EM CASE OF THE WEEK.

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Care Warriors

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Serotonin Syndrome

A 53-year-old male with a past medical history of depression and hepatitis C presents to the ED via EMS after being found obtunded aside empty bottles of sertraline, trazodone, and quetiapine. Patient was arousable only to extensive sternal rubbing. He was vomiting profusely and visibly aspirating. He was subsequently sedated with propofol and intubated in the ED. If serotonin syndrome was suspected, which of the following clinical pictures would most likely present in such a patient?

(A) Hyperthermia, agitation, altered mental status, mydriasis, dry mucous membranes, urinary retention, and decreased bowel sounds

(B) Hyperthermia, increased concentrations of end-tidal carbon dioxide, rigor mortis-like muscle rigidity, tachycardia, and acidosis

(C) Hyperthermia, altered mental status, leukocytosis, elevated creatine phosphokinase, elevated hepatic transaminases, metabolic acidosis, and sluggish neuromuscular responses (rigidity, bradyreflexia)

(D) Hyperthermia, altered mental status, leukocytosis, elevated creatine phosphokinase, elevated hepatic transaminases, metabolic acidosis, neuromuscular hyperreactivity (tremor, hyperreflexia, myoclonus)

Figure 1: A depiction of myoclonus

Serotonin syndrome is associated with increased serotonergic activity in the CNS seen with therapeutic medication use, inadvertent interactions between drugs, and intentional self-poisoning. The typical clinical triad is **mental status changes, autonomic hyperactivity, and neuromuscular abnormalities**.

EM Case of the Week is a weekly "pop quiz" for ED staff.

The goal is to educate all ED personnel by sharing common pearls and pitfalls involving the care of ED patients. We intend on providing better patient care through better education for our nurses and staff.

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The answer is (D). Serotonin Syndrome (SS) is a clinical diagnosis based on the patient's history and physical findings. Vital sign abnormalities typically include **tachycardia** and **hypertension**. In severe cases, patients may develop hyperthermia (accounted for by neuromuscular hyperactivity, not due to alteration in hypothalamic set point) and intense oscillations in pulse and blood pressure. Physical findings may include hyperthermia, agitation, ocular clonus, mydriasis, tremor, akathisia, **deep tendon hyperreflexia**, **spontaneous or inducible muscle clonus**, muscle rigidity, bilateral Babinski signs, dry mucus membranes, flushed skin and diaphoresis, and increased bowel sounds. Of note, the neuromuscular findings (hyperreflexia, clonus, rigidity, and etc.) are usually more pronounced in the lower extremities. Of the three agents that were found next to this particular patient, two can contribute to SS - sertraline and trazodone.

Answer (A) describes findings typical in **anticholinergic toxicity**.

Answer (B) describes findings typical in **malignant hyperthermia** secondary to halogenated volatile anesthetics and depolarizing muscle relaxants (e.g., succinylcholine).

Answer (C) describes findings typical **in neuroleptic malignant syndrome (NMS)** secondary to neuroleptic agents, most often seen with the "typical" high potency neuroleptic agents (e.g., haloperidol, fluphenazine).

The other answer choices are descriptions of selected differentials that are often confused with SS due to abundant overlap in clinical presentations - with NMS being the most common misdiagnosis. SS develops and resolves within 24 hours after withdrawal of the offending agent and is characterized by neuromuscular **hyperactivity**. NMS develops over days to weeks, takes longer to reach resolution, and involves **sluggish** neuromuscular responses with less hyperreflexia and myoclonus. Neuromuscular findings are often normal in other causes of an altered patient (e.g. anticholinergic poisoning and sympathomimetic toxicity).

Hunter Criteria for Serotonin Syndrome

[ ] Patient has taken a serotonergic agent

PLUS *One of the following:*

[ ] Spontaneous clonus
[ ] Inducible clonus AND agitation or diaphoresis
[ ] Ocular clonus AND agitation or diaphoresis
[ ] Tremor AND hyperreflexia
[ ] Hypertonia AND temperature above 38°C AND ocular clonus or inducible clonus

Discussion

Serotonin syndrome is defined by an increased in serotonergic activity in the CNS. It is often secondary to therapeutic medication use, inadvertent interactions between drugs, and intentional self-poisoning. SS presents as a spectrum of clinical findings and is associated with the triad of AMS, autonomic instabilities, and neuromuscular hyperactivities. The syndrome has been implicated in all age groups with the rising incidence correlating with the increasing use of serotonin reuptake inhibitors. It is a clinical diagnosis aided by the use of the **Hunter Criteria** (84% sensitive, 97% specific).

In the CNS, serotonin modulates attention, behavior and thermoregulation. In the PNS, the neurotransmitter regulates GI motility, vasoconstriction, uterine contraction, and bronchoconstriction. Serotonin also promotes platelet aggregation. The excess stimulation of two serotonin receptors (5-HT1A AND 5-HT2A) is implicated in SS. The syndrome is often a result of simultaneous administration of multiple (classically, two) serotonergic agents, but may also be due to an increase in dosage of a single serotonergic drug. Cases of SS that involve MAO inhibitors are associated with more severe clinical pictures and worse outcomes, including death. Other complications of SS include DIC, rhadomyolysis, myoglobinuria, RF, ARDS, and metabolic acidosis.

Serum serotonin concentrations do not correlate with clinical severity and associated laboratory findings are nonspecific (e.g. elevated WBCs, elevated CPK, and decreased bicarbonate.)

For a list of educational lectures, grand rounds, workshops, and didactics please visit ***BrowardER.com*** and **click** on the ***"Conference"*** **link**.

All are welcome to attend!

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January 2016 | Vol 3 | Issue 19

Table 1: Drugs that can precipitate Serotonin Syndrome (UpToDate)

Mechanism	Drug
Increases serotonin formation	Tryptophan
Increases release of serotonin	Amphetamines & Derivatives Cocaine MDMA (Ecstasy) Levodopa, Carbidopa-levodopa
Impairs synaptic serotonin reuptake	Cocaine MDMA (Ecstasy) Meperidine Tramadol Pentazocine SSRIs (**sertraline**, citalopram) SNRIs (duloxetine, venlafaxine) DA-NE reuptake inhibitors (bupropion) Serotonin modulators (**trazadone**) TCAs (amitriptyline) 5-HT3 receptor antagonists (ondansetron) Metoclopramide Valprotate Carbamazepine Dextromethorphan
Inhibits serotonin metabolism	MAO-Is (phenelzine, selegiline)
Direct serotonin agonist	Buspirone Triptans (sumatriptan) Ergots (ergotamine) Fentanyl Lysergic acid diethylamide (LSD)
Increases sensitivity of receptors	Lithium

Management and Antidote

Management of SS involves 5 key principles: (1) Discontinuation of all serotonergic agents, (2) Supportive care with the goals of normalizing VS, (3) Sedation via benzodiazepines, (4) Administration of antidotes/serotonin antagonists, and (5) Assessment of the need to resume the serotonergic agent. Supportive care includes oxygen (SaO2 goal ≥ 94%), IVFs (crystalloids), and continuous cardiac monitoring. IV benzodiazepines (lorazepam 2-4 mg or diazepam 5-10 mg) help in controlling agitation and may also ameliorate associated hypertension and tachycardia. Severe hypertension should be treated with titratable short-acting agents (esmolol or nitroprusside). Hypotension from MAO-Is should be treated with direct-acting sympathomimetics (phenylephrine, epinephrine, or norepinephrine). Hyperthermia can be controlled with cooling measures (lukewarm mist spray, cooling units/beds, and chlorpromazine if NMS is ruled out). Patients with temperatures above 41.1°C require immediate sedation, paralysis, and tracheal intubation.

Antidotal therapy with cyproheptadine is tried if supportive measures and benzodiazepines fail to normalize agitation and VS. An initial dose of 12 mg is followed by 2 mg every 2 hours until clinical response is observed.

Take Home Points

- SS is a clinical diagnosis. Hunter Criteria can help with the diagnosis.
- Patients often present with hypertension and tachycardia. Neuromuscular **hyperactivity** can help differentiate SS from NMS.
- Mainstay of management for SS is supportive care. Cyproheptidine is the antidote to SS.
- In cases of intentional overdose, consider simultaneous ingestion of salicylates (ASA) and acetaminophen (APAP).

ABOUT THE AUTHOR

This month's case was written by Nhan Do. Nhan is a 4th year medical student from NSU-COM. She did her emergency medicine rotation at BHMC in October 2016. Nhan plans on pursuing a career in Internal Medicine after graduation.

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