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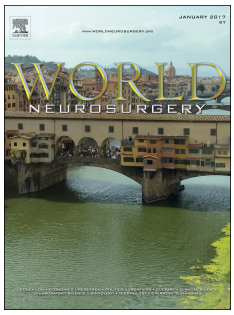

Reversible Cerebral Vasoconstriction Syndrome as an Unusual Complication of a Dural Arteriovenous Fistula treated with Onyx Embolization

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Reversible Cerebral Vasoconstriction Syndrome as an Unusual Complication of a Dural Arteriovenous Fistula treated with Onyx Embolization

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Abstract

Background. Reversible cerebral vasoconstriction syndrome (RCVS) is a rare entity with an unknown pathophysiology. RCVS has been reported to occur more frequently in women aged 20 to 50 years. Several mechanisms have been postulated involving transient deregulation of cerebral arterial tone, small vessel endothelial dysfunction, biochemical factors, hormonal deregulation, oxidative stress, and genetic predisposition. All these mechanisms and triggers are related with sympathetic over-activation which eventually produce vasoconstriction. RCVS is distinguished by acute severe recurrent thunderclap headaches with or without other neurological symptoms. However, the diagnosis can be challenging and most likely underdiagnosed requiring a high level of suspicion from the clinician.

Case Description. We present an unusual case of an 18-year-old female who developed RCVS after embolization of a dural arteriovenous fistula with onyx embolic material. A cerebral angiogram was performed and verapamil was administered intra-arterially demonstrating slight improvement of the constricted vessels with clinical improvement. The patient was maintained on oral verapamil during hospitalization. At 7-month follow-up, the patient was neurologically stable and a cerebral angiogram demonstrated no signs of vasoconstriction.

Conclusions. Endovascular procedures are a rare trigger for the development of RCVS and may be misdiagnosed. Prompt recognition of symptoms and diagnosis with treatment are necessary to reduce the risk of stroke. The management should follow the premise of discontinuing precipitating drugs and administering CCBs.

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is a rare entity with an unknown pathophysiology. RCVS has been reported to occur more frequently in women aged 20 to 50 years.[1] Several mechanisms have been postulated involving transient deregulation of cerebral arterial tone, small vessel endothelial dysfunction, biochemical factors, hormonal deregulation, oxidative stress, and genetic predisposition. It has also been reported to be associated with the use of vasoactive drugs including pseudoephedrine, triptans, ergotamine, and SSRI's. All these mechanisms and triggers are related with sympathetic over-activation which eventually produce vasoconstriction.[2-4] The clinical presentation usually consists of a severe headache with pain reaching maximum intensity in less than 1 minute (thunderclap headache) and it may be associated with nausea, vomiting, and photophobia.[4] However, the diagnosis can be challenging and most likely underdiagnosed requiring a high level of suspicion from the clinician.

RCVS may rarely occur in association with neuroendovascular procedures.[5,6] Herein, we report an unusual presentation of RCVS following endovascular embolization of a dural arteriovenous fistula (dAVF) using onyx material, rationale of management, and a short overview of the literature.

Case Report

An 18-year-old female presented to the hospital with a severe and incapacitating headache. Her past medical history included a remote craniotomy for an arachnoid cyst fenestration and migraine. Due to worsening of headache and a persistent audible bruit on the left side, neurosurgery was consulted. Patient underwent a cerebral angiogram that demonstrated a dAVF

at the junction of the left transverse sigmoid sinus fed by multiple external carotid artery branches (Figures 1A-E). Decision was made to intervene with endovascular embolization using onyx material.

Treatment

The intervention was performed with the patient under general anesthesia and via transfemoral arterial approach. In addition, a transfemoral vein access was performed for temporary balloon occlusion of the transverse sigmoid sinus to control sinus lumen while injecting embolization material into the arterial vessels leading to the fistula. The patient was neurophysiologically monitored during the procedure. Catheterization of the posterior branch of the left middle meningeal artery was done using a Scepter Dual Lumen Balloon (MicroVention, Aliso Viejo, CA). After gentle inflation of the balloon to prevent reflux, the vessel lumen was flushed with 10 ml of heparinized saline and subsequently the Onyx-18 material with DMSO were delivered. A second pedicle was catheterized, namely the left occipital artery with same process repeated. After second pedicle injection, completion of 6-vessel angiography demonstrated complete obliteration of the dAFV (Figures 1F-J). No complications were apparent at the conclusion of the procedure.

Outcome and Follow-up

On the 2nd day post-procedure, the patient developed a severe bilateral and diffuse headache without any focal neurological deficit. A non-contrast head CT was unremarkable. Bouts of severe headaches continued despite increase in analgesic doses. An occipital nerve block was

performed on day 4 post-surgery and nortriptyline was added to the medical management. Due to no improvement of symptoms, a cerebral angiogram was performed on post-operative day 10 and demonstrated complete obliteration of the left dAVF with disseminated spasm within the bilateral anterior circulation as well as the left superior cerebellar artery distribution. Subsequently, we administered 10 mg of verapamil intra-arterially into the left internal carotid artery and a 10-min period was allowed for vascular response (Figure 2A – D). A final angiogram run demonstrated partial improvement of the cerebral vasoconstriction confirming the diagnosis of RCVS. A brain MRI was performed after this intervention and showed no evidence of ischemic lesions.

Patient was transferred to the neurocritical care unit and was maintained on oral verapamil. Steroids and nortriptyline were discontinued due to their association with RCVS. On postoperative day 16, the patient was discharged home in a stable condition and improvement of symptoms. At 7-month imaging follow-up, a cerebral angiogram demonstrated a complete obliterated dAVF with no signs of vasoconstriction (Figure 2E – F).

Discussion

The mechanism of vasoconstriction in RCVS has not been elucidated but hypotheses suggest there is a deregulation of the cerebral vasculature secondary to endothelial dysfunction and oxidative stress rather than structural changes in the vessels.[3,7] However, the cause of this dynamic unbalance remains unknown and several predisposing factors have been reported (Table 1). There is uncertainty of which patients are more susceptible to develop RCVS but genetic polymorphisms have been associated with more severe presentations.[8]

RCVS usually resolves spontaneously within 3 months but approximately 30% of the cases may develop catastrophic complications such as subarachnoid hemorrhage, intraparenchymal hemorrhage, or ischemic strokes, which can lead to permanent neurological deficits.[1,9] In order to reduce morbidity, early diagnosis and prompt treatment should be warranted.[4] The diagnosis of RCVS should be considered in patients with thunderclap headaches whether in the presence or lack of neurologic signs. First step should be to perform a non-contrast head CT to rule out any hemorrhage. An MRI or MRA should be used as complement to identify any structural defect or early signs of RCVS such as intraparenchymal hemorrhage, subarachnoid hemorrhage or ischemia of watershed areas.[2,4] In addition, transcranial Doppler is a non-invasive neuroimaging modality that may have potential for the initial diagnosis and subsequent monitoring of patients with suspected RCVS.[10,11] Despite the lack of consensus, cerebral angiography demonstrating diffuse segmental vasoconstriction of arteries and response to intra-arterial calcium channel blockers (CCBs) remains the gold standard for the diagnosis of RCVS.[12] It is important to highlight that vasoconstriction in RCVS usually begins in peripheral arterioles progressing to larger vessels within days and an initial angiography may fail to demonstrate vasospasm. [13-15]

In our patient, the development of RCVS could be attributed to several factors: 1) history of migraine, reported in 17 to 30% of cases;[16,17] 2) history of head surgery (15 years before dAVF treatment); 3) the concomitant use of steroids and nortriptyline, and 4) neuroendovascular treatment for the dAFV with Onyx and organic solvent DMSO, which most likely triggered the deregulation in the cerebral vascular tone. DMSO is an efficient solvent for water-insoluble compounds and a hydrogen-bound disrupter.[18] Overall, DMSO is well distributed throughout the body by all routes, it is metabolized by oxidation to dimethyl sulfone ($DMSO_2$) or by reduction in dimethyl sulfide (DMS). $DMSO_2$ is primarily excreted in the urine and DMS is eliminated by

the lungs and skin. The estimated half time elimination of intravenous injected DMSO is 4 days, and within a week 80% is eliminated.[19,20] DMSO crosses the blood-brain barrier and has previously been shown to cause an inflammatory response, vasospasm, and endothelial necrosis.[21] Chaloupka *et al.* described in detail severe vasospasm related to superselective intra-arterial injection of DMSO in swine, while smaller volumes of DMSO were associated with subarachnoid hemorrhage.[22]

Although there is no standard of treatment for RCVS, discontinuing possible triggers should be the initial management, especially any type of sympathomimetic drug since abnormal reaction to vasoactive substances is considered a secondary cause of RCVS.[2,23,24] Additionally, small case series have suggested the use of glucocorticoids may potentially predict worse clinical outcomes and should be also discontinued.[25] In general, the treatment goal is to reduce the risk of stroke. Recent studies have reported favorable clinical outcomes by using oral CCBs such as verapamil or nimodipine, however, they only ameliorate the severity of headaches but the prognosis is not affected. To date, with the lack of strong evidence for RCVS treatment, the use of intra-arterial therapies or endovascular angioplasty should be reserved for patients with severe refractory RCVS or with clinical deterioration.[2,4,26] Due to the low incidence of RCVS cases, or perhaps under-recognized entity, further prospective studies are warranted to elucidate the natural history, pathogenesis, and treatment alternatives for this unique disease.

Conclusion

Endovascular procedures are a rare trigger for the development of RCVS and may be misdiagnosed. Prompt recognition of symptoms and diagnosis with treatment are necessary to

reduce the risk of stroke. The management should follow the premise of discontinuing precipitating drugs and administering CCBs.

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Figure Legends

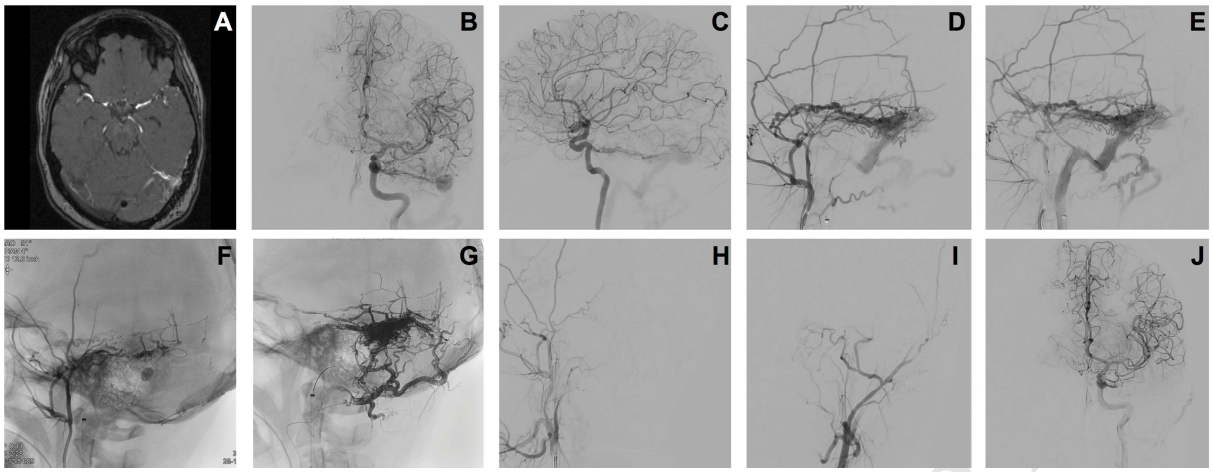
Figure 1. (A) MRA demonstrating a left dural arteriovenous fistula (dAFV). Cerebral angiogram in anteroposterior (B) and lateral (C) views demonstrating persistency of the artery of Bernasconi and Cassinari feeding the DAFV. Super selected angiographies (D and E) from the left external carotid artery demonstrating multiple feeding vessels that drain into the left transverse sigmoid junction DAFV. Temporary balloon occlusion (F and G) was performed while injecting Onyx embolization material trough the feeding arteries into the DAFV. Completion of angiography demonstrated absence of DAFV filling (H – J).

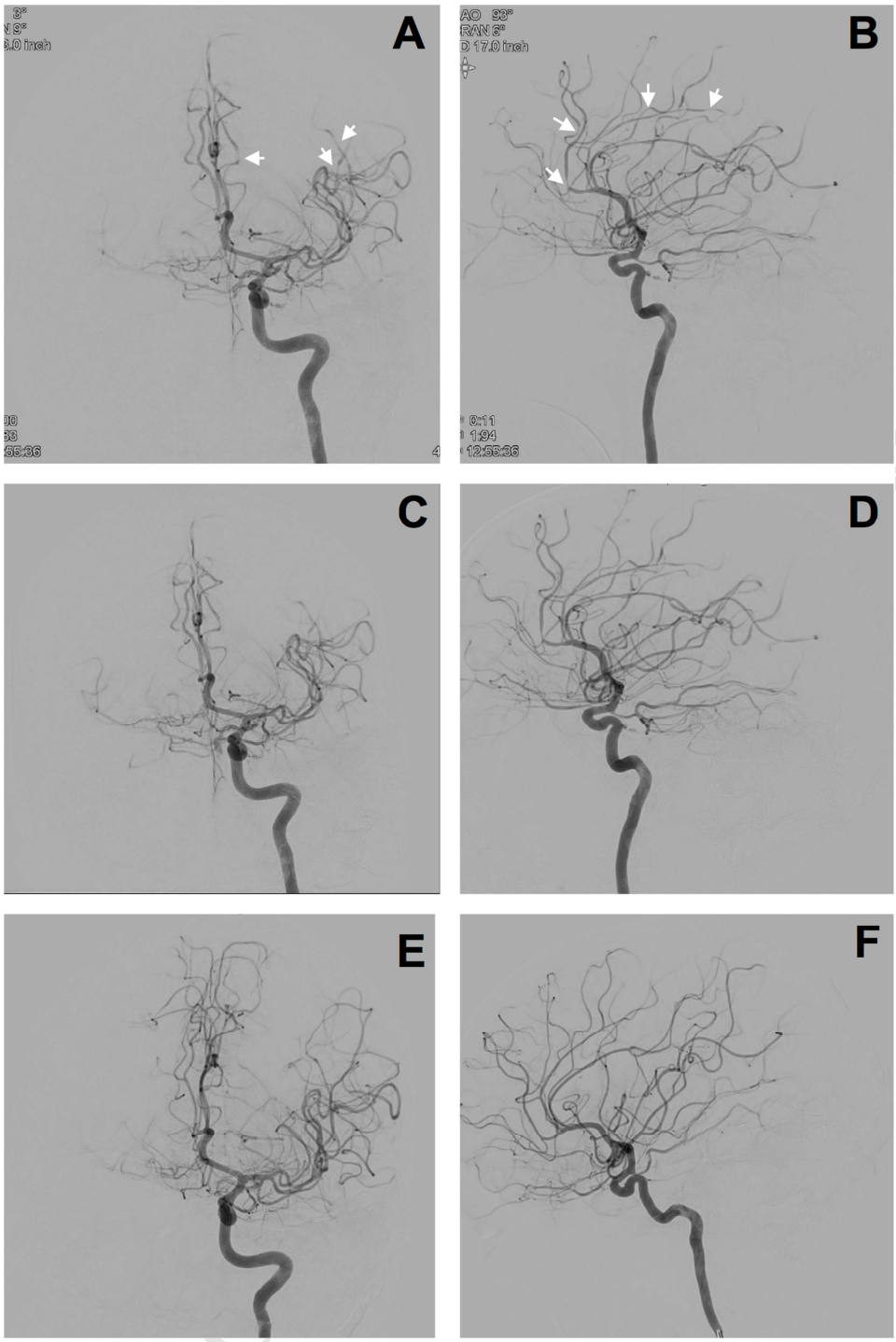
Figure 2. On postoperative day 10, a cerebral angiogram in anteroposterior (A) and lateral (B) views demonstrated several segments of vasospasm in the anterior and middle cerebral arteries (white arrows); 10 mg of verapamil was administered intra-arterially and after a 10-minute period a cerebral angiogram demonstrated slight improvement of the constricted vessels with clinical improvement (C and D). At 7-month follow-up, a cerebral angiogram demonstrated no signs of vasoconstriction (E and F).

Table 1. Precipitating factors associated with reversible cerebral vasoconstriction syndrome.

Medical Comorbidities
1. Post-partum (most cases)
2. Vascular: intracranial aneurysms, endovascular procedures, carotid endarterectomy, fibromuscular dysplasia, cervical artery dissection
3. Tumors: pheochromocytoma, glomus tumor, carcinoid tumors
4. Extra or intracranial disorders: head trauma, neurosurgery, head and neck surgery, spinal subdural hematoma
5. Autoimmune disorders: systemic lupus erythematous, antiphospholipid syndrome, thrombotic thrombocytopenic purpura
6. Headache disorders: migraine, exertional, benign sexual headache
7. Others: porphyria, hypercalcemia, macroangiopathic hemolytic anemia, autonomic dysreflexia, exercise, sexual activity
Drugs and Medications
1. Sympathomimetic drugs: ephedrine, pseudoephedrine, epinephrine
2. Ergotamine derivatives
3. MAO inhibitors
4. SSRIs
5. TCAs
6. Triptans
7. Dopaminergic: bromocriptine
8. Immunosuppressant and immunomodulatory drugs
9. Blood products: RBC transfusion, IVIG infusion
10. Illicit drugs: cocaine, LSD, amphetamines, ecstasy, marijuana
11. Others: indomethacin, OCPs, erythropoietin, caffeine withdrawal, binge alcohol, nicotine patches

IVIG: intravenous immunoglobulins; LSD: lysergic acid diethylamide; MAO: monoamine oxidase; OCPs: oral contraceptive pills; RBC: red blood cells; SSRIs: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressant.




A
B
C
D
E
F

Highlights

- Reversible cerebral vasoconstriction syndrome (RCVS) is a rare entity with an unknown pathophysiology characterized by thunderclap headaches
- Despite the lack of consensus, cerebral angiography demonstrating diffuse segmental vasoconstriction of arteries and response to intra-arterial calcium channel blockers remains the gold standard for the diagnosis of RCVS.
- Prompt recognition and treatment of RCVS are necessary to reduce the risk of stroke.

Abbreviations List

CT – Computed tomography

CCBs – Calcium channel blockers

dAVF – Dural arteriovenous fistula

DMS – Dimethyl sulfide

DMSO – Dimethyl sulfoxide

$DMSO_2$ – Dimethyl sulfone

IVIG – Intravenous immunoglobulins

LSD – Lysergic acid diethylamide

MAO – Monoamine oxidase

MRA – Magnetic resonance angiography

MRI – Magnetic resonance imaging

OCPs – Oral contraceptive pills

RBC – Red blood cells

RCVS – Reversible cerebral vasoconstriction syndrome

SSRI – Selective serotonin reuptake inhibitors

TCA – Tricyclic antidepressant