patients; there was some benefit in patients treated with calcium channel blockers alone. Others have suggested that calcium channel blockers may reduce the intensity and frequency of headache. The association between glucocorticoids and poor outcome is possibly explained by the fact that glucocorticoids were initiated in sicker patients with severe vasoconstriction or established brain lesions; yet, glucocorticoids appear ineffective in preventing clinical deterioration. Our study is limited by its retrospective nature, small number of patients with poor outcome, and possible selection bias. Until further studies are performed, it is prudent to focus on distinguishing RCVS from PACNS and to withhold brain biopsy or empirical glucocorticoid therapy in patients exhibiting the typical clinical imaging features of RCVS as highlighted by our study.

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