

# Extensive brain infarction involving deep structures during an acetazolamide-challenged single-photon emission computed tomography scan in a patient with moyamoya disease

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## Abstract

**Background** Acetazolamide-challenged brain single-photon emission computed tomography (SPECT) is used for the evaluation of cerebral perfusion in cerebrovascular diseases including moyamoya disease (MMD). Not a few patients experience adverse side effects during the acetazolamide-challenged brain SPECT, but most of the symptoms are mild and transient. To our knowledge, this is the first case report of severe brain infarction leading to death during the examination of an acetazolamide-challenged brain SPECT in a patient with MMD.

**Case presentation** An 11-year-old girl who had been diagnosed of MMD demonstrated sudden tonic movement during an acetazolamide-challenged brain SPECT as the preoperative examination for the second surgery. She had not experienced any adverse effect during the previous SPECT study and her first indirect bypass surgery on both left side and bifrontal area

was uneventful. After she had seizures twice, she became unconscious and her pupils were dilated and fixed. Acute infarction involving bilateral occipital lobes, thalami, brainstem, and cerebellum was observed on brain magnetic resonance images which led to brain death.

**Conclusion** We report a mortality case of patient with MMD after the administration of acetazolamide during the examination of brain SPECT that was accompanied by an extensive acute infarction involving the bilateral occipital lobes and thalami, brainstem, and cerebellum. Physicians should be aware of this rare but serious complication.

**Keywords** Acetazolamide-challenged single-photon emission computed tomography scan (SPECT) · Brain death · Brain infarction · Moyamoya disease (MMD)

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## Background

Moyamoya disease (MMD) is an idiopathic progressive stenooclusive cerebrovascular disease involving the distal internal carotid arteries with a network of hazy basal collaterals [13]. It is a common cause of pediatric stroke in East Asia and requires surgical treatment. Approximately 10–30% of MMD patients have an accompanied posterior cerebral artery (PCA) involvement during the initial presentation [5, 7].

Acetazolamide-challenged brain single-photon emission computed tomography (SPECT) is used for the evaluation of cerebral perfusion in MMD both preoperatively and postoperatively [12, 14]. The administration of acetazolamide, in particular, enables the assessment of vascular reserve in patients with chronic cerebral hypoperfusion. Up to 63% of patients may experience adverse side effects during the brain SPECT study in conjunction with acetazolamide, but most of the symptoms are mild and do not last long [9].

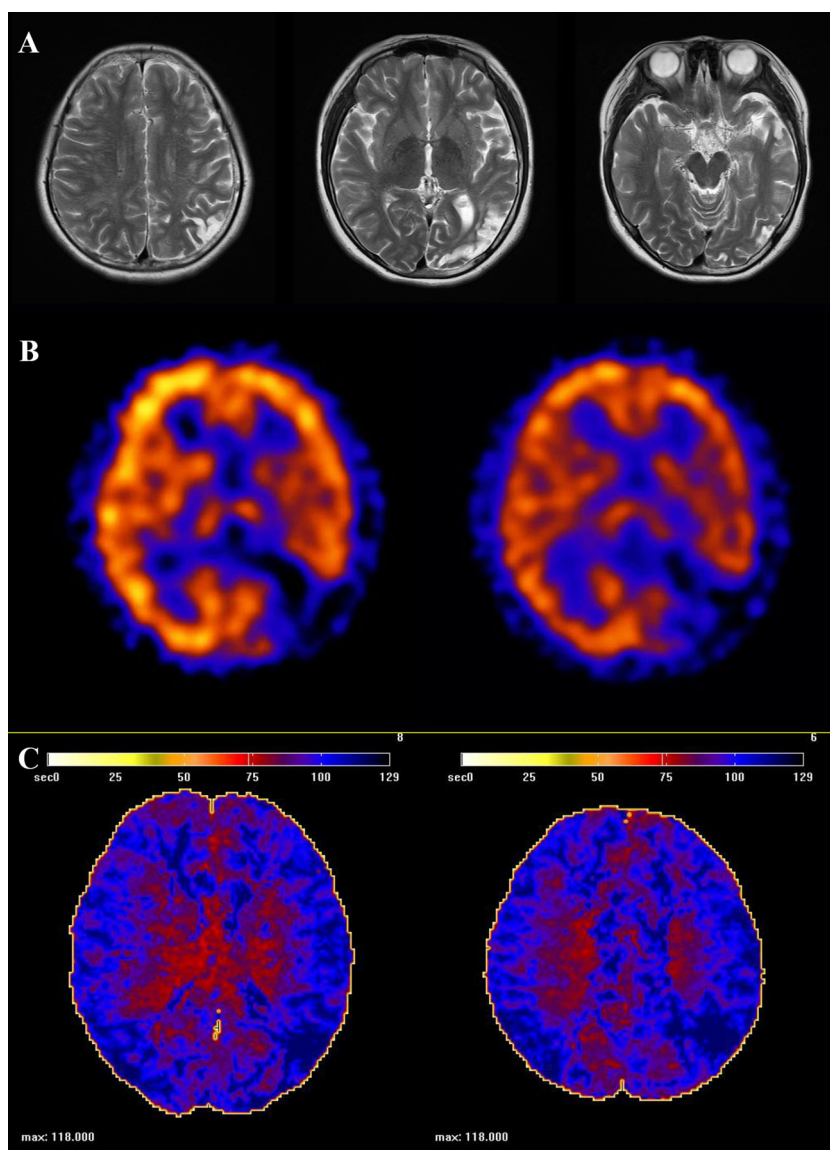
Therefore, it has been used for several decades without severe problems. We present a case of serious brain infarction during the examination of an acetazolamide-challenged brain SPECT in an 11-year-old female patient with MMD.

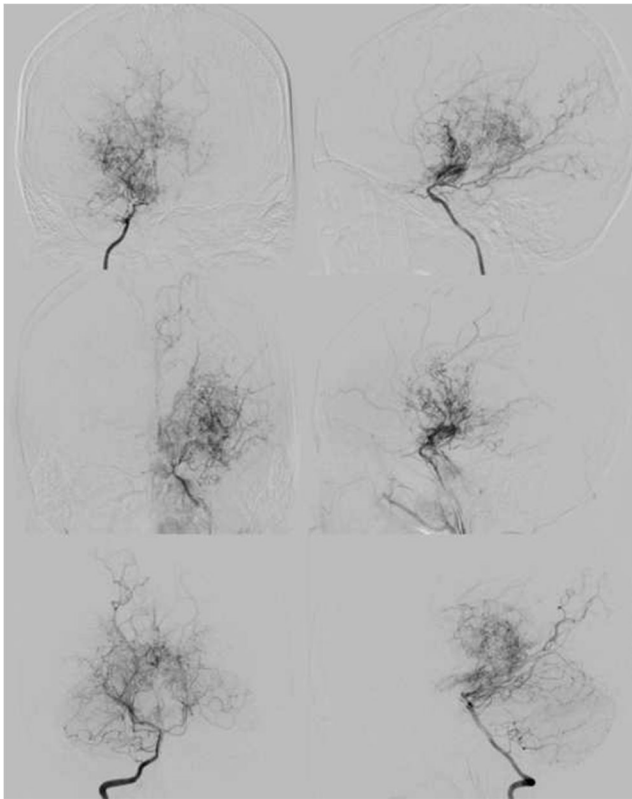
## Case presentation

An 11-year-old girl presented with a recurrent transient ischemic attack (TIA) on both lower extremities and the right upper extremity that started 1 year ago. The patient had also been suffering from a headache in the occipital area. Brain magnetic resonance (MR) images showed an old infarct in the left parietooccipital area, T2-high signal intensity lesions in the bilateral posterior border zone and basal moyamoya vessels (Fig. 1a). On MR angiography, bilateral internal carotid artery (ICA) occlusion with multiple collaterals was observed, and

the involvement of the posterior circulation was suspected. Brain SPECT including the acetazolamide challenge revealed basal hypoperfusion with decreased vascular reserve in the left middle cerebral artery (MCA) territory, and she did not experience any symptoms during the examination (Fig. 1b). Perfusion MR images demonstrated decreased perfusion in both the MCA territory, which was more severe on the left side (Fig. 1c). Transfemoral cerebral angiography (TFCA) confirmed the diagnosis of MMD. Bilateral occlusion of the terminal ICA involving the basal collaterals was observed, as well as stenosis of both PCAs (Fig. 2). Initially, she underwent an encephaloduroarteriosynangiosis (EDAS) using the superficial temporal artery on the left side and a bifrontal encephalogaleosynangiosis (EGS). The surgical procedure and postoperative recovery was uneventful, and the patient was discharged on the seventh postoperative day.

**Fig. 1** Preoperative images of the patient. **a** Axial T2-weighted MR images show an old infarction in the left parietooccipital area. Tiny moyamoya vessels are seen in the basal cistern (*right*). **b** Basal (*left*) and acetazolamide-challenged (*right*) SPECT images of the patient reveal hypoperfusion with decreased vascular reserve in the left cerebral hemisphere. **c** Perfusion MR images demonstrate a delayed time-to-peak of both whole cerebral hemispheres that is more severe on the left side



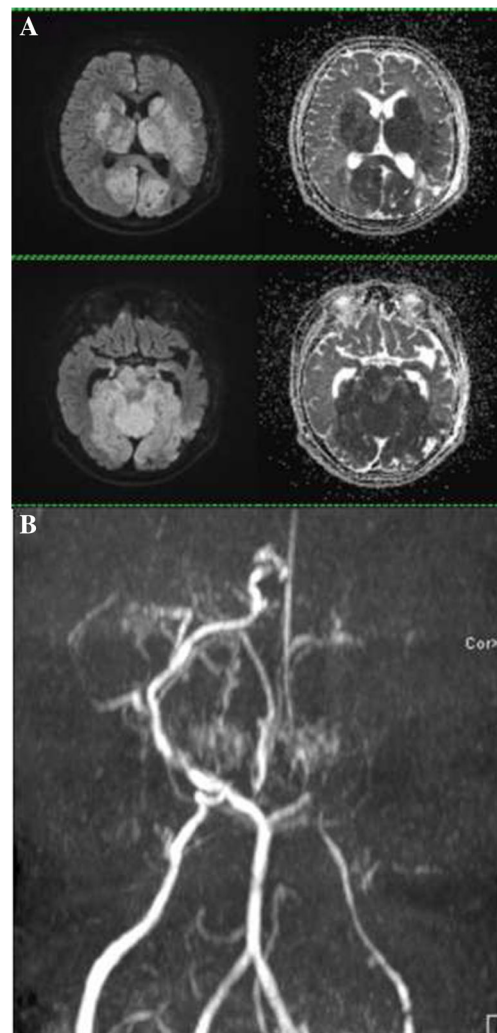


**Fig. 2** Cerebral angiography (upper; right internal cerebral artery, middle; left internal carotid artery, lower; vertebral artery, left column; anteroposterior view, right column; lateral view) confirms the diagnosis of moyamoya disease. A stenooclusive change of both posterior cerebral arteries is also found

Surgery for the right side was planned soon after, and an acetazolamide-challenged brain SPECT was taken again 1 month after the first surgery using the same protocol as that of the preoperative examination. After the basal images were obtained, 952 mg (14 mg/kg) of acetazolamide (Zoladin, BCWORLD Pharm Co., Ltd., Seoul, Korea) was injected over 2 min to obtain images for cerebral vascular reserve. Five minutes after the injection of  $^{99m}\text{Tc}$ -HMPAO and 1 min after the end of acetazolamide injection, she screamed and demonstrated tonic movement lasting 10 s. Following a neurological examination, which was performed 20 min after the acetazolamide infusion, she was given a Glasgow coma scale (GCS) of 3, and both of her pupils measured 3 mm and were equally reactive. Her vital signs were as follows: blood pressure, 227/108 mmHg; heart rate, 103 beats per minute; respiratory rate, 24 breaths per minute; body temperature, 36.4 °C.

Twenty-five minutes later, another generalized seizure occurred, which was controlled by the administration of lorazepam. Because the respiratory rate decreased and both pupils became fixed, she was intubated. Soon, her pupils were fully dilated and brainstem reflexes became absent. Brain computed tomography (CT) was taken 45 min after

the acetazolamide infusion and showed low attenuation in the thalamus, midbrain, pons, and cerebellum with obliteration of the perimesencephalic cistern and fourth ventricle. Subsequently, a brain MR was performed approximately 5 h after the acetazolamide infusion, and there was an extensive acute infarction involving bilateral occipital lobes and thalami, midbrain, pons, and cerebellum with an upward herniation. The structures supplied by the anterior circulation were relatively spared except for the bilateral caudate nuclei (Fig. 3). Her neurological status did not improve, and she was declared as brain dead 83 days after the event.



**Fig. 3** MR images and an MR angiogram taken immediately after the event. **a** Diffusion-weighted (*left*) and apparent diffusion coefficient map (*right*) images demonstrate extensive acute infarction in the brainstem, cerebellum, and thalami as well as the bilateral occipital lobes and caudate nuclei. Obliteration of the basal cistern is observed. **b** On MR angiogram, there was no change of the bilateral distal internal carotid artery obliteration and posterior cerebral artery stenosis compared to preoperative status. No evidence of new stenooclusive changes in the posterior circulation was found

## Discussion

One of the most unique findings in this unusual case is the dense infarction involving the thalamus, brainstem, and cerebellum. These areas are innocent regions that are not affected by MMD. This indicates that this phenomenon is not caused by the common pathophysiology of cerebral infarction that can be seen in MMD patients. There are several possibilities to consider as a cause of this unexpected event, such as vertebral or basilar artery dissection, vasculitis, adverse effects from the infused agents, or a coincidental new infarction during SPECT examination.

Vertebral artery or basilar artery dissection is a disease that can lead to a posterior circulation infarction and should be considered as a possible cause of death in this patient. Abe et al. [1] reported a case of a brainstem infarction caused by a basilar artery dissection in a patient with MMD 4 years after revascularization surgeries. The history of TFCA also supports the suspicion of a basilar artery dissection. However, there was no evidence of a basilar artery dissection such as intraluminal hemorrhage and a dissection flap upon reviewing the source images of MR angiography taken after the event compared to the preoperative images.

Considering luminal narrowing of the cerebral vessels and presentation of stroke, the possibility of unusual cerebral vasculitis should be ruled out. However, the results of laboratory tests for vasculitis were all negative and there was no predisposing medical abnormality to explain the cerebral infarction.

Acetazolamide is a carbonic anhydrase inhibitor which induces cerebral vasodilation and increases cerebral blood flow [2]. In MMD, autoregulatory vasodilation has already occurred within the affected brain territory, and administration of acetazolamide may lead to a paradoxical decrease of cerebral blood flow in the affected area called the steal phenomenon [6]. Therefore, it is utilized for the assessment of the vascular reserve in chronic ischemic cerebrovascular disease [15]. Aggravation of ischemic symptoms might be caused by an acetazolamide challenge, but it rarely causes brain infarction. There is only one case report of cerebral infarction caused by an acetazolamide-challenged SPECT in MMD patients. Sato et al. [10] reported a case of cerebral infarction during an acetazolamide-challenged brain SPECT; however, anemia predisposed to the typical watershed infarct. In this case, “extensive” brain infarction was developed in the regions with “preserved” blood flow, which are not affected by MMD, such as the brainstem and cerebellum. Moreover, there were no other predisposing factors except the acetazolamide challenge.

An adverse effect associated with brain SPECT should also be ruled out. Anaphylactic shock was unlikely due to the lack of rash and swelling, and the blood pressure was rather high during the event. An air embolism can rarely occur by intravascular injection, causing a fatal result, but there were no

demonstrable air emboli or scattered infarctions on brain CT or MR in this case. A side effect of the drug is a possible cause. Fever, flushing, rash, swelling, and warm skin are a few known side effects of  $^{99m}\text{Tc}$ -HMPAO [11]. The well-known side effects of acetazolamide are headache, malaise, and numbness [15]. Because most of the side effects are mild and transient, it is widely used. More severe damage in the areas with more spared perfusion suggests that the toxic effect caused by the infused agents is possible but it is also unlikely considering the long history of use of  $^{99m}\text{Tc}$ -HMPAO or acetazolamide. There is a small possibility of drug denaturation, but no one who was examined with the drug with the same lot number on that day showed any side effects. An injection error with the wrong drug is impossible because acetazolamide was the only drug in the scanning room. An overdose is also unlikely because the dose for the patient was not drastically different from that of an ordinary adult patient. All procedures during the examinations were performed following the guidelines for brain perfusion SPECT [3, 4].

The brainstem and cerebellum are not areas where cerebral infarction occurs in MMD considering the location of the stenooclusive lesions. In actual clinical observations of MMD patients, there is no case of infarctions within the brainstem or cerebellum in the course of disease [8]. Other than the aforementioned conditions, it is difficult to consider other diseases that can cause a dense infarction in these areas independently. Furthermore, when considering the chronological sequence of the events, one cannot exclude an association between the examination and the infarction. Therefore, the possibility of a coincidental infarction during the examination is remote.

This is our first case of a severe adverse effect related to an acetazolamide-challenged brain SPECT. We have never experienced such a case before this event despite approximately 5000 cases of brain SPECT being performed during the most recent 5 years. Regarding its rarity and severity, autopsy was considered. However, the parents refused to consent. Unfortunately, the exact cause of death was not determined in this patient. Thus, investigating the cause of death in this unusual case is limited to clinical inference.

After this experience, we began to obtain written consent forms for acetazolamide-challenged brain SPECT scan that explained the possible side effects, including cerebral infarction. Neurologists and neurosurgeons in our institute became cautious to order acetazolamide-challenged brain SPECT and now tend to utilize perfusion MR imaging more frequently for the assessment of cerebral perfusion.

## Conclusion

We report a mortality case of patient with MMD after the administration of acetazolamide during the examination of

brain SPECT that was accompanied by an extensive acute infarction involving the bilateral occipital lobes and thalami, brainstem, and cerebellum. Physicians should be aware of this rare but serious complication.

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**Compliance with ethical standards** This case report was approved by Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 1701-074-824).

**Conflict of interest** The authors declare that they have no conflict of interest.

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