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SLEEP MEDICINE PEARLS

A 76 Year-Old Woman with Sleep and Waking Stridor, Sleep Talking, Orthostatic Hypotension, and Imbalance

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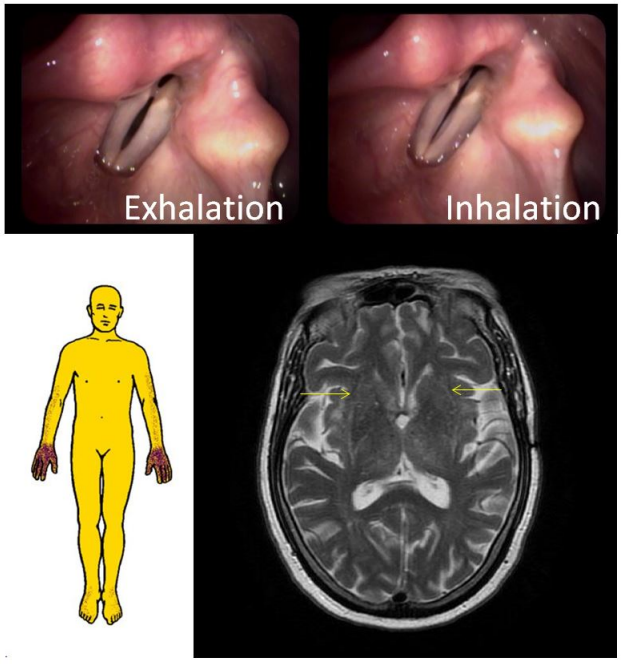
A 76-year-old woman presented with a three-month history of a harsh, high-pitched breathing noise during sleep, which had also recently begun to occur occasionally during the daytime while awake. Sleep talking had been noted for decades but recently had become louder and more agitated in character. No other nocturnal motor activity was noted. Over the last year, she had intermittent urinary urgency and incontinence; softer, imprecise speech; imbalance; and dizziness while standing, with severe supine hypertension. Midodrine was unhelpful. Her only medication was losartan 25 mg daily.

On examination, there was moderate hypomimia, hypokinetic dysarthria, inspiratory and phonatory stridor (**Video 1**), moderate symmetric rigidity and bradykinesia, and a 30-mm systolic blood pressure drop from sitting to standing. Also noted was loud waking stridor, particularly notable during inspiration, with use of accessory respiratory muscles (sternocleidomastoid and neck strap muscles) indicating increased effort as the patient breathes against dysfunctional vocal cords (**Video 1**).

Videolaryngoscopy showed significantly reduced vocal fold mobility bilaterally, with failure of abduction and paradoxical movement of true vocal fold tissue during inspiration. Autonomic reflex screen demonstrated severe orthostatic hypotension during head-up tilt table testing, and marked cardiovagal, cardiovascular adrenergic, and patchy postganglionic sympathetic sudomotor abnormalities. Thermoregulatory sweat testing demonstrated severe anhidrosis compatible with central autonomic failure. Brain MRI showed linear hyperintensities along the lateral aspects of the putamen (**Figure 1**).

Figure 1



Top: Laryngoscopy demonstrated bilateral, near total, vocal fold paralysis, associated with sleep and waking inspiratory and phonatory stridor. Bottom: Thermoregulatory sweat testing showed near complete anhidrosis with only light sweating over the hands. Brain MRI demonstrated linear hyperintensities along the lateral aspects of the putamen bilaterally, right more than left.

QUESTION: What diagnosis does the clinical presentation, laryngoscopic, brain MRI, and thermoregulatory sweat testing findings shown in Figure 1 suggest?

A. Parkinson disease
B. Huntington disease
C. Multiple system atrophy
D. Idiopathic REM sleep behavior disorder
E. Progressive supranuclear palsy

ANSWER: C. Multiple system atrophy.

Polysomnography recorded stridor during all positions and stages of sleep. Apnea-hypopnea index was 13/h, with oxyhemoglobin saturation nadir of 83%. Nasal continuous positive airway pressure was titrated to 13 cm H_2O, eliminating stridor, and further titration to 16 cm H_2O eliminated respiratory effort-related arousals. Manually quantified REM sleep without atonia (RSWA) analysis of combined phasic and tonic muscle activity in both submentalis (SM) muscle and tibialis anterior (TA) muscles was 83.5% (with muscle activity calculated as the total number of positively scored REM sleep 3-s mini epochs, divided by the total number of analyzable REM sleep 3-s mini-epochs). Control group combined RSWA muscle activity cutoff was previously defined as 43.4%.[1] Manually quantified RSWA tonic muscle activity in the SM and TA muscles was 69.7%, with control group tonic RSWA muscle activity cutoff previously defined as 1.2%.[1]

Computerized automated REM atonia index (RAI) in the SM EMG assessed using HypnoLab sleep scoring software (ATES Medica Labs, Verona, Italy) was 0.35%. The RAI was scored on a scale of 0–1, with a score of zero indicating complete absence of muscle atonia and one indicating completely preserved muscle atonia. Values < 0.8 are strongly indicative of RSWA, values between 0.81 and 0.90 indicate likely abnormal muscle activity, while an RAI > 0.9 indicates preserved muscle atonia; the diagnostic cutoff determined in our laboratory that best distinguished RBD cases from controls was 0.88.[1,2]

Nasal CPAP and melatonin 3 mg were initially prescribed; but given daytime stridor and poor vocal fold mobility, tracheostomy with a Passy-Muir valve to permit speech was recommended. Lee Silverman Voice Therapy program for hypokinetic dysarthria was also suggested.

DISCUSSION

Multiple system atrophy (MSA) is a neurodegenerative disorder with predominant brainstem α-synuclein deposition. MSA is clinically characterized by autonomic failure (orthostatic hypotension, bowel and bladder dysfunction, with sweating abnormalities) and motor impairment with parkinsonism (rigidity, bradykinesia, and postural instability) and/or cerebellar ataxia with prominent sleep disturbances including REM sleep behavior disorder (RBD) and sleep disordered breathing (SDB). SDB in MSA may include obstructive or central sleep apnea, central alveolar hypoventilation, and most characteristically, sleep and daytime stridor due to laryngeal weakness or dystonia. Stridor and obstructive and central SDB in MSA likely relate to dysregulation of inspiratory laryngeal and pharyngeal motoneurons and the pontomedullary respiratory network involving the lateral dorsal tegmental, pedunculopontine, parabrachial/Kölliker-Fuse, nucleus of solitary tract, and ventrolateral medulla, as well as degeneration of serotonergic medullary raphe chemosensitive neurons.[2–4]

The differential diagnosis for acutely evolving stridor includes allergic reactions, epiglottitis associated with *Haemophilus influenzae* type b, inhalation injury (e.g., due to cleaning agents, or smoke inhalation), laryngeal tumors, and idiopathic vocal cord dysfunction, although as distinguished from our patient where the temporal course involved initial sleep before waking stridor, most of these other conditions would present with initial waking stridor as well. When stridor is present, visualization of the vocal folds by laryngoscopy is crucial. In our opinion, tracheostomy should be strongly considered to help prevent the risk of sudden death if there is bilateral vocal fold paralysis, if stridor is present during the day, or if nocturnal stridor does not respond to nasal CPAP therapy, as tracheostomy may provide protection against breathing arrest during the awake state, since most patients without ventilatory failure would not choose to utilize CPAP while awake.[4–6] Nasal CPAP is a reasonable alternative when stridor is limited to sleep[7] and when vocal folds still demonstrate reasonable function, and even in some cases with complete vocal fold abduction restriction.[11] Future multicenter prospective observational and randomized trials between CPAP and tracheostomy will be necessary to define optimal evidence-based treatment approaches for sleep and daytime stridor in MSA.

Repeat laryngoscopy should be performed at regular intervals if CPAP therapy is selected to detect progressive laryngeal dysfunction. Cases of sudden death during sleep have still been reported following treatment with either nasal CPAP or tracheostomy, suggesting that other mechanisms of autonomic dysfunction may still be fatal in MSA.[4,6] RBD and REM sleep without atonia characterized by especially prominent excessive tonic muscle activity are frequent in MSA. Melatonin or clonazepam may be offered as therapies, with melatonin preferred to avoid exacerbating SDB and neurological dysfunction.[12] Taking a thorough medication history for any medications that could provoke or aggravate RSWA is important in all patients presenting with parasomnia behaviors. Several medications have been associated with RSWA, including tricyclic, selective serotonin reuptake inhibitors, and mixed mechanism antidepressants (i.e., mirtazapine and venlafaxine), and monamine oxidase inhibitors such as seligline.[13,14]

Unfortunately, no specific therapies to arrest the relentless progression of MSA neurodegeneration exist. Symptomatic treatments include levodopa-carbidopa or a dopamine agonist for parkinsonism (although MSA patients often respond poorly and fail to tolerate dopaminergic therapies due to worsened orthostatism) and midodrine (ProAmatine) or fludrocortisone (Florinef) for orthostatic hypotension.

MSA may present with sleep stridor and RBD in the absence of prominent parkinsonism or cerebellar ataxia,[15] so sleep specialists should consider prompt neurological and otorhinolaryngology referral when these signs are encountered.

SLEEP MEDICINE PEARLS

1. Sleep-related stridor can be the presenting manifestation of MSA and is associated with sudden death.
2. Sleep-related stridor associated with MSA may respond to nasal continuous positive airway pressure (CPAP) therapy.

3. The presence of waking stridor signals the need for consideration of prompt elective tracheostomy.

ABBREVIATIONS

MSA, multiple system atrophy
RBD, REM sleep behavior disorder
SDB, sleep-disordered breathing

CITATION

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