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CASE REPORT

Reversible Cerebral Vasoconstriction Syndrome Associated With Oxybutynin Use; a Brief Review of Pathophysiology

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Abstract

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by reversible vasospasm of the central nervous system vasculature. It usually presents as a classic thunderclap headache, but complications like a stroke, seizure, or intracranial hemorrhage may occur at the onset. Most cases are linked temporally to secondary agents. The most common suggested mechanism underlying the RCVS is vascular tone dysregulation. Our report describes the RCVS incidence associated with oxybutynin use in a young female. We aim to describe the potential pathophysiology linking oxybutynin use and RCVS.

Keywords: RCVS, Oxybutynin, Thunderclap headache, Pathophysiology, Vasoconstriction

1. Background

RCVS is a syndrome characterized by reversible vasospasm of CNS vasculature. It usually presents with multiple episodes of thunderclap headaches. RCVS mostly runs a benign clinical course, but major strokes leading to significant morbidity and mortality can happen in a minority of patients. Frequently, a secondary inciting event, such as pregnancy or an agent, usually a vasoactive substance like an SSRI, can be linked to RCVS. However, to our knowledge, no case of RCVS has been reported associated with the bladder relaxant oxybutynin.

2. Case

A 45-year-old female with a history of migraine headaches presented with acute onset severe, intermittent occipital headache of two weeks. Her headache would start as a dull occipital headache to become throbbing and generalized within a minute to involve the whole head. It would last for a few hours at maximum intensity and diminish over time to a persistent low-intensity headache with the help of medications, only to come back the next day. It was associated with photo- and phonophobia, nausea, and vomiting. Her current headache was much different from her prior migraines regarding the character, intensity, duration, and response to treatment. Previously, Her migraine headache would respond quickly to NSAIDs. She has not had any significant migraine-type headaches for about 20 years since a total abdominal hysterectomy, and bilateral salpingo-oophorectomy was performed for endometriosis. Her medications included estradiol 1 mg PO daily with no change in dose for >15 years. Two weeks prior to this headache onset, she was also prescribed oxybutynin 5 mg daily for chronic bladder hyperactivity. She denied recent viral illness, arthralgias, myalgias, skin lesions, or new onset

Abbreviations: Reversible cerebral vasoconstriction syndrome, RCVS; central nervous system, CNS; Nitric oxide, NO; Intracranial hemorrhage, ICH

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bladder/bowel dysfunction. On her frequent ER visits a week before the admission, repeated head CTs and labs were unremarkable, with multiple medications ((ketorolac, dexamethasone, diphenhydramine, nalbuphine, ondansetron, and metoclopramide)) only providing temporary and incomplete relief. Initial vitals in the ER included BP 131/67 mmHg, HR 71/min, RR 18/min, O2 Sat 94% on RA, T 98.2 F. CBC, CMP, ESR, and CRP were unremarkable. She was in severe distress due to a headache, and the physical examination was non-localizing with intact orientation. A CT scan of the head was unremarkable. CTA of the head and neck showed extensive long-segment intermittent or beaded stenosis involving anterior, middle, and posterior cerebral arteries without large vessel-filling defects (Fig. 1). MRI of the brain showed scattered nonspecific white matter changes without diffusion restriction. She was admitted with concern for vasculitis vs. FMD vs. viral encephalitis vs. RCVS. CTA of the chest, abdomen, and pelvis was unremarkable for radiologic evidence of vascular abnormalities. A lumbar puncture showed a protein of 53 mg/dL (15–45 mg/dL) and a positive HHV6 PCR. Other labs showed B12 level 477 pg/ml (180–914 pg/ml) and TSH 2.283 uIU/ml (0.450–5.330 uIU/ml). Urinalysis did not show hematuria. The urine toxicology screen was negative. Immunoglobulin levels, ANA, ANCA, AMA, cryoglobulins, APS panel, complement levels, protein electrophoresis, COVID-19 PCR, respiratory composite panel, HIV serology, hepatitis serology, homocysteine, and ACE level showed no significant abnormalities. On admission day two, a repeat MRI brain done for worsening mental status (confusion, lethargy, and decreased responsiveness) showed resolving areas of patchy non-enhancing nonspecific white matter hyperintensity and a new, more confluent hyperintensity over the parietal-occipital parts with focal areas of restricted diffusion indicative of developing infarct. Repeat CTA head and neck showed progressive areas of vessel caliber variation involving the anterior middle and posterior cerebral artery territories (Fig. 2). The cervical, thoracic, and lumbar spine MRI revealed no overt central or peripheral demyelinating, ischemic or inflammatory changes. She was initially treated with gabapentin followed by nimodipine and eventually discharged on verapamil with significant improvement of symptoms. Her oxybutynin was stopped. At the eight-week follow-up, she remains headache free.

3. Discussion

RCVS is characterized by a hallmark of reversible multifocal beading of the cerebral arteries with clinical features of thunderclap headache and sometimes neurologic deficits related to brain edema, stroke, or seizure. It is more prevalent in females, with ratios from 2:1 to 10:1 in different studies with a mean age of presentation around 42.5 years.[1] Most cases are temporally associated with a secondary agent or events like pregnancy. Most frequently associated agents are vasoactive substances, e.g., cannabis, antidepressants, nasal decongestants sumatriptan, SSRI, SNRI, pseudoephedrine, diet pills, and illicit drugs like ecstasy, amphetamines, and cocaine.[1-4] Recurrent sudden thunderclap (max intensity in <1min) headache often accompanied by nausea, vomiting, photo- and phonophobia is usually the most prominent feature.[5] Sometimes it may present as a complication in the form of a stroke, intracranial

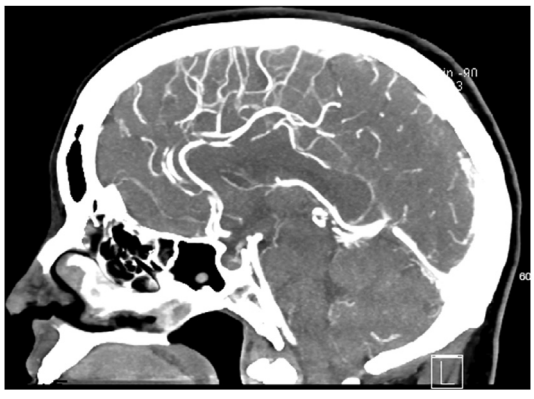

Fig. 1. CTA showing Mid and distal ACA stenoses.

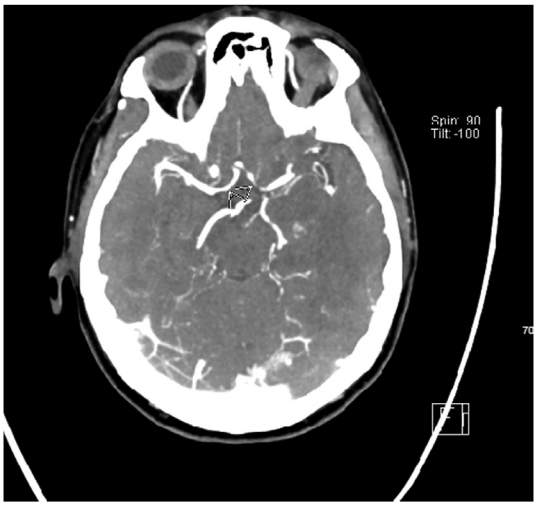

Fig. 2. Progressive and increased areas of caliber variation and stenosis are readily apparent within the A1 segments of both anterior cerebral arteries, left greater than right.

hemorrhage (ICH), seizures, and changes in mental status.

The exact pathophysiology remains ambiguous, but it is hypothesized to be related to exaggerated vascular receptor activity or sensitivity resulting from a cerebral vascular tone dysregulation that could be spontaneous or evoked central vascular discharge.[5,6] Genetic predisposition, sex hormonal influences (higher incidence in premenopausal females), and infections associated with hyperinflammatory states such as COVID-19 have been linked to RCVS.[7] Factors causing vascular tone dysregulation include sudden sympathetic overdrive (emotional, situational, drugs) and attenuated parasympathetic effect.[8] The sympathetic system acts differently on various locations of cerebral arteries; sympathetic drive causes vasodilation of distal arterioles through β2 receptors causing vasodilation that, in turn, leads to stretching of nociceptors causing thunderclap headaches. At the same time, the sympathetic activity causes vasoconstriction of larger arteries upstream, visible on imaging as characteristic lesions.[9] Nitric oxide (NO) from endothelium causes vasodilation and is one of the main mechanisms of vasodilation in non-innervated vascular trees. Endothelial dysfunction has been proposed to play a significant role in RCVS and other vascular pathologies of CNS. Finally, blood–brain barrier breach has also been well documented in patients with RCVS and may be related to endothelial dysfunction and blood pressure surges.[9]

In our patient, the only trigger seems to be the addition of oxybutynin. The significance of HHV6 PCR in CSF with no clinical viral illness is unknown. Oxybutynin is an antimuscarinic drug with moderate selectivity at the M3 receptor.[10] Of all five types of muscarinic receptors found in brain tissue, M1, M3, and M5 are the predominant types. All these receptors, when activated, lead to smooth muscle contraction in pericytes causing vascular contraction but also induce indirect vasodilation through endothelial NO. The effect of NO is usually humoral and not neurogenic. Generally, the balance is influenced by vascular tone; in dilated arteries, the constrictor effect predominates, but under high vascular tone, the vasodilatory response dominates. Thus, in pathologies where the endothelium is damaged or removed, the activation of M3 on the vascular smooth muscle cells causes vasoconstriction. Interestingly, experiments in bovine cerebral arteries reported M3 inhibiting the release of acetylcholine and norepinephrine, suggesting M3 has a regulatory function mediating both constriction and dilation of cerebral arteries.[11] By blocking M3 in a humoral fashion, oxybutynin may cause endothelial dysfunction tilting the balance towards vasoconstriction by innervated smooth muscles already affected by dysregulated tone.

Diagnosis of RCVS is made through a combination of appropriate clinical and radiographic findings. It includes the presence of typical headaches, the characteristic beading appearance of cerebral vessels, and the absence of aneurysmal ICH with benign CSF analysis.[12] Recently a tool called RCVS2 score has been devised for its diagnosis.[13] The clinical outcome is usually benign, although major strokes can result in severe disability or death in a minority.[1]

Many treatments have been described to alleviate the headaches of RCVS. The most used are calcium channel blockers with variable success.[14] IV magnesium is also reported, but it is unclear whether they prevent hemorrhagic or ischemic complications.[15] One common feature multiple studies highlighted was that steroids were associated with worse outcomes.

4. Conclusion

Most RCVS cases can be temporally associated with an inciting event or agent, usually a vasoactive substance. The dysregulated vascular tone in the settings of some predisposition to develop RCVS seems the most plausible of the pathophysiologic mechanisms described. In our case, we suggest oxybutynin could have been the agent that propelled this predisposed individual to manifest the clinical symptoms and radiographic findings of RCVS.

Disclosures

The authors have nothing to disclose.

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