Reversible cerebral vasoconstriction syndrome (RCVS) is a rare neurological condition, characterized by recurrent thunderclap headaches and neuroimaging findings of multifocal vasoconstriction of cerebral arteries. The Japanese authors in this study presented a patient who died of radiographically and pathologically confirmed reversible cerebral vasoconstriction syndrome one day after the third mRNA COVID (BNT162b2, Pfizer-BioNTech) vaccination.

RCVS is characterized by recurrent severe thunderclap headaches, with or without other acute neurological symptoms, and multifocal segmental vasoconstriction of cerebral arteries that resolves spontaneously within three months. Although RCVS is typically a transient condition with a generally benign clinical course, certain patients may develop severe complications like an ischemic stroke and intracerebral hemorrhage. The diagnosis of RCVS requires a high clinical suspicion and recognition of typical signs, symptoms, and common radiographic features. Brain scans of numerous patients diagnosed with RCVS look healthy despite the presence of diffuse vasoconstriction on concomitant cerebral angiograms.

Lesions include reversible brain edema and three types of stroke: subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction. To diagnose RCVS, cerebral angiography must demonstrate segmental narrowing and dilatation (a string of beads) of one or more arteries. Calabrese et al. established the diagnostic criteria for RCVS. (Calabrese LH, et al. Narrative review: reversible cerebral vasoconstriction syndrome. Ann Intern Med. 2007, 146:34-44.)

Two major pathophysiological mechanisms of RCVS currently under investigation are endothelial dysfunction and a transient disturbance of the regulation of cerebral arterial tone. Sympathomimetic agents such as cannabinoids, selective serotonin reuptake inhibitors, and nasal decongestants have been identified as potential precipitants in many cases. A recent study that used brachial arterial flow-mediated dilation assessment two weeks after the second BNT162b2 mRNA COVID-19 vaccination, showed endothelial dysfunction in relatively healthy participants. The authors suggested that endothelial dysfunction detected after the second dose of the BNT162b2 vaccine may be related, at least in part, to thrombotic events that develop early after vaccination. https://discovermednews.com/bnt162b2-mrna-vaccine-impairs-endothelial-function-for-six-months-after-the-second-vaccination/

Approximately 50-70% of patients experience headaches after receiving the SARS-CoV-2 mRNA vaccination. The causes of headaches range from tension-type headaches to intracerebral bleeding, subarachnoid hemorrhage, or venous sinus thrombosis. There are

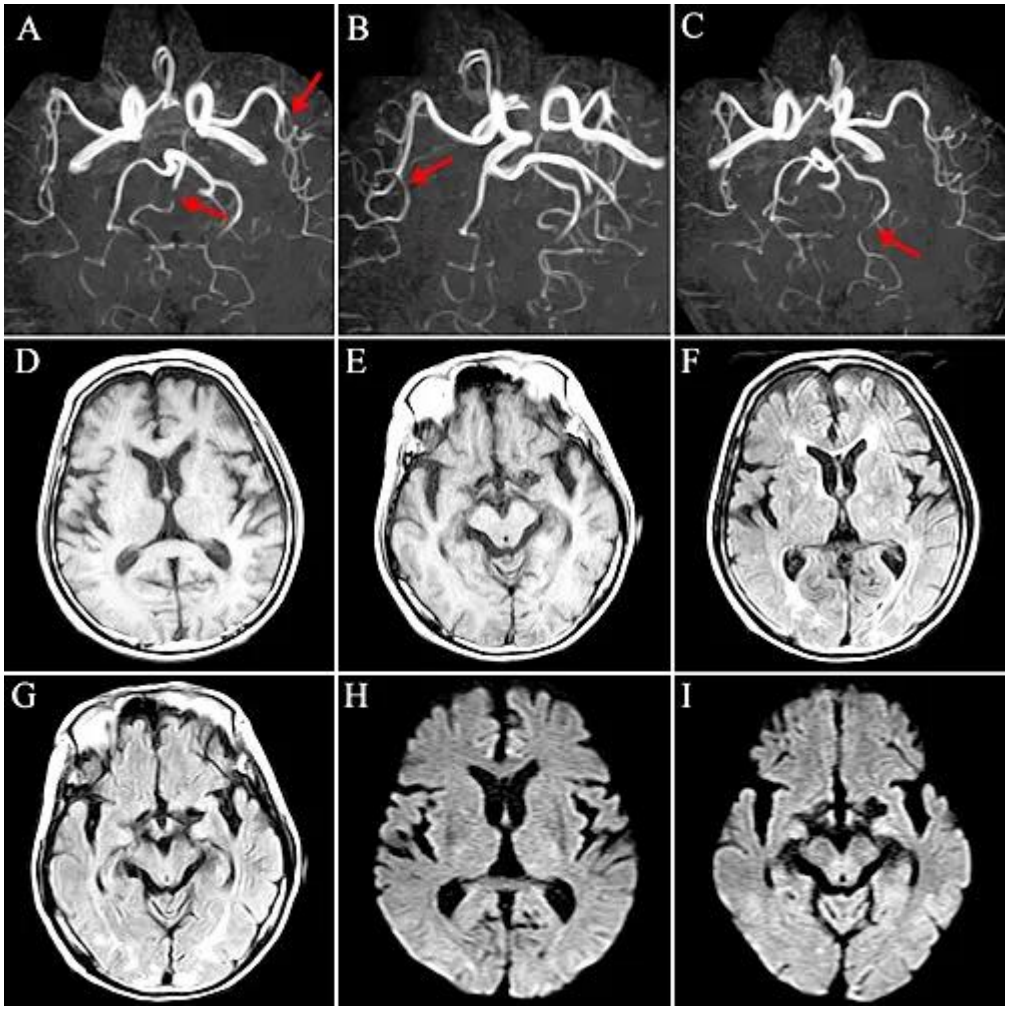
several case reports of RCVS after mRNA vaccination; however, its pathophysiology remains poorly understood.

Case report

A 73-year-old man was hospitalized for acute exacerbations of chronic obstructive pulmonary disease. In medical history, he had hypertension and osteoporosis, as well as giant cell arteritis. He was treated with salbutamol, ceftriaxone, and prednisolone.

On the 38th day of hospitalization, he developed hospital-acquired pneumonia and was treated with piperacillin and tazobactam. On the 46th day after admission, he received a third dose of the mRNA SARS-CoV-2 vaccine (BNT162b2, Pfizer-BioNTech, New York). The next morning, he experienced a moderate headache, tonic-clonic seizures, and a disturbance of consciousness. Neurological examination demonstrated a conjugate deviation of the eyes to the right.

Brain magnetic resonance imaging showed multiple vasoconstrictions of the middle and posterior cerebral arteries, without evidence of acute cerebral hemorrhage or infarction. Electroencephalography showed frequent spike activity, dominant in the right hemisphere, and diffuse high-voltage slow waves.



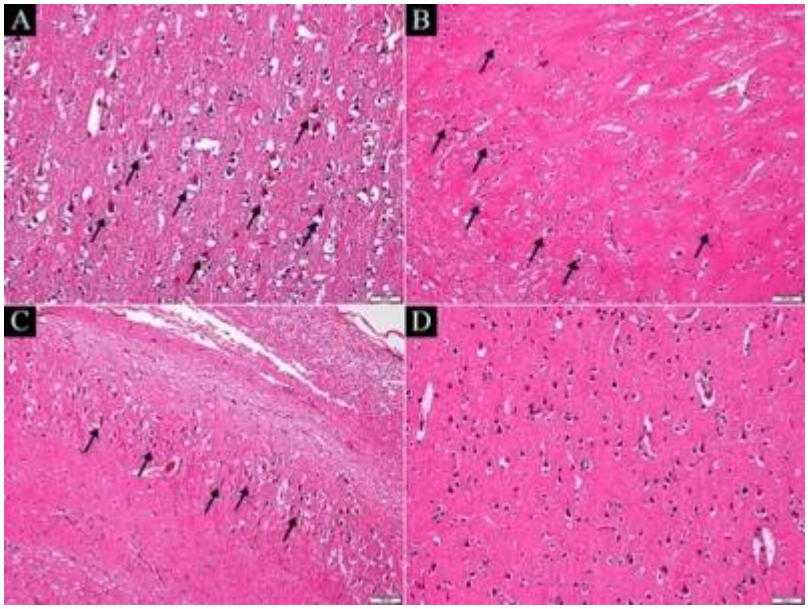
The original figure from the article of Shimura M et al. Head magnetic resonance angiography shows multiple vasoconstrictions involving the middle and posterior cerebral arteries (red arrows). T1-weighted (D-E), FLAIR (F-G), and diffusion-weighted (H-I) images show chronic ischemic changes without any acute intracranial hemorrhage or infarction.

The intravenous diazepam stopped the tonic-clonic seizures. Intermittent convulsions of the left upper extremity and the left side of the face persisted despite treatment with levetiracetam. His family was opposed to any other treatment except diazepam and levetiracetam. His cognitive and cardiorespiratory conditions gradually deteriorated, and he died 40 hours after the third mRNA COVID-19 vaccination.

Autopsy report

The brain autopsy revealed multiple fresh ischemic lesions in the cerebral cortices of the temporal and occipital lobes, and the Ammons horns (CA1-3) on both sides of the brain.

There were no pathological changes in the anterior lobe, basal ganglia, thalamus, brainstem, or cerebellum. Also, there was no evidence of thrombus formation or inflammatory cell infiltration in the main cerebral arteries. Based on these findings, the scientists concluded that the patient had acute ischemic brain injuries, mainly in the territory of the middle and posterior cerebral arteries, caused by multiple vasospasms of the bilateral cortical branches of the middle and occipital cerebral arteries. RCVS has been diagnosed radiographically and pathologically.



Original figure from the article of Shimura M et al. Pathological examinations at autopsy (hematoxylin and eosin stain). Severe perineuronal space enlargement and many eosinophilic neurons were observed in the temporal cortex (A), CA1 (B), and CA2–3 (C) (black arrows). Conversely, no pathological changes were observed in the anterior lobe (D).

Possible differential diagnoses included status epilepticus, hypoxic-ischemic encephalopathy, and systemic circulatory disturbances. The hippocampal injury due to status epilepticus typically occurs in the regions CA1, 3, and 4, whereas CA2 tends to be preserved. This is not consistent with the pathological findings in this case. There were no

apparent lesions in the cerebellum or thalamus (dorsal medial nuclei), frequently affected by epilepsy. Cerebellar, visual, motor, and sensory cortices, easily affected by hypoxic-ischemic encephalopathy, remained intact.

According to the PubMed database, this case is the first autopsy case report of RCVS following a SARS-CoV-2 infection or COVID-19 vaccination. Although the underlying mechanism remains unknown, the authors assumed that vaccine-expressed SARS-CoV-2 spike protein interacts with angiotensin-converting enzyme 2 (ACE2), which down-regulates ACE2 and increases the vasoconstrictive peptide angiotensin 2. This results in vasoconstriction and RCVS.

Conclusion

In this study, the Japanese authors presented a patient who died of radiographically and pathologically confirmed reversible cerebral vasoconstriction syndrome (RCVS) one day after the third mRNA COVID (BNT162b2, Pfizer-BioNTech) vaccination. The scientists recommended that magnetic resonance imaging and magnetic resonance angiography should be considered in individuals who develop headaches following the SARS-CoV2 vaccination. Future research is needed to understand the underlying mechanism of headache and RCVS, and the adverse effects associated with the SARS-CoV-2 vaccination.

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Journal Reference

Shimura M, Fujikawa H, Yazawa M, et al. An Autopsy Case of Reversible Cerebral Vasoconstriction Syndrome After a Severe Acute Respiratory Syndrome Coronavirus 2 Vaccination. Cureus 2024: 16(4): e59311. (April 29, 2024) (Open Access) https://www.cureus.com/articles/233306-an-autopsy-case-of-reversible-cerebral-vasoconstriction-syndrome-after-a-severe-acute-respiratory-syndrome-coronavirus-2-vaccination?score_article=true#!/