



RCVS and TGA: a common pathophysiology?

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Dear Sirs,

Reversible cerebral vasoconstriction syndrome (RCVS) is a rare and probably underdiagnosed condition of unknown pathophysiology, which presents with acute and severe headaches accompanied by transient multifocal constriction of the small cerebral arteries, which progresses to larger arteries later during the course [1, 2]. Typical trigger factors, such as physical activity or emotional stress, are associated with its manifestation. Interestingly, similar triggers have been reported in the context of transient global amnesia (TGA) and Takotsubo cardiomyopathy [3–5]. Therefore, there may be analogies in the pathophysiology, which have not been deciphered yet [6].

Here, we describe a case with a synchronous manifestation of RCVS and TGA, and a previous history of Takotsubo cardiomyopathy. A 62-year-old woman presented to the emergency department with a first-time holocephalic thunderclap headache (NRS 10/10) accompanied by an antero- and retrograde amnesia lasting for 2 h. She could not recall the transfer to the hospital and repeatedly asked the same questions. Her previous medical history was positive for an episodic migraine without aura, arterial hypertension, asthma, and curatively treated breast cancer. Five years earlier, Takotsubo cardiomyopathy had been diagnosed following the death of a close relative. The initial neurologic examination in the emergency department was unremarkable except for deficits of short-term verbal and figural memory. A cranial MRI detected focal lesions in diffusion-weighted

images (DWI) in both lateral hippocampal CA1 regions, indicative of TGA, and multifocal vasoconstrictions in MR angiography (Fig. 1a, b) [7]. Transcranial cerebral duplex ultrasonography (TCCD) indicated increased flow velocities up to 175 cm/s in both MCAs (Fig. 1c). EEG showed intermittent temporal slowing bilaterally. The RCVS₂ score was 9, suggesting high probability of RCVS [8]. Therapy with nimodipine (4 × 60 mg/day p.o.) was initiated. After 2 days, verbal and figural memory deficits had resolved in neuropsychological testing (CERAD plus test battery), but deficits of spatial orientation and memory persisted (error rates in real space navigation testing: 80%; 4-Mountains-Test: 53%). This cognitive profile was recently reported to be typical for TGA [9]. In the following weeks, three more episodes of thunderclap headaches were reported by the patient, which were induced by Valsalva maneuvers and emotional stress. The latest episode (24 days after RCVS onset) was accompanied by transient homonymous hemianopsia on the left. At this time, TCCD revealed increased flow velocities in both MCAs (270 cm/s right, 240 cm/s left) and both PCAs (102 cm/s). A cranial MRI showed a novel DWI lesion in the right occipital lobe, whereas the previous lesions in the hippocampus had resolved completely on DWI and FLAIR sections (Fig. 1a). MR angiography indicated multifocal vasoconstriction in the right PCA. The dosage of nimodipine was increased to 6 × 60 mg/day p.o. At follow-up 3 months later, the patient reported no further recurrence of thunderclap headaches or focal neurological symptoms. Flow velocities in TCCD had normalized and previous lesions were no longer seen in MRI, thus confirming the initial diagnosis of RCVS.

The combined acute presentation of RCVS and TGA in the light of a history of Takotsubo cardiomyopathy suggests a common pathophysiological background in our patient. To the best of our knowledge, concomitant occurrence of RCVS and TGA was described only once so far [10], while associations of RCVS or TGA with Takotsubo cardiomyopathy seem to be more frequent [3–5, 11]. The following observations may suggest common pathophysiological mechanisms in these disorders: (1) affected patients are of comparable

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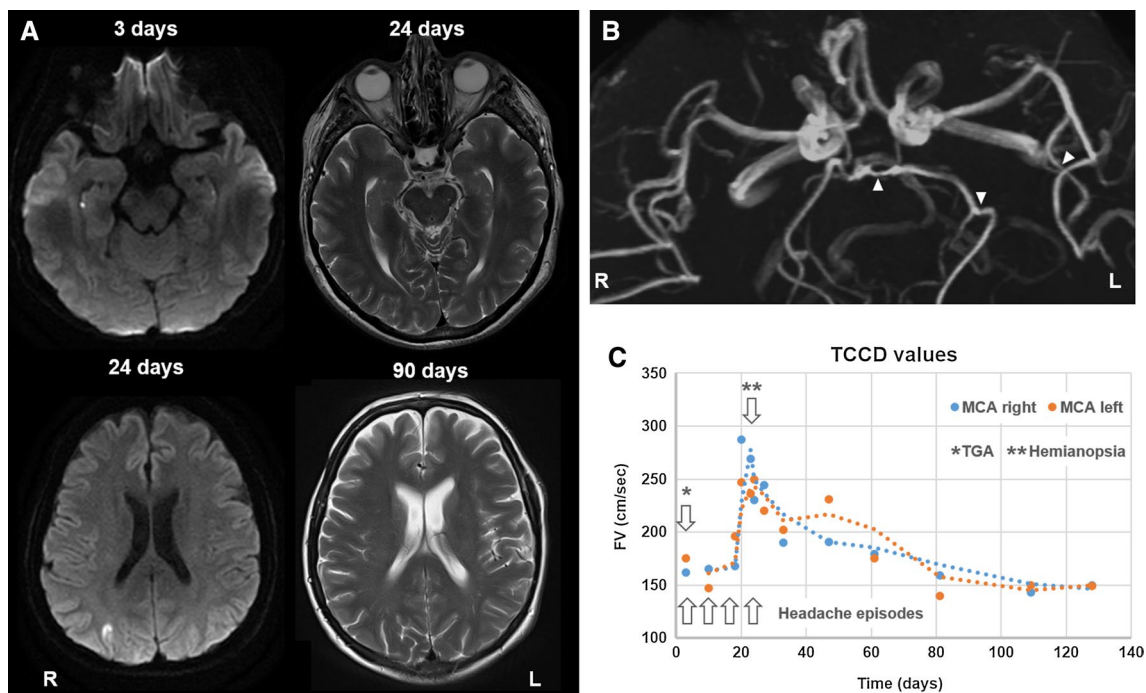


Fig. 1 **a** Serial MRI scans indicate focal DWI lesions in the lateral hippocampus (CA1 region) on both sides 3 days after symptom onset, which were not detectable by day 24 on FLAIR images. At this time, a new right occipital DWI lesion was found with no residuum on FLAIR images after 3 months. **b** MR angiography at day 3 indicated multifocal, short-segment vasoconstrictions (mainly in the left PCA

and MCA). **c** Results of consecutive TCCD measurements showed an increase of flow velocities in both MCAs at symptom onset, a peak at day 21, and a gradual normalization after the following month. *FV* flow velocity, *MCA* middle cerebral artery, *TCCD* transcranial cerebral duplex ultrasonography

age with a female preponderance. (2) Trigger factors preceding the attacks, such as physical or psychological stress, are of similar quality [2–5, 8]. (3) Transient dysregulation of arterial tone due to sympathetic overactivity and excess of stress hormones is assumed in all three disorders [2–6, 12]. (4) In RCVS and TGA, imaging features are similar [1, 7]. The lateral CA1 DWI lesions in TGA show the typical temporal evolution and spatial distribution of vasospasm-induced border zone ischemic lesions [13]. In acute TGA, bilateral hippocampal hypoperfusion is consistently reported and compatible with focal vasoconstriction, but less suggestive for embolic or lacunar stroke [14, 15].

In our patient, we hypothesize that vasoconstriction in RCVS began in distal small vessels supplying the hippocampal formation, thus causing the focal CA1 lesions in the Sommer's sector—a known border zone of arterial blood supply—and leading to the TGA presentation. CA1 neurons have a specific vulnerability to transient ischemia compared to other hippocampal neurons [16]. TCCD revealed only a slight increase of flow velocities in MCA, ACA, and PCA at that time. The propagation of vasoconstriction to more proximal vessel segments led to a small cortical infarct in the PCA territory accompanied by a more pronounced increase of flow velocities in TCCD at follow-up. Given the

chronology of signs and symptoms, it is conceivable that the patient had a susceptibility to triggers leading to cardiac and cerebral vasoconstriction and that the TGA was a presentation of hippocampal RCVS. It should be investigated whether signs of vasoconstriction can be seen in TGA patients without the full clinical picture of RCVS. Perfusion imaging may be more sensitive than TCCD for this purpose, because it can also depict signs of vasoconstriction of more distal arteries. In conclusion, several lines of evidences favor the idea of sympathetic overactivity or overresponsiveness to catecholamines as a common pathophysiological basis of RCVS and TGA.

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Compliance with ethical standards

Conflicts of interest Ms. Kamm reports no disclosures. Dr. Schöberl reports no disclosures. Mr. Grabova reports no disclosures. Prof. Straube reports no disclosures. Dr. Zwergal reports no disclosures.

Ethical approval The Ethics Committee of the Ludwig-Maximilians-University, Munich, approved the standardized testing of spatial orientation and memory. The patient participated after informed written consent.

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