Dear Sir,

Most patients with multiple system atrophy (MSA) die within 6–9 years after the onset of symptoms [1, 2]. Although the cause of death in MSA is commonly related to the development of bulbar palsy that predisposes a patient to aspiration pneumonia, it has also been demonstrated that sudden death during sleep is common [3]. A recent study revealed a significantly shorter survival for MSA patients with nocturnal stridor, which is commonly explained as the result of vocal cord abductor paralysis (VCAP), compared with those without stridor [4]. This finding suggests that upper airway obstruction caused by VCAP is associated with nocturnal sudden death; however, the mechanism by which VCAP causes nocturnal sudden death remains unknown, because the features of sleep-disordered breathing in patients with advanced-stage MSA have not been analyzed in detail to date. Here, we describe a patient with MSA presenting with progressive nocturnal hypoxemia, which may help us understand the mechanism underlying nocturnal sudden death in MSA.

Case Report
A 61-year-old woman, with no past history of cardiopulmonary diseases, developed a gait disturbance at age 57 and urinary incontinence and orthostatic hypotension at age 58, all of which steadily worsened. At age 59, she presented with nocturnal stridor and daytime sleepiness. At age 60, she was admitted to our hospital for the evaluation of the cause of her nocturnal stridor. Her height and weight were 146.5 cm and 54.5 kg, respectively (body mass index 25.4). A chest X-ray revealed normal findings, but arterial blood gas examination in room air showed a mild hypoxemia (PaO₂ 73.7 mm Hg) and hypercapnea (PaCO₂ 55.1 mm Hg). Pulmonary function tests were normal. Neurological examination revealed cerebellar ataxia, urinary incontinence, and parkinsonism that responded poorly to levodopa. We diagnosed her as having probable MSA-parkinsonism on the basis of the consensus statement criteria [5]. She presented with inspiratory laryngeal stridor during sleep. Fiberoptic laryngoscopy disclosed bilateral VCAP. A polysomnographic sleep study (Somnostar, SensorMedics) showed that baseline oxygen saturation was 93%, and the respiration rate was 20/min before sleep (fig. 1a). Two hours after sleep onset (23.30 h; fig. 1b), hypopnea and gradual oxygen desaturation with an increased respiration rate (30–35/min) were observed. Subsequently, oxygen desaturation and tachypnea (50–60/min) worsened further (2.00 h; fig. 1c), and respiration became extremely shallow (tidal volume was estimated to be 50–100 ml), although thoracic motion did not subside. At a later stage of sleep (4.30 h; fig. 1d), mixed-type sleep apnea and Cheyne-Stokes respiration-like periodic respiration were observed, and the oxygen level finally decreased to 65%. Slow-wave sleep (stages 3 and 4) and rapid eye movement sleep were reduced (4.1 and 4.1%, respectively).

The administration of continuous positive airway pressure (CPAP) resulted in a marked improvement in nocturnal oxygen desaturation (fig. 1e) and daytime alertness. She was discharged from the hospital with the recommendation of CPAP administration during sleep. Although she and her relatives did not report a recurrence of nocturnal stridor, she was found in the state of anoxic brain injury early one morning 1 month after the discharge. The
nasal mask for CPAP administration was dislodged on this occasion. She died 2 months after the incident.

Discussion
We report the case of an MSA patient with VCAP who succumbed to nocturnal sudden death 1 month after polysomnography. Polysomnography demonstrated progressive tachypnea and hypoxemia with a shallow respiration. We speculated that the progressively rapid and shallow respiration caused respiratory muscle fatigue resulting in hypoxemia, and that the progressive hypoxemia resulted in an anoxic brain injury or a fatal cardiovascular incident.

The mechanism underlying progressively rapid and shallow respiration remains unknown. One possibility is central neurogenic hyperventilation (CNH), which is a rare syndrome characterized by sustained hyperventilation without cardiac or pulmonary diseases that stimulate a compensatory hyperpnea [6], because the neurodegeneration of the brainstem might cause a dysfunction of the rhythmic modulation of respiration. However, it is difficult to explain the mechanism underlying progressive hypoxemia in our patient only by CNH, because CNH usually shows normal or elevated arterial oxygen levels. Another possibility is an adaptive response to prevent further obstruction of the vocal cords [7]. Because the increase in the kinetic energy of air flowing through the narrowed glottis, the Bernoulli effect, the phenomenon of internal pressure reduction with increased air velocity, further narrows the glottis. Furthermore, an impaired hypoxemic ventilatory response observed in MSA patients [8] might facilitate nocturnal hypoxemia.

This study indicates intriguing features of sleep-disordered breathing in advanced-stage MSA. Further study will be required to investigate whether nocturnal sudden death is caused by a severe nocturnal hypoxemia. In addition, it is important to investigate whether CPAP administration, which has been shown to have a long-term beneficial effect in MSA patients [9], improves patient prognosis, in part, by preventing nocturnal hypoxemia.
References