

Sustained Corticosteroid-Induced Mania and Psychosis Despite Cessation: A Case Study and Brief Literature Review

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Abstract

Objective: Corticosteroids generally result in short-lasting neuropsychiatric symptoms following cessation, but the following case highlights an unusually long-lasting course of symptoms in a patient following near immediate cessation of medication, despite medication management and electroconvulsive therapy. The case presentation will be followed by a discussion of the presentation, treatment, mechanism, and management of steroid induced neuropsychiatric symptoms.

Methods: The patient was followed from symptom onset to resolution.

Results: The patient's symptom course was unusually long and required a long course of multi-modal therapy.

Conclusions: Corticosteroids are commonly used medications both in a wide variety of medical settings, and despite this, their neuropsychiatric effects are poorly understood. The affective and behavioral symptoms, in particular mania and psychosis, can be unpredictable and challenging to treat as in our patient, who developed a long lasting psychotic episode on high dose steroids, despite having tolerated them multiple times in the past and whose very marked symptoms persisted, despite discontinuation and treatment for almost 6 months.

Keywords: Psychosis; Corticosteroid; Treatment; Duration; Risk

Introduction

Corticosteroids are very commonly prescribed among both hospitalized and outpatient medical and surgical patients. While many of the common endocrinological and pathological side effects of corticosteroids are well understood, the incidence, presentation, and treatment of neuropsychiatric manifestations have not been commonly characterized and studied. Though most practitioners are familiar with the term "steroid-induced psychosis," the affective and behavioral symptoms related to corticosteroid use are varied and can be unpredictable. In many cases, the appropriate treatment and its duration can be elusive. We present a case of corticosteroid induced mania and psychosis, highlighting a highly unusual course and resolution, as well as a prolonged duration despite an aggressive treatment course, including electroconvulsive therapy that has not been noted in medical literature based on our review. The case is followed by a discussion of incidence, risk factors, and treatment options.

Case Presentation

A 58 year old male with a history of general anxiety disorder who was brought into the emergency room on an involuntary hold for unusual behavior and an inability to care for himself. He had been seen wandering around a store parking lot with delusional thinking and pressured speech. On exam, his thought process was tangential, confused and circumstantial. The patient denied auditory or visual hallucinations at the time, and the patient and his family attributed his condition on admission to his current steroid use. His urine toxicology screen was negative, and there was no history of prior drug or alcohol use. Mr. A. was alert and oriented to person, place, time, and situation. The patient had no other significant prior psychiatric history, other than a diagnosis of anxiety, including no previous history of reported mania, psychosis or bipolar disorder. An MRI of his head, blood count with the exception of platelet count, chemistry panel, thyroid studies, and ammonia level were normal.

The patient had a history of idiopathic thrombocytopenic purpura which had been diagnosed 9 years prior to this admission. He had had

his first relapse two years after diagnosis and then again four years subsequent to that, and a third time about two years prior to this admission. He was on a 90 mg prednisone taper for his first two relapses, each just over two months in duration, and a 100 mg prednisone taper for the third, lasting about four weeks. He was on a taper for about four weeks just three months prior to this admission because of biopsy negative mediastinal lymphadenopathy which had subsequently resolved. The patient had never had a prior reaction to steroids. Then almost eight weeks prior to admission, he had a notable drop in platelets, and he was started on four day of 40 mg of dexamethasone bursts every three weeks. When he was on his third cycle, his behavior changed, and per his family, he was behaving in a bizarre manner and could not care for himself.

The patient was admitted to the medicine floor for low platelets, and his dexamethasone was stopped. He continued to be inappropriate and to demonstrate evidence of mania and psychotic symptoms. Psychiatry was consulted, and the patient was started low dose quetiapine. He was observed to be naked at night in his room, to be praying in unintelligible speech, and to have disorganized thoughts and manner of speaking.

After 10 days admission to medicine, the patient's platelets were stabilized, and he was transferred to inpatient psychiatry for further stabilization of his symptoms which included minimal sleep. The patient was started on a dose of nighttime quetiapine which was up-titrated to 200 mg in the morning and 600 mg at bedtime. Sleep improved, and the patient became more directable. However, he continued to engage in

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hyper-religious behaviors such as “speaking in tongues” and chanting for hours. A short course of aripiperazole to which he had a dystonic reaction followed by 5 days of electroconvulsive therapy brought about no additional improvement. High-dose quetiapine was re-started, and the patient gradually improved over a total of almost 6 months.

Conclusion

Corticosteroids have been in use for over six decades to treat a wide variety of pathologies from asthma and allergies to autoimmune diseases and dermatologic conditions. Corticosteroid use is common, and up to 10% of inpatients receive steroids, while about 2 to 3% of the general population is on long-term glucocorticoid treatment [1]. It is estimated that about 20% of patients who receive high dose corticosteroids, defined as greater than 40 mg of prednisone or its equivalent, will develop a psychiatric disorder like mania, psychosis, or depression severe enough that with condition will require pharmacotherapy [2,3]. In a large United Kingdom study that examined steroid use in over 350,000 patients, it was determined that suicides and suicide attempts were almost seven times as common in those who had been prescribed steroids for a condition when compared with those with the same condition who had not received the medication. Additionally, mania was over four times as common, and disorientation and confusion were noted at five times the rate. The overall incidence of neuropsychiatric effects of corticosteroids is not entirely known with reports ranging anywhere from 2 to 60%, and with a weighted average of 6% in meta-analyses. The majority of patients, 60 to 85%, will develop symptoms within the first week of treatment, and about 90% within six weeks of initiating treatment, with at least half noting symptoms within the first ten days as did our patient [4].

Manic episodes constitute the most common manifestations of corticosteroid-induced neuropsychiatric disorder (CIPD), accounting for about one-half of all psychiatric referrals and make up an estimated 40% or more of those with a neuropsychiatric manifestation. Psychotic symptoms are prominent among those with mania, seen in about 30 to 40% of those patients. The literature suggests that patients who suffer from steroid-induced mania are more likely to demonstrate psychotic features than are patients who have non-substance induced mania. Persecutory delusions, auditory hallucinations, and disorganized behaviors are prevalent psychotic symptoms among such patients. Patients usually present with prominent signs of mania including excitation, pressured speech, euphoria, hyperactivity, and irritability. In one study that reported on eighteen patients who were referred to for psychiatric consultation over a 10 year period, of the 2069 patients referred, 18 were noted to have met DSM IV criteria for CIPD and had no prior psychiatric history. The majority of those patients, fifteen of the eighteen in total, presented with mania, and three of those also had psychotic symptoms [5-8].

Even withdrawal of corticosteroids can initiate the commonly termed “withdrawal syndrome,” the latter resulting in anorexia, depression, fatigue, poor concentration, depersonalization, and psychosis with additional symptoms including lability, somatic concerns such as paresthesias and faintness, poor memory and focus, depersonalization, and in some case, suicide [8,9]. Such side effects of withdrawal are typically short-lived, but have been reported to last anywhere from two to eight weeks post-termination [8].

Prior psychiatric history, age, underlying disease, and gender have been postulated to serve as risk factors for the development of CIPD. However, studies have shown mixed results. Hall et al. found no correlation with a history of a previous psychiatric condition or

CIPD, while another study by Wada et al. nine of eighteen patients had recurring CIPD, suggesting that treatment with corticosteroids had induced a mood disorder that was self-propagating. With respect to age, there appears to be no association with CIPD. Neuropsychiatric manifestations also do not appear to be associated with a specific underlying disease either with the exception of systemic lupus erythematosus which increases the risk by a factor of two or more. Gender however does pose a risk. Even when controlling for the higher incidence of certain medical conditions requiring corticosteroid treatment in women, neuropsychiatric symptoms are up to six times more common in women when compared with men. However, as in our patient, previous tolerance of corticosteroids is not correlated with a reduced frequency of neuropsychiatric side effects on re-introduction of the medication [9,10].

There is also a dose dependent relationship that causes the development of neuropsychiatric symptoms with fewer than 2% of patients being affected at doses less than 40 mg per day of prednisone or its equivalent, while around 5% of those dosed between 40 and 80 mg will have psychiatric manifestations. Nearly 1 in 5 of those on 80 mg or more per day will be affected. Mr. A was taking the equivalent of just over 260 mg of prednisone daily. While there are case reports of psychiatric manifestations in patients on even very low doses, there does appear to be a dose dependent relationship, and the average dose of those who present with psychosis is around 60 milligrams [9-12].

There are no FDA-approved medications to manage steroid-induced neuropsychiatric symptoms. Therefore, treatment is based on anecdotal evidence and case reports as well as a few small, scattered case series. However, the first step in managing any steroid-induced psychiatric symptom is to reduce the dosage of the medication to that of less than 40 mg per day of prednisone or its equivalent, and ideally, if possible, to stop the drug. About three-fourths of psychiatric symptoms will remit on discontinuation alone [11,13]. Lewis and Smith [14] found that approximately 90% of patients treated with a taper only achieved recovery. Eighty-four percent of those treated with neuroleptics recovered. All of those treated with electroconvulsive therapy (ECT) or taper in addition to either lithium or neuroleptics had symptom resolution in case reports and small studies, but our patient appears to stand out in terms of his long duration of symptoms with minimal response to ECT.

For depressive symptoms, tri-cyclics are generally avoided as their anti-cholinergic effects can exacerbate or worsen delirium states which can often be coexistent. Serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors have been reported to have been successfully used in case reports. Lithium has also been used to treat depression alone.

Carbamazepine, lamotrigine, and valproate are effective in treating corticosteroid induced psychosis and/or mania. In multiple studies [4-6], phenothiazines have proven effective. Haloperidol can be used to control the majority of psychotic reactions to corticosteroids. Olanzapine and risperidone have been used to treat psychiatric reactions including mania and depression, and in one report, risperidone proved effective in treating a patient in whom a reduction in corticosteroids was not possible in the short term. In a case study of an adolescent steroid induced mania and psychosis showed Seroquel to be useful in resolving symptoms over a matter of weeks. Brown et al., [15] found that olanzapine was effective in 92% of patients who suffered from mania or mixed symptoms at doses ranging from 2.5 to 20 milligrams per day, resolving symptoms over no more than a five week period.

In half of patients, termination of the steroid will lead to symptom resolution within about two weeks, while in 90% of patients, symptoms will cease within 6 weeks of cessation. Complete recovery is ultimately expected in nearly all patients, though this can be out as far as six months from treatment cessation. It is not known whether the addition of anti-psychotics or other medications results in or hastens symptom resolution, but it is likely that, at least, its use controls symptoms [7,8,12].

There may be useful symptom prevention strategies when giving patients steroids, though none would have directly applied to our patient. Dosing plays a significant role in the development of neuropsychiatric symptoms, thus minimizing the dose is a primary preventive strategy with the goal of maintaining a 40 mg daily dose of prednisone or its equivalent. Patients who are at higher risk for psychiatric complications, specifically those with a damaged blood brain barrier and those with hypoalbuminemia, which increases the risk by a factor of two [16], should be carefully considered for steroid therapy. Avoiding other drugs that may increase circulating levels of corticosteroids is also important. For example, Clarithromycin, a P450 CYP 3A4 inhibitor that prevents breakdown of prednisolone, prednisone's biologically active metabolite, has been shown to incite mania [17]. There are small trials that have supported the use of prophylaxis, particularly in those with a prior history of steroid induced psychosis or mania using such agents as olanzapine and lithium [13]. Dosing regimen, such as pulsed dosing, daily divided dosing, and alternate day dosing, does not seem to reliably prevent the development of neuropsychiatric symptoms, and in fact the latter has been associated with rapid cycling of moods [18].

Corticosteroid induced neuropsychiatric symptoms are not uncommon. Despite this, there are few sizable studies on their presentation and management. Medication cessation or dosage should always be the first line of treatment, and the addition of anti-psychotics is supported by the literature. Though further research is needed to determine whether such medication hastens or causes symptom resolution, it would appear to contain symptoms, though it did not have an impressive effect in the patient described herein. ECT has, in small reports, been shown to be highly effective in treating steroid induced symptoms, though, again, this was not the case in this patient. The prognosis for patients in general is excellent with expected complete resolution in nearly all of those affected, though this may take several weeks or even many months.

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