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Reversible cerebral vasoconstriction syndrome: review of neuroimaging findings

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Abstract

Reversible cerebral vasoconstriction syndrome (RCVS) is a group of disorders characterized by segmental narrowing and dilatation of medium-to-large cerebral arteries, clinically presenting with recurrent episodes of sudden-onset thunderclap headaches, with or without focal neurological deficits. Cerebral vasoconstriction is typically reversible, with spontaneous resolution within 3 months. Although the syndrome has generally a benign course, patients with neurological deficits may experience worse outcome. The main imaging finding is segmental constriction of intracranial arteries, which can be associated with subarachnoid hemorrhage and/or ischemic foci. Other possible findings are intracranial hemorrhage, subdural bleeding and cerebral edema. The latter may have a pattern which can resemble that of posterior reversible encephalopathy syndrome, a condition that can overlap with RCVS. New imaging techniques, such as vessel wall imaging and arterial spin labeling, are proving useful in RCVS and are giving new insights into the pathophysiology of this condition. In this paper, we aim to review neuroimaging findings of RCVS.

Keywords Reversible cerebral vasoconstriction syndrome · Magnetic resonance imaging · Subarachnoid hemorrhage · Digital subtraction angiography · Vessel wall imaging

Abbreviations

RCVS	Reversible cerebral vasoconstriction syndrome
PRES	Posterior reversible encephalopathy syndrome
SAH	Subarachnoid hemorrhage
CT	Computed tomography
ICH	Intracranial hemorrhage
MR	Magnetic resonance
FLAIR	Fluid-attenuated inversion recovery
DWI	Diffusion weighted imaging
VWI	Vessel wall imaging
ASL	Arterial spin labeling
CBF	Cerebral blood flow
DSA	Digital subtraction angiography
PACNS	Primary angiitis of the central nervous system

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Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is a cerebrovascular disease characterized by diffuse, multifocal and segmental arterial constriction resolving within 3 months, clinically presenting with recurrent episodes of sudden-onset thunderclap headaches, with or without other neurological deficits [1]. The syndrome affects most commonly women aged between 20 and 50 years [2]. The exact incidence is still unknown, probably because RCVS is likely to be underdiagnosed. Ducros et al. reported that RCVS was the final diagnosis in approximately 0.26% of patients presenting to the emergency department due to headache [3].

It can occur spontaneously or can be caused by triggers. Puerperium and vasoactive medications (for instance, bromocriptine, ergotamine, pseudoephedrine, selective serotonin-uptake inhibitors and interferon) account for almost half of the cases [4]. Other known triggers are alcohol, drugs (such as amphetamines, cannabis, cocaine, ecstasy and nicotine), blood products, migraines, tumors (in particular, Pheochromocytoma and Paraganglioma), antiphospholipid

antibody syndrome and thrombotic thrombocytopenic purpura [5].

RCVS has also been described in the context of SARS-Cov-2 infection [6]. Although this association needs further validation, SARS-CoV-2 may trigger RCVS because of the direct interaction of the virus with endothelial cells and Angiotensin-converting enzyme type 2 receptors, with subsequent possible alterations of vessels caliber [7].

Pathogenesis is still unknown, although transient deregulation in cerebral vascular tone is thought to be a key feature, whereas active inflammation has not been shown on brain biopsy in these patients [4]. Sympathetic overactivity, oxidative stress and endothelial disfunction are probably the main factors involved in the pathogenesis of RCVS, although the specific contribution of each one probably varies depending on the specific trigger. For instance, in case of vasoactive medications and Pheochromocytoma, sympathetic overactivity is thought to play a crucial role [8]. Oxidative stress is probably involved in RCVS, as markers of this process have been reported to be elevated in the syndrome [9].

RCVS frequently overlaps with posterior reversible encephalopathy syndrome (PRES), which clinically presents with headache, visual alterations and seizure [10]. On imaging, cerebral edema is an important feature of PRES, and it usually involves the occipital lobes, with cortico-subcortical distribution [11]. Although pathogenesis of PRES is still unknown, endothelial disfunction with subsequent alteration of permeability may be the main pathological mechanism, especially in normotensive patients [12]. RCVS and PRES share clinical, radiological and pathophysiological features, therefore it has been recently proposed that they might represent a disease continuum [11].

Calabrese et al. have proposed diagnostic criteria for RCVS, which have been modified by the International Headache Society [1]. They include both clinical and neuroradiological findings, such as thunderclap headache and the presence of subarachnoid hemorrhage (SAH). Recently, diagnostic scores have been introduced to improve the diagnostic work-up of RCVS. Rocha et al. developed the RCVS$_2$ score, which is based on both clinical and imaging findings. It includes thunderclap headache, female gender, carotid artery involvement, presence of RCVS triggers and SAH [13]. It showed high specificity and sensitivity, mostly for higher score (specificity > 99% and sensibility > 90%, for score higher than 5). The RCVS-TCH score is only based on clinical features, such as thunderclap headache, female sex, presence of triggers and blood pressure surge [14]. It showed high sensitivity and specificity for score higher than 7 (sensitivity of 80% and specificity of 97%).

Clinically, patients with RCVS suffer from multiple episodes of thunderclap headache, recurring over 1–4 weeks in 94–100% of cases [15]. The headaches in RCVS may be the only clinical manifestation, and they are characterized by excruciating pain, with predominant bilateral and occipital distribution, duration around three hours and complete resolution within 2–3 weeks [16]. Focal neurological deficits may occur in 9–63%, and can be transient or permanent [1]. Other possible clinical manifestations are photophobia, phonophobia, nausea, vomiting and encephalopathy [17]. Seizures have been reported in 21% of patients and they can be focal or generalized [15].

RCVS is usually monophasic and self-limiting, with complete resolution of symptoms within 3 months [18]. Unfortunately, complications are reported in RCVS and therefore, neurological sequelae are possible. Hemorrhagic complications are described in up to 34% of cases, usually occur in the first week, and they are more frequent in women with history of migraine [19]. Hemorrhages in RCVS may be the consequence of vessel caliber dysregulation, with post-ischemic reperfusion injury and damage of arterial walls [20]. Another possible early complication is PRES, whereas ischemic events tend to appear during the second week [21]. RCVS may also have a fulminant course in the postpartum, with massive ischemia and brain edema leading to death in 8–24 days after delivery [22].

Early recognition of the syndrome is crucial to manage the symptoms effectively. Firstly, it is necessary to identify and eliminate any trigger. Calcium channel blockers including Nimodipine and Verapamil have been extensively used to relieve headache as a first-line therapy [21]. Intravenous magnesium sulfate may be considered in postpartum RCVS with eclampsia [23]. Retrospective data suggest significant risk of clinical worsening using steroids for treatment of RCVS [24].

Aim of this review is to describe neuroimaging findings of RCVS reported in the scientific literature so far (Table 1).

Computed tomography

Non-contrast computed tomography (CT) is usually the first imaging exam performed in patients with RCVS, as they present at the emergency department because of thunderclap headache. The exam may result negative in more than half of the cases [24]. Therefore, Fukaguchi et al. have proposed to perform clinical and imaging follow-up for at least 2 weeks to exclude the syndrome [25].

Hemorrhagic manifestations have been reported in 34–43% of cases and they may consist of SAH, intracranial hemorrhage and subdural bleeding, with possible overlapping of different types in the same patient [3, 26]. SAH (Fig. 1) is the most frequent hemorrhagic manifestation, representing almost 38% of all hemorrhagic complications in RCVS [26]. It is usually mild and located in the cerebral sulci near the vertex [27]. Topcuoglu et al. evaluated 162 patients with RCVS and the distribution of the blood was

Table 1 Neuroimaging findings reported in RCVS

Neuroimaging findings reported in RCVS
Subarachnoid hemorrhage in the cerebral sulci at the convexity
Intraparenchymal hemorrhage
Subdural hemorrhage
Ischemic stroke (usually with watershed pattern)
Cerebral edema
Posterior reversible encephalopathy syndrome
Hyperintensity of vessels along the cerebral sulci on FLAIR images
Segmental vasoconstriction of cerebral arteries with "string of bead" appearance
On VWI, concentric and diffuse pattern of involvement of arterial cerebral vessels, with possible wall enhancement
Multifocal areas of decreased perfusion with watershed pattern
On ASL, hypoperfusion in watershed areas and CBF increase within two weeks

FLAIR Fluid-attenuated inversion recovery; *VWI* vessel wall imaging; *ASL* arterial spin labeling; *CBF* cerebral blood flow

Fig. 1 Non-contrast coronal reformat CT shows left frontal SAH (*arrows*) within cortical sulci

bilateral in almost 38% of case [26]. Plus, there was involvement of one cortical sulcus in 36% of cases, two sulci in 26% of cases and more than three sulci in 38% of patients. Blood rarely extended to the Sylvian fissures and ambient cistern [26]. The most frequent location was the frontal lobe (79% of cases), followed by the parietal region (31% of cases), whereas the occipital and temporal lobes were rarely involved (only 23 and 10% of cases, respectively) [26]. In 90% of cases SAH was present in the initial imaging. SAH may also affect cerebellar hemispheres, although this location is rare [27]. In almost half of the cases, SAH is associated with intracerebral hemorrhage and/or ischemic stroke [28, 29].

Topcuoglu et al. also evaluated intracranial hemorrhages (ICH) in RCVS (Fig. 2), reporting them as rare (13%) [26]. They were usually associated with other hemorrhagic manifestations and were single in the majority of

Fig. 2 Non-contrast CT reveals a focal intraparenchymal hemorrhage in the subcortical white matter in the area of the inferior frontal gyrus (*arrow*)

cases [30]. The location was mainly lobar, but they could also occur in the deep gray nuclei and cerebellum [26]. They were of small amount (less than 10 mm^3) and usually preceded SAH, although they were both early complications, mainly occurring in the first week after clinical onset [26]. ICH in the context of RCVS seems to be more frequent in women, in particular with history of migraine [3].

Subdural hematoma are extremely rare in RCVS (prevalence of nearly 2% of cases) and they are usually acute and associated with other hemorrhagic events [3]. In particular, they appear in areas adjacent to ICH [26].

Fig. 3 Axial fat-suppressed FLAIR (**a**) and coronal reformat of 3D maximum intensity projection MR Angiography (**b**) showing a vast ICH in the right frontal region (*short black arrows* in **a**) with concomitant vasogenic edema (*white arrows* in A). There is concomitant vasoconstriction of anterior, middle and posterior cerebral arteries with alternating areas of vasodilatation (**b**)
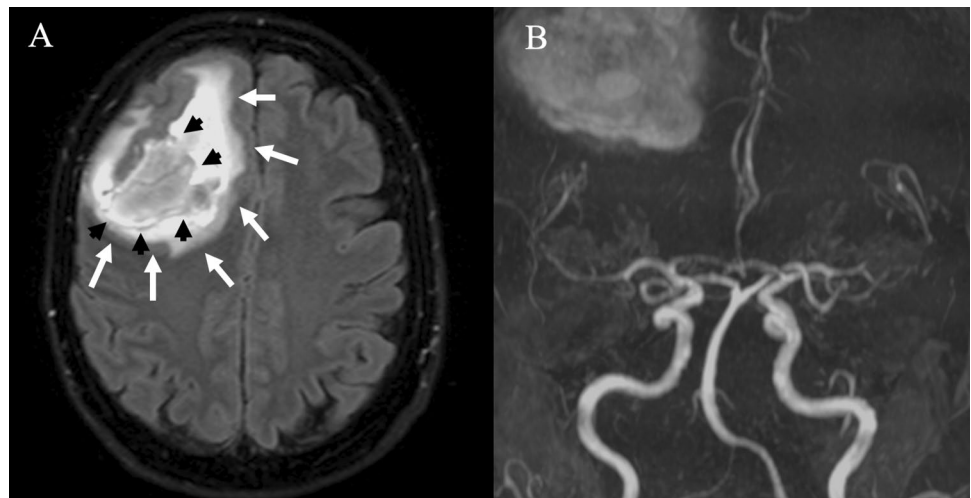
Wilson et al. have described a case of isolated intraventricular hemorrhage in a clinical setting compatible with RCVS, but further scientific reports are required to validate this finding as associated with the syndrome and not as a concomitant event [31].

Ischemic stroke can also occur in almost 50% of cases of RCVS and it may rarely overlap with cerebral hemorrhage [32].

In the setting of patients with acute severe headache, the American College of Radiology Appropriateness Criteria report unenhanced head CT as the initial imaging test [33]. If SAH is found or neurological examinations suggest a secondary headache, CTA is suggested to provide additional information in the diagnostic work-up and in particular to rule out vascular malformations, cerebral aneurysms, venous sinus thrombosis and RCVS [34].

Magnetic resonance imaging

Magnetic resonance (MR) is frequently performed in the setting of suspected RCVS to detect complications, such as intracerebral bleeding (Fig. 3), and exclude other differential diagnosis. Fluid-attenuated inversion recovery (FLAIR) sequences are useful to detect SAH (Fig. 4) and cerebral edema [35]. Furthermore, hyperintensity of cerebral vessels along the sulci on FLAIR images has been described [36]. It may be caused by vasoconstriction and can be differentiated from SAH using susceptibility weighted sequences.

Diffusion weighted imaging (DWI) may demonstrate the presence of ischemic stroke (Fig. 5) [37]. In RCVS, ischemic lesions are usually bilateral and manifest in arterial watershed distribution, probably due to cerebral
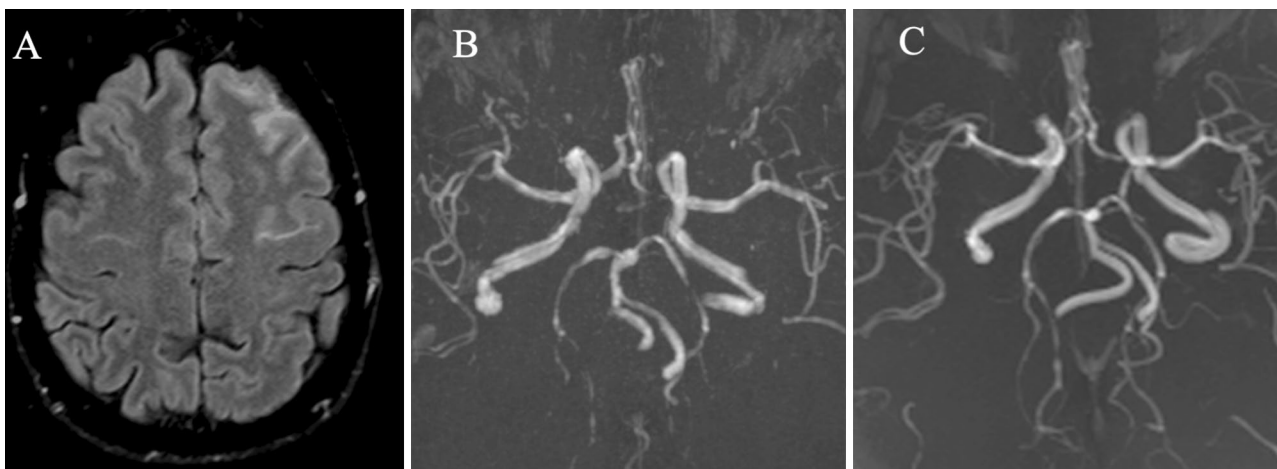

Fig. 4 Axial fat-suppressed FLAIR (**a**) and coronal reformat of 3D maximum intensity projection MR Angiography (**b**) showing SAH in the frontal region bilaterally. There is also vasoconstriction of the arteries of the circle of Willis (**b**) which resolved after 3 months (**c**)
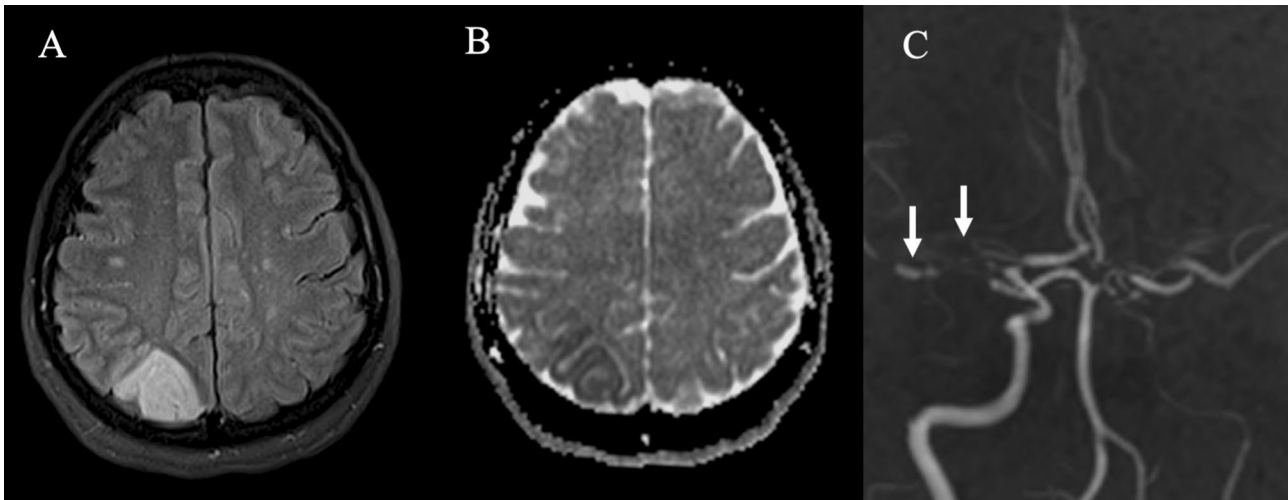
Fig. 5 Axial fat-suppressed FLAIR (**a**), Apparent Diffusion Coefficient (**B**) and coronal reformat of 3D maximum intensity projection MR Angiography (**c**) show an acute ischemic area in the right parietal region hyperintense in FLAIR (A) with low Apparent Diffusion Coefficient values (**b**). There is also vasoconstriction with "sausage on a string" appearance, more prominent in the right middle cerebral artery (*arrows* in **c**)

vasoconstriction (Fig. 6) [38]. Cerebellar stroke has also been described in RCVS, although it is a rare event [39].

Cerebral edema is a possible complication of RCVS and it has been reported in almost 10% of cases [40]. It usually occurs in the first week after clinical onset, showing complete resolution within 1 month [4]. Ischemic stroke and brain hemorrhages are frequently associated [3]. On FLAIR sequences, it appears as symmetrical areas of hyperintensity, usually in the parieto-occipital regions [10]. This pattern resembles that of PRES, suggesting a common pathophysiological mechanism underlying these two conditions [41].

MR angiography is extremely important to evaluate the presence of segmental vasoconstriction of cerebral arteries in RCVS. It usually affects large-to-medium-sized arteries with an appearance of alternating areas of constriction and dilatation, giving a typical "string of bead" or "sausage on a string"appearance (Fig. 7) [42] The peak of vasoconstriction is around 16 days after clinical onset, and it resolves within 3 months (Fig. 8) [2].

Vessel wall imaging (VWI) is a new MR technique which enables the evaluation of blood vessel wall of proximal intracranial arteries [43]. It requires specific high-resolution and black-blood sequences, high spatial
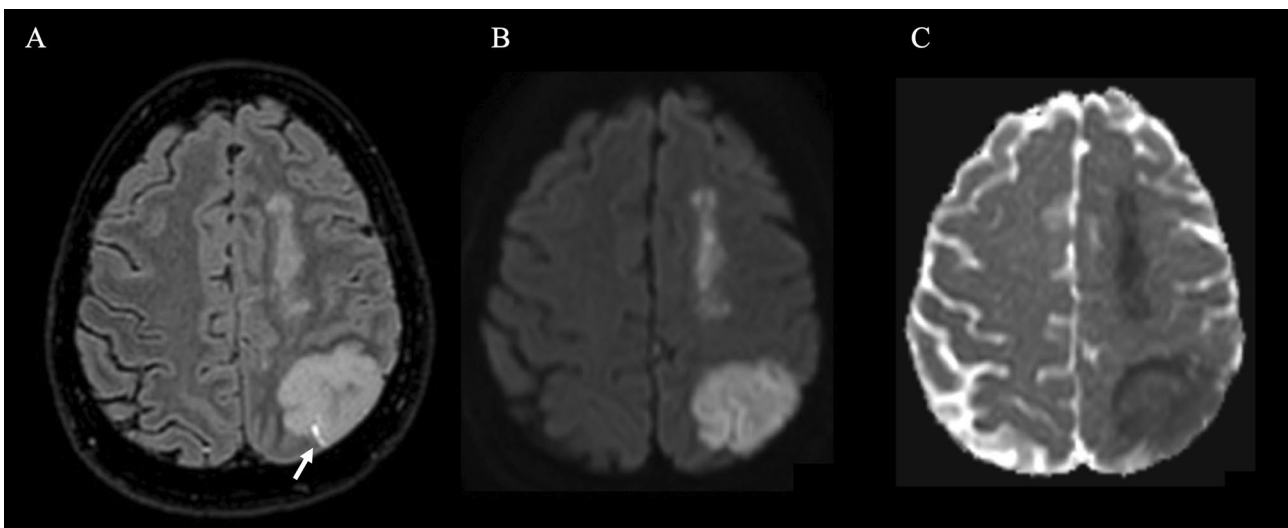

Fig. 6 Axial FLAIR (**a**), DWI (**b**) and Apparent Diffusion Coefficient (**c**) images show ischemic stroke with watershed distribution, involving left frontal parasagittal area and the left posterior parietal lobe. Note also SAH in the left parietal convexity (*arrow* in A)

Fig. 7 Coronal reformat of 3D maximum intensity projection MR Angiography reveals multiple and bilateral segmental arterial narrowing of anterior, middle and posterior cerebral arteries with a subtle "beaded" appearance

case there is thickening of the vessel wall with no or mild enhancement, whereas in vasculitis vessel wall enhancement tends to be prominent and persistent [46]. Chen et al. prospectively evaluated 48 patients with RCVS and 45.8% of them showed vessel wall enhancement on VWI, which was mild in 77.3% of cases and concentric in 72.7% of cases [47]. Interestingly, vessel wall enhancement not always co-localized with vasocontraction [47]. M1 tract of the middle cerebral artery was the most common affected vessel [47]. During follow-up, 35.7% of patients had persistence of vessel wall enhancement, whereas in 64.3% of cases there was complete resolution [47].

Perfusion MR imaging techniques, such as dynamic susceptibility contrast, are not routinely performed in RCVS. Rosenbloom et al. reported a case of RCVS where MR perfusion showed areas of hypoperfusion in watershed territories, which later evolved in ischemic areas [48].

Arterial spin labeling (ASL) is a perfusion MR technique, which enables cerebral blood flow (CBF) evaluation, without the need of Gadolinium injection [49]. Kano et al. performed ASL in five patients with RCVS, and it showed higher sensitivity than MR angiography in detecting hypoperfusion [50]. Vasoconstriction reached its peak in the second week with subsequent gradual normalization [50]. Furthermore, it showed a centripetal progression, beginning from distal arteries and affecting the central vessels later. In the area where PRES and SAH were present, CBF was lower than in other regions of the brain, probably because of breakdown of autoregulation [50].
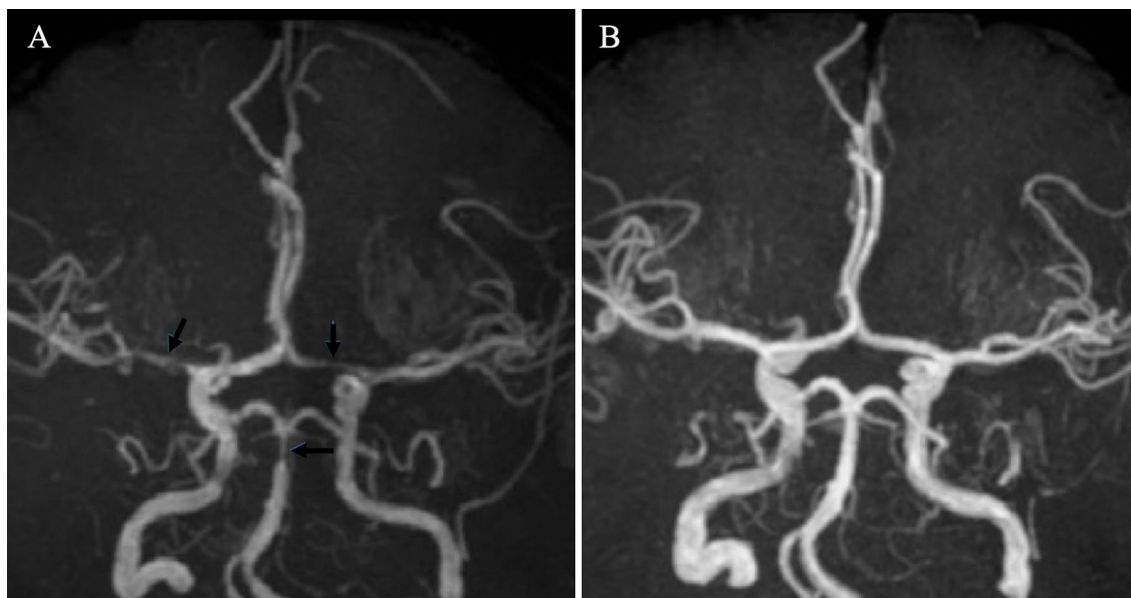
resolution and high-field-strength magnets, as cerebral vessels are only few millimeters thick [44]. In the past few years, VWI has proved to be useful in the setting of RCVS, in particular to differentiate this entity from other forms of arteriopathy [45]. For instance, VWI may be used to differentiate RCVS from vasculitis as in the first

Fig. 8 Coronal reformat of 3D maximum intensity projection MR Angiography (**a**) shows bilateral stenoses of anterior and middle cerebral arteries and of the basilar artery. At follow-up MR Angiography performed 9 weeks later, there is marked improvement in vessel caliber (**b**)
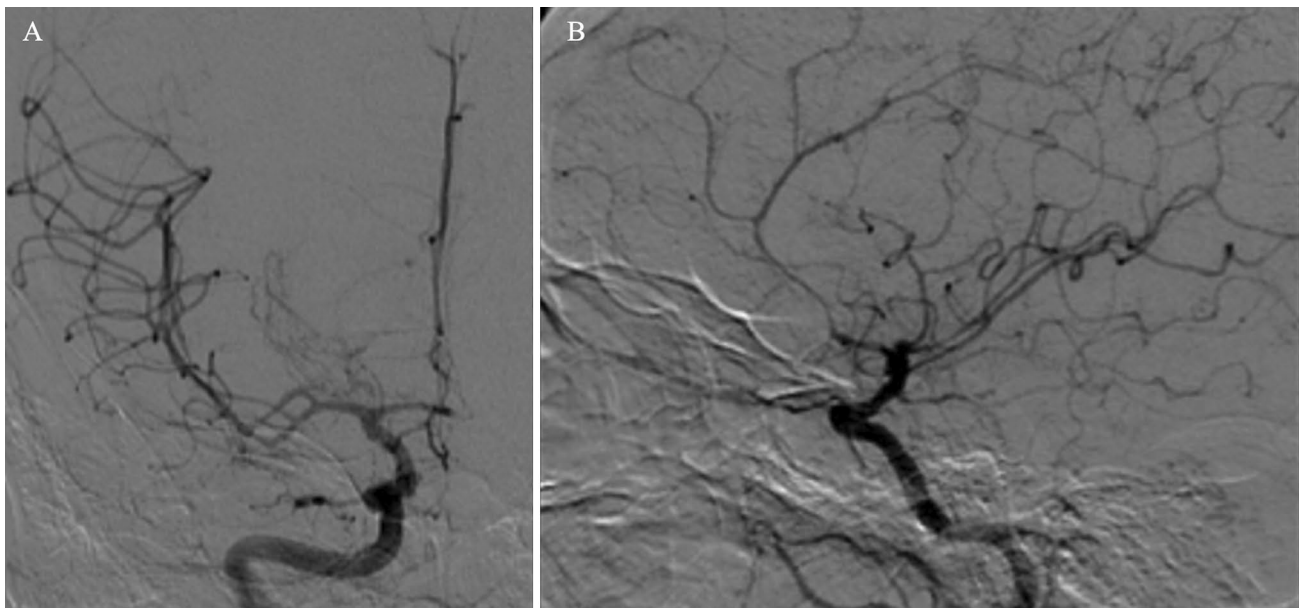
Fig. 9 DSA of the right internal carotid artery demonstrates subtle areas of narrowing

Digital subtraction angiography

Digital subtraction angiography (DSA) is the gold standard to evaluate cerebral arterial vasoconstriction (Fig. 9) [19]. Typically, it shows bilateral and diffuse areas of segmental narrowing and dilatation of medium-to-large arteries, which determines the typical "string of beads" pattern [51]. The most frequently affected vessels are the basilar artery and the carotid siphon [52, 53]. What is more, vasoconstriction does not constantly affects the same vessel tracts [54]. On repeated DSA, there might be resolution of some constrictions with new areas of narrowing, with centripetal progression during follow-up [52]. Furthermore, the conspicuity of vasoconstriction may fluctuate over time, with some areas showing dilatation and other narrowing [24]. In a minority of cases (prevalence of almost 16%), the pattern of vasoconstriction can be hemispheric or focal [32].

It is important to acknowledge that if DSA is performed within the first week after clinical onset, it may be normal [54]. This probably happens because vasoconstriction begins from small and peripheral vessels, which are not easily evaluated with DSA. In this case, it is suggested to repeat DSA in the second week, as the peak of vasoconstriction is reached at day 16 [55].

Furthermore, DSA can be used to prove reversibility of vasoconstriction after intra-arterial administration of vasodilator, such as Verapamil [56]. This finding is important to demonstrate reversibility of arterial vasoconstriction, which can help early diagnosis of RCVS [57].

Table 2 Differential diagnosis of RCVS

Differential diagnosis of RCVS
Aneurysmal rupture
Non Aneurysmal Subarachnoid hemorrhage
Primary angiitis of the central nervous system
Cortical vein thrombosis
Amyloid Angiopathy

Differential diagnosis

There are multiple clinical conditions which overlap with RCVS (Table 2). Firstly, it is important to rule out aneurysmal rupture as it may cause thunderclap headache [58]. Key elements to distinguish these two entities are clinical presentation and the pattern of distribution of SAH. RCVS is characterized by relapsing–remitting episodes of thunderclap headache, which is usually monophasic in case aneurysmal rupture or preceded by sentinel headache [59]. In case of aneurysmal SAH, blood distributes in cerebral cisterns near the ruptured aneurysm, in particular if middle cerebral artery or anterior communicating artery are interested [60]. The pattern of arterial vasoconstriction associated with aneurysmal rupture is not specific and therefore it is not easy to distinguish it from that of RCVS [61].

Nonaneurysmal SAH probably has a venous origin [62]. Blood is usually located in the perimesencephalic region, thus helping in differentiation with RCVS [63].

Primary angiitis of the central nervous system (PACNS) is in another condition to consider among the differential diagnosis of RCVS. PACNS causes a slowly progressive and very intense headache, and it is more frequent in middle-aged men [64]. Furthermore, this condition has dismal prognosis without adequate and rapid immunosuppressive therapy [65]. In PACNS, brain MR shows multiple cerebral infarcts of different ages, and hemorrhagic events are rare [66]. Furthermore, the pattern of vasoconstriction is different from that of RCVS as it is multi-focal and mainly interests mid-to-distal cerebral arteries [67]. Finally, VWI has proved useful to rule out PACNS, as it shows concentric wall thickening and enhancement of the affected vessels [68].

Cortical vein thrombosis should also be considered, as it shares clinic-radiological features with RCVS. In particular, they are both more frequent in pregnant women, usually determine thunderclap headache, may determine SAH at convexity and ischemic stroke [69]. An important clue to make the correct diagnosis is to look for cortical vein hypointensity on susceptibility-weighted sequences [70].

Finally, amyloid angiopathy may also determine cortical SAH, but it is more frequent in the elderly, and it does not cause thunderclap headache. Furthermore, it usually determines ICH and microbleeds with peripheral pattern [71].

Conclusions

RCVS is a not completely understood and under-diagnosed clinical syndrome, characterized by recurrence of thunderclap headache and reversible diffuse areas of narrowing and dilatation, mainly affecting large-to-medium cerebral arteries.

In the scientific literature multiple imaging findings have been reported in RCVS, such as SAH, intracranial hemorrhage, subdural bleeding, ischemic stroke, PRES and segmental vasoconstriction of cerebral arteries with a "string of bead" appearance. Furthermore, advanced imaging techniques, (namely, vessel wall imaging and ASL) could improve diagnostic work-up and possibly give new insights in the pathophysiology of this condition. The neuroradiologist should be aware of these imaging findings as rapid diagnosis is crucial to improve prognosis.

Declarations

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