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Research Article

Reversible Cerebral Vasoconstriction Syndrome (RCVS): Etiologies Related Radiological Findings

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Abstract

Objectives: Reversible cerebral vasoconstriction (RCVS) is a clinico-radiological syndrome with diverse diseases, but etiology remains unclear. This study was designed to analyze affected circulation territory and cerebral imaging under corresponding etiologies, aiming to provide mechanistic combination between differential etiologies and radiological findings. **Patients and Methods:** Case or series reports of RCVS were searched on PubMed from December 1, 2011, to December 31, 2017, using the following search terms: "RCVS" and "case" or "Reversible Cerebral Vasoconstriction syndrome" and "case". 69 reports with 86 cases were included under inclusion criteria and exclusion criteria. Etiologies of RCVS, blood vessel territories by cerebral magnetic resonance angiography (MRA), computed tomography angiography (CTA) or digital subtraction angiography (DSA), and brain imaging by cerebral computed tomography (CT), magnetic resonance imaging (MRI) and diffusion weighted imaging (DWI) were analyzed. **Results:** Combined anterior and posterior circulation is most affected in RCVS (67%), and solitary anterior circulation is more vulnerable than solitary posterior circulation in RCVS (26% *vs.* 7%). 38% convex subarachnoid hemorrhage (cSAH), 51% DWI/MRI (T2) hyperintensity and 23% other intracranial hemorrhage were identified. More than half cases with cSAH had etiologies of primary or idiopathic and vasoactive substances. Remaining etiologies of pregnancy and the postpartum period, blood products, extra- or intra- cranial arterial disorders or procedures and miscellaneous had more DWI/MRI (T2) and posterior reversible encephalopathy syndrome (PRES). **Conclusions:** Radiological findings were divergent under differential etiologies of RCVS. Sympathetic innervation, endothelial dysfunction, oxidative stress and other unknown reasons contribute to pathophysiological process.

Keywords: *RCVS, etiologies, radiological findings*

Introduction

Reversible cerebral vasoconstriction (RCVS), also called Call Fleming Syndrome, is a clinico-radiological syndrome in which patients presented headache and reversible segmental vasoconstriction of cerebral arteries that resolve spontaneously within 3 months [1]. Clinical manifestation included thunderclap headache (TCH) with or without neurological defects caused by cerebral ischemic infarct, hemorrhage, subarachnoid hemorrhage or vasogenic edema confirmed by brain imaging [2-5]. Reported etiologies of RCVS were diverse, including primary or idiopathic, vasoactive substances, pregnancy and postpartum, blood products, cranial arterial disorders or procedures, catecholamine secreting tumors, intracranial disorders or surgery and miscellaneous. As diverse etiologies mentioned above, patients with RCVS come from Department of gynaecology and obstetrics, psychiatry, hematology, cardiology, neurosurgery, head and neck surgery and neurology [3,4,6].

Although explicit clinical descripting of RCVS is outlined, underlying pathophysiology remains poorly understood. Endothelial dysfunction and sympathetic overactivity are implicated as key underlying mechanisms based on temporal relationship of symptom onset to vasoconstrictive drug exposure [7], the absence of arterial inflammation on pathology

[8] and overlapping with posterior reversible encephalopathy syndrome (PRES) [9]. Sympathetic innervation is much higher in anterior circulation compared to posterior circulation [10,11], indicating potential preferential anterior circulation in RCVS which was unconfirmed yet. This study was designed to analyze affected circulation territory and cerebral imaging under corresponding etiologies, aiming to provide mechanistic combination between differential etiologies and radiological findings.

Materials and Methods

Case or series reports of RCVS were searched on PubMed from December 1, 2011, to December 31, 2017, using the following search terms: "RCVS" and "case" to get 93 papers; "Reversible Cerebral Vasoconstriction syndrome" and "case" to get 162 papers. After screening 255 papers above under following inclusion criteria and exclusion criteria, 69 papers with 86 cases were included and analyzed with etiologies, circulation territories by cerebral magnetic resonance angiography (MRA), computed tomography angiography (CTA) or digital subtraction angiography (DSA), and brain imaging by cerebral computed tomography (CT), magnetic resonance imaging (MRI) and/or diffusion weighted imaging (DWI). **Inclusion criteria:** diagnosis of RCVS; explicit cerebral (CT/MRI/DWI) and angiography (MRA, CTA or DSA), or detailed description of above. **Exclusion criteria:** Incomplete cerebral imaging or description.

Results

Etiologies of RCVS were categorized into primary/idiopathic and secondary shown in Table 1.

Table 1. Categories associated with RCVS

Categories	Subcategories	Specific annotations	M	F	AA
Primary/Idiopathic	29	bath, exertional headache	10	19	47
Secondary	Vasoactive substances (28)	Illicit drugs: Cannabis, marijuana, cocaine, (meth)-amphetamine, lysergic acid diethylamide (LSD), ketamine	3	25	38
		Ergots: Ergotamine tartarate			
		Sympathomimetics: Pseudoephidrine, energy drink			
		Serotonergic drugs: Selective serotonine-reuptake inhibitors, triptans, MAOI			
		Immunosuppressants: Tacrolimus, cyclosporine A			
		Miscellaneous: Tobacco, NSAIDs, glucocorticoid, Slim food, plant extract			
	Pregnancy and the postpartum period	postpartum +/- vasoactive drugs	0	10	30
	Blood products	Blood transfusion, intravenous immunoglobulin	0	4	46
	Extra- or intra-cranial arterial disorders or procedures (3)	Carotid endarterectomy, aortic dissection, carotid paraganglioma	1	2	37
	Miscellaneous	systemic lupus erythematosus, takayasu, guillain barre syndrome, thrombotic thrombocytopenic purpura, repetitive transcranial magnetic stimulation, airplane descent, abdominal hysterectomy with bilateral salpingo-oophorectomy	2	10	42

M: Male; F: Female; AA: Average Age; RCVS: Reversible Cerebral Vasoconstriction

Specific annotations in primary/idiopathic were bath, exertional headache or no known predisposition. Secondary included vasoactive substances (illicit drugs, ergots, sympathomimetics, serotonergic drugs, immunosuppressants, miscellaneous), pregnancy and postpartum period (postpartum ± vasoactive drugs), blood products (blood transfusion, intravenous immunoglobulin), extra- or intra- cranial arterial disorders or procedures (carotid endarterectomy, aortic

dissection and carotid paraganglioma) and miscellaneous (systemic lupus erythematosus, Takayasu, Guillein Barre syndrome (GBS), thrombotic thrombocytopenic purpura (TTP), repeated transcranial magnetic stimulation (rTMS), airplane descent, abdominal hysterectomy with bilateral salpingo-oophorectomy). Average gender and age under each category were illustrated. More females were affected than males (70 *vs*. 16).

Affected anterior and/or posterior circulation were shown in Table 2 and Figure 2A. 26% solitary anterior circulation, 7% solitary posterior circulation and 67% combined anterior and posterior circulation were affected in RCVS.

Table 2. Angiographic territory in RCVS with differential categories

	Total	Anterior Circ. Alone				Posterior Circ. Alone				Anterior+Posterior Circ.			
		L	R	L+R	Total	L	R	L+R	Total	L	R	L+R	Total
Primary or Idiopathic	29	0	1	8	9	1	0	2	3	0	1	16	17
Vasoactive substances	28	0	1	3	4	1	0	1	2	1	2	19	22
Pregnancy and the postpartum period	10	0	0	2	2	0	0	1	1	0	0	7	7
Blood products	4	0	0	0	0	0	0	0	0	0	0	4	4
Extra- or intra-cranial arterial disorders or procedures	3	0	0	1	1	0	0	0	0	0	1	1	2
Miscellinious	12	1	2	3	6	0	0	0	0	0	0	6	6
Sum	86	1	4	17	22	2	0	4	6	1	4	53	58
Percentage					0.26				0.1				0.7
L: left; R: Right; Circ.: Circulation; RCVS: Reversible Cerebral Vasoconstriction													

Table 3. Brain imaging with RCVS

	Total	Normal	cSAH					DWI/MRI (T2)				Other intracranial hemorrhage			(+) PRES	
			F	P	O	T	To.	A	P	A+P	To.	PH	SDH	IVH		R
Primary or Idiopathic	29	4	12	2	1	0	15	3	6	3	12	10	2	0	2	0.1
Vasoactive substances	28	4	5	3	3	3	14	3	7	3	13	4	1	0	6	0.2
Pregnancy and the postpartum period	10	2	1	0	0	0	1	4	1	0	5	2	0	2	3	0.3
Blood products	4	0	0	0	0	0	0	1	3	0	4	1	0	0	3	0.8
Extra- or intra-cranial arterial disorders or procedures	3	0	1	1	0	0	2	1	2	0	3	1	0	0	1	0.3
Miscellinious	12	4	0	1	0	0	1	3	0	4	7	0	0	0	2	0.2
Sum	86	14	19	7	4	3	33	15	19	10	44	18	3	2	17	0.2
Percentage		0.16					0.38				0.51	0.21	0.03	0.02	0.2	
cSAH: Convex Subarachnoid Hemorrhage; F: Frontal Lobe; P: Parietal Lobe; O: Occipital Lobe; T: Temporal Lobe; To.: Total; DWI: Diffusion-Weighted Imaging; MRI: Magnetic Resonance Imaging; A: Anterior Territory; P: Posterior Territory; PH: Parenchymal Hemorrhage; SDH: Subdural Hemorrhage; IVH: Intraventricular Hemorrhage; PRES: Posterior Reversible Encephalopathy Syndrome; R: Ratio; RCVS: Reversible Cerebral Vasoconstriction																

Brain imaging included convex subarachnoid hemorrhage (cSAH), DWI/MRI (T2) hyperintensity, other intracranial hemorrhage (parenchymal hemorrhage, subdural hemorrhage or intraventricular hemorrhage) and combination with PRES (Table 3 and Figure 1). For RCVS patients with cSAH (33 in 86, 38%), frontal lobe was most vulnerable (19 in 33, 57%), followed by parietal (7 in 33, 21%), occipital (4 in 33, 12%) and temporal lobe (3 in 33, 9%) shown in Table 3 and Figure 2B. More than half of primary or idiopathic (15 in 29, 52%) and vasoactive substances (14 in 28, 50%) induced RCVS had cSAH. Few patients with pregnancy and postpartum period (1 in 10, 10%), blood products (1 in 4, 25%) and miscellaneous (1 in 12, 8%) in second category had cSAH. For RCVS patients with DWI/MRI (T2) hyperintensity (44 in 86, 51%), circulation territory preferential sequences were posterior territory, anterior territory and combination of both (19 (43%), 15(34%) and 10 (23%) in 44). Notably, all patients with blood products and extra- or intra- cranial arterial disorders or procedures as secondary etiologies had DWI/MRI (T2) hyperintensity. DWI/MRI (T2) occurred most in all RCVS cases (44 in 86, 51%), and followed with cSAH (33 in 86, 38%). Within other intracranial hemorrhages, parenchymal hemorrhage (21%) was much higher than subdural hemorrhage (3%) or intraventricular hemorrhage (2%). PRES were identified in 75% RCVS patients with blood products as secondary category (3 in 4).

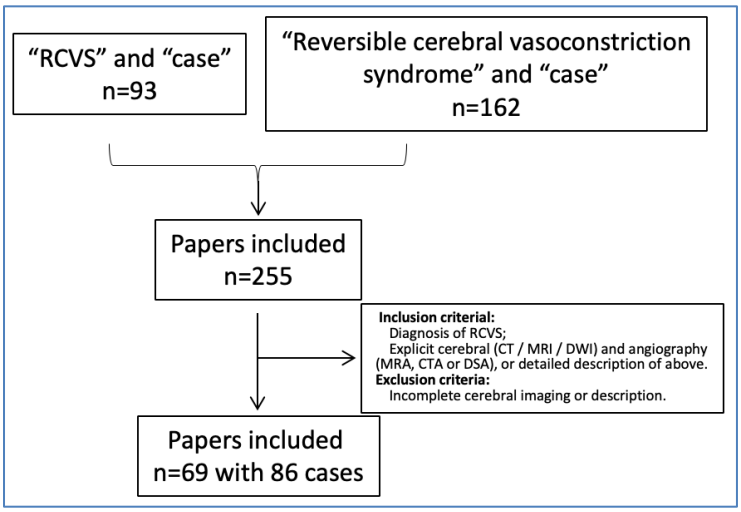

Figure 1. Searching flow chart on PubMed

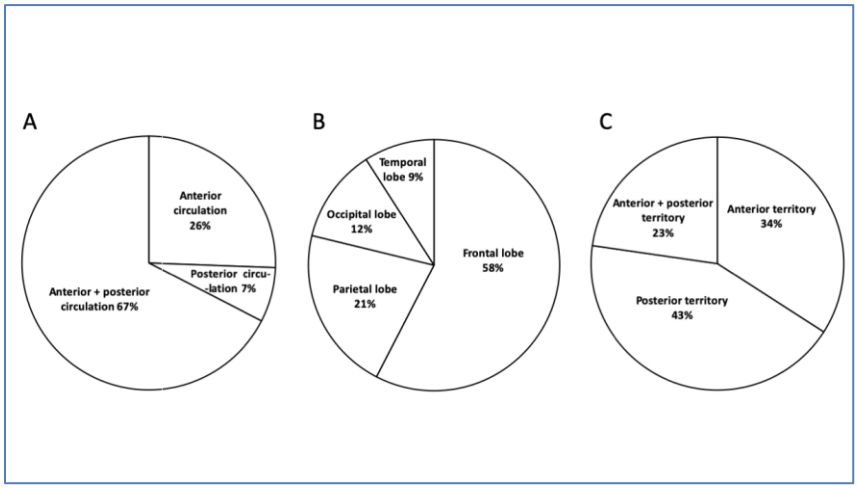

Figure 2. Angiographic, cSAH and DWI/MRI (T2) hyperintenstiy in RCVS. Angiographic territories, lobular compositions of cSAH and circulation territory of DWI/MRI (T2) hyperintensity in RCVS were shown in A, B and C respectively.
cSAH: Convex Subarachnoid Hemorrhage; RCVS: Reversible Cerebral Vasoconstriction.

Discussion

This study summarized radiological findings under etiologies of RCVS, aiming to provide mechanistic relationship between the above two.

Primary/idiopathic and vasoactive substances explained more than half of etiologies for RCVS, and the remaining included pregnancy and the postpartum period, blood products, extra- or intra- cranial arterial disorders or procedures and miscellaneous. Other etiologies like catecholamine secreting tumors and intracranial disorders or surgery were not included but mentioned in previous studies [3].

Pathophysiology of RCVS mainly relates to dysregulation of cerebral arterial tone triggered by sympathetic overactivity, estrogen modulation, endothelial dysfunction and oxidative stress [4,12-15]. Vasoactive substances produce direct vasoconstriction. Primary/idiopathic reasons like bathing, exertion, and other categories included pregnancy and the postpartum period, blood products and extra- or intra- cranial arterial disorders or procedures induce rapid increase in cerebral blood flow which beyond cerebral autoregulation capacity and result in vasoconstriction. During this procedure, over-perfusion damage may release free radicals and induce cerebral endothelial dysfunction, and further aggravates cerebral vasoconstriction and damage to the vasculo-endothelial system, leading to vicious cycle [16,17].

Sympathetic innervation is much higher in anterior circulation compared to posterior circulation [10,11], which explained more anterior circulation (92%) were affected than posterior circulation (74%) in nearly all categories of RCVS in this study. Female dominance indicated estrogen modulation of sympathetic tone as pathophysiologic etiologies [15]. Unexpectedly, two thirds (67%) cases with both anterior and posterior circulation were identified, indicating more mechanisms, such as endothelial dysfunction, oxidative stress and other unknown reasons participate to pathogenesis of RCVS [16].

38% cSAH, 51% DWI/MRI (T2) hyperintensity and 63% intracranial hemorrhage (including cSAH (38%) and other intracranial hemorrhage (26%)) were identified in 86 cases in this study, which matched one third to a half incidence of ischemic or hemorrhagic complications previously reported [2,4,6]. Due to dynamic nature of arterial changes as “reversible” in RCVS, initial angiography and imaging may be normal, thus repeat imaging is recommended if the diagnosis is highly suspected. Cases with etiologies of primary/idiopathic, vasoactive substances and extra- or intra-cranial arterial disorders or procedures tended to have more cSAH than DWI/MRI (T2) hyperintensity, whereas cases with etiologies of pregnancy and the postpartum period, blood products and miscellaneous presented more DWI/MRI (T2) hyperintensity than cSAH. cSAH related preferential etiologies above have greater potency to induce vasoconstriction, which occurred temporal, earlier and/or persisting longer (weeks), to make cSAH in RCVS distinguishable from SAH related vasospasm [2,4,18]. Etiologies of pregnancy and the postpartum period, blood products and extra- or intra- cranial arterial disorders or procedures induce cerebral autoregulation dysfunction and result in higher incidence of DWI/MRI (T2) hyperintensity and PRES. Posterior circulation region, which is lack of sympathetic innervation, is more vulnerable to rapid blood pressure raise and cause blood-brain barrier disruption [19]. Two main hypotheses were raised for pathogenesis of PRES: vasogenic and cytotoxic mechanism. Vasogenic hypothesis assumes that excessive blood pressure overcomes cerebral autoregulation capacity and cause cerebral vasodilation and vasogenic edema [20-23]. Cytotoxic hypothesis refers to direct toxic effects, which leads to vasoconstriction and cytotoxic edema [24-27].

Differential diagnosis includes aneurysmal SAH, PACNS, artery dissection, cerebral venous sinus thrombosis, intracranial hypotension, CADASIL, intracranial atherosclerosis, emboli, vasculitis, encephalitis and intravascular neoplasm [12,28,29].

There are 3 main shortcomings of this study. First, this study involved only reported cases, which might lead to publication bias. Second, DWI/MRI (T2) hyperintensity referred to either cytotoxic edema, vasogenic edema or both due to lack of ADC information. Third, case or series had different origination and description, from which it's hard to sequentially delineate radiological findings. We look forward to multi-center study in more sophisticated design to make RCVS clarified.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Abbreviations

RCVS: Reversible Cerebral Vasoconstriction Syndrome; TCH: Thunderclap Headache; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; MRA: Magnetic Resonance Angiography; CTA: Computed Tomography Angiography; DSA: Digital Subtraction Angiography; DWI: Diffusion Weighted Imaging; GBS: Guillein Barres Syndrome; rTMS: Repeated Transcranial Magnetic Stimulation; TTP: Thrombotic Thrombocytopenic Purpura; cSAH: Convex Subarachnoid Hemorrhage; PRES: Posterior Reversible Encephalopathy Syndrome

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