Clinical Reasoning:

A 46-year-old man with persistent hiccups, cognitive dysfunction, and imbalance

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SECTION 1

A 46-year-old, right-handed, African American man presented to the emergency department after 1 week of persistent hiccups and 3 days of nausea and vomiting. His family member also noted that he had been experiencing right-hand tremor and gait imbalance for the last 3 months. Over the 6 months prior to presentation, the patient's coworkers had noticed that he was completing his work more slowly, that he was forgetting how to perform simple tasks, and that several times he had come to work at the wrong hours. The patient had a history of HIV diagnosed 10 years earlier and reported good adherence to an antiretroviral regimen consisting of tenofovir, emtricitabine, and atazanavir boosted by ritonavir, without any changes for several years. His viral load was undetectable when tested 8 months prior to presentation.

The patient had experienced a 9-kg (20-lb) weight loss over the last 6 months and watery, nonbloody

diarrhea for 3 days. He denied illicit or IV drug use, new sexual partners, recent travel, ill contacts, or toxic exposures.

Neurologic examination revealed frequent hiccups; decreased short-term recall (1 of 5 words) after 5 minutes with normal registration; a 4–6 Hz, low-amplitude postural and action tremor of the right hand; appendicular ataxia of the upper limbs; and gait ataxia, especially prominent with tandem gait. The remainder of the physical examination was normal.

Questions for consideration:

1. Based upon the patient's history and neurologic examination, where do each of the patient's symptoms and signs localize?
2. Which are the most common neurologic causes of persistent or intractable hiccups?
3. What medications can be used for symptomatic treatments of persistent hiccups?

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SECTION 2

The patient's history and examination revealed executive dysfunction localizing to the frontal lobe and decreased recall localizing to the temporal lobe, both signs of cognitive dysfunction. The tremor of the right hand could localize to the left basal ganglia, the spinocerebellar tracts, or the rubrocerebellothalamic projections (Holmes rubral tremor). With the addition of cerebellar findings such as appendicular ataxia localizing to the lateral cerebellum, and gait ataxia localizing to the midline cerebellum, a cerebellar tremor is favored. However, rubral and cerebellar tremors can be difficult to distinguish because they have similar frequency and are present with action and at rest. The varying localizations should indicate to the clinician that this disease process is either multifocal or diffuse, rather than the result of a single, focal lesion.

Hiccups, also called singultus, are paroxysmal myoclonic activations of the diaphragm involving a reflex arc with afferent vagal input, central integration in the medulla area postrema, and efferent output via the phrenic nerves.¹ Ischemia, encephalitis, neuromyelitis optica,² or neoplastic lesions affecting the medullary integrating center including the area postrema are the most common primary neurologic causes, although many other causes have been described including direct phrenic nerve irritation from malignancy or surrounding structures.¹ We found no randomized controlled trials to

compare the effectiveness of drug therapies for persistent or intractable hiccups; however, chlorpromazine has been effective in clinical practice and is the only medication approved by the US Food and Drug Administration for hiccups. Several alternative medications have been reportedly effective in the medical literature, including gabapentin. All are proposed to act on the GABAergic or dopaminergic neurons of the medulla.¹

The patient was admitted to the hospital neurology service and a course of chlorpromazine was administered. His hiccups, nausea, and vomiting resolved in less than 24 hours. MRI of the brain with and without gadolinium contrast revealed diffuse T2/fluid-attenuated inversion recovery hyperintensities involving the right frontal cortex, cerebral white matter, right external capsule and caudate nucleus, left midbrain, pons, medulla, and bilateral peridentate cerebellum. None of these lesions was contrast-enhancing. MRI of the cervical and thoracic spine demonstrated nonenhancing increased T2 signal intensity involving the right side of the thoracic cord from C4 through T1 (figure).

Questions for consideration:

1. In light of the patient's history, examination findings, and MRI abnormalities, what are the top 5 considerations in your differential diagnosis?
2. Which laboratory assays would you order for CSF analysis?

Figure MRI of the brain and cervical and thoracic spine

(A–D) Axial T2-weighted fluid-attenuated inversion recovery sequence MRI of the brain without contrast demonstrates multifocal hyperintensities of the bilateral deep nuclei, white matter, and cerebral cortex. (E) Midsagittal T2-weighted MRI of cervical spine without contrast demonstrates central cervical spinal cord hyperintensity.

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SECTION 3

The differential diagnosis is broad considering the patient's history of HIV with subacute and acute symptoms. The MRI findings are suggestive of multifocal leukoencephalopathy, involving the cortex, deep nuclei, and spinal cord. In a study of nearly 250 AIDS-affected patients who underwent stereotactic biopsies for cerebral lesions found on imaging, the most common diagnoses were cytomegalovirus encephalitis, HIV encephalitis, CNS lymphoma, and CNS toxoplasmosis. Many patients had more than 1 active diagnosis concurrently.³ This patient's history of preceding diarrhea raises clinical concern for cytomegalovirus with concurrent colitis and encephalitis. In addition, his history of good adherence to antiretroviral therapy does not exclude the diagnoses of opportunistic infections or malignancies such as CNS toxoplasmosis, progressive multifocal leukoencephalopathy, tuberculosis, fungal infections, HIV encephalitis, or CNS lymphoma.⁴

If the patient had been more recently diagnosed with HIV and begun on antiretroviral therapy, immune reconstitution syndrome would be another

consideration. Other noninfectious or HIV-related etiologies that could account for this patient's clinical picture include demyelinating illness such as neuromyelitis optica spectrum disorder, neurosarcoidosis, and other rheumatologic disorders with CNS involvement or autoimmune encephalitis.

The patient's plasma CD4 count was 724 cells/ μ L (>400 cells/ μ L). Plasma HIV RNA viral load was measured at 406 copies/mL, which is slightly above the expected range for patients who have been on stable antiretroviral therapy. A lumbar puncture revealed lymphocytic pleocytosis and elevated protein. Subsequent infectious assays including herpesviridae, Gram stain, JC virus, *Toxoplasma*, *Cryptococcus*, and venereal disease research laboratory were negative, with the exception of CSF HIV RNA PCR (2,520 copies/mL). Plasma and CSF were negative for neuromyelitis optica antibodies (table e-1 at Neurology.org).

Question for consideration:

1. Based on the laboratory profile, what treatment would you recommend for this patient?

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SECTION 4

Based on the preliminary CSF laboratory results, the patient was not started on any empiric therapies. The patient's HIV RNA load in CSF exceeded 2,000, while the plasma HIV viral load was below 500, confirming HIV CSF viral escape syndrome. Infectious diseases experts recommended changing his antiretroviral regimen to abacavir, lamivudine, and dolutegravir.

The patient's tremor, cognitive dysfunction, and imbalance had resolved at 6-month follow-up. He completed comprehensive neuropsychometric testing, which did not reveal evidence of cognitive dysfunction. Repeat MRI scans demonstrated interval improvement of the leukoencephalopathy.

DISCUSSION We present a case of symptomatic HIV CSF viral escape syndrome causing subacute HIV-associated neurocognitive disorder and acute HIV encephalomyelitis. HIV CSF viral escape syndrome is a rare manifestation of HIV infection in patients who are actively on antiretroviral therapy with discordance between plasma and CSF viral load.^{5,6} The pathophysiologic mechanism is not fully understood, but it has been proposed that a distinct HIV clonality with resistance to the antiretroviral regimen evolves in the CSF compartment after initial infection or by the failure to achieve therapeutic concentrations in the CNS.^{6–9}

In most reported cases of HIV CSF viral escape syndrome, patients present with variegated focal or nonfocal neurologic symptoms with insidious onset despite longstanding antiretroviral therapy. These presentations have included neurocognitive disorders, behavioral changes, fatigue, headache, cerebellar dysfunction, and focal motor or sensory symptoms.⁶ Visualized radiographic abnormalities are typically similar to our case presentation, with diffuse T2-weighted hyperintensities involving the white matter, cerebellum, basal ganglia, and periventricular parenchyma. Awareness of this condition and clinical suspicion of HIV CNS infection despite antiretroviral therapy and viral suppression is the key to diagnosis and management. Treatment is contingent upon HIV RNA resistance testing from the CSF compartment and changes of the antiretroviral therapy incorporating agents with higher CNS penetration capable of overcoming the resistance profile of the CSF HIV population.⁶

There are no expert consensus recommendations regarding routine CSF screening for HIV viral load. It is reasonable to reserve CSF HIV RNA and genotype resistance testing only for cases where CSF viral escape syndrome is suspected and alternative diagnoses have been evaluated. Follow-up evaluation of CSF HIV RNA after antiretroviral modification can be

performed after 4–6 weeks, based on the recommendation for follow-up of plasma HIV response.¹⁰

AUTHOR CONTRIBUTIONS

Dr. Lamb contributed to the conception and design of the article; collection, analysis, synthesis, and interpretation of the data; drafting and critical revision of the article; and generation/collection of the figure. Drs. Lopez Chiriboga, Sotello Aviles, Mendez, and Robinson contributed to the design and critical revision of the article. All authors gave final approval of the article.

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