Received: 27 September 2021 | Revised: 27 October 2021 | Accepted: 30 November 2021

DOI: 10.1002/emp2.12627

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
Open Access
WILEY

CASE REPORT

Toxicology

Reversible cerebral vasoconstriction syndrome associated with tetrodotoxin poisoning: A case report

Eiichi Kakehi MD, PhD[1] | Makoto Matsumoto MD[1] | Shohei Taniguchi MD[1] | Yukinobu Akamatsu MD[1] | Shigehisa Sakurai MD[1] | Akane Hirotani MD[1] | Takafumi Nozaki MD[1] | Keisuke Shoji MD[1] | Seiji Adachi MD[1] | Kazuhiko Kotani MD, PhD[2] | Masami Matsumura MD[2]

[1] Department of General Medicine, Tottori Municipal Hospital, Tottori-City, Tottori, Japan

[2] Center for Community Medicine, Jichi Medical University, Shimotsuke-City, Tochigi, Japan

Correspondence
Eiichi Kakehi, MD, PhD, Department of General Medicine, Tottori Municipal Hospital 1-1 Matoba, Tottori-City, Tottori 680-8501, Japan.
Email: openwater_swimming5933@yahoo.co.jp

Funding and support: By *JACEP Open* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist

Abstract

An 81-year-old woman with a history of hypertension and Alzheimer's disease presented to the emergency department because of impaired consciousness. Physical examination revealed acute progressive generalized flaccid paralysis, hypertension, respiratory failure, and pupillary dilation. Although the patient did not complain of headache, head magnetic resonance angiography and magnetic resonance imaging showed multifocal segmental cerebral vasospasm and cerebral infarction in the left occipital lobe. Her family reported that although she did not have a license to cook pufferfish, she was in the habit of eating pufferfish. We subsequently detected tetrodotoxin in the patient's urine, and she was diagnosed with tetrodotoxin poisoning. As the symptoms of tetrodotoxin intoxication improved, head magnetic resonance angiography showed the disappearance of the multifocal segmental cerebral vasospasm. The patient's clinical course and imaging findings were consistent with reversible cerebral vasoconstriction syndrome (RCVS). Sympathetic overactivity after tetrodotoxin intoxication possibly caused the development of RCVS, and RCVS could not be ruled out even in the absence of the typical thunderclap headache. Magnetic resonance angiography is a useful modality when performing repeated examinations.

KEYWORDS

ischemic stroke, magnetic resonance angiography, multifocal segmental cerebral artery vasoconstriction, pufferfish, reversible cerebral vasoconstriction syndrome, sympathetic over-activity, tetrodotoxin

1 | INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS) typically manifests as an acute-onset, recursive, severe headache that continues for about 1 month.[1] The pathophysiology involves reversible segmental vasoconstriction of cerebral arteries that is frequently associated with focal cerebral ischemia. Angiographic studies (eg, cerebral angiography, computed tomography angiography, or magnetic resonance angiography [MRA]) typically show segmental or diffuse spasms in the cerebral artery that resolve within 12 weeks.[1]

Although the onset of RCVS may occur spontaneously, clinical associations with pregnancy (postpartum vasculopathy) and ingestion of vasoactive medications, recreational drugs, and substances have been noted.[2] Furthermore, RCVS is typically accompanied by a thunderclap

Supervising Editor: Kenneth Katz, MD.

headache, but cases without headache have also been reported.[3] We herein describe a patient with RCVS who did not have the typical thunderclap headache after the onset of tetrodotoxin (TTX) intoxication and for whom repeated MRA examination was useful for the diagnosis.

2 | CASE PRESENTATION

The patient was an 81-year-old Japanese woman with hypertension and Alzheimer's dementia. However, she was receiving no medical treatment. She lived alone in a rural fishing village.

One day after dinner, she became sick and called her son in the neighborhood for help. When her son visited her house, she complained of numbness around her mouth and paresis of her extremities. She was transferred to our hospital with suspected cerebrovascular disease.

On arrival at our hospital, she was conscious but complained of dysarthria and weakness in her extremities. Her Glasgow Coma Scale score was 13 points (E4V3M6). Her vital signs were a blood pressure of 205/104 mmHg, pulse rate of 88 beats per minute, body temperature of 36.0°C, respiratory rate of 22 breaths per minute, and oxygen saturation of 97% on room air. Blood analysis showed no clinically relevant abnormalities. Both ECG and chest roentgenography revealed no specific findings. The results of a substance abuse test (phencyclidines, benzodiazepines, cocaine narcotics, stimulants, cannabis, morphine narcotics, barbiturates, and tricyclic antidepressants) were negative.

The patient was suspected to have cerebrovascular disease, but the initial brain computed tomography was unremarkable. She subsequently underwent brain magnetic resonance imaging (MRI) with MRA. Brain MRA revealed multifocal segmental irregularities in the M2 base of the right middle cerebral artery and the left posterior cerebral artery with no evidence of aneurysmal subarachnoid hemorrhage (Figure 1A, B). On the way back to the emergency department from the laboratory room, the patient developed respiratory arrest and required intubation and ventilation management. Her left and right pupils were dilated, and the light reflex had disappeared. She rapidly developed complete quadriplegia. The tendon reflexes in her extremities disappeared, and her Babinski reflexes were negative. Her circulatory dynamics were maintained with hypertension. She was admitted to the ICU and continued ventilation management.

A careful review of the patient's life history, provided by her family, revealed that she was an unqualified but routine consumer of pufferfish. She lived in a fishing village in rural Japan, where she was able to easily obtain pufferfish. We subsequently performed a urinary TTX test, which was positive (29 μg/dL). The urine sample was extracted using a C18 column and a small solid phase column and then analyzed by liquid chromatography with tandem mass spectrometry.[4] The patient was diagnosed with TTX poisoning. Later, a remnant of a *Takifugu* pufferfish was found in the kitchen of her house.

On day 2 of hospitalization, the patient exhibited movement of her extremities and spontaneous breathing, and on day 3, extubation was possible. At the 2-day follow-up, MRA and MRI showed partial disappearance of the vasoconstriction and ischemic stroke in the left posterior artery lesion (Figure 1C–F). Her consciousness could not be assessed while on mechanical ventilator management with sedation for respiratory paralysis, but she started breathing spontaneously and remained conscious when the sedative dose was reduced. We also did not use antihypertensive drugs because the use of sedatives lowered her blood pressure. Typically, visual field defects are neurological deficits at the site of infarction affected by vasoconstriction, but she had no such deficits. Although the patient did not develop a thunderclap headache and a cerebrospinal fluid examination was not performed, her imaging findings were consistent with RCVS.[1] She was therefore diagnosed with RCVS. After 14 days in the ICU without complaint, she was discharged, and drug treatment for her chronic hypertension was begun. The patient provided informed consent, and both the patient and our hospital approved using the patient's clinical data.

3 | DISCUSSION

We have herein reported a case of RCVS that developed after TTX intoxication. This case indicates that patients with chronic hypertension may develop transient further blood pressure elevation due to TTX intoxication, which may be associated with cerebral vasoconstriction. MRA is a useful modality for repeat examinations.

TTX is a potent neurotoxin originating from a wide array of taxonomic animal groups from almost all regions of the world.[5] This toxin has been detected in pufferfishes of the family Tetraodontidae, which is the origin of the name "tetrodotoxin." Pufferfish is a prevalent dish worldwide, particularly in coastal regions. In Japan, pufferfish (called *fugu*) is considered a delicacy and occasionally causes severe intoxication and even death if not correctly prepared for consumption. TTX blocks the pore region of fast voltage-gated sodium channels, thereby blocking stimulus conduction and acting on the central and peripheral nervous systems and the autonomic motor and sensory nerves.[6] Typical autonomic symptoms are hypotension and bradycardia. TTX poisoning is treated by relieving the ventilatory failure and hypoxia caused by respiratory muscle paralysis.

The exact pathogenesis of RCVS remains unclear; however, sympathetic overactivity may play a role.[2] Vasoconstrictive substances that might serve as triggers for RCVS reportedly include vasoactive medications and vasoactive recreational drugs, among others.[2] Although the typical autonomic nervous system findings of TTX poisoning are hypotension and bradycardia,[7] TTX may result in hypertension secondary to sympathetic dysfunction.[8] Deng et al.[8] postulated that individuals with preexisting hypertension responded to relatively small doses of TTX with a dramatic rise in blood pressure. The hypertension in patients with TTX intoxication might be explained by either an exaggerated response to sympathetic stimuli or by various responses of the vasomotor center to a small dose of TTX.[9] In patients with chronic hypertension, TTX can cause transient further elevation of blood pressure and induce vasoconstriction due to sympathetic overactivity, which may lead to RCVS.

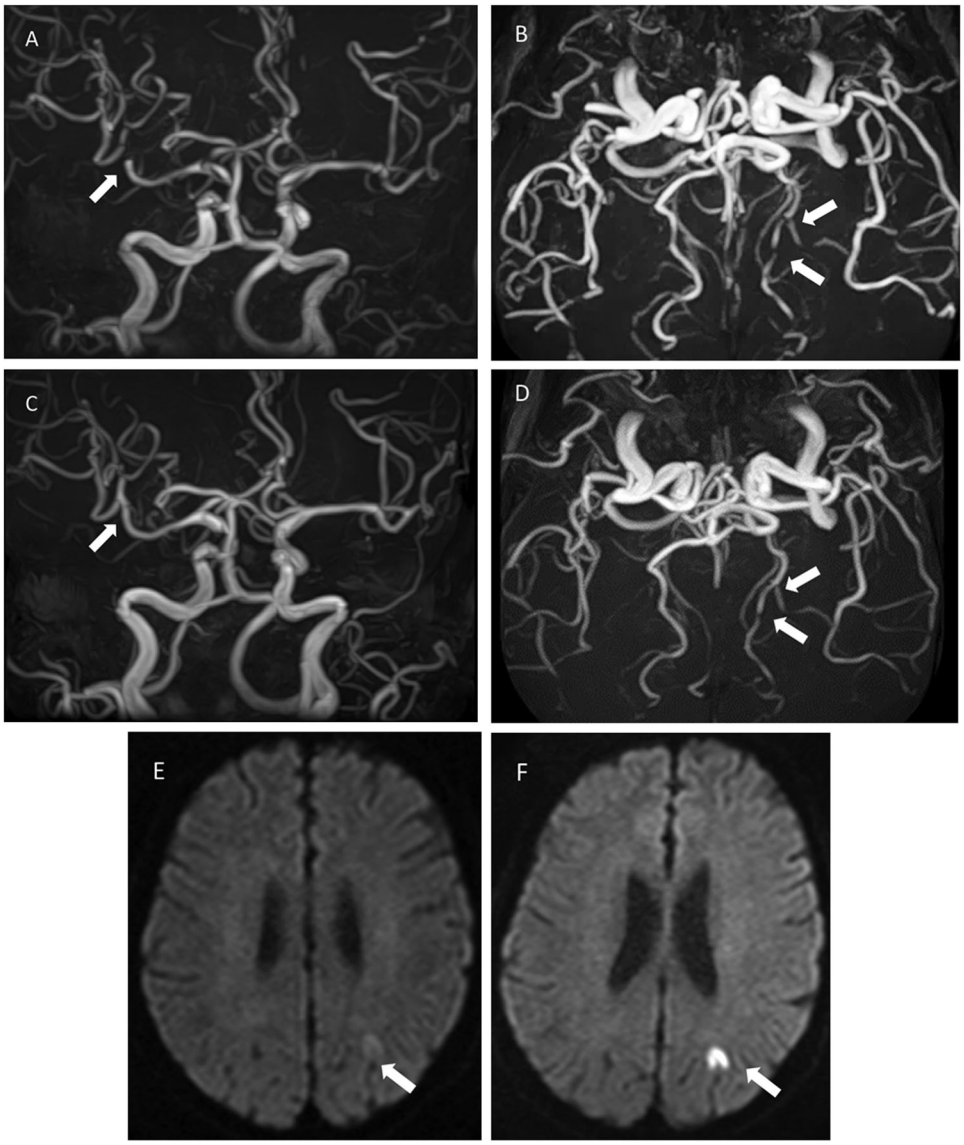

FIGURE 1 Initial and follow-up magnetic resonance angiography of an 81-year-old woman with reversible cerebral vasoconstriction syndrome following tetrodotoxin poisoning. (A, B) Magnetic resonance angiography revealed multifocal segmental irregularities in the M2 base of the right middle cerebral artery and the left posterior cerebral artery (arrows). (C, D) These irregularities had diminished 2 days later. (E) Initial magnetic resonance imaging revealed an indistinct subcortex lesion in the left occipital lobe (arrow). (F) However, an acute ischemic stroke was observed 2 days later (arrow)

The reversible vasoconstriction in our patient differed from classic RCVS in that a thunderclap headache was absent. Some patients with severe RCVS have seizures, focal neurological deficits, confusion, and coma-like stroke or posterior reversible encephalopathy syndrome without headache.[3] Wolff et al.[10] reported that RCVS without a thunderclap headache is a variant of RCVS. The patient in this case developed generalized flaccid paralysis due to TTX poisoning and was unable to explain her medical history. Furthermore, she had dementia and might have forgotten whether she had experienced a headache. Although thunderclap headache is a clinical feature of RCVS, we consider that its absence should not preclude the diagnosis.

Stroke, a major complication of RCVS, can result in persistent neurological disability. Ducros[11] found that cerebral infarction was present in 6% to 39% of patients with RCVS. In our patient, cerebral infarction was associated with vasoconstriction of the left posterior cerebral artery. Although headache was not evident in our patient, RCVS should be considered if cryptogenic ischemic cerebral infarction is accompanied by headache. With appropriate early treatment of RCVS, stroke is likely to be a preventable complication.[12]

Imaging plays a critical role in the diagnosis and management of RCVS. Digital subtraction angiography is the gold standard investigation.[1] However, it is invasive and impractical for frequent imaging examinations, which may be required to assess the reversibility of the vasospasm.[13] Non-invasive techniques such as MRA are being increasingly used in clinical practice, although cerebral angiography remains the standard criterion for the detection of cerebral

vasoconstriction.[14] When RCVS is suspected, MRA is a useful modality in actual clinical practice because repeated imaging follow-up over time is necessary.

The clinical and imaging features of RCVS can considerably overlap with those of other central nervous system disorders, mainly primary angiitis of the central nervous system.[15] Patients with primary angiitis of the central nervous system present with a history of dull headaches and usually have an insidious course of progressive neurological deterioration; these characteristics differ from those of RCVS, which manifests as acute headaches and is typically a self-limiting disease. Other potential differential diagnoses for RCVS include aneurysmal subarachnoid hemorrhage, migraine, cortical vein thrombosis, pituitary apoplexy, amyloid angiopathy, hypertensive hemorrhage, posterior reversible encephalopathy syndrome, giant cell arteritis, arterial dissection, spontaneous intracranial hypotension, and meningitis.[1,16]

Current treatment recommendations for RCVS include withdrawal of any suspected exogenous triggers, including vasoactive medications, ICU-level care, symptom relief with analgesics, blood pressure control, and seizure prophylaxis. In our patient, the respiratory muscle paralysis and elevated blood pressure due to TTX intoxication improved only with sedation for ventilatory control, and the RCVS findings subsequently improved. Early use of nimodipine, a calcium-channel antagonist, has been proposed for the management of RCVS.[17] Other vasodilators, such as phosphodiesterase inhibitors, have also been used with anecdotal success as described in case reports.[18] Glucocorticoid steroids have been administered to patients with RCVS, without improvement in either the symptoms or sequelae of the disease.[16]

4 | CONCLUSION

The present case suggests that RCVS can be caused by transient sympathetic overactivity after TTX intoxication in patients with chronic hypertension. MRA is a useful modality when performing repeated tests.

ACKNOWLEDGMENT

We thank Angela Morben, DVM, ELS, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

ORCID

Eiichi Kakehi MD, PhD https://orcid.org/0000-0002-4556-8412

REFERENCES

1. Calabrese LH, Dodick DW, Schwedt TJ, et al. Narrative review: reversible cerebral vasoconstriction syndromes. *Ann Intern Med*. 2007;146(1):34-44.
2. Miller TR, Shivashankar R, Mossa-Basha M, et al. Reversible cerebral vasoconstriction syndrome, part 1: epidemiology, pathogenesis, and clinical course. *AJNR Am J Neuroradiol*. 2015;36(8):1392-1399.
3. Wolff V, Ducros A. Reversible cerebral vasoconstriction syndrome without typical thunderclap headache. *Headache*. 2016;56(4):674-687.
4. Fong BM, Tam S, Tsui SH, et al. Development and validation of a high-throughput double solid phase extraction-liquid chromatography-tandem mass spectrometry method for the determination of tetrodotoxin in human urine and plasma. *Talanta*. 2011;83(3):1030-1036.
5. Lorentz MN, Stokes AN, Rößler DC, et al. Tetrodotoxin. *Current biology : CB*. 2016;26(19):R870-R872.
6. Lee CH, Ruben PC. Interaction between voltage-gated sodium channels and the neurotoxin, tetrodotoxin. *Channels (Austin, Tex)*. 2008;2(6):407-412.
7. How CK, Chern CH, Huang YC, et al. Tetrodotoxin poisoning. *Am J Emerg Med*. 2003;21(1):51-54.
8. Deng JF, Tominack RL, Chung HM, et al. Hypertension as an unusual feature in an outbreak of tetrodotoxin poisoning. *J Toxicol Clin Toxicol*. 1991;29(1):71-79.
9. Yang CC, Han KC, Lin TJ, et al. An outbreak of tetrodotoxin poisoning following gastropod mollusc consumption. *Hum Exp Toxicol*. 1995;14(5):446-450.
10. Wolff V, Armspach JP, Lauer V, et al. Ischaemic strokes with reversible vasoconstriction and without thunderclap headache: a variant of the reversible cerebral vasoconstriction syndrome?. *Cerebrovasc Dis*. 2015;39(1):31-38.
11. Ducros A. Reversible cerebral vasoconstriction syndrome. *The Lancet Neurology*. 2012;11(10):906-917.
12. Nath AF, Kanodia AK, Nair P, et al. Reversible cerebral vasoconstriction syndrome (RCVS): a transient condition being underdiagnosed?. *BMJ Case Rep*. 2016:bcr2016214641.
13. Dodick DW. Thunderclap headache. *J Neurol Neurosurg Psychiatry*. 2002;72(1):6-11.
14. Miller TR, Shivashankar R, Mossa-Basha M, et al. Reversible cerebral vasoconstriction syndrome, part 2: diagnostic work-up, imaging evaluation, and differential diagnosis. *AJNR Am J Neuroradiol*. 2015;36(9):1580-1588.
15. Koopman K, Uyttenboogaart M, Luijckx GJ, et al. Pitfalls in the diagnosis of reversible cerebral vasoconstriction syndrome and primary angiitis of the central nervous system. *Eur J Neurol*. 2007;14(10):1085-1087.
16. Singhal AB, Hajj-Ali RA, Topcuoglu MA, et al. Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. *Arch Neurol*. 2011;68(8):1005-1012.
17. Cho S, Lee MJ, Chung CS. Effect of nimodipine treatment on the clinical course of reversible cerebral vasoconstriction syndrome. *Front Neurol*. 2019;10:644.
18. Bouchard M, Verreault S, Gariépy JL. Dupré N. Intra-arterial milrinone for reversible cerebral vasoconstriction syndrome. *Headache*. 2009;49(1):142-145.

How to cite this article: Kakehi E, Matsumoto M, Taniguchi S, et al. Reversible cerebral vasoconstriction syndrome associated with tetrodotoxin poisoning: a case report. *JACEP Open*. 2021;2:e12627. https://doi.org/10.1002/emp2.12627