Central Neurogenic Hyperventilation

A Case Report and Discussion of Pathophysiology

Andrew W. Tarulli, MD; Chun Lim, MD, PhD; Jonathan D. Bui, MD, PhD; Clifford B. Saper, MD, PhD; Michael P. Alexander, MD

Background: Central neurogenic hyperventilation is a rare condition with poorly understood pathophysiology.

Objective: To describe a patient with central neurogenic hyperventilation caused by an infiltrative brainstem lymphoma.

Conclusion: Based on analysis of this patient and other case reports, we propose that central neurogenic hyperventilation is uniquely the result of infiltrative tumors that stimulate pontine respiratory centers and central chemoreceptors.

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An 87-year-old man was seen with decreased appetite and weight loss for 3 months and shortness of breath for 1 month. Medical history included remote bladder and prostate cancers and very remote tobacco use. Examination revealed cachexia and tachypnea (respiratory rate, >25/min), but other findings were normal. Arterial blood gases (ABGs) were pH, 7.60; PaCO₂, 14 mm Hg; and PaO₂, 115 mm Hg. The chest radiograph, noncontrast head computed tomographic scan, torso computed tomographic scan, electrocardiogram, and echocardiogram were normal. He was sent to a rehabilitation hospital without a clear diagnosis.

He remained tachypneic. Neurological examination demonstrated a mild confusional state. Pulmonary function tests showed mild restrictive lung disease not substantial enough to produce his hyperventilation. Magnetic resonance imaging of the head revealed T2 prolongation in the vertex of the right frontal lobe, right lateral frontal lobe, right dorsal midbrain, medial left cerebellar hemisphere, and left superior and middle cerebellar peduncles (Figure). No enhancement was seen with gadolinium.

On transfer to Beth Israel Deaconess Medical Center (Boston, Mass), he was afebrile, tachypneic (respiratory rate, 32/min), and uncomfortable. Oxygen saturation was 100% on room air. His lungs were clear. He was awake, inattentive, and disoriented, but there were no other significant neurological findings.

Laboratory studies disclosed the following values: ABGs, pH, 7.67; PaCO₂, 8 mm Hg; and PaO₂, 129 mm Hg; hematocrit, 33.3%; white blood cell count, 10 900/µL; neutrophils, 81%; erythrocyte sedimentation rate, 40 mm/h; sodium, 134 mEq/L; potassium, 4.2 mEq/L; chloride, 105 mEq/L; bicarbonate, 14 mEq/L; serum urea nitrogen, 37 mg/dL (17 mmol/L); creatinine, 1.3 mg/dL (114 µmol/L); and glucose, 112 mg/dL (6.2 mmol/L). Liver function test results, including those from the ammonia test, were normal; the carcinoembryonic antigen level was slightly elevated at 4.5 ng/mL; and protein electrophoresis and urinalysis results were normal. Lumbar puncture opening pressure was 13 cm. Cerebrospinal fluid (CSF) contained the following values: 6 white blood cells, 44% neutrophils, 33% lymphocytes, 6% monocytes, and 16% “other” cells; the CSF protein level was 26 mg/dL; glucose level, 37 mg/dL (2 mmol/L); and pH, 7.32. Cytologic examination of CSF showed rare, atypical, nucleated cells. Repeat CSF analysis 5 days after hospital admission showed a white blood cell count of 0, protein level of 24 mg/dL, and glucose level of 95 mg/dL (5.5 mmol/L).

Doses of 1 mg of intravenous morphine every 12 hours did not reduce the respiratory rate. A 5-day course of methylprednisolone, 1 g intravenously per day, was initiated on hospital day 7 when the patient’s
ABGs were pH, 7.67; PaCO$_2$, 15 mm Hg; and PaO$_2$, 114 mm Hg on room air. On hospital day 15, the patient's breathing was comfortable at 18 breaths per minute with ABGs of pH, 7.59; PaCO$_2$, 23 mm Hg; and PaO$_2$, 100 mm Hg. A right frontal brain biopsy specimen from day 18 showed diffusely infiltrating B-cell lymphoma. Colonoscopy for lower gastrointestinal bleeding revealed adenocarcinoma of the cecum. After discussion with his family, he was transferred to hospice care.

Plum and Swanson proposed that “central neurogenic hyperventilation in man results from the uninhibited stimulation of both the inspiratory and expiratory centers in the medulla by the lateral pontile reticular formation and by laterally located descending neural pathways.”

Of the 21 cases reported since, 15 had tumors clearly involving the pons (Table). Persistent CNH was seen in 19 cases and transient CNH, in 2. A bias for reporting patients with pontine tumors must be considered because a diagnosis of CNH is rarely entertained without evidence of brainstem infiltration. Pathologic features have rarely been restricted to the pons; medullary infiltration ($n=11$) or tumor involvement outside the brainstem ($n=11$) are also common. In addition to pontine infiltration, our patient had substantial lesions in the right frontal lobe, the midbrain, and the left cerebellar hemisphere.

Of the 18 reported cases that specified tumor histopathologic characteristics, there were 9 with lymphoma, 6 with slow-growing astrocytoma, 1 with metastatic tumor invading through the skull base, 1 with medulloblastoma, and 1 with aggressive astrocytoma (Table). As with the current report, CNH is consistently associated with slowly infiltrative tumors. There have been no reported cases of CNH caused by stroke and no single electrolytic lesion has produced CNH in animal models.

The mechanisms by which infiltrative pontine lesions cause CNH are not completely understood. Plum and Swanson proposed a functional disconnection of pontine and medullary respiratory centers. Pontine respiratory group neurons modulate the respiratory rhythm, but animal models that disconnect the pontine respiratory group from the medulla have not resulted in CNH. There are multiple pathways from the pneumotaxic centers in the pons to the medullary respiratory centers.

### Table. Cases of Central Neurogenic Hyperventilation in the Literature

<table>
<thead>
<tr>
<th>Source</th>
<th>Age, y</th>
<th>Diagnosis</th>
<th>CSF pH</th>
<th>Pons</th>
<th>Medulla</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzuki et al.² 1964</td>
<td>5</td>
<td>Astrocytoma</td>
<td>+</td>
<td>+</td>
<td>Unclear</td>
<td>Midbrain, occipital lobes</td>
</tr>
<tr>
<td>Lange and Laszlo.³ 1965</td>
<td>51</td>
<td>Lymphoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Goulon et al.¹ 1969</td>
<td>22</td>
<td>Astrocytoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Cerebellar hemispheres</td>
</tr>
<tr>
<td>Tinaztepe et al.⁴ 1982</td>
<td>53</td>
<td>Lymphoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Rodriguez et al.⁵ 1982</td>
<td>8</td>
<td>Not stated</td>
<td>7.27</td>
<td>+</td>
<td>Unclear</td>
<td>-</td>
</tr>
<tr>
<td>Plum,⁶ 1982</td>
<td>39</td>
<td>Not stated</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bilateral cerebral hemispheres</td>
</tr>
<tr>
<td>Plum,⁶ 1982</td>
<td>41</td>
<td>Lymphoma</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Bilateral posterior fossa mass</td>
</tr>
<tr>
<td>Cohn et al.⁷ 1985</td>
<td>84</td>
<td>Astrocytoma</td>
<td>7.53</td>
<td>+</td>
<td>+</td>
<td>Right cerebral hemispheres</td>
</tr>
<tr>
<td>Bateman et al.,⁸ 1985</td>
<td>62</td>
<td>Lymphoma</td>
<td>7.42</td>
<td>+</td>
<td>-</td>
<td>Bilateral cerebral hemispheres, hypothalamus, midbrain</td>
</tr>
<tr>
<td>Gottlieb et al.,⁹ 1987</td>
<td>23</td>
<td>Medulloblastoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bilateral parieto-occipital</td>
</tr>
<tr>
<td>Nakasu et al.,¹⁰ 1988</td>
<td>7</td>
<td>Astrocytoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bilateral frontal and parietal</td>
</tr>
<tr>
<td>Pauzer et al.,¹¹ 1989</td>
<td>61</td>
<td>Lymphoma</td>
<td>7.7</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Bilateral parieto-occipital</td>
</tr>
<tr>
<td>Salvesen,¹² 1989</td>
<td>48</td>
<td>Possible pontine glioma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Widespread</td>
</tr>
<tr>
<td>Dubaybo et al.,¹³ 1991</td>
<td>55</td>
<td>Laryngeal carcinoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Bilateral frontal and parietal</td>
</tr>
<tr>
<td>Krendel et al.,¹⁴ 1991</td>
<td>52</td>
<td>Lymphoma</td>
<td>7.33</td>
<td>-</td>
<td>-</td>
<td>Bilateral frontal and parietal</td>
</tr>
<tr>
<td>Tobias and Heideman,¹⁵ 1991</td>
<td>11</td>
<td>Astrocytoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bilateral cerebral hemispheres, hypothalamus, temporal lobes, midbrain</td>
</tr>
<tr>
<td>Shibata et al.,¹⁶ 1992</td>
<td>72</td>
<td>Lymphoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bilateral cerebral hemispheres, hypothalamus, temporal lobes, midbrain</td>
</tr>
<tr>
<td>Siderowf et al.,¹⁷ 1996</td>
<td>57</td>
<td>Astrocytoma</td>
<td>7.6</td>
<td>+</td>
<td>+</td>
<td>Bilateral cerebral hemispheres, hypothalamus, temporal lobes, midbrain</td>
</tr>
<tr>
<td>Sakamoto et al.,¹⁸ 2001</td>
<td>69</td>
<td>Lymphoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bilateral cerebral hemispheres, hypothalamus, temporal lobes, midbrain</td>
</tr>
<tr>
<td>Current study, 2005</td>
<td>88</td>
<td>Lymphoma</td>
<td>7.32</td>
<td>+</td>
<td>-</td>
<td>Bilateral cerebral hemispheres, hypothalamus, temporal lobes, midbrain</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; +, present; -, absent.
Destructive lesions are unlikely to disrupt all of these pathways and spare adjacent brainstem structures.

Carcinomatous and lymphomatous meningiides have also been implicated as causes of CNH. The rarity of CNH in patients with these conditions suggests that diffuse meningiitis is not its mechanism. Our patient’s second lumbar puncture demonstrated no cells during a period of persistent hyperventilation. Although this does not conclusively exclude meningiitis as the cause of CNH, alternative explanations implicating the neuroanatomy of respiration are perhaps more satisfactory.

Stimulation of intrinsic respiratory control centers in the pons and medulla could explain CNH. In both rats and cats, stimulation of the lateral parabrachial nucleus increased the respiratory rate. Injection of glutamate into the cat parabrachial nucleus produced tachypnea followed by restoration of eupnea, making it more likely that a stimulatory rather than a lesioning effect caused the tachypnea. Our patient had involvement in the region of the parabrachial nucleus on magnetic resonance imaging. Two other case reports with autopsy data also note specific involvement of the brachium conjunctivum, adjacent to the parabrachial nucleus. The nature of the stimulatory effect is not clear. In some cases, the tumor or associated inflammatory infiltrates may secrete cytokines or other molecules that activate hyperpnic responses from the parabrachial nucleus. We believe this to be the mechanism in our patient because there was a normalization of breathing after the initiation of corticosteroid treatment.

In other cases, the tumor may reduce local pH in the brainstem, thus activating respiratory chemoreceptors that are located in the ventral brainstem at the junction of the pons and the medulla. Tumors that cause CNH are slow growing and may be more likely to alter local tissue pH without altering overall CSF pH. Although the CSF pH varied considerably in the reported cases and was normal in our case, when measured, CSF pH has tended toward the alkaline (Table). Nevertheless, it is the tumor microenvironment and not the CSF pH that is relevant to the production of CNH.

Hyperventilation could theoretically result from seizure activity that activates the ventilatory response, but this would be more likely in cases of intermittent hyperventilation. Functional magnetic resonance imaging may have demonstrated ongoing brainstem seizure activity but was not performed on this patient.

CONCLUSIONS

The majority of CNH cases in the literature, including the 1 reported herein, had infiltrative tumors involving the pontine tegmentum and medulla. We propose that slowly infiltrating neoplastic lesions may activate central respiratory pathways that produce CNH. This is compatible with the known anatomy of respiratory control in animals and humans, prior reported cases of the syndrome, and the limited experimental evidence.

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Correspondence: Andrew W. Tarulli, MD, Department of Neurology, Israel Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 (atarulli@caregroup.harvard.edu).

Author Contributions: Study concept and design: Tarulli, Lim, Bui, Saper, and Alexander. Acquisition of data: Tarulli, Lim, Bui, Saper, and Alexander. Analysis and interpretation of data: Tarulli, Lim, Bui, Saper, and Alexander. Drafting of the manuscript: Tarulli. Critical revision of the manuscript for important intellectual content: Tarulli, Lim, Bui, Saper, and Alexander. Study supervision: Saper and Alexander.

REFERENCES