The Spectrum of Nontraumatic Convexity Subarachnoid Hemorrhage

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Background: Nontraumatic convexity subarachnoid hemorrhage (cSAH) is a nonaneurysmal variant that is associated with diverse etiologies. *Methods:* With IRB approval, we retrospectively reviewed consecutive nontraumatic cSAH from July 1, 2006 to July 1, 2016. Data were abstracted on demographics, medical history, neuroimaging, etiology, and clinical presentation. *Results:* We identified 94 cases of cSAH. The cases were classified according to the following etiologies: reversible cerebral vasoconstriction syndrome (RCVS) 17 (18%), cerebral amyloid angiopathy (CAA) 15 (16%), posterior reversible encephalopathy syndrome 16 (17%), cerebral venous thrombosis 10 (11%), large artery occlusion 7 (7%), endocarditis 6 (6%), and cryptogenic 25 (27%). Early rebleeding occurred in 9 (10%) patients. Time from initial imaging to CT rebleeding was 40 hours (range, 5-74). CAA was associated with the highest mean age at 75.8 and RCVS the lowest at 47.6 years ($P < .0001$). Among patients with RCVS, initial vascular imaging was negative in 6 (35%), and repeat imaging documented vasoconstriction at a mean delay of 5 days (range, 3-16). *Conclusion:* There were significant differences among the subgroups in cSAH, with CAA presenting as older men with transient neurological deficits, and RCVS presenting as younger women with thunderclap headache. Rebleeding was seen in 10% of cSAH patients. One-third of RCVS patients with cSAH required repeat vascular imaging to diagnose vasoconstriction.

Key Words: Convexity subarachnoid hemorrhage—rebleeding—reversible cerebral vasoconstriction syndrome—RCVS—posterior reversible leukoencephalopathy syndrome—cerebral amyloid angiopathy

Introduction

Nontraumatic convexity SAH (cSAH) is a recognized distinct subset that makes up approximately 6% of all SAH.[1] It has been associated with a wide spectrum of etiologies, notably cerebral amyloid angiopathy (CAA), posterior reversible encephalopathy syndrome (PRES), and reversible cerebral vasoconstriction syndrome (RCVS).[1,2]

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Methods

With approval from the Institutional Review Board, we retrospectively reviewed cSAH patients admitted to our institution from July 1, 2006 to July 1, 2016. We defined cSAH as radiographic hemorrhage isolated to the cerebral convexities, without significant cisternal component. Traumatic SAH was excluded. We collected data on patient demographics, symptoms, timing of symptom onset, triggers for RCVS (i.e., postpartum state and/or medication usage), neuroimaging results and timing, cSAH etiology, rebleeding events, and clinical outcomes. All neuroimaging were reviewed by study author (VL) to confirm diagnosis of cSAH. We categorized cSAH by diagnosis as CAA, PRES, RCVS, cerebral venous thrombosis (CVT), large artery occlusion, endocarditis, or cryptogenic (undetermined etiology or incomplete work-up). Large artery occlusion included patients with carotid occlusion or Moyamoya. Cryptogenic subgroup included

patients with unknown etiology, negative work-up, incomplete work-up, or unconfirmed suspected diagnosis. Patients included in the confirmed RCVS diagnosis required neuroimaging evidence of dynamic cerebral vasoconstriction. CAA diagnosis was based upon the modified Boston criteria for probable or possible CAA.[3] Good clinical outcome was defined as modified Rankin Score of 0-2 at 3 months. Rebleeding was defined as new intracerebral hemorrhage or extension of prior hemorrhage within 3 days of initial cSAH diagnosis.

Results

We identified 94 cases of cSAH. The mean age was 57.6 ± 16.3 years (range, 20.6-89.9) and 69.1% were female. There were 43.6% white, 30.8% black, 25.5% other/unknown, and 23% Hispanic patients. The presenting symptoms included sudden severe headache in 50 (53%), seizure in 16 (17%), transient neurological symptoms in 30 (32%), and mental status changes in 23 (24%). The time from symptom onset to neuroimaging diagnosis of cSAH was mean 2.1 days (range, 0-21 days). The mean hospital length of stay was 6.9 ± 5.9 SD days (range, 0-28 days). The overall in-hospital mortality rate was 7.4%. Most patients, 68 (73%), were discharged to home, 12 (13%) to acute rehabilitation facilities, and 6 (6%) were discharged to other skilled facility.

Among the cases of cSAH, 25 (27%) were cryptogenic, and among those, 7 were suspected clinical RCVS but vascular imaging did not document vasoconstriction. In cSAH patients with confirmed diagnosis, the etiology subgroups were as follows: RCVS 17 (18%), PRES 16 (17%), CAA 15 (16%), CVT 10 (11%), large artery occlusion 7 (7%), and endocarditis 6 (6%; Table 1). Among the 15 patients with CAA, 12 (80%) underwent MRI brain and 11/12 (93%) had MRI susceptibility weighted imaging that confirmed the presence of multiple microhemorrhages. Five patients had overlap of both RCVS/PRES.

Among diagnosed cSAH, there were significant differences in clinical presentation (Table 1). CAA was associated with the highest mean age at 75.8 and RCVS the lowest at 47.6 years ($P < .0001$). CAA were majority male (64%) whereas PRES and RCVS were exclusively female (100%; $P < .0001$). Transient neurologic symptoms were common in CAA (73%) but rare in RCVS (6%; $P.0037$), whereas headache was common in RCVS (88%) but unusual in CAA (13%; $P < .0001$).

Early rebleeding occurred in 9 (10%) patients (Table 2). The mean age of patients with rebleeding was 55.6 years (range, 24-68) and the majority 8 (89%) were women. The majority 6 (67%) were Hispanic. Rebleeding based on etiology was as follows: 6 (67%) RCVS, 1 (11%) CAA, 1 (11%) CVT, and 1 (11%) cryptogenic. Two of the RCVS patients also had concomitant PRES. Initial rebleeding included new remote subarachnoid hemorrhage in 1 (11%) and intracerebral hemorrhage in 8 (89%). Clinical symptoms of rebleeding were isolated worsening headache in 2 (22%), focal neurological deficits in 4 (44%), and no clinical change in 2 (22%). Time from initial neuroimaging documenting cSAH to CT rebleeding was 40 hours (range, 5-74), and rebleeding occurred within 60 hours in most patients (89%). Two patients had a subsequent 3rd rebleeding episode (due to CVT and RCVS) documented at 1.9 and 11.8 hours after the initial rebleeding CT (Fig 1). Among patients with rebleeding, good clinical outcome was seen in 7 (78%).

Among the 17 patients with confirmed RCVS, all were female and the majority and the racial subgroups were as follows: white (5), black (5), Asian (3), and other (4) (Table 3.) Five (29%) were Hispanic, and the non-Hispanic white proportion was only 13%. RCVS triggers were identified in 6 (35%) and included postpartum state in 4 (24%) and SSRI/decongestant use in 3 (18%). Initial vascular imaging was negative for vasoconstriction in 10 (59%), and repeat vascular imaging was necessary to diagnosis vasoconstriction at a mean delay of 6.7 days after initial imaging (range, 2-16; Fig 3). Among the RCVS patients, unusual features were noted including rebleeding in 6 (35%; Fig 2), concomitant PRES in 5 (29%), and concomitant cervical arterial dissection in 2 (12%). One patient had bilateral carotid dissections and a second patient had bilateral vertebral artery dissections.

Table 1. *Confirmed diagnosis of cSAH (69)*

	RCVS (17)†	CAA (15)	PRES (17)†	CVT (10)	LAO (7)	Endocarditis (6)	Cryptogenic (27)*	*P* value
Age mean (years)	47.6	75.8	50.9	49.3	54.0	59.3	58.9	<.0001
Sex female	17 (100%)	5 (36%)	17 (100%)	3 (30%)	4 (50%)	3 (50%)	20 (74%)	<.0001
HA	15 (88%)	2 (13%)	13 (76%)	12 (75%)	4 (57%)	0 (0%)	16 (59%)	<.0001
TNS	1 (6%)	11 (73%)	4 (24%)	3 (30%)	3 (43%)	1 (17%)	8 (30%)	.004
MS	2 (12%)	4 (27%)	4 (24%)	3 (30%)	1 (14%)	6 (100%)	4 (15%)	.001
Seizure	1 (6%)	4 (27%)	4 (24%)	2 (20%)	1 (14%)	1 (17%)	3 (11%)	.69

Abbreviations: HA, headache; MS, mental status changes; TNS, transient neurologic symptoms.
*Cryptogenic (includes 7 patients with suspected RCVS clinically without vasoconstriction documented).
†Five overlap RCVS/PRES patients.

Table 2. *cSAH patients with rebleeding (9)*

Case	Age/sex Hispanic	Medical history	Symptom	Diagnosis	Rebleeding (hours)*	3-month mRS
1	46 F White Hisp F	None	HA	RCVS	45.6	2
2	67 Hisp F	ESRD, DM, HTN	HA, SZ	CAA	5.2	1
3	68 Hisp F	HTN, aneurysm stent-coiling	HA	Cryptogenic	48.8	0
4	54 White M	DVT on xarelto	HP	CVT	12.6, 11.8†	6
5	55 Other Hisp F	HTN, CAD, prior stroke	HA	RCVS	50.8	4
6	24 White F	HTN, HL, prior stroke	HA	RCVS/PRES	53.1	0
7	61 Other Hisp F	None	HA	RCVS/PRES	45.8	1
8	61 Asian F (Fig 2)	Crohns, Sjorgens	HA	RCVS	26.0, 1.9†	2
9	61 White Hisp F	HL	HA	RCVS /PRES	73.8	0

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; DVT, deep vein thrombosis; ESRD, end-stage renal disease; HA, headache; HL, hyperlipidemia, HP, hemiparesis; HTN, hypertension; SZ, seizure.
*Hours are initial neuroimaging.
†Hours after initial rebleeding on neuroimaging.

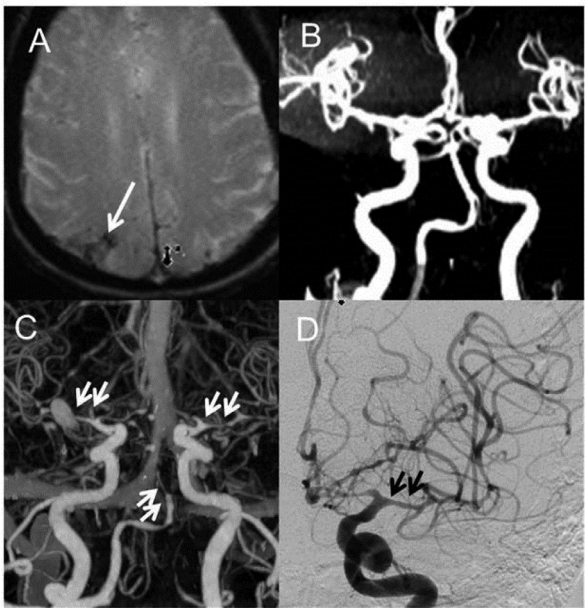

Figure 1. *Case 10. RCVS with delayed vasoconstriction. A 68-year-old female with depression on sertraline who developed thunderclap headache. (A) MRI SWI (day 4) shows cSAH (white arrow). (B) MRA head (day 4) shows normal vessels. Severe vasoconstriction is confirmed on day 7 on (C) CTA head (double white arrows) and (D) cerebral angiogram (double black arrows).*

Discussion

In our study, RCVS, PRES, and CAA were the most common diagnosis, which is consistent with previously published series. Unique to the literature is our finding of rebleeding rates after cSAH. Rebleeding in aneurysmal SAH is an important factor in mortality and the highest risk of rerupture is within the first 24 hours.[4,5] Despite modern treatment, aneurysmal rebleeding still occurs in nearly 7% of SAH.[6] However, the risk of early rebleeding after spontaneous cSAH is not well described. In our series, rebleeding occurred in 10% of cSAH patients and was predominantly seen in RCVS subgroup. Rebleeding occurred typically within 2.5 days of hospitalization. Two patients had a subsequent 3rd rebleeding (1.9 and 11.8 hours after the 1st rebleeding; Fig 1). Although cSAH is generally considered to be a benign subset of SAH, our series shows the risk of early rebleeding to be around 10%. Unlike aneurysmal SAH where rebleeding is typically a catastrophic event that increases morbidity and mortality, cSAH patients with rebleeding generally maintained good clinical outcomes.

RCVS is characterized by symptoms of thunderclap headache associated with reversible radiographic vasospasm in the cerebral arteries, and overall has a favorable prognosis.[7] Among patients with cSAH, RCVS is observed in younger patients (<60 years old) and females.[8] Our study confirms that RCVS patients with cSAH were universally female and younger compared to other subtypes of cSAH. In patients who cSAH is the presenting feature of RCVS, the diagnosis of RCVS was not immediately apparent, as initial vascular imaging at the time of cSAH was negative for vasoconstriction in over half of these patients. Most patients required repeat vascular imaging to document evidence of delayed cerebral vasoconstriction. In our series, we included noninvasive vascular imaging (CTA, MRA) for the diagnosis of RCVS per diagnostic criteria recommended by Calabrese in 2007.[9] Noninvasing imaging (especially CTA) is accurate compared to cerebral angiogram for the detection of severe vessel narrowing, and has been shown to be 80% sensitive for detecting vasoconstriction due to RCVS compared to cerebral angiogram and has become an acceptable modality for work-up of RCVS, as invasive imaging may not be clinically pursued.[10-12] Our series suggests that RCVS may be underdiagnosed in cSAH, as vasoconstriction may be dynamic and delayed after presentation. Clinicians should be aware that negative initial vascular imaging in cSAH does not exclude RCVS,

Table 3. *cSAH patients with confirmed RCVS (17)*

	Age race sex/trigger	Vascular imaging	Unusual feature
1.	49.7 Other F on SSRI	CTA neg (D#6), Angio +RCVS (D# 9)	PRES
2.	46 White Hispanic F	CTA neg (D#1), Angio + RCVS (D#3)	Rebleeding
3.	24 Black F postpartum	CTA neg (D# 0), Angio + RCVS (D#3)	
4.	27 Black F postpartum	CTA neg (D#3), Angio + RCVS (D#4)	BICA dissection PRES
5.	45 Asian F on SSRI	CTA neg (D#0), Angio neg (D#1), CTA + RCVS (D# 16)	
6.	34 Black F postpartum	CTA neg (D#3), Angio neg (D#4), CTA + RCVS (D#8)	
7.	37 White F postpartum	CTA and Angio dissection (D#0), MRA + RCVS (D#8), CTA + RCVS (D#10), MRA neg (3.5 months)	BVA dissection
8.	53 Other F Hispanic	CTA + RCVS (D#3), Angio (D#4) + RCVS, CTA + RCVS, CTA neg (2 months)	
9.	59 Black F	MRA + RCVS (D#9), CTA + RCVS (D#10)	
10.	68 Asian F on SSRI (Fig 1)	MRA neg (D#4), CTA and Angio + RCVS (D#7). Angio neg (D#14)	
11.	55 Other F Hispanic	CTA + RCVS (D#1), Angio + RCVS (D #3)	Rebleeding
12.	24 White F	MRA neg (D#2), Angio neg (D#3), MRA + RCVS (D#8), MRA improved (D#11).	PRES Rebleeding
13.	39 White F	Angio + RCVS (D#5) dissection	BICA dissection
14.	61 Other Hispanic F	MRA + RCVS (D#11), MRA resolved (D#38)	PRES Rebleeding
15.	61 Asian F on decongestant	CTA + RCVS (D#2), Angio (D#4) CTA + RCVS, (D#17)	Rebleeding
16.	61 F White Hispanic (Fig 2)	CTA neg (D#4), CTA + RCVS (D#6)	PRES Rebleeding
17.	59.6 F Black	CTA + RCVS (D#12)	

Abbreviations: BICA, bilateral carotid artery; BVA, bilateral vertebral artery; D#, number of days after onset of symptoms.

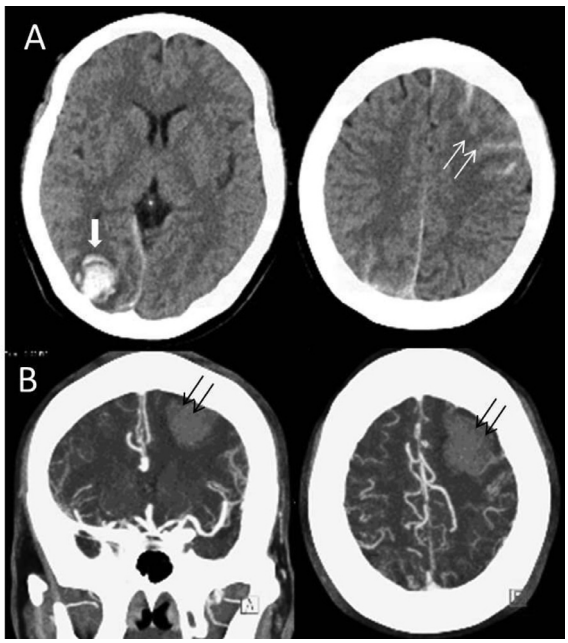

Figure 2. *Case 15. RCVS with rebleeding. A 61-year-old female developed thunderclap HA. Outpatient MRI 2 days later showed only left frontal cSAH. (A) CT brain that day showed stable cSAH (double white arrows) and new right occipital ICH (white arrow). Ten minutes after CT the patient developed right hemiparesis and aphasia. (B) CT angiogram 1.9 hours after CT brain showed new left frontal ICH (black double arrows).*

and repeat vascular imaging should be considered. RCVS is reported with other overlapping conditions, including concomitant cervical artery dissection in 12% and PRES in 9%.[13,14] In our series, RCVS presenting as cSAH was associated with concomitant dissection (12%) and PRES (24%). RCVS presenting as cSAH may represent a more severe variety on the spectrum of RCVS, and as such is associated with increased risk of complications such as dissection and PRES.

Our series differs from other large reports likely due to background racial variance, as our population included a larger proportion of black and Hispanic patients compared with other large series that were majority white or non-Hispanic populations.[1,2] The strength of this study is that it represents a large series of mixed case cSAH that is seen in a urban metropolitan community. The limitations of our project include those inherent to a retrospective study and tertiary referral bias. In the subset with negative work-up (cryptogenic), several patients were clinically suspected of having the RCVS diagnosis, but did not have imaging confirmed vasoconstriction, which likely led to an under ascertainment of RCVS.

Conclusion

The common etiologies of cSAH are RCVS, PRES, and CAA. CAA is typically older men with transient neurological

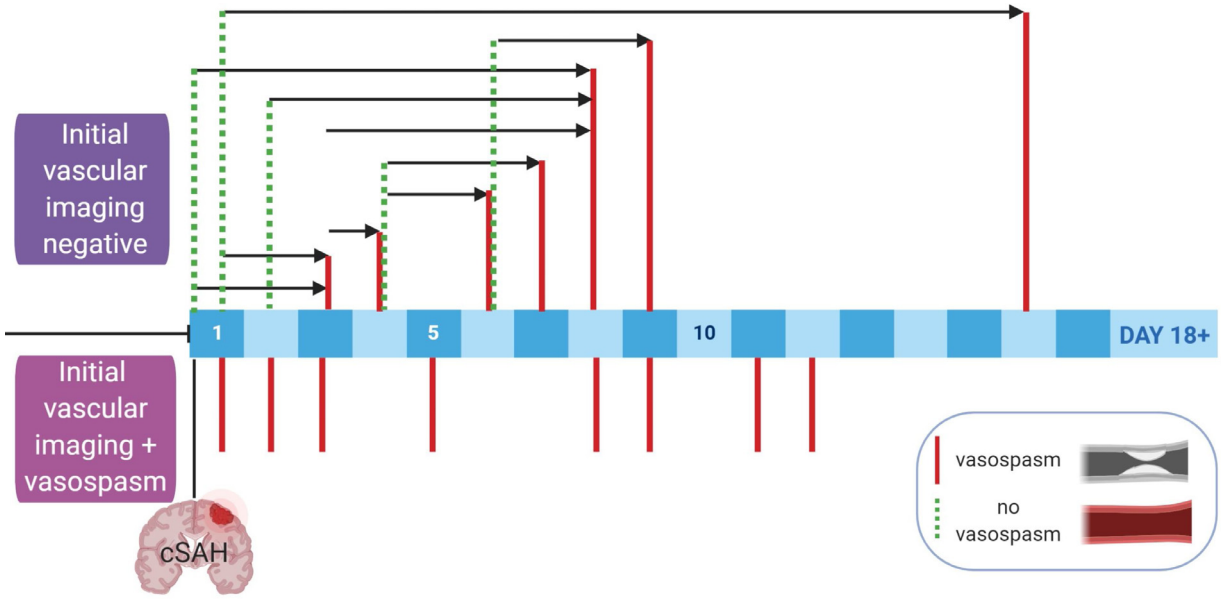

Figure 3. *Timing of vascular imaging documenting vasospasm in cSAH patients with RCVS (17 patients). Above the timeline includes 10 patients with negative initial vascular imaging, below the timeline includes 7 patients with initial vascular imaging documenting vasospasm.*

deficits, and RCVS presents as younger women with thunderclap headache. Early rebleeding was seen in 10% of cSAH patients, predominantly in those with RCVS. The diagnosis of RCVS presenting with cSAH may require repeat vascular imaging as the development of vasoconstriction may be delayed. Further studies are warranted to better understand the natural history of cSAH.

Conflicts of Interest

Dr. Garg receives funding from Instrumentation Laboratories for an unrelated study

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