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Letter to the Editor

Continuous intravenous milrinone for severe reversible cerebral vasoconstriction syndrome (a case report)

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Dear Editor,

Reversible cerebral vasoconstriction syndrome (RCVS) is a segmental constriction of cerebral arteries which exposes the patient to cerebral ischaemia and haemorrhage. Its pathophysiology is unknown. Disequilibrium in the regulation of the cerebral arterial tone (sympathetic overactivity) seems to be involved [1]. The postpartum period is a frequent contributor to severe RCVS [1]. Since there is no proven treatment, one may consider milrinone, a vasodilator occasionally used for vasospasm treatment after aneurysmal subarachnoid haemorrhage (ASAH) [2]. Since the pathophysiology of RCVS may differ, the vasodilatory effects of milrinone during RCVS are uncertain. We herein report a case of severe postpartum RCVS, treated with the combination of intravenous calcium channel-blocker nimodipine and a prolonged infusion of intravenous milrinone, a phosphodiesterase III isoenzyme inhibitor. Written patient consent was obtained for this publication. This case report fulfils the CARE checklist (http://www.care-statement.org/) except for the timeline figure, deemed not necessary herein.

The medical history of this 23-years-old woman was unremarkable, including two previous uncomplicated childbirths. Gestational diabetes developed during the third pregnancy. The third childbirth was initially uncomplicated (vaginal delivery, epidural anaesthesia, no inhibition of lactation). On postpartum day 6, a headache heralded the gradual occurrence of other signs: right hemiplegia and hemianesthesia, aphasia, homonymous hemianopsia, mild consciousness impairment and arterial hypertension (220/95 mmHg). National Institutes of Health Stroke Scale (NIHSS) score was 23 and the Glasgow score was 9. MRI and computed tomography (CT) angiography displayed a subarachnoid and intracerebral haemorrhage (left frontoparietal haematoma of 57 × 57 × 35 mm causing mild cerebral herniation, Fig. 1a), a diffuse but irregular narrowing of the left middle cerebral artery (MCA) and to a lesser extent, of the contralateral MCA (Fig. 2). There was no sign of arterial aneurysm, arteriovenous malformation, venous thrombosis, or posterior reversible encephalopathy syndrome. There was no biological sign of thrombotic microangiopathy. A toxicological screening did not reveal any toxic cause to the disorder. There was no echographic evidence of pelvic complication of the delivery. The diagnosis of RCVS was retained. Owing to its risks and to uncertainty about its diagnostic added value in our patient, no digital subtraction angiogram was performed. After urgent surgical evacuation of the haematoma, sedation was pursued in the intensive care unit (ICU). An intravenous infusion of nimodipine (10 mg per hour) was initiated. Even if arterial hypertension (spontaneous or pharmacologically induced) is desirable in vasospasm after ASAH [3], we preferred targeting intermediate levels of arterial pressure. Indeed, owing to the risks of rebleeding or worsening of cerebral edema, a mean arterial pressure of 85–100 mmHg was targeted *via* dose adjustments of urapidil. On day 2, CT-scan confirmed the postoperative decrease in the haematoma volume and revealed that the surrounding cerebral oedema has expanded (Fig. 1b). The CT-angiography displayed a worsening of the vasoconstriction of the right MCA, of the anterior and posterior cerebral arteries, while vasoconstriction of the left MCA territory remained stable (Fig. 2). Owing to the multifocal nature of the vasoconstriction, a systemic (intravenous) rather than *in situ* (intra-arterial) vasodilator treatment has been administered. A continuous intravenous infusion of milrinone was initiated (1 μg/kg/min with no bolus, as previously reported [4]) and was well tolerated: according to our beat-to-beat monitoring, there was neither arrhythmia (except an expected sinus tachycardia [4]) nor arterial hypotension despite the concomitant administration of nimodipine and urapidil. The CT-angiography showed a progressive resolution of the vasoconstriction on day 4 and on day 8 (Fig. 2). Sedation was stopped, allowing the tracheal extubation on day 3. Milrinone was tapered from day 7 and then stopped (total duration of 8 days). Nimodipine (intravenous then enteral) was withdrawn five weeks later. Most of the neurologic symptoms resolved within the first week. At ICU discharge (day 9), the NIHSS and the Glasgow scores were 3 and 15, respectively. Recovery of the haematoma-induced hemiplegia was observed within the subsequent weeks with no recurrence of RCVS.

In this case of severe postpartum RCVS, which worsened despite nimodipine administration, a prolonged intravenous infusion of

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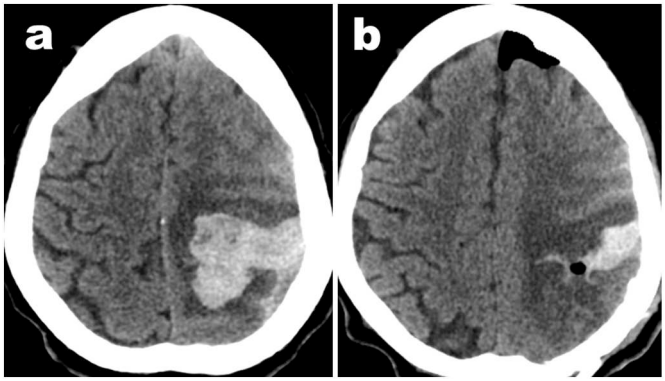

Fig. 1. Axial CT images before (a) and the day after (b) the surgical evacuation of a haematoma in the left frontoparietal area.

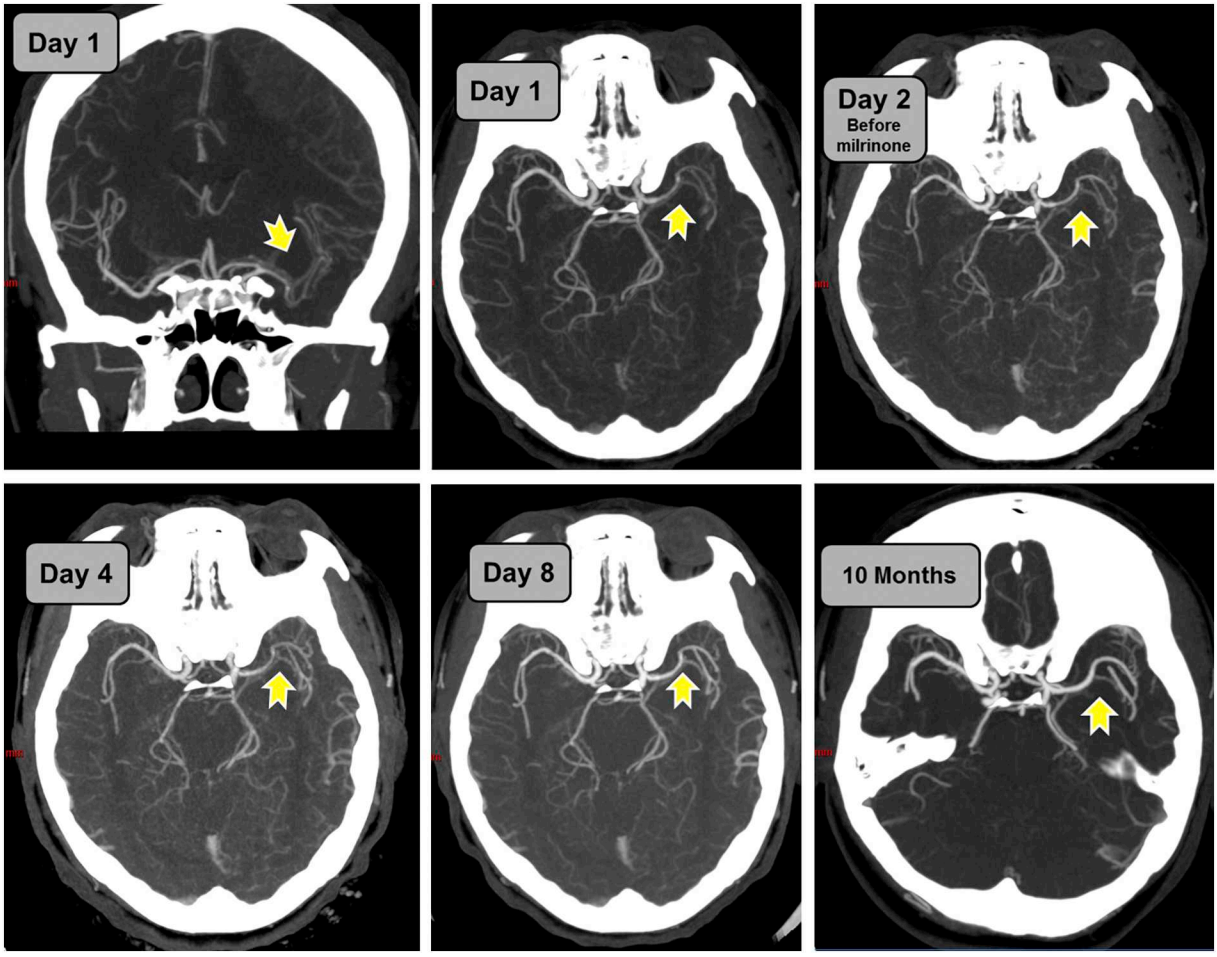

Fig. 2. Coronal and transverse CT images at day 1 (hospital admission) displaying diffuse vasospasm (with segmental narrowing) of the left middle cerebral artery (MCA) and its branches. Intravenous nimodipine was initiated. At day 2, the vasospasm of the left MCA remained stable but a vasospasm of the right MCA occurred. Milrinone has been administered. Subsequently, the vasospasm aspect gradually vanished (CT images at day 4, 8 and 10 months after).

milrinone was well tolerated and was associated with both angiographic and clinical improvements.

Milrinone is a phosphodiesterase III isoenzyme inhibitor therefore increasing cytosolic cAMP in vascular smooth muscle cells and cardiomyocytes. Besides its well-known inotropic effects used for heart failure treatment, its vasodilatory effects may reverse a life-threatening narrowing of cerebral vessels. In ASAH-related vasospasm, milrinone is increasingly used for this purpose [2] and encouraging efficacy has been reported [5]. Milrinone is then administered *in situ* into the internal carotid artery, *i.e.*, upstream the constricted arteries. Such intra-arterial invasive procedure is sometimes followed by a continuous intravenous infusion of milrinone in order to sustain its vasodilatory effects [4–6]. However, whatever its route of administration, milrinone has been insufficiently assessed [5] and is therefore only barely [3] or not mentioned at all [7] in latest international guidelines. In 2011 guidelines for ASAH management, it was stated that, along with induced arterial hypertension, endovascular treatment using intra-arterial vasodilators –including milrinone or calcium-channel blockers- and/or balloon angioplasty may be considered for refractory vasospasm [3]. The intravenous route for milrinone was not mentioned in these

guidelines.

Since the pathophysiology of RCVS remains unknown, the effects of milrinone during RCVS may differ from that of milrinone during vasospasm after ASAH. Milrinone therefore deserves to be specifically assessed during RCVS but its use in this setting is even more anecdotal than in ASAH-related vasospasm and no specific recommendation exists. The *in situ* administration of a *single dose* of milrinone and/or calcium-channel blockers (nicardipine or nimodipine, for instance) was very occasionally used as a treatment for RCVS [8] but was also proposed as a diagnostic test: vasodilation after milrinone or calcium-channel blocker intra-arterial infusion suggests RCVS rather than other intracranial stenotic diseases [9,10]. In one patient, Bouchard et al. reported a favourable outcome after the intra-arterial injection of milrinone followed by a short intravenous infusion of low dose of milrinone (0.5 μg/kg/min for 6 h and then weaned slowly over 13 h) [11]. In our patient, RCVS was severe, initially treated with intravenous nimodipine (which use is deemed reasonable despite a lack of evidence of its benefit in RCVS [12]), but its improvement was coincident with the administration of milrinone. Therefore, owing to its short duration of action (terminal elimination half-life of approximately 2 h [13]), we prolonged the infusion of milrinone to guarantee a sustained vasodilatory effect over 8 days. Milrinone exposes the patient to arrhythmia and hypotension [4,6]. In our patient, milrinone was remarkably well tolerated, despite a relatively high dose (1 μg/kg/min) over 8 days. Furthermore, the intravenous route prevented the invasive intra-arterial route-related complications: arterial access-related complications, ischaemic stroke, intracranial haemorrhage, contrast medium-related side effects, *e.g.* [14].

To prevent drawing any definitive conclusion on the basis of this case report, it is important to underscore that RCVS is a transient disorder, usually resolving spontaneously within 3 months [1]. Hence, we are unable to firmly state that the positive outcome we observed was undoubtedly related to milrinone use.

In summary, milrinone in RCVS deserves specific evaluation, but it may be a ready option to consider in refractory life-threatening vasoconstriction.

Competing interests

Karim Lakhal has no conflict of interest in connection with the work submitted. In addition, KL received, during the past 3 years, lecture fees from MEDTRONIC (once, in 2017), congress registration fees from SANOFI AVENTIS (once in 2018), travel fees from MSD France (once, in 2017), NOVEX PHARMA (once, in 2016) and GILEAD SCIENCES (twice, 2016 and 2017).

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The other authors declare that they have no competing interests.

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Ethical considerations

The written patient consent is attached.

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