CASE REPORT

Rare case of severe serotonin syndrome leading to bilateral compartment syndrome

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SUMMARY

The term 'serotonin syndrome' describes a constellation of symptoms caused by serotonergic overstimulation. Its characteristic clinical presentation consists of encephalopathy, neuromuscular signs and autonomic hyperactivity. After removal of the offending agent, the clinical course is usually self-limited but can occasionally lead to severe symptoms. We report the case of a 68-year-old woman who presented emergently with encephalopathy. Home medications included paroxetine and dextroamphetamine/amphetamine. Physical examination revealed tachycardia, tachypnoea, diaphoresis, rigidity, hyperreflexia and clonus. Given the fast onset of symptoms, a diagnosis of serotonin syndrome was made. Laboratory studies showed acute-on-chronic kidney injury and elevated creatine kinase. The patient's mental status quickly returned to baseline with supportive care. Her rhabdomyolysis, however, persisted and led to acute compartment syndrome in her lower extremities. After bilateral leg fasciotomies and treatment of a severe wound infection with intravenous antibiotics, the patient has now recovered with complete resolution of her symptoms.

BACKGROUND

Serotonin syndrome (SS) is a likely underdiagnosed side effect of agents that increase serotonergic stimulation in the nervous system. It has been associated with a number of different medications but is most commonly caused by selective serotonin reuptake inhibitors (SSRI). Clinical presentation ranges from mild confusion to life-threatening symptoms including hyperthermia and rhabdomyolysis. We report the case of a patient with severe SS leading to progressive, significant rhabdomyolysis requiring bilateral fasciotomies for limb salvage. This case illustrates the potential for severe symptoms due to excessive stimulation of serotonin receptors. Although severe rhabdomyolysis as seen in this case is rare, it is important to recognise SS early in the disease course so that appropriate treatment can be initiated and potential limb-threatening and life-threatening symptoms can be prevented.

CASE PRESENTATION

A 68-year-old woman with a history of chronic kidney disease, back pain, hypertension and depression presented with altered mental status.

On initial presentation, the patient was unable to provide the history secondary to encephalopathy. She lived independently but had a phone conversation the previous morning with a friend who

noticed that she sounded tired and confused. The friend then attempted several calls on the morning of presentation. After failing to contact the patient, the friend went to her house around 09:00 and found her in her nightgown on the ground next to her bed, which appeared to have been slept in. The patient was awake but unable to get up or walk. She was diaphoretic and slow to answer questions. Emergency medical service was called and the patient was taken to the emergency room, where she was found to be somnolent and diaphoretic. She demonstrated shallow breathing. Her oxygen saturation was 84% on room air, which normalised after intravenous administration of naloxone. Her mental status also improved but continued to wax and wane. She reported of a new pain in her feet and increased back pain. According to the patient's family, she had been taking trazodone for insomnia as well as psychiatric medications. She had prescriptions for paroxetine 40 mg orally every day (qd) and dextroamphetamine/amphetamine 50 mg orally once a day. She was tapering off risperidone, having decreased from taking 3 mg to 2 mg several weeks ago, then most recently taking 1 mg tablets on and off. Additional medication bottles found in the patient's house were: omeprazole 20 mg orally once a day, hydromorphone 4 mg orally once a day 8 hours and the dietary supplement Zendocrine (Tangerine, Rosemary, Geranium, Juniper Berry and Cilantro Herb essential oils).

Her physical examination was notable for the following: tachycardia, tachypnoea, diaphoresis, somnolence; disorientation to place, situation and time; rigidity in all four extremities with profound rigidity in the lower extremities, hyperreflexia in the lower extremities, spontaneous clonus of the upper extremities and inducible clonus of the lower extremities; no nystagmus.

INVESTIGATIONS

Laboratory investigations showed several abnormalities: white cell count 20.47 k/uL, creatinine 2.44 mg/dL, blood urea nitrogen 46 mg/dL, potassium 7.4 mmol/L, aspartate aminotransferase 866 U/L, alanine transaminase 318 U/L and creatine kinase (CK) 11 955 U/L.

DIFFERENTIAL DIAGNOSIS

Two important conditions within the differential diagnosis of the clinical presentation are SS and neuroleptic malignant syndrome (NMS). There are no clear diagnostic tools to help differentiate between these two diagnoses. There are, however, differences in the initial clinical presentations that

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Table 1 Comparison of neuroleptic malignant syndrome and serotonin syndrome (modified after²)

	Serotonin syndrome	Neuroleptic malignant syndrome
Most commonly associated with	Serotonergic agents (SSRI)	Dopamine antagonists
Onset	Variable, <12 hours	Variable, 1–3 days
Identical clinical features	Hypertension Tachycardia Tachypnoea Hyperthermia Hypersalivation	Hypertension Tachycardia Tachypnoea Hyperthermia Hypersalivation
Overlapping clinical features	<ul style="list-style-type: none"> Diaphoresis Mental status: variable; agitation, coma; encephalopathy can occur (~ 50%) Muscle examination: increased tone in lower extremities 	<ul style="list-style-type: none"> Diaphoresis Mental status: variable; ranges from alert to stupor and coma, encephalopathy occurs frequently (>90%) Muscle examination: 'lead-pipe' rigidity in all muscle groups
Distinct clinical features	Hyperreflexia Clonus Dilated pupils	Hyporeflexia Normal pupils
Laboratory abnormalities	Elevated creatine kinase Elevated hepatic transaminases Leucocytosis	Elevated creatine kinase Elevated hepatic transaminases Leucocytosis

SSRI, selective serotonin reuptake inhibitors.

help distinguish the diagnoses. Typically, SS presents faster, within minutes to hours, compared to a more subacute clinical course in NMS, which usually develops within days. Encephalopathy, muscle rigidity and hyperthermia are commonly more pronounced in NMS, whereas SS more commonly shows myoclonus (table 1).^{1 2}

Given the rapid onset of her symptoms, the observed clinical signs and her history of taking several medications with the potential to increase serotonin activity, a diagnosis of SS was made. NMS was less likely but could not be excluded definitively given her elevated CK, which is more commonly seen in NMS, and her previous treatment with antipsychotics.

TREATMENT

Given the rapid onset of her symptoms and the observed clinical signs, the diagnosis of SS was made and all possibly offending agents were withheld. With adequate intravenous fluid treatment, the patient's acute renal failure slowly resolved but her CK level continued to rise (peaked at 84 166 U/L 2 days after initial presentation) and she reported worsening leg pain. As her leg compartments were firm and difficult to compress indicating elevated compartment pressures, she was taken to the operating room (OR) for immediate release via bilateral fasciotomies and returned to the OR the following day for debridement of necrotic muscle tissue.

With adequate pain management, the patient's mental status slowly returned to baseline. On reviewing her most recent history, she reported that she was in her normal state of health 2 days prior to presentation. On the day prior to presentation, she felt a little tired and unwell so she took a nap but otherwise pursued her usual daily activities. She remembered going to bed at her usual time, and then waking up in the early morning hours to use the restroom. She could not remember subsequent details. She admitted to taking several extra doses of both dextroamphetamine/amphetamine and hydromorphone on the days leading up to admission.

OUTCOME AND FOLLOW-UP

After discharge from the inpatient setting, the patient was treated with empiric antibiotics (vancomycin/meropenem) for superinfection of her wounds. She received hospice care for

several weeks but then slowly recovered. She returned to her home with home health ~6 weeks after her initial presentation. Despite bilateral leg fasciotomies and extensive debridement, she is now again able to ambulate. Her mental status has remained at baseline.

DISCUSSION

SS is a potentially life-threatening constellation of symptoms caused by excessive stimulation of serotonin receptors in the central nervous system as well as the periphery.

Serotonin, or 5-hydroxytryptamine, is a monoamine neurotransmitter that is mostly synthesised in the enterochromaffin cells in the gastrointestinal (GI) tract where it regulates GI motility.³ Serotonergic neurons in the central nervous system (CNS) are mainly located in the Raphe nuclei⁴ and connect via ascending projections to various CNS regions, which allows them to be involved in a variety of regulatory functions, which include mood, attention, memory, depression, anxiety and thermoregulation.⁵ In the periphery, serotonin is involved in a number of additional functions including emesis, vasoconstriction, uterine contraction, bronchoconstriction and platelet aggregation.^{6 7}

Overstimulation of serotonin receptors has been reported with an increasing number of prescription drugs, herbal supplements and recreational drugs. These include agents that increase serotonergic neurotransmission like SSRI, serotonin and norepinephrine reuptake inhibitors, lithium, triptans, agents that increase the release of serotonin such as ecstasy or cocaine and agents that inhibit serotonin degradation, like monoamine oxidase inhibitors.⁸ Discontinuation of drugs has also been associated with SS, as has ingestion of single doses of medications that stimulate serotonin receptors. The most commonly associated medications in the literature have been SSRI.

While it is possible that taking only a single drug can significantly increase serotonin levels, SS is more commonly seen in patients who take one serotonergic agent at baseline, for example, an SSRI for depression, and then take additional serotonergic medications, like an antiemetic agent for nausea.

SS is diagnosed based on clinical symptoms. It typically presents with a triad of cognitive-behavioural (encephalopathy, agitation), autonomic (diaphoresis, diarrhoea, hyperthermia) and neuromuscular signs (clonus, hyperreflexia, tremor, rigidity).⁸

Even though it is a diagnosis of exclusion, the use of diagnostic criteria helps establish the correct diagnosis. The most commonly used and most accurate⁹ diagnostic criteria are the Hunter Criteria¹⁰ which require one or more of the following clinical signs in addition to the presence of a serotonergic agent: (1) Spontaneous clonus (2) Inducible clonus with agitation or diaphoresis, (3) Ocular clonus (ie, slow roving horizontal eye movements) agitation or diaphoresis, (4) Tremor and hyperreflexia, and (5) Hypertonia, temperature above 100.4°F (38°C) and ocular clonus (see table 2).

The severity of symptoms is thought to correlate with the extent of serotonergic activation at the nerve ending. It does not necessarily correlate with blood levels of serotonergic agents but rather with the amount of intrasynaptic serotonin.¹¹ SS is likely the most severe clinical presentation of a spectrum of disorders associated with serotonergic overstimulation.^{12 13}

Several abnormal laboratory findings can be seen, including leucocytosis and elevation of CK, aminotransferases, creatinine and potassium.¹¹

Most cases of SS resolve within 24–72 hours after discontinuing the offending agent but some patients go on to develop complications including seizures, hypotension, tachycardia, disseminated intravascular coagulation and myoglobinuria.¹⁰

Rhabdomyolysis associated with severe cases of SS has been reported. However, in some cases the distinction between SS and NMS was unclear.¹⁴ Also described are several cases of rhabdomyolysis associated with venlafaxine therapy with¹⁵ or without^{14 16} the clinical development of actual SS. Several other SSRIs have been associated with the development of rhabdomyolysis, including sertraline^{17 18} and escitalopram.¹⁹

Severe cases of rhabdomyolysis can lead to compartment syndrome. Rhabdomyolysis is defined as muscle necrosis leading to release of intracellular components into the extracellular compartment and the circulation.²⁰ It can be caused by a number of different processes that can be categorised as either hypoxic (prolonged pressure during an unconscious state, vascular occlusions), physical (trauma, overexertion), chemical (medications, illicit drugs) or biological (infectious or toxic myositis, muscular dystrophies),²¹ which all lead to increased intracellular calcium.^{22 23} Both SS and NMS can lead to rhabdomyolysis due to severe skeletal muscle rigidity leading to muscular necrosis.²⁴

Severe cases of rhabdomyolysis can lead to compartment syndrome as the oedema and inflammation in the limbs lead to increased local pressure which in turn compromises blood flow.^{22 25} Thick fascia, bones and other structures separate so-called compartments from each other. These contain muscles, and the nerves and blood vessels that supply those muscles. They are inflexible and cannot expand in response to a local process. The increased intracellular calcium in rhabdomyolysis leads to a shift of

large amounts of fluid from the extracellular to the intracellular space which causes swelling of muscle cells and increased local pressure.²² This in turn leads to a self-perpetuating cycle: as swelling increases, venous outflow of the blood is impaired, leading to further swelling. Once the pressure within the muscle compartment is greater than the end-arteriolar pressure, arterioles collapse.²⁶ Muscle necrosis will occur when the difference in compartment pressure and systemic diastolic pressure is <20 mm Hg.²⁷

If there is any suspicion for acute compartment syndrome, the pressure within the compartments should be measured. Patients often need to undergo emergent fasciotomies to prevent critical ischaemia resulting in irreversible damage of the muscles and nerves.²⁸

A diagnosis of SS in the presented patient seems likely given the rapid onset of her symptoms, mental status changes, typical features observed on her physical examination (spontaneous clonus on admission, rigidity and hyperreflexia in the lower extremities, diaphoresis, autonomic instabilities) and her history of taking several medications with the potential to increase serotonin activity. Elevated concentrations²⁹ and overdoses^{30 31} of paroxetine have been associated with SS. Given the patient's baseline chronic kidney disease and her significant acute-on-chronic renal failure, an increased blood level of paroxetine is possible as this medication is extensively hepatically metabolised, but renally cleared. Even though there is no clear relationship between blood levels of serotonergic agents and risk for SS,¹¹ her renal failure put the patient at increased risk for ongoing SS even after removing the offending agent (paroxetine was withheld after admission) as she likely required more time to clear this medication completely.

Overall, her presentation is clouded by her rhabdomyolysis leading to acute-on-chronic renal failure with reduced ability to clear her medications, including chronic narcotics and psychiatric medications, both of which likely contributed to her encephalopathy. The most likely cause for our patient's rhabdomyolysis was her SS, though muscular compression due to immobility was considered. As the patient was only 'down' for a few hours, immobility seems unlikely to be the only aetiology but may be contributing to the overall picture.

Learning points

- ▶ Serotonin syndrome has been associated with a number of different medications but is most commonly caused by selective serotonin reuptake inhibitors.
- ▶ The clinical course of serotonin syndrome is usually self-limiting but in some patients severe complications are observed (tachycardia, hyperthermia, seizures).
- ▶ Serotonin syndrome can lead to rhabdomyolysis as ongoing severe rigidity leads to muscle breakdown due to overstimulation and overuse.
- ▶ Rhabdomyolysis in turn may lead to acute compartment syndrome via oedema and inflammation in skeletal muscles leading to increased local pressure and compromised blood flow.
- ▶ Early recognition of serotonin syndrome is important as this is potentially life-saving and limb-saving.

Box 1 Hunter criteria (modified after¹⁰)

Hunter Serotonin Toxicity Criteria

Presence of a serotonergic agent and one or more of the following:

- ▶ Spontaneous clonus
- ▶ Inducible clonus and agitation or diaphoresis
- ▶ Ocular clonus and agitation or diaphoresis
- ▶ Tremor and hyperreflexia
- ▶ Hypertonia and temperature >38°C and ocular clonus or inducible clonus

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