Central Neurogenic Hyperventilation

A Case Report and Discussion of Pathophysiology

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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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CENTRAL NEUROGENIC HY- 

erperventilation (CNH) is a rare condition first de- 
scribed by Plum and Swanson.1 Diagnostic cri-
teria for CNH are hyperventilation that persist- 
s during sleep, low arterial PaCO2, high ar- 
terial PaO2, and high arterial pH in the absence of drug or metabolic causes.

REPORT OF A CASE

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 × 10³/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; ammonia level, 52 mg/dL (3 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 (5.3 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; PaCO₂, 15 mm Hg; and PaO₂, 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; PaCO₂, 23 mm Hg; and PaO₂, 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.7

The mechanisms by which infiltrative pontine lesions cause CNH are not completely understood. Plum and Swanson1 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.7,21 There are multiple pathways from the pneumotaxic centers in the pons to the medullary respiratory centers.22

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>Unclear</td>
<td></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>Midbrain</td>
<td>Pons</td>
</tr>
<tr>
<td>Goulon et al.4 1969</td>
<td>22</td>
<td>Astrocytoma</td>
<td>+</td>
<td>+</td>
<td>Midline posterior fossa mass</td>
<td></td>
</tr>
<tr>
<td>Tinaztepe et al.5 1981</td>
<td>7</td>
<td>Lymphoma</td>
<td>+</td>
<td>+</td>
<td>Bilateral parieto-occipital</td>
<td></td>
</tr>
<tr>
<td>Rodriguez et al.6 1982</td>
<td>53</td>
<td>Astrocytoma</td>
<td>+</td>
<td>−</td>
<td>Bilateral cerebral hemispheres</td>
<td></td>
</tr>
<tr>
<td>Plum,7 1982</td>
<td>8</td>
<td>Not stated</td>
<td>7.27</td>
<td>+</td>
<td>Bilateral cerebral hemispheres</td>
<td></td>
</tr>
<tr>
<td>Plum,7 1982</td>
<td>39</td>
<td>Not stated</td>
<td>+</td>
<td>+</td>
<td>Bilateral cerebral hemispheres</td>
<td></td>
</tr>
<tr>
<td>Sunderrajan and Passamonte,8 1984</td>
<td>41</td>
<td>Lymphoma</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Bilateral parietal</td>
<td></td>
</tr>
<tr>
<td>Cohn et al.9 1985</td>
<td>84</td>
<td>Astrocytoma</td>
<td>7.53</td>
<td>+</td>
<td>Widespread</td>
<td></td>
</tr>
<tr>
<td>Bateman et al.10 1985</td>
<td>62</td>
<td>Lymphoma</td>
<td>7.42</td>
<td>−</td>
<td>Hypothalamus, midbrain</td>
<td></td>
</tr>
<tr>
<td>Gottlieb et al.11 1987</td>
<td>23</td>
<td>Medulloblastoma</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Midline posterior fossa mass</td>
<td></td>
</tr>
<tr>
<td>Nakasu et al.12 1988</td>
<td>7</td>
<td>Astrocytoma</td>
<td>+</td>
<td>+</td>
<td>Bilateral parietal</td>
<td></td>
</tr>
<tr>
<td>Pauzer et al.13 1989</td>
<td>61</td>
<td>Lymphoma</td>
<td>7.7</td>
<td>Unclear</td>
<td>Widespread</td>
<td></td>
</tr>
<tr>
<td>Salvesen,14 1989</td>
<td>48</td>
<td>Possible pontine glioma</td>
<td>7.7</td>
<td>Unclear</td>
<td>Bilateral parietal</td>
<td></td>
</tr>
<tr>
<td>Dubayto et al.15 1991</td>
<td>55</td>
<td>Laryngeal carcinoma</td>
<td>7.33</td>
<td>−</td>
<td>Hypothalamus, temporal lobes, midbrain</td>
<td></td>
</tr>
<tr>
<td>Kendel et al.16 1991</td>
<td>52</td>
<td>Lymphoma</td>
<td>7.63</td>
<td>+</td>
<td>Hypothalamus, temporal lobes, midbrain</td>
<td></td>
</tr>
<tr>
<td>Tobias and Heideman,17 1991</td>
<td>11</td>
<td>Lymphoma</td>
<td>+</td>
<td>+</td>
<td>Bilateral frontal and parietal</td>
<td></td>
</tr>
<tr>
<td>Shibata et al.18 1992</td>
<td>72</td>
<td>Lymphoma</td>
<td>+</td>
<td>+</td>
<td>Widespread</td>
<td></td>
</tr>
<tr>
<td>Siderowf et al.19 1996</td>
<td>57</td>
<td>Astrocytoma</td>
<td>7.32</td>
<td>+</td>
<td>Right frontal lobe, midbrain, and left cerebellar hemisphere</td>
<td></td>
</tr>
<tr>
<td>Sakamoto et al.20 2001</td>
<td>69</td>
<td>Lymphoma</td>
<td>+</td>
<td>+</td>
<td>Right frontal lobe, midbrain, and left cerebellar hemisphere</td>
<td></td>
</tr>
<tr>
<td>Current study, 2005</td>
<td>88</td>
<td>Lymphoma</td>
<td>7.32</td>
<td>+</td>
<td>Right frontal lobe, midbrain, and left cerebellar hemisphere</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; +, present; −, absent.
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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REFERENCES