Reversible Cerebral Vasoconstriction Syndrome Treated by Continuous Intravenous Milrinone

Hilaire de Malleray[1] Sebastien Gazzola[2] Eric Meaudre[1] Pierre Esnault[1]

[1] Intensive Care Unit, Sainte Anne Military Teaching Hospital, Toulon, France
[2] Department of Neurology, Sainte Anne Military Teaching Hospital, Toulon, France

Address for correspondence Hilaire de Malleray, MD, Fédération d'Anesthésie, Réanimation, Hôpital d'Instruction des Armées Sainte-Anne, Boulevard Sainte-Anne, BP 20545, 83041 Toulon Cedex 9, France (e-mail: hmalleray@hotmail.fr).

J Neuroanaesthesiol Crit Care 2023;10:69–71.

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headaches, with or without other acute neurological symptoms, and diffuse segmental constriction of cerebral arteries that resolves spontaneously within 3 months.[1] It can occur spontaneously, especially in middle-aged women[1]; at least half the cases occur after exposure to vasoactive drugs or post-partum. This syndrome is often associated with a favorable outcome in 95% of cases.[1] However, the prognosis of RCVS is especially determined by stroke occurrence. Its management is inspired by what is applied in aneurysmal subarachnoid hemorrhage (aSAH), whose main complication is vasospasm and delayed cerebral ischemia (DCI). Although the physiopathology of RCVS is unclear, it appears to be distinct from aSAH. Indeed, the vasoconstriction in RCVS may be dependent on the activity and sensitivity of vascular receptors, which can lead to a more systemic effect on all brain vessels, as opposed to being dependent on the vasospasm induced by local clot lysis, as has been suggested in aSAH.[2] As cerebral arteries are densely innervated, the release of norepinephrine or neuropeptide Y from the sympathetic nerve endings may cause vasoconstrictions.[3] Angiographically, SAH-induced vasospasm is more commonly long-segmental and mainly around the bleeding focus, compared with the multiple, short-segmental, and diffuse changes seen in RCVS.[4] However, by analogy, RCVS is treated by nimodipine, and in some rare cases, the use of milrinone might be considered.[3]

Milrinone is a phosphodiesterase III inhibitor leading to smooth muscle relaxation in both arterial and venous vasculatures. Intra-arterial and intravenous administration of milrinone has been evaluated for the treatment of DCI and appears safe and associated with improved clinical outcomes.[5] The role of intravenous milrinone in reversing arterial vasospasm refractory to oral nimodipine is highlighted in the literature.[6] However, whatever its route, mode, and duration of administration, milrinone has been insufficiently assessed. Therefore, no specific recommendation exists.

A 54-year-old woman with no past medical history except for smoking and cannabis use began suffering from sustained and unusual headaches. They lasted about 20 minutes and recured twice daily. At first examination, the patient had no focal neurological deficit with a Glasgow coma score (GCS) of 15. A computed tomography angiography was performed and demonstrated a reduction in the caliber of both middle cerebral arteries and both posterior cerebral arteries without repercussion on the parenchyma. The patient was admitted to the neurology department for suspicion of either vasculitis or reversible vasoconstriction syndrome. Vessel wall-magnetic resonance imaging (MRI) after gadolinium injection demonstrates absent arterial enhancement (►**Fig. 1E**) ruling out the differential diagnosis of vasculitis. Antiplatelet therapy (75 mg of aspirin-based drug Kardegic) was initiated.

A digital subtraction angiography (DSA) performed 4 days from the beginning of the symptoms demonstrated diffuse irregularity with multifocal narrowings throughout the cerebral vasculature with a beaded appearance, most pronounced in bilateral distal middle cerebral arteries, bilateral proximal posterior cerebral arteries, right proximal superior cerebellar artery, and right proximal posterior inferior cerebellar artery (►**Fig. 1A**). RCVS was diagnosed as DSA is the gold standard. The patient received nimodipine, 60mg orally every 4 hours.

At 10 days from the onset of symptoms, the patient was still experiencing repeated headaches two to three times a day for approximately 20 minutes. Despite treatment, she experienced for the first-time weakness of the right lower limb, bilateral apraxia, ataxia and central right facial paralysis. Time-of-flight MR angiography showed multiple narrowing of both middle cerebral arteries and both posterior cerebral arteries (►**Fig. 1B**). As such, the patient was

article published online
April 24, 2023

DOI https://doi.org/10.1055/s-0043-1761248.
ISSN 2348-0548.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

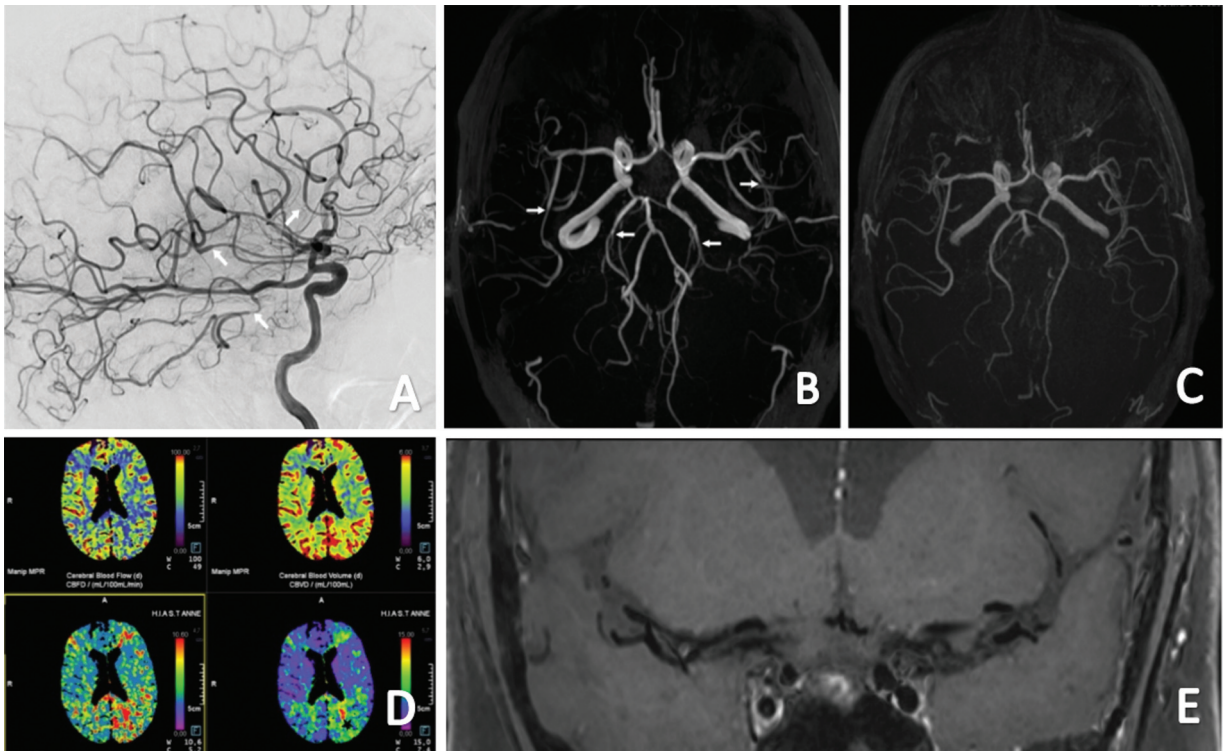

Fig. 1 (**A**) Cerebral digital subtraction angiography: diffuse, multifocal, segmental narrowing of large/medium-sized arteries with dilated segments that appear like string of beads or sausage strings (arrows). (**B**) Time of flight (TOF) magnetic resonance (MR) angiography: Initial TOF shows multiple narrowing (arrows) of both middle cerebral arteries and posterior cerebral arteries. (**C**) Resolution of abnormalities at 3 months. (**D**) Computed tomography perfusion: Axial CBF (cerebral blood flow), CBV (cerebral blood volume), MTT (mean transit time), and TTD (time to drain) parametric maps show MTT and TTD prolongation with CBF decrease and normal CBV in the parieto-occipital lobe. (**E**) Coronal three-dimensional vessel wall-MRI after contrast injection: no vessel wall enhancement.

transferred to intensive care unit (ICU) to receive a continuous intravenous infusion of milrinone (1µg/kg/min) with no bolus via central access with continuous monitoring of blood pressure. A mean arterial pressure of 90 mm Hg was targeted via dose adjustments of noradrenaline. The clinical response was immediate. A weaning attempt was undertaken at day 2 with a decrease to 0.75µg/kg/min but with immediate reappearance of headache. Computed tomography perfusion, which was performed on day 15 of the beginning of symptoms (day 5 of milrinone administration), showed delayed cerebral perfusion in the left parieto-occipital territories. (►**Fig. 1D**). Milrinone was progressively weaned with success from day 5 within 30 hours. At ICU discharge (day 7), the GCS score was still 15 with no residual deficit and without headache.

Through this case, we wish to point out the utility of milrinone in severe RCVS complicated by DCI. The use of this treatment in ICU is based on experience gained in the management of DCI following aSAH. This report is among the few on nonobstetric patients where milrinone could help treat severe RCVS and potentially prevent the occurrence of DCI. Continuous administration of milrinone seems to be safe. The main adverse effects (hypotension, rhythm disorders, hyponatremia) have not been observed despite a relatively high dose from 0.5 to 2µg/kg/min.[5] An intra-arterial injection during DSA could help differentiate RCVS from vasculitis and thus allow the choice of appropriate etiological treatment.[7]

To avoid drawing definitive conclusions about this case, we remind that RCVS resolves itself spontaneously within 12 weeks with substantial or complete normalization of arteries (►**Fig. 1C**). Therefore, it is possible that the clinical improvement is not totally due to the use of milrinone.

In summary, RCVS, in most cases, is benign. By analogy to the treatment of the vasospasm due to aSAH, milrinone, by its inodilatory properties, seems to be an attractive therapeutic option to consider in a severe form of RCVS.

Conflict of Interest
None declared.

References

1 Ducros A. Reversible cerebral vasoconstriction syndrome. Lancet Neurol 2012;11(10):906–917
2 Muehlschlegel S, Kursun O, Topcuoglu MA, Fok J, Singhal AB. Differentiating reversible cerebral vasoconstriction syndrome with subarachnoid hemorrhage from other causes of subarachnoid hemorrhage. JAMA Neurol 2013;70(10):1254–1260

3 Chen SP, Wang SJ. Pathophysiology of reversible cerebral vasoconstriction syndrome. J Biomed Sci 2022;29(01):72
4 Tan LH, Flower O. Reversible cerebral vasoconstriction syndrome: an important cause of acute severe headache. Emerg Med Int 2012;2012:303152
5 Bernier TD, Schontz MJ, Izzy S, et al. Treatment of subarachnoid hemorrhage-associated delayed cerebral ischemia with milrinone: a review and proposal. J Neurosurg Anesthesiol 2021;33(03):195–202
6 Hawkes MA, Hlavnicka AA, Wainsztein NA. Reversible cerebral vasoconstriction syndrome responsive to intravenous milrinone. Neurocrit Care 2020;32(01):348–352
7 Lakhal K, Rodie-Talbere PA, Alexandre PL, Testard N, Rozec B, Daumas-Duport B. Continuous intravenous milrinone for severe reversible cerebral vasoconstriction syndrome (a case report). J Neurol Sci 2019;397:55–57