A Case of Nemaline Myopathy with Sleep-Related Hypoventilation Diagnosed Using Polysomnography During Daytime Napping

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Abstract

This is a case of a 49-year-old woman who was admitted to the hospital for a close examination of pulmonary hypertension; however, the next morning, she developed carbon dioxide (CO$_2$) narcosis and was started on artificial ventilation. As pulmonary arterial hypertension was ruled out, the patient was extubated, and 24-hour transcutaneous PCO$_2$(TcPCO$_2$) monitoring was performed to diagnose sleep-related hypoventilation. Polysomnography (PSG) during daytime napping revealed markedly decreased chest motion and a “pseudo-central event”, which was neither central nor obstructive hypopnea. Based on the PSG results and physical examination findings, a neuromuscular disorder was suspected, and a muscle biopsy was performed to diagnose nemaline myopathy. Neuromuscular diseases are widely recognized for their association with sleep-disordered breathing, thus sleep-related hypoventilation should also be considered. TcPCO$_2$ monitoring and PSG are useful tools in identifying the cause of hypoventilation; however, overnight PSG may cause CO$_2$ narcosis in some diseases. In such cases, PSG may be beneficial during daytime napping.

Categories: Internal Medicine, Pulmonology
Keywords: transcutaneous pco2, pseudo central event, nemaline myopathy, polysomnography, sleep related hypoventilation

Introduction

In the International Classification of Sleep Disorders, Third Edition, sleep-related breathing disorders are classified into five groups. Among them, there is the sleep-related hypoventilation disorder group, further divided into six conditions (obesity hypoventilation syndrome, congenital central alveolar hypoventilation syndrome, late-onset central hypoventilation with hypothalamic dysfunction, idiopathic central alveolar hypoventilation, sleep-related hypoventilation due to a medication or substance, and sleep-related hypoventilation due to a medical disorder) [1]. The American Academy of Sleep Medicine suggested the following criteria for sleep-related hypoventilation in adults: the arterial PCO$_2$(or surrogate) during sleep increases > 55 mmHg for ≥ 10 minutes or the arterial PCO$_2$(or surrogate) during sleep increases > 10 mmHg compared with awake supine values exceeding 50 mmHg for ≥ 10 minutes [2]. This case was finally diagnosed as nemaline myopathy and falls into the category of “sleep-related hypoventilation due to a medical disorder”. In this report, we focus on the diagnostic process of determining the cause of hypoventilation.

Case Presentation

The patient, a 49-year-old woman, had been aware of mild breathlessness on exertion since she was 20 years old, had leg edema since the age of 38 years, and hypertension since the age of 48 years, both of which were treated with antihypertensive drugs and diuretics. At the age of 47, while dozing in a chair, she fell off the chair and fractured her collarbone. She had no noteworthy family history, and she had never smoked. She worked in an office. She was referred to the Department of Cardiology at our hospital for the evaluation of increased leg edema and hypoxia. At the time of the initial examination, she presented with facial edema and mucocutaneous cyanosis in addition to leg edema, and her peripheral capillary oxygen saturation (SpO$_2$) was 90%. Respiratory sounds were clear and no sputum or cough was noted. Chest radiography displayed cardiac enlargement (Fig.1), and echocardiography displayed preserved contractility with no evidence of valvular disease. However, her tricuspid regurgitation pressure gradient (TRPG) had increased to 55 mmHg. Chest computerized tomography (CT) showed no abnormality in the lung field, and the pulmonary artery enlargement(Fig.2), but no thrombus was found in the pulmonary artery on chest contrast-enhanced CT, therefore, pulmonary arterial hypertension was suspected, and the patient was admitted to the hospital. The patient was treated with an additional diuretic and 1 L/min of oxygen. The next morning, she was found to have altered mental status with a Glasgow Coma Scale (GCS) of 5.
FIGURE 1: Chest radiograph on admission.
The blood gas value was PH 7.04, the arterial PCO2 PaCO2 was 170 mmHg, the arterial PO2 PaO2 was 100 mmHg in O2 3L/min, the alveolar to arterial oxygen pressure difference was -77 mmHg, indicating respiratory acidosis. Treatment was started with NPPV, but her mental status did not improve, therefore artificial ventilation was started.

The cause of hypoventilation was unknown, but the cardiologist in charge of her thought the loss of consciousness was due to pulmonary arterial hypertension. Therefore, she was transferred to a specialized cardiology hospital with a pulmonary circulation department while on a ventilator. At the hospital where she was transferred, her TR-PG had decreased to 15 mmHg, and it was concluded that she did not suffer from pulmonary arterial hypertension. She remained intubated and was readmitted to our hospital the next day, where respiratory physicians were assigned to her.

The patient weighed 56 kg with a body mass index of 21 and a GCS score of E4VTM6 (on ventilatory management). Moreover, edema was observed on her face and in both lower legs. Chest radiography revealed cardiomegaly and scoliosis, with a Cobb angle of 28° (Fig. 1, Fig. 2). No blood gas analysis was...
performed before the onset of CO\textsubscript{2} narcosis, and post-intubation blood gases revealed values within the PH, 7.5 PaCO\textsubscript{2}, 40 mmHg range.

Sleep-related hypoventilation was suspected because she had no abnormality in her lung field and pulmonary blood vessels and developed CO\textsubscript{2} narcosis after sleep, furthermore according to her husband, she has frequently dozed off during the day for the past two years. Her mental condition had improved with artificial ventilation, and if the hypoventilation was sleep-related, some ventilation was expected to be maintained upon awakening; therefore, the patient was extubated. After extubating, non-invasive positive pressure ventilation (NPPV) was initiated for 24 hours, and SpO\textsubscript{2} and TcPCO\textsubscript{2} were monitored. Anticipating severe hypoventilation for several days after extubation, the staff checked on her if the TcPCO\textsubscript{2} was above 70 mmHg, to assess her level of consciousness, even at night. TcPCO\textsubscript{2} monitoring on the 5\textsuperscript{th} day after extubation is displayed in Fig. 2. Under NPPV (S/T mode, inspiratory positive airway pressure (IPAP)/expiratory positive airway pressure (EPAP): 15/5 cmH\textsubscript{2}O, fraction of inspired O\textsubscript{2}:20-30%, respiratory rate (RR): 20 cycles/min), TcPCO\textsubscript{2} remained in the 40-mmHg range upon awakening but increased to 60-70 mmHg upon falling asleep, accompanied by hypoxia.

The patient’s spontaneous breathing was barely detectable during sleep, and forced ventilation was triggered. She had been aware of daytime sleepiness for two years, although she had not complained of it at the time of admission. Suspecting obstructive sleep apnea (OSA), we raised the EPAP during sleep from 4 cmH\textsubscript{2}O to 8 cmH\textsubscript{2}O, which only slightly improved oxygenation and did not increase spontaneous breathing. Therefore, we concluded that obstructive apnea is not the only cause of hypoventilation, although obstructive apnea may be present during sleep.

With the increase in TcPCO\textsubscript{2} during sleep, a diagnosis of sleep-related hypoventilation was established; however, the cause was unknown. Obesity hypoventilation, hypothalamic dysfunction, and drug-induced hypoventilation were excluded as causes of sleep-related hypoventilation. Therefore, the cause was narrowed down to alveolar hypoventilation due to a medical disorder or late-onset congenital central alveolar hypoventilation (CCHS). The patient had scoliosis with a Cobb angle of 28°; however, the thoracic deformity was mild and not considered a cause of severe hypoventilation. Based on these findings, we strongly suspected an late-onset form of CCHS.

The patient was able to wean off NPPV when awake but continued to utilize it at night. We wanted to perform a nighttime polysomnography (PSG) for close examination of sleep disturbance but decided that if the patient had CCHS, an overnight PSG without NPPV would put the patient at risk of developing CO\textsubscript{2} narcosis. Therefore, the attending physician observed the patient at the bedside and performed PSG during daytime napping without NPPV.
During naps, the PSG revealed chest movements that were significantly attenuated compared to abdominal movements, although post-onset snoring was slight. The examination was terminated when SpO\textsubscript{2} dropped to 60% 2 hours after the start of the examination. Her blood gas level before the examination was pH 7.33, PaCO\textsubscript{2} 53 mmHg; however, immediately after the examination, her blood gas level was pH 7.28, PaCO\textsubscript{2} 68 mmHg. Fortunately, the patient was conscious. The results of the 2-hour PSG demonstrated an apnea/hypopnea index of 35/h, all of which were hypopneas (Fig. 3, Fig. 4).

**FIGURE 4:** Polysomnography performed in 2 hours during daytime napping.

REM: rapid eye movement; Cn.A: central apnea; Ob.A: obstructive apnea; Mx.A: Mixed apnea; Hyp: hypopnea

**FIGURE 5:** Electromyograph recording during polysomnography.

The waveform of chest motion is smaller than that of the abdomen in rapid eye movement (REM) sleep. This waveform can be considered a “pseudo-central event”.

Hypopnea was defined as central hypopnea, according to the guidelines [3]. However, it could not be determined whether this indicated the presence of CCHS. However, the patient’s chest movements were...
significantly weakened during PSG, prompting suspicion of neuromuscular disease. Therefore, we considered ruling out neuromuscular disease necessary before proceeding with the diagnosis of CCHS. Upon commencing rehabilitation, we discovered that the patient’s neck was drooping, she had an agitated gait, and her limb muscle strength had decreased. The patient’s developmental history revealed that her neck control developed slowly, and she started walking several months later than the average during infancy. Results of the pulmonary function test displayed a restrictive pattern with a forced vital capacity of 61% and a forced expiratory volume in 1 second to forced vital capacity ratio of 89.8% (table1). Furthermore, six-minute walk distance was 320m, which was quite short even taking age into account.

<table>
<thead>
<tr>
<th>parameters</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>1.78</td>
</tr>
<tr>
<td>FEV1(L)</td>
<td>1.6</td>
</tr>
<tr>
<td>FVC (%predicted)</td>
<td>61.0</td>
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<tr>
<td>FEV1/FVC (%)</td>
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<td>TLC (L)</td>
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<tr>
<td>DLCO (ml/min/mmHg)</td>
<td>14.5</td>
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<td>DLCO/VA (ml/min/mmHg/L)</td>
<td>5.26</td>
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<tr>
<td>6MWD (m)</td>
<td>320</td>
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</table>

Based on these findings, we suspected sleep-related hypoventilation due to neuromuscular diseases, particularly congenital myopathy. Blood gases during daytime awakening without NPPV were PH 7.3-7.4 and PaCO2 50-55 mmHg, with type 2 respiratory failure even when awake, but PH was in the normal range when awake. She was treated with NPPV (S/T mode, IPAP/EPAP 16/8.4 cmH2O, RR 15 cycles/min, no oxygen) only while sleeping. After discharge from the hospital, she was referred to the Department of Neurology at Nara Medical University, where a diagnosis of nemaline myopathy was made based on a biopsy of the biceps brachii muscle. She still continues to receive NPPV treatment only during sleep without recurrence of loss of consciousness, but her general muscle weakness has worsened.

**Discussion**

Nemaline myopathy is the most common form of congenital myopathy, and currently 12 types of genetic abnormalities have been identified [4]. There is still no fundamental treatment for this disease, which has a wide range of severity. There are reports of cases of nemaline myopathy diagnosed in adulthood due to respiratory failure and pulmonary hypertension [5]. This patient also had pulmonary hypertension on admission. It is widely known that hypoxia causes pulmonary arteriole vasospasm, which increases pulmonary arterial pressure. Since the pulmonary hypertension in this case was quickly improved by intubation and ventilation, we considered that persistent hypoxemia due to sleep-disordered breathing caused pulmonary arteriole spasm.

CCHS is a representative disease of sleep-related hypoventilation and a genetic disorder that presents with impaired ventilatory response. PHOX2B mutations are found in most of the patients with CCHS [6]. We have late-onset CCHS patients, and we consider it as a disease that should be kept in mind when hypoventilation of unknown cause occurs.

On the other hand, patients with neuromuscular diseases have a different mechanism of sleep-related hypoventilation from that of CCHS. In general, diaphragm movements are more involved in ventilation during REM than intercostal muscles and other auxiliary respiratory muscle activities [7]. Normal patients can maintain ventilation volume only by diaphragm movements even if other respiratory muscle activities are decreased, but patients with neuromuscular diseases with diaphragm weakness cannot compensate ventilation volume only by diaphragm movements [8]. In relation to this, a peculiar type of hypopnea called "pseudo-central event" has been reported during the REM period in patients with neuromuscular diseases [9]. This type of hypopnea is neither obstructive nor central, and is said to be caused by a decrease in chest movement during sleep compared to that in the abdomen due to a decrease in diaphragm muscle strength. The hypopnea in this case showed the same characteristics, and it is possible that a "pseudo-central event"
was observed (Fig. 4).

Finally, we would like to discuss why the patient developed CO₂ narcosis after hospitalization. There were two possible causes of her daytime hypercapnia: one was due to restrictive lung function, and the other was due to hypercapnia from sleep-related hypoventilation that carried over into the daytime. She has always been hypercapnia, and her ventilatory response to CO₂ would be expected to have been reduced. Therefore, we believe that the administration of oxygen after hospitalization induced CO₂ narcosis. Other cases of CO₂ narcosis induced by administering oxygen to patients with neuromuscular diseases have been reported [10]. We must first check for ventilation when treating a hypoxic patient, even if we do not suspect respiratory disease.

Conclusions
In the practice of sleep-related hypoventilation, it is essential to exclude hypoventilation due to obstructive or restrictive ventilation disorders of the lungs, such as COPD, interstitial pneumonia, and thoracic restrictive disease. In this case, we ruled out respiratory disease based on breath sounds, chest imaging, and respiratory function tests.

Since respiratory disease could be ruled out, the cause of sleep-related hypoventilation was assumed to be late onset congenital central hypoventilation syndrome or neuromuscular disease or other medical conditions. We suspected neuromuscular disease due to the “pseudo-central event” on PSG during daytime napping and restrictive patterns in the pulmonary function test.

Sleep-related breathing disorders are well-known to coexist with neuromuscular disorders, whereas sleep-related hypoventilation may be less well-recognized. TcPCO₂ and PSG are extremely useful in searching for the cause of hypoventilation; however, some patients having PSG overnight are at risk of developing CO₂ narcosis. In such cases, PSG in a safe environment, even for a short time during daytime napping, may be useful for diagnosis.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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