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Case Report

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Serotonin Syndrome on a Low Dose SSRI and an Atypical Antipsychotic Agent in a Patient with Cirrhosis of Liver

Trishna Sharma, MD, Hemraj Anand Persaud, MD and Rupal D Shah, MD*

ETSU Department of Psychiatry, East Tennessee State University, USA

Abstract

Background: Serotonin syndrome (SS) is a life-threatening condition that develops in a short span of time. It is clinically diagnosed and supportively managed. Severe clinical manifestation is sometimes treated with cyproheptadine to suppress the serotonin surge. Although it resolves spontaneously, the potential to take a fatal course and preventable adverse reaction are important reasons to recognize SS.

We present a case of a 50-year-old male patient who presented to the ER with altered mental status and within 6 hours of his arrival developed autonomic instability and neuromuscular dysfunction. Neurological exam revealed hyperreflexia, rigidity and inducible clonus. Based on medication use history, neurologically significant finding and hunter's criteria we diagnosed the patient with SS. Patient's neurological findings and autonomic symptoms resolved within 24 hours after administration of fluids and benzodiazepine.

This case of serotonin syndrome developed with low dose a SSRI and atypical antipsychotic use in the setting of poor hepatic function. Although most SSRI depend on hepatic oxidation the awareness of underlying hepatic dysfunction is crucial because this deficit decreases hepatic CYP isoenzyme production inhibiting metabolism of serotonergic drugs leading to build up in the system. This knowledge may guide customized dosing and mitigate development of adverse drug reactions.

Introduction

Serotonin syndrome (SS) is a potentially fatal condition occurring as a result of inordinate serotonergic activity within the central and the peripheral nervous system [1]. Presentation is commonly with a triad of symptoms including neuromuscular hyper excitability, autonomic disturbance and altered mental status [2]. Clinically SS ranges in a spectrum of presentation from mild to fatal, making early diagnosis and intervention crucial [3]. Although the incidence is unknown, SS is seen across all age groups and this occurrence may have to do with increase in selective serotonin reuptake inhibitor (SSRI) use in clinical practice [4].

Among the seven different family of serotonergic receptors SS is reported to be precipitated by exaggerated stimulation of 5HT1A and 5HT 2A receptors [5]. Typically, a serotonergic agent overdose, drug interaction or simultaneous use of two serotonergic agents are the common etiology behind precipitating SS [4]. However, some papers have reported SS precipitated by normal dose serotonergic medication too [4]. Moreover, second generation antipsychotics have a synergistic effect when used together with an SSRI and can also increase the chances of precipitating SS. One implicated mechanism may be due to partial agonism of 5HT-1A receptor [5].Diagnosing SS is based on clinical presentation guided by diagnostic classification systems namely the Sternbach, Randomski and hunter Serotonin toxicity criteria [4].

Case Report

We present a case of 50-year-old male patient with a known history of cirrhosis of liver, hepatic encephalopathy, hepatitis C, stimulant use disorder, methamphetamine type and major depressive disorder, with psychotic features who presented to the emergency department for altered mental status.

Patient was previously admitted 5 days ago for acute encephalopathy to medicine service and after stabilization, transferred to a psychiatry inpatient service for worsening depression. He was started on Lexapro 5 mg and Zyprexa 5 mg for major depressive disorder with psychotic features and at the time of presentation he had already been taking these medications for the past 10 days.

When the patient was seen at the ER, he was lying in

***Corresponding author:** Trishna Sharma, MD, ETSU Department of Psychiatry, East Tennessee State University, USA

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bed unresponsive to physical and verbal stimuli. Most of the history was obtained from a behavioral health aide who was in the ER exam room and had seen the patient since that morning, while en route of transfer from the psychiatric facility.

She reported that the patient was mumbling a little, partially oriented, and agitated. He was also agitated and snapped at a nurse who tried to secure an IV line in the ER.In an effort to rule out any causes for rapidly altered mental status and decline, Patient was taken for CT of the head without contrast, and after returning from scan, he started shaking vigorously. He was also reported to be shivering and sweating with copious amounts of salivation which moderately soaked his gown. Patient received 1mg ativan and 1mg benztropine IV at that point and since then had been sedated and unresponsive.

On exam patient was a febrile with elevated BP in the 180/100's. His pulse rate and respiratory rate were normal. During physical examination he was unresponsive to physical or verbal stimuli. He did not even respond to sternal rub. He was stiff and lying with his knees flexed. Pupils examined B/L were round and dilated but responsive to light. Chest, cardiac and GI exam were within normal limit. On neuro exam UE and LE rigidity were appreciated. UE reflexes were normal 2+B/L biceps jerk. LE Knee jerk was hypereflexive 4+ B/L ankle jerk were 3+ B/L and right foot elicited sustained inducible clonus along with moderate to severe non-sustained clonus over left foot.

While in the ER patient received IV fluid and a total of 2.5mg IV Ativan. CT head was obtained which did not show any acute intracranial abnormalities. Labs revealed the following:

- Labs hgb:11.2, PLT 138
- ABG showed PH of 7.51 with pCO_2 28.4 and PO_2 104 reflecting metabolic alkalosis.
- Kidney function: Cr 0.55
- Liver function: Alt 74, AST 97, ALP 123, Total bili 1.4 and ammonia level of 110.

UA showed urobilinogen with decreased urine specific gravity, UDS was negative and BAL < 10. After initial assessment patient was admitted as inpatient and treated with supportive care including IV fluids NS 150ml/hr and PRN Ativan. All serotonergic medications were held along with psychiatry and neurology consult. Neurology recommended getting MRI brain and EEG.

MRI brain did not reveal any acute intracranial abnormalities but showed some chronic findings of basal ganglia T1 hyper intensity. Differential included hepatocellular degeneration, hepatic encephalopathy, hyper alimentation, hyperglycemia, and hypoxia. This was followed by EEG which showed abnormal electroencephalogram during sleep and wakeful states. These findings were deemed consistent with a toxic, metabolic, or hypoxic/ischemic encephalopathy. No epileptiform pathology was noted and neurology signed off.

Labs on day 1 of hospital admission

- Hgb: 12.1, PLT: 134
- Creatinine: 0.51, CK: 90
- AST: 77, ALT: 62, ALP: 106, Total bilirubin: 2.0

Diagnosis

Our diagnosis was based clinically with the use of hunter's criteria. We diagnosed the patient with serotonin syndrome given the history of use of a serotonergic agent along with presence of inducible clonus +agitation. Besides meeting the minimum criteria for diagnosis, he also met additional symptoms of tremor and hyperreflexia.

Clinical course

Patient improved within 2 days of supportive therapy with IV fluids and benzodiazepines. He received a total of 2.5 mg IV lorazepam within 48 hours of admission. Patient gradually started responding to verbal stimuli and commands, but he remained oriented only to self. Psychiatry consult was placed and on day 3 patients was started on Zyprexa 5mg PO QHS while still holding SSRI. Patient was very sedated during daytime and Zyprexa was further reduced to 2.5mg after supper. This helped the patient with daytime sedation, but he continued to be partially oriented and exhibited thought block, delayed recall and confusion along with failure to understand the circumstances of hospital admission. While serotonin syndrome resolved, Psychiatry team deemed inpatient stay less beneficial at this point and recommendations for skilled nursing facility was made.

Past medical history

Patient had multiple admissions related to altered mental status in the last 6-months secondary to grade 1 hepatic encephalopathy. He was mostly managed on lactulose titrated to bowel movements and his ammonia levels trended in the 150-200's. He also recently had GI bleed and a TIPS procedure for the same.

Discussion

Alteration in hepatic blood flow, including the development of portal-systemic shunting, will significantly decrease the pre-systemic elimination [first pass effect] of drugs metabolism [6].This leads to a higher proportion of drug build up in the system [6]. Additionally, most medications in general are metabolized by hepatic cytochrome p450 isoenzymes [7]. Chronic liver disease inevitably leads to decreased production and activity of CYP isoenzymes effecting multiple drug metabolism [8].

In the background of hepatic impairment, high risk psychotropics are not recommended [9].Olanzapine however has extensive first pass metabolism but it is also mostly metabolized by second phase glucuronidation which is preserved in liver diseases and our patient was restarted on Olanzapine at 2.5 mg to manage MDD with psychotic features [9].

Table 1: Adapted from [8] Hunter's criteria:

Hunter Criteria-serotonin syndrome
Presence of a Serotonergic agent + one of the following below:
a) Spontaneous Clonus
b) Inducible Clonus + agitation OR diaphoresis
c) Ocular Clonus+ agitation OR diaphoresis
d) Hypertonia + Temperature >38˚C + ocular OR inducible clonus
e) Tremor + Hyperreflexia

Gollapudy, et al. reported a patient with acute decompensation of nonalcoholic steatohepatitis cirrhosis treated with citalopram and tramadol that served to highlight points that could be translated to this patient studied with serotonin syndrome (Table 1) [8]. In our patient with chronic cirrhosis and decreased CYP450 activity, serotonergic toxicity was manifested by mental status changes, autonomic instability and neuromuscular hyperactivity. Another important point to consider is that our patient's chronic cirrhosis in the setting of untreated hepatitis C, with hepatic encephalopathy, could have been masking some of the initial symptoms of serotonin syndrome in this patient as they both present clinically similar with some aspects of mental status changes, akathisia and diarrhea [10].

Kumar, et al. reported a case of SS precipitated by intentional overdose on escitalopram and concomitant use of cocaine [11]. Their case also had spontaneous resolution of symptoms after 24 hours of IV fluids and benzodiazepine and did not require cyproheptadine. This indicates that diagnosing SS timely and holding the offending agent will reasonably guide towards resolution of SS.

As appropriately used in the literature, diagnosis of SS was made in our patient using Hunter's criteria. The patient had history of use of a serotonergic agent [Lexapro 5mg, albeit a low dose, and Olanzapine 5 mg, that blocks 5HT2 receptor] along with presence of inducible clonus +agitation and/ or diaphoresis. Besides meeting the minimum criteria for diagnosis, he also met additional symptoms of tremor and hyperreflexia.

Given the history of use of relatively low dose of an antidepressant (Lexapro 5 mg), & antipsychotic (Olanzapine 5 mg) in our patient, there raises a question that there could have been some variation in the metabolism of these agents to increase the possibility that yielded a product of Serotonin Syndrome.

To address what could have contributed to this patient's diagnosis; factors such as past relevant medical history must be addressed to fully understand the picture of why this case presented the way it did. This patient already had an extensive history of cirrhosis of the liver secondary to hepatitis C with chronic hyperammonemia reflected over the course of multiple hospitalizations over the past 6 months requiring supplementation of Lactulose 20 mg TID every day.

In previous hospitalization encounters, the patient had presented somewhat similarly, though with gradual decline in mental status, moderate responsiveness, intermittent episodes of mild agitation, without any serotonergic or antipsychotic medication use. Previous hospitalizations deemed hepatic encephalopathy to be the likely etiology of symptoms. However, what made this presentation unique this time was

1) A rapid status of mental decline with minimal unresponsiveness on initial presentation with agitation, restlessness, confusion, disorientation,
2) Autonomic instability with hypertension, diaphoresis, tachycardia, and
3) neurological exam findings of UE and LE rigidity, LE Knee jerk was hyper- reflexive 4+ B/L ankle jerk were 3+ B/L and right foot elicited sustained inducible clonus along with moderate to severe non-sustained clonus over left foot.
4) Above findings coupled with the fact that patient had been recently started on Lexapro and Olanzapine, made suspicion and diagnosis for serotonin syndrome more suggestive.

In addition, depression with psychotic features, as was diagnosed in our patient can also mimic symptoms congruent with hepatic encephalopathy with features of similar cognitive deficits including delayed recall, thought blocking and psychomotor retardation [12]. The theory behind this is that cirrhotic patients with depression may have more challenging social circumstances than those without etiologies of cirrhosis (alcohol misuse, hepatitis C infection), having a social underpinning [12].

Social history in our patient is also noteworthy. He did not have family members or friends to report to staff; he had been homeless living off the streets for several years in and out of various psychiatric institutions, jails, and hospitals. As if depression and cirrhosis interplay is not supporting enough, studies, [12] have found that a significant proportion of patients have synonymous Hepatitis C and depression both of which are present in our patient with overlapping symptoms of neuropsychiatric manifestations including cognitive impairment, fatigue, and a "brain fog" that cannot be fully explained by liver disease associated with infection.

It is also note worthy to rule out Neuroleptic malignant syndrome as patient did have antipsychotic [Olanzapine] use for psychotic features with depression, and can mimic serotonin syndrome, though patients develop this after a gradual onset of using antipsychotics [dopaminergic antagonist use], high fever, altered mental status, rigidity, increased white blood cell count, and increased creatine kinase [3-4 fold higher than normal], with absence of myoclonus and hyperreflexia.

With escalation of symptoms following recent antidepressant use, normal white blood cell count, presence of myoclonus and hyperreflexia.Patient responded to treatment with discontinuation of serotonergic agent with supportive fluids, and benzodiazepines, neuroleptic malignant syndrome was ruled out with CK being 90.

Conclusion

Serotonin syndrome is an important diagnosis clinicians must be aware of as it can be easily overlooked in a timely fashion.

Having knowledge of

a) Serotonergic agents

b) Drug-drug interactions

c) Relevant past medical history with conditions affecting metabolism of CYP450 enzymes [e.g. hepatic encephalopathy, cirrhosis, hepatitis C] and

d) Rapidity of symptoms that can present with triad of mental status changes, autonomic instability and neuromuscular excitability are all factors to be cognizant of in making a timely diagnosis.

Declarations

Ethics approval and consent to participate

The ETSU IRB has decided the need to waiver patient consent based on the type of project. This case report has used all deidentified data.

Consent for publication

Yes

Competing interests

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Authors' contributions

Sharma Trishna- literature review, introduction and case report

Persaud, Hemraj Anand MD- Literature review discussions and conclusion

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