

## CASE REPORT

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### Central Neurogenic Hyperventilation with Primary Cerebral Lymphoma: A Case Report

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We report a case of a bright, alert patient with central neurogenic hyperventilation (CNH) associated with cerebral malignant lymphoma. CNH is a syndrome comprising normal or elevated arterial oxygen tension, decreased arterial carbon dioxide tension, and respiratory alkalosis in the absence of cardiac or pulmonary disease that stimulates a compensatory hyperpnea.

A 72-year-old man with recurrent central nervous system lymphoma presented with hyperpnea, showing a respiratory rate over 30 per minute. He was fully awake and conscious. Routine laboratory studies and chest X-ray were normal, but arterial blood gas examination on room air showed respiratory alkalosis, regardless of wakefulness or sleep. Pulmonary infarction was denied by pulmonary flow scintigram. Rebreathing from a paper bag, intravenous administration of diazepam, and oxygen inhalation failed to alter the respiratory pattern. Brain MRI demonstrated two mildly enhanced lesions within the left side of the medulla oblongata and right side of the pons.

CNH is rare in patients with normal consciousness. It seems to be caused by brainstem injury that includes the respiratory center.

*Key words:* central neurogenic hyperventilation, CNH, central nervous system lymphoma

#### INTRODUCTION

**H**YPERVENTILATION occurs as a result of peripheral and central causes. Peripheral causes such as pulmonary diseases stimulate the central respiratory center of the brainstem indirectly via chemical or mechanical receptors. Central factors include hypoxia, psychogenesis, drugs such as salicylic acid or prostaglandin, central nervous system disorders with disturbance of consciousness, and central neurogenic hyperventilation (CNH).

CNH was defined by Plum and Swanson in 1959 as a

syndrome comprising normal or elevated arterial oxygen tension, decreased arterial carbon dioxide tension, and respiratory alkalosis in the absence of cardiac or pulmonary disease that stimulates a compensatory hyperpnea.<sup>1</sup> It seems to be caused by brainstem injury that includes the respiratory center. CNH is rare in patients with a normal level of consciousness. To date, only 18 cases have been reported.

We report a bright, alert patient with CNH associated with cerebral malignant lymphoma.

#### CASE REPORT

In December 1994, a 69-year-old man previously in good health complained of generalized headache and diplopia. He consulted his family doctor and was referred to the Department of Neurosurgery of Kyoto University Hospital. Computed tomography and magnetic resonance imaging (MRI) revealed a deep-seated mass lesion well enhanced by contrast medium in the left cerebral occipital lobe. The patient refused a diagnostic biopsy, however, the imaging findings and responsiveness to corticosteroid therapy strongly

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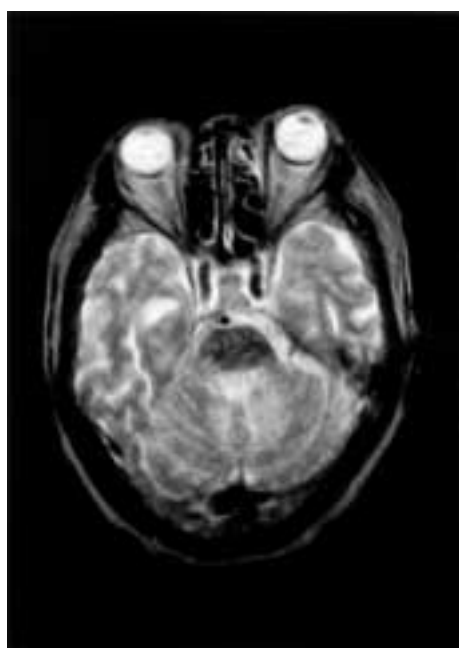
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**Table. Results of arterial blood gas analysis in the patient.**

| Date                          | 9/25/98       | 10/14/98      | 10/14/98                     | 10/14/98     |
|-------------------------------|---------------|---------------|------------------------------|--------------|
|                               | During waking | During waking | Rebreathing from a paper bag | During sleep |
| Lactate (mg/dl)               | 26.6          | 24.9          | 23.8                         | 33.6         |
| pH                            | 7.58          | 7.61          | 7.61                         | 7.61         |
| pCO <sub>2</sub>              | 16.7          | 8.3           | 12.5                         | 9.8          |
| pO <sub>2</sub>               | 89.0          | 110.9         | 113.5                        | 106.3        |
| HCO <sub>3</sub> <sup>-</sup> | 15.3          | 8.2           | 12.1                         | 9.6          |
| SaO <sub>2</sub>              | 98.7          | 99.8          | 98.9                         | 98.7         |

**Fig. 1.** T2-weighted brain MRI at the level of the pons.

suggested central nervous system (CNS) lymphoma. He was treated with 54 Gy of irradiation in 30 fractions, followed by four courses of VEPA regimen chemotherapy,<sup>2</sup> and the tumor responded completely to the treatment.

In July 1996, the first recurrence was observed in the left frontal lobe. He received stereotactic radiosurgery of 12 Gy to the lesion, followed by two courses of combination chemotherapy of etoposide and cisplatin (VP). Although MRI in October indicated regrowth of the lesion, thallium single photon emission computed tomography suggested that the area had brain necrosis due to radiosurgery.

Between March 1998 and July 1998, four recurrences were noted in the supratentorial region. Because all

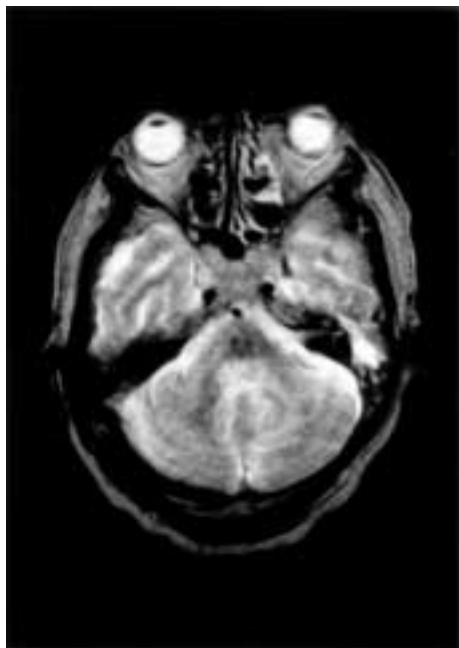
lesions were in previously untreated sites, they were each treated individually with radiosurgery of 10 to 12 Gy, followed by one course of VP regimen chemotherapy after the last recurrence. Complete remission was obtained each time. After these treatments, the patient was fine and worked as the president of a company until September 1998.

On September 25, he presented with hyperpnea, showing a respiratory rate of over 30 per minute on exertion. Routine laboratory studies and chest X-ray were normal, but arterial blood gas examination on room air showed respiratory alkalosis (Table). Pulmonary infarction caused by deep phlebothrombosis was denied by pulmonary flow scintigram. Thereafter, his respiratory pattern returned to normal.

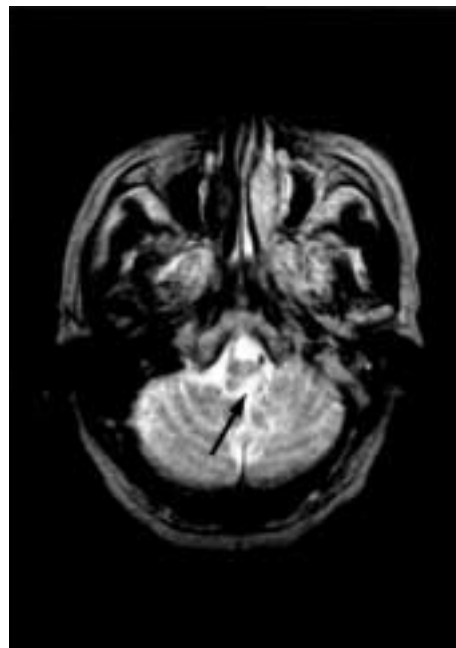
However, on October 11, he presented with hyperpnea and nasal alar breathing. Arterial blood gas analysis during room air breathing showed severe respiratory alkalosis, regardless of wakefulness or sleep (Table). Surprisingly, he was still fully awake and conscious. There were no significant alterations in blood pressure or heart rate. Rebreathing from a paper bag, intravenous administration of diazepam, and oxygen inhalation failed to alter the respiratory pattern. The hyperpnea continued until his death.

Brain MRI on September 29 demonstrated two mildly enhanced lesions measuring 5 mm and 10 mm within the left side of the medulla oblongata and right side of the pons, respectively. These showed iso-intensity on T1-weighted imaging and high-intensity on T2-weighted imaging (Fig. 1). The MRI images and results of arterial blood gas analysis strongly suggested CNH with CNS lymphoma relapsed in the brainstem.

On October 16, the value of C-reactive protein rose to 18.0 mg/dl, but his temperature was below 36.5°C, and respiratory sounds were normal. He presented with brownish sputum on October 18. On October 19, his temperature increased to 37.8 °C, and rale sounds were present in the bilateral lung. Chest X-ray photograph



**Fig. 2.** T2-weighted brain MRI at the level of the cerebellar peduncle.



**Fig. 3.** T2-weighted brain MRI at the level of the medulla. This image shows a high-intensity lesion of 5 mm in the left side of the medulla oblongata (*arrow*).

revealed no obvious pneumonia, however, he was diagnosed with *Klebsiella pneumoniae* by sputum examination. One week later, his arterial oxygen saturation decreased to 35%. The patient died on October 27, 1998. Autopsy was not permitted.

#### DISCUSSION

For the clinical diagnosis of CNH, elevated arterial oxygen tension, decreased arterial carbon dioxide tension, respiratory alkalosis, and lack of stimulation from the periphery to the central respiratory center are mandatory. Moreover, it is essential that this alkalosis persist during sleep, to exclude a psychogenic cause.<sup>3</sup>

In this case, arterial blood gas analysis showed severe alkalosis with decreased serum bicarbonate level. These data suggested three possibilities: primary respiratory alkalosis with compensatory decrease of bicarbonate, primary metabolic acidosis with compensatory decrease in respiratory carbon dioxide tension, and mixed disorder involving respiratory alkalosis and metabolic acidosis. A nomograph of acid-base equilibrium showed that the actual  $p\text{CO}_2$  level was extremely low, below the standard deviation of the estimate of  $p\text{CO}_2$  at the given bicarbonate level.<sup>4</sup> This means that the decrease in  $p\text{CO}_2$  was not due to respiratory compensation for metabolic acidosis. Furthermore, the hypothalamus is considered a metabolic center, and it controls ketone metabolism.<sup>5</sup> There was no extension of lymphoma to the

hypothalamus on MRI, and nothing caused metabolic acidosis; therefore, primary respiratory alkalosis was strongly indicated in this case.

Regarding stimulation from the periphery to the central respiratory center, hyperventilation results from increased afferent drives from the chemical receptors in the lung or arterial walls. In our case, however, evidence of pneumonia, pulmonary edema, or enlargement of the heart was not seen on chest X-ray or electrocardiogram. Further, there was no apparent dyspnea and normal arterial oxygen tension. He did not receive any respiratory-stimulating drugs, and the abnormal respiration rate persisted during sleep. Therefore, this disorder fulfilled all the criteria of CNH.

The pathophysiological mechanism of CNH remains unclear. There are three hypothesis:<sup>6</sup> first, Plum's initial hypothesis of dysfunction of the pontine reticular formation and laterally located descending neural pathway; second, Plum's second hypothesis of reflected central hyperventilation with lactic acid acidosis; and, finally, the hypothesis of unknown stimulating factors. Review of the literature indicated that all but one of the autopsied cases had brain lesions. These lesions were located in the pons and midbrain, lower pontine tegmentum and medulla oblongata, pons alone, and above the level of the superior colliculus with meningeal dissemination.<sup>7</sup> With such a range of distribution it seems

impossible to try to confine the anatomical site responsible for CNH to a single locus.

The lactic acid acidosis theory is that local lactic acid production by tumor cells could stimulate medullary chemoreceptors and cause CNH. Krendel *et al.*<sup>8</sup> described that the lactic acid acidification of cerebrospinal fluid (CSF) and decrease of lactic acid in CSF as treatment was observed in a patient with diffuse cerebral lymphoma, supporting this theory. They suggested that local acidification resulted in an increase in hydrogen ions and stimulated chemosensitive respiratory neurons. However, *in-vivo* studies measuring the pH in brain neoplasms by positron emission tomography have demonstrated that the pH in gliomas is higher than that in the rest of the brain, thus ruling out the theory of local lactic acid acidosis as the sole cause of CNH.<sup>9</sup>

Although we did not measure the CSF lactic acid level, the blood lactic acid level was extremely high. Huckabee reported that hyperventilation caused a 2 mEq/l rise in the arterial lactic acid level.<sup>10</sup> This means that hyperventilation does not result from lactic acid acidosis, but rather results in lactic acid acidosis in CNH. In addition, the nomogram findings demonstrated that hyperventilation did not compensate for metabolic acidosis. Therefore, the lactic acid acidosis theory was negated.

The location and histological findings seen in our patient were consistent with previous reports. CNH did not occur when lymphoma extensively invaded the cerebral cortex and basal ganglia, but was initiated when lymphoma infiltrated within the upper brainstem according to MRI findings. Therefore, it is clear that the upper brainstem lesion resulted in CNH. Lange and Laszlo reported a case of CNH with a central nervous system tumor involving the pons and midbrain, but sparing the medulla oblongata.<sup>11</sup> However, this was not consistent with our case, because hyperventilation persisted until the patient died. Permission for autopsy was not obtained, so pathological involvement remains unclear. A higher respiratory center or involvement of another structure above the brainstem does not seem to induce CNH. It is significant that the upper brainstem is involved. Our case suggests that CNH results from a structural mechanism, however, the precise nature of the structural lesion necessary to cause CNH remains unclear.

Pauzner *et al.* reported that cerebral lymphoma accounted for half of all brain tumors that induced CNH, despite the rarity of this tumor, which represents less than 1% of all brain tumors.<sup>12</sup> The relatively high frequency of lymphoma among cases of tumor-induced CNH appears significant. One possible reason is

localization to the nervous system and diffuse involvement where the lesions are multifocal and more commonly involve the corpus callosum compared with other brain tumors.

For remission of hyperventilation, rebreathing from a paper bag, intravenous administration of diazepam, and oxygen inhalation failed to alter the respiratory pattern, as others have reported. Administration of morphine slowed respiration moderately, but did not obtain a complete effect. A patient who returned to normal respiratory patterns as the tumor contracted after surgical therapy has been reported.<sup>13</sup> Treatment of primary cerebral lymphoma is essential to induce regression of the tumor and remission of CNH. The patient must be followed after radiation therapy and/or radiosurgery and chemotherapy penetrating the central nervous system.

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