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Reversible Cerebral Vasoconstriction Syndrome Associated with Vasospasm of the Colic Arteries and Possibly Coronary Vasospasm

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 48-year-old
Final Diagnosis: Reversible systemic vasoconstriction syndrome
Symptoms: Chest pain • epigastric pain • headache
Clinical Procedure: —
Specialty: Cardiology • General and Internal Medicine • Physiology

Objective: Rare disease
Background: Reversible cerebral vasoconstriction syndrome (RCVS) is a disorder characterized by recurrent thunderclap headaches and reversible cerebral vasoconstriction.
Case Report: Herein, we present the case of a man in his forties with a disease entity related to RCVS accompanied by vasospasm of the extracerebral blood vessels throughout the body. The patient presented to the Emergency Department with a severe headache and epigastric pain. Initially receiving a misdiagnosis of functional pain, he continued to experience severe recurrent headaches, most often after urinating or defecating and was referred to our department. Suspecting RCVS, we performed magnetic resonance angiography, which revealed beaded irregularity in the right anterior cerebral and V4 vertebral arteries. The patient also had epigastric pain that coincided with each headache. Electrocardiography revealed pronounced ST-segment elevation in leads I and aVL and inverted T wave in lead III, while abdominal computed tomography angiography showed narrowing of the colic arteries. We named this disease "reversible systemic vasoconstriction syndrome" (RSVS) as a potential suggested terminology for the future.
Conclusions: RSVS is a clinical syndrome characterized by thunderclap headaches and simultaneous unbearable pain in extracerebral organs. To the best of our knowledge, this is the first case report of RCVS with coronary and colic artery vasospasm. We need to take great care of patients with chest or abdominal pain accompanied by recurrent thunderclap headaches, since they can be misdiagnosed with functional or psychogenic disorders.

Keywords: Vasospasm, Intracranial • Headache Disorders, Primary • Cerebrovascular Disorders

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Background

Reversible cerebral vasoconstriction syndrome (RCVS) is an acute-onset clinical syndrome characterized by recurrent thunderclap headaches (severe pain that peaks in seconds) and diffuse reversible segmental narrowing of at least 2 cerebral arteries. In 2007, Calabrese et al [1] introduced the concept of syndromic reversible cerebral vasoconstriction, a clinical syndrome that was first reported in 1970, and further proposed the diagnostic criteria for it. The vasospasm involved in RCVS generally resolves within 3 months and is not associated with primary angiitis of the central nervous system or aneurysmal subarachnoid hemorrhage [2]. More than half of RCVS cases are thought to occur postpartum or upon exposure to adrenergic and serotonergic drugs [3]. In addition, several cases of RCVS associated with extracerebral vasospasm in the coronary and renal arteries have been reported [4-9]. However, there are few reports of coronary and abdominal artery vasospasm [5,8]. Herein, we report a case of RCVS accompanied by coronary and colic artery vasospasm, which we termed, as a potential suggested terminology for the future, "reversible systemic vasoconstriction syndrome" (RSVS) that manifested as a predictable extracranial vasospasm coinciding with cerebral vasoconstriction. To the best of our knowledge, this is the first case report of RCVS with coronary artery vasospasm revealed by coincident ST segment changes on electrocardiogram (ECG) and colic artery vasospasm visualized on abdominal computed tomography (CT) angiography.

Case Report

A 48-year-old man with hypertension and hyperuricemia presented to the Emergency Department (ED) with a sudden-onset throbbing headache and severe crampy pain in the epigastric region. He smoked 1 pack of cigarettes daily for 8 years in his twenties but had since quit. He reported drinking 400 mL of Japanese sake every week. Hyperuricemia had been diagnosed when he was in his forties, and he had been taking 20 mg of febuxostat daily for 4 years. He denied taking any other drugs, including cocaine, amphetamines, caffeine, or medications that constrict blood vessels.

The current episode began with sudden epigastric pain while washing dishes, followed within 1 min by a severe occipital headache. The intensity of the headache and the epigastric pain was initially described on a numerical rating scale (NRS) score of 5/10, increasing to an NRS score of 10/10 within 30 min. The patient described no provoking factors preceding the sudden onset of the pain and no palliative factors. The pain in both areas persisted for 3 to 4 h without fluctuations in intensity. The patient was alert and oriented with a blood pressure of 155/103 mmHg, temperature of 36.3°C, pulse of 64 beats per min, respiratory rate of 13 breaths per min, and oxygen saturation of 99% on room air. A physical examination revealed no neurological abnormalities. No nuchal rigidity, accentuation of knee jerk, allodynia, or neuralgia was observed. His abdomen was soft, without tenderness on palpation, and bowel sounds were present. No masses, rebound, or guarding were observed. The creatine kinase-myoglobin binding level was 11 U/L, while the troponin T level was 0.008 ng/mL. We did not conduct a urine toxicology screen since illicit drugs are extremely hard to obtain in Japan. No obvious ST-T changes were observed on ECG, and no asynergy was seen on echocardiography. A CT scan from the head to the pelvis was unremarkable. The patient was treated with 1000 mg of acetaminophen, and the pain disappeared a few hours thereafter. Given the normal workup and spontaneous resolution, functional pain was diagnosed and he was discharged home.

Upon returning home, the patient's headache reappeared for 1 min during micturition and then resolved before he could take any acetaminophen. On the subsequent day, similar symptoms occurred while the patient was driving, again beginning with sudden epigastric pain, followed by an occipital headache (NRS 6/10) that peaked within a few minutes. He returned immediately to the ED and was again treated with acetaminophen and monitored, with the pain disappearing within 3 h. Before discharge, he was referred to our outpatient Internal Medicine Clinic for further investigation the following day.

The evaluation in the clinic corroborated the normal physical examination findings of the ED. Suspecting RCVS based on the sudden and severe nature of his symptoms, we arranged a brain magnetic resonance angiography (MRA) on the day of referral, which demonstrated irregular beading of the right anterior cerebral artery (**Figure 1A**) and mild stenosis at the distal V4 vertebral artery (**Figure 1B**). Stenosis at multiple sites confirmed the diagnosis of RCVS. There were no parenchymal abnormalities on brain magnetic resonance imaging, such as edema or infarction. Given that he was asymptomatic at the time of consultation, we decided to follow him and observe his clinical course on an outpatient basis. We did not recommend medical treatment because only 2 episodes were confirmed at that time.

A third episode of headache following epigastric or chest pain occurred again 3 days later while the patient was straining during defecation, and he returned to the ED. He was alert and oriented with a blood pressure of 150/99 mmHg, temperature of 36.2°C, pulse of 85 beats per min, respiratory rate of 18 breaths per min, and oxygen saturation of 99% on room air. Suspecting the presence of vasoconstriction in other organs causing the epigastric pain, we performed abdominal imaging. Abdominal CT angiography revealed narrowing of the right colic and ileocolic arteries (indicated by the red arrows in **Figure 2**). Electrocardiography revealed remarkable ST-segment elevation in leads I and aVL; inverted T waves were observed in lead III

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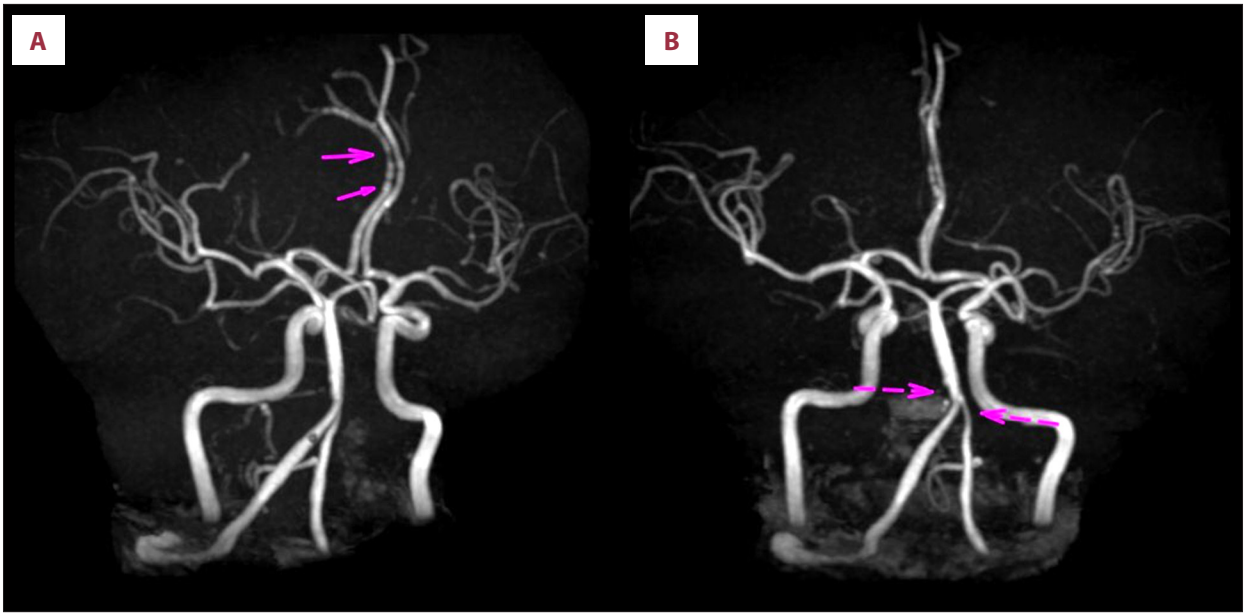

Figure 1. (**A**) Brain magnetic resonance angiogram showing beaded stenosis in right anterior cerebral artery (arrows). (**B**) Brain magnetic resonance angiogram showing stenosis in the V4 segment of the vertebral artery (arrows).

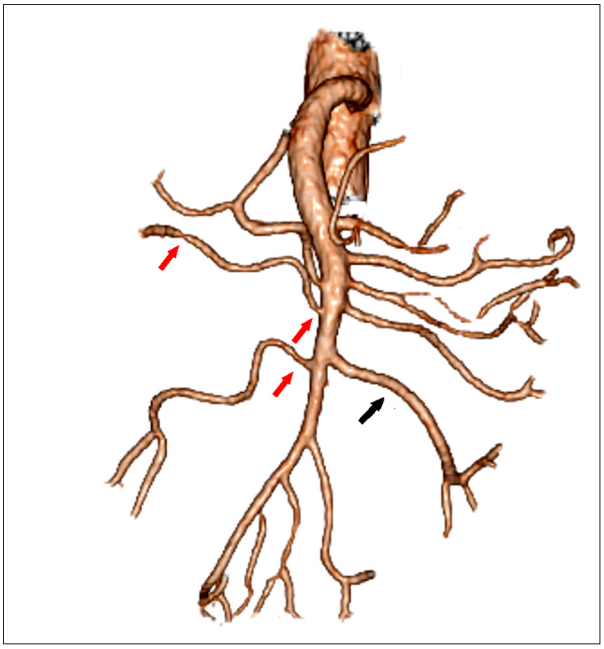

Figure 2. Abdominal computed tomography angiography showing stenosis of the right colic and ileocolic arteries (red arrows). For comparison, we attached the black arrow that indicates an intact branch of the jejunal artery.

(**Figure 3A, 3B**). The ST elevation was transient, and the electrocardiography was normalized 1.5 h after the onset of symptoms (**Figure 3C**). The creatine kinase-myoglobin binding level was 12 U/L, while the troponin T level was 0.006 ng/mL. Coronary angiography was performed 4 h after the onset of symptoms without the use of antithrombotics or aspirin, but no spasm or stenosis of the coronary arteries was observed; moreover, no changes in the caliber of the coronary arteries were noted after nitroglycerin administration.

The differential diagnoses of epigastric pain accompanied by ST-segment changes on electrocardiography, but without elevation of cardiac enzymes, include vasospastic angina and unstable angina pectoris. In this case, the coronary angiography findings were inconsistent with unstable angina pectoris. The absence of stenosis, transient electrocardiography changes, and chest pain strongly suggested ephemeral coronary artery vasospasm consistent with vasospastic angina, although it is one of the diagnostic possibilities since we did not conduct the intracoronary acetylcholine test. We also noted simultaneous vasospasm in the colic arteries, suggestive of RSVS. Other differential diagnoses of headache included intracerebral hemorrhage, cerebral venous thrombosis, cervical or cerebral arterial dissection, pituitary apoplexy, and aneurysmal subarachnoid hemorrhage, which were ruled out using a cerebral CT scan. We also considered antiphospholipid antibody syndrome, but the activated partial thromboplastin time was 26.7 s, which was within the normal range. We did not measure antiphospholipid antibody levels because no findings were suggestive of thrombotic predisposition. We also listed the differential diagnoses of headache accompanied by chest or abdominal pain (**Table 1**). We ruled out giant cell arteritis since he did not have typical signs, such as temporal headache, abrupt onset of visual disturbances, limb claudication, asymmetric blood pressures, and jaw claudication. We also ruled out Takayasu arteritis since he did not have constitutional symptoms, arthralgias,

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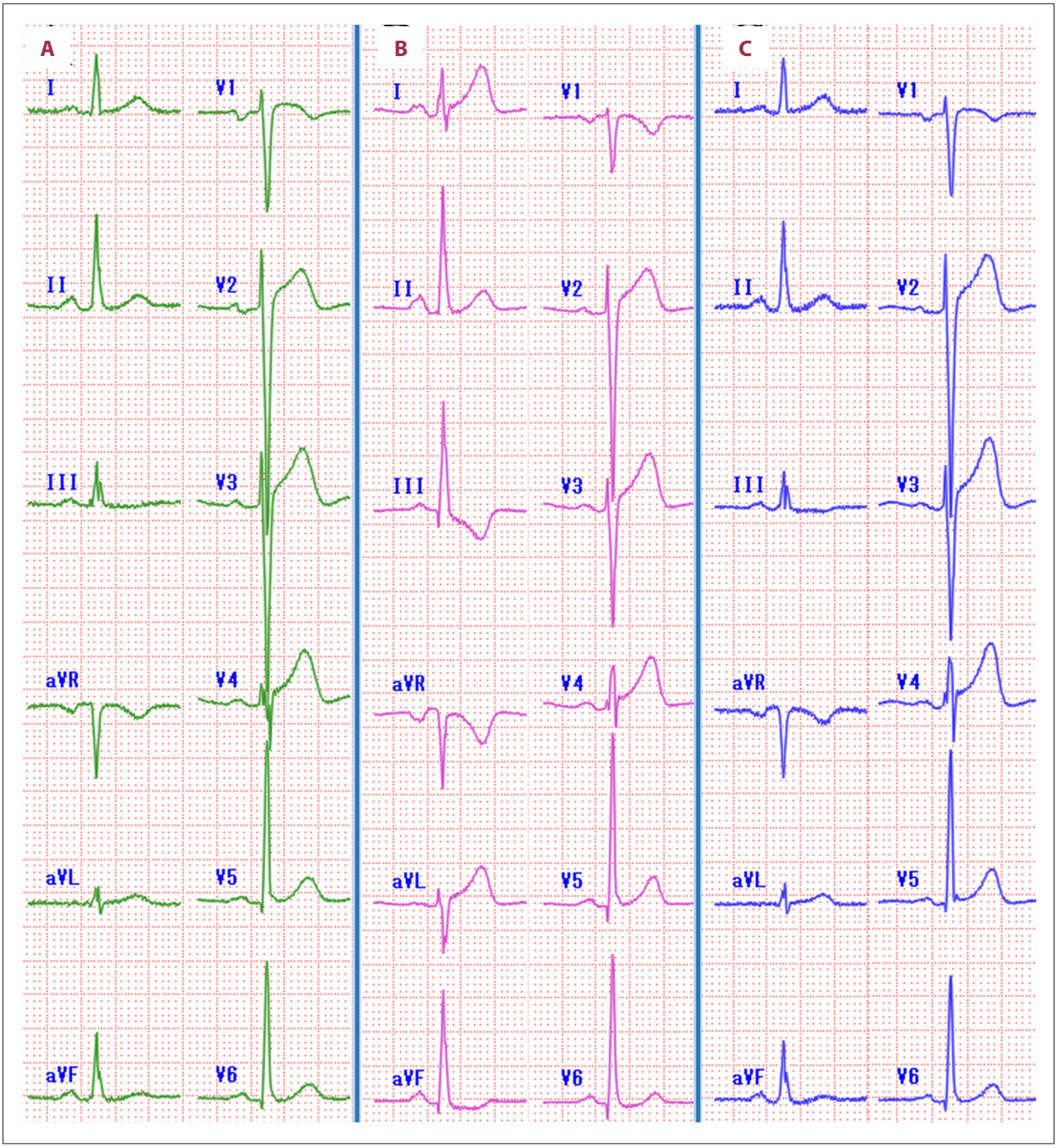

Figure 3. (**A**) Electrocardiogram recorded at the first visit showing no abnormal findings. (**B**) Electrocardiogram of the third attack showing remarkable ST-segment elevation in leads I and aVL and inverted T waves in lead III. (**C**) Electrocardiogram (ECG) after 1.5 h of the third attack showing normalized ECG.

carotidynia, absent or weak peripheral pulse, limb claudication, arterial bruit, and discrepant blood pressure between arms.

Given that we observed narrowing of the arteries on brain MRA and abdominal CT angiography in addition to changes in the ECG consistent with vasospasm, we assumed that this patient likely had systemic arterial vasoconstriction. Thus, we pursued treatment for vasospastic angina in the cerebral, coronary, and colic arteries, prescribing 20 mg of sustained-release nifedipine orally to prevent vasospasm and for blood pressure control, as well as 40 mg of isosorbide dinitrate by patch for antianginal effects and seizure prevention. Nitroglycerin was prescribed for further attacks. At follow-up 2 weeks after coronary angiography, the patient had only 1 additional attack, which occurred 2

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Table 1. Differential diagnoses of reversible cerebral vasoconstriction syndrome (RCVS) plus syndromes.

Differential diagnoses of RCVS plus syndromes

• Reversible cerebral vasoconstriction syndrome
  • Vasospastic angina
  • Renal arteries vasospasm
• Systemic vasculitis
  • Large vessels
  • Giant cell arteritis
  • Takayasu arteritis
  • Secondary causes
• Antiphospholipid antibody syndrome
• Migraine
  • Cardiac cephalalgia
  • Abdominal variants of migraine
• Intoxication
  • Alpha-adrenoceptor agonists
  • Vasopressin analogs
  • Epinephrine
  • Norepinephrine
  • Phenylephrine
  • Serotonin 5-hydroxytryptamine agonists
  • Almotriptan
  • Eletriptan
  • Frovatriptan
  • Naratriptan
  • Rizatriptan
  • Sumatriptan
  • Zolmitriptan
  • Dobutamine
  • Dopamine
  • Drugs
  • Cocaine
  • Amphetamine
• Psychosomatic disorder
  • Somatoform disorders

days after angiography. During this episode, headache and epigastric pain (NRS 6/10) began immediately after defecation. The pain resolved within 30 min after taking nitroglycerin, confirming reversible vasospasm in the colic arteries as the cause of his pain. At follow-up, we increased the dose of sustained-release nifedipine to 40 mg orally. Upon telephone follow-up 2 months after the first dose of nifedipine, he denied experiencing further thunderclap headaches. Nimodipine is commonly used as a treatment for RCVS, while calcium-channel blockers in general, such as nifedipine, nimodipine, and verapamil, have been reported to be effective [13]. It should be noted that the patient was started on nifedipine because nimodipine is not available in Japan.

Discussion

RSVS is characterized by the presence of systemic vasospasm involving extracerebral organs in addition to cerebral vasoconstriction. Several case reports have discussed the spectrum of extracerebral involvement in RCVS [4-9]. Renal artery vasospasm accompanying RCVS has been described twice previously [4,9]. In addition, dissection of the internal and external carotid arteries is associated with RCVS [5,9-11]. In a retrospective case series of patients with RCVS who underwent transthoracic echocardiography (TTE) during ictus [5], 17% had signs of wall motion abnormalities; however, ECG data were unavailable. In a case report of a 50-year-old woman with chest pain and thunderclap headache [8], elevated serum cardiac enzymes and wall motion abnormalities on TTE indicated coronary artery vasospasm, but no ischemic changes on 12-lead ECG or coronary artery disease on angiography were observed. Few reports have been published on coronary artery vasospasm with RCVS [5,8], and this is the first reported case of the sequelae of vasoconstriction captured on ECG despite the fact that no elevation of biomarkers or frank stenosis was observed on coronary angiography. Furthermore, this case revealed evidence of narrowing of the colic arteries, which has not been previously described in the literature. However, this case report does not include information on stenosis in other parts of the vascular endothelium because we did not conduct digital angiography throughout the body, considering its invasiveness. There is still room to consider that symptoms may differ by location.

The pathogenesis of RCVS remains unknown; however, a previous study suggested that triggering cerebral endothelial dysfunction increased vascular tone, and this may contribute to RCVS [12]. We expect a similar etiology to be applicable to blood vessels throughout the body given the evidence of vasoconstriction occurring in extracranial arteries during RCVS ictus. We suspect that the scarcity of studies characterizing RSVS, especially those with cardiac involvement, is due to the fact that patients presenting with headache who have pain in other parts of the body are more likely to be misdiagnosed with other diseases. In this case, functional or psychogenic headache was diagnosed on both the first and second visits to the ED before the patient was referred to Internal Medicine, where he was diagnosed with RSVS. Moreover, vasoconstriction in RCVS is typically believed to resolve within 3 months [2]; however, misdiagnoses may not have been identified since patients may have had to endure symptoms for only a few months. It is necessary to recognize RSVS as part of the RCVS spectrum involving noncerebrovascular vasospasm that may not have been thoroughly addressed or investigated. Furthermore, the symptoms, such as headache, chest pain, and abdominal pain, could repeat again and again in cases of RSVS. More data are necessary to investigate the prevalence and pathogenesis of RSVS. Given that we observed headaches associated with pain in other parts of the body, such as abdominal variants of migraine [14] or cardiac cephalalgia [15], such migraines could be derived from the same pathology as RSVS.

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Conclusions

RSVS is characterized by cerebral vasoconstriction and simultaneous systemic vasospasm manifesting as sudden-onset unbearable pain in a variety of extracerebral organs. Although several cases of RCVS with coronary artery vasospasm have been reported, this is the first case describing simultaneous colic artery vasoconstriction. Patients with chest or abdominal pain due to RSVS, in addition to recurrent thunderclap headache, may be at a higher risk of receiving a misdiagnosis of functional or psychogenic headache than those with classic RCVS manifesting as headache alone.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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