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Case Reports

Rapid-Onset Steroid-Induced Psychosis

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Steroid-induced psychosis is a known adverse effect of treatment with corticosteroids. On average, the time of onset is several days after exposure to the steroid. A 91-year-old man presented with left buttock pain with radicular features and was found to have severe left lateral recess spinal canal stenosis on MRI. He was started on a prednisone taper and developed steroid-induced psychosis one day later. He was treated with a short course of antipsychotic medication. This case discusses the unusually rapid onset of steroid-induced psychosis at a dose of prednisone that does not commonly cause this adverse effect. It emphasizes important considerations when starting steroids in patients with advanced age and comorbidities that may impact the metabolism of steroids.

BACKGROUND

Corticosteroids, a medication class used to treat an array of inflammatory, allergic, and immunological conditions, have well-studied adverse effects, including weight gain, poor wound healing, and skin thinning. Steroid-induced psychosis is often taught as an adverse effect but typically begins several days after initiation of the steroid. Here we report a case of rapid-onset steroid-induced psychosis.

CASE PRESENTATION

A 91-year-old male with a past medical history of end-stage renal disease (ESRD) on hemodialysis and compensated cirrhosis due to Hepatitis C presented to the emergency department after three mechanical falls due to severe left buttock pain radiating into his left lower extremity. Vital signs at presentation demonstrated a temperature of 36.8°C, heart rate of 52 beats/min, blood pressure of 155/68 mm Hg, respiratory rate of 18 breaths/min, and O_2 saturation of 98% on ambient air. Physical exam revealed a positive straight leg raise on the left and positive contralateral straight leg raise on the right, 4/5 strength in left lower extremity plantar flexion and knee flexion, 5/5 strength of the right lower extremity, absent deep tendon reflex in the left Achilles tendon, and reduced sensation in the left S1 dermatome. MRI without contrast of the lumbar spine showed L5-S1 disc extrusion extending 0.5 cm into the spinal canal and 1 cm along the posterior S1 vertebral body resulting in severe left lateral recess spinal stenosis, moderate-severe spinal stenosis at L3-4 and L4-5, and severe neural foraminal stenosis on the left at L4-5.

Pain management options such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids were limited by the patient's ESRD, cirrhosis, and advanced age. Oral medications included hepatically- and renally dosed acetaminophen, methocarbamol, and gabapentin. Topical medications, including diclofenac and lidocaine, were also trialed without significant effect. Given his advanced age and complex medical history, including thrombocytopenia and a history of atrial fibrillation on chronic anticoagulation, he was not a candidate for an epidural steroid injection.

The inpatient pain service was consulted, and a four-day prednisone taper was recommended to treat his significant radicular pain. He received prednisone 40 mg/day on hospital day 5 and 30 mg/day on hospital day 6 with some interval improvement in his symptoms. However, shortly after his second dose on hospital day 6, the patient developed visual hallucinations, delusions, disorganized speech, agitation, confusion, and insomnia. Workup, including labs and imaging, were unremarkable, and there were no localizing signs or symptoms of infection (**Table 1**).

A Chest X-ray showed atelectasis but no focal consolidations. A CT head showed no acute intracranial hemorrhage or mass effect, though probable chronic microvascular ischemic disease, and age-related brain volume loss. Medications were reviewed, and in the context of the symptomatology, there was a high suspicion for steroid induced psychosis (**Table 2**). The prednisone taper was discontinued immediately. Due to increased agitation and combativeness, a hospital response team came to assess the patient, and he was started on standing haloperidol per psychiatry's recommendation. After 1-2 days of treatment with antipsychotic medication, his acute agitation resolved. His symptoms of psychosis significantly improved seven days after stopping prednisone.

Table 1. Laboratory test results at the onset of psychosis.

Laboratory Tests	Reference	Units	Value	Interpretation
Anion Gap	3-11	mmol/L	10.3	
Sodium	136-146	mmol/L	135	L
Potassium	3.5-4.3	mmol/L	4.2	
Chloride	95-110	mmol/L	95	
Carbon Dioxide	24-31	mmol/L	29.7	
Urea Nitrogen	5-25	mg/dL	21	
Creatinine	0.52-1.28	mg/dL	4.2	H
Glu	70-110	mg/dL	130	H
Magnesium	1.8-2.4	mg/dL	2.1	
Phosphorus	2.5-4.9	mg/dL	3.5	
WBC	4.5-11.0	k/uL	5.67	
RBC	4.4-5.9	M/uL	3.24	L
Hgb	13.3-17.7	g/dL	10.7	L
Hct	39-52	%	33.0	L
Plt	150-440	k/ul	120	L
Neutrophil %	41-85%	%	81.0	
Lymphocyte %	20-40%	%	12.9	L
Monocyte %	2-10%	%	5.6	
Eosinophil %	1-6%	%	0	L
Basophil %	0-1%	%	0	
Ig %	0.0-0.9%	%	0.5	

DISCUSSION

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) classifies steroid-induced psychosis under Substance/Medication-Induced Psychotic Disorders. To meet DSM-5 criteria, steroid-induced psychosis must include hallucinations or delusions after steroid exposure, and other causes cannot explain symptoms.[1] In the literature, various steroid-induced psychiatric syndromes, including affective, behavioral, and cognitive symptoms that do not meet the criteria for psychosis, are often conflated under the term steroid-induced psychosis.[2] Thus, it is difficult to investigate the true incidence, onset, duration, and risk factors specific to steroid-induced psychosis.

Given this broad categorization, the reported incidence of steroid-induced psychosis ranges from 2% to 60%.[2] Meta-analyses have found that 6% of patients exposed to steroids develop severe psychiatric syndromes.[3] In a study by Lewis and Smith reviewing 79 cases of steroid-induced psychiatric syndromes, 40% had depression, 28% had mania, 14% had psychosis, 10% had delirium, and 8% had depression and mania.[4] Bolanos et al. found that patients receiving short-term prednisone therapy were more likely to develop mania, while long-term treatment patients were more likely to develop depression[5]

The time of onset of steroid-induced psychosis is highly variable, though Lewis and Smith noted a median onset of 11.5 days, and Nishimura et al. reported a mean of 12.5 days.[4,6] In this case, the patient developed psychosis one day after exposure to steroids, a much shorter onset time than reported in the literature. The duration of steroid-induced psychosis depends on the time of discontinuation of the steroid and pharmacologic treatment of psychosis. Lewis and Smith reported that 90% of cases were resolved within six weeks.[4] In a review of adolescent steroid-induced psychosis, symptoms can last from several days to several weeks.[3] In this case, the patient's psychosis significantly improved after seven days.

Evidence supports that the dose of steroids is a risk factor for developing steroid-induced psychosis. Multiple studies have shown that increased doses of prednisone are positively correlated with the incidence of psychiatric syndromes.[2,4,7] In one study, 1.3% of patients receiving prednisone ⩽40 mg/day developed this condition, compared to 4.6% of patients receiving prednisone 41-79 mg/day and 18.4% receiving prednisone ⩾80 mg/day.7 Despite receiving a relatively low dose of prednisone ⩽40 mg/day, the patient in this case still developed profound psychosis.

There may be evidence that female sex is a risk factor, as Lewis and Smith showed that 68% of patients in their reviewed case reports were female. Data from clinical trials showed that 19.7% of females treated with steroids developed psychiatric conditions compared to 3.3% of males. These differences remained significant even after excluding patients with SLE and RA, which are more common in females.[4] There is no clear relationship between this condition and age: clinical trials showed a mean of 42.7 years of 1,400 control subjects.[2] Nor was there a clear association between this condition and a previous history of psychiatric disorders.[2]

Table 2. Timeline of medication changes prior to onset of psychosis.

Timeline of Interventions	
Day of Admission	In the ED: ketorolac 15 mg IM once, acetaminophen 1 g IV once Started: Acetaminophen 1g IV Q12H, topical lidocaine 5% ointment BID PRN, topical diclofenac 1% gel TID PRN, methocarbamol 500 mg TID PRN
HD 1	Changes: Oxycodone 5 mg PO once, changed acetaminophen to 650 mg PO Q8H Continued: Topical lidocaine 5% ointment BID PRN, topical diclofenac 1% gel TID PRN, methocarbamol 500 mg TID PRN
HD 2	Continued: Acetaminophen 650 mg Q8H, topical lidocaine 5% ointment BID PRN, topical diclofenac 1% gel TID PRN, methocarbamol 500 mg TID PRN
HD 3	Changes: Cyclobenzaprine 5 mg PO once, gabapentin 100 mg QHS Continued: Acetaminophen 650 mg Q8H, topical lidocaine 5% ointment BID PRN, topical diclofenac 1% gel TID PRN, methocarbamol 500 mg TID PRN
HD 4	Changes: Changed gabapentin to 100 mg BID, changed acetaminophen to 650 mg Q8H PRN Continued: Topical lidocaine 5% ointment BID PRN, topical diclofenac 1% gel TID PRN, methocarbamol 500 mg TID PRN
HD 5	Changes: Prednisone 40 mg once Continued: Acetaminophen 650 mg Q8H PRN, topical lidocaine 5% ointment BID PRN, topical diclofenac 1% gel TID PRN, methocarbamol 500 mg TID PRN, gabapentin 100 mg BID
HD 6* *Onset of psychosis	Changes: Prednisone 30 mg once** Continued: Acetaminophen 650 mg Q8H PRN, topical lidocaine 5% ointment BID PRN, topical diclofenac 1% gel TID PRN, methocarbamol 500 mg TID PRN, gabapentin 100 mg BID **Prednisone discontinued after 30 mg dose
Onset of Symptoms to Resolution	Continued: Acetaminophen 650 mg Q8H PRN, topical lidocaine 5% ointment BID PRN, topical diclofenac 1% gel TID PRN, methocarbamol 500 mg TID PRN, gabapentin 100 mg BID

Further definitive risk factors have yet to be elucidated; however, a patient's comorbidities must be considered when assessing their susceptibility to the neuropsychiatric effects of steroids. The kidney and liver metabolize prednisone.[8] The clearance of prednisolone (an active metabolite of prednisone) depends on plasma protein binding, which is also affected by kidney and liver function.[8] Interestingly, kidney and liver disease have not been evaluated as potential risk factors for steroid-induced psychosis. Further studies investigating the relationship between the comorbidities mentioned earlier, and steroid-induced psychosis should be conducted, given their implications on the pharmacodynamics of steroids.

Along with discontinuing or reducing the steroid dose, treatment of steroid-induced psychiatric syndromes includes antidepressants, mood stabilizers, and antipsychotics.[2,9,10] For depressive symptoms, some case reports have shown the use of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors. Davis et al. showed that low-dose antipsychotics successfully treated psychosis in 83% of patients, with symptoms resolving in one week in 60%.[10] In a review of adolescent steroid-induced psychosis, combination therapy followed by monotherapy with risperidone, chlorpromazine, quetiapine, diazepam, sertraline, or olanzapine has been a typical regimen.[9] In this case, the patient's agitation and combativeness resolved after only 1-2 days of antipsychotic medication.

The other possible causes of psychosis in this patient were also considered, including metabolic derangements and hospital-induced delirium. The patient's metabolic panel was stable compared to baseline in the context of end-stage renal disease, making this a less likely cause of his delirium. Hospital-induced delirium is ultimately a diagnosis of exclusion, and due to its multifactorial etiology, a multi-modal approach, including delirium precautions, sleep hygiene, and bowel regimen, was implemented to address this potential cause.

The described incidence, risk factors, manifestations, definitions, implicated dosages, and study subjects of steroid-induced psychosis are highly variable in the literature. This highlights the need for further investigation to establish consensus criteria for this disease entity to diagnose steroid-induced psychosis more quickly and accurately. In summary, practitioners should have a high degree of caution when prescribing corticosteroids to the elderly population, particularly patients with renal and liver comorbidities. This case illustrates the need to maintain a high index of suspicion for steroid-induced psychosis, even when the tempo does not fit the classic illness. The mainstay of treatment for steroid-induced psychosis is stopping or reducing the steroid dose and administering low-dose antipsychotic medication. In addition to pharmacologic measures, it is essential to consider environmental and behavioral interventions for a multi-pronged approach to treatment.

AUTHOR CONTRIBUTIONS

All authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the International Committee of Medical Journal Editors criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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