Psychiatric Impact of Glucocorticoids in Organ Transplantation

34

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Introduction

Despite advances in immunosuppression, the use of glucocorticoids in different phases of transplantation remains common. Pulses of high doses of steroids are regularly employed in the peri-operative period and for treatment of acute rejection. Lower dose regimens are routinely used for maintenance therapy. Organ-specific regimens may differ in their usage of these agents [1]. While glucocorticoids' efficacy has been demonstrated in randomized controlled trials [2], there are numerous associated adverse effects, both acute and chronic.

While the somatic effects of glucocorticoids are well understood, the mechanisms of neuropsychiatric complications are less well characterized [3, 4]. Numerous symptoms have been reported, including, but not limited to agitation, anxiety, distractibility, dysphoria, fear, hallucinations, hypomania, indifference, insomnia, irritability, lethargy, labile mood, paranoia, pressured speech, restlessness, and tearfulness [5]. In clinical practice, subsyndromal anxiety, insomnia, and irritability are very common.

The prevalence of neuropsychiatric side effects ranges in the literature from 2 to 62% with 3–6% suffering from severe symptoms [6–8]. A majority of patients develop neuropsychiatric symptoms early in treatment. Hall et al. found 86% of symptoms occurred within 2 weeks of initiation of treatment, with up to two-thirds of patients developing symptoms within the first 5 days [9]. Lewis and Smith's review found a median time to onset of symptoms of 11.5 days with 62% developing symptoms in the first 2 weeks and 89% developing symptoms within 6 weeks of initiation of steroids [7].

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Multiple authors have come to the conclusion that affective symptoms appear to be the most common psychiatric adverse effects of corticosteroids [7], [10–12]. In the early stages of steroid treatment and those on higher doses, patients are more likely to experience manic or hypomanic symptoms. Long-term therapy, similar to Cushing's Disease, is more likely associated with depressive symptoms [4, 8, 13]. Steroid-induced affective disorders appear to be accompanied by psychotic symptoms more frequently than primary mood disorders [7, 11]. Suicide risk is also increased; in a national database UK study, the hazard ratio for suicide or suicide attempt in patients exposed to steroids as compared to controls was 6.89 [14]. Cognitive deficits (especially impairment in verbal and declarative memory, and particularly recall deficits in the elderly) are also common with glucocorticoid treatments [9, 15, 16].

Duration of affective or psychotic symptoms has been reported with significant variability likely relating to variation in discontinuation and intervention [3]. Patients with delirium may recover more quickly, with one study reporting a mean duration of 5.4 days vs. 19.3 days in those with depression, mania, or psychosis [17]. Varney and colleagues noted that cognitive deficits resolved within 3 to 11 months after discontinuation of glucocorticoids, though Hall and colleagues noted 7% had persisting deficits [9, 17].

There appears to be a clear dose relationship between glucocorticoids and neuropsychiatric symptoms [18]. The Boston Collaborative Drug Surveillance Program studied 718 consecutive patients receiving steroid therapy and found that 1.3% of patients receiving doses up to 40 mg per day, 4.6% of patients receiving doses between 41 and 80 mg per day, and 18.4% of patients receiving doses greater than 80 mg per day developed neuropsychiatric side effects [6]. Similarly, Lewis and Smith found that 77% of patients with neuropsychiatric symptoms had received 40 mg per day or more of prednisone [7]. Most patients undergoing organ transplantation who receive steroids receive high doses.

P. C. Zimbrean et al. (eds.), *Transplant Psychiatry*, https://doi.org/10.1007/978-3-031-15052-4_34

In addition to the steroid dose, other speculated risk factors for development of neuropsychiatric side effects include hypoalbuminemia, disruption of the blood–brain barrier, prior steroid-induced neuropsychiatric symptoms, cytochrome p 450 inhibition, longer acting corticosteroid preparations, female sex, and increasing age [4, 14]. Many of these factors are common in patients requiring transplant: many patients with liver failure have hypoalbuminemia; the blood–brain barrier can be compromised during large surgeries; and other medications involved may affect the cytochrome p 450 system.

Withdrawal of glucocorticoid agents can also lead to neuropsychiatric symptoms. This can be due to suppression by exogenous steroids or endogenous production leading to a derangement in the hypothalamic–pituitary–adrenal (HPA) axis, but also may represent a stand-alone withdrawal syndrome with preserved HPA function [5]. This syndrome has been characterized by sleep and appetite disturbance, depression, anhedonia, fatigue, irritability, depersonalization, poor concentration, anorexia, agitation, psychosis, and suicide [3]. Secondary mania, psychosis, and delirium are also possible [19, 20]. While symptoms improve and often resolve within 2–8 weeks [21], symptoms can persist and may require a second, more gradual taper [19].

Several agents have been trialed as prophylaxis for neurocognitive side effects during glucocorticoid administration. Trials of mood stabilizers, such as lithium carbonate and lamotrigine, have been published which show efficacy, although the trials have limitations including small sample sizes, low doses of prednisone, or lack of quantification of symptoms [3, 22, 23]. There is limited case literature showing possible efficacy for valproate as a prophylactic agent [24]. Phenytoin, levetiracetam, and amantadine did not show significant differences for affective symptoms when compared to placebo in small studies [3, 25–27].

When symptoms do arise, a number of different steps can be taken to manage the symptoms. Discontinuing or decreasing steroids to less than 40 mg per day equivalent dose of prednisone is suggested generally, though this may not be possible in many transplant cases. Mood stabilizers have not only shown efficacy in prophylaxis but also in treatment [3]. Their use is often limited in transplant populations by need for other nephrotoxic agents, significant fluid balance shifts in the peri-operative window, and drug–drug interactions.

Antipsychotics have also been shown to be effective in treatment of both mood and psychotic symptoms. Davis and colleagues found symptom resolution with low-dose antipsychotic treatment in 83% of patients with psychosis, including 33% in 3 days and 60% in 1 week [28]. Similarly, Brown and colleagues found olanzapine effective in 11 of 12 patients with manic or mixed symptoms with mean daily dose of 9.2 mg per day [29]. Since many antipsychotics are usually well tolerated in the short term, not dependent on fluid balance, and have relatively fewer drug interactions, they often represent first-line treatment for both manic and psychotic symptoms associated with steroids in transplant patients.

Case History

A 31-year-old woman with a history of liver failure secondary to primary sclerosing cholangitis was admitted to the hospital for liver transplantation. Her medical history was significant for hepatic microabscesses on chronic antibiotics (most recently ciprofloxacin and metronidazole) and Crohn's disease being treated with vedolizumab. She has a psychiatric history of bipolar affective disorder, type 2, in remission prior to surgery and previously on lamotrigine but off medications for 10 years, with no previous history of substance abuse. Prior to transplantation, laboratory tests were notable for hemoglobin and hematocrit of 10.9 and 34.9, respectively, total bilirubin of 3.9, alkaline phosphatase of 531, alanine aminotransferase of 383, and aspartate aminotransferase of 585. She underwent an orthotopic liver transplant during which multiple hepatic microabscesses were appreciated and thought to be consistent with known lesions. No major operative complications were noted and blood loss was estimated to be 800 cc. She was extubated and off pressor supported on post-operative day 0. She was given 160 mg of methylprednisolone on the day of her transplant, followed by a 4-day taper down to 40 mg before transitioning to a 6-day prednisone taper from 20 mg daily to 10 mg daily. She was also started on tacrolimus. She did well during the initial post-operative period with no signs of affective, psychotic, or cognitive disturbance though developed a mild tremor. Opioids were discontinued by post-operative day 5, with no more than one dose daily of as needed tramadol administered thereafter.

On post-operative day 8, she was diagnosed with an acute rejection with signs of hepatic damage. A dose of methylprednisolone 500 mg was administered and prednisone was increased to 20 mg daily 3 days later. On post-operative day 13, she became intermittently disoriented and had trouble sleeping. Vital signs and laboratory investigations, including comprehensive metabolic panel, complete blood count, and liver enzymes, were stable or improved from previous days. During the following 2 days she developed auditory and visual hallucinations, paranoid ideation, insomnia, rapid and illogical speech, inattention, distractibility and significant anxiety, and intermittent mild agitation. Her mood ranged from dysphoric to irritable and her tremor worsened. Brain magnetic resonance imaging (MRI) did not show any abnormality. Tacrolimus levels were noted to be in the lower range of therapeutic.

Psychiatry was consulted on post-operative day 16. Quetiapine was initiated and titrated over the next 3 days to 200 mg nightly with 50 mg as needed doses with limited

effect on sleep and continued psychotic and manic features. On post-operative day 20, the decision was made to discontinue quetiapine and olanzapine was started and titrated to 10 mg over the next 2 days with good effect on sleep and improvement in attention, orientation, as well as manic and psychotic symptoms. Blood glucose initially became elevated with the second methylprednisolone pulse, with daily ranges from 140 to 220, and this was exacerbated when olanzapine was titrated with resulting ranges between 150 and 250. Full resolution of symptoms was achieved on day 24 and olanzapine was tapered over the next 4 days due to increasing day time sedation with no relapse in symptoms. Blood glucose normalized within 1 week after discontinuation of olanzapine and continued steroid taper.

Clinical Questions

1. What factors in the patient's history raise her risk for developing a glucocorticoid-induced affective disturbance?
2. After the patient's mental status changed on post-operative day 13, what would your differential diagnosis include, and what investigations might you pursue to clarify it?
3. Why was it important to obtain brain magnetic resonance imaging in regard to the worsening tremor and altered mental status?
4. In this patient, what considerations would you consider in choosing whether to initiate a pharmacologic agent and which one to start?
5. Would you consider prophylactically prescribing a medication to the patient in the future if she required another pulse of steroids, and if so, which medication?

Discussion

This case presents a number of the difficulties that can be associated with diagnosing and treating glucocorticoid-induced neuropsychiatric symptoms in the setting of transplantation. When the patient developed new cognitive and mood symptoms on post-operative day 13, the differential was broad and included hepatic encephalopathy in the setting of acute rejection, delirium due to new infection or other post-operative complication, side effects from co-administered immunosuppressants (in this case, concern for tacrolimus-induced neurotoxicity), side effects from high-dose steroids, or an exacerbation of a previously diagnosed bipolar disorder.

When the patient went into acute rejection, her liver enzymes became elevated and her international normalized ratio (INR) began to increase, suggesting hepatic damage and malfunction. Interestingly, her mental status did not worsen until 5 days after acute rejection was first noted and treated with a second pulse and taper of steroids. When symptoms did develop, her liver function was improving. This made hepatic encephalopathy less likely as a cause for the changes in her mood and cognition.

With the onset of disorientation and alteration in sleep, delirium was suspected and a medical work-up was started which demonstrated stable or improved complete blood count, comprehensive metabolic panel, and liver enzymes. Her mental status deteriorated and was accompanied by worsening tremor, raising concern for a tacrolimus-induced neurotoxicity and posterior reversible encephalopathy syndrome (PRES). With regard to tacrolimus-induced neurotoxicity, it was reassuring that her tacrolimus levels were not elevated, though this does not rule out a tacrolimus-related neurotoxicity. In addition, her blood pressures were not elevated and the MRI ruled out PRES. However, given the evolution of her symptoms following the second steroid pulse and her relative tolerance of tacrolimus up until this point, her new neuropsychiatric symptoms were thought to be more likely related to glucocorticoids.

The patient had multiple factors that raised her risk for adverse effects with high-dose steroids. She had been previously diagnosed with bipolar disorder, which has not been consistently shown to be a risk factor, but was not currently treated. Her sex also raises her risk. Due to her pre-existing liver disease, she also had hypoalbuminemia prior to transplant and this had not yet recovered post-transplant before the second steroid pulse was given. Since methylprednisolone is bound to albumin, low albumin levels can lead to increased free methylprednisolone levels in the blood and has been associated with an increased frequency of steroid-related side effects [30]. She was also given two pulses of high-dose steroids within a relatively short period of time, and the second pulse and taper were followed 5 days later by changes in mood and cognition. As discussed earlier, most patients develop symptoms within the first week of starting steroids, and two-thirds within 5 days.

On exam, the patient showed a mixed picture of manic, psychotic, and inattentive features. While visual hallucinations are rare in primary psychiatric conditions, they are common in the case literature surrounding glucocorticoid-induced psychoses. Her neuropsychiatric symptoms were worsening with more prominent psychotic features, persisting insomnia, and concern that she would soon be unable to participate in care. In addition, steroid discontinuation was deemed to be too high risk by the primary team, and thus, another pharmacologic intervention was necessary. An antipsychotic was favored over a mood stabilizer due to the presence of psychotic symptoms, the need for improved sleep, evidence of hepatic damage, and continued concern for fluid shifts. Quetiapine was initially trialed for both its sedating effects and relatively lower anticholinergic activity as compared to other more sedating antipsychotics.

When symptom improvement was not attained with escalating doses of quetiapine, the medication was changed to olanzapine to allow for a faster titration to therapeutic doses. Olanzapine was titrated with good effect and eventual full symptom resolution. The patient did not experience anticholinergic side effects. Olanzapine was tapered off slowly while the patient was monitored for relapse of symptoms in the hospital. Blood glucose did show elevation with steroid taper with mild exacerbation while olanzapine was administered, but returned to normal after discontinuation of the latter. No further symptoms were noted.

In the peri-transplant period, some of the common side effects of atypical antipsychotics can become more impactful. Anticholinergic side effects can also lead to increased urinary retention in the post-operative period which could increase the risk of urinary tract infection in a population already at higher risk. Many atypical antipsychotics can also have metabolic effects, including impairing insulin sensitivity leading to increases in blood glucose, compounding with the effects of steroids. QT prolongation can also be exacerbated by other transplant medications (e.g., tacrolimus, antibiotics), as well as post-operative electrolyte shifts. Antipsychotics' ability to lower seizure threshold is also worth considering since some of the immunosuppressants can also lower this threshold.

The patient previously had wanted to remain off medications for her bipolar illness as she had been symptom free for the last 12 years and without medications for the past 10 years. The consultation service discussed with the patient the options of re-initiating a maintenance mood stabilizing medication or starting treatment in the future if she were to need another course of steroids. It is unclear whether her risk of another mood episode due to her primary psychiatric condition is increased by this glucocorticoid-induced episode; though given the hardship this episode caused and her desire to avoid a similar event in the future, she ultimately agreed to pursue prophylaxis in the event of another course of high-dose steroids.

In recommending a prophylactic medication to this patient if future need did arise, multiple factors were considered. She had previously done well with mood stabilization on lamotrigine, but this medication takes a long time to titrate to therapeutic doses and if the need for a higher steroid dose is urgent or emergent, we may not be able to titrate quickly enough to attain prophylaxis. Valproic acid, while rapidly titratable, also has risk for hepatotoxicity. In addition, antipsychotics are easy to titrate and often reliable in these cases. If she did require another dose of steroids, it would likely relate to hepatic transplant rejection which would make a medication with risk for hepatotoxicity less desirable. Atypical antipsychotics were discussed with the patient, and she chose olanzapine for possible future use given her experience with its efficacy and tolerability.

Take Home Points

1. High-dose glucocorticoids are commonly used in transplant patients.
2. While steroid-induced anxiety and insomnia are quite prevalent, affective disorders are the most common major disturbance.
3. There are several risk factors for glucocorticoid neuropsychiatric effects that are common in patients requiring transplant. The most validated risk factor is the higher dose of glucocorticoids, with other contributing factors, including hypoalbuminemia, disruption to the blood brain barrier, and co-prescribed medications that may affect the cytochrome p450 system.
4. Given the comorbidities involved in organ transplantation, management options require careful consideration of their potential risks and benefits.

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