Central neurogenic hyperventilation

A sign of CNS lymphoma

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Practical Implications

Central neurogenic hyperventilation is often caused by CNS lymphoma; the eyes may be involved in 20% of cases, and the diagnosis may be confirmed in the appropriate setting by vitreous or aqueous aspiration.

A 69-year-old man complained of “breathing too fast” for 6 weeks. He was a recovered alcoholic with essential tremor, hypertension, depression, and history of stage IE diffuse large B-cell lymphoma of the left femur diagnosed 3.5 years earlier and treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone. Six weeks prior to presentation, the patient noted an increased respiratory rate and shortness of breath, and was found to have new atrial fibrillation; he underwent unsuccessful atrial ablation. He had a 3-month history of malaise, cold intolerance, and a 10-pound weight loss. He also complained of occasional floaters in his right eye, and had become more agitated with increasing forgetfulness.

Examination revealed normal sinus rhythm and respiratory rate between 25 and 35 breaths per minute that persisted during sleep. The patient was alert and oriented to person and place but not to date. He had hypometric horizontal pursuit bilaterally, mildly hypometric horizontal saccades, and impaired convergence. There was no papilledema, and lower cranial nerves were normal. Strength was full. There was a postural high-frequency, low-amplitude bilateral hand tremor. He had no dysmetria or ataxia. He had diminished lower extremity vibration and proprioception, 1+ upper extremity and knee reflexes, and absent ankle jerks. Differential diagnosis at the time of initial examination included recurrent lymphoma, progressive multifocal leukoencephalopathy, glioma, and paraneoplastic encephalitis.

Evaluation over 2 weeks included arterial blood gas (pH 7.63, pCO₂ 9, pO₂ 184, HCO₃ 9.5 on room air); the following studies were unremarkable: complete blood count, complete metabolic panel, thyroid function tests, rapid plasma reagin, serum protein electrophoresis, HIV, erythrocyte sedimentation rate, angiotensin-converting enzyme, vitamin B₁₂, and thiamine. Serum CD4 was 354. Spirometry, cardiac catheterization, CT chest (pulmonary embolism protocol), abdomen, and pelvis (IV/oral contrast), bilateral lower extremity ultrasound, whole spine MRI, noncontrast head CT, and routine EEG were unrevealing. CSF analysis yielded 1/0 leukocytes, 0/0 erythrocytes, protein 97 mg/dL, and glucose 58 mg/dL. CSF Gram stain, cytology, electrophoresis, JC virus PCR, and anti-Hu antibody were negative. Brain MRI with gadolinium and PET CT studies are shown in figure 1. Confluent areas of nonenhancing signal abnormality were noted in bilateral cerebral hemispheres, thalami, and brainstem. Slit-lamp examination revealed cells in the vitreous on the right. Right vitreous biopsy (figure 2) was consistent with diffuse large B-cell lymphoma.

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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Figure 1 Brain MRI with gadolinium

(Upper panel, fluid-attenuated inversion recovery): Large confluent areas of nonenhancing signal abnormality within the genu of corpus callosum extending to the left greater than right frontal lobes, with suggestion of cortical involvement in the medial/anterior aspects of the left frontal lobe. In addition, multiple areas of signal abnormality are noted in bilateral cerebral and cerebellar hemispheres, bilateral thalami, and dorsal midbrain and pons. The right frontal lobe lesion showed restricted diffusion, consistent with hypercellularity (not shown). PET CT (lower panel): FDG avid foci in the basal ganglia, dorsal pons, and mid cerebellum, with relative hypometabolism in the remainder of the cortical structures. Non-FDG avid right retroocular soft tissue lesion is noted.

Upon diagnosis, IV methylprednisolone was started without clinical improvement. The patient declined further therapy with methotrexate or radiation, and was transferred to hospice. He became progressively disoriented, and died 5 days after entering hospice. Autopsy was refused.

DISCUSSION

Our patient had systemic diffuse large B-cell lymphoma with ocular and CNS infiltration manifesting with central neurogenic hyperventilation (CNH). This entity was first described by Plum and Swanson¹ in 1959. Diagnostic criteria for CNH include hyperventilation (respiratory rate > 25) persisting during sleep; low arterial PaCO₂; high arterial PaO₂; and high arterial pH in absence of cardiac, pulmonary, and metabolic/iatrogenic causes. CSF lactate and pH may be elevated.

Plum and Swanson¹ postulated that CNH may result from destructive medial pontine lesions (as observed in our patient) interrupting descending inhibitory impulses to the medullary respiratory centers. Another hypothesis posits that local lactate production and a low pH stimulates ventral medullary chemoreceptors, leading to hyperventilation.^{2,3} In animals, Chamberlin⁴ found that stimulation of the lateral parabrachial neurons with glutamate may increase the respiratory rate/tidal volume.

CNH is usually observed in comatose patients; there are fewer than 30 case reports of conscious patients with CNH in the literature. Most patients have lesions involving the pontine tegmentum and medulla. CNS involvement outside the brainstem is common, occurring in about 50% of patients.² CNS lymphoma accounts for 50% (9/18 in the largest review) of reported cases of CNH.² CNS lymphoma may involve the eye in 20% of cases; it is estimated that 60%–80% of patients with intraocular lymphoma will develop CNS disease within a mean of 29 months of diagnosis.⁵ CSF cytology is positive in only 25% of patients with MRI

Figure 2 Vitreous biopsy

(A) Cytology: Hypercellular specimen contains large atypical mononuclear cells, with oval to irregular nuclei and multiple prominent nucleoli. Apoptotic cells and necrotic debris are noted. (B, C) Immunohistochemistry: CD20 and PAX5 positivity, consistent with B-cell population. Diagnosis: Diffuse large B-cell lymphoma with ocular and CNS infiltration. Slides courtesy of Franz Fogt, MD, MBA, and Bo Jian, MD, PhD.

lesions,⁶ which typically enhance in primary CNS lymphoma, but did not in our patient. There has been one reported case of CNH due to Richter transformation of chronic lymphocytic leukemia to diffuse large B-cell lymphoma.⁷ Other reported etiologies of CNH include slow-growing astrocytoma,² medulloblastoma, invasive laryngeal carcinoma, systemic histiocytosis, bilateral medial thalamic infarctions, acute intermittent porphyria, brainstem encephalitis, anti-NMDA receptor encephalitis, and multiple sclerosis (MS).

Treatment of CNH consists of repeated or continuous IV administration of midazolam, propofol, morphine, or mechanical ventilation and therapy for the underlying tumor. One reported case of MS with CNH improved clinically and radiographically after plasma exchange. Prognosis in cancer-associated CNH is poor, with average survival of several months after diagnosis.

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ACKNOWLEDGMENT

The authors thank the patient's wife for recording his breathing during sleep and allowing use of his data and the Hospital of the University of Pennsylvania Neurology Ward team that took care of the patient: Judy Jia, MD, Megan Richie, MD, Yan Yan, MD, and Arun Padmanabhan, MD; University of Pennsylvania ophthalmology consultants: Joshua Ney, MD, and Albert Maguire, MD; and University of Pennsylvania pathologists Franz Fogt, MD, MBA, and Bo Jian, MD, PhD.

STUDY FUNDING

No targeted funding reported.

DISCLOSURES

A. Pantelyat reports no disclosures. S. Galetta serves on the editorial boards of *Neurology*[®] and the *Journal of Neuro-ophthalmology* and serves as a consultant for Genzyme, Vaccinex, and Biogen Idec. A. Pruitt serves on the editorial board of *Journal Watch Neurology*, has received speaker honoraria from the American Academy of Neurology, receives research support from Teva, and her spouse has participated in medico-legal cases. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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