

CASE REPORT



Delayed onset serotonin syndrome in the setting of polypharmacy

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ABSTRACT

Serotonin syndrome is a rare but well-known condition that can be life-threatening if not diagnosed early. Onset is usually within 4 to 13 h of starting the offending medication. We present a case of delayed onset of serotonin syndrome that presented after 48 h. Polypharmacy played a role in causing the onset of symptoms. Clinicians should keep a high index of suspicion for serotonin syndrome when dealing with elderly confused patients who take multiple medications even when the onset is delayed or atypical because the outcome can be disastrous.

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KEYWORDS

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1. Case



A 76-year-old female with multiple comorbidities including scleroderma, chronic anemia, fibromyalgia, hypertension, chronic kidney disease stage 3, interstitial lung disease on 3 L oxygen, Raynaud's phenomenon, inflammatory bowel disease, hypothyroidism presented to the hospital with black discoloration of right second and third toe. She was started on intravenous linezolid and cefepime for presumed necrosis of toes. Arterial duplex study ruled out acute ischemia of lower extremities. On third day (55 h) of admission, she had a change in her mental status. She was agitated and disoriented on examination. Neurological exam revealed 3 + reflexes on bilateral lower extremities along with clonus and increased muscle rigidity. Blood pressure was 131/75 mmHg, Heart rate 104/min, respiratory rate 20/min, oxygen saturation 98% on 3 L oxygen, temperature was 36°C at the time but increased to 38.1°C few hours later.

Computed Tomography (CT) of the head was done which was unremarkable. Upon reviewing the home medications with the husband, we found that she was chronically on tramadol, cyclobenzaprine, oxycodone, pantoprazole and amlodipine. In the hospital, in addition to Linezolid, she was on metoclopramide as well. Though the presentation was atypical, we suspected serotonin syndrome (SS) based on Hunter's Criteria. Acute delirium was ruled out after determining no acute electrolyte abnormalities, drug overdosing, substance abuse, and acute alcohol or opiate withdrawal. Her metoclopramide and linezolid were stopped, and the

antibiotic was switched to vancomycin. CT head was repeated in next 24 h which was again unremarkable. Magnetic Resonance Imaging (MRI) of the brain did not reveal any acute pathology. Cerebrospinal fluid (CSF) cell count was within normal limits, with normal protein and negative gram stain and culture. Herpes simplex virus 1 & 2 PCR, cryptococcus antigen, varicella antibody, measles antibody, mumps antibody, rubella antibody, and West Nile virus antibody were negative. Serum Human Immunodeficiency Virus (HIV) ELISA test was non-reactive for HIV 1 & 2. Her laboratory results are tabulated in Table 1. The patient was managed on the telemetry floor with frequent mental status assessment and intravenous lorazepam as needed for agitation. On fourth day of stopping Linezolid and metoclopramide, her mental status started to improve. Her clonus and hyperreflexia resolved. A day later, the mental status returned to baseline. Her gangrenous change was deemed to be a dry gangrene due to chronic ischemia secondary to Raynaud's phenomenon and thus antibiotics were stopped. She had full mental and neurological recovery as was discharged on day 8 of hospitalization. Her tramadol and cyclobenzaprine were stopped on discharge (timeline depicted in Table 2).

2. Discussion

Serotonin syndrome is a serious condition that may be due to overdose, drug interaction, or occasionally therapeutic use of drugs [1]. Overstimulation of postsynaptic 5-hydroxytryptophan receptors (5HT1A and 5HT1B) in the central and peripheral nervous system

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Table 1. Laboratory Results.

Cell count	4/uL	WBC	19500/uL	Sodium	132 mmol/L
Protein	30 mg/dL	Differential	N78%, L8%	Potassium	4.5 mmol/L
Glucose	83 mg/dL	Hemoglobin	8.2 g/dL	Bicarbonate	18 mmol/L
Culture	Negative	MCV	86.3 FL	BUN/Cr	28.8/1.9 mg/dL
CrAg, VDRL, HSV 1/2 PCR, WNV IgG/IgM, MMR IgG/IgM	Negative	Platelets	472000/uL	Total protein/Albumin	7.4/1.9 g/L
		PT/APTT	30/10.5 sec	CK	67 U/L
		HIV 1/2	Non-reactive	Total Bilirubin	0.3 mg/dL
		Blood culture	Negative	AST/ALT/ALP	11/15/134 U/L

CSF: cerebral spinal fluid, CrAg: cryptococcal antigen, VDRL: Venereal Disease Research Laboratory Test, HSV: herpes simplex virus, MMR: measles, mumps and rubella, WNV: West Nile virus, PT: prothrombin time, APTT: activated partial thromboplastin time, CK: creatine kinase, AST: aspartate aminotransferase, ALT: alanine aminotransaminase, ALP: alkaline phosphatase.

Table 2. Timeline of the events.

	Started on linezolid		<ul style="list-style-type: none"> • MRI negative • CSF negative for infection 		Mental status back to baseline	
Home medicines: Tramadol, cyclobenzaprine	Day 1	Day 3	Day 4	Day 7	Day 8	On discharge: Tramadol and cyclobenzaprine stopped
		<ul style="list-style-type: none"> • AMS with new onset clonus and hyper-reflexia around fifty-five hours • Linezolid and metoclopramide stopped • CTH negative 		<ul style="list-style-type: none"> • Mental status improving • Clonus, Hyper-reflexia resolved 		

from single or multiple drugs can cause overwhelming serotonin response [2]. Though mostly caused by drug interaction, few cases of serotonin syndrome are reported with monotherapy of selective serotonin reuptake inhibitors (SSRI) or related drug [3,4]. Linezolid, a monoamine oxidase inhibitor is a well-known antibiotic to be a cause [5]. Drugs that are used frequently which can result in overwhelming serotonin response are listed in Table 3. The incidence of serotonin syndrome is unknown as there is no confirmatory test to diagnose serotonin syndrome. It is probably underdiagnosed as it is a diagnosis of exclusion. However, a few diagnostic criteria have been developed Hunter’s criteria is one of the widely

used criteria. Hunter’s criteria has a sensitivity of 84% and specificity of 94%. It is relatively simple to use. It uses physical examination findings as minor criteria, and exposure to serotonergic agents is the major criteria (Table 4) [6]. Symptoms generally appear within 4–6 h and all cases reported are within 24 h [7].

The population of patients who enters 65 years of age group is increasing everyday not only in the USA but globally. This age group usually has chronic medical conditions for which they are dependent on daily medicines from which they experience substantial side-effects also. To counteract the side-effects, another medicine is introduced quickly leading to polypharmacy [8]. One study revealed that polypharmacy tripled in 10 years in the Spanish population [9]. A study revealed that chronic pain syndrome, arthritis, insomnia, depression are common medical

Table 3. Common Medicines associated with Serotonin Syndrome.

Mechanism	Drugs
Increased serotonin Formation	Tryptophan
Increases release of serotonin	Amphetamine, cocaine, levodopa
Impairs reuptake in junction	TCA, SSRI, SNRI, St John’s wort, 5-HT3 antagonist, Dextromethorphan, Metoclopramide, Tramadol, Cyclobenzaprine
Decreased Metabolism	MAOI
Direct agonist	Tryptans, Fentanyl

TCA: tricyclic antidepressant, SSRI: selective serotonin reuptake inhibitor, SNRI: selective norepinephrine reuptake inhibitor, MAOI: monoamine oxidase inhibitor, 5-HT3: 5-hydroxytryptophan type 3.

Table 4. Hunter Serotonin Toxicity Criteria (Sensitivity 84%, specificity 94%).

Major Criteria	Minor Criteria (one of the following)
Serotonergic agent exposure	Spontaneous clonus
	Inducible clonus PLUS agitation or diaphoresis
	Ocular clonus PLUS agitation or diaphoresis
	Tremor PLUS hyperreflexia
	Hypertonia PLUS temperature above 38°C PLUS ocular clonus or inducible clonus

conditions for which this age group takes medicines such as anticholinergics, sedatives, anti-psychotics, and anti-depressants that are commonly associated with SS [8]. Chronic pain affects up to one-fifth of the population and depression is the third global burden disease and treatment is usually medicines that belong to tricyclic antidepressants, selective serotonin reuptake inhibitors selective norepinephrine reuptake inhibitors, and monoamine oxidase inhibitor [10]. As mentioned earlier, anti-depressants, antiemetics, opioids, muscle relaxants, over the counter cough medications can have interactions that can lead to serotonin syndrome [11]. As generally witnessed hospitalized patients are on one or more than one such medicines for chronic medical conditions.

The presented case was unique in a few ways. As far as we know it is one of the first cases that reports delayed presentation, i.e., more than 48 h. Another case has been reported in which the onset was after 72 h, but the late-onset was attributed to the concomitant use of short-acting cyproheptadine which counteracted the ongoing serotonin response caused by long-acting serotonin agonists. SS was obvious in that case only after 72 h, time enough for most of the cyproheptadine to be metabolized and excreted [12]. Another case was reported where the onset was at around 24 h [7]. In our case, no such medication was involved that could delay the presentation.

The treatment of SS is mainly supportive. The benzodiazepines are first line for agitation. Cyproheptadine, a histamine-1 receptor antagonist is widely used as antidote though there is no strong evidence to support its use. Antipsychotics are generally advised to avoid due to their anticholinergic property which can further complicate hyperthermia. Resistant hyperthermia should be managed in intensive care unit with sedation, muscle paralysis and mechanical intubation [1].

Lastly, we want to emphasize the need to have high index of suspicion to diagnose SS. In our case, diagnosis was made only after a thorough evaluation of patient by multiple specialties for a broad differential diagnosis.

3. Conclusion

Serotonin syndrome is an uncommon but well-known syndrome that can be life-threatening if there a delay in diagnosis. It should always be in the differential while evaluating an elderly acutely altered patient. It should be kept in mind that the onset might be delayed like in our case. Special attention to polypharmacy in elderly and medication review during hospitalization, including over the counter drugs, is of utmost importance in trying to prevent new cases. Whenever possible,

physicians should attempt to minimize the polypharmacy, if necessary, with the help of a pharmacist.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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