Clinical Reasoning: A 72-year-old man with nocturnal stridor

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SECTION 1

Initial presentation. A 72-year-old man was admitted to the hospital with a 5-day history of shortness of breath. He initially presented to the emergency department and was found to have significant difficulty with respiration. On the day after admission, the patient developed stridor, tachypnea, and hypoxia, requiring bilevel positive airway pressure (BiPAP) use. ENT was consulted for evaluation of new-onset stridor; direct fiberoptic laryngoscopy revealed proper vocal cord function while awake but bilateral vocal cord abduction paralysis while asleep. Collateral history revealed that the patient had experienced progressive dysphagia, ataxia, and bradykinesia for the previous 3 years. He also experienced constipation, erectile dysfunction, and orthostatic hypotension.

His medical history was remarkable for hypertension, diabetes, heart failure, and left frontal and cerebellar strokes.

Examination revealed flattening of the right nasolabial fold, hypomimia, hypophonia, and severe spastic dysarthria. He also had rigidity of the right upper extremity that increased with activation, and bradykinesia bilaterally. Mild weakness of the right triceps was noted. Sensory examination demonstrated decreased vibratory sense up to the ankles. Stretch reflexes were 2+ in the upper extremities and 3+ at the knees with crossed adduction bilaterally. The left Achilles was 2+ and the right Achilles had sustained clonus. Plantar responses were down on the left and up on the right. Action tremor and dysmetria were noted in both upper extremities.

Questions for consideration:

1. What is the differential diagnosis?
2. What is the most likely anatomical localization of the lesion responsible for these symptoms?

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SECTION 2

Differential and localization. In a patient with bilateral vocal fold paralysis, the differential diagnosis includes a number of nonneurologic and neurologic disorders. Nonneurologic disorders include, but are not limited to, trauma, mass lesions, laryngospasm secondary to asthma or gastroesophageal reflux disease, and inflammation from an upper respiratory infection.¹ Acute-onset neurologic disorders that cause stridor include ischemic or demyelinating events, as well as botulinum.^{1,2} Guillain-Barré syndrome, its variants, and myasthenia gravis may also cause stridor in the acute to subacute setting.¹ Chronic neurologic causes of stridor include amyotrophic lateral sclerosis (ALS) and other causes of motor neuron disease, as well as spinocerebellar ataxia type 3 (SCA) and multiple system atrophy (MSA).^{1,3-7}

In this case, the initial step is to identify the tracts that regulate the various neurologic complaints and then localize the dysfunction. Vocal cord control is mediated by motor fibers from the primary motor cortex that travel along the corticospinal tracts and synapse bilaterally in the nucleus ambiguus. Fibers then emerge ipsilaterally from the medulla and travel with the vagus nerve. These then travel along the carotid arteries in the neck and branch into the recurrent laryngeal nerves at the level of the aortic arch. These nerves innervate the ipsilateral posterior cricoarytenoid muscles, which mediate vocal cord abduction. Clinically, stridor may occur as a result of disruption of any part of this pathway.

The combination of bradykinesia and rigidity are likely representative of dysfunction in the direct

pathway of the basal ganglia. Excitatory cortical input to the putamen and caudate is relayed as inhibitory fibers to the globus pallidus pars interna and substantia nigra pars reticulata. Inhibitory fibers are then sent to the ventral anterior and ventral lateral nucleus of the thalamus, where excitatory fibers are relayed to the motor areas of the cortex. Disruption of this pathway leads to hypokinesia and is commonly seen in the setting of neurodegenerative issues where onset of symptoms is insidious.

Ataxia localizes to either cerebellar lobe, as well as the output pathway from the dentate nucleus. Fibers exit through the superior cerebellar peduncle and then decussate in the midbrain to reach the contralateral red nucleus. These synapse in the contralateral ventral lateral nucleus of the thalamus, which then project to the contralateral cortex to modulate motor systems. Clinically, ipsilateral ataxia would occur with disruption of this pathway.

The selective paresis of the bilateral vocal cords that occurred only during sleep is a unique feature to this case. This would argue against an acute process such as ischemia, demyelination, or toxic exposure, which would cause persistent dysfunction of the vocal cords. Subacute to chronic neurologic processes would also be expected to cause persistent dysfunction as well. However, given the diffuse nature of the symptoms and localization for each of these, a diffuse neurodegenerative process was suspected.

Question for consideration:

1. What investigations would you recommend?

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SECTION 3

Initial workup. In the acute setting, workup should begin with imaging of the head and neck to evaluate for lesions in the cerebral hemispheres, brainstem, cervical cord, and soft tissue of the neck. MRI would be the preferred study, because this can urgently evaluate soft tissue structures with the ability to highlight acute damage to the CNS. It also serves as comparison to prior imaging for various neurodegenerative disorders. An MRI of the brain was obtained, which demonstrated no evidence of tumor, hemorrhage, or ischemia. However, progression of cerebellar and new pontine atrophy was noted when compared with a brain MRI from 5 years prior (figure, A and B). MRI of the neck demonstrated spondylosis of the cervical spine but no tumor.

Given the various life-threatening neurologic disorders that can cause vocal cord paralysis, electrodiagnostic evaluation should also be urgently considered. EMG and nerve conduction studies can be useful in evaluating for ALS, botulism, Guillain-Barré syndrome, and myasthenia gravis.

Question for consideration:

1. How would you interpret the results of the MRI?

Tumor and acute stroke were ruled out based on the MRI. The presence of progressive atrophy confirmed suspicion of a neurodegenerative process. Specifically, marked atrophy of the cerebellum was seen when compared with 5 years prior (figure, A and B). This can be seen in a number of disorders including, but not limited to, SCA and MSA cerebellar subtype (MSA-C).³⁻⁵ However, atrophy of the olivary nuclei was prominent, in addition to atrophy of pontocerebellar fibers traversing the mid pons, known as a “hot cross bun” sign (figure, B and C).⁴⁻⁶ These findings were suggestive of MSA-C.

DISCUSSION MSA is an adult-onset, neurodegenerative α -synucleinopathy characterized by parkinsonism, cerebellar ataxia, pyramidal signs, and autonomic dysfunction.^{4,6} The diagnosis of possible MSA is based on clinical evidence of parkinsonism (MSA-P) or a cerebellar syndrome (MSA-C) in the presence of at least one autonomic feature of urinary dysfunction, erectile dysfunction, or orthostasis.⁴⁻⁶ In addition, corticospinal tract involvement, stridor, or a poor response to levodopa can be found in either subtype of MSA. Findings of cerebellar ataxia in the MSA-P subtype or parkinsonism in the MSA-C subtype further support the diagnosis.⁶ Probable MSA is characterized by autonomic failure defined as urinary incontinence or orthostasis in combination with poorly levodopa-responsive parkinsonism or cerebellar syndrome.⁶ In a review of 203 patients with MSA, 59% of patients presented with an initial motor complaint of parkinsonism while 29% presented with ataxia.⁵

A definite diagnosis of MSA can only be made on histopathologic examination, with findings dependent on the parkinsonism or cerebellar subtype.⁶ Degeneration of the substantia nigra and putamen is found in patients with severe parkinsonism, while inferior olive and cerebellar Purkinje cell atrophy is seen with prominent cerebellar dysfunction. Intermediolateral cell column degeneration and atrophy of the nucleus of Onuf are found with autonomic dysfunction.⁴⁻⁶ In the absence of an autopsy, the clinical presentation of stridor in the setting of progressive parkinsonism and ataxia in our patient, with MRI findings of olivopontocerebellar atrophy, was highly suggestive of a diagnosis of MSA-C.

Recognition of stridor can help distinguish MSA from other neurodegenerative diseases, including Parkinson disease, ALS, SCA, and progressive supranuclear palsy. Stridor in MSA is thought to occur from degeneration

Figure Brain and brainstem MRI without contrast

(A) Sagittal T1-weighted MRI from 2008 demonstrates a normal-appearing pons and mild atrophy of the cerebellum. (B) Sagittal T1-weighted MRI from 2013 demonstrates progression of cerebellar atrophy, in addition to new olivary nucleus and pontine atrophy. (C) Axial T2-weighted MRI from 2013 demonstrates hyperintense lines traversing the mid pons, known as a “hot cross bun” sign.

of the nucleus ambiguus, which leads to atrophy of the posterior cricoarytenoid muscles. Selective laryngeal abductor weakness follows, leading to stridor.^{1,4,6} Although posterior cricoarytenoid muscle atrophy has been demonstrated on histopathologic examination, corresponding changes in the nucleus ambiguus were not definitive.⁸ One study demonstrated that 4% of patients presented with stridor as the initial symptom.⁷ Another study showed that 42% of patients with MSA were diagnosed with vocal fold dysfunction.⁹ Overall, stridor is present in 13% to 19% of patients with MSA and potentially higher rates when studied with polysomnography, often coinciding with severe disease and higher rates of mortality.¹⁰ This highlights the need for early recognition of stridor in MSA, as treatment with tracheostomy or BiPAP leads to significant improvement in mortality.¹⁰ In our case, the patient was referred for polysomnography and prescribed a continuous positive airway pressure (CPAP) machine. Significant reduction in nocturnal stridor was noted at 3-month follow-up.

The clinical presentation of MSA can be highly variable and easily mistaken for other neurodegenerative diseases. However, recognition of stridor in the context of parkinsonism can assist with the diagnosis of MSA.^{7,9} Early recognition allows for prompt treatment with tracheostomy or CPAP.¹⁰

AUTHOR CONTRIBUTIONS

Dr. Zuzuárregui, Mr. Shah, and Dr. Saint-Hilaire contributed to drafting and revising the manuscript. Dr. Zuzuárregui was responsible for the study concept.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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