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CASE REPORTS

Non-REM sleep–predominant reversible paradoxical breathing effort indicates dysregulation of diaphragm movements in multiple system atrophy

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Study Objectives: In multiple system atrophy, sleep-disordered breathing has a broad spectrum of phenotypes, among them inspiratory stridor and obstructive sleep apnea being most frequent.

Methods: We present a case of a 59-year-old woman with cerebellar-type multiple system atrophy, who showed transient paradoxical breathing effort during non–rapid eye movement sleep on diagnostic polysomnography. Because this thoraco-abdominal paradox was atypical for and did not coincide with upper airway obstruction, it most likely indicated central dysregulation of the diaphragm.

Results: Continuous positive airway pressure therapy with low pressure (5 cm H_2O) was sufficient to completely resolve this type of respiratory dysregulation.

Conclusions: This case extends the clinical spectrum of sleep-disordered breathing in multiple system atrophy.

Keywords: sleep-disordered breathing, multiple system atrophy, thoraco-abdominal paradox, dysregulation of diaphragm movements, continuous positive airway pressure therapy

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INTRODUCTION

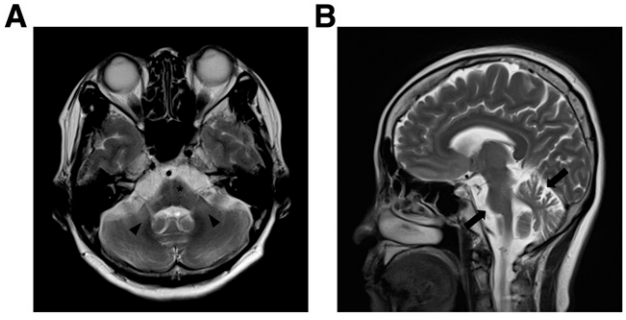
Sleep-disordered breathing (SDB) is the most frequently reported nocturnal disorder in multiple system atrophy (MSA), along with rapid eye movement (REM) sleep behavior disorder. SDB can manifest as obstructive sleep apnea, inspiratory stridor, or less often as central sleep apnea, Cheyne-Strokes respiration, or dysrhythmic respiration; the phenotype may change over time with disease progression.[1] Dysregulation of diaphragm movements, on the other hand, is a rarely debated phenomenon in MSA. Here, we present a patient with cerebellar-type MSA, with motor symptom onset less than a year from diagnostic workup, exhibiting reversible non-REM (NREM) predominant paradoxical breathing effort, suggestive of central dysregulation of the diaphragm during full-night polysomnography (PSG).

REPORT OF CASE

A 59-year-old woman visited our sleep disorder clinic to address her REM sleep behavior disorder and excessive daytime sleepiness (Epworth Sleepiness Scale 12). Her sleep disturbances began in 2017, with recurrent episodes of "screaming and acting out in bed as if possessed by a demon," as reported by her bed partner. Motor symptoms began to manifest in July 2018. She complained of having difficulty pronouncing words and sentences, writing with her dominant right hand, and maintaining balance during gait. She also complained of urinary incontinence, which was especially bothersome during the night. She denied having orthopnea while awake or dyspnea on exertion. Her body mass index was 21.1 kg/m^2. She never smoked or consumed alcohol throughout her life. There was no history of chest wall trauma or neuromuscular disease. No family history of movement disorder, neuromuscular disease, or stroke was identified. Neurologic examination revealed bilateral dysmetria and dysdiadochokinesia in the upper extremities, scanning dysarthria, and ataxic gait, collectively suggesting cerebellar ataxia in both her limbs and trunk. A brain magnetic resonance imaging scan was obtained, and olivopontocerebellar atrophy was evident in T2-weighted images (**Figure 1**). On autonomic function study, a moderate degree of adrenergic and cardiovagal dysfunction including orthostatic hypotension was found; systolic blood pressure dropped 31 mm Hg after 3 minutes of standing during a tilt-table test. The patient was diagnosed with cerebellar-type MSA in August 2018. Initial full-night PSG performed 8 months after motor symptom onset revealed mild obstructive sleep apnea with an apnea-hypopnea index of 14.9 events/h (no apnea; hypopnea only), 1 episode of REM sleep behavior disorder, and REM sleep without atonia. The patient slept supine throughout the study, except during an REM sleep behavior disorder episode. Neither inspiratory stridor nor dysrhythmic respiration was noted. Snoring was present to a moderate degree. Mild airflow limitation, which did not satisfy the criteria for hypopnea or apnea, was detected through airflow signal traces at baseline. In NREM sleep, during inspiration, the thorax moved upward, but the abdomen moved downward in the piezoelectric belt trace and vice versa during exhalation; this is an atypical paradoxical breathing effort that indicated central dysregulation of the diaphragm or diaphragmatic palsy (**Video 1** in the supplemental material). This was accompanied by augmented flow limitation and hypopneas.

During this abnormal period of respiration, which lasted as long as 62 minutes, oxygen saturation decreased to as low as 84% without the patient awakening. In REM sleep, however, the paradoxical breathing effort present during NREM sleep disappeared, whereas mild short-lasting hypopneas increased in frequency (Table 1). The plain chest radiograph revealed no abnormal unilateral or bilateral diaphragmatic elevation, increase in acuteness of costophrenic angle, or bibasilar subsegmental atelectasis in the lung parenchyma. A subsequent PSG with split-night design and end-tidal CO_2 measurement was performed a week after the initial study. The first half of the study was performed without intervention and revealed a slight airflow limitation with End tidal CO_2 level increase from 32 to 40 mm Hg (a 25% increase) preceding the thoraco-abdominal paradox. The End tidal CO_2 levels stagnated between 42 and 43 mm Hg while the paradoxical breathing effort prevailed. In the second half of the study performed with continuous positive airway pressure (CPAP) titration, the patient's paradoxical breathing effort and oxygen desaturation were completely resolved with CPAP therapy (5 cmH_2O) (**Video 2** in the supplemental material). Furthermore, she reported her daytime sleepiness was much improved with CPAP therapy (Epworth Sleepiness Scale 3). Table 1 summarizes the respiratory data obtained from the PSG studies that were performed.

Figure 1—Brain MRI findings of the patient with MSA-C.



(A) "Hot cross-bun sign" (asterisk) in the pons, hyperintensity of the bilateral middle cerebellar peduncles (black arrowheads), and ex vacuo dilatation of the fourth ventricle in axial T2-weighted image. **(B)** Olivo-pontocerebellar atrophy (black arrows) and prominent cerebellar folia in parasagittal T2-weighted image. MRI = magnetic resonance imaging, MSA-C = multiple system atrophy cerebellar-type.

DISCUSSION

The features that distinguish our case from other well-recognized SDBs in MSA are that (1) the patient's paradoxical breathing effort suggested dysregulation of diaphragm movements that were detected only during sleep in the absence of clinical symptoms or signs of diaphragmatic palsy while awake; (2) this type of thoraco-abdominal paradox was prevalent in her NREM sleep only; and (3) it was completely reversible with low-pressure CPAP therapy. To our knowledge,

Table 1—Summary of respiratory data from the polysomnography studies.

	Initial PSG	Split-Night PSG	
		No Intervention	CPAP Titration
Longest apnea/hypopnea time (s)	Hypopnea, 166.0	Hypopnea, 62.0	Apnea, 31.4; hypopnea, 17.6
Total apnea-hypopnea events (no.)	113	29	4
Total AHI (events/h)	14.9	14.6	1.1
Apnea index	0.0	0.0	0.8
Hypopnea index	14.9	14.6	0.3
AHI in REM	23.5	23.1	1.6
AHI in NREM	11.4	13.6	1.0
RDI (events/h)	16.7	15.6	1.4
Lowest SpO_2 (%)	84.0	87.0	92.0
ODI (events/h)	13.5	15.1	0.5
SpO_2 < 90% (min, %)	61.4, 13.5	35.3, 29.6	0.0, 0.0
Respiratory arousal (events/h)	7.3	5.0	0.8
Paradoxical breathing effort	+	+	–
Total events (no.)	6	4	—
Total duration (min)	213.4	76.3	—
Longest duration (min)	62.0	40.6	—
AHI (events/h)	5.1	11.8	—
Lowest SpO_2 (%)	84	87	—
ODI (events/h)	7.9	11.0	—
SpO_2 < 90% (min, %)	61.4, 28.8	35.3, 46.3	—

AHI = apnea-hypopnea index, CPAP = continuous positive airway pressure, NREM = non–rapid eye movement, ODI = oxygen desaturation index, PSG = polysomnography, RDI = respiratory disturbance index, REM = rapid eye movement, SpO_2 = oxygen saturation.

this is the first report of NREM-dominant paradoxical breathing indicating dysregulation of diaphragm movements without definite airflow limitation, tachypnea, dysrhythmic breathing, or inspiratory stridor, with complete reversal of the phenomenon by low-pressure CPAP therapy.

From the first diagnostic full-night PSG, we suspected that central dysregulation of the diaphragm was at play. We were confident that technical caveats such as false thoraco-abdominal paradox artifact were thoroughly addressed so that the integrity of our results were not compromised. Despite some degree of flow limitation, the paradoxical breathing effort seen in our patient does not comply with the type of thoraco-abdominal paradox seen in upper airway obstruction, where the thorax contracts while the abdomen expands during inspiration, creating negative pressure in the thoracic cavity to compensate for the collapsed airway and vice versa during expiration. In our patient, her thoracic signal coincided with the airflow signal, meaning the inspiratory and expiratory effort overcame the airway resistance, yet the abdomen moved in the opposite vector; this is a paradox, but a different type of paradox. Moreover, the respective apnea-hypopnea index during the thoraco-abdominal paradox episodes in the first diagnostic PSG was only 5.1 events/h compared with 11.4 events/h during NREM sleep and 14.9 events/h during total sleep time (**Table 1**). This collectively suggests that upper airway resistance did not account for the whole SDB in our patient nor did it trigger the type of paradoxical breathing effort typically attributable to upper airway obstruction. In turn, this led us to an independent pathophysiology involving the key muscle driving the abdominal movement during breathing—the diaphragm. The first differential diagnosis was to consider diaphragmatic palsy. If this was the case, abdominal motion in the opposite direction to the airflow or thoracic motion should suggest bilateral complete diaphragmatic palsy. Nevertheless, the patient had no clinical symptoms to suggest complete diaphragmatic palsy during exercise or at rest, and her chest radiograph did not support that diagnosis.[2] Moreover, the fact that low-pressure CPAP therapy resolved this phenomenon disproves the possibility of complete bilateral diaphragmatic palsy, which is a fixed weakness and usually requires high level or bilevel positive airway pressure therapy. Central dysregulation of the diaphragm was another entity to consider. Tonic and phasic overactivation and paradoxical movement of the diaphragm and intercostal muscles were previously reported in an electromyography study of patients with MSA and inspiratory stridor.[3] Also, MSA is known to involve a number of respiratory brainstem nuclei including the pre-Bötzinger complex, a respiratory pattern generator that exerts control over diaphragmatic activity during inspiration.[4] Therefore, we suspected that dysregulated diaphragm movements generated by malfunctioning relevant brainstem nuclei dynamically hindered respiration during sleep, causing prolonged periods of oxygen desaturation. We did consider central dysregulation of the diaphragm as the more likely etiology that took place during NREM sleep, but an electromyography of respiratory muscles would be needed to reveal its true physiologic profile.

The paradoxical breathing effort in our case also draws attention to its NREM-dominant nature. The diaphragm is suggested to be the main respiratory muscle during REM sleep, so in case of immanent or structural malfunction of the diaphragm, we expect SDB to be worse during REM sleep. Although short-lasting hypopneas were more dominant during the patient's REM sleep, they were a minor contribution to her sleep-disordered breathing as a whole in terms of length and degree of desaturation compared with paradoxical breathing during NREM sleep (**Table 1**). In a study on patients with bilateral diaphragmatic palsy and SDB, extra-diaphragmatic muscle activities persisted during REM sleep, suggesting brainstem reorganization.[5] Therefore, it is possible that extra-diaphragmatic muscles still assisted our patient during REM sleep, assuming the reorganization process in the brainstem had already taken place. Nevertheless, the diaphragm is still the key muscle during respiration, and worsening during REM sleep seems inevitable if we exclusively consider static, structural malfunctions of the diaphragm. Central pattern dysregulation of diaphragm movements is a more suitable fit for the whole picture; a dynamic hindrance of the diaphragm can better explain why SDB was worse in this patient during NREM sleep. Specifically, paradoxical diaphragmatic contraction upward during inspiration can reduce the amount of inward airflow by decreasing lung capacity. Conversely, increased tonicity of muscles during REM sleep without atonia may be protective against SDB caused by dysregulation of diaphragm movements via 2 factors: REM sleep without atonia can (1) buffer and tone-down phasic dysregulated diaphragmatic movements by providing a steady stream of tonic discharges to both agonist and antagonist muscles and (2) recruit pharyngeal upper airway dilator muscles during paradoxical breathing efforts.[6] Therefore, paradoxical breathing effort caused by dysregulation of the diaphragm movements, partially compensated by thoracic movement driven by extra-diaphragmatic accessory respiratory muscles and REM sleep without atonia, may be a more probable interpretation of our patient's thoraco-abdominal paradox.

We suggest 2 mechanisms by which CPAP therapy could have resolved this patient's dysregulated diaphragm movements, both at the cortical and peripheral levels. First, in keeping with the possibility of central causation, CPAP therapy may have acted as a pneumatic splint for obstructive sleep apnea and as a sensory trick at the cortical level. Although the exact pathophysiology of this sensory trick is still elusive, several compelling mechanisms have been suggested, one of the more popular hypotheses being the balancing of facilitation-to-inhibition ratio.[7] Upper airway mucosal proprioceptive receptors will convey information to cranial nerve V, IX, and X nuclei in the pons and the medulla, relaying information to the somatosensory cortex, which may interact with motor cortices to ameliorate the abnormal intracortical facilitation, ultimately putting the dysregulated diaphragm under control. Second, CPAP therapy may alleviate proprioceptive triggers of dysregulated breathing at the peripheral level. CPAP therapy aids in effective ventilation during sleep by widening the gap between upstream airway pressure and critical closing pressure; it increases the former substrate allowing airflow into the lungs. Mounting evidence suggests that proprioceptive feedback from mechanoreceptors the in upper airways help maintain pharyngeal lumen width by activating pharyngeal dilator muscles

during inspiration.[8] Also, it has been suggested by Nonaka et al[9] that, in patients with MSA, to compensate for their narrow glottic aperture, pathologically elevated afferent activity and subsequent dystonic thyroarytenoid vocal cord adductor muscle output may push the narrowing even further, creating a vicious cycle of "airway reflex" that precipitates inspiratory stridor. Dysregulation of diaphragm movements in our patient may have occurred independently or in combination with vocal cord dystonia, but it is worth noting that vocal cord dystonia has been associated with abnormal overactivation of respiratory muscles in a previous study.[3] By providing support to upstream airway pressure, CPAP therapy can aid in maintaining passive pharynx width, preventing the generation of mechanoreceptor signals that initiate both vocal cord dystonia and dysregulation of diaphragm movements.

Although we stand by our data, there were some diagnostic shortcomings worth mentioning. Dysregulation of diaphragm movements in our case was inferred from a minimal diagnostic workup as the dominant mechanism behind the patient's paradoxical breathing effort. Although normal chest radiograph and lack of respiratory symptoms do lessen the possibility of diaphragmatic palsy, obtaining measures such as vital capacity and maximum inspiratory pressure, twitch diaphragmatic pressure, and performing esophageal manometry could have provided a more solid set of objective evidence, whether her condition was attributable to local vs higher-order etiology concerning the degeneration of central regulators of the diaphragm or other causes such as transient airflow limitation below detection threshold. For further evaluation of the dysregulation of diaphragm movements, an electromyography of the diaphragm, accessory respiratory muscles, and vocal cord muscles could have aided in demonstrating the patient's specific phenomenology, in particular, diaphragmatic dystonia.

In conclusion, NREM-dominant dysregulation of diaphragm movements may be one of the many faces of SDB in MSA, and CPAP therapy can effectively resolve this phenomenon. Studies on therapeutic approaches for SDB in MSA center on managing inspiratory stridor. A previous study in the literature enrolled patients with MSA with disease durations ranging from 5 to 13 years from disease onset.[10] CPAP therapy was prone to adjustment failure, and most patients eventually received tracheostomy to deal with CPAP-unresponsive sleep apnea syndrome, daytime hypoxia symptoms, hypoventilation, and recurrent aspiration pneumonia.[11] The advent of inspiratory stridor, however, may connote that vocal cord pathology has already evoked an irreversible fast track to deterioration, rendering the patient increasingly resistant to CPAP therapy. Further investigation of patients with early-stage MSA with SDB without notable inspiratory stridor is warranted to confirm the effect of CPAP therapy for improving their sleep quality, and hopefully quality of life, in a limited time window.

ABBREVIATIONS

CPAP, continuous positive airway pressure
MSA, multiple system atrophy
NREM, non–rapid eye movement
PSG, polysomnography
SDB, sleep-disordered breathing

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