

# Acetazolamide therapy for symptomatic plateau waves in patients with brain tumors

## Report of three cases

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✓ In this report, the authors describe three patients with malignant gliomas who experienced paroxysmal neurological symptoms triggered by standing. The symptoms were attributed to acute elevations of intracranial pressure, an uncommon phenomenon called “plateau waves.” In each instance, the attacks occurred despite the fact that the patient was receiving dexamethasone therapy and stopped promptly with the addition of acetazolamide. Acetazolamide, an orally administered carbonic anhydrase inhibitor, appears to be a specific and effective therapy for this uncommon neurological disorder.

**KEY WORDS** • plateau wave • acetazolamide

**P**LATEAU waves, first described by Lundberg,<sup>7</sup> are acute elevations of ICP that may cause stereotypical, paroxysmal neurological symptoms. Plateau waves occur in situations in which baseline ICPs are already moderately elevated. During plateau waves, ICP readings may reach 100 mm Hg, markedly reducing cerebral blood flow. Intracranial pressures remain at high levels for several minutes before they diminish spontaneously. These acute elevations of ICP have been observed in patients with brain tumor,<sup>9</sup> subarachnoid hemorrhage,<sup>3,5</sup> acute hydrocephalus,<sup>6</sup> and benign intracranial hypertension,<sup>4</sup> and may be triggered in ambulatory patients by postural changes.<sup>8</sup> Sometimes misinterpreted as seizures, the symptoms that accompany plateau waves may include headache, visual disturbances, impairment of postural or motor control, and altered consciousness.<sup>8,10</sup> In this report, we describe three patients with brain tumors and symptomatic plateau waves who responded to treatment with acetazolamide.

### Case Reports

#### Case 1

*History.* This 56-year-old woman who harbored a glioblastoma multiforme in the left frontal region was treated with cranial radiotherapy and chemotherapy with lomustine. Phenytoin was prescribed early in the course of her illness because two generalized seizures had occurred shortly after brain biopsy, and throughout her illness the patient

*Abbreviations used in this paper:* CPP = cerebral perfusion pressure; CSF = cerebrospinal fluid; ICP = intracranial pressure; MR = magnetic resonance.

had been dependent on a regimen of dexamethasone. Five months after diagnosis, while taking 16 mg of dexamethasone daily, the patient began to experience episodes of a pressure sensation in the head, blurred vision, diplopia, and imbalance precipitated by standing. The symptoms began within 30 seconds after she assumed the upright posture, and resolved after she sat or lay down. The attacks, which occurred multiple times each day, did not improve when the dose of phenytoin was increased.

*Treatment.* Suspicious that the attacks might be plateau waves, we prescribed acetazolamide (250 mg by mouth two times/day). Within 2 days, the frequency of the attacks diminished; the attacks ceased entirely when the dose of acetazolamide was increased (250 mg three times/day).

*Course of the Disease.* Despite treatment, the patient's neurological symptoms worsened and a computerized tomography scan demonstrated relentless tumor growth. Salvage therapy in which temozolomide was administered was unsuccessful. Death occurred 7 months after diagnosis. Once initiated, the acetazolamide treatment was maintained until the patient's death and there was no recurrence of the attacks.

#### Case 2

*History.* This 57-year-old man with a left frontal glioblastoma multiforme received cranial radiotherapy and chemotherapy that included tamoxifen as well as procarbazine, lomustine, and vincristine. Five months after diagnosis, he began to experience episodes of headache, altered consciousness, and loss of postural tone, which was always triggered by standing. Countless attacks occurred each day.

## Acetazolamide for symptomatic plateau waves in brain tumor patients

*Treatment.* The spells were unresponsive to therapeutic doses of phenytoin. The attacks ceased temporarily when the dose of dexamethasone was increased to 8 mg daily, but then recurred. Because of the multiple side effects associated with the steroid, the patient declined to have the dose of dexamethasone increased further. Instead, acetazolamide was prescribed (250 mg two times/day), after which the postural attacks ceased entirely.

*Course of the Disease.* Despite the treatment outlined earlier, the patient experienced worsening neurological symptoms and MR imaging revealed tumor growth. Death occurred 1 year after diagnosis.

### Case 3

*History.* This 41-year-old left-handed man presented with complex partial seizures with secondary generalization. Although the neurological examination yielded normal findings, MR images demonstrated a large, diffuse, nonenhancing mass involving the right temporal and inferior frontal lobes. The imaging appearance of the mass was consistent with that of a low-grade glioma. The patient was asymptomatic, apart from frequent simple partial seizures until 5 months later, when he began to have difficulties in selecting appropriate words and experienced weakness on his left side. A repeated MR imaging study revealed tumor growth and contrast enhancement. A stereotactic biopsy revealed an anaplastic astrocytoma, and cranial radiotherapy was recommended. Following the biopsy, but before radiotherapy, the patient experienced episodic headache and dizziness triggered by standing. Although the attacks were associated with his diminished awareness and responsiveness, they differed from the seizures he had experienced previously and resolved within minutes after he sat or lay down.

*Treatment.* The spells occurred two or three times daily, despite a regimen of dexamethasone (16 mg daily) and therapeutic doses of phenytoin. Physical examination revealed a mild left hemiparesis with no papilledema or postural change in blood pressure. Acetazolamide was prescribed (250 mg two times/day), and the episodes ceased abruptly.

*Continued Treatment and Course of the Disease.* The patient subsequently completed a course of cranial radiotherapy (5760 cGy in 32 fractions). Tumor progression was apparent on MR images obtained 6 weeks after completion of radiotherapy, and treatment with temozolomide was initiated. To date, there is evidence that the patient's disease has stabilized in response to the temozolomide. He continues to receive acetazolamide, and remains free from these posturally precipitated episodes.

## Discussion

Acute elevations in ICP ("plateau waves") may produce paroxysmal symptoms in patients with brain tumor. Awareness of this uncommon paroxysmal disorder and a careful history will often assist the clinician in reaching the correct diagnosis. The symptoms associated with plateau waves are easily misinterpreted to be seizures because alterations in consciousness and motor control are cardinal symptoms of both disorders. Under ideal circumstances, plateau waves can be distinguished from seizures because they oc-

cur shortly after the patient assumes the erect posture and are frequently accompanied by headache or a pressure sensation in the head. In practice, however, the distinction can be difficult because the patient is often unable to describe the attacks accurately and caregivers may not have appreciated the relationship between postural change and the onset of symptoms. Orthostatic hypotension due to occult, steroid-induced gastrointestinal bleeding, vincristine neuropathy, or other causes in patients with brain tumor might also produce symptoms similar to those associated with plateau waves, but can be excluded by a thorough physical examination. Furthermore, orthostatic hypotension would be unlikely to respond favorably to a diuretic such as acetazolamide.

In the individuals we describe, the episodes were consistently precipitated by postural change, clearly differed from the phenomenological characteristics of previous seizures, and failed to respond to therapeutic doses of standard anticonvulsant medications. In Cases 1 and 3, the presence of orthostatic hypotension was specifically sought, and was excluded by the results of the physical examination. Interestingly, on standing, the patient in Case 1 did not experience hypotension and tachycardia, but rather hypertension and bradycardia, a cardiovascular response consistent with the acute onset of raised ICP. These clinical features provided important clues to the true nature of the paroxysmal attacks in these patients. Ultimately, of course, our diagnosis that these events were plateau waves remains speculative in the absence of objective documentation. In individuals with suspicious, frequent, and reproducible symptoms, transcranial Doppler ultrasonography might provide a non-invasive means of demonstrating characteristic changes in ICP and establishing the diagnosis of plateau waves with greater certainty.

The relationship between plateau waves and postural change merits further mention. Magnaes<sup>8</sup> studied the effect of rapid postural change on CSF pressure in individuals with elevated ICP due to neurological disease, including subarachnoid hemorrhage and hydrocephalus, and in control patients without elevated ICP. Sitting up rapidly produced transient CSF pressure waves in all control patients; these were considered to be normal postural CSF pressure waves. In some patients with brain disease and elevated ICP, however, sitting up rapidly produced a more sustained pattern of CSF pressure elevation, similar to a plateau wave. Magnaes postulated that in individuals with brain disease and impaired autoregulation, the normal transient CSF pressure wave associated with the rapid assumption of upright posture might trigger a plateau wave.<sup>8</sup>

Plateau waves develop as a result of a rapid increase in intracerebral blood volume. A prerequisite for their occurrence is a reduction in intracranial compliance, such as that which occurs with mass lesions, cerebral edema, or hydrocephalus.<sup>2</sup> Sluggish CSF flow and defective CSF absorption may be important contributors to this lack of intracranial compliance.<sup>6</sup> In this setting, slow increases in ICP are associated with compensatory decreases in CPP, which trigger vasodilation through the normal process of autoregulation, resulting in a slow rise in cerebral blood volume. When CPP drops below a critical level, however, the rate of vasodilation increases dramatically, resulting in a rapid increase in cerebral blood volume and a sudden and sustained increase in ICP. Termination of these plateau waves requires

an increase in CPP, which might occur when the patient is recumbent, which triggers autoregulatory vasoconstriction and a reduction in ICP. The increase in CPP required to abort plateau waves may be generated by the Cushing phenomenon, which is activated when brainstem ischemia triggers systemic hypertension, thus increasing CPP.<sup>10</sup>

Experimentally, plateau waves can produce irreversible cerebral ischemia and brain injury. Hyperventilation, catecholamine infusion, CSF drainage, and intravenous administration of mannitol will abort individual plateau waves, but these effective measures are impractical therapies for ambulatory patients. Moreover, the ideal therapy would prevent the occurrence of plateau waves, rather than simply abort individual episodes. By reducing cerebral edema, dexamethasone may lessen the severity and frequency of plateau waves,<sup>1</sup> and, perhaps, more aggressive dosing of dexamethasone in our patients would have achieved control of their paroxysmal symptoms. Serious side effects may occur when dexamethasone is used on a long-term basis, however, and corticosteroid medications alone may not afford complete protection from attacks in all patients. Our experience in these three cases would suggest that acetazolamide may be a highly effective therapy for symptomatic plateau waves in patients with brain tumor and, in this respect, a highly useful addition to the pharmacological armamentarium in neurooncology. Although the improvement in our patients may have been due to factors other than acetazolamide, this possibility seems unlikely, given that in all three cases control of symptomatic plateau waves was maintained in the face of progressive disease.

Acetazolamide is an orally administered carbonic anhydrase inhibitor used in the treatment of a variety of illnesses that are associated with paroxysmal symptoms, including glaucoma, Meniere disease, migraine, hypokalemic periodic paralysis, and certain of the episodic ataxias. Acetazolamide can also be an effective therapy for benign intracranial hypertension, a related disorder in which plateau waves can occur.<sup>4</sup> The mechanism by which acetazolamide prevents plateau waves in patients with brain tumor is incompletely understood. Nevertheless, acetazolamide is known to decrease CSF production, which may in turn improve intracranial compliance, thus lessening the risk that plateau waves would occur or become symptomatic. It is also conceivable that acetazolamide produces a beneficial effect by reducing brain tumor-induced cerebral edema or

works by other mechanisms. Acetazolamide should be administered with caution in patients with a history of allergy to sulfonamides and may cause unpleasant paresthesias of the fingertips or toes in some individuals.

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