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Conservative management of severe serotonin syndrome with coma, myoclonus, and crossed-extensor reflex complicated by hepatic encephalopathy

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ABSTRACT

Serotonin syndrome (SS) is an underrecognized and potentially fatal disorder that occurs secondary to combinational use or overdose of a single serotonergic medication. The presentation may be complicated by hepatic encephalopathy in cirrhotic patients, which may also affect metabolism of these serotonergic agents. The authors report a rare case of severe SS complicated by hepatic encephalopathy secondary to cirrhosis in a 52-year-old woman after an increase in her home dosage of fluoxetine and addition of other psychiatric medications.

KEYWORDS Cross-extensor reflex; hepatic encephalopathy; management; myoclonus; serotonin syndrome

Serotonin syndrome (SS) is an underrecognized and potentially fatal disorder caused by drug-induced excess serotonin. It most often occurs when two or more serotonergic medications are inadvertently administered in combination or through overdose of a single agent.[1] Tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors are most commonly implicated. SS may present via the triad of altered mental status (agitation, confusion), autonomic instability (hyperthermia, tachycardia, mydriasis), and neurologic derangements (hyperreflexia, myoclonus, tremor, rigidity).[1] Treatment of mild to moderate cases involves withdrawal of implicated agents and supportive care.[2] Some reports have used antidotes for severe cases.[1,3] We report a case of severe serotonin syndrome with coma, myoclonus, and crossed-extensor reflexes complicated by hepatic encephalopathy.

CASE STUDY

A 52-year-old woman with cirrhosis, cluster bipolar disorder, major depressive disorder, polysubstance abuse (alcohol, cocaine, and phencyclidine), and hypertension presented to our service after transfer from psychiatry for acute changes in her mental status.

Seven days prior, the patient was admitted to psychiatry for suicidal ideation with auditory and verbal hallucinations. On day 3 of admission, the patient's home fluoxetine dose was increased from 10 to 20 mg 4 times per day. She was also initiated on aripiprazole 5 mg 3 times per day and cyclobenzaprine 10 mg 4 times per day for her symptoms. Home medications were continued *(Table 1)*. Her psychiatric symptoms improved, but she endorsed new-onset mild tremors 2 days after increasing fluoxetine. At the time, the tremors were attributed to alcohol withdrawal. However, after 4 days of increased fluoxetine, she became more withdrawn, fatigued, and confused. On the seventh day, she became somnolent but arousable. She was subsequently transferred to the medicine service for further evaluation.

On initial evaluation, the patient was somnolent and uncooperative. Vital signs were within normal limits. Examination revealed 1+/3+ edema bilaterally in her legs and a neurological exam not indicative of a focal lesion. She was tremulous, oriented only to self, and somnolent. The platelet count was 53,000/μL, with a leukocyte count of 2,600/μL, ammonia 82 μmol/L, aspartate aminotransferase 76 U/L, and alanine aminotransferase 81 U/L. A complete metabolic panel was otherwise unremarkable. A head computed tomography scan was unremarkable.

The patient was started on lactulose 10 mg 3 times per day for suspected hepatic encephalopathy and was continued on her psychiatric medications *(Table 2)*. On day 2 of admission to the medicine service, the patient was still altered and became more delirious. On examination, she was tremulous with flushing of her skin and increased muscle tone (lower limbs greater than upper limbs). Neurological exam now demonstrated 4+/4+ reflex patellar reflexes with extensor crossover. Furthermore, she

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Table 1. The patient's scheduled medication list at the time of transfer from the psychiatry service to the medicine service

Medication	Dosage
Amlodipine	5 mg QD
Aripiprazole	5 mg QD
Cyclobenzaprine	10 mg TID
Fluoxetine	20 mg QD
Folic acid	1 mg QD
Gabapentin	400 mg QID
Hydroxyzine	25 mg TID
Lisinopril	10 mg QD
Naproxen	500 mg BID
Thiamine	100 mg QD
Trazodone	100 mg QD

QD indicates once daily; TID, 3 times per day; QID, 4 times per day; BID, twice per day.

had inducible lower extremity clonus and 3+/4+ biceps and brachioradialis reflexes. Aripiprazole, cyclobenzaprine, fluoxetine, and lactulose were held. The creatinine kinase, salicylate, valproic acid, and thyroid-stimulating hormone levels were normal. The patient was treated with normal saline and lorazepam as needed for agitation and was started back on lactulose 10 mg 3 times per day on day 3.

For the next 3 days, the patient was more arousable but still intermittently delirious and somnolent. Exam showed persistent hyperreflexia and clonus. Lorazepam 1 mg was given 3 times in the first 3 days for agitation. Her lactulose was uptitrated to 20 mg 4 times per day. She received labetalol 10 mg for elevated blood pressures 3 times.

On day 10, the patient became alert and orientation to person, place, purpose, and time and was no longer somnolent. Neurologic exam disclosed 4+/4+ reflex patellar reflexes with extensor crossover but without clonus. On day 13, the patient was discharged on fluoxetine 10 mg 4 times per day. Other psychiatric medications were discontinued.

DISCUSSION

The United States Toxic Exposure Surveillance System noted 93 deaths due to SS in 2002.[4] The most common differential diagnosis of SS includes neuromalignant syndrome, anticholinergic toxicity, malignant hyperthermia, encephalitis, meningitis, and delirium tremens. The gold standard for diagnosis is evaluation by a medical toxicologist. SS can also be diagnosed with an appropriate history and physical examination with use of the Hunter serotonin toxicity criteria, which has an 84% sensitivity and 97% specificity[5] *(Table 2)*. Offending medications should be promptly discontinued. Supportive care with goals to normalize vital signs by oxygen administration, continuous cardiac monitoring, and intravenous crystalloid solution is key.[6] Benzodiazepines are preferred for mild-to-moderate agitation, tachycardia, and hypertension.[7] In some case reports, the

Table 2. The Hunter serotonin toxicity criteria

The patient must be taking a serotonergic agent AND experience one of the following:
Spontaneous clonus
Inducible clonus + [agitation or diaphoresis]
Ocular clonus + [agitation or diaphoresis]
Tremor + hyperreflexia
Hypertonia + temperature above 38°C + [ocular or inducible clonus]

antidote cyproheptadine, a 5-HT_{2A} inhibitor, has been used in moderate and severe cases when supportive care fails.[8]

The patient's elevated ammonia level at presentation (82 μmol/L) led to consideration of hepatic encephalopathy. The correlation of hyperammonemia and hepatic encephalopathy has been questioned because it is the level of ammonia in the cerebrospinal fluid that is the determinant of hepatic encephalopathy.[9] Nevertheless, increased levels of ammonia in the serum have been shown to be a predictor of hepatic encephalopathy.[10] Worsening symptoms over 24 hours despite aggressive lactulose treatment and bowel movements prompted investigation of other causes. The patient's medication list revealed 3 drugs that may precipitate SS and worsen SS symptoms when taken in combination. Fluoxetine, a selective serotonin reuptake inhibitor, and its metabolite norfluoxetine were most likely the major cause of the patient's prolonged SS course, because they have the longest half-lives (1 week and 2.5 weeks, respectively) when taken for prolonged periods of time.[11] Aripiprazole is an atypical antipsychotic that acts as partial agonist at 5-HT_{1A} receptor and antagonist at 5-HT_{2A} receptor. Cyclobenzaprine has tricyclic properties and interacts with pro-serotonergic drugs to cause SS.[12] Aripiprazole and cyclobenzaprine have shorter half-lives (72 and 32 hours, respectively). As such, a synergistic effect was likely due to the different serotonergic pathways implicated. Thus, despite normal doses, the combination induced SS.[12,13]

Our patient had features consistent with severe SS, including coma, cross-extensor hyperreflexia (4+), myoclonus, and increased tone in the lower limbs. Daily meticulous physical exams are crucial in the diagnosis and monitoring response to treatment, as observed in this patient. Despite her severe SS features, our patient was successfully treated supportively with intravenous fluids, benzodiazepines, and short-acting beta-blockers. Cyproheptadine, for which the evidence is limited to case reports/series, was not needed.[14] Minimal use of lorazepam and labetalol was required, highlighting the success of conservative management in this severe case.

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Reader comments

Dr. Roberts,

I received the copies of *Baylor University Medical Center Proceedings* from Tom Gore that you sent to him for me. I thank you very much. Also, thank you for publishing his review in the *Proceedings*.[1] I hope that it may stimulate some physicians to become a little more politically involved. While medicine is and always has been my first love, I found politics to be interesting and challenging. The decisions made there have a great deal to do with how we deliver care. Thanks again and my very best regards.

J. Roy Rowland, MD
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