CASE REPORT

A Complex Case of Suspected Serotonin Syndrome

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Serotonin syndrome is a potentially life-threatening state caused by an excess of serotonergic activity in the nervous system. Symptoms include mental status changes, autonomic instability, and neuromuscular hyperactivity (1). The present case report is of an elderly woman with moderate-to-severe presentation following psychotropic medication use.

CASE

"Ms. A" is a 60-year-old single, unemployed woman with a history of hypertension, hypothyroidism, and obstructive sleep apnea and a psychiatric history of bipolar I disorder, borderline personality disorder, and cannabis/alcohol/sedative/hypnotic (benzodiazepine) use disorder. She has had multiple psychiatric admissions since the age of 22 resulting from suicide attempts via overdose. Since this age, she has had 20 sessions of ECT. She was brought to the hospital for suicide attempt via drug overdose in the context of her husband's death.

The patient was medically cleared (temperature=36°C–36.5°C, heart rate=98–104 beats per minute, blood pressure=114–135 mm Hg/63–71 mm Hg, respiratory rate=20, and blood oxygen saturation level=95%–99%), fully oriented, and admitted to psychiatry. Urine toxicology, blood alcohol, acetaminophen, and salicylate levels were unremarkable. It is unclear whether over-the-counter medications were ingested. Past medications include lithium, divalproex, lamotrigine, phenelzine, vorioxetine, risperidone, and olanzapine. Prior to presentation, her psychiatrist placed her on phenelzine after a 3-week wash-out period from olanzapine and vorioxetine due to remission on phenelzine in the past. Phenelzine was titrated to 30 mg every morning and 45 mg every evening. Quetiapine was added for mood stabilization and for treatment of chronic, paranoid delusions that others intensely disliked her. Quetiapine was titrated to 50 mg every morning and 300 mg every evening. She was on these medications for 6 months preceding decompensation.

After admission, phenelzine was increased to 45 mg twice daily. Levothyroxine for hypothyroidism and modafinil for obstructive sleep apnea were continued. Amlodipine was discontinued, since the patient was normotensive. Following further titration, quetiapine was discontinued due to orthostatic hypotension. Risperidone was started, then cross-titrated to haloperidol at 2 mg every morning and 3 mg every evening due to the patient's concern of weight gain side effect and persistent psychotic symptoms on other antipsychotics. She was maintained on benztropine for extrapyramidal symptom prevention. Lamotrigine was started and titrated to a therapeutic level for further mood stabilization.

After 3 months of the above medication adjustments, Ms. A was noted over a couple of days to be oriented to herself only and resistant to passive flexion and extension of extremities. These symptoms, in combination with the recent addition of a neuroleptic, raised concern for neuroleptic malignant syndrome. However, the patient's vital signs were unchanged. Delirium workup revealed only a positive urinalysis that was subsequently treated. Catatonia was suspected, but the patient did not respond to a trial of benzodiazepines. Haloperidol was decreased to 2 mg at bedtime.

Overnight, the patient developed spontaneous, bilateral ocular and ankle clonus, mild diaphoresis, tremulousness, and diffuse 4+ hyperreflexia more pronounced in the lower extremities. Her 24-hour vitals were as follows: temperature=36.2°C–37.4°C, heart rate=77–107 beats per minute, blood pressure=108–158 mm Hg/52–105 mm Hg, respiratory rate=17–46, and blood oxygen saturation level=92%–98%. The rapid emergence of hyperreflexia and spontaneous clonus were suggestive of serotonin syndrome. Additionally, the patient remained afebrile, whereas temperatures of more than 38°C are typical in 87% of neuroleptic malignant syndrome cases. The patients' creatine phosphokinase levels oscillated between 200 IU/L and 400 IU/L and peaked at 693 IU/L, lower than the 1,000 IU/L–100,000 IU/L in neuroleptic malignant syndrome (2).

Psychotropic medications were discontinued. Supportive management with intravenous fluids was started with lorazepam as needed. The clonus and diaphoresis resolved. The patient's laboratory workup was normal. Video EEG showed nonspecific generalized slowing. However, the patient became intermittently tachycardic to 110 beats per minute and hypertensive to 170/90. She remained afebrile.

The patient was transferred to an intensive care unit for administration of cyproheptadine by nasogastric tube. Over several days, her heart rate and blood pressure normalized. Over the following week, her symptoms resolved, and she returned to baseline mental status. She was transferred back to psychiatry where she was stabilized on divalproex, vortioxetine, haloperidol, lorazepam, and benztropine.

DISCUSSION

Serotonin syndrome was first described in the 1960s in a patient with tuberculosis who had received meperidine with iproniazid (3). Since the death of Libby Zion, the daughter of a powerful attorney, in 1984 (4), there have been hundreds of case re-

TABLE 1. Common Drugs Associated With Serotonin Syndrome[a]

Drug	Mechanism of Action
Amphetamine, amphetamine derivatives	CNS stimulant: blocks presynaptic reuptake of norepinephrine and dopamine
Analgesics: fentanyl, meperidine, tramadol	CNS opioid receptor agonist, NRIs, SRIs
Antidepressants	SSRIs, SNRIs, MAOIs
Mood stabilizers	Lithium: unknown, alters nerve and muscle cell Na+ transport VPA: unknown, increases CNS concentrations of GABA
Antimigrane drugs: ergots, triptans	Ergots: 5-HT1D agonist; triptans: 5-$HT_{1B/1D}$ agonist
Antiemetics: metoclopramide, ondansetron	CNS and PNS: antagonizes dopamine receptors; modulates serotonin receptors
Dextromethorphan	Centrally acting antitussive; active at multiple receptor types
Linezolid	Oxazolidinone antibacterial, reversible MAOI
Methylene blue	Potent MAO-A inhibitor, MAO-B inhibition at higher levels
Cocaine	CNS dopamine transporter protein blockade. 5-HT_3 antagonist
St. John's wort	Multiple mechanisms, including reuptake inhibition of multiple monamines
Tryptophan supplements	Amino acid, involved in biosynthesis of serotonin

[a] For further details, see references 13–17. CNS=central nervous system; GABA=gabaaminobutyric acid; MAO=monoamine oxidase; MAOI=monoamine oxidase inhibitor; Na+=sodium; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; PNS=peripheral nervous system; VPA=valproate.

ports describing serotonin syndrome. A literature review published in 2000 examined 226 cases from the 1960s to the 1990s (5). The age of individuals with serotonin syndrome spanned from 5 years old to 82 years old but occurred commonly between ages 20 and 50. The male-to-female ratio was 1:1.7, and 90% of patients had at least one of the following disorders: depression (65.8%), headaches (19%), obsessive-compulsive disorder (9.7%), alcohol abuse (7.3%), and generalized anxiety (7.3%) (5).

Ingestion of multiple drugs that block serotonin reuptake can cause serotonin syndrome (see Table 1). Patients with no exposure to a selective serotonin reuptake inhibitor (SSRI) who acutely ingest an SSRI in large doses are at higher risk (6). Hunter's Criteria is one instrument used in making this clinical diagnosis and captures 84% of cases. Diagnosis using Hunter's Criteria requires any of the following symptoms in the setting of serotonergic agent use: spontaneous clonus, clonus induced by sudden dorsiflexion of the ankle plus agitation or diaphoresis, ocular clonus (slow continuous lateral eye movements) plus agitation or diaphoresis, tremor plus hyperreflexia, or hypertonia plus temperature above 38°C plus ocular clonus or inducible clonus (1). These symptoms may develop later, and presenting symptoms can include lethargy and disorientation (5).

There is no specific test for serotonin syndrome. Laboratory abnormalities are nonspecific but include elevated creatine phosphokinase, leukocytosis, transaminitis, and low serum bicarbonate (7). Measurement of serotonin levels has not been shown to be helpful (4).

Clinical presentation can range from mild to moderate to severe symptoms. Intensity of symptoms reflects the degree of serotonin toxicity. Consequently, intensity of treatment depends on clinical findings. Mild cases with hyperreflexia, intermittent tremor and without fever or tachycardia can be managed by discontinuing the offending agent and supportive care. Lack of improvement warrants transfer to a medical unit. Moderate cases involving tachycardia, hypertension, fever, diaphoresis, or clonus and severe cases involving rigidity, seizures, and unstable hemodynamics require additional treatment: hydration, sedation, and intubation (4, 8). Controlling repetitive isometric muscle contractions in episodes of agitation with benzodiazepines is crucial to prevent morbidity and mortality (4, 8). Restraints are contraindicated and may contribute to mortality. Cyproheptadine, a 5-HT_{2A} antagonist, is often given, although efficacy has not been clearly established (4, 8).

The presentation of the patient in the above case was moderate to severe. Additionally, the patient was taking phenelzine, a monoamine oxidase inhibitor (MAOI) strongly associated with severe cases due to irreversible inhibition of the enzyme (1). Because of this, the body must regenerate monoamine oxidase to resume prior levels of enzymatic activity, a process that may take weeks. Effects of the MAOI can persist after the drug has been cleared (9). A limitation of the present case re-

KEY POINTS/CLINICAL PEARLS

- Symptoms of serotonin syndrome include mental status changes, autonomic instability, and neuromuscular hyperactivity.
- Hunter's Criteria (sensitivity 84% and specificity 97%) is a measure commonly used to diagnose serotonin syndrome.
- Laboratory abnormalities seen are nonspecific but can include elevated creatine kinase, leukocytosis, transaminitis, and low serum bicarbonate.
- Treatment includes removal of the offending agent and supportive care.; cyproheptadine, a 5-HT_{2A} antagonist, is often given, although efficacy has not been clearly established.

port, however, is that discontinuation of all psychiatric medications would treat both serotonin syndrome and neuroleptic malignant syndrome and that timing of the improvement would correspond to both neuroleptic malignant syndrome (10) and severe serotonin syndrome with MAOI involvement (9). Moreover, it is possible that the patient had co-occurring substance use on the unit or an acute ingestion. Urine toxicology repeated on readmission to psychiatry was negative, but this test does not detect agents such as synthetic opiates and SSRIs (11).

There are no clear guidelines as to which psychiatric medications to restart in patients with a history of serotonin syndrome (12). The patient in the above case report was restarted on a regimen without an MAOI.

Most of the literature on serotonin syndrome dates from the 1990s to the 2000s. Future areas of investigation include the creation of risk assessments for serotonin syndrome, which include details correlating morbidity and mortality with symptom timing, type and dose of drug ingested, and diagnoses. Objective measures such as vital signs warrant inclusion.

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