Daytime Hypoxemia, Sleep-Disordered Breathing, and Laryngopharyngeal Findings in Multiple System Atrophy

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Background: The mechanism underlying nocturnal sudden death in patients with MSA remains unclear. It may be explained by upper airway obstruction, such as vocal cord abductor paralysis; an impairment of the respiratory center, such as Cheyne-Stokes respiration; or an impaired hypoxic ventilatory response.

Objective: To investigate the mechanism of sleep-disordered breathing in multiple system atrophy (MSA).

Design: We recruited 21 patients with probable MSA who were admitted sequentially to our hospital, and performed daytime blood gas analysis, pulmonary function tests, polysomnography, and fiberoptic laryngoscopy during wakefulness and with the patient under anesthesia.

Results: A decrease in arterial oxygen pressure and an increase in alveolar-arterial oxygen gradient significantly correlated with disease duration (P = .045 and .046, respectively). Polysomnography demonstrated Cheyne-Stokes respiration in 3 (15%) of 20 patients. Fiberoptic laryngoscopy during wakefulness showed that 3 (14%) of the 21 patients exhibited vocal cord abductor paralysis, and laryngoscopy under anesthesia showed that 9 (45%) of 20 patients exhibited vocal cord abductor paralysis. Laryngoscopy under anesthesia also revealed that 11 (55%) of 20 patients showed upper airway obstruction in places other than the vocal cords, including obstruction at the base of the tongue or soft palate. In addition, it demonstrated novel laryngopharyngeal findings, such as floppy epiglottis and airway obstruction at the arytenoid.

Conclusions: We observed daytime hypoxemia with an increased alveolar-arterial oxygen gradient, Cheyne-Stokes respiration, and novel abnormal laryngopharyngeal movements in patients with MSA. We also found that laryngoscopy under anesthesia might be useful for evaluating upper airway obstruction. The significance of these findings to the mechanism of sudden death in those with MSA needs to be examined.

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Most patients with multiple system atrophy (MSA) die within 6 to 9 years after symptoms begin to appear. Although the cause of death in MSA is commonly related to the development of bulbar palsy, predisposing a patient to aspiration pneumonia, sudden death during sleep is also common. The mechanism underlying nocturnal sudden death remains unclear; however, it may be explained by upper airway obstruction, such as vocal cord abductor paralysis (VCAP), or by abnormal respiration, resulting from an impairment of the respiratory center, such as Cheyne-Stokes respiration (CSR). An impaired hypoxic ventilatory response may also be involved, because it can aggravate hypoxemia during sleep. Despite our better understanding of sleep-disordered breathing in MSA, several unanswered questions remain. Do patients with MSA have abnormal laryngopharyngeal movements other than VCAP that contribute to upper airway obstruction? What is the prevalence of CSR? Do patients with MSA have daytime respiratory impairments that aggravate nocturnal hypoxemia? To elucidate these questions, we recruited patients with probable MSA and performed daytime blood gas analysis, pulmonary function tests, polysomnography, and laryngoscopy.

METHODS

We recruited patients admitted sequentially to the Department of Neurology, Niigata University, who were diagnosed as having MSA between May 1, 2001, and April 30, 2004. All the patients fulfilled the diagnostic criteria of probable MSA according to the consensus statement. A hyperintense putaminal rim and a “hot cross bun” sign on magnetic resonance imaging were used to support the diagnosis. Patients...
we were excluded from the study if they showed evidence of being positive for spinocerebellar ataxia types 1, 2, 3, and 6; dentatorubral pallidolysian atrophy; or fragile X tremor/ataxia syndrome by a molecular genetic test.18 The selection of hospitalized patients with MSA in this study is likely to be biased toward patients with a more severe condition. A patient with a history of recent respiratory infections (patient 21) was excluded from blood gas analysis, pulmonary function tests, and polysomnography. The severity of ataxia was evaluated using the International Cooperative Ataxia Rating Scale.9

Arterial oxygen pressure (PaO2) and arterial carbon dioxide pressure (PaCO2) were analyzed using an automatic acid-base analyzer. Severe hypoventilation was defined as PaCO2 greater than 50 mm Hg. The alveolar-arterial oxygen gradient ([A-a]DO2) was calculated as follows: [A-a]DO2 = (150 − PaCO2)/HbO2. Conventional spirometry was performed, and vital capacity and forced expiratory volume in 1 second were determined. These values were expressed as percentages of predicted values.

Polysomnographic findings were classified according to the recommendations of the American Academy of Sleep Medicine Task Force in 1999. Sleep apnea syndrome was defined as an apnea-hypopnea index (AHI) of greater than 10 per hour. Severe nocturnal oxygen desaturation was defined as having greater than 10% of sleep time with an oxygen saturation level of less than 90%. The CSR was defined as a crescendo-decrescendo pattern of hyperpnea, alternating with central apnea and hyperpnea, and was determined to be present when the central AHI was 10 or more per hour.10

Fiberoptic laryngoscopy was performed under video monitoring during wakefulness in all the patients. It was also performed with the patient under anesthesia induced by an intravenous injection of 5 to 10 mg of diazepam (patients 1-3) or 100 to 200 mg of propofol (patients 4-21). We could not perform laryngoscopy under anesthesia for 1 patient (patient 1), because he did not fall asleep after receiving 10 mg of diazepam. Vocal cord abductor paralysis was defined as the restriction of vocal cord movement in abduction. The severity of VCAP was expressed as partial or complete, corresponding to fixation at the midline in abduction.

The relationships between disease duration and variables related to sleep-disordered breathing were analyzed by the Spearman rank correlation test. The effects of continuous positive airway pressure on polysomnographic findings were analyzed by the paired t test when the variables were normally distributed. The Wilcoxon signed rank test was used when the normality test failed to show a normal distribution of the data. Statistical significance was defined as P<.05.

PATIENT CHARACTERISTICS

We recruited 21 consecutive patients (9 men and 12 women) with probable MSA. The mean±SD age of the patients was 59.8±8.3 years (range, 44-72 years); the mean±SD age at onset of MSA was 56.3±9.2 years (range, 41-72 years); and the mean±SD duration of disease was 3.8±1.8 years (range, 1-7 years). The mean±SD International Cooperative AtaxiaRating Scale score was 45.7±13.2 (range, 26-73). Of these 21 patients, 18 (86%) had MSA of the cerebellar subtype (MSA-C) and the remaining 3 (14%) had MSA of the parkinsonian subtype (MSA-P). Twelve patients were able to walk without help, 2 were able to walk with the help of a walker, and 7 could not walk. All the patients showed autonomic failure or urinary dysfunction; 14 of the 21 patients had orthostatic hypotension (defined as a fall in blood pressure of ≥30 mm Hg systolic or ≥15 mm Hg diastolic) and 16 had urinary incontinence. No patients were receiving hypnotic or antidepressant agents, but the 3 patients with MSA-P were receiving dopaminergic agents during the study. Six patients (29%) experienced daytime sleepiness. All patients produced inspiratory noises during sleep: snoring in 21 (100%) and laryngeal stridor in 5 (24%) (Table 1). Their mean±SD body mass index (calculated as weight in kilograms divided by height in meters squared) was 22.9±4.2 (range, 17.9-34.7), and obesity (body mass index, >25) was observed in 2 patients (patients 3 and 13).

DAYTIME PULMONARY FUNCTION

Blood gas analysis revealed PaO2 and PaCO2 mean±SD values of 70.8±6.5 and 43.8±3.4 mm Hg, respectively. Daytime hypoxemia (PaO2 <80 mm Hg) was observed in 14 (70%) of 20 patients. Severe hypoventilation was observed in 1 patient (5%) (Table 1). The mean±SD [A-a]DO2 increased (24.9±7.0 mm Hg; normal, ≤10 mm Hg), and 11 (55%) of 20 patients showed an [A-a]DO2 of greater than 20 mm Hg. Eighteen (90%) and 20 (100%) of 20 patients had a normal percentage vital capacity and a normal percentage forced expiratory volume in 1 second, respectively. Chest x-ray film findings were normal in the patients with daytime hypoxemia.

POLYSOMNOGRAPHIC FINDINGS

The apnea index and AHI were a mean±SD of 4.1±4.5 and 20.1±19.9 per hour, respectively. Of 20 patients, 13 (65%) fulfilled the criteria of sleep apnea syndrome; 3 (15%) had CSR (Table 1). Five patients, including 3 with CSR, presented with central sleep apnea, although the percentage of obstructive sleep apnea was higher than that of central sleep apnea in these patients. Future studies are necessary to investigate the involvement of central neurogenic respiratory disturbances. The sleep architectures were characterized by a decreased percentage of slow-wave sleep (mean±SD with stage 3 plus 4, 13.3±13.8%; normal value, 20%-35%) and a decreased percentage of rapid eye movement sleep (mean±SD with rapid eye movement, 8.2±7.6%; normal value, 20%-25%). Sleep efficiency also decreased (mean±SD, 47.7±19.5%; normal value, >85%). The mean±SD oxygen saturation was 94.3±17.2%, with the lowest value at 88.0%. Of 20 patients, 4 (20%) fulfilled the criteria of severe nocturnal oxygen desaturation.

We investigated the relationships between disease duration and variables related to the clinical features, daytime blood gas analysis findings, and polysomnographic findings (Table 2). The International Cooperative Ataxia Rating Scale score significantly correlated with disease duration. A significant inverse correlation was observed between PaO2 and disease duration, and a significant correlation was observed between [A-a]DO2 and disease duration. Polysomnographic variables, includ-
ing apnea index, AHI, and mean oxygen saturation, showed no correlation with disease duration. Furthermore, there was no significant correlation between increased [A-a]DO2 and abnormalities in apnea index (r = -0.02, P = .92) or AHI (r = 0.27, P = .27).

**FIBEROPTIC LARYNGOSCOPY**

Fiberoptic laryngoscopy during wakefulness was performed on all 21 patients (Table 3). We found VCAP in 3 patients (14%). Although upper airway obstruction at levels other than the vocal cords was not observed, bilateral rhythmical tremulous movements of the arytenoid were observed in 6 patients (29%).

Laryngoscopy while patients were under anesthesia showed that 9 (45%) of 20 patients exhibited VCAP. Interestingly, all the patients presenting with the rhythmical tremulous movements of the arytenoid during wakefulness exhibited VCAP under anesthesia.

Laryngoscopy under anesthesia also revealed that 11 (55%) of 20 patients showed upper airway obstruction at levels other than the vocal cords. The obstruction was observed at the base of the tongue (in 4 patients) and at the soft palate (in 4 patients). Five patients showed floppy epiglottis, a condition in which the epiglottis is sucked into the glottis during inspiration.11 Three patients showed airway obstruction at the arytenoid, characterized by prolonged, sustained muscle contractions during inspiration, resulting in glottic stenosis (Figure, E and F). Although we have performed laryngoscopy on patients with sleep apnea syndrome or laryngopharyngeal disorders using intravenous diazepam and propofol (in >80 and 70 patients, respectively), we have never encountered patients presenting with VCAP, floppy epiglottis, or airway obstruction at the arytenoid, suggesting that these drugs do not cause such conditions. Although we do not have experience in fiberoptic laryngoscopy in patients under anesthesia.
with other neuromuscular disorders, we have sufficient experience in fiberoptic laryngoscopic examination on otorhinolaryngological patients under anesthesia (150 patients). We found that the abnormal movements of the arytenoid and epiglottis described in this study have been observed only in patients with MSA.

Concerning the relationship between the increase in \([A-a]DO_2\) and abnormal findings on fiberoptic laryngoscopy, there was no significant correlation between the increase in \([A-a]DO_2\) and laryngoscopic abnormalities, such as VCAP \((P=.99)\). In addition, there was no significant difference in apnea index or AHI between patients with and those without VCAP under anesthesia \((P=.71\) and .33, respectively).

### Table 3. Summary of Laryngoscopic Findings of Patients With MSA

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Wakefulness</th>
<th>Under Anesthesia</th>
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<tbody>
<tr>
<td></td>
<td>VCAP</td>
<td>Stenosis of the Base of the Tongue</td>
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<tr>
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<td>+ (UP)</td>
<td>+ (BP)</td>
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<tr>
<td>4</td>
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<td>−</td>
</tr>
<tr>
<td>5</td>
<td>+ (BP)</td>
<td>−</td>
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<td>6</td>
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<td>7</td>
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<td>21</td>
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Abbreviations: BC, bilateral complete abduction restriction of vocal cords; BP, bilateral partial abduction restriction of vocal cords; MSA, multiple system atrophy; NE, not examined; UP, unilateral partial abduction restriction of vocal cords; VCAP, vocal cord abductor paralysis; +, present; −, absent.

### DAYTIME HYPOXEMIA IN MSA

To our knowledge, this is the first study evaluating daytime pulmonary function in MSA. We observed daytime hypoxemia with an increased \([A-a]DO_2\) in the advanced stage of MSA, which suggests that daytime hypoxemia can exacerbate nocturnal hypoxemia caused by upper airway obstruction.

The mechanism underlying hypoxemia with an increased \([A-a]DO_2\) remains to be elucidated. The \([A-a]DO_2\) reflects the efficiency of oxygen exchange between pulmonary alveoli and pulmonary capillaries and reflects increases in the presence of a ventilation/perfusion mismatch, a shunt, or a diffusion impairment. Shunts or diffusion impairments are unlikely to be considered the cause of an \([A-a]DO_2\) increase because these conditions are associated with organic changes in the alveolovascular system. Although it is conceivable that a ventilation/perfusion mismatch, such as a pulmonary microembolism, is the cause, additional studies should be performed to elucidate the mechanism.

### RESPIRATORY DYSFUNCTION DURING SLEEP IN MSA

We found that patients with MSA had decreased sleep efficiency and abnormal sleep architectures, including decreased percentages of slow-wave sleep and rapid eye movement sleep, as demonstrated in a recent study. Cheyne-Stokes respiration was observed in some pa-
patients (3 [15%] of 20 patients). This was not the focus of much attention in previous studies, although there is 1 report in which a patient presenting with CSR is described. Further studies should be performed to determine whether CSR is associated with nocturnal sudden death in MSA, which occurred in 1 of our patients with CSR despite the fact that he underwent tracheotomy.

ABNORMAL LARYNGOPHARYNGEAL FINDINGS IN MSA

We showed that laryngoscopy under anesthesia might be useful for evaluating upper airway obstruction. We have never encountered patients with sleep apnea syndrome or other laryngopharyngeal disorders who presented with VCAP, floppy epiglottis, or airway obstruction at the arytenoid, suggesting that these conditions are not caused simply by the muscle relaxation effects of diazepam and propofol. Instead, it is possible that these drugs may intensify potentially abnormal conditions in the laryngopharynx in patients with MSA. The data obtained by fiberoptic laryngoscopy under anesthesia may need careful interpretation. Although we do not have sufficient experience in treating patients with other neuromuscular disorders, we have never observed these abnormal findings in any patients other than those with MSA.

Using this method, we observed laryngopharyngeal movements that, to our knowledge, have not previously been reported in patients with MSA. Floppy epiglottis was observed in 5 (25%) of 20 patients. Although congenital floppy epiglottis, which is caused by an abnormality in laryngeal cartilage, is a common cause of laryngeal stridor in infants, adult-onset floppy epiglottis is a rare condition. It has been observed in patients following a head injury or stroke syndrome, and the resulting central nervous system damage has been thought to be the cause of the loss of laryngeal motor tone with coordination impairments. In MSA, an abnormality in laryngeal motor tone caused by the degeneration of the nucleus ambiguous may influence the development of floppy epiglottis, although the relationship between the abnormality in laryngeal motor tone and the degeneration of the nucleus ambiguous still remains controversial. A recent study demonstrated that continuous positive airway pressure does not improve the airway patency of congenital floppy epiglottis; on the contrary, continuous positive airway pressure may exacerbate upper airway obstruction by further promoting the downward displacement of the epiglottis into the laryngeal inlet. It may be safer to avoid continuous positive airway pressure and to recommend partial epiglottidectomy in patients with floppy epiglottis.

Airway obstruction at the arytenoid during inspiration was also observed in 3 (15%) of 20 patients. Regarding the mechanism of the obstruction, 1 possibility is arytenoidal muscle dystonia because the movement was characterized by prolonged sustained contractions of arytenoid muscles during inspiration, resulting in glottic stenosis; also in patient 21, expiration is shown. Arrows indicate the arytenoid; arrowheads, the vocal cords.

In conclusion, we observed daytime hypoxemia, with an increased [A-a]Do₂ and CSR during sleep, and novel abnormal laryngopharyngeal movements, including floppy epiglottis and airway obstruction at the arytenoid, in patients with MSA. Further study is required to confirm whether these findings are involved in the mechanism of nocturnal sudden death in patients with MSA.

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Announcement

Online Submission and Peer Review System Available. The Archives of Neurology editorial office has introduced an online manuscript submission and peer review system developed by ejournalPress that will serve the needs of authors, reviewers, and editors. The new system went live on November 14, 2005. See http://archneur.ama-assn.org for more detailed information.