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BRIEF REPORT

Possible overlap between reversible cerebral vasoconstriction syndrome and symptomatic vasospasm after aneurysmal subarachnoid hemorrhage

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Abstract A 34-year-old woman with a previous history of severe headache ("thunderclap") was admitted with a diagnosis of aneurysmal subarachnoid hemorrhage (SAH). The patient developed symptomatic vasospasm on day 5 that resolved rapidly after having increased arterial blood pressure. She experienced also short-lasting excruciating headache. On day 12, while velocities had normalised, as revealed by transcranial Doppler (TCD), for more than 48 h, she developed aphasia and right hemiplegia associated with diffuse segmental vasospasm on the left middle cerebral artery. Intra-arterial infusion of vasodilatory agents was required. Recurrence of symptomatic vasospasm was noted on day 25, with a great number of territories involved as shown in the cerebral angiogram. A second intra-arterial treatment was needed. The patient complained of multiple episodes of extremely severe headache ("thunderclap"), with also transient dysarthria and hemiparesia on day 30. She was discharged on day 38 after full recovery. The clinical and TCD/radiological findings were consistent with a reversible cerebral vasoconstriction syndrome overlapping SAH related symptomatic vasospasm.

Keywords Reversible cerebral vasoconstriction syndrome · Aneurysmal subarachnoid hemorrhage · Vasospasm

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Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is a rare vasculopathy of unknown etiology [1, 2]. It was mainly reported in young women with a history of severe "thunderclap" headache. The clinical picture may mimic subarachnoid hemorrhage (SAH). In addition, unruptured aneurysms have been reported in some patients with RCVS, but not clear causal relationship has been documented [3–5]. We describe a case of aneurysmal SAH for which the differential diagnosis has to be discussed between RCVS and symptomatic vasospasm.

Case report

A 34-year-old woman developed acute-onset occipital headache with loss of consciousness. She had a history of episodic severe headache treated by nonsteroidal anti-inflammatory drugs. There was no clear precipitating factor. The headache was described as generalised and bilateral. The pain was excruciating and lasted usually less than 1 h, being sometimes accompanied by nausea and vomiting.

On arrival, she had a GCS of 15, and also with a mild hypo-esthesia in the left arm. The brain CT confirmed the

diagnosis of SAH (Fisher 3 radiological score), with a focal hematoma in the territory of the left anterior cerebral artery (ACA), blood in the subarachnoid spaces of the left sylvian fissure and into the occipital horn of the left lateral ventricle. The cerebral angiography revealed four distinct aneurysms. The ruptured aneurysm (8 mm × 9 mm) was located on the junction of the A1–A2 segments of the left ACA. The three unruptured aneurysms were on the A1 segment of the left ACA (1.5 mm diameter), on the A2 segment (3 mm × 2 mm) and at the origin of the posterior communicating artery. The clipping of the four aneurysms was performed without peri-operative complications and after extubation the patient presented only neck stiffness and photophobia. She received oral nimodipine and continuous infusion of magnesium sulphate. On day 5 from bleeding, she was found drowsy, with a slurry speech, and a vasospasm on the left middle cerebral artery (MCA) was suspected on transcranial Doppler (TCD). Systolic arterial pressure was increased to 150 mmHg by norepinephrine infusion followed by rapid neurological improvement. She complained on days 9 and 10 of acute-onset but short-lasting excruciating headache. Norepinephrine infusion was tapered down and stopped on day 12. Velocities normalised on TCD performed on days 7 and 10. She was discharged from ICU on day 12 with a normal neurological examination but was readmitted the same night with right hemiplegia and aphasia. The diffusion-weighted imaging (DWI) during brain MR showed a limited hyperintense lesion in the left cingulum. As the symptoms persisted after 12 h of intensive treatment, rescue therapy with intra-arterial vasodilatory agents was considered. Nimodipine (3 mg over 20 min) was infused in loco (left MCA) during cerebral angiography, followed by intravenous continuous infusion of milrinone (0.75 μg/kg per min). There was a prompt recovery of aphasia and a regression of the motor deficit in the upper right limb. The patient was able to move the right lower limb on day 16. Milrinone infusion was continued for a period of 11 days, and during this treatment, norepinephrine infusion had to be increased to 2 μg/kg per min to obtain an arterial systolic blood pressure of 150 mmHg. The evolution of the clinical course and of the TCD/radiological investigations is summarised in Table 1. On day 25, the patient became drowsy and complained again from severe headache. Bilateral vasospasm was demonstrated by TCD and angiography (Fig. 1a, b). Intra-arterial infusion of milrinone (15 mg over 60 min, divided in two doses in both MCA) was performed, and intravenous infusion was started again as in the previous episode, for a total of 5 days (together with high doses of norepinephrine). Symptoms regressed, except for headache (multiple episodes every day). Finally, on day 30, dysarthria and right hemiparesia were transiently noted. Magnesium sulphate infusion and norepinephrine (as a part of the triple H therapy) were stopped on day 32. The patient was discharged from the ICU on day 38 after a normal neurological examination but with persisting high velocities at TCD examination of the right MCA. The velocities normalised completely only on day 43. The patient made a complete recovery (including headache) at 3 months follow-up.

Discussion

The idiopathic RCVS is a disease with cerebral vasoconstriction that is usually documented by CT or MR angiography. The syndrome should be differentiated from other identified causes of arterial narrowing including CNS vasculitis, pheochromocytoma or the use of vasoactive substances like cocaine [1, 2]. In some patients, the presence of an associated intracranial abnormality can be demonstrated, as in our patient who had a ruptured aneurysm leading to SAH.

Obviously, vasospasm, symptomatic or not, is a common complication following aneurysmal SAH. The presence of blood close to the site of the aneurysm locally triggers the vasospasm. The maximal duration of vasospasm, when installed, is usually 4 weeks. However, a delayed recurrence of symptomatic vasospasm is infrequent. Also the clinical symptoms and the TCD and radiological findings were unusual. Recurrent excruciating headache ("thunderclap") was the main clinical feature. It lasted for approximately one hour and was poorly influenced by major analgesics. It occurred several times during the same journey and seemed to be partly correlated with increased velocities on TCD examination. Cerebral angiography demonstrated migrating segmental vasoconstriction in different cerebral arteries.

We suspected that cerebral vasoconstriction could be triggered by two different mechanisms and postulated that the patient presented an overlap between RCVS and SAH-related vasospasm.

It has been suggested that some factors known to be involved in SAH-related vasospasm (catecholamines, endothelin-1, serotonin, nitric oxide, and prostaglandins) could play a similar role in the pathophysiology of vasoconstriction in RCVS [1, 2].

SAH without intracranial aneurysm is not infrequently encountered in RCVS, perhaps in up to one in four cases, and typically overlies the lateral-superior cortical surface [3–6]. In RCVS, SAH is usually minimal or moderate in amount and should not be considered the cause of the segmental vasoconstriction, which affects artery remote to the site of bleeding. An association between RCVS and unruptured intracranial aneurysm has also be reported [5].

By definition, RCVS usually shows diffuse areas of multiple stenosis and dilatation involving intracranial

Table 1 Clinical course, TCD and radiological findings, and therapy

Day from bleeding	TCD Mean velocity (cm/s) (left MCA/right MCA)	Symptoms	Brain CT or MR angiography Vasospasm	Treatment
D1		Headache, loss of consciousness		Nimodipine
D2		(Clipping)		Nimodipine, $MgSO_4$
D3				Nimodipine, $MgSO_4$
D4	130/111	Headache		Nimodipine, $MgSO_4$
D5	154/123	Headache	Left MCA(P)	Nimodipine, $MgSO_4$, THT
D6	160/135			Nimodipine, $MgSO_4$, THT
D7	105/88			Nimodipine, $MgSO_4$, THT
D8				Nimodipine, $MgSO_4$, THT
D9				Nimodipine, $MgSO_4$, THT
D10	95/88			Nimodipine, $MgSO_4$, THT
D11				Nimodipine, $MgSO_4$
D12				Nimodipine, $MgSO_4$
D13	174/109	Aphasia, right hemiplegia	Left ACA(C), diffuse D on left M1 and right M1–M2	Nimodipine, $MgSO_4$, THT-IA nimodipine, IV milrinone
D14	99/62	Right leg plegia		Nimodipine, $MgSO_4$, THT, milrinone
D15	92/63	Motor recovery		Nimodipine, $MgSO_4$, THT, milrinone
D16				Nimodipine, $MgSO_4$, THT, milrinone
D17	105/60			Nimodipine, $MgSO_4$, THT, milrinone
D18	140/60	Headache		Nimodipine, $MgSO_4$, THT, milrinone
D19	145/88	Headache		Nimodipine, $MgSO_4$, THT, milrinone
D20	121/80			Nimodipine, $MgSO_4$, THT, milrinone
D21	122/62			Nimodipine, $MgSO_4$, THT, milrinone
D22				Nimodipine, $MgSO_4$, THT, milrinone
D23				Nimodipine, $MgSO_4$, THT, milrinone
D24	89/71			Nimodipine, $MgSO_4$, THT
D25	150/220	Confusion, agitation, headache +++	See Fig. 1	Nimodipine, $MgSO_4$, THT-IA + IV milrinone
D26	109/165	Headache		Nimodipine, $MgSO_4$, THT, milrinone
D27	96/100	Headache		Nimodipine, $MgSO_4$, THT, milrinone
D28	78/130	Headache		Nimodipine, $MgSO_4$, THT, milrinone
D29				Nimodipine, $MgSO_4$, THT, milrinone
D30		Transient dysarthria and right hemiparesia	RP1, focal BT, segmental left M1, right M1	Nimodipine, $MgSO_4$, THT
D31	96/166			Nimodipine, $MgSO_4$, THT
D32	83/152			Nimodipine, $MgSO_4$, THT
D33				Nimodipine
D34	94/171			Nimodipine
D35				Nimodipine
D36				Nimodipine
D37				Nimodipine
D38	87/145	Full recovery		Nimodipine

TCD transcranial Doppler, *left ACA* left anterior cerebral artery, *left MCA* left middle cerebral artery, *right MCA* right middle cerebral artery, *LM1* segment M1 of left MCA, *RM1–2* segments 1–2 of right MCA, *RP1* segment P1 of the right posterior cerebral artery, *BT* basilar trunk, *P* proximal, *C* complete, *D* distal, *THT* triple-H therapy, *IA* intra-arterial (in loco), *IV* intravenous

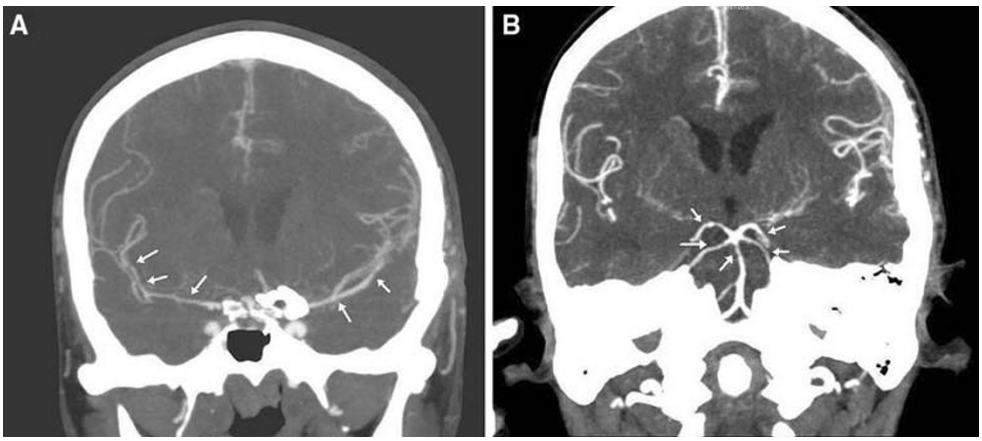

Fig. 1 Angio-CT, three-dimensional reconstruction, coronal view. **a** Diffuse segmental stenosis of the proximal and distal (*arrows*) right middle cerebral artery. Segmental stenosis of the distal (*arrows*) left middle cerebral artery. **b** Diffuse narrowing (*arrows*) of the distal basilar trunk, of both posterior cerebral arteries, and of both superior and anterior cerebellar arteries

arteries [1, 2, 6]. These abnormalities are reversible within days to weeks. In SAH, vasospasm typically is not multifocal, affects one or two medium arteries, and peaks between days 4 and 11.

The pharmacological treatment of SAH-related vasospasm relies on the so-called "triple-H therapy" (hypertension, hypervolemia, hemodilution), where hypertension induced by norepinephrine may play a major role. It can not be excluded that vasoactive substances like norepinephrine may aggravate RCVS [6]. The place of "rescue" therapy with intra-arterial vasodilatory agents is not yet defined [7].

Conflict of interest None.

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