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Review article

Treatment challenges in idiopathic extracranial ICA vasospasm case report and review of the literature

Edith Graham [a,*], Karen Orjuela [a,b], Sharon Poisson [b], Jose Biller [a]

[a] Department of Neurology, Loyola University Chicago, Stritch School of Medicine, Maywood, IL, United States of America
[b] Department of Neurology, Neurohospitalist & Stroke Division, University of Colorado, Anschutz Medical Campus, United States of America

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ABSTRACT

Idiopathic extracranial internal carotid artery (ICA) vasospasm is a rare pathological phenomenon that may lead to stroke in young patients. We report a case of an 18 year-old female with recurrent extracranial ICA vasospasm since age thirteen. We summarize published data related to this condition including all twenty-three reported cases of extracranial ICA vasospasm. We describe the various proposed pathophysiological mechanisms underlying this disorder. Various treatment modalities have been attempted but there is no known long-term effective treatment.

1. Introduction

Idiopathic extracranial internal carotid artery (ICA) vasospasm is a rare pathological phenomenon that may lead to stroke in young patients. The pathophysiology of this reversible vasospasm remains poorly defined. One possible etiology involves adrenergic hypersensitivity of the extracranial ICA due to different autonomic innervation of the intracranial versus extracranial ICA that occurs during embryologic development [1]. The intracranial ICA uniquely receives parasympathetic innervation from the internal carotid nerve plexus which results in dilation [2]. The lack of parasympathetic innervation in the extracranial ICA may predispose to sensitivity to sympathetic vasomotor stimuli that may contribute to vasospasm [3].

2. Case description

An 18-year-old woman with history of migraines with aura and extracranial internal carotid arteriopathy presented to our institution due to left sided weakness upon awakening. Initial examination showed a blood pressure of 118/64 mmHg, heart rate of 77 bpm, left central facial paresis, left hemiparesis and left hemisensory impairment. Magnetic resonance imaging (MRI) of the brain showed a right middle cerebral artery (MCA) and posterior cerebral artery (PCA) border-zone acute ischemic infarct. Magnetic resonance angiography (MRA) showed severe right ICA stenosis at the level of the C1 vertebral segment (Bouthillier classification). The distal petrous, cavernous and clinoid segments of the ICA were patent bilaterally. CT angiography (CTA), confirmed a long segment severe right ICA stenosis at the same level; the contralateral ICA was normal on both MRA and CTA (see Fig. 1).

She initially received aspirin 81 mg and clopidogrel 300 mg in the emergency department. She was admitted to the Neurointensive Care Unit where she continued with clopidogrel 75 mg daily and enoxaparin 40 mg subcutaneous daily. During her hospital stay, non-invasive monitoring with transcranial Doppler (TCD) ultrasound showed normal intracranial velocities. Transthoracic echocardiogram (TTE) demonstrated normal ejection fraction and redundant/myxomatous mitral valve leaflets and mitral valve prolapse. A continuous video-EEG showed evidence of electrographic seizures originating from right hemisphere. She received lacosamide 100 mg twice daily.

Her initial symptoms started at thirteen years of age, when she presented with acute left-sided transient numbness and weakness associated with moderate intensity right occipital headaches. Neurological examination on initial presentation to the emergency department showed dysarthria, sialorrhea, left homonymous hemianopia, and left hemiparesis. Her exam returned to normal within two hours after onset of symptoms. MRA of the extracranial circulation showed concentric stenosis of the cervical right ICA at the C1 level (see Fig. 2). Her initial radiological findings were concerning for a non-traumatic cervical right ICA dissection. MRI of the brain showed restricted diffusion on the right parietal region; follow up MRI obtained the following day did not demonstrate an area of ischemia.

In light of a possible spontaneous cervical right ICA dissection, she

* Corresponding author.
E-mail address: edith.graham@northwestern.edu (E. Graham).

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received anticoagulation with enoxaparin 1.25 mg/kg dose twice daily. Follow up MRA ten days later demonstrated partial resolution of the right ICA stenosis and another area of focal narrowing of the right ICA located 2 cm above the carotid artery bifurcation and new findings of left ICA stenosis at the skull base. She was placed on enoxaparin 50 mg twice daily for five weeks and then, transitioned to aspirin 81 mg thrice daily. Follow up imaging four weeks after the initial event showed mild narrowing of the left ICA just below the skull base and resolved right ICA stenosis.

Since her index event at age 13, she has continued to have recurrent episodes of weakness and/or numbness sometimes associated with headaches. These stroke-like events have been associated with restricted diffusion on MRI, but usually return to normal on repeat imaging. However, at age 17, she had a right parietal lobe ischemic stroke. The patient has had several neuroimaging studies throughout her life, with multimodal techniques, CTA, MRA and catheter cerebral angiography of the intracranial and extracranial circulation demonstrating fluctuating evidence of the cervical ICAs narrowing.

A comprehensive evaluation by Neurology, Vascular Surgery, Rheumatology and Medical Genetics was done. Extensive imaging and laboratory tests have ruled out multiple possibilities of systemic disease. General examination showed hyperelastic tissue joints with a Beighton score of 7/9. However, she had no history of joint subluxations, dislocations, or sprains. She underwent genetic studies for connective tissue disorders including Ehlers-Danlos (COL1-A and COL3-A) and Fibromuscular Dysplasia (FMD) and was also tested for Fabry disease, Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS), Myoclonic epilepsy with ragged-red fibers (MERRF), which were all negative. Additionally, an area of possible systemic vasospasm involving her left upper extremity digits and possible right ulnar arterial occlusive disease was discovered but no cause of inflammatory or vasculitic process was found. ANA was positive at 1:40 titer, but other inflammatory markers and ENA panel were negative. Ancillary tests for acquired and primary thrombophilia, pheochromocytoma, and familial hemiplegic migraine were negative. Chest MRA and a CT-PET excluded systemic involvement of large arteries. Multiple therapies have been attempted such as low molecular weight heparin, dual antiplatelet medications, calcium channel blockers, alpha blockers, topiramate, gabapentin, and methylprednisolone. At five-year follow-up, our patient has not had further strokes or known vasospastic events on a regimen of gabapentin, nimodipine, aspirin and clopidogrel. She does, however, suffer from seizures as a result of her stroke. Her migraines are well-controlled.

3. Literature review

A PubMed literature search was performed for articles containing the following terms: “recurrent extracranial ICA vasospasm”, “reversible ICA stenosis”, and “idiopathic cervical ICA vasospasm.” Patients with intracranial ICA vasospasm or those with identifiable cause such as post-surgical, post-traumatic, or vasculitis were excluded. To our knowledge, there have been twenty-three case reports of extracranial ICA vasospasm since 1984, including our patient. There are earlier case reports of alternating hemiplegia or hemiplegic migraine; however, these were before reliable angiography and also concluded lack of effective treatment. All reported cases of extracranial vasospasm to date with their treatments and outcomes are summarized in Table 1 [4–22].

In this retrospective review on 23 patients with extracranial ICA vasospasm, 12 were female and 11 were male suggesting a lack of gender predisposition. The mean age was 35.5, though the average age at symptom onset was 31.7. Nineteen patients presented with alternating or bilateral vasospasm and four had unilateral vasospasm. The most common treatments attempted were calcium channel blocker (11), antiplatelet (10), corticosteroids (6), anticoagulation (5), nitrates (4), carotid stenting (4), beta-blocker (3), balloon angioplasty (3), intra-arterial vasodilator (2), alpha-1-blocker (2). The following treatments were used in 1 patient each: stellate ganglion block, phenytoin, valproate, diazepam, edaravone, intranasal dihydroergotamine (DHE), midodrine, fludrocortisone and gabapentin. Reported benefits were noted in the four patients who underwent carotid artery stenting with an average follow up time of 19.5 months. Of note, one author noted stent placement at the carotid bifurcation did not prevent recurrence, though additional stenting in the pre-petrous segment was successful at preventing vasospasm. Outcomes did not significantly vary by age, though the oldest patient at onset was 67 and had the worst outcome of coma and ultimate death.

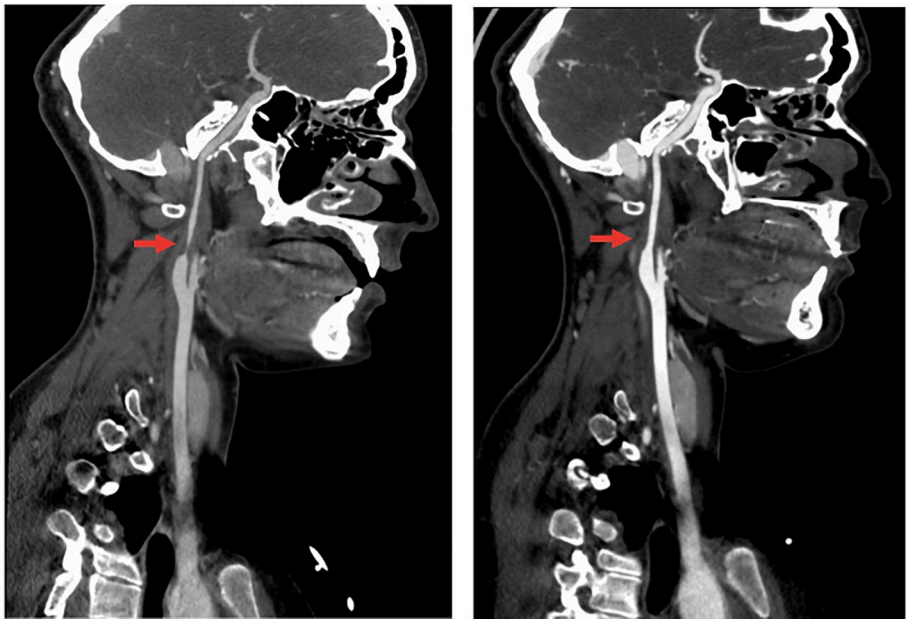

Fig. 1. CTA of the neck on admission (left) shows severe stenosis of the cervical segment of the right ICA. CTA of the neck three days later (right) shows recovery of the stenosis.

4. Discussion

Our patient had cervical carotid artery vasospastic disease with no apparent dissection or intracranial vessel involvement. Laboratory studies for connective tissue, inflammatory, and genetic disorders were unremarkable. Her recurrent, variable stenosis is highly suggestive of ICA vasospasm.

Differential diagnosis of reversible extracranial ICA vasospasm includes cervical arterial dissection, complex migraines, reversible cerebral vasoconstriction syndrome (RCVS), post-viral arteriopathy, drugs of abuse, localized vascular inflammation, and systemic inflammatory disease.

The pathophysiology of recurrent ICA vasospasm remains poorly understood. Vasospasm of the extracranial ICA has been documented following catheter angiography and trauma. Other processes including sympathetic activation, inflammation and genetic factors have been postulated. A case of recurrent alternating ICA vasospasm has also been attributed to recreational marijuana use in a patient with history of traumatic left ICA dissection [19].

Whether or not there is a relationship between extracranial ICA vasospasm and migraine is unknown. A link between RCVS and migraine has been described, with up to 27% of patients with RCVS having a history of migraine. This could be due to a shared pathophysiology or due to vasoactive drugs used in acute migraine treatment such as triptans and ergots which may facilitate the occurrence of RCVS. There is also a link between cannabis, sympathomimetic and serotonergic substances with RCVS [23]. While similar mechanisms could play a role in extracranial ICA vasospasm, the autonomic innervation of the extracranial vasculature differs from the intracranial vasculature affected in RCVS [1–3]. Moreover, our patient was not taking any vasoactive substances that may have contributed to her episodes.

Genetic factors may play a role in extracranial ICA vasospasm. A recently identified heterozygous mutation in ACOX3 gene (p.F79V and p.G222E) could cause recurrent ICA vasospasm via disruption in autoregulation of smooth muscle endothelium. Kim et al. identified these mutations in two Korean twin brothers affected by recurrent extracranial ICA vasospasm via whole-exome sequencing. They found that knockdown of ACOX3 in vitro prolonged loss of vascular myogenic tone which they proposed is necessary for maintaining vascular patency [22].

A second possibility is that recurrent extracranial ICA vasospasm may be similar to Prinzmetal's variant angina, another recurrent vasoconstrictive disease. Prinzmetal's has been shown to be associated with endothelial nitric oxide synthase (eNOS) T-786C polymorphism, leading to reduced nitric oxide (NO) production [24]. This condition is treated with nitrites and/or calcium channel blockers. Glueck et al. described the nitric oxide-elevating l-arginine to be a treatment for Prinzmetal's variant angina with eNOS T-786C mutation [24]. Interestingly, the T-786C polymorphism has also been found to be an independent risk factor for the development of moderate to severe cervical ICA stenosis [25].

Third, ICA vasospasm may also be associated with other vasospastic disorders, such as Raynaud's phenomenon. Sinici et al. found that polymorphism in the T-786C promoter region may predispose to systemic sclerosis (SSc) via reduced availability of NO. [26] Our patient had evidence of vasospasm involving her left upper extremity digits, suggesting a Raynaud's phenomenon.

A fourth proposed mechanism regulating peripheral and cerebral vessel constriction involves the production of 20-hydroxyeicosatetraenoic acid (20-HETE), which triggers to astrocyte-regulated vasoconstriction. 20-HETE blocks calcium-activated Kþ channels in smooth muscle cells, leading to depolarization, increased Ca2þ influx and contraction. Patients with increased 20-HETE activity have been found to have polymorphism in the CYP1A1 gene. Additionally, 20-HETE formation is inhibited by nitric oxide. Thus, treatment with nitric oxide containing compounds may promote vasodilation [27]. We would advise caution with prolonged treatment with nitrates as rebound coronary vasospasm has been reported to occur after cessation of therapy [28].

In summary, recurrent extracranial ICA vasospasm remains a diagnostic and therapeutic challenge. Multiple possible mechanisms have been described, most of which implicate dysfunction of the vascular endothelium. The most serious complication of ICA vasospasm is cerebral infarction. Various treatment modalities have been attempted but

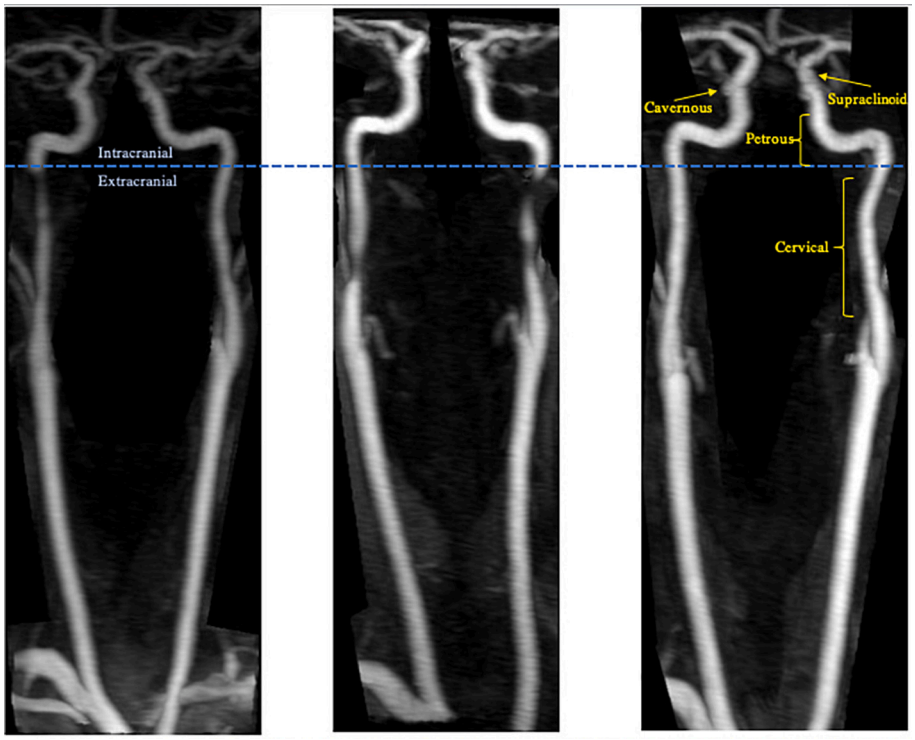

Fig. 2. MRA at symptom onset age 13 (left) compared to MRA 3 weeks later (center) and MRA 3 months later (right). On the initial MRA, there is concentric right ICA stenosis just inferior to the skull base at C1 (Bouthillier classification). This short segment of stenosis is resolved in the center image, but there is new mild-to-moderate right ICA stenosis 2 cm above bifurcation a new moderate-to-severe left ICA stenosis at the inferior skull base and a separate area of milder left ICA stenosis just below. The MRA on the right is nearly normal except for very mild tapered narrowing on the right ICA above the bifurcation.

Table 1
Summary of treatment and outcomes in extracranial ICA vasospasm (Case Reports Data)*.

Reference	Age/ Sex	Location and Timing of Vascular Abnormalities	Treatment	Outcome
Lieberman et al., 1984 [4]	39/F	RICA petrosal segment followed 2 days later by LICA cervical segment	1. Aspirin	No follow up data given
Arning et al., 1998 [5]	32/F	RICA stenosis preceded by LICA 13 months earlier	1. Prednisone up 30 mg/day	Recurrence of visual disturbance after 6 weeks
			2. Molsidomine (nitric oxide producer) + Nifedipine	Brief attacks of visual impairment
			3. Nitrendipine	Brief attacks of visual impairment
Janzarik et al., 2006 [6]	30/ M	RICA followed by bilateral ICA 2 years later	1. CCB - Nitrendipine 20 mg + phenprocoumon	Recurrence of stenosis, alternating sides
			2. Intraarterial papaverine	Brief dilation with recurrence
Janzarik et al., 2006 [6]	48/F	Bilateral cervical ICAs alternating weekly	1. CCB – Flunarizine 5 mg/d	Recurrent vasospasm
			2. CCB + Methylprednisolone	Benefit for 3 weeks with steroids, but recurrence after they were stopped
Yokoyama et al., 2006 [7]	35/ M	Alternating ICA stenosis almost monthly since age 20	1. Propranolol, Arotinolol, Nifedipine, Diltiazem, Isosorbide, Nicorandil, Nisoldipine, Diazepam, Phenytoin, Valproate, and Aspirin for at least 3 months each	Recurrent vasospasm
			2. Stellate ganglion block	Temporary amelioration of vasoconstriction though frequency of attacks unchanged
Mosso et al., 2007 [8]	45/ M	Alternating ICA stenosis (16 left and 7 right over 42 months)	1. Aspirin 100 mg daily	Recurrent vasospasm
			2. Sublingual nitroglycerin	Immediate, but not long-term relief
			3. Isosoribide dinitrate 100 mg daily + diltiazem 180 mg daily	Not tolerated due to headache
			4. Flunarizine 10 mg daily	Recurrent vasospasm
Magnin et al., 2011 [9]	39/ M	Bilateral ICA stenosis at onset	1. Propranolol 40 mg daily + acetaminophen	Recurrent vasospasm
			2. Intranasal DHE	Recurrent vasospasm
Dembo et al., 2012 [10]	24/F	Filiform stenosis of the right ICA about 4 cm above the origin, recurring every 1–4 months	1. CCB	Symptoms increased
			2. CCB + beta-blocker	No change
			3. Intra-arterial Isosorbide Dinitrate	No change
			4. Balloon angioplasty	Immediate relief, no follow-up data given
Moeller et al., 2012 [11]	25/ M	Bilateral ICA between 2 cm cranially of the carotid bulb and skull base, recurring every few days	1. Oral anticoagulation (phenprocoumon) + a1-blocker (prazosin) 10 mg/d	Reduced vasospasm frequency
			2. Metronomic deep breathing (used to counteract vasospasm from cold pressor test)	Immediately reduced vasospasm
Fujimoto et al., 2013 [12]	47F	RICA cervical segment every 3 months × 3	1. Carotid artery stenting	No recurrence at 24 months
Fujimoto et al., 2013 [12]	46F	LICA cervical segment	1. Carotid artery stenting	No recurrence at 24 months
Sawa et al., 2013 [13]	67/F	Bilateral extracranial ICA at onset	1. IV Argatroban (60 mg/day, 3 days)	Worsening
			2. Edaravone (60 mg/ day x 11 days)	Worsening
			3. IV Dexamethasone (12 mg/day, 5 days)	Decorticate posturing, paradoxical breathing, cardiopulmonary arrest, death
Wopking et al., 2013 [14]	34/F	LICA followed by RICA 3 days later	1. CCB Nicardipine (240 mg/day) and Phenprocoumon	Recurrence in 5 years
			2. CCB and Aspirin	Recurrence in 6 years
Huisa and Roy, 2014 [15]	55/F	RICA cervical segment. Many similar episodes alternating sides in prior 30 years	1. Aspirin, long-acting nitrate, and a tapering course of prednisone	7 recurrent episodes of unilateral hemiparesis in 12 months
Shimoda et al., 2014 [16]	25/F	RICA followed by LICA at 12 days and recurrent RICA at 14 days	1. Catheter angiography	Relief of right ICA, left remained partially stenosed
			2. Intra-arterial 15 mg fasudil hydrochloride	No change
			3. Intra-arterial 1 mg nicardipine	Dilation of left ICA
			4. Oral benidipine	No follow-up data given
Yoshimoto et al., 2014 [17]	40/F	LICA cervical segment	1. Carotid artery bifurcation stenting	Recurrent vasospasm
			2. Additional stent in prepetrous portion of carotid artery	No recurrence at 24 months
Takeuchi et al., 2016 [18]	25/ M	LICA followed by RICA cervical segments 3 days later	1. CCB + nitrate (unspecified)	Vasospasm lasting up to one week
			2. Methylprednisolone 250 mg/d x 3 days, followed by slow steroid taper	Initial resolution of vasospasm in one day but recurrence of spasm 14 months later on prednisone 15 mg/ d
Vaccani et al., 2016 [19]	24/ M	Alternating RICA and LICA 3× per year then once a month	1. Low dose aspirin and midodrine	No follow-up data given
			2. Marijuana cessation	
Takahira et al., 2017 [20]	40/ M	Alternating RICA and LICA 1-2× per month since age 29	1. RICA stenting followed by LICA stenting one month later	No vasospasm at 6 month follow up
Hirayama et al., 2018 [21]	38/ M	LICA followed by RICA cervical segments 9	1. CCB and antiplatelet	Discharged home day 39, no follow-up data given

(continued on next page)

Table 1 (*continued*)

Reference	Age/ Sex	Location and Timing of Vascular Abnormalities	Treatment	Outcome
		days later. Similar episodes age 27 and 35		
Kim et al., 2020 [22]	18/ M	Alternating RICA and LICA cervical segments monthly since age 13	1. Antiplatelets, warfarin, vasodilators, steroids, balloon angioplasty	Multiple bilateral recurrences
Kim et al., 2020 [22]	22/ M	RICA and LICA cervical segments at onset	1. Balloon angioplasty RICA, aspirin and CCB	Bilateral recurrent stenosis at one year
Our case	18/F	Alternating RICA and LICA ranging from above bifurcation to below skull base	1. Aspirin 81 mg TID	Recurrent subclinical vasospasm
			2. Lovenox 50 mg BID	Recurrent clinical vasospasm
			3. Verapamil 120 mg BID	Recurrent clinical vasospasm
			4. Nifedipine 60 mg + prazosin 1 mg bid	Lightheadedness
			5. Prazosin 1 mg bid	Recurrent clinical vasospasm
			6. Cardene 30 mg TID	Recurrent clinical vasospasm
			7. Midodrine, Florinef 0.1 mg, salt tablets	Recurrent clinical vasospasm
			8. Gabapentin, nimodipine, aspirin and clopidogrel	No vasospasm x 5 years

* One abstract/case report published in Japanese was not included in this table.

there is no known long-term effective treatment at this point. This study is limited due to retrospective nature and treatments were often done in combination making it difficult to determine which mechanism may be of highest benefit. Randomized control trials and large observational studies are difficult given the rarity of this condition. Further research is warranted into the mechanisms of vasospasm and possible genetic etiologies.

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