

# The many faces of the reversible cerebral vasoconstriction syndrome (RCVS)

## Introduction

The reversible cerebral vasoconstriction syndrome (RCVS), a recently recognized syndrome, is a common cause of sudden headache and of recurrent thunderclap headache (TCH).<sup>1</sup> A recently recognized syndrome characterized by recurrent TCH attacks. Many reports of this condition began accumulating these last ten years. This syndrome has also been called: Call-Flemming syndrome, benign cerebral angiopathy, post-partum angiopathy. These terms has been unified as RVCS. This name of RVCS was first proposed by Calabrese et al.<sup>2</sup> in 2007, and these authors define the diagnostic criteria of this clinical-radiological syndrome.<sup>2</sup> (i) multifocal segmental cerebral artery vasoconstriction documented by angiographic imaging tests; (ii) no evidence of aneurysmal subarachnoid hemorrhage; (iii) normal cerebrospinal fluid analysis; (iv) severe and acute headaches with or without additional neurologic signs or symptoms; and (v) reversibility of angiographic abnormalities within 12 weeks after onset.

The laboratory findings have received some recent modifications. Cerebrospinal fluid (CSF) may be normal or near-normal (protein concentration <100 mg/dL, <15 white blood cells/ $\mu$ L, normal glucose).<sup>3</sup> There is a characteristic pattern of radiographic features alongside suggestive clinical manifestations, which lead to a diagnosis of RVCS. This syndrome is characterized: 1-clinically by acute-onset and very severe headache, often thunderclap headache, ie headache peaking in one minute, and with or without acute neurological signs and symptoms, such as seizures, hemiparesis or encephalopathy. 2-radio logically by multifocal and segmental narrowing of multiple cerebral arteries corresponding to vasoconstriction that can affect the proximal, middle, and distal arterial segments and posterior predominant brain edema. The vasoconstriction is demonstrated by a characteristic diffuse "beaded" appearance identified on magnetic resonance angiography (MRA), angio-CT (ACT) or catheter cerebral angiography.<sup>4,5</sup> This syndrome is also defined by the complete resolution of the vasoconstriction shown by follow-up on MRA, CTA or catheter cerebral angiography within 12 weeks after onset, together with the total clinical normalization. Epidemiology RVCS affects patients of all ages, with a middle-aged female preponderance, between 20 and 50; the sex ratio varies among the series. The RVCS seems rare and perhaps under-recognized in children.<sup>6</sup> Causes: There are various precipitants of RCVS including, sexual activity, exertion, pregnancy-related conditions (early puerperium, pre-eclampsia, and eclampsia; post-partum), sympathomimetic or vasoactive substances, including nasal decongestants, serotonin-reuptake inhibitors, catecholamine-secreting tumors and ergoline derivatives, intravenous immunoglobulin, blood products, immune suppressants, and the use of illicit drugs (cannabis, cocaine) or comorbid autoimmune disorders. Many other putative precipitants have been reported. In 2/3 of patients, one or multiple precipitating factors are identified.

## Neuroimaging

In clinical practice, non-enhanced CT scan is the initial performed

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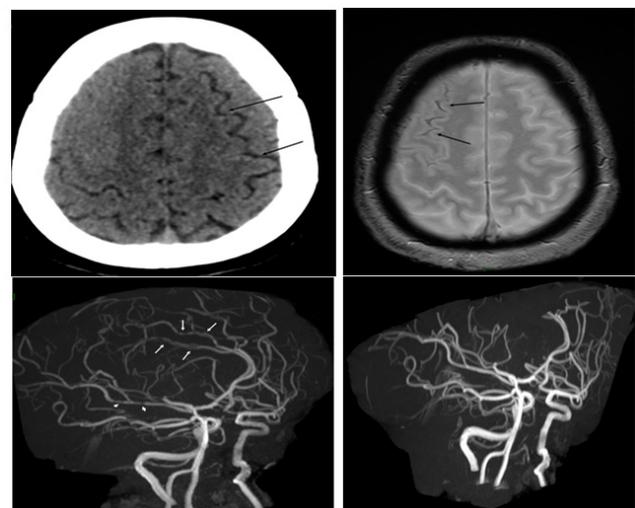
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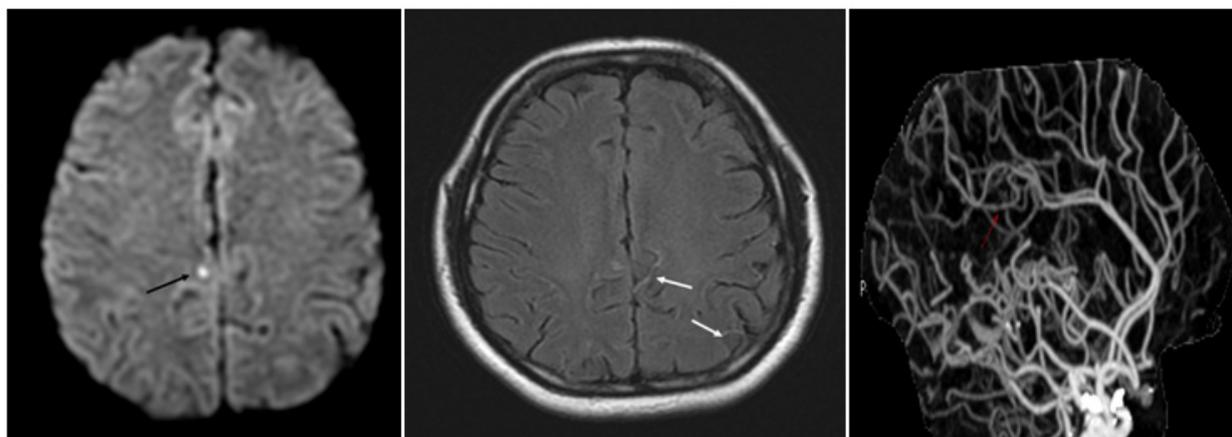
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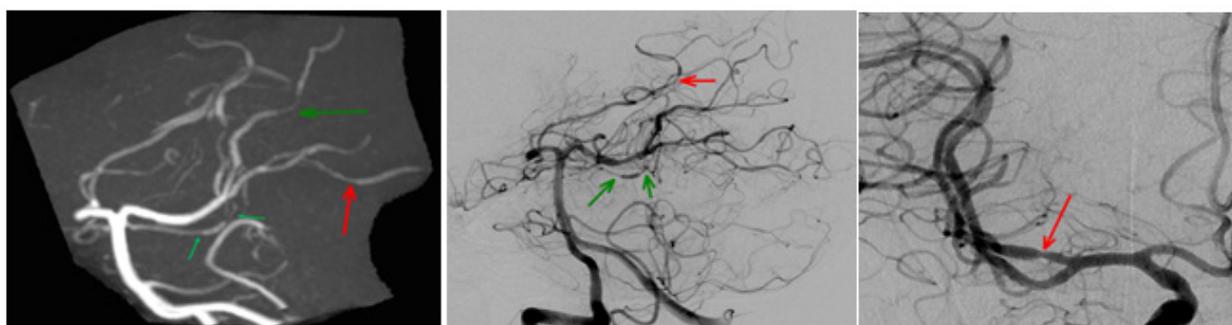
examination. When convexal subarachnoid hemorrhage (cSAH) is present but with small amounts of blood, the diagnosis of cSAH is not suggested. The arterial vasoconstriction is necessary for the diagnosis. Cerebral angiography was the standard criterion for the detection of cerebral vasoconstriction, but noninvasive techniques such as CT-angiography (Figure 1) (Figure 2) and MRA can be used for the diagnosis and follow-up of RCVS-related vasoconstriction. MRA is increasingly being used and is an effective imaging evaluation for the diagnosis and follow-up (Figures 3–5).<sup>6,7</sup>



**Figure 1** RVCS and SAH- Case 3. (A) Non-contrast CT shows a subtle hyperattenuation in the right anterior frontal sulcus favoring a minimal SAH. Note that on the left side the Superior frontalsulcus well identified (arrows) T2\* (GRE T2) sequence confirms the localized convexal SAH, showing a focal linear hypointense signal in the superficial layers of the right anterior frontal lobe related to superficial siderosis (B). (C) Oblique antero-posterior view from a 3D time-of-flight (TOF) magnetic resonance angiography (MRA) shows multiple segmental narrowing of proximal and distal anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) branches. (D) 3-month follow-up MRA reveals resolution of the multiple areas of arterial narrowing, consistent with RCVS.



**Figure 2** RVCS and Ischemia – Case 4: DWI sequence reveals a dot hyper intensity, related to focal ischemia in the right anterior cerebral artery territory (A) visualized on FLAIR (B, arrowhead). FLAIR shows also distal vessel hyperintensities. Angio-CT shows multiple arterial stenosis of distal arterial branches of anterior and middle cerebral arteries (C, arrow).



**Figure 3** Isolated RVCS- Case 1: 3D Time-of-flight (TOF) magnetic resonance angiography (MRA) shows multiple segmental stenosis and dilatations on the proximal left superior cerebellar artery (SCA) (Small green arrows) and the distal branches of the left posterior cerebral artery (PCA) branches (long arrows) (A). The same stenoses and dilatations are visualized on catheter cerebral angiography on (left SCA (green arrows) and on the distal branches of the right PCA (red arrow) as on the M2 segment of the right middle cerebral artery (MCA) (C, arrow).

In most cases CT scan and MRI do not show other intracranial abnormalities.<sup>8-10</sup> In most cases, the RVCS is isolated (Case 1). However, this syndrome may be associated with cSAH (Case 2, Case 3, Case 5), ischemic (Case 4) or hemorrhagic stroke, or PRES. Occasionally, cSAH and infarct, brain hemorrhage and infarct, PRES and cSAH or cerebral hemorrhage may be associated with the clinical-radiological characteristic features of RVCS (Case 5). Some cSAH (30%) are focal SAH, circumscribed to few sulci along the cerebral convexity. 30% of patients present with cSAH with or without brain hemorrhage. CSAH appears on non-contrast CT as a slight sulcal hyperdensity (Figure 4) or hyperattenuation (Figure 1), and on FLAIR as sulcal hyperintensity (Figure 1) (Figure 5). The sensitivity of CT decreases with time, especially if hemorrhage is minimal. FLAIR is more sensitive than CT to depict localized cSAH and the sulcal hyperintensity persists much longer. Susceptibility sequences (T2\* or GRE T2 and SWI sequences), may be very useful to confirm the hemorrhagic nature of the sulcal hyperintensity, showing a linear hypointense signal at the surface of the cortex (ie focal cortical superficial siderosis) (Figure 4). Intracerebral hemorrhagic complications (13-20%) occur early in the course of RCVS (mainly in the first week after onset), whereas ischemic events occur preferentially later (two and three weeks after onset).<sup>10,11</sup> Hemorrhages are focal and often associated with cSAH. They are rarely localized in the deep structures.<sup>12</sup> Infarcts are usually

localized to watershed areas, and are localized in the carotid or vertebral-basilar territories (Figure 2) and occur a mean of 9 days after onset (Ducros, 2007). The frequency of the RCVS-related infarcts varies among the series, ranging from 6 to 12%.<sup>2,7,8</sup>

The frequency of the RCVS-associated PRES varies greatly among the series (12%). PRES typically includes acute headache, visual disturbance, seizures, variable focal neurological deficits, altered mental status, associated with a unique and typical clinical-radiological pattern of dominant parieto-occipital vasogenic edema. Other structures including the brain-stem, cerebellum, basal ganglia, and frontal lobes can be also involved. Minute focal hemorrhages, cSAH and hematoma may occur with the same frequency (15%) in PRES (Figure 5). The incidence of hemorrhagic lesions varies among the series, 20% for Sharma & Kastrup<sup>13,14</sup> PRES and RCVS share many imaging characteristics, suggesting possible similar mechanisms. Ducros (2007) and colleagues (8) reported that 9-38% of patients with RCVS are associated with PRES lesions. Chen<sup>7</sup> found that vasoconstrictions are important determinants for PRES and ischemic stroke. More rarely, dissection of the cervical arteries may also be associated with the RVCS.<sup>15</sup> These complications (brain infarction, brain hemorrhage, dissection) may cause substantial morbidity and even mortality.<sup>8</sup> Distal hyper intense vessels on FLAIR sequence may

be present in RCVS (Figure 2), indicating low flow and markers of arterial narrowing. They have been reported as more frequent when ischemic infarcts are present.<sup>16</sup> The pathophysiology of RCVS is uncertain. RCVS may be related to a disturbance in the regulation of cerebral arterial tone. This disturbance may be spontaneous or secondary to precipitant conditions or substances, as described previously.

Clinical variants isolated thunderclap headache may be 75% of cases the single symptom of RCVS and accounts for most benign TCH. However the incidence of isolated headache varies within large published series.<sup>7-9</sup> *Post-partum RCVS* starts within one month from the delivery. In 67% of cases, prior pregnancy has been uneventful. Neurological symptoms begin on day 5 post-partum. In most cases post-partum RCVS has a good prognosis, but fulminant cases and fatal cases have been reported.<sup>17-19</sup>



**Figure 4** RCVS and SAH- Case 2: Non-contrast CT shows hyperattenuation at the anterior part of the right sylvian fissure (A, arrow). MRI Fluid-attenuated inversion recuperation (FLAIR) sequence reveals hyper intensities in the sulci of the right anterior frontal lobe (B) and temporal lobe (C) suggestive of convexal subarachnoid hemorrhage (cSAH (arrows)). 3D Time-of-flight (TOF) magnetic resonance angiography (MRA) shows multiple segmental stenosis of A1 segment of the right anterior cerebral artery (red arrow), of branches of the right middle cerebral artery (MCA) (black arrows) (B) and of the first segment of the left superior cerebellar artery (SCA), (C). Angio-CT reveals on midline sagittal reformat multiple stenoses of the pericallosal and callosal branches of the anterior cerebral artery (D).

### Evolution-prognosis

Most patients with RCVS have a good clinical outcome. However, deterioration is not uncommon. Clinical worsening is usually associated with ischemic infarctions and may result in permanent deficits.<sup>20</sup>

### Differential diagnosis

When cSAH is present, the differential diagnosis with aneurysmal SAH (aSAH) is challenging. Patients with aSAH usually present an acute onset and a progressive neurologic worsening. Vasospasm in aSAH is in the vicinity of the SAH, and involves long segments of arteries near the polygone of Willis. Younger age, prior history of headache, lower Fisher SAH grade, more diffuse segmental arterial narrowing, and the presence of bilateral vasoconstriction seem in favor of RCVS rather than of aSAH.<sup>21</sup> Another differential diagnosis usually evoked is the primary angiitis of the central nervous system (PACNS). In PACNS headaches have not the characteristics of TCH, ischemic infarcts are multiple, associated with subacute cognitive

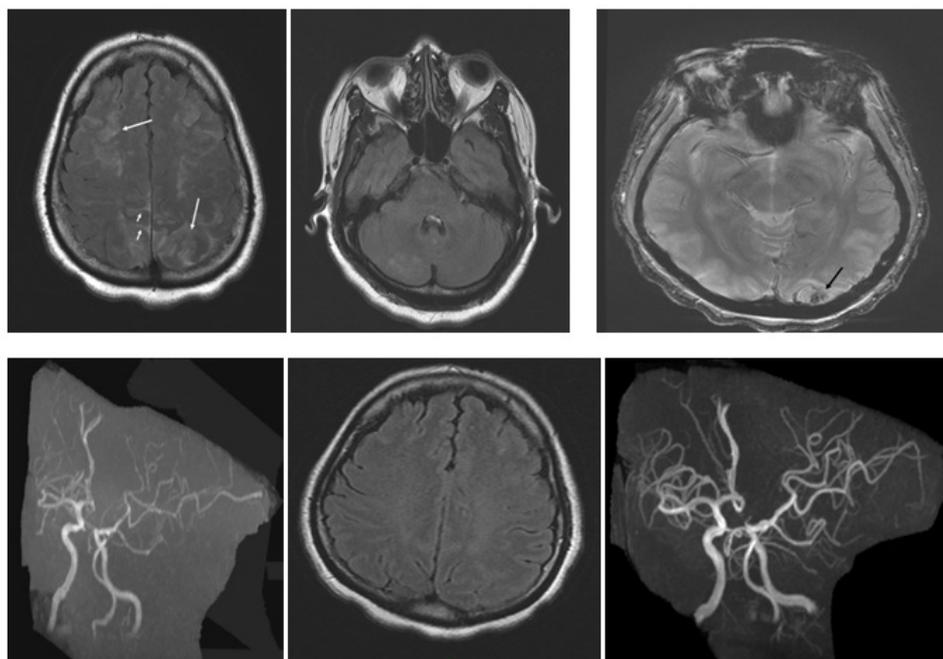
decline whereas MRI reveals old and recent infarcts along with white matter abnormalities. Analysis of CSF is helpful. Post-contrast high resolution MRI vessel wall imaging of the cerebral arteries reveals in PACNS a strong circumferential vessel wall enhancement and thickening, while in RCVS vessel wall imaging shows a diffuse, uniform and minimal wall thickening, corresponding to artery stenosis with mild enhancement, along with total resolution at 3-month control.<sup>22-25</sup> Furthermore, MRI can depict other causes of TCH, ie, cerebral venous thrombosis and cerebral artery dissection. The primary treatment of patients with RCVS should be the identification and elimination of aggravating factors including drugs (cessation of vasoactive agents), the recommendation of rest, and empirically the administration of drugs targeting vasospasms, calcium channel blockers such as nimodipine and verapamil. This treatment does not affect the course of the disease.<sup>3</sup>

We present 6 illustrative cases of RCVS that highlight the various presentations of this syndrome. All patients had clinical and neuroradiological follow-up at 3 months, and these controls show the

complete disappearance of the clinical and radiological abnormalities. In all presented cases, reversal of vasoconstriction was noted on follow-up 3-month MRA.

**Case 1:** A 34-year-old man, cannabis user, presented a TCH. He denied similar headaches in the past. Clinical examination was unremarkable. MRI/MRA showed arterial vasoconstriction, with no SAH nor parenchymal lesion. MRA shows multiple arterial stenosis of proximal and distal branches of the middle cerebral arteries and the vertebral and basilar arteries (Figure 3).

**Case 2:** A 46-year-old woman with previous history of migraine was admitted to Emergency Department because of a sudden-onset severe headache reaching peak intensity within one minute and associated with nausea. Her medication included Seroplex (10mg daily) and Imigran in case of migraine. Clinical examination was normal. Non-contrast CT showed subtle sulcal SAH which was confirmed on T2\* (T2GRE) sequence. MRA showed the multiple segmental narrowing of the cerebral arteries and 3-month MRA follow-up showed the total regression of the vaso-constriction (Figure 4).



**Figure 5** RVCS and PRES- Case 5: FLAIR images demonstrate cortical and subcortical areas of hyperintensities in the frontal and parietal lobes, (a, long arrows) and sulcal hyperintensities in the right para sagittal fronto-parietal sulci, consistent with focal convexal subarachnoid hemorrhage (A, Small arrows). FLAIR hyperintensities are also present in the pons and the cerebellar lobes (B). T2\* (GRE T2) sequence shows an area of hemorrhage as hypo intensity in the left occipital lobe. Oblique antero-posterior view from a 3D TOF MRA show wide spread, progressive narrowing of proximal and distal anterior cerebral artery and middle cerebral artery branches (C). Follow-up MRI at day 9 of admission: FLAIR shows the resolution of the parenchymal hyperintensities (vasogenic edema) and of sulcal hyperintensities (convexal SAH). At 3-month follow-up, MRA shows the complete resolution of the vasoconstriction.

**Case 3:** A 60-year-old woman with migraine and smoking history presented with thunderclap headache during defecation. The headaches were recurrent during last week, accompanied with vertigo. Her medication included Seroplex. Clinical examination was normal. FLAIR showed sulcal SAH in the right anterior frontal and temporal areas. MRA showed multiple segmental narrowing of the cerebral arteries and 3-month MRA follow-up showed the total regression of the vaso-constriction (Figure 1).

**Case 4:** A 41-year-old woman presented with acute onset of severe headache and nausea. There was no neurological deficit. There was no previous history of migraine. Previous medication included Seroplex (20mg/day) for depression. Non-contrast CT at admission was unremarkable and ACT showed segmental arterial narrowing. MRI/MRA one day later confirmed the vaso-constriction and revealed dot ischemia on FLAIR and Diffusion images (DWI) with ADC restriction. This ischemic infarct was clinically silent (Figure 2). The outcome was favorable.

**Case 5:** A 31-year-old woman, gravida 2, presented 2 weeks after caesarean section with headache of progressive onset, phosphenes,

rapid decline of visual acuity and vomiting. She had an otherwise uneventful pregnancy. She was found to have an elevated blood pressure of 220/120 mm Hg. Ten hours later the patient developed one episode of generalized tonic-clonic seizure. Emergency MRI showed on FLAIR images extensive vasogenic edema, multifocal sulcal SAH, small right occipital hematoma and extensive vasoconstriction of the cerebral arteries on MRA (Figure 5). These findings were consistent with PRES. The clinical normalisation was observed at day 7, vasogenic edema resolved on 9-day MRI control. Follow-up MRI at 3 months showed a normal aspect of cerebral arteries.

## Conclusion

The diagnosis of RCVS should be made on the basis of the typical imaging appearance of cerebral vasoconstriction, in addition to the characteristic clinical onset, and results of CSF analysis. As early diagnosis is crucial to avoid invasive workups and inappropriate treatments, it is critical for emergency physicians to detect the RCVS in patients with TCH, when there is no evidence of aneurysmal SAH, and for radiologists to recognize the imaging pattern of RCVS. Delay

in diagnosis may cause clinical deterioration, especially ischemic infarcts and unnecessary diagnostic investigations. Furthermore, timely demonstration of complete or near-complete reversibility of vasoconstriction within 3 months, in addition to clinical resolution is useful to confirm the diagnosis.

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## Conflict of interest

Authors declare there is no Conflict of interest towards this manuscript.

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