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# Reversible Pontine Ischemia Caused by Acetazolamide Challenge

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**Summary:** We report the findings in a patient with a midbasilar artery stenosis in whom reversible ischemic neurologic deficits developed during cerebral blood flow imaging with acetazolamide challenge. The potential for ischemic complications from acetazolamide challenge is discussed.

**Index terms:** Brain, ischemia; Cerebral blood flow; Iatrogenic disease or disorder

Acetazolamide, widely used to assess cerebral hemodynamic reserve capacity in patients with ischemic brain disease, increases cerebral blood flow (CBF) when given intravenously (1–9). However, intravenous injection of acetazolamide can cause circumoral numbness, tingling of the palms, and headache (1, 6, 9). We report a case of reversible ischemic neurologic complications caused by acetazolamide challenge in a patient with stenosis of the basilar artery. We present this case to warn physicians of the potential for ischemic complications stemming from acetazolamide challenge during CBF examination.

## Case Report

A 48-year-old man began experiencing dizziness and numbness in the circumoral region and left upper and lower extremities 1 month before admission. He had no numbness in the body trunk and no motor weakness. Episodes of dizziness and numbness, occurring about once a week, would begin suddenly, last 1 to 3 hours, and then disappear completely. One day before admission, the onset of these symptoms was followed by left-sided motor weakness. The patient came to our hospital because the numbness and hemiparesis persisted.

On admission, blood pressure was 158/120 mm Hg. Neurologically, the patient was alert and dysarthric with mild hemiparesis on the left. Mild central left-sided facial paresis was noted. The patient had been undergoing treatment for hypertension and insulin-dependent diabetes mellitus for the past 6 years. Laboratory data were within

normal limits except for elevated fasting blood sugar at 162 mg/dL and hemoglobin A<sub>1c</sub>, 8.1%.

Computed tomographic (CT) findings of the brain on admission were normal. We began antiplatelet treatment with 100 mg ticlopidine hydrochloride twice a day and 160 mg sodium ozagrel per day intravenously. Magnetic resonance (MR) images on day 9 showed an infarction in the right side of the pons (Fig 1A). Digital subtraction angiography showed a stenosis of the midportion of the basilar artery (Fig 1B and C). CBF imaging at rest on day 4 with technetium-99m hexamethylpropyleneamine oxime (<sup>99m</sup>Tc-HMPAO) showed normal distribution of the CBF. The blood flow in the pons was normal (Fig 1D). Regional CBF was measured according to the method elucidated by Matsuda et al (10). Measured CBF in the pons was 62.4 mL/100 g per minute, while that in the left middle cerebral artery territory was 59.9 mL/100 g per minute.

Five days after the baseline study, acetazolamide challenge with <sup>99m</sup>Tc-HMPAO was carried out. Acetazolamide was given intravenously at a dose of 1 g. One minute after injection of acetazolamide, the patient experienced circumoral numbness, followed by numbness in the left upper and lower extremities. Upon leaving the examination table, he noticed deterioration of left-sided motor performance and gait, as well as dysarthria. Blood pressure before and after the CBF examination was stable. The CBF images showed increased blood flow in the cerebellum and in the supratentorial regions, but decreased flow in the pons (Fig 1E). Measured CBF in the left middle cerebral artery territory was 74.1 mL/100 g per minute (a 24% increase relative to baseline), while that in the pons was 54.5 mL/100 g per minute (a 9% decrease relative to baseline). Within about 4 hours, the patient's numbness had disappeared completely, but 3 to 4 days were required before motor performance, gait, and speech were restored to baseline level. Follow-up MR imaging revealed no new infarction.

## Discussion

Although the mechanism by which acetazolamide induces cerebral vasodilatation has not been fully elucidated, it is commonly recognized that acetazolamide inhibits carbonic an-

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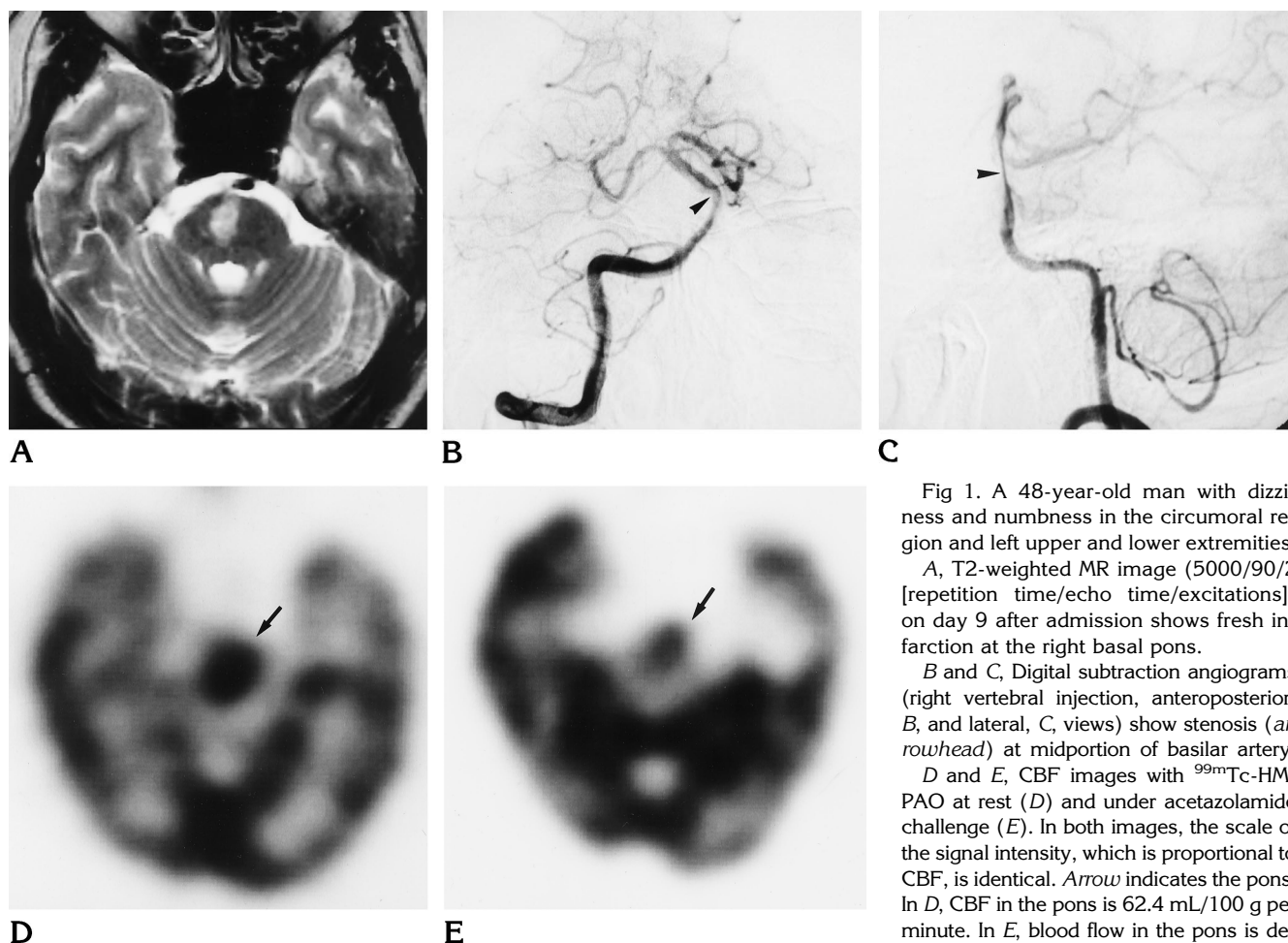


Fig 1. A 48-year-old man with dizziness and numbness in the circumoral region and left upper and lower extremities.

A, T2-weighted MR image (5000/90/2 [repetition time/echo time/excitations]) on day 9 after admission shows fresh infarction at the right basal pons.

B and C, Digital subtraction angiograms (right vertebral injection, anteroposterior, B, and lateral, C, views) show stenosis (arrowhead) at midportion of basilar artery.

D and E, CBF images with  $^{99m}\text{Tc}$ -HMPAO at rest (D) and under acetazolamide challenge (E). In both images, the scale of the signal intensity, which is proportional to CBF, is identical. Arrow indicates the pons. In D, CBF in the pons is 62.4 mL/100 g per minute. In E, blood flow in the pons is decreased (54.5 mL/100 g per minute, a 9% reduction from baseline).

hydrase, which results in a decrease of brain tissue pH (11). Acidosis in the brain induces a vasodilatory effect, increasing CBF (12). In combination with single-photon emission CT or transcranial Doppler sonography, this phenomenon has been put to use in evaluating cerebrovascular diseases (3–5, 7–9).

Acetazolamide at a dose of 0.5 to 1.0 g does not have a significant effect on blood pressure, pulse rate, respiratory rate, oxygen tension, carbon dioxide tension, or cerebral metabolic rate for oxygen (1, 4, 6, 8, 13, 14). Reported untoward effects related to acetazolamide administration can be classified into two groups: chronic side effects resulting from oral administration and acute side effects resulting from intravenous administration. Chronic side effects are caused by an abnormally elevated serum level of acetazolamide. Since acetazolamide is eliminated entirely by renal excretion, renal dysfunction may reduce acetazolamide clear-

ance, resulting in elevation of the serum acetazolamide level (15, 16). Drug interaction with salicylates also elevates unbound plasma acetazolamide (17). Chronic side effects are due to metabolic acidosis, and include malaise, fatigue, weight loss, depression, anorexia, loss of libido, confusion, somnolence, and delirium (3, 15–18). Acute side effects are circumoral numbness or tingling of the palms of the hands, headache, malaise and fatigue, giddiness, cranial fullness, altered taste, nausea, anorexia, vertigo, and polyuria (1, 6, 9). These symptoms start within a few minutes after acetazolamide injection and last for several hours (6). In one case, a feeling of generalized malaise and fatigue is reported to have lasted 24 to 36 hours (6). One patient had bronchospasm after intravenous acetazolamide (9). Patients with hepatic encephalopathy have become lethargic and confused after receiving 2 g of acetazolamide, beginning 20 to 30 minutes after the injection

and lasting from 6 to 24 hours (1). All these acute adverse effects are temporary and reversible. Piepgras et al (8) reported no acute ischemic complications in more than 1000 examinations with acetazolamide challenge.

In healthy subjects, increases in CBF ranging from 13% to 75% have been observed after intravenous acetazolamide administration (1, 2, 4, 6, 13, 14). However, in patients with stenosis or occlusion of the intracranial vessels or brachiocephalic vessels, different responses to acetazolamide challenge have been reported (3–9). One is a uniform increase in regional CBF. Another is lack of response or a small increase in CBF (redistribution). Other patients have exhibited paradoxically decreased CBF, which has been designated the steal phenomenon (4).

Possible explanations for the occurrence of cerebral ischemia after acetazolamide challenge in our patient are that either the pons became ischemic as a result of the steal phenomenon or the ischemic episode was a coincidental event. Although we cannot rule out coincidental occurrence of ischemia, we believe that acetazolamide-induced ischemic symptoms in our patient were based on the following: (1) Regional CBF in the pons decreased 9% from the baseline after acetazolamide administration, while in the other regions, including the cerebellum, CBF increased over 20% from the baseline level. Although gross reduction of blood flow in the pons was 9%, regional blood flow in some areas within the pons might have been greater than 9%, which was enough to produce ischemic symptoms. (2) Ischemic symptoms began within a few minutes of acetazolamide administration. (3) Systemic blood pressure was stable during the examination. (4) The clinical manifestation after acetazolamide administration was quite similar to the symptoms of the initial stroke. (5) Finally, during the 4-month period between the initial ischemic episode and the last follow-up after initiation of antiplatelet treatment, no recurrent ischemic episode occurred except for the attack on the occasion of acetazolamide challenge.

The effect of intravenous acetazolamide on CBF can persist for more than 1 to 2 hours, but maximal effect occurs about 25 to 30 minutes after injection (1, 13). The half-life of the declining phase of the response has been observed to be 95 minutes (13). Neurologic deficits lasting more than 1 day could be attributable to secondary effects of acetazolamide. The neurologic

deficits experienced by our patient were completely reversed within several days.

Our case illustrates a potential complication of acetazolamide challenge. Should ischemic complications occur, immediate appropriate treatment is essential.

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