

## Efficacy of Tracheostomy for Central Alveolar Hypoventilation Syndrome Caused by Lateral Medullary Infarction

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### Abstract

Central alveolar hypoventilation syndrome (CAHS) is a rare and potentially fatal condition. However, respiratory care for patients with CAHS caused by lateral medullary infarction (CAHS-LMI) remains an important unsolved problem. We describe 2 patients with CAHS-LMI and review the case reports for 17 previously described patients. Patient 1 was a 78-year-old man who was referred to our hospital because of dizziness. After admission, Wallenberg syndrome developed. Magnetic resonance imaging showed left LMI. He had hypercapnia and respiratory acidosis the next afternoon and temporarily received mechanical ventilation. A tracheotomy was performed on the 12th hospital day, and the patient was weaned from the ventilator on the 18th hospital day. Patient 2 was 72-year-old man who was referred to our hospital because of dizziness and gait disturbance. Wallenberg syndrome was diagnosed after admission, and magnetic resonance imaging showed right LMI. His consciousness deteriorated, and hypercapnia developed on the ninth hospital day. The patient received ventilatory support, and a tracheotomy was performed on the 12th hospital day. He was weaned from the ventilator by the 16th hospital day. Consistent with our findings, most previously reported cases of CAHS-LMI were initially associated with mild symptoms, which subsequently worsened. Five of the 19 patients (26.3%) died within 1 month after onset, and 7 patients (36.8%) died within 1 year. Tracheotomy was performed in 12 patients, 2 of whom died 1 month after onset (16.7%); another patient died of chronic renal failure after 2 years. Tracheotomy seemed to be an effective procedure in patients with CAHS-LMI. We speculate that tracheotomy assists alveolar ventilation by reducing dead space ventilation. Closure of the tracheotomy should, therefore, be avoided in patients with CAHS-LMI, even if respiratory status is good.

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**Key words:** lateral medullary infarction, Ondine's curse, tracheostomy

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## Introduction

The respiratory center is a collection of neurons with unclear boundaries and consists of various components, such as the dorsal and ventral respiratory group in the reticular formation of the medulla oblongata and the apneustic and pneumotaxic center in the pons<sup>1</sup>. In humans, respiratory control involves 2 functional elements: the metabolic control system and the behavioral control system. The metabolic control system is located in the medulla oblongata and receives inputs from chemoreceptors in the carotid body and medulla oblongata and from respiratory proprioceptors. The behavioral control system governs waking behavior, such as talking, laughing, and crying, and adjusts the respiratory rhythm and the amount of ventilation, both voluntarily and involuntarily. Respiratory control involves both the metabolic and behavioral control systems in the waking state, rapid eye movement (REM) sleep, and light non-REM sleep. During sound non-REM sleep, only the metabolic control system regulates respiratory control.

The pathogenesis of Ondine's curse<sup>2</sup>, also called central alveolar hypoventilation syndrome (CAHS), is attributed to dysfunction of the metabolic control system, involving the medullary respiratory center itself or its neural pathways. The ventilatory response to increased levels of carbon dioxide in plasma is lost or diminished. Patients fall into hypoventilation if they not breathe voluntarily via the behavioral control system. In the waking state, therefore, the patient can continue to breathe by means of the breathing behavioral regulatory system and thereby compensate for hypoventilation. During sound non-REM sleep, however, both the metabolic and behavioral control systems do not work, and patients fall into potentially fatal, severe chronic hypoventilation.

Previous studies<sup>3-16</sup> have documented 17 patients with CAHS caused by lateral medullary infarction (CAHS-LMI, **Table 1**). Although CAHS is often fatal, respiratory care for CAHS-LMI remains an important unsolved problem. We describe 2

surviving patients who presented with CAHS-LMI. We also review 17 previously documented patients with CAHS-LMI and discuss strategies for respiratory control in CAHS-LMI.

## Material and Methods

### Patient 1

A 78-year old man was referred to our hospital because of dizziness at 10 p.m. and was admitted. There were no clinically significant abnormalities on neurological examination or chest radiography (**Fig. 1A**). Because the oxygen saturation had decreased at midnight, we increased the oxygen dose of the patient. The next morning, dizziness became milder. However, disturbed consciousness developed at 2 p.m. Arterial blood gas analysis showed hypercapnia and respiratory acidosis (PO<sub>2</sub>, 106 mm Hg; PCO<sub>2</sub>, 101 mm Hg; pH, 7.124). Tracheal intubation was immediately performed, and the patient received ventilatory support. He then regained consciousness. We also diagnosed Wallenberg syndrome, associated with left blepharophimosis, miosis, incoordination, right superficial sensation disorder of the upper extremity, and severe dysphagia. Therefore, his neurological status as well as his respiratory status had deteriorated. Only mild atelectasis of the right lower lung field was seen on a chest X-ray film (**Fig. 1B**). On the third hospital day, magnetic resonance imaging (MRI) of the head showed a high-intensity region in the left lateral medulla oblongata on diffusion-weighted images (DWI, **Fig. 2A**) and T<sub>2</sub>-weighted images (T<sub>2</sub>WI, **Fig. 2B**). **Figure 3** shows the distribution of the lesion and the anatomy of the medulla oblongata. Magnetic resonance angiography (MRA) demonstrated weak signals for the left vertebral artery (**Fig. 2C and 2D**). We diagnosed CAHS-LMI due to atherothrombosis. The endotracheal tube was removed on the fourth hospital day, because the respiratory status had been good during the daytime. On the sixth hospital day, however, hypercapnia (PCO<sub>2</sub>, 96 mmHg) recurred at midnight, and the endotracheal tube was reinserted. A tracheotomy was performed on the 12th hospital day. On the 18th hospital day, ventilatory support was discontinued. While the

Table 1 Clinical profiles of our patients and the 17 patients with central alveolar hypoventilation syndrome due to lateral medullary infarction

No	Age, gender	Initial symptoms	Respiratory failure after onset	Ischemic lesion	Vascular lesion	Remarks	Tracheotomy	Paper
1	36, F	Dyspnea	0 hour	Left lateral medulla oblongata and cerebellum (autopsy)	Dissection of left vertebral artery (autopsy)	Died suddenly on the 31st hospital day.	Yes	Devereaux <i>et al.</i> <sup>3</sup>
2	58, F	Dyspnea, left Wallenberg syndrome	0 hour	Unknown	Unknown	Tracheotomy several hours after admission.	Yes	Devereaux <i>et al.</i> <sup>3</sup>
3	52, M	Dizziness, nausea, headache	5 hours	Left lateral medulla oblongata (autopsy)	90% stenosis of left vertebral artery (autopsy)	Artificial respiration more than 30 days. Spontaneous breathing eventually. Merger of myocardial infarction. Died after a month.	Yes	Levin <i>et al.</i> <sup>4</sup>
4	49, M	Left Wallenberg syndrome	Unknown	Unknown (CT)	Unknown	CPAP was efficacious.	Unknown	Askenasy <i>et al.</i> <sup>5</sup>
5	71, M	Dizziness, double vision.	3 days	Left lateral and dorsomedial medulla oblongata (MRI)	Unknown	Separated from ventilator after a month.	Yes	Hashimoto <i>et al.</i> <sup>6</sup>
6	73, M	Ataxic gait	4 days	Left lateral medulla oblongata and lower pons (autopsy)	Stenosis of bilateral vertebral and carotid arteries (autopsy)	Died of pneumonia with ventilator after a month.	Unknown	Bogousslavsky <i>et al.</i> <sup>7</sup>
7	65, M	Dizziness, nausea, headache	1 day	Left lateral medulla oblongata (autopsy)	Occlusion of left vertebral artery (autopsy)	Died of pneumonia with ventilator after 12 days.	Unknown	Bogousslavsky <i>et al.</i> <sup>7</sup>
8	64, M	Gait disturbance	3 days	Right lateral medulla oblongata (MRI)	Unknown	Separated from ventilator after 48 days. Died of chronic renal failure after 2 years.	Yes	Takehara <i>et al.</i> <sup>8</sup>
9	49, M	Bradycardia, dysphagia, dysarthria, hypoesthesia of left face, right hemiparesis	2 days	Bilateral thalamus, occipital lobe, pons and medulla oblongata, and left cerebellum and cerebral peduncle (MRI)	Occlusion of left vertebral artery (angiography)	Temporary artificial respiration. Possible to walk with assistance, and the cavity of tracheotomy was closed after 6 months.	Yes	Kraus <i>et al.</i> <sup>9</sup>
10	78, M	Dizziness, gait disturbance	7 days	Right lateral and dorsomedial medulla oblongata (MRI)	Occlusion of right vertebral artery (angiography)	Temporary artificial respiration, and nasal CPAP.	Unknown	Iwasaki <i>et al.</i> <sup>10</sup>
11	70, M	Ataxic gait, nausea	15 hours	Left lateral medulla oblongata (autopsy)	Occlusion of left vertebral artery due to arteriosclerosis (autopsy)	Separated from ventilator with alprostadil. Died 16 hours after onset.	No	Terao <i>et al.</i> <sup>11</sup>
12	55, M	Dizziness, nausea, dysarthria, headache, left hemiparesis	12 hours	Bilateral cerebellum, and right thalamus, pons, medulla oblongata (MRI)	Unknown	BIPAP was efficacious. Died of sepsis after 23 months.	Unknown	Schestatsky <i>et al.</i> <sup>12</sup>
13	59, M	Dysarthria, dysphagia, numbness of left body.	1 day	Left lateral medulla oblongata (MRI)	Dissection of left vertebral artery (angiography)	Temporary artificial respiration. Separated from ventilator with acetazolamide after 25 months.	Yes	Takabatake <i>et al.</i> <sup>13</sup>
14	86, M	Gait disturbance, hoarseness, dysarthria	5 days	Right lateral medulla oblongata (MRI)	Unknown	Tracheotomy on the 8th hospital day. Separated from ventilator daytime after 9 months.	Yes	Arai <i>et al.</i> <sup>14</sup>
15	83, F	Dysphagia	3 days	Right lateral medulla oblongata (MRI)	Unknown	Separated from ventilator after 2 months.	Yes	Arai <i>et al.</i> <sup>14</sup>
16	79, F	Dizziness, dysarthria.	Unknown	Left lateral medulla oblongata (MRI)	Normal (MRA)	Died of pneumonia and sepsis with ventilator after 2 months.	Unknown	Pedroso <i>et al.</i> <sup>15</sup>
17	73, F	Right blepharophimosis, dizziness,	3 days	Right lateral medulla oblongata (MRI)	Occlusion of right vertebral artery (MRA)	Tracheotomy on the 18th hospital day. Separated from ventilator daytime after 2 months.	Yes	Fukushima <i>et al.</i> <sup>16</sup>
18	78, M	Dizziness	2 days	Left lateral and dorsomedial medulla oblongata (MRI)	Low signal of left vertebral artery (MRA)	Separated from ventilator on the 18th hospital day.	Yes	Case 1
19	72, M	Dizziness, gait disturbance	9 days	Right lateral medulla oblongata (MRI)	Low signal of right vertebral artery but normal BPAS (MRA).	Separated from ventilator on the 16th hospital day.	Yes	Case 2

BPAS=basisparallel anatomical scanning; CPAP=continuous positive airway pressure; BIPAP=bilevel positive airway pressure.

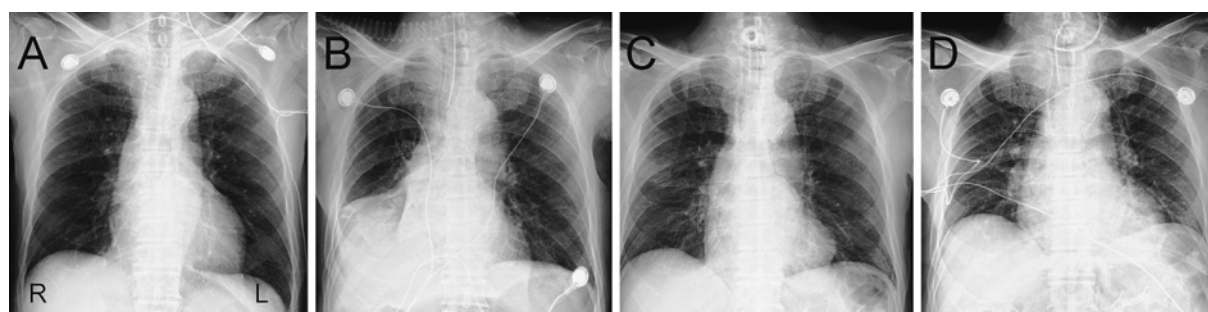


Fig. 1 Chest X-ray films on the first (A), second (B), 109th (C), and 158th (D) hospital days.

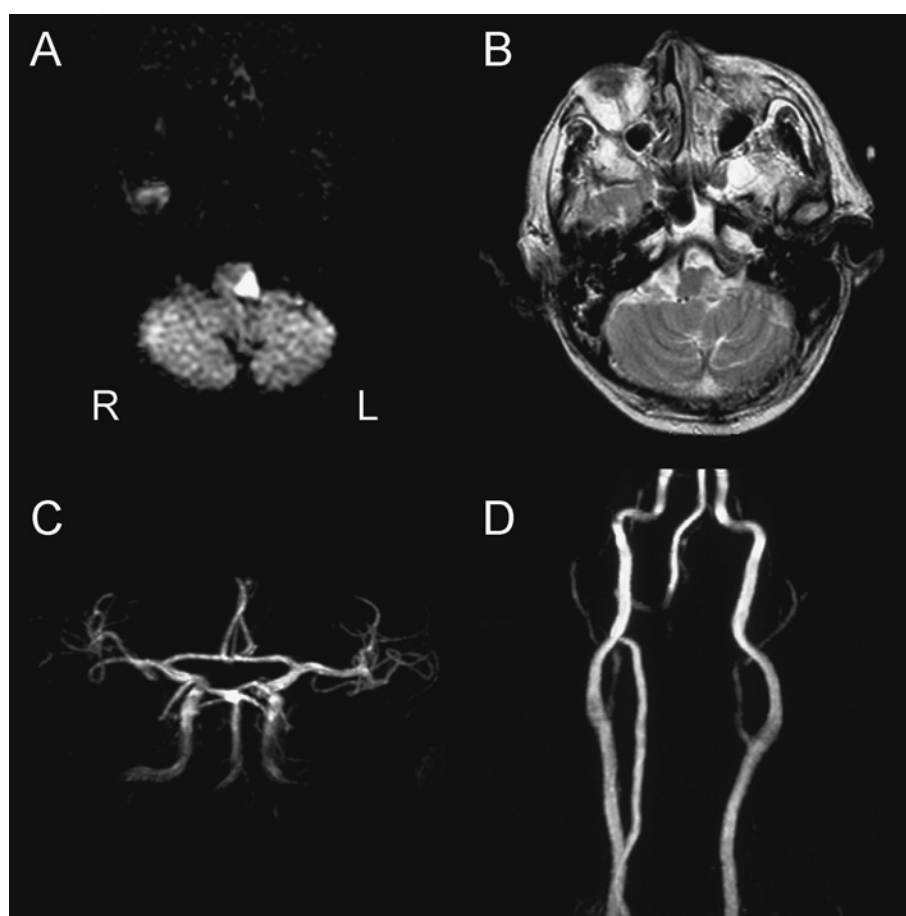


Fig. 2 A diffusion-weighted image (A) and a T<sub>2</sub>-weighted image (B) obtained with magnetic resonance imaging on the third hospital day and magnetic resonance angiograms of the head (C) and neck (D) obtained on the sixth hospital day. Magnetic resonance imaging shows a high-intensity region in the left lateral medulla oblongata. Magnetic resonance angiograms show weak signals for the left vertebral artery.

patient was breathing room air, the PO<sub>2</sub> was about 60 mm Hg, and the PCO<sub>2</sub> was about 40 mm Hg. A speaking-type tracheotomy tube was inserted on the 39th hospital day. Because dysphagia was severe, gastrostomy was performed on the 98th hospital

day.

The patient was transferred to a rehabilitation hospital on the 116th hospital day. Because his respiratory status was good, the tracheotomy tube was removed, and the tracheostoma site was

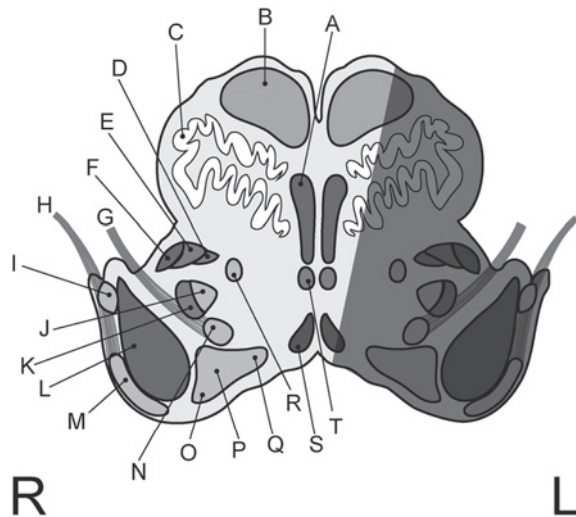


Fig. 3 An illustration of the medullary lesion in patient 1. A=medial lemniscus, B=pyramid, C=inferior olivary nucleus, D=anterior spinothalamic tract, E=lateral spinothalamic tract, F=anterior spinocerebellar tract, G=glossopharyngeal nerve, H=cochlear nerve, I=ventral cochlear nucleus, J=trigeminal nucleus, K=spinal tract of trigeminal nerve, L=inferior cerebellar peduncle, M=dorsal cochlear nucleus, N=solitary fasciculus and nucleus, O=lateral vestibular nucleus, P=inferior vestibular nucleus, Q=medial vestibular nucleus, R=nucleus ambiguus, S=medial longitudinal fasciculus, T=ventral spinothalamic tract.

covered with gauze on the 150th hospital day. His consciousness and respiratory status deteriorated again, and he was transferred to our hospital on the 158th hospital day. Laboratory examinations revealed hypercapnia ( $\text{PCO}_2$ , 73.1 mm Hg) and mild inflammation (white blood cell count,  $9,310/\mu\text{L}$ ; C-reactive protein, 1.1 mg/dL). A chest X-ray film showed only mild pneumonia in the left lower lung field (**Fig. 1D**). We performed artificial respiration by means of a tracheotomy tube, and his condition soon improved. We decided that the tracheotomy tube should not be removed because the reduction in airway dead space due to the tracheotomy had apparently improved the CAHS. After that, the patient could again breathe without the ventilator during the daytime but used a portable ventilator at night.

## Patient 2

A 72-year old man had dizziness and nausea on waking and rested at home. However, his symptoms worsened, and he could not walk. He was then transported to our hospital by ambulance at noon. On admission, the consciousness was clear. Neurologic examination revealed right hemiparesis, saccadic eye movements, and dysarthria. After 1 hour, his symptoms worsened, and he presented with right blepharophimosis, miosis, curtain sign, deviation of the tongue, absence of the gag reflex, incoordination, and severe dysphagia. Wallenberg syndrome was diagnosed. He also had disturbed superficial sensation of the left side of the face and upper and lower extremities. A DWI (**Fig. 4A**) showed a high-intensity region in the right lateral medulla oblongata, although a  $\text{T}_2\text{WI}$  (**Fig. 4B**) showed no abnormalities. A chest X-ray film on admission showed no abnormalities (**Fig. 4C**). MRA demonstrated occlusion of the right vertebral artery, but basiparallel anatomical scanning<sup>17</sup> showed both the right and left vertebral arteries with no stenosis. Right lateral medullary infarction caused by atherothrombosis was thus diagnosed. On the ninth hospital day, his consciousness deteriorated in the early morning, and the  $\text{PCO}_2$  was 115 mm Hg. Tracheal intubation was immediately performed, and he regained consciousness. Tracheotomy was performed on the 12th hospital day. Ventilatory support was discontinued on the 16th hospital day, and the patient was transferred to a rehabilitation hospital on the 41st hospital day. Because swallowing function was not restored, a cricopharyngeal myotomy with laryngeal suspension was performed on the 166th hospital day.

## Results

Nineteen patients with CAHS-LMI<sup>3-16</sup>, including our patients, have been described (**Table 1**). Two patients described by Devereaux *et al.*<sup>3</sup> were transported to the hospital because of respiratory failure. The other patients initially had mild symptoms, such as dizziness and gait disturbance, on admission but their condition subsequently deteriorated. Seven patients presented with CAHS

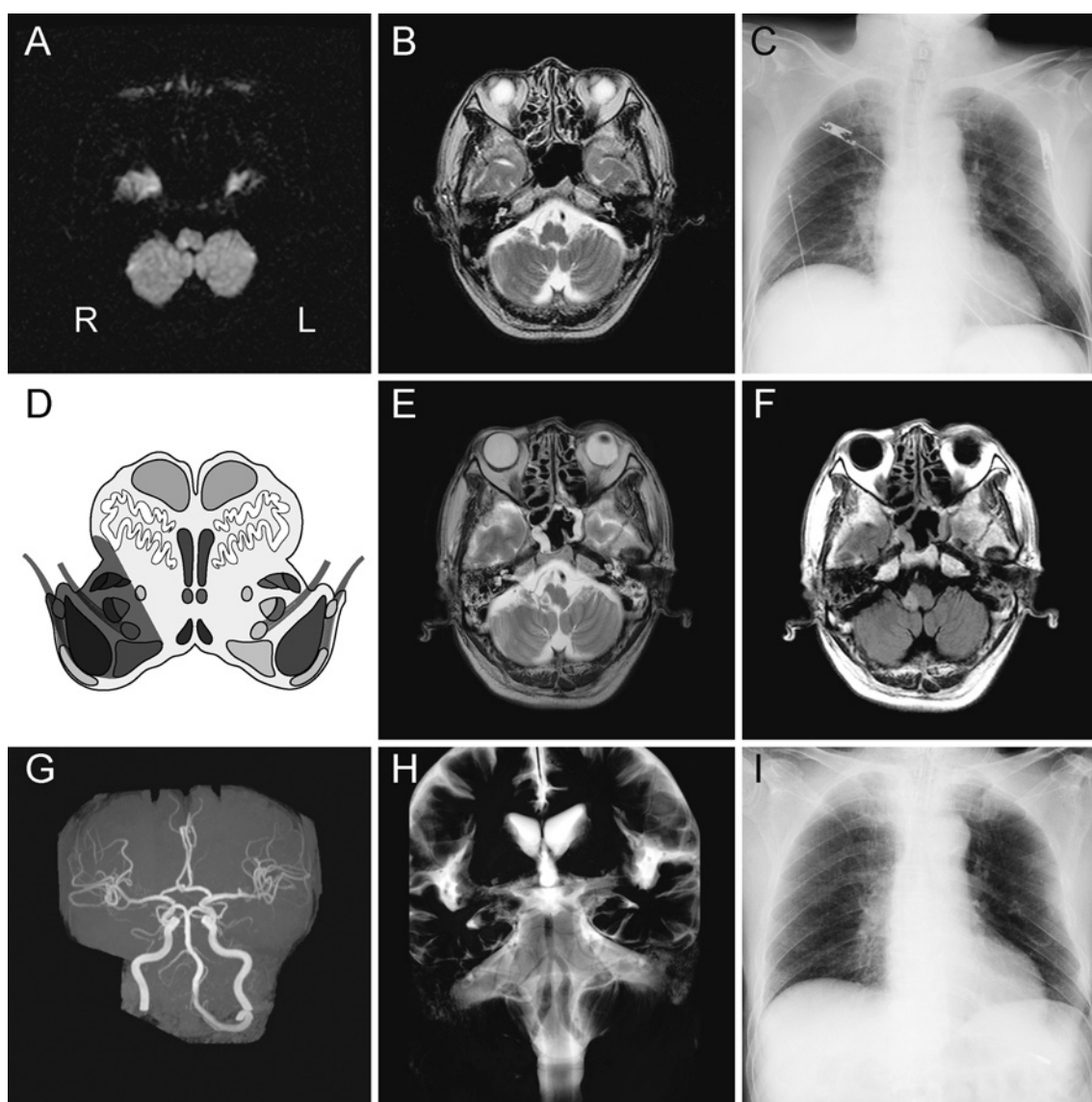


Fig. 4 A diffusion-weighted image (DWI, A) and a T<sub>2</sub>-weighted image (T<sub>2</sub>WI, B) obtained with magnetic resonance imaging (MRI) and a chest X-ray film (C) on the first hospital day, an illustration of the medullary lesion in patient 2 (D), a T<sub>2</sub>WI (E), and a fluid attenuation inversion recovery image (F) obtained with MRI, a magnetic resonance angiogram (MRA, G), a basiparallel anatomical scan (BPAS, H), and a chest X-ray film (I) obtained on the 26th hospital day. The DWI obtained on the first hospital day shows a slightly high intensity region in the left lateral medulla oblongata, although the T<sub>2</sub>WI showed no abnormalities. The later MRIs show an obvious medullary lesion. The MRA shows the right posterior inferior cerebellar artery but not the right vertebral artery, although the BPAS demonstrates both the right and left vertebral arteries. The BPAS revealed the outer contour of the intracranial vertebrobasilar artery, whereas conventional MRA showed the inner contour of the vessel. Therefore, the right vertebral artery was not hypoplastic.

within 20 hours after onset, and 2 patients presented with CAHS more than 7 days after onset. One patient had bilateral medullary lesions, 11 had left medullary lesions, and 7 had right medullary lesions. Dissection of the vertebral artery was found in 2 patients. Stenosis or occlusion of the vertebral artery with atherosclerosis was confirmed in 4 patients at

autopsy. Five (26.3%) of the 19 patients died within 1 month after onset, and 7 (36.8%) died within 1 year. Tracheotomy was performed in 12 patients. Two (16.7%) of these patients died 1 month after onset, and another patient died of chronic renal failure after 2 years. It is unclear whether a tracheotomy was performed in 6 patients.



## Discussion

Previous studies have reported that obstructive sleep apnea syndrome (OSAS) is a risk factor for death in patients with stroke<sup>18,19</sup>. As mentioned earlier, CAHS-LMI has a higher mortality rate than does stroke with OSAS. Five of 19 patients with CAHS-LMI died within 1 month after onset. However, only 2 of the 12 patients who underwent tracheotomy died within 1 month. We speculate that the patients who died without undergoing tracheotomy were in poor general health. We further speculate that tracheotomy improves alveolar hypoventilation by reducing dead space ventilation, as described later.

Alveolar hypoventilation is caused by failure of the respiratory center, neural and neuromuscular transmission, muscle, chest wall, lung, and airways<sup>20</sup>. Arterial carbon dioxide tension ( $PaCO_2$ ) is defined as:

$$PaCO_2 = k V_{CO_2}/V_A, \quad (1)$$

where factor  $k$  (0.863) is the constant of proportionality,  $V_{CO_2}$  is the volume of carbon dioxide eliminated per minute, and  $V_A$  is alveolar ventilation. Therefore, reduced alveolar ventilation causes hypercapnia. Alveolar ventilation is defined as:

$$V_A = V_E - V_{ds} \quad (2)$$

where  $V_E$  is minute ventilation, and  $V_{ds}$  is dead space ventilation<sup>20</sup>. Expansion of the dead space leads to decreased alveolar ventilation, such as that associated with breathing with a snorkel. On the other hand, a reduction in the dead space assists alveolar ventilation. Tracheotomy shortens the airway and reduces dead space ventilation. Therefore, we believe that the tracheotomy effectively promotes alveolar hypoventilation. Some patients with the CAHS-LMI, including our patients, did not require ventilatory support after tracheotomy.

We suggest that closure of the tracheotomy should be avoided in patients with CAHS-LMI, even if respiratory status is good. Alveolar ventilation in patient 1 deteriorated after removal of the tracheotomy tube. In one previous patient, however, the tracheostoma site could be closed 6 months after onset<sup>9</sup>. Continuous positive airway pressure (CPAP)

was reported to be efficacious in 3 patients with CAHS-LMI<sup>5,10,12</sup>. CPAP is now often used in patients with OSAS<sup>21,22</sup>. Alveolar hypoventilation might resolve without a reduction in dead space in some patients with CAHS-LMI. We speculate that CPAP may not be indicated for every patient with CAHS-LMI, because in contrast to tracheotomy, CPAP does not reduce dead space. As mentioned earlier, the distribution of neurons in the respiratory center is unclear, and differences in recovery might be related to individual differences in the distribution of neurons participating in respiratory function.

The respiratory center is thought to exist bilaterally in the brainstem<sup>1,23</sup>. Only 1 of the 19 patients with CAHS-LMI had bilateral lesions of the medulla oblongata<sup>9</sup>, and all other patients had unilateral lesions. Twice as many patients had left-sided lesions as had right-sided lesions. The left medulla oblongata might play a dominant role in respiratory control. While awake, patients with unilateral lesions can potentially compensate for alveolar hypoventilation by means of the behavioral control system. We could not delineate characteristic differences in the distribution of lesions between usual medullary infarction and CAHS-LMI because some case reports did not include images or describe the pathological features of lesions. The lesions in some patients did not include the inferior cerebellar peduncle<sup>3,4,7,11</sup>. The region surrounding the nucleus ambiguus, the solitary tract, and the trigeminal nucleus may be a common focus<sup>16</sup>. However, we do not assume that hypoventilation develops in all patients with lesions in regions of the brain involved in respiratory control. The brain must include a "safety net," which acts to prevent the development of alveolar hypoventilation. The safety net may be related to the "obscure" nature of the respiratory center. Mild alveolar hypoventilation might not be diagnosed in some patients. Further studies are needed to achieve a better understanding of these matters.

The development of CAHS is apparently related to initial symptoms in patients with CAHS-LMI (Table 1). Two patients were brought to the hospital because of respiratory failure<sup>3</sup>. The others had mild initial symptoms, such as dizziness and gait

disturbance, but their condition deteriorated later. In patient 2, CAHS developed on day 9. Perhaps the patient could not sleep soundly because of the stress and noise in the intensive care unit for stroke, and his behavioral control system might have compensated for alveolar hypoventilation for a prolonged time. In any case, respiratory status should be closely monitored, particularly at night, in patients in poor condition who have LMI. Many patients had prolonged stenosis or occlusion of the vertebral artery, although LMI was caused by dissecting aneurysms in 2 patients. Dissection is the second most common cause of LMI; atherothrombosis of the vertebral artery is the most common cause<sup>24</sup>. Our findings suggest that atherothrombotic infarction can cause CAHS-LMI.

### Conclusion

We have described 2 patients with CAHS-LMI and reviewed previous case reports of CAHS-LMI. CAHS-LMI is a rare and potentially fatal condition. Although many patients with CAHS-LMI had a progressive course, there were no characteristic findings of the initial symptoms of the patients. We did not find also characteristic of the distribution of medullary lesions in the patients with CAHS-LMI. This fact may be related to the obscure distribution of neurons in the respiratory center. In patients with progressive LMI, respiratory status should be closely monitored at night. Tracheotomy was efficacious in patients with CAHS-LMI. We speculate that a reduction in airway dead space after tracheotomy improves alveolar hypoventilation.

**Conflict of Interest:** There is no possible conflict of interest related to this paper.

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