CLINICAL VIGNETTE

Sheehan Syndrome and Secondary Panhypopituitarism Unmasked by COVID-19

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Introduction

Hypopituitarism is rare and while true incidence is unknown, one study has suggested an incidence of approximately 29 to 45 people per 100,000.[1] Sheehan syndrome, where severe postpartum hemorrhage and hypotension can lead to infarction of the pituitary gland, is one of the less common causes of hypopituitarism, accounting for only approximately 6% of cases.[2]

The hypopituitary effects of Sheehan syndrome can often present many years after the initial incident of postpartum hemorrhage. In a study of women in France, the average time until diagnosis was nine years.[3] Additionally, COVID-19 has been shown to interact with, and at times suppress, the pituitary hormonal axis. We present a patient presenting with hypopituitarism nearly 30 years after suspected Sheehan syndrome possibly triggered by infection with COVID-19.

Case Report

A 60-year-old woman with hypertension, hyperlipidemia and recently diagnosed squamous cell carcinoma of the right forearm presented with 1 day of chest pressure and left flank pain, which resolved by the time of evaluation, as well as nausea, dizziness and bilateral frontal headache, all present at the time of evaluation. Review of systems was otherwise negative. However, additional history obtained from the patient's daughter noted leg cramps and fever of 102°F two days prior and weakness and confusion with disorientation the morning of presentation. The daughter reported the patient was normally independent with activities of daily living. Remainder of the history was unremarkable, including denial of tobacco, alcohol or recreational drug use. She had no surgical history nor significant family history. Though a life stressor was identified with the recent death of the patient's sister three weeks ago. The daughter reported the patient had distrust of taking medications for fear of addiction. She was prescribed daily amlodipine 2.5mg, aspirin 81mg, atorvastatin 20mg and sertraline 25mg, but was only taking aspirin and atorvastatin.

Vitals include T 98.1° F, heart rate 65, BP 139/63, P 65, and oxygen saturation was 100% on room air. She has low speech and appeared fatigue, though she answered questions appropriately and was able to follow commands. Neurological exam included orientation to year, but otherwise without focal neurological deficit or abnormality. The remainder of the physical exam was unremarkable. Initial labs included sodium of 120, decreased from 139 one month prior, but otherwise normal basic metabolic panel. Serum osmolality was 254, urine osmolality 271 and urine sodium 77. COVID-19 PCR returned positive. Initial imaging with chest radiograph and abdominal CT without contrast were unremarkable. ECG was unremarkable. She was admitted to Medicine for further evaluation and management of hyponatremia suspected secondary to SIADH, possibly induced by COVID-19 infection, new medications or social stressors.

On day 2 further studies included uric acid 2.3 (normal 2.6-8.0), TSH 2.061 (normal 0.35-4.94) and random serum cortisol of 3.9. Nephrology advised, fluid restriction and salt tabs with a minor, below expected correction of sodium. To evaluate the low random cortisol, a cosyntropin stimulation test was normal. Additional thyroid studies included low T4 and T3 with below <0.40. Normal range (0.70-1.49) and free T3 <0.40 (normal 0.58-1.59). Further investigation for central hypopituitarism included FSH 0.6 (normal 25-135), prolactin 1.6 (normal 4.8-23.3), and IGF <10 (normal 41-279). Afternoon ACTH was 11 with reference ranges for morning samples.

Additional history identified two previous episodes of hyponatremia, 3 and 6 years prior. The patient reported her last vaginal delivery 30 years prior, she developed life-threatening hemorrhage due to a retained placenta requiring multiple transfusions. She has remained amenorrheic since this event.

In light of her history and the evaluation suggestive hypopituitarism, an MRI pituitary showed an empty sella without pituitary mass. She was diagnosed with hypopituitarism likely secondary to Sheehan Syndrome and levothyroxine was started. Sodium slowly corrected and was 132 on day of discharge. After discharge, patient reported nausea and weight loss with low morning cortisol (2.5, normal 4.8-10.5). Hydrocortisone was started with symptom improvement.

Discussion

Our patient was diagnosed with hypopituitarism secondary to prior Sheehan syndrome 30 years after her postpartum hemorrhage. Delayed presentation is known, and delay in diagnosis can be attributed to nonspecific symptoms. Some women may recover pituitary function after delivery,[4] and most will be asymptomatic until an acute stress or illness exacerbates symptoms and reveals the underlying disease. Our patient may have

had partial hypopituitarism for many years, with more recent hospitalizations representing recurrent exacerbations.

Establishing the diagnosis was made difficult by the normal serum TSH. Although TSH levels can be normal, obtaining the free T4 is useful instead of relying on reflex studies when evaluating possible hypopituitarism. The patient's prior TSH tests had all been normal, but when she was first tested for free T4 during this admission was found to have a nearly undetectable level. The abnormally high or "normal" levels of TSH may have been due to increased sialylation and reduced metabolic clearance.[5]

COVID-19 may have been an acute stressor. Our patient was incidentally diagnosed with COVID-19 but was otherwise asymptomatic. Prior reports have detailed hypophysitis associated with COVID-19.[6] Previous SARS-CoV has been associated with hypocortisolism,[7] and it is possible that COVID-19 may also interfere with the hypothalamic-pituitary-adrenal axis.

In conclusion, our patient was diagnosed only after many years, multiple presentations, and development of symptoms that required repeated diagnostic testing. It is important to consider the limitations of reflex testing and the impact of different diseases such as COVID-19 on secondary panhypopituitarism.

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