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Review article

Laryngeal stridor in multiple system atrophy: Clinicopathological features and causal hypotheses

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ABSTRACT

Laryngeal stridor is recognized as a characteristic clinical manifestation in patients with multiple system atrophy (MSA). However, the pathogenic mechanisms underlying this symptom are controversial. Neurogenic atrophy of the posterior cricoarytenoid muscle has been identified in cases of MSA, suggesting that laryngeal abductor weakness contributes to laryngeal stridor. However, dystonia in the laryngeal adductor muscles has also been reported to cause laryngeal stridor. Depletion of serotonergic neurons in the medullary raphe nuclei, which exert tonic drive to activate the posterior cricoarytenoid muscle, has recently been identified in MSA cases. This adds weight to the possibility that laryngeal abductor weakness underlies laryngeal stridor in MSA. Continuous positive airway pressure therapy is currently used in the treatment of laryngeal stridor, but should be used with caution in patients showing contraindications. Current knowledge of the clinical and neuropathological features of laryngeal stridor is summarized in this paper, and the hypothesized causes and possible therapeutic options for this symptom are discussed.

Contents

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1. Introduction

Multiple system atrophy (MSA) is an adult-onset neurodegenerative disease characterized by parkinsonism, cerebellar ataxia, pyramidal signs, and autonomic dysfunction [1]. In MSA patients, glottic stenosis in the inspiratory phase of respiration causes laryngeal stridor, usually during sleep [2]. Laryngeal stridor frequently accompanies MSA, but is rare in patients with Parkinson's disease (PD) or other forms of atypical parkinsonism [3]. The current diagnostic criteria for MSA indicate that laryngeal stridor can be used in the diagnosis of possible MSA [1]. Furthermore, the European MSA Study Group categorized laryngeal stridor as a red flag or warning sign, raising the clinical suspicion of MSA [4]. Laryngeal stridor is thus an important sign in the clinical diagnosis of MSA.

The classic descriptions of laryngeal stridor in MSA patients are typified by Case 4 reported by Bannister et al. in 1967 [5] and Case 4 described by Martin et al. in 1968 [6], which are considered as the earliest descriptions of the symptom. In a famous study of MSA by Shy and Drager [7], Case 2 was described as showing mild neuronal cell loss and gliosis in the nucleus ambiguus, but the clinical record was lacking information about laryngeal stridor in that case.

A basic neurological examination is insufficient for assessing laryngeal stridor, which is associated with airway symptoms characterized by laryngeal movement disorders during respiration. Interdisciplinary approaches to the assessment of laryngeal movement disorders are required to understand the significance of this symptom in patients with MSA.

This review paper summarizes the current state of knowledge regarding laryngeal stridor in MSA, with special reference to results from fiberoptic laryngoscopy and electrophysiological examinations, as well as the neuropathological and biochemical characteristics associated with the symptom. We also address the therapeutic aspects, as well as hypotheses regarding the cause of laryngeal stridor in patients with MSA.

2. Clinical features

2.1. Natural history

Several studies have considered the epidemiology and natural history of laryngeal stridor in MSA. Wenning et al. reported that 34 of 100 MSA cases showed laryngeal stridor [8]. Regarding the appearance of laryngeal stridor during the course of MSA, Isozaki et al. studied 23 cases of MSA with laryngeal stridor and reported that the symptom occurred at a mean of 5.8 years after disease onset [9]. The severity of glottic stenosis leading to laryngeal stridor reportedly worsens with the progression of MSA [10]. However, other studies reported this symptom emerging early in the course of MSA. Uzawa et al. evaluated symptoms in 200 serial cases of MSA and reported that eight (4%) exhibited laryngeal stridor as the initial symptom, and as the solitary manifestation of MSA in six of these eight cases [11]. According to a report from the Mayo Clinic in Minnesota, six of all MSA cases from 1996 to 2005 displayed respiratory insufficiency, including laryngeal stridor, as an early presenting symptom [12]. Sakuta et al. recently described the presence of laryngeal stridor during the premotor stage in a patient with MSA [13]. These observations indicate that laryngeal stridor can be an early symptom of MSA.

2.2. Stridor sound

The sound of laryngeal stridor is produced by air passing through a chink in the vocal cords during inspiration. The pitch of the sound is 260–330 Hz, higher than the pitch of ordinary snoring produced in the upper pharyngeal territory [14]. In MSA patients, laryngeal stridor has a distinctive sound that is often compared to the sound of nickering. However, patients are unlikely to notice this sound, which usually occurs during sleep, and a bed partner or other family member is likely to be the first person to bring this issue to the attention of the patient. Occasionally, this symptom can be difficult to detect, because the sound becomes thin or faint if respiration is weak [15]. In such cases, the boundary between laryngeal stridor and ordinary snoring is also difficult to identify based on auditory inputs alone. The presence or absence of laryngeal stridor in a patient with MSA is thus sometimes equivocal.

2.3. Contribution of intrinsic laryngeal muscles

The intrinsic laryngeal muscles are a group of smooth muscles attached to the laryngeal cartilages. Fig. 1 shows the fundamental functional anatomy of the intrinsic laryngeal muscles that may play a role in laryngeal stridor. The adductor group of intrinsic laryngeal muscles consists of the transverse arytenoid, oblique arytenoid, and lateral cricoarytenoid muscles, and is responsible for adduction of the vocal cords, while the posterior cricoarytenoid muscle is the only intrinsic laryngeal muscle causing abduction of the vocal cords. These four intrinsic laryngeal muscles are innervated by the recurrent nerve, which is a branch of the vagal nerve. The vagal nerve that innervates these muscles originates from branchimotor neurons in the nucleus ambiguus of the medulla oblongata. The cricothyroid and thyroarytenoid muscles are other intrinsic laryngeal muscles, but are responsible for adjusting the tone of the vocal cords and their contribution to laryngeal stridor is therefore limited.

2.4. Fiberoptic laryngoscopy findings

Fiberoptic laryngoscopy can be used to detect the presence of glottis stenosis, which is a potential cause of laryngeal stridor. In MSA patients with laryngeal stridor, fiberoptic laryngoscopy findings of glottic stenosis have occasionally been termed “vocal cord abductor paralysis”, but whether the glottic stenosis in MSA is always caused by a “paralytic” disorder of the laryngeal muscles remains unclear. As a result, the present paper has avoided using this term to avoid any confusion about the pathophysiology of laryngeal stridor in MSA.

In 1979, Williams et al. performed fiberoptic laryngoscopy on 12 patients with MSA [15]. They found that moderate or severe glottis stenosis was present in eight of the 12 patients, while laryngeal stridor was present in six of these eight patients with glottis stenosis. However, this article lacked information about whether fiberoptic laryngoscopy was performed with the patient awake or asleep. Generally, fiberoptic laryngoscopy needs to be performed during sleep, because laryngeal stridor is more evident during sleep than during wakefulness. Very few reports have described MSA patients who have undergone fiberoptic laryngoscopy during physiological sleep [16], because such examinations may disturb the continuity of physiological sleep in patients. Fiberoptic laryngoscopy is therefore usually performed on patients who have been sedated using diazepam or propofol. Isozaki et al. performed fiberoptic laryngoscopy on seven patients with MSA during wakefulness and under diazepam-induced sedation [17]. Three of the seven patients exhibited normal laryngeal movements during wakefulness, but all seven patients displayed severe glottic stenosis under sedation, and one showed fixation of bilateral vocal cords at the midline during inspiration. Based on these findings, Isozaki et al. proposed a multi-stage classification of glottic stenosis to estimate the risk of