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Editor's Comments: The possibility of sudden death is a constant threatening thundercloud hovering over the heads of patients with multiple system atrophy, their family, and their physicians. Shimohata and colleagues provide an important and enlightening service by bringing to our collective attention the fact that sudden death in multiple system atrophy may be the result of multiple potential mechanisms and that a system, or team, approach is likely to provide the best means of preventing this devastating complication.

Ronald F. Pfeiffer, Editor-in-Chief, Dept. of Neurology, Oregon Health and Science University (OHSU), 3181 SW Sam Jackson Park Rd, Portland, OR 97201-3098, Oregon, USA.

Review article

Mechanisms and prevention of sudden death in multiple system atrophy

Takayoshi Shimohata [a, *], Naotaka Aizawa [b], Hideaki Nakayama [c], Hiroshige Taniguchi [d], Yasuyoshi Ohshima [e], Hitoshi Okumura [f], Tetsuya Takahashi [a], Akio Yokoseki [g], Makoto Inoue [h], Masatoyo Nishizawa [a]

[a] Department of Neurology, Brain Research Institute, Niigata University, Aahimachi-dori 1-757, Chuo-ku, 951-8585, Niigata City, Niigata, Japan
[b] Department of Otorhinolaryngology, Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, Minami-uonuma, Japan
[c] Department of Respiratory Medicine, Tokyo Medical University, Tokyo, Japan
[d] Department of Dentistry, School of Medicine, Fujita Health University, Toyoake, Japan
[e] Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[f] Division of Otolaryngology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[g] Department of Molecular Neuroscience, Resource Branch for Brain Disease Research, Brain Research Institute, Niigata University, Niigata, Japan
[h] Division of Dysphagia Rehabilitation, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

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ABSTRACT

Background: Sudden death in multiple system atrophy (MSA) usually occurs during sleep and was therefore attributed to suffocation resulting from vocal cord abductor paralysis, a characteristic laryngeal finding of MSA. This led to the use of tracheostomy and noninvasive positive pressure ventilation (NPPV) for the prevention of sudden death. However, neither method has been able to prevent sudden death, and both have occasionally precipitated treatment-related complications, including central sleep apneas and exacerbation of floppy epiglottis. Therefore, it is important to determine the mechanisms and prevention of sudden death in MSA.

Methods: We reviewed the literature on the mechanisms and prevention of sudden death in patients with MSA.

Results: Sudden death in MSA is hypothesized to be a consequence of disordered central respiration, suffocation caused by sputum and food, upper airway obstruction from NPPV acting on a floppy epiglottis, cardiac autonomic disturbance, or a combination of these factors.

Conclusion: Various factors may be involved in the mechanism of sudden death in MSA. A multidisciplinary approach is needed to prevent sudden death, and this requires an organized system of several medical specialties. Neurologists require a cooperative network that includes experts in otorhinolaryngology, sleep medicine, dysphagia rehabilitation, and cardiology.

1. Introduction

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by any combination of cerebellar ataxia,

* Corresponding author. Department of Neurology, Brain Research Institute, Niigata University, 1-757 Asahimachi-dori, Chuo-ku, Niigata City, Niigata, 951-8585, Japan.
E-mail address: t-shimo@bri.niigata-u.ac.jp (T. Shimohata).

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parkinsonism, and autonomic disturbance [1,2]. Various sleep disorders have been observed as complications of MSA, including sleep-disordered breathing (SDB) [3,4], REM sleep behavior disorder [5], restless legs syndrome [6], and excessive daytime sleepiness [7,8]. An additional manifestation of MSA is sudden death, in which patients die of no apparent reason 24 h after the onset of symptoms [9]. Sudden death in MSA usually occurs during sleep [10] and may occur at an early disease stage [11]. The possibility of sudden death is a very serious concern of both the patient at risk and their family; however, issues such as informing the patient on prognosis and treatment autonomy in patients with MSA have not been adequately discussed in the published literature. In recent years, some progress has been made toward a better understanding of the diverse mechanisms of sudden death, the available preventive treatment options, and their outcomes. This review aims to provide an overview of the current understanding, treatment, and clinical ethical issues associated with sudden death in MSA.

2. Methods

References were identified using searches of PubMed with key words. The following combinations were used in a search of titles and abstracts in September 2015:

1. "Multiple System Atrophy" [Mesh]) AND "Death, Sudden" [Mesh]
2. "Multiple System Atrophy" [Mesh]) AND "Mortality" [Mesh]
3. "Multiple System Atrophy" [Mesh]) AND "Sleep" [Mesh]

The abstracts of these articles were screened and full texts of those potentially relevant articles to the review were obtained. After articles were reviewed, a hand search was also conducted using their reference lists.

3. Features and mechanisms of sudden death in MSA

Retrospective studies have reported a survival duration of 7–10 years for patients with MSA [12,13], and prospective studies in Europe and USA each reported a duration of 9.8 years [14,15]. Autonomic disturbances at diagnosis or early in the disease course have been suggested as useful factors for predicting a poor prognosis [15,16]. Although laryngeal stridor is not a useful predictor of poor prognosis, including sudden death [17], a recent study reported that the degree of vocal fold motion impairment is inversely correlated with the survival duration [18].

At first, sudden death in MSA was attributed to suffocation resulting from vocal cord abductor paralysis (VCAP), a characteristic laryngeal finding of MSA [19,20]. This led to the therapeutic use of tracheostomy [11,21] and noninvasive positive pressure ventilation (NPPV) [22,23], which included continuous positive airway pressure (CPAP), bi-level positive airway pressure (BPAP), and adaptive servo-ventilation (ASV), to prolong the survival duration. To determine whether these treatments could prevent sudden death, we prospectively studied 47 patients with probable MSA, according to the consensus criteria [2,10]. In this study, NPPV was selected as the therapeutic intervention in patients with SDB when the apnea-hypopnea index (AHI) exceeded 30/h and in patients with a nocturnal oxygen desaturation that fulfilled a CT90 (cumulative percentage of time spent at saturations below 90% over total sleep time) >10%. Patients with recurrent aspiration pneumonia were treated via conventional surgical tracheostomy. Ten patients died during the five years of observation: seven from sudden death (six during sleep), and one each from pneumonia, suffocation by food, and lung cancer (Fig. 1). Among the seven patients with sudden death, two patients had been treated via tracheostomy and three were treated with NPPV during sleep, suggesting that these treatments do not prevent sudden death in patients with MSA, and suggest that sudden death occurs via mechanisms other than upper airway obstruction. Although the pathogenesis of sudden death is not yet fully understood, the following possibilities merit consideration.

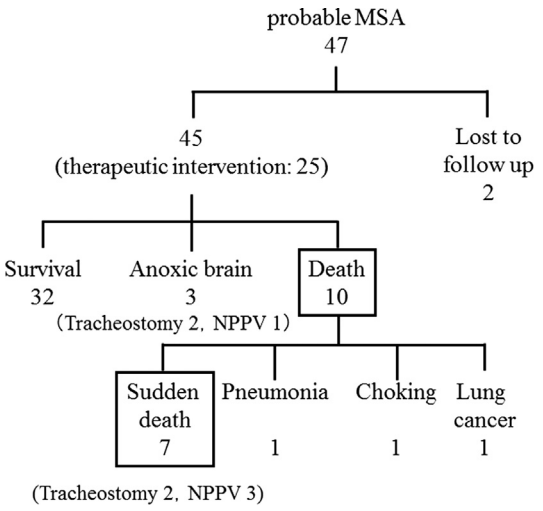

Fig. 1. Causes of death in multiple system atrophy (MSA) and effectiveness of therapeutic interventions. Of 47 patients with MSA, seven succumbed to sudden death. Two of the patients had undergone tracheostomy, and three were using noninvasive positive pressure ventilation (NPPV). Three patients developed anoxic brain injury, despite that two had undergone tracheostomy and one was using NPPV. This is previously published [10].

3.1. Abnormal control of breathing

Hirano et al. reported a patient who died suddenly during an overnight polysomnography (PSG) evaluation, thus providing useful information regarding the time course of sudden death [24]. Although sleep apnea was not observed in this patient, the breathing cycle became irregular at one point, and subsequently transitioned into tachypnea. Respiration stopped following tachypnea, and cardiac arrest occurred 4 min later.

In addition, we previously reported a patient whose PSG revealed marked tachypnea that turned into Cheyne–Stokes respiration (CSR) and caused progressive severe hypoxemia during sleep [25]. We examined the frequency of CSR in patients with probable MSA [2], and found that it was observed in three out of 20 patients (15%) [4].

Tachypnea during sleep and CSR are thought to be caused by neurodegeneration of the respiratory center; pathological analyses demonstrated the depletion of medullary serotonergic neurons that regulate the respiratory and cardiovascular systems in MSA patients who died suddenly [26]. The importance of these medullary serotonergic neurons was confirmed in a study of MSA model mice that expressed human wild-type α-synuclein in oligodendroglial cells [27]. In our experience, serotonergic therapy with selective serotonin reuptake inhibitors (SSRIs) may maintain the glottal opening in patients with MSA for a limited period of time [28]. Future studies are needed to determine whether SSRI-based serotonergic therapy could also ameliorate respiratory disorders with a central origin.

In summary, abnormal control of breathing during sleep might be a cause of sudden death. Because tracheostomy alone cannot prevent the occurrence of sudden death [10], the use of tracheostomy-intermittent positive pressure ventilation (TPPV) may be considered.