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Acute Mania in a Patient With Primary Adrenal Insufficiency Due to Autoimmune Adrenalitis: A Case Report

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We describe a rare case of acute mania in the setting of autoimmune adrenalitis. A 41-year-old male with no previous psychiatric diagnoses presented with impulsivity, grandiosity, delusions of telepathy, and hyperreligiosity following a previous hospitalization for an acute adrenal crisis and 2 subsequent days of low-dose corticosteroid treatment. Workups for encephalopathy and lupus cerebritis were negative, raising concern that this presentation might represent steroid-induced psychosis. However, discontinuation of corticosteroids for 5 days did not resolve the patient's manic episode, suggesting that his clinical presentation was more likely new onset of a primary mood disorder or a psychiatric manifestation of adrenal insufficiency itself. The decision was made to restart corticosteroid treatment for the patient's primary adrenal insufficiency (formerly known as Addison disease), coupled with administration of both risperidone and valproate for mania and psychosis. Over the following 2 weeks, the patient's manic symptoms resolved, and he was discharged home. His final diagnosis was acute mania secondary to autoimmune adrenalitis. Although acute mania in adrenal insufficiency is quite rare, clinicians should be aware of the range of psychiatric manifestations associated with Addison disease so that they can pursue the optimal course of both medical and psychiatric treatment for these patients.
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KEY WORDS: mania, psychosis, Addison disease, autoimmune adrenalitis, corticosteroids

BACKGROUND

Autoimmune adrenalitis is the most common cause of primary adrenal insufficiency (PAI), formerly known as Addison disease, in the Western world, affecting an estimated 35 to 60 million people.[1–3] Adrenal insufficiency has been associated with a myriad of potential neuropsychiatric manifestations including psychosis, depression, mania, and anxiety.[4–6] While the role of hypercortisolemia (Cushing disease) in psychiatric conditions and the association between corticosteroids and psychosis have been well documented,[6,7] there is a paucity of literature regarding the relationship between adrenal insufficiency and psychotic[8] or manic syndromes. Cases of psychosis or mania secondary to PAI are even rarer, with the cases that have been reported primarily involving *secondary* adrenal insufficiency caused by hypopituitarism. For this reason, we present an interesting case of acute mania in the setting of autoimmune adrenalitis.

CASE DESCRIPTION

A 41-year-old male with no previous psychiatric history and a recent hospitalization for adrenal insufficiency but no other significant medical history presented to the emergency department with symptoms of acute mania including impulsivity, grandiosity, delusions of telepathy, hyperreligiosity, and decreased need for sleep. The patient had been hospitalized for 2 weeks at a neighboring hospital for undifferentiated shock, during which he was admitted to the intensive care unit after experiencing hypotension, tachycardia, fever, and chills. A full infectious diseases workup was completed and was unremarkable. An echocardiogram was obtained which showed a normal ejection fraction and no evidence of systolic/diastolic dysfunction. The

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patient was ultimately diagnosed with acute adrenal crisis secondary to adrenal insufficiency and was maintained on high-dose steroids while in the hospital. After his acute adrenal crisis resolved, the patient was discharged on hydrocortisone 10 mg twice daily. Approximately 2 days later, the patient began developing the manic symptoms described above and presented to a tertiary care hospital.

Results of an encephalopathic workup (HIV, rapid plasma reagin, B_{12} level, complete blood count, complete metabolic panel, catalytic transfer hydrogenation, urine drug screen, urinalysis, blood alcohol, salicylate, and acetaminophen levels) were all negative, and results of an autoimmune workup for lupus cerebritis, including antinuclear antibody test, anti-double-stranded DNA antibodies, and complement component C3/C4 blood tests, were within normal limits. Results from a cosyntropin stimulation test strongly suggested PAI, and 21-hydroxylase antibodies were positive several days later, consistent with autoimmune adrenalitis.

Also, an endocrine workup detected low levels of insulin-like growth factor-1, although the patient had no history of growth hormone deficiency as a child and had never been on growth hormone replacement therapy. Furthermore, the patient exhibited low testosterone levels (90 ng/dL) despite normal levels of follicle-stimulating hormone and luteinizing hormone. However, the patient did not exhibit symptoms of hypogonadism such as decreased libido or muscle mass. Furthermore, magnetic resonance imaging of the brain without contrast revealed no large pituitary mass, decreasing the concern for a central cause of the patient's laboratory results.

On presentation, steroid-induced psychosis was originally suspected given the patient's newly initiated treatment; thus, steroids were discontinued. However, steroid-induced psychosis is uncommon at the very low doses administered to the patient (10 mg hydrocortisone twice a day) and normally has a longer latency time to symptom onset.[9] According to the Boston Collaborative Drug Surveillance Program, 18% of patients receiving a dose of prednisone higher than 80 mg/d exhibited severe psychiatric disturbances (including psychosis), compared with 4% of patients receiving between 41 and 80 mg/d and 2% of patients receiving <41 mg/d.[10]

An underlying or new onset primary mood disorder was also considered. Although the patient had no documented psychiatric history of depression, his family reported that he had exhibited a gradually worsening dysphoric mood and fatigue over the previous 4 years, suggesting that his most recent symptoms could have been suggestive of a manic episode in the setting of an underlying mood disorder. However, neither the patient nor his family reported any history of manic or hypomanic symptoms, and the patient's dysphoric mood could have been the result of adrenal insufficiency, which is commonly associated with fatigue and depression.[8] Although less likely, the patient's presentation could have been consistent with late-onset bipolar disorder, as a recent theoretical model proposed that there are 3 age-of-onset subgroups within bipolar disorder (onset at mean ages of 17, 27, and 46).[11] The patient, at 41 years of age, would have fallen into the third subgroup; however, the timing of symptom onset following an acute Addisonian crisis points to medical causes as the likely culprit. Five days after the steroids were discontinued, the patient's symptoms had not improved and he began to develop hyponatremia and hypotension. At this point, the diagnosis pointed more heavily toward psychosis secondary to PAI.

The patient was started on risperidone 1 mg twice a day for acute mania and psychosis, which was later increased to 1 mg in the morning and 2 mg in the evening. Valproate 1500 mg at bedtime was also started for mania. After 5 days off steroids and no reduction in his manic symptoms, the patient was started on hydrocortisone 10 mg in the morning and 5 mg in the evening and 0.2 mg/d of fludrocortisone for adrenal insufficiency. Two days later, his hydrocortisone was switched to prednisone 5 mg due to patient preference. On the eighth day of his hospital stay, the patient was transferred to an inpatient adult psychiatric unit where he would remain for 11 days.

Upon transfer to the inpatient psychiatric unit, the patient continued to exhibit symptoms of mania such as pressured speech, flight of ideas, loosening of associations, distractibility, and overfamiliarity and intrusiveness with peers. His symptoms slowly diminished throughout the hospitalization and the patient was discharged home on risperidone 3 mg at bedtime, valproate 1500 mg at bedtime, prednisone 5 mg/d, and fludrocortisone 0.2 mg/d, with instructions to follow up with outpatient endocrinology and psychiatry.

At an outpatient psychiatric appointment, the patient reported complete resolution of his psychiatric symptoms—including paranoia and delusions. On examination, the patient was euthymic, and no

auditory or visual hallucinations or delusions were reported. The patient demonstrated circumstantial thought process at times but was overall coherent and logical with fair insight and judgment. He was adherent to the prescribed psychiatric medications and was tolerating them with minimal side effects. He admitted to mild dizziness when standing from a seated position but denied lightheadedness or abdominal pain. However, the patient had endorsed dizziness before his adrenal crisis and hospitalizations, suggesting that the dizziness may have been related to his adrenal insufficiency. In addition, the patient reported sleeping 6 hours every night (his normal amount), and his family concurred that the patient had returned to his baseline mental status.

DISCUSSION

PAI, also known as Addison disease, is a rare endocrine disorder in which the adrenal gland fails to produce both cortisol and mineralocorticoids in adequate amounts. Present in roughly 1/100,000 people in the United States,[12] Addison disease is well known to be associated with depressed mood and fatigue secondary to deficient levels of cortisol and mineralocorticoids.[8] However, there is a dearth of literature describing other psychiatric manifestations of PAI, including psychosis and/or mania. When reported, these symptoms have generally presented in the setting of secondary adrenal insufficiency (hypopituitarism).[6,13]

Although Addison disease itself was first described in 1849, its association with psychosis was not reported until almost a century later in 1942, when Engel and Margolin described the frequency of "abnormal psychic states" observed in patients with the disease.[14] In 1958, McCulloch and Calverley became the first to provide long-term documentation of psychosis in a patient treated for an Addisonian crisis.[14] Once the patient's serum chemistry normalized, he became acutely psychotic and was thereafter in and out of the Provincial Mental Hospital in British Columbia over the course of 2 years. Since McCulloch and Calverley's documentation of this case of acute psychosis, reports of similar manifestations in PAI have been few and far between. As years have come and gone, descriptions of psychiatric symptoms of PAI have become an historic relic of the medical literature, a "forgotten phenomenon."[7]

In another of the handful of cases that have been reported, Farah et al[8] described the case of a 63-year-old male with Addison disease and psychosis that was resistant to treatment with antipsychotic medications. The psychosis only resolved following 3 days of hydrocortisone treatment. In 2021, Abdulla[15] reported the first case of a psychiatric manifestation of Addison disease resembling bipolar disorder in a 53-year-old male with tuberculous adrenalitis. This patient's mania resolved after treatment with steroids, illustrating the association between his manic symptoms and hypocortisolic state. Similar to our case, that patient's presentation was unique in terms of its classification of the psychiatric symptoms as mania (impulsivity, grandiosity, pressured speech, elevated mood), which is distinct from psychosis (auditory and visual hallucinations) and/or unipolar depression previously described in Addisonian crises. In another unique case, a 51-year-old female presented with catatonia attributed to PAI.[16] Interestingly, her symptoms did not improve following first-line treatment with IV lorazepam for catatonia, but she did improve following treatment with methylphenidate and hydrocortisone. It was suspected that the resolution of the patient's catatonia was mostly associated with the corticosteroid treatment (as the patient continued to demonstrate significant improvement over the week before her discharge after discontinuation of methylphenidate).[16]

Although they are tentative, several theories have been proposed to explain the relationship between psychiatric symptoms and PAI. First, it is possible that hyponatremia-induced swelling of the brain could yield a myriad of neurologic disorders related to consciousness and cognition. As areas of the brain become compressed, compression of certain regions such as the hippocampus can cause a wide range of psychiatric manifestations. Second, decreased cerebral glucocorticoid stimulation from brain swelling can increase overall neural excitability, lower hippocampal glucocorticoid levels, and impair function of the frontal circuit and processing of memory.[8,17–20] Finally, decreased feedback inhibition from glucocorticoids results in greater release of propiomelanocortin (POMC). Since POMC from the anterior pituitary is ultimately processed to yield endorphins, it is apparent that increased POMC production could be responsible for hallucinations, mania, and other elements of psychosis. In general, continued investigation is necessary to further elucidate mechanisms responsible for mania and psychosis in hypocortisolism.

While acute mania and adrenal insufficiency are both well known in the psychiatric and endocrinologic fields, respectively, it is important for practicing physicians to be aware of the rare connection between adrenal insufficiency and psychiatric symptoms. A major factor responsible for the relative lack of familiarity among clinicians is related to the fact that the correlation between corticosteroid treatment (and states involving excess steroids) and psychosis is a well-established phenomenon that is encountered fairly commonly during medical training and practice.[6] Because this association is so well known, many physicians do not consider the fact that the opposite state—steroid deficiency—can produce similar psychiatric manifestations.

CONCLUSIONS

Both the primary condition, PAI, and its treatment (steroids) are associated with acute psychosis. It is thus important to consider the timing of the symptoms and the patient's corticosteroid dose when considering initial treatment. Although theoretically possible, low-dose steroids are unlikely to induce psychosis. Regardless of the cause of acute psychosis (primary psychiatric condition versus steroid-induced versus a manifestation of adrenal insufficiency), atypical antipsychotics and mood stabilizers represent the first-line approach to treatment. When adrenal insufficiency is present, steroid treatment should be added to the psychiatric treatment regimen. It can be difficult to determine the exact cause of psychosis. Doing so may require months to years of monitoring before it can be concluded that the psychosis manifested without the presence of a primary mood disorder. However, time course and duration of symptoms can help inform one's differential diagnosis. In the case described here, the patient's manic symptoms resolved quite abruptly with treatment, further suggesting a medical cause rather than an underlying bipolar disorder for his symptoms. Ultimately, the clinical presentation described in this case report blurs the line between physiological medicine and mental health. A multidisciplinary team involving primary care physicians, psychiatrists, and endocrinologists is essential for timely management so that both factors can be accounted for during treatment of PAI.

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