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Long-Term Stabilization of Respiratory Conditions in Patients with Spinal Muscular Atrophy Type 2 by Continuous Positive Airway Pressure: a Report of Two Cases

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ABSTRACT

Spinal muscular atrophy (SMA) type 2 is a motor neuron disease that leads to severe congenital muscle atrophy. The majority of adult patients are at risk of death due to respiratory failure. Here, we report on two patients with SMA type 2 who repeatedly developed bronchitis and pneumonia. The patient in Case 1 was a 48-year-old female lacking exon 7 of the survival motor neuron gene (SMN) 1. The patient in Case 2 was a 37-year-old female lacking exons 7 and 8 in SMN 1 and exon 5 in the neuronal apoptosis inhibitory protein (NAIP) gene.

We applied continuous positive airway pressure (CPAP) in both cases because their data on polysomnography showed obstructive sleep apnea (OSA). CPAP treated their respiratory symptoms as well as those due to OSA. Moreover, CPAP stabilized the respiratory condition of Case 1 for seven years and seven months and that of Case 2 for five years and four months. These findings suggest that CPAP alone can achieve long-term improvement in the respiratory condition in patients with SMA type2.

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CPAP stabilizes respiratory condition in SMA type 2

INTRODUCTION

Spinal muscular atrophy (SMA) is a congenital motor neuron disease that shows an autosomal recessive hereditary pattern (1, 2). It was previously reported that the genes responsible for SMA were the survival motor neuron gene (SMN) 1(1) and the neuronal apoptosis inhibitory protein (NAIP) gene (2). Patients with SMA usually develop severe deformity of the thorax with severe scoliosis due to muscle atrophy from infancy (3). Therefore, these patients develop severely restrictive ventilatory defect complicated by repetitive episodes of bronchitis and pneumonia (4-6).

However, noninvasive mechanical ventilation (NIV) was reported to control the respiratory problems of patients with neuro-muscular disorder containing SMA (7). NIV has two modes: continuous positive airway pressure (CPAP) and biphasic positive airway pressure (BiPAP) (8). CPAP sends the patient airway a constant level of positive pressure during breathing. CPAP is mainly used to treat the obstructive sleep apnea (OSA). OSA is reported to be associated with hypertension, cardio-vascular disorder, stroke and chronic bronchitis (9-11). BiPAP provides the patient airway at a higher level of pressure during inspiration, and a lower pressure during expiration. BiPAP is applied to OSA that cannot be adequately managed by CPAP and is utilized for sleep-associated disorders involving central sleep apnea, heart failure, COPD and respiratory failure due to neuromuscular disorders (8,9). Generally, BiPAP is applied to assist respiratory function in patients with of neuromuscular diseases such as SMA (7, 8, 12). However, whether CPAP is effective for respiratory disorders in patients with SMA has remained unknown until now.

We applied CPAP to our patients with SMA to treat OSA and found an unexpected overall effect on their respiratory disorder. Here, we examine the usefulness of CPAP for respiratory problems in patients with SMA type2.

CASE 1

The patient was a 48-year-old right-handed woman who was diagnosed with SMA type 2 at two years of age. She lacked SMN 1 gene exon 7, and demonstrated the neuronal apoptosis inhibitory protein (NAIP) gene (Figure 1a) and three copies of SMN 2 exon 7. In addition, she was reported to have a hybrid SMN involving the fusion of SMN 2 intron 7 and SMN 1 exon 8 (13). She could not hold her back upright in a chair without support, and could not raise her limbs upwards or raise her head to an upright position. Her spinal column showed severe scoliosis and kyphosis due to muscle atrophy since infancy (Figure 2a). Examination demonstrated an alert and well- oriented woman with normal speech and eye movements. Her tongue showed slight fasciculation and moderate atrophy (Figure 3). She could not open her mouth completely. The muscles of all extremities showed severe atrophy. Motor strength was 1/5 in all extremities; deep-tendon reflexes were 0/4 distally and 0/4 proximally. There was no Babinski's sign. Sensory perceptions were normal. Her mother had recognized the physical weakness of the patient at three to four months of age; she was unable to raise her lower limbs or brace her feet. She could not roll over even at six months of age. She showed poor muscular development and was diagnosed with SMA at two years of age. She could sit by herself until seven years of age, but she could never stand by herself. Her older brother also had SMA type 2. He died of respiratory failure after developing severe pneumonia and chest emphysema at 32 years of age.

The patient had shown a gradual increase in the frequency of coughing fits along with episodes of bronchitis and pneumonia since 30 years of age. She also had to struggle with severe respiratory problems every morning, which was the worst time of the day. After awakening, she could not cough up the phlegm by herself abundantly accumulated sour

phlegm by herself, and needed the assistance of someone to repeatedly push against her abdomen to enable her to expel the phlegm. The phlegm was abundantly, and then the taste was sour.

In addition, when she tried to ingest tablets, beans, hijiki seaweed or rice crackers, she often felt as if these were caught in her throat.

Following an episode of severe pneumonia, the patient was referred to our hospital in May 2001 at 38 years of age. In June 2001, she started to inhale a bronchodilator (β-agonist: salbutamol sulfate) for continuous wheezing. She developed bronchitis with high fever five times during 2001, six times during 2002 and three times between January and September in 2003. In December 2002, she was hospitalized with severe pneumonia. In April 2003, gastroesophageal reflux disease (GERD) was suspected as the cause of her cough, but she refused to be examined by esophagogastroduodenoscopy at that time. Ranitidine hydrochloride and dried aluminum hydroxide gel・magnesium hydroxide were prescribed, but respiratory symptoms were not improved.

In October 2003, we analyzed the cycle of her respiratory symptoms in detail and found that the condition was worst in the morning, and then gradually recovered during the day. In addition, medical examination by interview disclosed that she was frequently awakened by coughing during the night, snored while sleeping and showed fatigue and sleepiness during the day. Polysomnography demonstrated obstructive sleep apnea (OSA). The apnea and hypopnea index (AHI) was 11.9 (supine: 7.9, non-supine: 14.0). The minimal arterial oxygen saturation (SaO_2) was 69%. In September 2003, arterial blood gas analysis performed during the daytime showed normal values. Pulmonary function tests demonstrated severe restrictive and mild obstructive ventilatory impairment (forced vital capacity (FVC): 0.93 L; forced expiratory volume in 1 second ($FEV_{1.0}$): 0.84 L; 50%FVC/25%FVC: 3.6). CPAP was initiated because of an extremely low minimal SaO_2 during sleep. The positive pressure was set to 5.0 cmH_2O. The morning after the initiation of CPAP, she immediately showed recovery from severe respiratory symptoms including coughing, wheezing, and sputum production. Between October 2003 and December 2004, she developed upper respiratory infection twice due to a cold. Between January 2005 and October 2010, she developed upper respiratory infection only once per year. CPAP has stabilized her respiratory condition for seven years seven months to date. In addition, she became able to naturally swallow tablets, beans, hijiki seaweed and rice crackers, and her swallowing ability normalized. The patient reported that sputum often stayed in her throat before she used CPAP, and the sputum affected her ability to swallow foods, but she has not felt sputum in her throat since the initiation of CPAP, and has become able to swallow foods naturally.

In July 2008, she underwent esophagogastroduodenoscopy because she showed severe anemia (red cell count $353x10^4/\mu$ l, Hb 7.7 g/dl Ht 25.7%) and appetite loss. The procedure demonstrated stenosis at the lower esophagus similar to esophageal achalasia (Figure 4). The cause of her anemia was hemorrhoids.

CASE 2

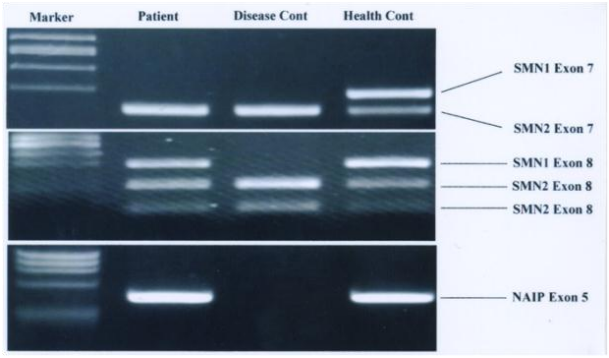
The patient was a 37-year-old right-handed woman who was diagnosed with SMA type 2 at one year of age. She lacked SMN 1 gene exons 7 and 8 and the NAIP gene exon 5 (Figure 1b), but she had three copies of SMN 2 exon 7.

She could not hold her back upright in a chair without support, and could not raise her limbs upwards or hold her head in an upright position. Her spinal column showed severe scoliosis and kyphosis (Figure 2b). Examination demonstrated an alert, and well-oriented

woman with normal speech and eye movements. Her tongue showed fasciculation and moderate atrophy on the left side. She could not open her mouth completely. The muscles of all extremities showed severe atrophy. Motor strength was 0/5 in all extremities, although motor strength was 1/5 in fingers; deep-tendon reflexes were 0/4 distally and 0/4 proximally. There was no Babinski's sign. Sensory perceptions were normal. Muscle strength in her limbs was weak from birth. She could raise her head, and roll over at six months of age, but she could not roll over at 10 months of age. She was diagnosed with SMA at one year of age. After the diagnosis, atrophy and decrease in muscle strength gradually progressed. She underwent tracheal incision during an episode of pneumonia at 15 years of age. The situation recovered thereafter the tracheal cannula was removed. She developed pneumonia twice at 25 years of age, and was admitted to the hospital due to pneumothorax twice at 29 years of age.

She reported that she felt choked by food and that her breath stopped at night, and she developed bronchitis more than three times per year before CPAP was initiated. She consulted a doctor specializing in sleep disorder. Portable polysomnography demonstrated AHI at 26.4, and then minimal SaO_2 was 74%. Therefore, she received a diagnosis of OSA. However, based on her overall condition, it was speculated that she would have had considerable difficulty in recovering from sleep apnea. It was also thought that apnea might become fatal. Therefore, in January 2006, CPAP was initiated. The patient has not felt choked by food, and has been able to sleep soundly since the initiation of CPAP. In addition, she has had only one episode of bronchitis after the start of CPAP up to October 2010. CPAP has stabilized her respiratory condition for five years and four months to date.

a



b

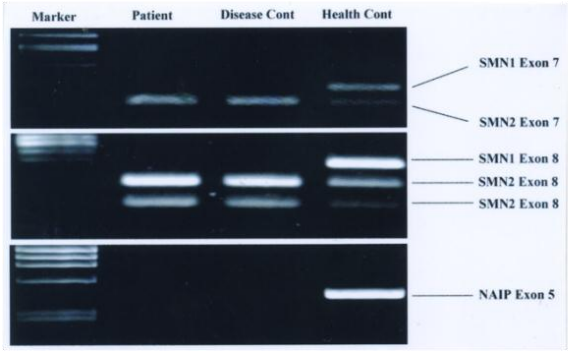


Figure 1. Detection of SMN1, SMN2 and NAIP gene deletion by polymerase chain reaction (PCR). (a) Data from Case 1. (b) The data from Case 2. The marker is ϕ X174 Hae III digest.

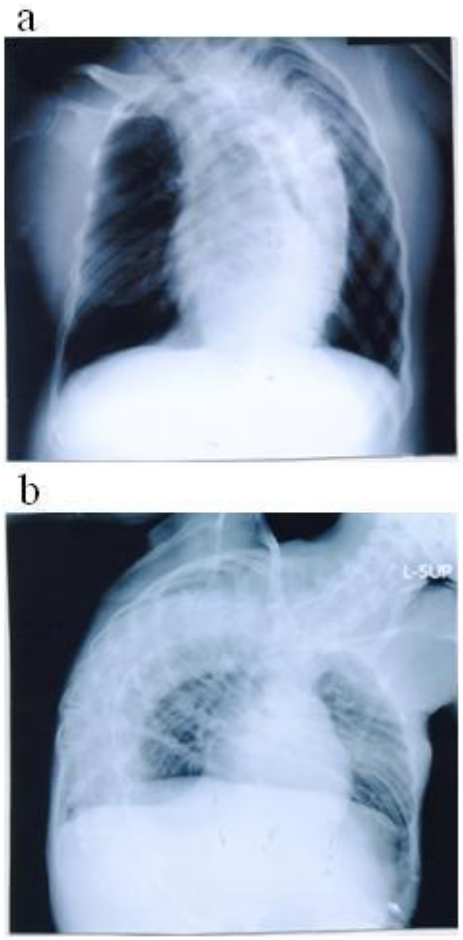


Figure 2. Deformed thorax on chest X-ray. (a) Chest X-ray of Case 1. (b) Chest X-ray of Case 2.

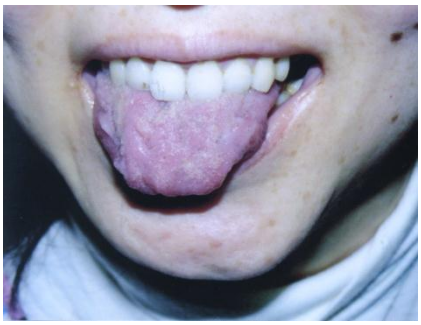


Figure 3. The tongue of Case 1.

Figure 4. Stenosis at the lower esophagus of Case 1 on esophagogastroduodenoscopy.

DISCUSSION

When we diagnose patients as having SMA, we must consider their symptoms, course and genetic abnormality. Our patients started to show muscle atrophy of the extremities before one year of age, and then they could not stand and walk without support. Symptoms and course were characteristic for SMA type 2 (4-6). In addition, Case 1 was lacked the SMN 1 exon 7, and Case 2 was lacked the SMN 1 exons 7 and 8 as well as the NAIP gene exon 5. Therefore, we diagnosed our patients as having SMA type2.

Coincidently, each features three copies of SMN 2 exon 7. However, it remains unknown whether the number of the copies of SMN2 exon 7 affects the course of SMA (14). Furthermore, Case 1 had a hybrid SMN (13). However, the impact of that finding also remains unknown.

Patients with SMA demonstrate OSA as a complication. It was previously reported that when patients with SMA demonstrate OSA, their OSA-related symptoms could be treatable by CPAP (15-17).

Our patients had chronic bronchitis and repeated pneumonia. However, their respiratory state had not yet progressed to respiratory failure. Therefore, we applied CPAP for the treatment of OSA. As a result, CPAP not only improved the sleep apnea, but also suppressed the occurrence of chronic bronchitis and pneumonia. Moreover, CPAP achieved long-term stabilization of their respiratory condition.

Here, we discuss the effect of CPAP on chronic bronchitis and pneumonia of the patients with SMA type 2. First, Case 1 demonstrated chronic bronchitis and repeated pneumonia. In addition, she had expectorated sour sputum every morning before CPAP was initiated. It is highly possible that sour sputum was mainly composed of gastric juice. Therefore, we can speculate that gastric juices had further damaged the lung due to gastroesophageal reflux. In addition, she had severe scoliosis and kyphosis as complications. It was reported that the deformed spine causes deterioration of reflux esophagitis (18, 19). However CPAP can inhibit OSA, and therefore, lessen the reflux esophagitis (20, 21).

Thus, we speculate that CPAP was able to prevent the reflux of gastric juice to bronchi, and then stabilized the respiratory condition of Case 1. In addition, the patient had a swallowing disorder before CPAP, but the symptom disappeared after CPAP was initiated. She had complained that she constantly felt residual sputum and that the sputum mixed with the bolus of food, preventing her from fully swallowing the food before CPAP. Hence, it is highly possible that the swallowing disorder of the patient was related to chronic bronchitis. That is, CPAP may have improved the swallowing disorder because CPAP successfully suppressed the chronic bronchitis.

In Case 2 as well as in Case 1, the repeated occurrence of pneumonia ceased and both the chronic bronchitis and the swallowing disorder were improved after the initiation of CPAP. The patient had a deformed spine and sleep apnea, although she did not have symptoms of reflux esophagitis. Therefore, Case 2 had milder symptoms of chronic bronchitis than Case 1.

However, the deformed spine and sleep apnea may increase the severity and frequency of gastric reflux to the bronchi in Case 2 because these diseases can aggravate reflux esophagitis (18-21). That is, we speculate that the aggravated reflux might contribute to chronic bronchitis and pneumonia as one of the silent symptoms in Case 2. In addition, it is possible that the improvement of swallowing disorder in Case 2 was associated with the same mechanism as in Case 1.

One of the serious respiratory disorders caused by neuromuscular disorders was reported to be atelectasis (22, 23, 24). CPAP is also effective in preventing the atelectasis (25, 26). The effect may be also associated with the stabilization of the respiratory condition in our patients after CPAP.

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