Clinical Reasoning:

A 44-year-old man with a 3-month history of hiccups

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SECTION 1

A 44-year-old right-handed African American man with a 1-year history of seizures was admitted for further evaluation. During a previous hospitalization for status epilepticus, MRI revealed a brain lesion, but the patient refused biopsy. Over a 3-month period, he developed unrelenting hiccups which fluctuated in frequency. His only other symptom was headache relieved by acetaminophen. The patient denied photophobia, phonophobia, and visual changes associated with the headache.

He had a history of hypertension and a left above-the-knee amputation (AKA) for osteosarcoma as a child.

His general medical examination revealed the left AKA but was otherwise unremarkable. He was alert, oriented, and executive functions were intact. Vision was 20/20 in both eyes, extraocular movements were intact, and pupils were equal and reactive. There was no papilledema. He had a flattened right nasolabial fold. Motor, sensory, and cerebellar function were intact. Hiccups persisted throughout the interview. Their frequency remained relatively constant, and they often interrupted the patient's speech.

Questions for consideration:

1. How are hiccups classified based on their time course?
2. How are hiccups generated and what is the pathophysiology in this patient?

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SECTION 2

Hiccups, or singultus, result from sudden closure of the glottis along with contraction of the inspiratory muscles.¹ Bouts of hiccups lasting up to 48 hours are considered physiologic. However, persistent (lasting up to 2 months) or intractable (lasting greater than 2 months) hiccups have various etiologies.²

The pathophysiology of hiccups is not entirely clear, but it is thought to involve a reflex arc and unilateral contraction of the diaphragm. The afferent limb of the reflex arc consists of the phrenic nerve, vagus nerve, and sympathetic chain, and the efferent limb consists of the phrenic nerve with connections

to the glottis and inspiratory intercostal muscles. Centrally, hiccups are thought to be mediated by a combination of the phrenic nerve nuclei, respiratory centers, reticular formation in the brainstem, and the hypothalamus.^{2,3} Furthermore, the temporal lobe, hypothalamus, and reticular activating substance have been proposed as stimulatory or inhibitory modulators of the reflex arc.⁴

Questions for consideration:

1. What are the possible etiologies of persistent or intractable hiccups?
2. What laboratory tests and studies would you pursue?

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Fluid-attenuated inversion recovery MRI demonstrates involvement by the infiltrating astrocytoma of (A) the pons and right temporal lobe, (B) the right temporal and frontal lobes, and (C) the right parietal lobe and thalamus.

SECTION 3

Etiologies of intractable and persistent hiccups can be divided into 4 categories: vagus or phrenic nerve irritation, toxic-metabolic disorders, CNS disorders, and psychogenic causes. Peripheral nerve irritation is the most common cause, and it also causes most bouts of hiccups. The vagus and phrenic nerves can be irritated by a variety of processes, including pharyngitis, laryngitis, and masses in the neck. Diaphragmatic disorders, such as hiatal hernias or subphrenic abscesses, can cause irritation of the phrenic nerve. In AIDS, hiccups may be caused by esophageal candidiasis. They may also be caused by multiple sclerosis (MS), syringomyelia, hydrocephalus, neoplasms, and other disorders that result in cerebral or brainstem lesions. Toxic metabolic disorders such as alcohol intoxication, uremia, and general anesthesia are known to cause hiccups. Psychogenic factors such as anxiety, stress, excitement, and malingering can also be the cause of hiccups.^{2,3}

The workup of persistent or intractable hiccups addresses these etiologies. A complete medical, surgical, and substance abuse history is important. A neurologic examination and thorough assessment of the

ears, nose, throat, thorax, and abdomen should be done. Laboratory tests include electrolytes, creatinine, and a complete blood count to look for occult infection or malignancy. A chest x-ray may detect a structural cause in the mediastinum and diaphragm. Other tests may include an MRI of the head and CT of the chest.^{2,3} Laboratory values were normal in this patient.

MRI of the brain demonstrated a large, confluent, hyperintense region in the right temporal and frontal lobes extending into the right basal ganglia and thalamus on T2 and fluid-attenuated inversion recovery (figure). Another smaller hyperintense region was seen in the inferior left frontal lobe. Abnormal signal intensity was also seen in the optic chiasm and the prechiasmatic optic nerves. Finally, there was a focal area of hyperintensity in the pons. The differential included malignancies such as glioma or lymphoma and demyelinating processes.

Biopsy showed a grade II infiltrating astrocytoma.

Question for consideration:

1. How would you treat this patient's hiccups?

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SECTION 4

Holding one's breath and being frightened are examples of home remedies for hiccups, but there is little evidence as to their efficacy. The treatment of intractable hiccups begins with chlorpromazine. The IV form, infused slowly to avoid hypotension, is most effective, but oral doses 25–50 mg 3 to 4 times per day have been used. The latter was effective in our patient. Side effects include drowsiness, and less commonly, acute dystonic reactions. A second-line treatment is metoclopramide, 10 mg 3 to 4 times per day. A known side effect of both chlorpromazine and metoclopramide is tardive dyskinesia. Other possibly effective treatments include baclofen, phenytoin, carbamazepine, valproic acid, gabapentin, tricyclic antidepressants, methylphenidate, and quinidine. Alternative therapies include hypnosis and acupuncture for hiccups refractory to medical treatment.^{2,3} Surgical ablation of the phrenic nerve is also mentioned in the literature,³ but several recent reports describe improvement with ultrasound-guided anesthesia of the phrenic nerve at the cervical level. In one report, 3 of 5 patients had cessation of hiccups, and the remaining patients had improvement of their symptoms.⁵

DISCUSSION The differential diagnosis for persistent or intractable hiccups is extensive. Grade II infiltrating astrocytoma is an unreported cause of intractable hiccups. In this patient, it is difficult to determine whether the hiccups arose from temporal or pontine involvement by the tumor. There is one report of persistent hiccups that resolved following resection of a temporal lobe glioblastoma multiforme.⁶ There is also a case of periodic hiccups following a right temporal brain abscess.⁷ Finally, a study on the use of MRI for intractable hiccups demonstrated that 3 of 9 patients had temporal lobe lesions.⁴

There are also reports of intractable hiccups in patients with pontine lesions. One patient was found to have involvement of the right lateral tegmentum of the lower pons by MS.⁸ In another report of stroke rehabilitation patients, 3 patients with persistent hiccups had pontine infarcts.⁹

We present a patient with intractable hiccups resulting from a grade II infiltrating astrocytoma. Intractable hiccups caused by CNS malignancies are rare, and this case is the first that reports infiltrating astrocytoma as the etiology.

AUTHOR CONTRIBUTIONS

M. Lee contributed to drafting and revising the manuscript and is the corresponding author. Dr. Pritchard contributed to drafting and revising the manuscript. Dr. Weiner contributed to drafting and revising the manuscript.

DISCLOSURE

M. Lee and Dr. Pritchard report no disclosures. Dr. Weiner served on scientific advisory boards for Santhera Pharmaceuticals and Rexahn Pharmaceuticals, Inc.; serves on the editorial boards of *Parkinsonism and Related Disorders* and *Current Treatment Options in Neurology*; and receives publishing royalties for *Neurology for the Non-Neurologist* (6th edition, Wolters Kluwer/Lippincott, 2010), *Parkinson's Disease: A Complete Guide for Patients and Family* (2nd edition, Hopkins University Press, 2007), and *Handbook of Clinical Neurology Hyperkinetic Disorders* (Elsevier, 2011).

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