Triptan-induced Reversible Cerebral Vasocclusion Syndrome: Two Case Reports with a Literature Review

Yuji Kato, Takeshi Hayashi, Satoko Mizuno, Yoohsuke Horiuchi, Masayuki Ohira, Norio Tanahashi and Masaki Takao

Abstract

We encountered two patients with sumatriptan-induced reversible cerebral vasocclusion syndrome (RCVS). The present patients were taking sumatriptan for the first time because they had been tentatively diagnosed with a migraine. On reviewing the literature, we found nine other cases of triptan-induced RCVS, predominantly among women aged 30 to 40 years. RCVS has been precipitated by triptan at the first ever use, after daily use, and even with long-term use at anormal dose. Patients with acute onset of severe headache should be thoroughly evaluated, and triptan should be administered appropriately. If triptan-induced RCVS is suspected, vascular imaging should be repeated after several days.

Key words: reversible cerebral vasocclusion syndrome, triptan, migraine, thunderclap headache

(Intern Med 55: 3525-3528, 2016)
(DOI: 10.2169/internalmedicine.55.7185)

Introduction

Reversible cerebral vasocclusion syndrome (RCVS) is a clinical entity characterized by severe headaches with or without acute neurological symptoms, the radiological features of which include multifocal segmental constriction of the cerebral arteries that resolves spontaneously within three months (1-4). RCVS is considered a rare syndrome, but the growing use of vasoactive drugs combined with the more frequent use of non-invasive neurovascular imaging has increased the incidence (4). Triptan is one of the drugs that triggers RCVS (2, 4), but triptan-induced RCVS cases are relatively rare. We herein describe two cases of sumatriptan-induced RCVS and review the clinical features of triptan-induced RCVS.

Case Reports

Case 1

A 43-year-old woman with a history of uncontrolled hypertension began suffering from a bifrontal-throbbing headache every other day, associated with neither nausea, photophobia, nor phonophobia. Three weeks later, she sought medical attention when over-the-counter medications failed to relieve the headaches. The results of a computed tomographic (CT) scan of the head were normal, and she was prescribed oral sumatriptan. One hour after taking the drug, she experienced a sudden exacerbation of her headache, followed by a seizure, which caused her to fall and hit her head against the floor. She was subsequently admitted to our institute.

On admission, her blood pressure was 171/72 mmHg, and she was afebrile. Shortly thereafter, she again experienced a generalized epileptic seizure that was treated by intravenous administration of diazepam and phenytoin. The laboratory findings, including a blood count, coagulation parameters, and the results of liver and renal tests, were normal. Magnetic resonance imaging (MRI) of the brain using fluid-attenuated inversion recovery (FLAIR) revealed a left parietal cortical subarachnoid hemorrhage (SAH) (Fig. 1a, small white arrow) and multiple high-intensity lesions in the bilateral occipital lobes (Fig. 1a, large black arrows). Diffusion-weighted MRI and magnetic resonance angiography (MRA) revealed no abnormalities (Fig. 1b). On Day 6, MRA showed narrowing of the bilateral middle and posterior cerebral arteries (Fig. 1d, white arrows), although the lesions on
the occipital lobes had improved (Fig. 1c). Her blood pressure was controlled within a normal range through administration of first amlodipine and then lomerizine. On Day 14, her headache had improved, and findings on MRI and MRA were normal (Fig. 1e and f). She was diagnosed with a headache attributed to arterial hypertension before sumatriptan administration, and RCVS associated with posterior reversible encephalopathy syndrome (PRES). The cortical SAH might have been due either to the head trauma or to RCVS.

**Case 2**

A 30-year-old woman developed a bifrontal-throbbing headache 4 days after spontaneous delivery. The pregnancy had been uneventful, and she never had signs of eclampsia. She had no remarkable medical history. On admission, her blood pressure was 180/104 mmHg. The findings from a neurological examination and initial CT scan were normal. The brain MRI with MRA findings were also normal (Fig. 2a and b). She was treated with nasal sumatriptan, but the headaches initially showed no response. The headaches then gradually resolved following the administration of acetaminophen over a few days, and the patient was discharged. A repeat MRI with MRA performed on Day 6 after her discharge showed narrowing of the bilateral anterior, middle, and posterior cerebral arteries (Fig. 2c and d, white arrows), which were normalized on Day 25 (Fig. 2e and f). In this case, the headache peaked during the first few days following sumatriptan administration and disappeared before the peak of cerebral vasoconstriction. She was retrospectively suspected of having had a postpartum headache before starting sumatriptan administration.

**Discussion**

Sumatriptan is often used to treat migraines and occasionally induces cerebral vasoconstriction. Our two patients were taking sumatriptan for the first time because they had been tentatively diagnosed with a migraine. It was difficult to show any clear evidence of sumatriptan-induced RCVS in both of these cases. Sumatriptan seemed to play a primary role in Case 1, but a secondary role or even an incidental role due to the postpartum period in Case 2. However, sumatriptan likely either induced or exacerbated RCVS in both cases.
The recent literature reflects a growing interest in RCVS. Four studies including more than 10 cases have been published (5-8). However, only nine cases in the literature have described the association between triptans and RCVS in detail (Table) (7, 9-14). The mean age among these 9 cases was 36 years, and 6 (66.7%) were women. Sumatriptan, administered either subcutaneously, orally, or nasally, was the most commonly implicated drug. RCVS was precipitated at the first ever use, or after daily use of one or several drugs, or even after long-term use of triptan at normal doses. Two patients presented with RCVS within the first week after delivery, suggesting that triptans must be used carefully in patients with headache in the postpartum period. The most frequent finding on cerebral imaging was ischemic stroke (four cases). Only two patients presented with thunderclap headache. Most patients had good recovery, but severe stroke seemed to induce poor outcomes.

The underlying mechanisms of RCVS are unknown. Triptan can precipitate RCVS when administered to susceptible patients. An individual’s susceptibility to developing RCVS may be influenced by genetic predisposition (e.g., brain-derived neurotrophic polymorphism, female gender) and precipitating factors (e.g., vasoactive substances, pregnancy/postpartum) (15). Triptan-induced RCVS may be more frequent than previously thought. Regardless of the presence of a migraine, patients presenting with acute onset of severe headache should be thoroughly evaluated, and triptan should be administered carefully, as it could precipitate RCVS or aggravate cerebral vasoconstriction. If triptan-induced RCVS is suspected, vascular imaging should be performed after several days.

| Reference | Age/sex | Trigger drug | Postpartum period | Subarachnoid hemorrhage | Stroke | Headache characteristics | Clinical outcome |
|-----------|---------|--------------|-------------------|------------------------|--------|-------------------------|-----------------|
| 9         | 43M     | Sumatriptan† (T), Midrin† | No | No | Ischemic | Bioccipital-throbbing | Recovery |
| 10        | 20F     | Sumatriptan* (I), Ergotamine* | Yes | No | Ischemic | Severe frontal and occipitomacial | Recovery |
| 11        | 37F     | Sumatriptan† (I), Ergotamine† | No | No | Hemorrhage | Frontal throbbing | Impairment |
| 12        | 34M     | Sumatriptan (I) † | No | No | Ischemic | Nonconscious | Recovery |
| 13        | 12M     | Eletriptan (T) | No | Yes | No | Severe acute | Recovery |
| 14        | 39F     | Naratriptan (T) †, SNRI, SSRI | No | Yes | No | Severe bifrontal-throbbing | Recovery |
| 7         | 68F     | Sumatriptan (?) | No | No | Ischemic | Thunderclap | Death |
| Present case 1 | 44F | Sumatriptan* (T) | No | Yes | PRES | Thunderclap | Recovery |
| Present case 2 | 30F | Sumatriptan* (N) | Yes | No | No | Bifrontal-throbbing | Recovery |

(T) Tablet, (N) Nasal spray, (I) Injection, * First ever use, † Abuse or daily use, SNRI: serotonin norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor, PRES: posterior reversible encephalopathy syndrome
The authors state that they have no Conflict of Interest (COI).

References

1. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative review: reversible cerebral vasoconstriction syndromes. Ann Intern Med 146: 34-44, 2007.
2. Ducros A. Reversible cerebral vasoconstriction syndrome. Lancet Neurol 11: 906-917, 2012.
3. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33: 629-808, 2013.
4. Yancy H, Lee-Iannotti JK, Schwedt TJ, Dodick DW. Reversible cerebral vasoconstriction syndrome. Headache 53: 570-576, 2013.
5. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain 130: 3091-3101, 2007.
6. Singhal AB, Haji-Ali RA, Topcuoglu MA, et al. Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. Arch Neurol 68: 1005-1012, 2011.
7. Robert T, Kawakabani Marchini A, Oumarou G, Uské A. Reversible cerebral vasoconstriction syndrome identification of prognostic factors. Clin Neurol Neurosurg 115: 2351-2357, 2013.
8. Katz BS, Fugate JE, Ameriso SF, et al. Clinical worsening in reversible cerebral vasoconstriction syndrome. JAMA Neurol 71: 68-73, 2014.
9. Meschia JF, Malkoff MD, Biller J. Reversible segmental cerebral arterial vasospasm and cerebral infarction: possible association with excessive use of sumatriptan and Midrin. Arch Neurol 55: 712-714, 1998.
10. Granier I, Garcia E, Geissler A, Boespflug MD, Durand-Gasselin J. Postpartum cerebral angiopathy associated with the administration of sumatriptan and dihydroergotamine: a case report. Intensive Care Med 25: 532-534, 1999.
11. Nighoghossian N, Derex L, Trouillas P. Multiple intracerebral hemorrhages and vasospasm following antimigrainous drug abuse. Headache 38: 478-480, 1998.
12. Singhal AB, Caviness VS, Begleiter AF, Mark EJ, Rordorf G, Koroshetz WJ. Cerebral vasoconstriction and stroke after use of serotoninergic drugs. Neurology 58: 130-133, 2002.
13. Yoshioka S, Takano T, Ryujin F, Takeuchi Y. A pediatric case of reversible cerebral vasoconstriction syndrome with cortical subarachnoid hemorrhage. Brain Dev 34: 796-798, 2012.
14. Ba F, Giuliani F, Camicioli R, Saqqur M. A reversible cerebral vasoconstriction syndrome. BMJ Case Rep 2012: bcr0920114841, 2012.
15. Chen SP, Fuh JL, Wang SJ, Tsai SJ, Hong CJ, Yang AC. Brain-derived neurotrophic factor gene Val66Met polymorphism modulates reversible cerebral vasoconstriction syndromes. PLoS One 6: e18024, 2011.