CLINICAL VIGNETTE

An Elusive Antibody Causing Hypercapnic Respiratory Failure

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Introduction

Hypercapnic respiratory failure carries a broad differential diagnosis. While narcotics and chronic obstructive pulmonary disease (COPD) exacerbations are among the most common etiologies in hospitalized patients, it is important to be aware of the broader list of possible etiologies.

Case presentation

A 60-year-old female non-smoker without significant past medical history presented to establish care with a primary care physician with the chief complaint of progressive dyspnea on exertion. She ambulated without limitation but was found to be hypoxemic with room air oxygen saturation of 88%. She was sent to the emergency department where she found to have a severe hypercapnia and respiratory acidosis with a pH of 7.14, pCO_2 of greater than 114 mmHg (laboratory maximum), and bicarbonate of 48 mEq/L. She failed a brief trial of non-invasive positive pressure ventilation (NIPPV) and was intubated. Gas exchange quickly normalized with mechanical ventilation. Family then arrived and provided additional history.

The patient experienced progressive dyspnea for over one year. Four months prior to presentation, she traveled to New York where she was able to hike in the mountains. She denied any tick bites. In the past two months, she was noted to have waxing and waning episodes of facial weakness with occasional drooling, difficulty keeping her head elevated and often falling asleep inappropriately. In the past two weeks, she had developed an acute gastroenteritis. Computed tomography (CT) scans of the chest and head were unrevealing. Given the history, serum testing was sent for myasthenia gravis, Guillain-Barre syndrome (possible Miller-Fisher variant), and Lyme disease. Since these results routinely take days to weeks to return, empiric therapy was started. The patient's most prominent symptoms were bulbar and most consistent with myasthenia gravis. She was started on corticosteroids and pyridostigmine. She clinically improved and was extubated the following day. Neurologic exam was only positive for diplopia and limited adduction of the right eye with leftward and upward gaze. She was started on plasmapheresis and within a few days had significant improvement in serial vital capacity (VC) and maximal inspiratory pressure (MIP) measurements. She was breathing without assistance and was even able to do squats at the bedside. After a few days, acetycholine receptor (AChR) binding, modulating, and blocking antibodies all resulted negative as did Lyme titers. A few weeks later, the antibody to muscle-specific kinase (MuSK) and GQ1b anti-ganglioside antibodies resulted positive. Given the patient's dramatic response to traditional myasthenia treatment with cholinesterase inhibitor and plasmapheresis, the diagnosis of myasthenia gravis was strongly favored. On outpatient follow-up, the patient was continued on pyridostigmine, completely off of corticosteroids and was symptom free.

Discussion

Hypercapnic respiratory failure carries a broad differential diagnosis including disorders of central control, motor neurons, peripheral nerves, neuromuscular junction, respiratory muscles, and primary disorders of the chest wall. This encompasses many conditions including narcotic overdose, medullary stroke, hypothyroidism, amytrophic lateral sclerosis, Guillain-Barre syndrome, critical illness polyneuropathy, tick paralysis, myasthenia gravis, Lambert-Eaton myasthenic syndrome, botulism, hyperinflation from COPD, and severe kyphosis - to name a few.[1] Once a complete history and neurologic exam was obtained, it was clear that our patient had predominantly oculomotor and bulbar symptoms, indicating a neuromuscular disorder, specifically myasthenia gravis as the etiology of the hypercapnic respiratory failure.

In patients with a neuromuscular etiology of respiratory distress, it is imperative to properly assess respiratory muscle function. These patients often have more severe respiratory dysfunction than is clinically apparent. In a hospitalized patient, measurements of the VC and MIP, also called the negative inspiratory force (NIF), can evaluate respiratory muscle strength. The VC is the maximum volume of gas that can be expelled from full inspiration. Once the VC falls below 15 to 20 mL/kg, 60 percent of predicted, or 1 L, the risk of respiratory failure increases significantly. The MIP/NIF is a measure of how strong a patient can inhale. Once the MIP/NIF is less negative than -30 cm H_2O (i.e., -20 cm H_2O), there is a high risk of hypercapnic respiratory failure.[2,3] These values predict the risk for hypercapnia and respiratory failure in patients with Guillain-Barre syndrome and have been extrapolated for use in myasthenia gravis and other neuromuscular diseases.

Myasthenia gravis, in particular, is a disorder of neuromuscular transmission. It is an antibody-mediated, T-cell dependent immunologic attack directed at proteins in the postsynaptic membrane of the neuromuscular junction (i.e., acetylcholine

receptors or receptor-associated proteins). Symptoms include a fluctuating degree and variable combination of weakness in ocular, bulbar, limb, and respiratory muscles. These symptoms progress over weeks to months and often fluctuate with repetitive actions. Diagnostic measures include a decremental response to repetitive nerve stimulation and antibody positivity.[4,5,6]

The AChR antibodies are present in 80-90% of patients affected with myasthenia gravis. Of the 10-20% of patients that lack AChR antibodies, 40-70% have antibodies directed against the MuSK receptor.[4,7] The clinical features common to patients with MuSK antibody positivity include an oculobulbar symptom predominance, though not purely ocular myasthenia gravis. These patients have more prominent respiratory and/or proximal weakness, especially with neck extension. They commonly have no thymic pathology and the role of thymectomy is uncertain. They are less responsiveness to acetylcholinesterase inhibitors but do have a good response to plasma exchange and immunosuppression. Fewer patients with MuSK antibody positivity achieve remission and more remain dependent on immunosuppressive therapy than individuals with typical myasthenia gravis.[4,7,8]

Our patient clearly had features common to myasthenia gravis and particularly the MuSK antibody variant, which was confirmed weeks later when the laboratory tests resulted. Due to the early clinical recognition of these features, our patient received timely treatment, minimizing potential morbidity and mortality.

Conclusion

Hypercapnic respiratory failure is not uncommon, but many clinicians are not familiar with the broader differential diagnoses that can lead to it. Early recognition of the common signs and symptoms of these various diagnoses can significantly alter therapy and be life-saving.

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