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Rapid change of estrogen levels induce reversible cerebral vasoconstriction syndrome and cerebral venous sinus thrombosis: A report of two cases

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Abstract

Reversible cerebral vasoconstriction syndrome (RCVS) presents with characteristic clinical, brain imaging, and angiographic findings. The most common clinical feature of RCVS is a severe acute headache, which is often referred to as a thunderclap headache owing to the nature of its presentation. It may occur spontaneously or may be provoked by various precipitating factors. We present two cases of RCVS concomitant with cerebral venous sinus thrombosis (CVST). Patient 1 was a 42-year-old woman admitted to our hospital with severe headache radiating to the neck, with associated vomitting. She had a history of ovarian cancer and underwent an operation for resection of the tumor a month prior to presentation. After resection, her estradiol (E2) levels were reduced from 288 pg/ml to 31 pg/ml (normal range, 0-49 pg/ml). Initial imaging upon admission to our hospital revealed left posterior convexity subarachnoid hemorrhage. Magnetic resonance angiography (MRA) showed findings consistent with RCVS affecting the left posterior cerebral artery. Magnetic resonance venography (MRV) showed CVST of the left transverse and sigmoid sinuses. Single photon emission computed tomography (SPECT) showed a left posterior ischemic lesion. These findings improved following treatment with nimodipine and anticoagulant. Patient 2 was a 39-year-old woman presented with holocranial headache associated with vomiting. She was diagnosed with an ovarian tumor. She underwent an operation three months prior to presentation. After tumor resection, her E2 level decrease from 193 pg/ml to 19 pg/ml (normal range, 0-49 pg/ml). MRA confirmed the presence of a vasospasm involving the right anterior cerebral artery. MRV confirmed the presence of thrombosis involving the superior sagittal sinus. She was discharged on postpartum day 31 without neurological deficits after treatment with anticoagulants. At 3 month follow-up, both MRA and MRV were within the normal limits. In conclusion, this is the first report of two women diagnosed with RCVS with concomitant CVST following ovarian tumor resection. The rapid change of perioperative E2 levels may have contributed to the development of CVST and RCVS.

Keywords: Reversible cerebral vasoconstriction syndrome (RCVS), cerebral venous sinus thrombosis (CVST), ovarian tumor; single photon emission computed tomography (SPECT), edoxaban

INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS) is a unifying term used to describe a group of disorders sharing angiographic and clinical features, such as reversible segmental and multifocal vasoconstriction of cerebral arteries and severe headaches with or without focal neurological deficits or seizures.[1] Patients presenting with these features were previously described using diverse terminology. The most common clinical feature of RCVS is a severe acute headache, which is often referred to as a thunderclap headache owing to the nature of its presentation.[2] RCVS has been reported in association with ischemic stroke and convexity subarachnoid hemorrhage (SAH)[3]; however, few reports have described RCVS concomitant with cerebral venous sinus thrombosis (CVST). This is the first case report that describes RCVS concomitant with CVST in a woman who underwent ovarian tumor resection and was followed-up with single photon emission computed tomography (SPECT) and 3.0 T magnetic resonance imaging (MRI).

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CASE REPORTS

Patient 1

A 42-year-old woman presented with a 3-week history of headache showing recent progression, as well as disorientation and reduced level of consciousness. She revealed a medical history of ovarian tumor resection (Figure 1A,B,C). After resection, her estradiol (E2) level decreased from 288 pg/ml to 31 pg/ml (normal range, 0-49 pg/ml). Neurological examination revealed bilateral papilledema without focal neurological deficit. MRI (FLAIR and T2* images) revealed left occipital cortical SAH and dural venous sinus thrombosis involving the left transverse and sigmoid sinuses (Figure 2A). MR angiography (MRA) revealed high-grade left posterior cerebral artery (PCA) stenosis (Figure 2B). Notably N-isopropyl-p-[123I]iodoamphetamine (IMP)-SPECT imaging performed on day 2 revealed left posterior ischemic lesions (Figure 2C); however, these ischemic lesions disappeared on day 28 (Figure 2D). The IMP-SPECT findings were correlated with vasoconstriction on cerebral angiography and MRA. Routine laboratory investigations revealed anemia (serum hemoglobin level 8.8 g/dL) without any other abnormality. All blood tests for thrombophilic conditions showed negative or normal results, including tests for antinuclear antibodies, anti-DNA antibodies, antiphospholipid antibodies, C protein, S protein, and antithrombin-3. Moreover, genetic screening for mutation G1691A in the gene for Factor V, mutation G20210A in the gene for Factor II, mutation V617F in *JAK2,* and mutation in the *MTHFR* gene revealed no abnormalities. Cerebrospinal fluid (CSF) analysis revealed minor abnormalities including a marginally increased white blood cell count and mildly elevated protein levels. Therapy was initiated with nimodipine, magnesium sulfate, simvastatin, and unfractionated heparin (activated partial thromboplastin time: 2-2.5 times of the normal level.).

Over the following 2 weeks, gradual improvement in the stenosis was observed on repeat ultrasonography and MRA (Figure 2E). Edoxaban was initiated, and following tapering of nimodipine, she was discharged on day 28 without neurological deficits. Her MRV revealed no abnormalities a month later (Figure 2F).

Patient 2

A 39-year-old female with a recent history of ovarian tumor resection developed holocranial headache associated with vomiting. After tumor resection, her E2 level decreased from 193 pg/ml to 19 pg/ml (normal range, 0-49 pg/ml). Neurological examination revealed no focal neurologic deficits. The next day she experienced repeat onset of severe headache, followed by right-lower limb paresis. Upon presentation to our department, she underwent a clinical examination which revealed all vital signs to be within the normal ranges. Magnetic resonance angiography (MRA) confirmed the presence of a vasospasm involving the right anterior cerebral artery (Figure 3A). Magnetic resonance venography (MRV) confirmed the presence of a thrombosis involving the superior sagittal sinus (Figure 3B). All blood tests for thrombophilic conditions were negative or normal. We subsequently initiated anticoagulation with low molecular weight heparin (enoxaparin) and nimodipine. Her subsequent clinical course was uneventful with slow recovery of right limb

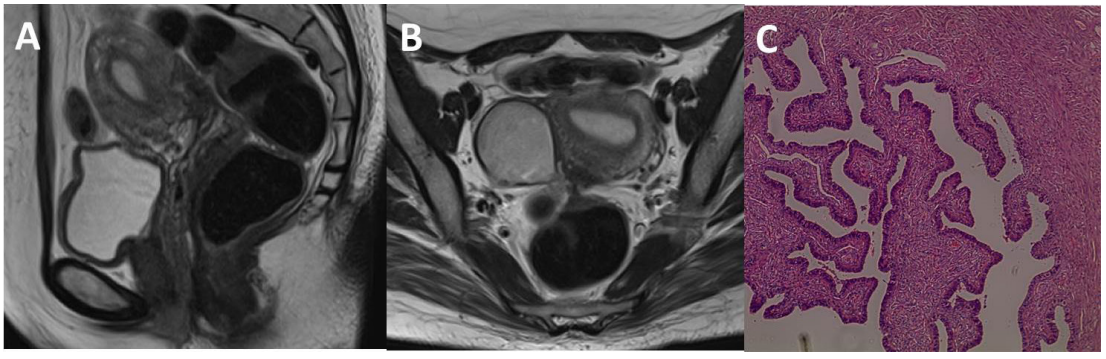

Figure 1. A, B. Sagittal and axial T2-weighted MR image shows a large cystic ovarian tumor of 5 cm at maximum diameter. The tumor had arisen from the right ovary, the margin was smooth and the uterus was normal size. C. Ovarian endometrioid tumor of low malignant potential showing glands similar to the complex hyperplasia of the uterine endometrium.

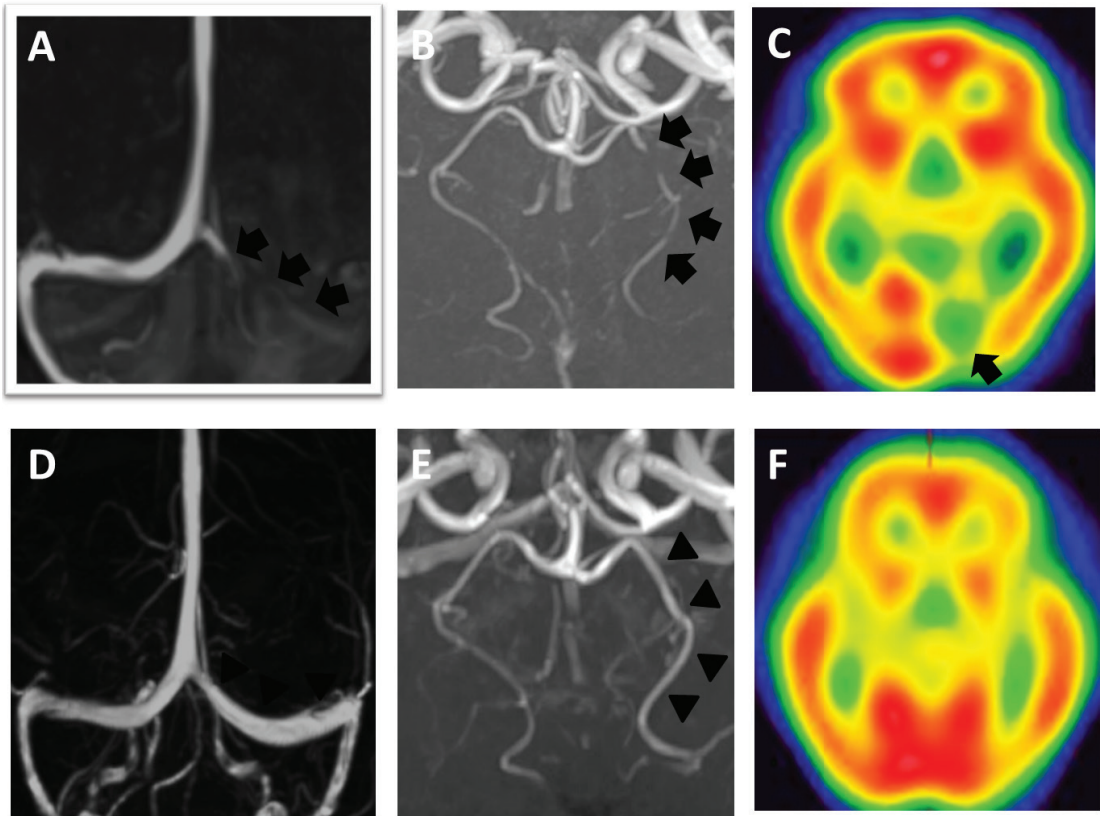

Figure 2. A. Brain magnetic resonance venography image obtained upon admission showing occlusion of the left transverse and sigmoid sinuses. Magnetic resonance venography image obtained 28 days after admission showing recanalization of the venous sinus (D).
B. 3D TOF MRA showing high-grade left PCA stenosis. Improvement in vasoconstriction is observed on day 14 from ictus (E).
C. SPECT images obtained on day 2 from ictus showing left posterior ischemic lesion. SPECT image obtained on day 28 from ictus showing absence of the ischemic lesion (F).

paresis. Over the following weeks, there was a gradual improvement of the stenoses, as assessed by repeated MRI. She was started on a different anticoagulant (edoxaban) and discharged on postpartum day 31 without neurological deficits; we additionally tapered her nimodipine. At 3 month follow-up MRA and MRV were normal (Figure 3C, D). She was ultimately diagnosed with postpartum stroke, wherein CVT was followed in quick succession by RCVS.

DISCUSSION

CVST is an uncommon form of stroke that presents with a wide range of clinical manifestations. Risk factors include ovarian tumor, iron deficiency anemia, pregnancy, intravenous drug abuse, infection, and dehydration.[4] Headache is the predominant symptom reported in 90% of cases. Papilledema occurs in approximately 30% of cases and is attributed to elevated intracranial pressure. Focal neurological deficits occur in patients with CVST, primarily as a consequence of infarction and less commonly, secondary to hemorrhage.[5] RCVS is a rare form of angiopathy, and childbirth is a known precipitating factor for this condition. RCVS is characterized by reversible segmental vasoconstriction of medium- and large-sized cerebral arteries.[1,6,7] SAH is not a necessary criterion to diagnose RCVS, although approximately 22–34% of cases with RCVS are associated with convexity SAH.[8] To our knowledge, no reports have described IMP-SPECT findings in patients presenting with RCVS concomitant with CVST. In our patient (Case1), using IMP-SPECT imaging, we identified left posterior ischemic lesions on day 2, which disappeared on day 28.

The following pathomechanisms should be considered in the present case: RCVS and CVST

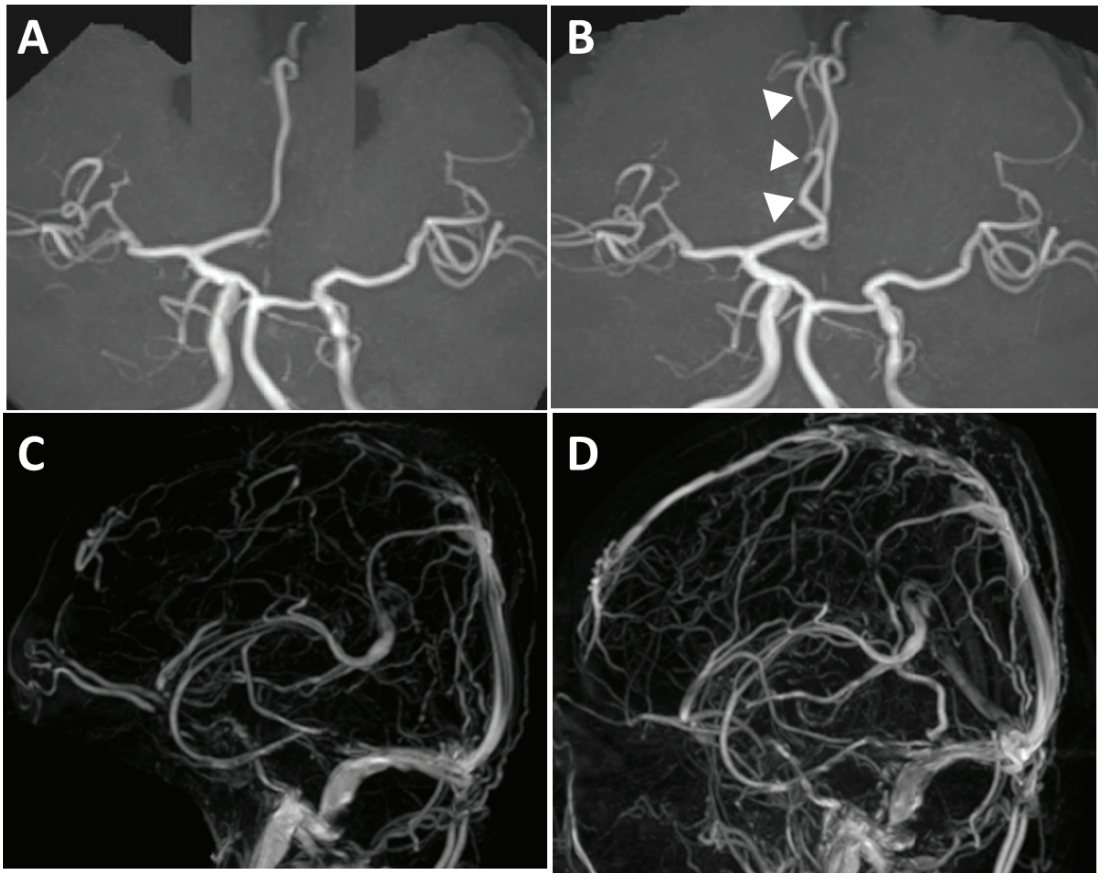

Figure 3. A, C. Magnetic resonance angiography (MRA) confirmed the presence of a vasospasm involving the right anterior cerebral artery. On admission, MRA revealed vasoconstriction of the anterior cerebral artery (ACA). Vasoconstriction was normalized within 3 months. B, D: Magnetic resonance venography (MRV) confirmed the presence of a thrombosis involving the superior sagittal sinus. On admission, MRV revealed thrombosis of the superior saggital sinus (SSS), which normalized within 3 months.

coexisted in this woman or CVST resulted in RCVS. An association between CVST and RCVS has previously been reported in 2 women immediately postpartum.[9] Another case report has described such an association between these 2 forms of angiopathy in a young woman who underwent stenting of the lateral venous sinus for the management of idiopathic intracranial hypertension.(Table 1).[10-12] In these cases, the authors concluded that CVST and RCVS were perhaps distinct pathophysiological entities. Soo *et al*. reported that extremely elevated estrogen levels due to ovarian tumors contribute significantly to the development of CVST before surgery[13]. RCVS may have been triggered by the rapid reduction of estrogen in the serum after surgery, which is perhaps associated with loss of vasodilatation and other changes within the endothelium and the vessel wall.[14] In our patients, resection of the ovarian tumor led to dramatically reduced estrogen levels (Patient 1: 288 pg/ml to 31 pg/ml, Patient 2: 193 pg/ml to 19 pg/ml), which could have contributed to the development of CVST and RCVS. Our patient showed concomitant venous thrombosis and arterial vasospasm in the setting of severe acute headache. This is the first report that describes RCVS concomitant with CVST in the perioperative period of ovarian tumor surgery.

In conclusion, our cases highlight that both RCVS and CVST should be considered perioperatively in women undergoing ovarian tumor resection. In our patients, the ovarian tumor increased estrogen levels which induced CVST. Resection of the ovarian tumor led to dramatically reduced E2 levels which may have contributed to the development of RCVS.

DISCLOSURE

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Conflict of interest: None

Table1: Summary of patients with co-occurrence of RCVS and venous sinus thrombosis

Case no.	Study	Age/ Sex	Symptoms	Risk factor	Affected veins	Affected arteries	Associated condition	Therapy	mRS (Admission)	mRS (Discharge)
1	Katzin *et al.* (2007)[10]	37/F	Headache, Vomitting	Pregnancy	Trolard	ACA, MCA, PCA	Infarction	Warfarin	2	1
2	Markus *et al.* (2011)[11]	38/F	Headache	Pregnancy	SSS, TS, SS	PCA	None	Nimodipine, Magnesium, Statine, Warfarin	1	0
3	Bourvis *et al.* (2016)[12]	24/F	Headache, Vomitting	Pregnancy	TS,SS	PCA, MCA	SAH, Infarction	Nimodipine, Warfarin	3	1
4	Our cases	42/F	Headache	Ovarian tumor, Anemia	TS,SS	PCA	SAH	Nimodipine, Edoxaban	2	0
5		39/F	Headache	Ovarian tumor	SSS	ACA	None	Nimodipine, Edoxaban	1	0

REFERENCES

1. Singhal AB, Bernstein RA. Postpartum angiopathy and other cerebral vasoconstriction syndromes. *Neurocrit Care* 2005; 3(1):91-7.
2. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain* 2007; 130(12):3091–101.
3. Robert T, Oumarou G, Villard J, *et al*. Call-Fleming syndrome associated with convexity subarachnoid hemorrhage. *Clin Neurol Neurosurg* 2013; 115(6): 796-8.
4. Silvis SM, Middeldorp S, Zuurbier SM, Cannegieter SC, Coutinho JM. Risk factors for cerebral venous thrombosis. *Semin Thromb Hemost* 2016; 42(6):622-31.
5. Dash D, Prasad K, Joseph L. Cerebral venous thrombosis: an Indian perspective. *Neurol India* 2015; 63(3):318-28.
6. Bousser MG. Antithrombotic strategy in stroke. *Thromb Haemost* 2001; 86(1):1-7.
7. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative review: reversible cerebral vasoconstriction syndromes. *Ann Intern Med* 2007; 146(1): 34-44
8. Matano F, Murai Y, Adachi K, *et al*. Reversible cerebral vasoconstriction syndrome associated with subarachnoid hemorrhage triggered by hydroxyzine pamoate. *Clin Neurol Neurosurg* 2013; 115(10): 2189-91.
9. Hoeren M, Hader C, Strümpell S, Weiller C, Reinhard M. Peripartum angiopathy with simultaneous sinus venous thrombosis, cervical artery dissection and cerebral arterial vasoconstriction. *J Neurol* 2011; 258(11): 2080-2.
10. Katzin LW, Levine M, Singhal AB. Dural puncture headache, Postpartum angiopathy, pre-eclampsia and cortical vein thrombosis after an uncomplicated pregnancy. *Cephalalgia* 2007;27(5):461-4.
11. Markus H, Claudia H, Sandra S, Cornelius W, Matthias R. Peripartum angiopathy with simultaneous sinus venous thrombosis, cervical artery dissection and cerebral arterial vasoconstriction. *J Neurol* 2011;258(11):2080-2.
12. Bourvis N, Franc J, Szatmary Z, *et al.* Reversible cerebral vasoconstriction syndrome in the context of recent cerebral venous thrombosis: report of a case. *Cephalalgia* 2016; 36(1): 92-7.
13. Soo Y, Singhal AB, Leung T, *et al*. Reversible cerebral vasoconstriction syndrome with posterior leucoencephalopathy after oral contraceptive pills. *Cephalalgia* 2010; 30(1): 42-5.
14. Freilinger T, Schmidt C, Duering M, *et al*. Reversible cerebral vasoconstriction syndrome associated with hormone therapy for intrauterine insemination. *Cephalalgia* 2010; 30(9):1127-32.