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【 CASE REPORT 】

Post-hyperventilation Apnea with Spindle Activity on Electroencephalogram

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Abstract:
Loss of consciousness occurs in post-hyperventilation apnea, but its pathophysiology remains unclear. We herein report a patient with post-hyperventilation apnea showing spindle activity on electroencephalogram (EEG). The patient was alert and breathing spontaneously before the hyperventilation test, but loss of consciousness and apnea with spindle activity on EEG occurred when the end-tidal CO_2 decreased during the hyperventilation test. She recovered consciousness and spontaneous breathing with the disappearance of the spindle activity on EEG when the end-tidal CO_2 increased after the hyperventilation test. The loss of consciousness during post-hyperventilation apnea might be due to the focal involvement of the ascending-activating mesodiencephalic reticular formation.

Key words: post-hyperventilation apnea, hyperventilation syndrome, spindle coma

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Introduction

Hyperventilation syndrome (HVS) is characterized by functional hyperventilation attacks with no underlying organic abnormalities and generally carries a good prognosis (1). However, HVS has occasionally been associated with severe symptoms, including apnea. Post-hyperventilation apnea (PHA) with sustained cyanosis, hypoxemia, and loss of consciousness (LOC) has been previously reported (2), but the pathophysiology of LOC in PHA is not fully understood.

We herein report a patient with PHA showing spindle activity on EEG in the hyperventilation test (HVT) and speculate on the pathophysiology of LOC in PHA.

Case Report

The patient was a right-handed, 27-year-old woman. She had experienced HVS several times. Her first apnea attack occurred when she was a high school student. In 2009 and 2012, she experienced the second and third apnea attacks, respectively, after drinking alcohol. Each episode occurred subsequent to HVS, and she recovered spontaneously without treatment.

In 2016, she was rushed to the emergency department of another hospital on day 1 due to HVS after consuming alcohol and was treated with intravenous hydroxyzine. Subsequently, her respiratory rate (RR) gradually decreased, and she was intubated and artificially ventilated due to apnea, which continued for up to 1 minute. She was transferred to our medical center on day 2. On arrival, she had been intubated, but she was breathing spontaneously, and no sedative drugs were being used. Her RR was 11 breaths/min, and percutaneous oxygen saturation (SpO_2) was 97% on room air. She was alert, and showed no neurological abnormalities. A blood examination revealed no abnormalities aside from an elevated white blood cell count (16,000/μL). No abnormal signals were observed on brain or cervical magnetic resonance imaging (MRI).

As the etiology of apnea remained unclear in our patient, we performed an HVT with monitoring of the SpO_2, end-tidal CO_2 ($etCO_2$), and electroencephalogram (EEG) in order to exclude other diseases, such as epilepsy, and assess the correlation between hyperventilation and apnea (Fig. 1). The patient provided her informed consent. While she had been intubated on admission and was breathing spontaneously, we prepared a mechanical ventilator to ensure the patient's

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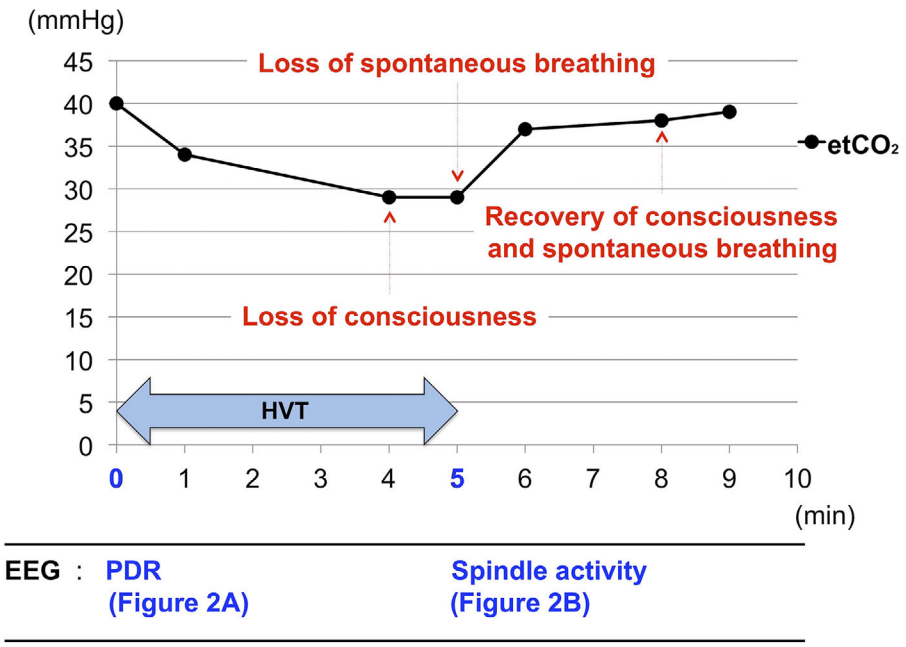

Figure 1. **The time course of the patient's consciousness, respiration, and electroencephalography on the hyperventilation test. Before the HVT, the patient was alert and breathing spontaneously (corresponding to EEG in Fig. 2A). When the $etCO_2$ decreased to 29 mmHg during the HVT, LOC and apnea occurred (corresponding to EEG in Fig. 2B). Later, when the $etCO_2$ gradually increased to 38 mmHg after the HVT, she recovered consciousness and spontaneous breathing. $etCO_2$: end-tidal CO_2, HVT: hyperventilation test, LOC: loss of consciousness, PDR: posterior dominant rhythm**

safety in case of apnea during the HVT. Before the HVT, she was alert, and EEG showed a 9- to 11-Hz posterior-dominant rhythm (Fig. 2A). We performed the HVT using volume-controlled assist-control mechanical ventilation (tidal volume 430 mL, RR 28 breaths/min, and FiO_2 0.21). After the HVT was started, the $etCO_2$ gradually decreased. Four minutes later, the $etCO_2$ decreased to 29 mmHg, and the patient lost consciousness. The HVT was stopped after 5 minutes, but the patient did not resume spontaneous breathing, and EEG revealed spindle activity without slow activity (Fig. 2B). Mechanical ventilation was started again due to apnea. Three minutes later, the $etCO_2$ gradually increased to 38 mmHg, and she recovered consciousness and spontaneous breathing, with the disappearance of the spindle activity on EEG. During the HVT, the SpO_2 was maintained at more than 95% on room air. The results of the HVT suggested a correlation between hyperventilation and apnea, so we diagnosed her with PHA.

Thereafter, she was extubated and showed no relapse of PHA. Since the previous relapses of PHA had occurred after alcohol consumption, we advised her not to consume alcohol in order to prevent PHA. The patient was discharged on day 5.

Discussion

We herein report the case of a patient with PHA showing spindle activity on EEG during the HVT. In our patient, when LOC associated with PHA occurred during the HVT, EEG revealed spindle activity, which disappeared in parallel with the recovery of consciousness and spontaneous breathing. Some patients with HVS are known to develop PHA in conjunction with hypoxia, cyanosis, or LOC, requiring intubation and artificial ventilation (2). Most patients spontaneously recover from PHA, but prolonged PHA is associated with severe outcomes, including death (3).

There have been only a few reports of PHA, but breath-holding spell (BHS), which resembles PHA, is a common disease in infants causing apnea, cyanosis, and LOC following crying induced by pain, anger, and fear (4). Although PHA and BHS differ in terms of the age of onset, BHS resembles PHA in terms of the development of apnea after HVS.

Apnea is generally caused by the dysfunction of the respiratory centers in the medulla and pons (5), and several studies have speculated the mechanism of PHA to be as follows: PHA occurs when the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) is reduced to the threshold of spontaneous breathing (6); hypocapnia resulting due to HVS causes respiratory alkalosis, and this leads to reduced hydrogen ions acting on chemoreceptors and subsequent respiratory depression (6). In addition, even if hypocapnia following hyperventilation is normalized, the breathing may not immediately restart for several possible reasons. First, the threshold level of $PaCO_2$ is elevated after hyperventilation (7). Second, hypocapnia in the brain persists even when arterial and alveolar $PaCO_2$ are normalized (8). Third, the hypoxic ventilatory drive is attenuated by hypocapnia due to

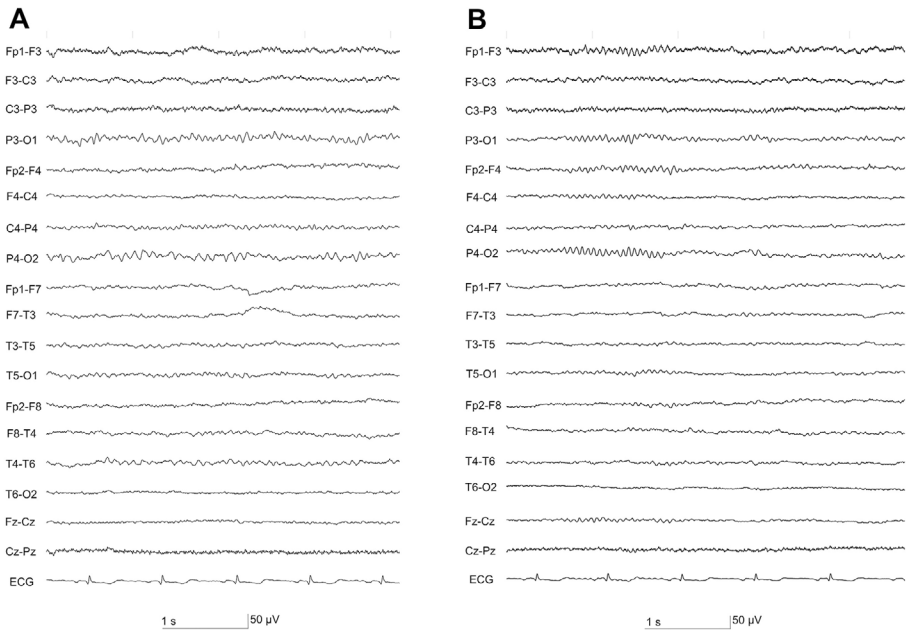

Figure 2. **EEG findings. (A) EEG performed before the HVT showing a 9- to 11-Hz posterior-dominant rhythm. High-pass filter, 0.5 Hz; low-pass filter, 70 Hz. (B) EEG at the end of the HVT showing spindle activity. High-pass filter, 0.5 Hz; low-pass filter, 70 Hz. HVT: hyperventilation test**

HVS (9). Furthermore, our patient repeatedly experienced PHA after drinking alcohol. Since a high blood alcohol concentration can cause respiratory depression (10), alcohol consumption might increase the risk of PHA.

To our knowledge, this is the first reported case of PHA with EEG monitoring during the HVT. The pathophysiology of LOC in PHA is unknown; PHA is often associated with hypoxia caused by apnea (2), and LOC in BHS is speculated to be a result of hypoxia (4). However, in our patient, SpO_2 did not decrease during the HVT. Although the possibility of decreased cerebral tissue pressure of oxygen (pO_2) could not be excluded, as the arterial pO_2 does not reflect the cerebral tissue pO_2 in acute respiratory alkalosis after HVS (11), LOC in PHA might not be due to hypoxia.

In our patient, when LOC and apnea occurred during the HVT, EEG revealed spindle activity, which disappeared in parallel with the recovery of consciousness and spontaneous breathing. The EEG findings in our patient resembled "spindle coma," which is a term used to refer to an EEG pattern of spindle activity, often with vertex sharp waves and K-complexes, observed in patients with coma. Spindle coma was described first in a patient with neoplasms of the hypothalamus and midbrain, sparing the thalamus (12). Subsequently, spindle coma has been observed in various diseases, such as head injury, hypoxia, drug intoxication, and brain infarctions and hemorrhaging (13). The precise pathophysiology of spindle coma is not clear, but in animal models, spindle coma is produced by lesions of the hypothalamus, midbrain tegmentum, or subthalamus (14). Some authors have speculated that because human sleep spindle generators are located in the thalamus (15), disorders leading to spindle coma must alter the function in regions caudal to the thalamus. Therefore, spindle coma may occur due to the involvement of the ascending-activating mesodiencephalic reticular formation, leaving the thalamocortical connections intact (13, 16). The appearance of spindle activity with LOC and the disappearance of the spindle activity with the recovery of consciousness in our patient might therefore suggest that the LOC in PHA occurs due to the transient and focal involvement of the ascending-activating mesodiencephalic reticular formation with intact thalamocortical connections.

Furthermore, the almost simultaneous occurrence of LOC and apnea in our patient might suggest that PHA is correlated with the focal involvement of the brainstem, which includes the ascending-activating mesodiencephalic reticular formation and respiratory centers in the medulla and pons. In addition, hypocapnia causes a decreased cerebral blood flow (CBF) (17), and the CBF reactivity to hypocapnia in the vertebral artery in particular is larger than that in the other cerebral arteries (18). Therefore, a decreased CBF in the brainstem might be correlated with LOC and apnea in PHA, although this is only speculative, as we did not monitor the changes in the CBF during hyperventilation.

Conclusion

We herein report the case of a patient with PHA showing spindle activity on EEG during the HVT. Our clinical and EEG observations suggested that the occurrence of LOC in PHA was due to the focal involvement of the ascending-activating mesodiencephalic reticular formation. Although we have speculated on the pathophysiology of PHA from various viewpoints in this report, why PHA occurs repeatedly in only a few patients while most people never experience PHA even after HVS remains unclear. More detailed

clinical analyses and a greater number of cases are necessary to elucidate the pathophysiology of PHA.

Informed consent was obtained from the patient.

This study was approved by the ethics committee of Kobe City Medical Center General Hospital.

The authors state that they have no Conflict of Interest (COI).

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