

## Original Investigation

# Clinical Worsening in Reversible Cerebral Vasoconstriction Syndrome

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**IMPORTANCE** Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by recurrent thunderclap headaches and evidence of vasoconstriction with subsequent resolution. The clinical course of RCVS is traditionally considered monophasic and benign. However, recurrent episodes of focal neurological symptoms have been described after initial presentation.

**OBJECTIVE** To define the frequency, timing, and consequences of clinical worsening in patients with diagnosis of RCVS.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective observational study of consecutive patients with RCVS at 2 referral institutions for neurological disease.

**MAIN OUTCOME AND MEASURE** Clinical worsening after diagnosis of RCVS. We defined clinical worsening as new permanent or transient neurological deficits (compared with presenting signs and symptoms) or new onset of seizures. We performed a logistic regression analysis to assess associations between patient characteristics and clinical worsening. Functional outcome was assessed at 1 to 3 months using the modified Rankin score.

**RESULTS** We identified 59 patients (median age, 47 years; interquartile range, 32-54 years) with RCVS. Twenty patients (34%) experienced clinical worsening after a median of 2.5 days (range, several hours to 14 days). Eight of the 20 patients who worsened had permanent deficits, including 4 who died. We did not find an association between age, sex, smoking, migraine, acute or chronic hypertension, peripartum state, or use of serotonergic drugs with clinical worsening. Clinical worsening was associated with radiological infarction ( $P = .001$ ) and worse functional outcome ( $P < .004$ ). Functional outcome was favorable (modified Rankin score 0-2) in 51 patients (86.4%).

**CONCLUSIONS AND RELEVANCE** Clinical worsening after diagnosis is common in patients with RCVS. Thus, RCVS is self-limited but not strictly monophasic. Most patients have a very favorable outcome, but clinical worsening may result in permanent deficits.

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Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by recurrent thunderclap headaches, radiographic evidence of vasoconstriction with subsequent resolution, and a normal or near-normal cerebrospinal fluid profile. More than one-half of cases of RCVS occur postpartum or in association with exposure to serotonergic or adrenergic medications.<sup>1</sup> The syndrome is considered relatively rare, but its exact incidence is unknown. Because cerebral angiography—a requisite for diagnosis—is not always performed in symptomatic patients with recurrent thunderclap headache and/or transient neurological symptoms, the disorder is probably underrecognized. A high index of suspicion is

necessary to diagnose RCVS, especially on initial presentation. The initial presentation of RCVS is not limited to recurrent thunderclap headache but can also include encephalopathy and seizures. Brain imaging can show cortical subarachnoid hemorrhage, intraparenchymal hemorrhage, or vasogenic edema.<sup>1-6</sup>

Reversible cerebral vasoconstriction syndrome is traditionally considered to have a monophasic and benign clinical course. However, the clinical course after the establishment of the diagnosis has not been thoroughly studied. Previous reports detail transient ischemic attacks and cerebral infarction occurring as late as 2 weeks after the diagnosis of RCVS, some-

**Box. Criteria for Reversible Cerebral Vasoconstriction Syndrome**

Acute and severe headache (often thunderclap) with or without focal deficits or seizures

Uniphasic course without new symptoms more than 1 month after clinical onset

Segmental vasoconstriction of cerebral arteries shown by noninvasive angiography (eg, MRA or CTA) or direct catheter angiography

No evidence of aSAH

Normal or near-normal CSF profile (protein level <0.1 g/dL, WBC count <15 cells/ $\mu$ L)

Complete or substantial normalization of arteries on follow-up angiography within 12 weeks of clinical onset

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; CSF, cerebrospinal fluid; CTA, computed tomography angiogram; MRA, magnetic resonance angiogram; WBC, white blood cell.

SI conversion factors: To convert protein to grams per liter, multiply by 10; and WBC count to  $\times 10^9/L$ , multiply by 0.001.

Adapted from the International Headache Society criteria for acute reversible cerebral angiopathy and the criteria proposed in 2007 by Calabrese et al<sup>7</sup> as proposed by Ducros.<sup>1</sup>

times after the headache has improved or resolved.<sup>2,3</sup> A monophasic course has previously been applied as a criterion for diagnosis of RCVS,<sup>7</sup> likely to exclude patients with new symptoms after 1 month of clinical onset. This is often misinterpreted, casting some doubt about the correct diagnosis of RCVS when new symptoms occur, especially if severe or associated with persistent deficits.

In this study, we reviewed our experience with RCVS and examined the temporal course of clinical worsening after the initial diagnosis.

## Methods

We retrospectively identified consecutive patients with RCVS at 2 institutions serving as referral centers for acute neurological diseases: Mayo Clinic (Rochester, Minnesota) and FLENI Institute (Buenos Aires, Argentina). The study was approved by the institutional review boards of these 2 participating centers. We reviewed the records of 59 patients who met definite or probable criteria for RCVS (Box). Reversible cerebral vasoconstriction syndrome was considered probable normalization of cerebral arteries that was not documented on delayed angiography.<sup>8</sup>

At Mayo Clinic, medical records were searched for the terms *reversible cerebral vasoconstriction syndrome*, *cerebral angiopathy*, *CNS angiitis*, *CNS angiopathy*, *cerebral angiitis*, *cerebral vasoconstriction*, *Call-Fleming syndrome*, *eclampsia*, *posterior reversible encephalopathy syndrome*, or *reversible posterior leukoencephalopathy syndrome* in all patients from January 1, 2004, to October 31, 2012.

At the FLENI Institute, an electronic discharge database was used to search for all female patients aged 15 to 55 years admitted to the cerebrovascular section from January 1, 2009, to October 31, 2012. Records of patients aged 15 to 75 years who

attended the vascular neurology clinic during the same period were reviewed by diagnosis. For all cases identified, we analyzed medical records to ensure that they met the inclusion criteria.

We defined clinical worsening as the new occurrence, following initial diagnosis of RCVS, of permanent or transient neurological deficits or new onset of seizures. Patients who only had isolated recurrent thunderclap headaches without new or worsening vasoconstriction and a new neurological deficit after diagnosis were not classified as having clinical worsening.

We collected the following data: age, sex, history of hypertension (defined by use of antihypertensive medications), migraine headaches, smoking history, peripartum state, use of vasoactive and serotonergic medications, acute hypertension (defined as documented blood pressure greater than 140/90 mm Hg at the time of first evaluation), duration of symptoms prior to establishment of diagnosis, date of established diagnosis, presence of clinical worsening after diagnosis, brain imaging findings and noninvasive and conventional angiography imaging results on diagnosis and on clinical worsening, time to angiography, and treatments. We assessed functional outcome using the modified Rankin score at hospital discharge and at 1 to 3 months. The primary outcome was the presence of clinical worsening after diagnosis of RCVS.

We calculated frequencies to summarize categorical variables and means (or medians, in the case of skewed data) to summarize continuous variables. Univariate logistic regression analysis was performed to assess associations between patient characteristics and clinical worsening. A *P* value <.05 was considered statistically significant.

## Results

### Clinical Characteristics

Fifty-nine consecutive patients met inclusion criteria (41 had definite RCVS and 18 had probable RCVS): 33 from Mayo Clinic and 26 from the FLENI Institute. Fifty-two of the cases were diagnosed with RCVS at the time of their clinical presentation by one of us (B.S.K.) (ie, they were prospectively identified) while the other 7 were only identified retrospectively by our data search and they all met full criteria for definite RCVS.

Median age was 47 years (interquartile range, 32-54 years) and 52 (88.1%) were women. Reversible cerebral vasoconstriction syndrome was diagnosed at a median time of 6 days from symptom onset (interquartile range, 3-10 days). Nearly half of the patients were taking a serotonergic medication (*n* = 24, 41%), with the most common medications including selective serotonin reuptake inhibitors or triptans. Additional clinical characteristics are summarized in Table 1.

### Radiological Characteristics

The most frequent abnormal initial radiographic finding was intracranial hemorrhage, identified in 21 patients (36%). These hemorrhages included 15 cortical subarachnoid hemorrhages and 6 intraparenchymal hemorrhages. Bilateral areas of hypodensity in the occipital lobes suggestive of posterior reversible encephalopathy syndrome were seen in 4 patients (7%),

Table 1. Baseline Reversible Cerebral Vasoconstriction Syndrome Patient Characteristics<sup>a</sup>

Characteristic	No./Total No. (%)			
	All (n = 59)	None (n = 39)	Worsening	
			Temporary (n = 12)	Permanent (n = 8)
Age, y, median (range)	47 (15-75)	44.5 (16-75)	52 (29-65)	31.5 (15-50)
Female	52 (88.1)	33 (84.6)	12 (100)	7 (87.5)
Hypertension				
Acute	29/52 (55.8)	20/34 (58.8)	5/11 (45.4)	4/7 (57.1)
Chronic	13 (22.0)	9 (23.1)	2 (16.7)	2 (25)
Smoking status				
Current	12/57 (21.1)	9/38 (23.7)	2/12 (16.7)	1/7 (14.3)
Former	21/57 (36.8)	13/38 (34.2)	4/12 (33.3)	4/7 (57.1)
Never	24/57 (42.1)	16/38 (42.1)	6/12 (50.0)	2/7 (28.6)
Migraine headaches	16 (27.1)	9 (23.1)	5 (41.7)	2 (25)
Peripartum	17 (28.8)	11 (18.6)	1 (8.3)	5 (62.5)
Serotonergic drugs	24 (40.7)	15 (38.5)	8 (66.7)	1 (12.5)

<sup>a</sup> The denominator indicates the number of patients for whom the data were available when data were not available for all patients in the group.

and 1 patient had diffuse cerebral edema. One patient presented with ischemic strokes. In the subset of 10 patients who had clinical worsening that was permanent, 3 had hemorrhagic infarctions, 4 had ischemic infarctions, and 3 had a combination of ischemic and hemorrhagic strokes. When ischemic infarctions occurred, 5 of the 7 were in an arterial watershed distribution. Case illustrations of imaging findings are shown in **Figure 1** and **Figure 2**.

Noninvasive angiograms documenting vasoconstriction were obtained in 24 patients. Of these, 7 also had a conventional cerebral angiogram. Of the 17 who had only noninvasive angiograms, 9 patients worsened after diagnosis, and 3 of these worsened within 24 hours of the noninvasive angiogram.

Of the 42 patients who underwent conventional cerebral angiogram, 14 patients worsened after the diagnosis, and 6 of these had worsening within 24 hours of the angiogram. New deficits were persistent in 5 patients. Forty-four patients had follow-up angiography (noninvasive or invasive) performed.

Forty-four patients (74.6%) had 1 or more follow-up angiograms. Complete resolution of vasoconstriction was demonstrated in 38 (86%) and improvement was seen in 3 (7%). No improvement was seen on the latest angiographic study in 3 cases, all of whom had fulminant courses that were eventually fatal. There were 15 patients who had no follow-up angiogram; 14 of them had a benign course (making the expense of the repeated angiogram dispensable) and 1 died before a follow-up angiogram could be performed.

### Clinical Worsening

Overall, 20 patients (34%) had clinical worsening after the diagnosis of RCVS, with a median time from diagnosis to worsening of 2.5 days (range, several hours to 14 days). Of the patients who worsened, 12 (55%) had transient focal deficits with normal brain imaging, and their symptoms lasted several minutes to 5 hours. In 11 patients, the symptoms were new (different from those at presentation), and in 1, they were only worsening of previous symptoms in the setting of hypotension resulting from an episode of atrial fibrillation with rapid

ventricular response. These transient symptoms were encephalopathy/seizure in 2, visual in 5, sensorimotor in 2, and purely sensory in 3. These patients also had recurrent thunderclap headaches. Two of these patients had new sulcal subarachnoid hemorrhage and 1 had a new area of ischemia on repeated brain imaging.

Eight patients (40%) had clinical worsening that resulted in permanent neurological deficits. In all these cases, the symptoms were new and included motor deficits with some change in mental status. On repeated brain imaging, a new combination of hemorrhage and ischemia was observed in 3; new ischemic areas only, in 3, new hemorrhage only, in 1; and extension of previous ischemic areas, in 1.

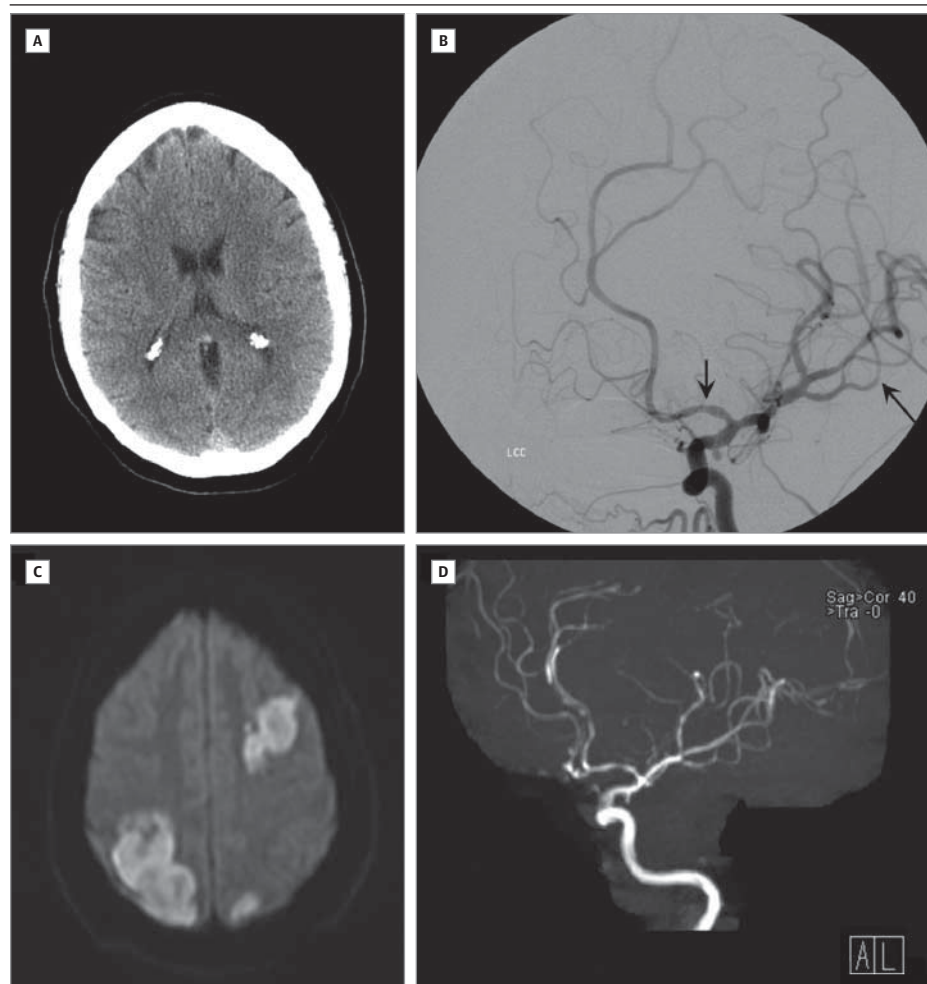
Eighteen of the 20 patients with clinical worsening had repeated angiograms after the clinical worsening. Vasoconstriction remained diffuse and often appeared more severe in these repeated studies. However, in the absence of a validated scale to assess angiographic severity of vasoconstriction and without serial perfusion scans to evaluate for progression of hypoperfusion, we were unable to perform a reliable correlation between new symptoms and severity/progression of vasoconstriction.

When excluding the 18 patients classified as having probable RCVS because of lack of documentation of resolution of vasoconstriction (either because of early death or benign clinical course), the rate of clinical worsening remained relatively unchanged: clinical worsening was observed in 16 of 41 patients (39%) with definite RCVS vs 4 of 18 patients (22%) with probable RCVS.

### Statistical Associations

Radiological evidence of ischemic infarction was significantly associated with clinical worsening after diagnosis ( $P = .001$ ). Neither the presence of intracranial hemorrhage nor posterior reversible encephalopathy syndrome were associated with clinical worsening. Undergoing a conventional catheter angiogram was not statistically associated with clinical worsening ( $P = .89$ ). We did not find an association between age, sex, smoking status, history of migraine, peripartum state,

Figure 1. A 52-Year-Old Woman Presented With Recurrent Thunderclap Headaches, Visual Changes, and Mild, Transient Left Hemiparesis



A, Axial, non-contrast-enhanced computed tomography obtained at initial presentation demonstrated no evidence for acute or chronic ischemia. B, Oblique anteroposterior view of the left internal carotid artery angiogram showed subtle narrowing of distal middle cerebral artery and anterior cerebral artery branches (arrows). C, One week later, the patient developed recurrent, persistent left hemiparesis. Axial diffusion-weighted magnetic resonance imaging performed at that time demonstrated bilateral areas of restricted diffusion within the cortex and associated sulcal effacement. D, Oblique anteroposterior view from a time-of-flight magnetic resonance angiogram of the left intracranial circulation showed widespread, progressive narrowing of proximal and distal anterior cerebral artery and middle cerebral artery branches.

acute or chronic hypertension, or use of serotonergic medications with clinical worsening. The results of the univariate logistic regression analysis are summarized in Table 2.

### Treatments and Outcomes

Given that there is no established, standardized treatment for RCVS, management in our cohort varied. The most common agents used were calcium channel blockers, which were given to 42 patients (70%). Nineteen of the 20 patients who worsened after the diagnosis of RCVS were taking calcium channel blockers when clinical worsening occurred. Other therapies included short-term corticosteroids ( $n = 12$ , 20%) and intravenous magnesium ( $n = 9$ , 16%). Of the 12 patients treated with corticosteroids, 8 had clinical worsening, and 10 of the 12 patients treated with corticosteroids were treated concurrently with calcium channel blockers.

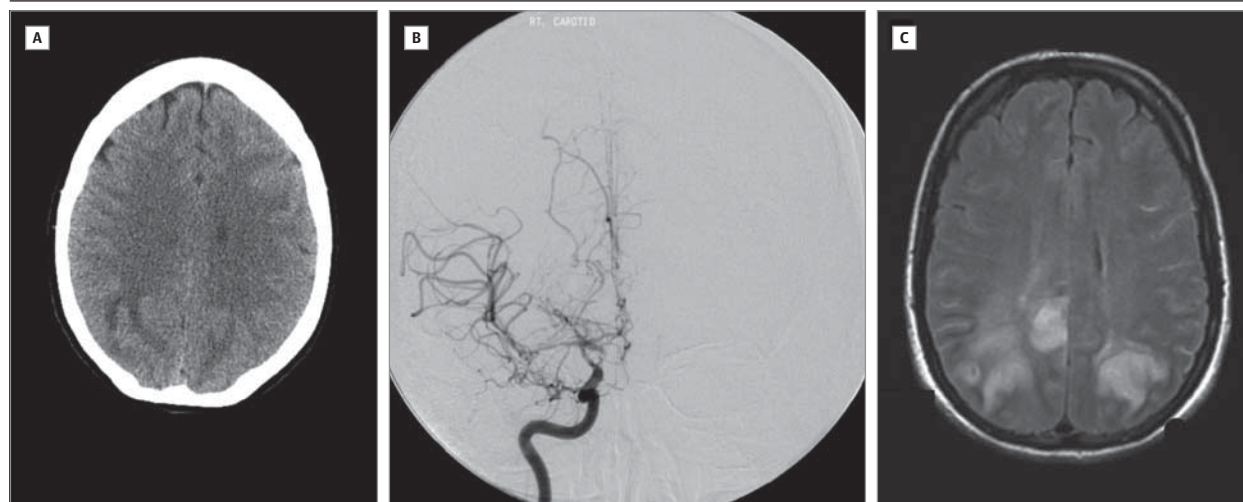
Functional outcome was generally favorable. However, 8 patients (13.6%) had disability at 1 to 3 months or in-hospital death (Table 3). Four of these patients died in the hospital (all were post partum); 2 had a combination of hemorrhage and ischemic insults; and the other 2 had ischemic insults with massive edema. Functional outcome (modified Rankin score at 1-3

months) was worse in patients with episodes of clinical decline (odds ratio, 1.9; 95% CI, 1.2-3.0;  $P = .004$ ). Four patients required readmission to the hospital within 30 days of presentation, including 3 cases in which the readmission was prompted by worsening symptoms of RCVS.

### Discussion

In this retrospective series of 59 patients from 2 institutions, we sought to characterize the clinical course of patients with RCVS following their initial diagnosis. Despite the prevailing conception that this disorder is generally monophasic, we found that approximately one-third of patients with RCVS clinically deteriorated after the initial diagnosis. This finding is relevant for several reasons. First, the understanding that clinical worsening is common in RCVS is important so that if it occurs, clinicians do not unnecessarily revisit the diagnosis and pursue further unnecessary and invasive tests or therapies. For example, central nervous system vasculitis is often considered in the differential diagnosis for patients with cerebral arterial vasoconstriction. This condition is treated with potent

Figure 2. A 33-Year-Old Woman Who Was 3 Weeks Post Partum Presented With Recurrent Headaches, Altered Mentation, and Left-Sided Numbness and Weakness



A, Non-contrast-enhanced computed tomography demonstrated mild subcortical hypodensity in the right parietal region. Hemorrhagic infarction of the left caudate head was present as well (not shown). Magnetic resonance angiogram of the brain showed widespread moderate narrowing of all vascular territories. Over the following 24 hours, she worsened rapidly to the point of developing spastic quadriplegia and requiring intubation for airway protection. B, An emergent conventional angiogram (anterior-posterior view of the right internal carotid artery injection shown) showed severe, near-occlusive, widespread stenoses, which were markedly worse than in the previous

magnetic resonance angiogram. C, The patient was treated with angioplasty and intra-arterial injection of calcium channel blocker, but her clinical condition continued to deteriorate. Magnetic resonance imaging of the brain confirmed the presence of new infarctions, and the axial fluid-attenuated inversion recovery sequence showed new bilateral frontoparietal cortical infarctions. She became comatose after developing severe cerebral edema. After failure of aggressive medical therapy, the family requested withdrawal of life support measures.

chemotherapeutic agents such as cyclophosphamide, which has potentially serious adverse effects. Second, this finding provides insight into the temporal course of RCVS, which may be useful for future studies. Ideally, the subset of patients who are at highest risk for secondary deterioration could be identified at the time of diagnosis so that patients could be appropriately triaged to an appropriate level of care and monitored.

The phenomenon of post-angiographic acute worsening in patients with RCVS has been previously alluded to. In 1 study, 9% of patients undergoing conventional angiogram experienced transient neurological deficits within 1 hour after angiography.<sup>3</sup> We found that 14% of patients who underwent a conventional cerebral angiogram deteriorated within 24 hours of the procedure. Since we also observed a similar proportion of cases of clinical worsening within 24 hours of a noninvasive angiogram, our data do not confirm a causal association between catheter angiography and clinical worsening.

Previous studies have mostly focused on the clinical and radiological presentations of RCVS, but none has detailed the clinical course after the diagnosis of RCVS was established, as was done in the current series. Most prior series concluded that the prognosis in RCVS is generally excellent, with most patients recovering completely or near completely within days to weeks.<sup>3-8</sup> One study reported that 90% to 95% of patients with RCVS have a benign and self-limited syndrome despite the presence of severe angiographic vasoconstriction and ischemic or hemorrhagic brain lesions.<sup>8</sup> Although severe progression of vasoconstriction resulting in ischemic symptoms (transient ischemic attacks and strokes) and even death

Table 2. Univariate Logistic Regression Analysis Evaluating Associations Between Clinical and Radiological Characteristics of Reversible Cerebral Vasoconstriction Syndrome and Presence of Clinical Worsening

Patient Variable	Odds Ratio (95% CI)	P Value
Age	0.10 (0.96-1.04)	.83
Female	3.45 (0.39-30.89)	.27
Hypertension		
Acute	0.84 (0.26-2.70)	.78
Chronic	0.83 (0.22-3.15)	.78
Smoking status		
Current	0.67 (0.14-3.17)	.61
Former	1.23 (0.36-4.18)	.74
Migraine headaches	1.74 (0.53-5.67)	.36
Peripartum	0.92 (0.28-2.99)	.89
Serotonergic drugs	1.31 (0.44-3.90)	.63
Acute ischemia	11.00 (2.53-47.91)	.001
Acute hemorrhage	1.05 (0.36-3.09)	.93
PRES	2.00 (0.26-15.38)	.51

Abbreviation: PRES, posterior reversible encephalopathy syndrome.

has been reported, this clinical course is deemed very infrequent.<sup>8-13</sup> The great majority of our patients had an excellent outcome, but some developed brain infarctions with persistent deficits and a few postpartum cases were fatal. The presence of clinical worsening was associated with the occurrence of radiologically demonstrated ischemic infarctions. Thus, patients with RCVS who worsen after diagnosis should be carefully monitored.

Table 3. Functional Outcomes Grouped by Presence and Type of Clinical Worsening

Functional Outcome	No. (%)			
	All (n = 59)	None (n = 39)	Worsening	
			Temporary (n = 12)	Permanent (n = 8)
mRS 0-2 at 1-3 mo	51 (86.4)	38 (97.4)	11 (91.7)	2 (25)
mRS 3-5 at 1-3 mo	4 (6.8) <sup>a</sup>	1 (2.6)	1 (8.3)	2 (25)
In-hospital death	4 (6.8)	0	0	4 (50)

Abbreviation: mRS, modified Rankin score.

<sup>a</sup> One patient was last seen at 1 month with an mRS of 5 and multiterritorial brain infarctions that made favorable recovery over time very unlikely. The

other 3 patients were last evaluated more than 1 year after the admission for reversible cerebral vasoconstriction syndrome and had persistent functional disability.

This study has limitations. The results of this retrospective (albeit the great majority of patients were prospectively diagnosed by one of the investigators) observational study do not allow determination of the true incidence of clinical worsening after a diagnosis of RCVS. Many of our patients were referred from other institutions. This could create a bias of more severe or complex cases compared with the general population of patients with RCVS and thus could possibly lead to an overestimation of the frequency of abnormal brain imaging results and poor clinical outcomes. We did not uniformly require radiological proof of reversibility of the vasoconstriction because in practice not all patients with RCVS have follow-up imaging and vasoconstriction may occasionally persist beyond 12 weeks even in patients with the typical clinical course.<sup>8</sup> Also, angiographic proof of resolution of the vasoconstriction may not be possible in patients who follow a fulminant course and may not be financially justified in patients

who have a very favorable clinical course. Nonetheless, the rate of clinical worsening remained similarly high when patients without angiographic proof of resolution of vasoconstriction were excluded from our analysis. Whether patients with more severe or fulminant courses could have progressive rather than reversible vasoconstriction and a different pathophysiology than the much more common milder cases deserves further investigation.

In conclusion, our study shows that neurological deterioration after diagnosis of RCVS is fairly common. Clinical worsening was transient in more than half of the patients. Knowing that these patients can have early recurrent or worsening symptoms after diagnosis is important to avoid misdiagnosis with its potential for unnecessary testing and incorrect, hazardous treatments. Patients with recurrent symptoms should be closely monitored because they are at risk of developing permanent ischemia and may rarely have a fulminant course.

#### ARTICLE INFORMATION

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**Acquisition of data:** Katz, Fugate, Ameriso, Pujol-Lereis, Rabinstein.

**Analysis and interpretation of data:** Fugate, Ameriso, Pujol-Lereis, Mandrekar, Flemming, Rabinstein.

**Drafting of the manuscript:** Katz, Fugate, Ameriso, Pujol-Lereis.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Mandrekar.

**Administrative, technical, or material support:** Ameriso, Pujol-Lereis.

**Study supervision:** Ameriso, Pujol-Lereis, Flemming, Kallmes, Rabinstein.

**Conflict of Interest Disclosures:** None reported.

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