Title: A Rare Presentation of Catatonia due to Primary Adrenal Insufficiency

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Introduction

Primary adrenal insufficiency (PAI), also called Addison's disease, is an endocrine disorder in which the adrenal glands are unable to produce an adequate amount of glucocorticoids and/or mineralcorticoids. Acute adrenal insufficiency can present with neuropsychiatric symptoms including depression, anxiety, cognitive complaints, and changes in mental status progressing from decreased responsiveness to stupor and coma(1). It has been estimated that the prevalence of neuropsychiatric symptoms in PAI ranges from 64-84%. Though there are no case reports in the recent literature, catatonia has been associated with PAI in historical case reports(2). Therefore, PAI as a cause of catatonia may be under-recognized by psychiatrists and endocrinologists. As PAI can be potentially life threatening, it is important for the consultation-liaison psychiatrist to be able to recognize the condition in the context of vague, nonspecific neuropsychiatric complaints. Here, we present a case of catatonia presenting secondary to PAI and review the literature of neuropsychiatric symptoms associated with PAI.

Case

Ms. G was a 51 year old Caucasian female with PAI, type I diabetes, gastroparesis, neuropathy, and retinopathy. She also had a history of depression and anxiety managed with sertraline 75mg for several years. Just prior to admission to our hospital, Ms. G had been at an outside hospital for 30 days for management of diabetic ketoacidosis (DKA). Unfortunately, detailed records from that hospitalization were not available.

The day after Ms. G was discharged from the outside hospital she returned to the outside emergency department for intractable nausea and vomiting. She was afebrile, had a blood pressure of 130/59, pulse of 144, and normal respiratory rate and oxygen saturation. Labs were notable for sodium of 135 (reference 136-145), potassium of 3.2 (reference 3.5-5.1), bicarbonate 19 (reference 22-29), glucose 220 (reference 70-110), and a venous blood gas pH of 7.58 (reference 7.32-7.43). DKA was ruled out based on laboratory results. Due to the inability to explain her nausea and vomiting, she was subsequently transferred to our quaternary referral hospital for further evaluation and treatment of presumed gastroparesis.

Upon arrival Ms. G was only minimally responsive to questioning and staring spells were noted. Home medications included dronabinol 5mg three times daily, Humalog insulin, hydrocortisone 20mg twice daily, furosemide 40mg three times daily, pregabalin 200mg twice daily, pantoprazole 40mg twice daily, simvastatin 20mg nightly, and ondansetron 4mg three times daily as needed. On exam, she was oriented to person and place only and mute; otherwise the physical exam was documented as normal. Admission labs were significant for potassium of 2.9 (reference 3.5-5.5), glucose of 218 (reference 70-99), and magnesium of 1.1 (reference 1.6-2.9). She was continued on home sertraline 75 mg for depression. For unclear reasons, home steroids for PAI (hydrocortisone 20 mg BID) were not continued on admission. Ms. G was given dronabinol, ondansetron, granisetron, and mirtazapine for management of nausea and vomiting, symptoms that were attributed to gastroparesis. Oral intake was poor during Ms. G's early hospitalization and she had notable urinary retention. On hospital day (HD) 8 she had a syncopal episode due to hypotension.

Initially it was suspected by Ms. G's medicine teams that her chronic gastrointestinal symptoms, lack of response, and staring spells were due to an underlying psychiatric disorder or malingering. The gastroenterology consult service did not feel that her pain and nausea were consistent with gastroparesis due to their persistence and chronicity. Due to these concerns, our psychiatry consult team was consulted and saw the patient on HD 8. Ms. G was unresponsive to questions during the initial consult. Vital signs were within normal limits with the exception of blood pressure of 115/46. On exam Ms. G was lying in bed with arms crossed. The exam was also notable for immobility, mutism, staring, catalepsy, posturing, rigidity, negativism, and waxy flexibility, scoring 21 on the Bush Francis Catatonia Rating Scale. Mood, thought process, thought content, and perceptions were unable to be obtained due to mutism. The physical exam was otherwise unremarkable.

Further history obtained from the patient's mother revealed that Ms. G had many hospitalizations for DKA and usually experienced staring spells and decreased reactiveness during those hospital stays. Up until the current presentation the spells had lasted only a few days and Ms. G had maintained some interaction with her mother. Her mother reported that the spells had never been as severe as the current one. She had been treated for depression by her primary care physician, but there was no known history of psychiatric hospitalizations or suicide attempts.

Our team recommended an Ativan challenge of 2 mg intravenously. The challenge did not yield improvement in catatonic symptoms yet also did not sedate Ms. G. Higher doses of Ativan also were not helpful. At this time the patient was no longer able to take medication by mouth, so trials of other medications, such as memantine or zolpidem, were not able to be attempted.

Neurology was consulted and saw the patient on HD 9. The neurological exam was significant for eyes that open spontaneously but not to auditory stimuli; the patient was nonverbal, did not follow commands, was resistant to eyelid opening, and had varying tone in upper extremities, sometimes normal and sometimes waxy in character. The exam was also notable for a positive palmomental reflex. Reflexes were normal and clonus was not elicited. Neurology suspected either catatonia or akinetic mutism and recommended an EEG and a brain MRI w/o contrast to investigate for a primary CNS pathology such as stroke or malignancy. EEG showed the presence of moderate generalized slowing, indicating moderate diffuse encephalopathy. MRI revealed no evidence of acute hemorrhage, mass effect, or infarct. By HD

11 the patient had a nasogastric tube and neurology recommended starting methylphenidate 5 mg daily as a trial for akinetic mutism versus catatonia. She was noted to be slightly more alert the following day, so methylphenidate 5 mg was increased to 10 mg.

Endocrinology initially saw Ms. G on HD 13 for blood glucose management while on nasogastric tube feeds. Endocrinology also noted that the patient had been off her home dose of steroids which she takes for PAI. However, there was no record of when or where the patient was diagnosed with PAI. To confirm the diagnosis, endocrinology recommended a random morning cortisol and ACTH to verify the diagnosis. The cortisol level was <0.4 mCg/dL (reference 8-25), and she was started on hydrocortisone, 20 mg daily and 10 mg in the evening on HD 14.

The patient's responsiveness after being treated with hydrocortisone was variable at first though nursing reports noted that the patient's wakefulness was slowly improving. On HD 16 neurology increased methylphenidate to 10 mg BID to further improve alertness. On HD 18 her ACTH level returned at 82 pg/mL (reference 7.2-63), confirming PAI. Fludrocortisone 50 mCg by mouth was subsequently added. Ms. G gradually became more interactive and conversant by the end of the third week of her hospitalization. She did not recognize her providers or remember earlier aspects of her hospitalization. Of note, she had a relapse of catatonic symptoms for a two-day period when she removed her NG tube and did not receive steroids, though had an improvement in mental status when steroids were resumed.

Ms. G was started on methylphenidate and hydrocortisone in close succession. To ensure that improvement was due to treatment of PAI rather than treatment with methylphenidate, the latter was discontinued on HD 24. Ms. G continued to improve over the remaining week of her hospitalization and was at baseline at time of discharge. Given her improvement in the absence of methylphenidate it was determined that the catatonia resolved due to treatment of PAI.

Discussion

PAI results in inadequate production of endogenous corticosteroids. These steroids are involved in electrolyte balance and have a variety of effects on the endocrine, cardiovascular, musculoskeletal, central nervous, hematologic, and immune systems(3). The prevalence of PAI in Western countries is estimated to be 100-140 cases per million, and PAI is most commonly due to autoimmune disease. Untreated PAI can be life threatening as corticosteroids are involved in energy, salt, and fluid homeostasis. Physical symptoms of an acute PAI crisis are nonspecific and include weakness, fatigue, orthostatic hypotension, abdominal pain, nausea, vomiting, and musculoskeletal pain(2,3). Lab abnormalities include hyponatremia and hypokalemia, though normal electrolyte levels may be seen in 20-30% of patients(4).

In this case, Ms. G's symptoms of mutism, negativism, waxy flexibility, and catalepsy/posturing met the diagnostic criteria of catatonia in the DSM-V, and her Bush-Francis Catatonia Rating Scale score of 21 supported this diagnosis(5). Additionally, the patient was inattentive, disoriented, and had generalized slowing on EEG, consistent with a diagnosis of delirium. These findings reinforce recent research that shows that delirium and catatonia can coexist, despite the DSM-V criteria that preclude the diagnosis of both conditions concurrently(6).

Although Ms. G did take several serotonergic medications during her hospital stay her symptoms were more consistent with catatonia than serotonin syndrome. Serotonin (5HT) syndrome is a clinical diagnosis that is a triad of autonomic instability, neuromuscular changes, and altered mental status due to increased 5HT in the CNS. Using the Hunter Toxicity Criteria to assess for serotonin syndrome, she did take serotoninergic agents but she did not have spontaneous, inducible, or ocular clonus, and did not have tremor or hyperreflexia on multiple neurological examinations(7).

Much of our knowledge about the neuropsychiatric symptoms of PAI derives from case series and case reports published primarily from the 1940s-1960s. These studies recognized a variety of neuropsychiatric symptoms associated with PAI including irritability, depression, anxiety, memory impairment, disorientation, delusions, and hallucinations. A 2006 article published in *The Journal of Neuropsychiatry and Clinical Neurosciences* by Anglin et al. summarized case reports of 25 patients with neuropsychiatric findings associated with Addison's disease that were published since 1940. In these case reports 14 patients had delusions, 11 had depression, 10 had hallucinations, 6 had anxiety, 5 had disorientation, 2 had catatonia, and 2 demonstrated self-mutilation. In the majority of these cases symptoms improved within one week of starting steroid replacement. However, in some cases the mood symptoms reoccurred when the patients had another PAI crisis, which is similar to Ms. G who has had milder symptoms associated with PAI crisis in the past before this current episode. Mood symptoms were common in milder cases while psychosis and mental status changes were associated with severe PAI crisis. Of note, EEGs often were abnormal in patients with neuropsychiatric symptoms due to PAI and the most common abnormality was diffuse slowing, similar to Ms. G's EEG findings(2).

PAI as a cause of neuropsychiatric symptoms, including catatonia, is likely under-recognized. A review of the recent literature yielded only one 2012 article published in the *Journal of ECT* by Grover et al. In this case report, a patient had PAI with hyponatremia and catatonia, and catatonia was attributed to hyponatremia, though the catatonia persisted even with resolution of hyponatremia. In that case, catatonia remitted with ECT and treatment of PAI, suggesting that treatment of PAI rather than resolution of hyponatremia alone resolved the catatonia. In the article PAI was not explicitly considered as a cause of the catatonia(8). It is worth noting that though PAI is most commonly associated with electrolyte abnormalities, normal electrolyte levels can be seen in 20-30% percent of patients with PAI, making the diagnosis even more challenging to recognize(4).

This case was presented at an endocrinology case conference at our institution, and the endocrinologists present were unaware of catatonia as a potential manifestation of PAI. Indeed, due to the historical nature of the literature, the neuropsychiatric symptoms of PAI have been called a “forgotten phenomenon”(2). Catatonia as a manifestation of PAI is acknowledged in textbooks however, which may serve as a better resource for synthesizing historic literature that online databases(9,10).

In Ms. G’s case, her PAI diagnosis and the hydrocortisone she took at home were documented in the electronic medical record. Chart review shows that the patient was intended to be continued on her home dose of hydrocortisone, but this was not ordered. It is unclear how long the patient went without her home dose of hydrocortisone prior to admission to our hospital.

Had medical providers been more aware of the complications of untreated PAI, and with greater scrutiny of the patient’s medications, catatonia may have been recognized earlier or even prevented altogether. Though catatonia is an uncommonly reported symptom of severe PAI, it is important for the consult-liaison psychiatrist to recognize the cause early as untreated PAI can lead to severe complications, including coma and death. This unique case equips psychiatrists and other medical providers to recognize, diagnose, and treat catatonia secondary to PAI, and highlights the value of familiarity with both historic and recent medical literature.

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