Acute Psychosis Following Corticosteroid Administration

Sana Elham Kazi, Sheikh Hoque

1. Psychiatry, Brookdale University Hospital Medical Center, Brooklyn, USA

Corresponding author: Sana Elham Kazi, elhamkazi@gmail.com

Abstract

Glucocorticoids are commonly used to treat endocrine as well as non-endocrine disorders. Unfortunately, these agents are associated with multiple adverse effects affecting various organ systems. A 55-year-old woman with type 2 diabetes mellitus and hypertension with no past psychiatric history was admitted to the hospital for acute hypoxic respiratory failure secondary to coronavirus disease 2019 (COVID-19) pneumonia. The patient did not exhibit any psychiatric symptoms during the initial admission. However, she was re-admitted three days after the initial discharge, presenting with acute psychosis following the intravenous dexamethasone administration for seven days. Neuropsychiatric effects of glucocorticoids include depression, mania, agitation, mood lability, anxiety, insomnia, catatonia, depersonalization, delirium, dementia, and psychosis. Clinicians should be aware of the acute neuropsychiatric side effects of corticosteroids and evaluate patients for delirium if clinically indicated. Further research is needed to identify the pathophysiology and predisposing factors contributing to neuropsychiatric side effects of corticosteroid administration. The use of atypical antipsychotics in the management of these sequelae needs to be explored as well.

Categories: Endocrinology/Diabetes/Metabolism, Internal Medicine, Psychology

Keywords: acute hypoxic respiratory failure, covid, covid vaccine, corticosteroid, glucocorticoid, steroid induced psychosis, acute psychosis

Introduction

Corticosteroids are endogenous steroid hormones produced in the adrenal cortex. There are two main classes of corticosteroids: mineralocorticoids and glucocorticoids. Mineralocorticoids are regulated by the renin-angiotensin system and have salt-retaining properties, whereas glucocorticoids are regulated by adrenocorticotropic hormone (ACTH). Fludrocortisone is the most common mineralocorticoid, and glucocorticoids are further classified into short-acting, intermediate, and long-acting based on the duration of action. Glucocorticoids are commonly used to treat endocrine and non-endocrine disorders, including inflammatory, allergic, immunologic, and malignant conditions [1,2]. Numerous studies have shown that long-term glucocorticoid use, even in low doses, is an independent predictor of various adverse effects. The risk is both dose- and duration-dependent [3].

Dexamethasone is a long-acting, potent glucocorticoid with no mineralocorticoid activity (no salt-retaining properties). It is metabolized in the liver with a half-life of one to five hours with intravenous administration. Neuropsychiatric effects of glucocorticoids, including dexamethasone, comprise depression, mania, agitation, mood lability, anxiety, insomnia, catatonia, depersonalization, delirium, dementia, and psychosis. In this case report, we describe the onset of acute psychosis, in a patient with no prior history of psychiatric illnesses, associated with the administration of intravenous dexamethasone for a week.

Case Presentation

The patient, Ms. A, was a 55-year-old woman of Caribbean descent with a history of type 2 diabetes mellitus and hypertension with no past psychiatric history. Before admission, she had not been on any medications for her diabetes or hypertension. Ms. A initially presented to the hospital with shortness of breath, intermittent productive cough with white sputum, chest tightness, chills, sporadic headaches, anosmia, loss of taste, and malaise for one week in the context of receiving the first dose of Moderna coronavirus disease 2019 (COVID-19) vaccine (Moderna, Inc, Cambridge, MA) nine days ago. She reported a gradual worsening of the symptoms mentioned above and denied any recent travel or sick contact. On arrival to the emergency room, the patient tested positive for COVID-19 and was noted to have hypoxia with oxygen saturation of 87% and tachypnea with a respiratory rate of 24 bpm. On physical examination, the patient was alert and oriented, in distress, with normal heart rate and regular rhythm with the presence of rhonchi. Motor strength and sensations were intact with no focal neurological deficits. Laboratory evaluation showed positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and
Glucocorticoids are listed below in Table 1 [4].
### TABLE 1: Glucocorticoid dose equivalents and duration of action

| Activity          | Glucocorticoids       | Duration of action (hours) | Dose equivalent (mg) |
|-------------------|-----------------------|---------------------------|----------------------|
| Short-acting      | Hydrocortisone        | 8-12                      | 20                   |
|                   | Cortisone             | 8-12                      | 25                   |
| Intermediate-acting| Prednisone            | 12-36                     | 5                    |
|                   | Prednisolone          | 12-36                     | 5                    |
|                   | Methylprednisolone    | 12-36                     | 4                    |
|                   | Triamcinolone         | 12-36                     | 4                    |
| Long-acting       | Dexamethasone         | 36-72                     | 0.75                 |
|                   | Betamethasone         | >48                       | 0.6                  |

### TABLE 2: Adverse effects of corticosteroids

| Organ systems                  | Adverse effects                                                                 |
|--------------------------------|---------------------------------------------------------------------------------|
| Neuropsychiatric               | Mood changes – mania/depression/dysphoria/euphoria, psychosis, insomnia, seizures, vertigo, headache, increased motor activity (akathisia) |
| Ophthalmologic                 | Posterior subcapsular cataract, glaucoma, ocular nerve damage, exophthalmos, ophthalmic fungal, or viral infections |
| Cardiovascular                 | Hypertension, fluid retention, thromboembolism, arrhythmias, arteriosclerosis, thrombophlebitis |
| Gastrointestinal               | Nausea/vomiting, gastritis, esophagitis, peptic ulcer disease, steatohepatitis pancreatitis |
| Endocrine/metabolic            | Hyperglycemia, weight gain, secondary adrenal insufficiency                       |
| Female reproductive            | Amenorrhea, post-menopausal bleeding                                             |
| Musculoskeletal                | Osteoporosis, myopathy, muscle wasting, avascular necrosis of femoral head        |
| Dermatologic                   | Hirsutism, acne, skin atrophy, striae, ecchymoses/purpura                         |
| Hematologic/immune             | Leukocytosis, increased susceptibility to infections                               |

In addition, glucocorticoids are associated with multiple adverse effects affecting various organ systems, as listed in Table 2.[5]

Long-term therapy with glucocorticoids results in depression or apathy, whereas short-term use induces psychosis, mood lability, delirium, and other excitatory psychiatric disturbances. These include agitation, anxiety, distractibility, fear, hypomania, insomnia, irritability, lethargy, labile mood, pressured speech, restlessness, and tearfulness. Risk factors for the development of neuropsychiatric issues include higher doses, a dose equivalent to ≥80 mg prednisone. Other risk factors include female gender, age >30 years, history of alcohol use disorder, bipolar disorder, depression, or neuropsychiatric disorders [6,7].

The patient described in the case report developed acute psychosis more than three weeks after receiving the COVID-19 vaccine, two weeks after being diagnosed with acute respiratory failure, and one week after completing a week-long course of intravenous dexamethasone. She did not exhibit any psychiatric symptoms during the initial hospital admission and had no prior psychiatric history.

Psychiatric side effects most commonly occur early in the therapeutic course, within five days of initiation of glucocorticoids, averaging 11.5 days. However, these can occur at any time during steroid therapy and can persist even after stopping the treatment. The most common psychiatric disorders were depression (35%),...
mania (31%), psychosis (14%), and delirium (13%), based on a retrospective study of 14 cases of steroid-induced psychiatric disorders [8].

**Pathophysiology of steroid-induced neuropsychiatric effects**

The possible pathophysiology includes glucocorticoid-induced hippocampal dysfunction associated with decreased hypothalamic corticotropin-releasing hormone (CRH) and circulating ACTH hormone levels. Dementia associated with steroid use is attributed to hippocampal and frontal-cortex impairment [9].

The incidence of steroid-induced severe neuropsychiatric effects is variable and was noted in about 5.7% of patients in a meta-analysis of 2,555 patients. The occurrence of any psychiatric symptoms was 18.6% in patients receiving >80 mg/day of prednisone (12 mg/day dexamethasone). Of note, the steroid dose was not predictive of the time of onset, severity, type, or duration of symptoms. Symptoms usually resolved with dose reduction or stopping the steroid. The use of atypical antipsychotics or mood stabilizers was found beneficial as well [10].

Recurrent cases of steroid-induced mood disorder have been reported in patients with a previous history of bipolar disorder. Therefore, the use of antidepressants and mood stabilizers can be considered in these patients [11].

**Other possible causes of psychosis**

The other possible mechanism for psychosis in this patient was due to SARS-CoV-2 infection. This virus causes COVID-19, affects multiple organ systems, and leads to psychiatric and neurocognitive symptoms [12]. These symptoms include depressed mood, anxiety, insomnia, anger, and fear in mild disease, depression, and post-traumatic stress disorder in moderate illness, and exacerbation of psychiatric disorders in severe disease [13].

The onset of neuropsychiatric symptoms with COVID-19 is also variable. For example, one case report has discussed a patient with no history of psychiatric illness who developed a delayed onset of manic-like symptoms related to SARS-CoV-2 viral infection on day 17 of the disease [14]. On the other hand, 5-8% of COVID-19 patients had newly diagnosed psychiatric illness between 14-90 days, based on a review of 62,354 COVID-19 cases [15]. Our patient presented with psychosis about 23 days after receiving the COVID-19 vaccine and 21 days after the onset of other COVID-19 symptoms.

Autoimmune mechanisms with the involvement of several immune loci and lymphocyte markers are linked to the pathophysiology of COVID-19 psychosis. These include the major histocompatibility complex, CD4, CD8, CD19, and CD20 [16]. The other mechanism of neuroinflammation in COVID-19 is related to the dysregulation of cytokine systems. Proinflammatory cytokines including interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, IL-8, and IL-10 are triggered in response to COVID-19 infection, resulting in the derangement of the blood-brain barrier [17]. Therefore, the role of testing for inflammatory biomarkers and the use of non-steroidal anti-inflammatory medications for COVID-19-related psychiatric illness needs to be evaluated. In addition, further research may be required to assess the role of the detection of antigens, antibodies, and immune complexes in the cerebrospinal fluid (CSF) of patients with neuropsychiatric manifestations of COVID-19.

The patient was also given remdesivir for five days for COVID-19; however, there have been no reports of remdesivir-induced psychosis [18].

The third possible reason for acute change in mental status with paranoid behavior is delirium secondary to hypoxic respiratory failure. The usual instrumental tools to diagnose delirium include the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). Unfortunately, clinicians often do not recognize delirium. In one study, over 40% of patients referred to a psychiatrist to manage depression were eventually noted to have delirium [19]. Nevertheless, delirium was ruled out by history, physical exam, and laboratory evaluation in our patient.

Given that the patient presented with psychiatric symptoms one week after steroid administration, that is the most likely cause of the patient’s acute psychosis. In addition, the patient’s brother had recently been diagnosed with steroid-induced mania and psychosis. However, the other two variables - SARS-CoV-2 viral infection and delirium - present a crucial challenge in diagnosing and treating patients with neuropsychiatric symptoms in the context of steroid use.

**Conclusions**

Glucocorticoids are associated with multiple adverse effects impacting various organ systems. This case report highlights the importance of paying close attention to neuropsychiatric side effects in patients treated with corticosteroids. In this case report, we discussed a previously normal patient with no prior psychiatric history who developed acute psychosis in the context of steroid administration. Based on our
findings, we recommend that clinicians perform a detailed assessment of all patients presenting with psychiatric symptoms, including evaluating for signs and symptoms of delirium and obtaining a thorough history of current and past medication use. Further research is needed to identify the pathophysiology and predisposing factors contributing to neuropsychiatric side effects of corticosteroid administration. The use of antipsychotics in the management of these sequelae needs to be explored as well.

**Additional Information**

**Disclosures**

**Human subjects:** Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

**References**

1. Becker DE: Basic and clinical pharmacology of glucocorticoids. Anesth Prog. 2013, 60:25-31. 10.2544/0003-3006-60.1.25
2. Zoorob R, Cender D: A different look at corticosteroids. Am Fam Physician. 1998, 58:443-50.
3. Liu D, Ahmet A, Ward L, et al.: A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2015, 9:30. 10.1186/s11701-1492-9-50
4. Kapugi M, Cunningham K: Corticosteroids. Orthop Nurs. 2019, 38:536-9. 10.1097/NOR.0000000000000595
5. Huscher D, Thiele K, Gronmica-Uble E, et al.: Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis. 2009, 68:1119-44. 10.1136/ard.2008.092163
6. Warrington TP, Bostwick JM: Psychiatric adverse effects of corticosteroids. Mayo Clin Proc. 2006, 81:1361-7. 10.4065/81.10.1361
7. Ciriaci M, Ventrice P, Russo G, Scicchitano M, Mazzitello G, Scicchitano F, Russo E: Corticosteroid-related central nervous system side effects. J Pharmacol Pharmacother. 2013, 4:394-8. 10.4103/0975-500X.120975
8. Lewis DA, Smith RE: Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. J Affect Disord. 1983, 5:319-32. 10.1016/0165-0327(83)90022-8
9. Wolkowitz OM, Burke H, Epel ES, Reus VI: Glucocorticoids. Mood, memory, and mechanisms. Ann NY Acad Sci. 2009, 1179:19-40. 10.1111/j.1749-6632.2009.04980.x
10. Dubovsky AN, Arvika S, Stern TA, Axelrod L: The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. Psychosomatics. 2012, 53:105-15. 10.1016/j.psym.2011.12.007
11. Wada K, Yamada N, Suzuki H, Lee Y, Kuroda S: Recent cases of corticosteroid-induced mood disorder: clinical characteristics and treatment. J Clin Psychiatry. 2000, 61:261-7. 10.4088/jcp.v61n0404
12. Wilson BA, Betteridge S, Fish J: Neuropsychological consequences of Covid-19. Neuropsychol Rehabil. 2020, 30:1625-8. 10.1080/09602011.2020.1808483
13. Hellmuth J, Barnett TA, Askem BM, et al.: Persistent COVID-19-associated neurocognitive symptoms in non-hospitalized patients. J Neurovirol. 2021, 27:191-5. 10.1007/s13365-021-00995-4
14. Lu S, Wei N, Liang J, et al.: First report of manic-like symptoms in a COVID-19 patient with no previous history of a psychiatric disorder. J Affect Disord. 2020, 277:557-40. 10.1016/j.jad.2020.08.031
15. Taquet M, Luciano S, Geddes JR, Harrison PJ: Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry. 2021, 8:130-40. 10.1016/S2215-5366(20)30463-4
16. Al-Diwani AA, Pollak TA, Irani SR, Lennox BR: Psychosis: an autoimmune disease?. Immunology. 2017, 152:388-401. 10.1111/imm.12795
17. Ferrando SI, Klepacz L, Lynch S, et al.: COVID-19 psychosis: a potential new neuropsychiatric condition triggered by novel coronavirus infection and the inflammatory response?. Psychosomatics. 2020, 61:551-5. 10.4103/0976-500X.120975
18. Marcantonio E, Ta T, Duthie E, Resnick NM: Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair. J Am Geriatr Soc. 2002, 50:850-7. 10.1046/j.1532-5415.2002.05210.x
19. García CA, Sánchez EB, Huerta DH, Gómez-Arnau J: Covid-19 treatment-induced neuropsychiatric adverse effects. Gen Hosp Psychiatry. 2020, 67:163-4. 10.1016/j.genhosppsych.2020.06.001