



# Concomitant reversible cerebral vasoconstriction syndrome and transient global amnesia

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## Abstract

**Background** Reversible cerebral vasoconstriction syndrome (RCVS) is a common cause of thunderclap headache (TCH), mainly recurrent, sometimes associated with seizures and/or neurological deficit. Association with amnesia is exceptional. We report a case series of RCVS concomitant with transient global amnesia (TGA) and propose pathophysiologic hypotheses.

**Methods** We retrospectively reviewed clinical and radiological features of patients diagnosed with confirmed concomitant RCVS and TGA between 2012 and 2018 in two specialized institutions.

**Results** Two women aged 67 and 53, and a 64-year-old man had a first thunderclap headache triggered by an acute emotional stress, rapidly followed by TGA. Amnesia resolved within a few hours and RCVS was proven for all, with complete resolution of vasospasms within 3 months. All three patients had excellent outcome.

**Conclusions** RCVS and TGA can occur simultaneously, which suggests common mechanisms such as aberrant responses to physical or emotional stress and cerebral vasoconstriction.

**Keywords** Thunderclap headache · Transient global amnesia · Vasospasm · Reversible cerebral vasoconstriction syndrome

## Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headache, often thunderclap headaches (TCH), and reversible segmental constriction of the cerebral arteries, with or without cortical subarachnoid hemorrhage, infarction or intracerebral hemorrhage [1]. On top of TCH, seizures and neurological deficit are commonly observed [1]. Conversely, amnesia is exceptional. Transient global amnesia (TGA) is defined by a sudden transient

anterograde amnesia [2]. To our knowledge, co-occurrence of RCVS and TGA has been described in two patients [3, 4]. We report the first series of three cases of RCVS with TGA, implying a causal relationship between these two pathologies.

## Methods

We retrospectively reviewed clinical and radiological features of patients diagnosed with concomitant RCVS and TGA between 2012 and 2018 in two specialized institutions. Confirmed RCVS was defined by (1) recent severe headaches of sudden onset; (2) cerebral vasoconstriction on computed-tomography angiography (CTA) or MRA or TCD; (3) normalized arteries within 3 months. TGA was defined as sudden, transient deficit of anterograde memory without any other neurological impairment, in the absence of another cause.

All patients agreed to participate to this observational study, which was approved by the ethics committee.

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## Results

### Case 1

A 67-year-old woman, with a history of migraine with aura and hypertension, had a thunderclap headache (TCH) while feeling distressed during a trial. A few minutes later, she developed typical anterograde amnesia in the presence of witnesses that resolved within 3 h. Upon examination at the local emergency department (ED), memory was normal, headache had disappeared, and diagnosis at discharge was a TGA. On day 2, she relapsed with two episodes of TCH, and returned to the ED. Non-contrast computed tomography (CT) was normal. A fourth TCH recurred while bending, and a fifth the next morning, during showering. She was admitted to the Lariboisière emergency headache center. Blood pressure was 150/100 mmHg. During examination, she experienced a sixth TCH, followed by a persistent throbbing pain. Cerebral CTA showed distal vasospasms. Magnetic resonance imaging (MRI) showed a tiny right temporal foci of restricted diffusion. Blood tests and CSF analysis were normal. Nimodipine was started and no new TCH occurred. On day 4, transcranial Doppler (TCD) disclosed increased peak systolic velocities on the terminal right internal carotid artery and left anterior cerebral artery (120 cm/s and 145 cm/s, respectively). One month after onset, control TCD showed normalized flow velocities.

One year later, she experienced a second TGA triggered by acute emotional stress (speaking out loud during a ceremony), without any headache. A cerebral MRI was performed, and was normal. There was no other relapse for 6 years thereafter.

### Case 2

A 53-year-old woman, without medical history, presented a first TCH while she and her daughter were victims of a sudden flood in their house. The patient took paracetamol, and did not remember anything afterward. Upon arrival to the ED in Montpellier, she had severe headaches with vomiting, and anterograde amnesia without any other neurological deficit. Blood pressure was 180/90 mmHg. Non-contrast cerebral CT and blood tests were normal. Lumbar puncture was subnormal (white cell count of 20/mm<sup>3</sup>). Headache resolved within 3 h and amnesia within 6 h. She had a second TCH during the evening, and a third on day 3, both lasting a few hours and followed by a moderate persistent headache. On day 3, CTA was normal. MRI showed bilateral small diffusion-restricted hippocampal lesions (Fig. 1a, b) and mild bilateral occipital hypersignals on

fluid-attenuated inversion recovery (FLAIR). On day 5, cerebral MRI showed persistent temporal abnormalities, multiple cortical subarachnoid FLAIR hypersignals, and diffuse cerebral vasoconstriction on MRA (Fig. 1e, f). Nimodipine was started without recurrence of significant headache. On day 11, MRI showed complete resolution of cerebral abnormalities (Fig. 1c, d, g–i). CTA at 3 months showed normalized arteries (Fig. 1j, k).

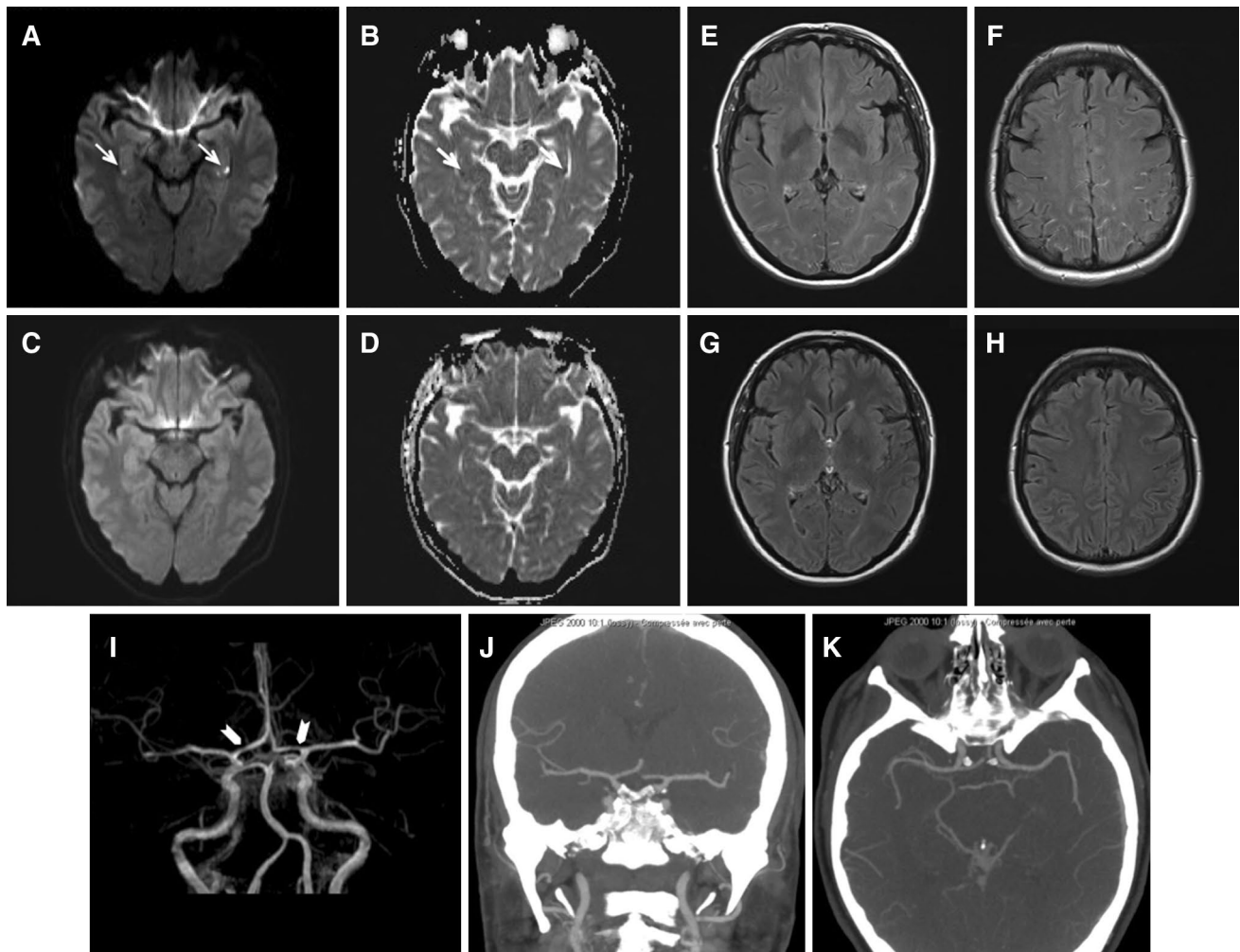
### Case 3

A 64-year-old man had a TCH while showering, just after a sudden contrariety in the setting of physical activity on a warm day. Then, he experienced amnesia for 40 min, during which he remained alone in his bedroom, but dressed up and prepared a bag, without remembering it. His wife witnessed him just after he regained a normal memory. There was no any clue to loss of consciousness. Severe headache lasted all night long, and he presented to the ED in Montpellier the day after. He had history of sleep apnea, dyslipidemia, and used nasal decongestants three times a week. Physical examination and standard biology were normal. Cerebral CT with CTA was normal (Fig. 2d). MRI showed a small right temporal diffusion-restricted lesion (Fig. 2a–c). He was treated with low-dose aspirin and nimodipine. Constant headache with paroxysms persisted for 10 days then decreased gradually to disappear on day 16. CTA on day 16 showed mild stenosis of a branch of the left posterior cerebral artery (Fig. 2e). Cerebral MRI at 1 month was normal. CTA at 3 months showed normal arteries (Fig. 2f). While vasospasm was seen only in one artery, association of severe headache during 10 days and reversible cerebral vasospasm made the diagnosis of RCVS.

Because of clinical and imaging course, the three patients were diagnosed with RCVS and concomitant TGA, associated with a posterior reversible encephalopathy syndrome in case 2.

## Discussion

RCVS and TGA are two acute and reversible neurological conditions, whose exact pathological mechanisms are still unknown. In 2017, a case of TGA accompanying proven RCVS was reported in a 65-year-old man who used reserpine 2 weeks before onset [3]. In 2019, a second case has been described [4]. Herein, we report three more cases of TGA with RCVS, suggesting this association is not fortuitous. While RCVS predominates in females and peaks around 45 years [1], TGA equally affects both genders and peaks between 50 and 70 years [2, 5]. In our series, there were two women and one man, all of them within typical age range of TGA.



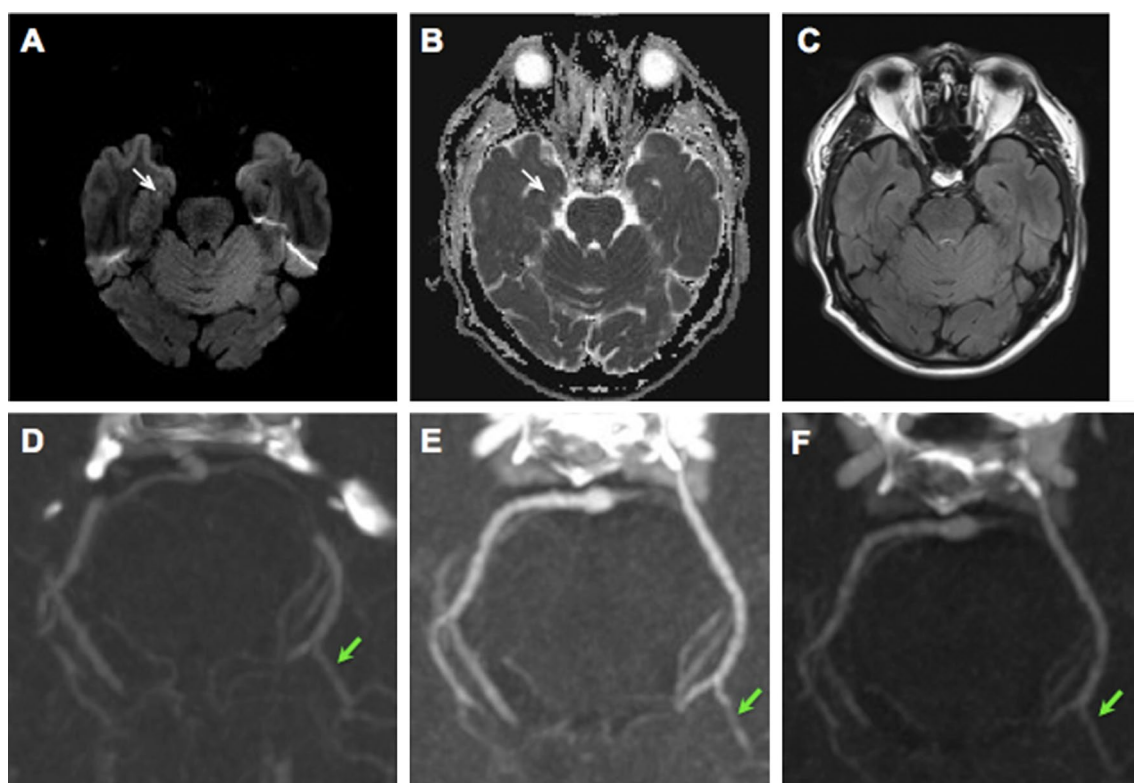
**Fig. 1** Brain MRI (**a**, **b**) at day 5 showed bilateral temporal foci of restricted diffusion and corresponding diminished apparent diffusion coefficient. Temporal abnormalities have normalized on MRI (**c**, **d**) at day 11. Axial FLAIR (**e**, **f**) at day 5 disclosed multiple cortical subarachnoid hypersignals. These multiple cortical subarachnoid hyper-

signals had disappeared on day 11 (**g**, **h**). MR angiography (**i**) at day 5 showed segmental vasoconstriction of proximal anterior and right middle cerebral arteries (arrowheads). Computed tomography angiography (**j**, **k**) at 3 months disclosed normal cerebral arteries

RCVS is attributed to a transient deregulation of cerebral arterial tone [1]. Hypothetic mechanisms of transient hippocampal hypoxia in TGA involve venous congestion, spreading depression or transient ischemia [2, 4, 6]. TGA is associated with transient foci of restricted MRI diffusion of the hippocampal CA1 regions, which are highly vulnerable to hypoxia, in 0 to 84% of the cases [2, 6]. These variables figures may reflect an incomplete sensitivity of MRI for punctate hypersignal foci on diffusion-weighted imaging (DWI), potentially due to differences in timing of MRI acquisition, resolution of DWI sequences, thickness of MRI slices, and mono- versus multiplanar acquisition, as already described in MRI studies of small infarcts or TIA [6].

Headache is the most common symptom associated with TGA (up to 40%) but usually has unspecific features, not consistent with TCH [2]. In our three patients and in the

case reported by Kamm et al. [4], TCH was the presenting manifestation of RCVS, and was accompanied or followed within minutes by TGA. The patient described by Isahaya et al. [3] presented with TGA and concomitant non-TCH headache, then had TCH and neurological deficit a few days later, and was diagnosed with RCVS. In addition, this patient had a history of TGA without headache 15 years before, suggesting TGA can recur with or without RCVS in some patients. Moreover, 50 to 90% of TGA are provoked by various triggers including strenuous physical exertion, emotional stress, sudden immersion in cold or hot water, pain, medical procedures, sexual intercourse, or Valsalva maneuvers [2, 5]. Notably, exactly the same triggers provoke 80% of the TCH in RCVS [1]. High altitude has also been reported as a trigger for both RCVS [7], and high-altitude global amnesia, a condition similar to TGA [8]. In 2016, the



**Fig. 2** Right temporal foci of restricted diffusion (a) and corresponding diminished apparent diffusion coefficient (b), not visible on FLAIR (c), are shown on MRI at day 1. Computed tomography angiography (d) at day 1 showed a normal left posterior cerebral artery

(arrow). Computed tomography angiography (e) at day 16 disclosed vasoconstriction of the P2 segment of the left posterior cerebral artery (arrow). Computed tomography angiography (f) at 3 months showed normalization of the left posterior cerebral artery

striking similarities of triggers of RCVS and TGA have been highlighted, suggesting that emotional and physical stress might cause acute neuronal or vascular dysfunction through sympathetic overactivity [9]. The concomitant occurrence of both conditions further strengthens this hypothesis. All our patients reported that an emotional stress preceded the onset of TGA and RCVS. The excruciating pain of TCH might also have contributed to provoke TGA.

Another condition with similarities to RCVS and TGA is takotsubo stress cardiomyopathy (TKC) [10], which predominates in females aged 65–70 years. Emotional and physical triggers, which predominate in women and men, respectively, provoke more than two-thirds of TKC. One case of RCVS and TKC occurring successively has been reported [11]. Four women with concomitant TGA and TKC have been described [12–15]. Finally, the patient with RCVS and TGA reported by Kamm et al. had a history of TKC 5 years earlier [4].

Cases with TGA concomitant to RCVS or TKC may represent a rare association affecting only a minority of susceptible patients. Conversely, patients affected by a combination of TGA, TKC and/or RCVS may have been underreported, because recognition of thunderclap headache might be

hampered by transient amnesia in the setting of TGA, cerebral angiogram is not systematic in patients presenting with either TGA or TKC, and cardiac investigations are not systematic in patients presenting with either RCVS or TGA.

Common triggers as well as overlapping occurrence of TGA, RCVS and TKC strongly suggest common mechanisms. In some susceptible persons with or without predisposing factors such as vasoactive drug intake, migraine, or anxiety, an acute emotional or physical stress may trigger a wave of sympathetic overactivity leading to an abrupt and sustained arteriolar and microvascular constriction with subsequent ischemic or hypoxic injury leading either to TGA with DWI hypersignals in vulnerable hippocampal tissue, to thunderclap headache and RCVS, when cerebral vasculature is involved, and to TKC when cardiac microarterial vasoconstriction is affected [4, 9, 10, 15].

Given that some patients can develop any combination of RCVS, TGA and TKC simultaneously or in succession, we suggest that clinicians facing patients with TGA should carefully check for the presence of associated thunderclap headache and chest pain to promptly identify associated RCVS and TKC, respectively. Conversely, thunderclap headache associated with anterograde amnesia should bring up



a possible RCVS. Large studies of patients presenting with one of the three conditions with detailed assessment of headache, memory and cardiac symptoms, as well as systematic cerebral angiography, cerebral MRI with DWI sequences, and cardiac echography would be necessary to determine the degree of overlap between them. Further work is needed to elucidate the exact biological mechanisms underlying relationship between these disorders.

**Acknowledgements** We acknowledge all the patients for their agreement to participate in this observational study.

## Compliance with ethical standards

**Conflicts of interest** Nothing to report.

**Ethical standards** All patients agreed to participate to this observational study, which was approved by the local ethics committee.

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