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BRIEF RESEARCH REPORT

The serotonin syndrome—the need for physician's awareness

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Abstract
Background Serotonin syndrome is a potentially life-threatening adverse drug reaction that results from therapeutic drug use, usually of selective serotonin reuptake inhibitors (SSRIs), intentional excessive use or interactions between various drugs.
Case presentation A 16-year-old Caucasian boy presented to our emergency department (ED) with alteration in his mental status for 6 h prior to arrival. On physical examination in our ED, he was combative and disoriented to time, place and person. He was febrile, hypertensive and tachycardic as well. He had intermittent rigid extremities with myoclonus of both lower extremities. A diagnosis of serotonin syndrome (SS) was made based on history of intake of fluoxetine and clinical signs, which included presence of inducible clonus and agitation. The child received supportive care involving intravenous fluids and intravenous lorazepam. The child was back to his baseline mental status and had a normal neurological exam by 24 h and was discharged home later for follow-up with a psychiatrist.
Conclusions SS occurs with increasing frequency, and most cases resolve with prompt recognition and supportive care. Failure to make an early diagnosis and to comprehend adverse pharmacological effects of therapy can lead to adverse outcomes.

Keywords Serotonin syndrome · Toxidrome · SSRIs

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Case presentation

A 16-year-old Caucasian boy presented to our emergency department (ED) with alteration in his mental status for 6 h prior to arrival. According to his parents, he was found in his uncle's garage in a state of confusion. They were uncertain as to what he was doing in the garage. He was not found sniffing anything. They said that he was not responding appropriately to verbal commands and was very agitated and confused. There was no history of trauma, fever or any recent illness. There was no witnessed seizure-like activity or bowel or bladder incontinence. The parents were not sure if he had ingested any drugs. The child had a history of depression diagnosed 1 year ago and was on treatment with fluoxetine (10 mg) since then. There was no history of suicidal ideations or attempts in the past. He was also on loratidine and lansoprazole for seasonal allergies and gastroesophageal reflux disease, respectively. There had been no recent changes in his medications. He had also completed a rehabilitation program for tobacco and alcohol abuse. He had no drug allergies, and his immunizations were up to date. His mother has a history of anxiety, seizure disorder, hypothyroidism and asthma. She was on multiple medications, including lorazepam, dilantin, synthroid and advair.

The child was initially taken to a nearby adult ED. Their impression was some type of drug ingestion versus meningoencephalitis. The child was given a dose of lorazepam and transferred to our ED for further management. On physical examination in our ED, he was combative and disoriented to time, place and person. His temperature was 38.3°C, heart rate 146/min, respiratory rate 22/min, blood pressure 145/84 mmHg and pulse oximetry 98% on room air. The pupils were equally dilated, 6 mm in size, and reactive to light and accommodation. There was

no nystagmus or ocular clonus noted. His neck was supple and he had a good cough and gag reflex. The abdomen was soft with no organomegaly, but bowel sounds were exaggerated. The skin was warm and flushed. On central nervous system examination, his speech was unclear with few words, and he was confused. The cranial nerves were grossly intact, and meningeal signs were negative. He was moving his extremities symmetrically without any appreciable weakness. He had intermittent rigid extremities with myoclonus of both lower extremities. His deep tendon reflexes were exaggerated, and he also had a patellar as well as ankle clonus. Based on his history and physical examination, the differential diagnosis included central nervous system infections like meningitis/encephalitis, toxic ingestions including sympathomimetic, anticholinergic, ingestions, salicylate toxicity, alcohol and benzodiazepine withdrawal, serotonin syndrome, carbon monoxide poisoning, neuroleptic malignant syndrome, trauma and endocrine disorders like thyroid storm.

His laboratory results at our ED showed normal serum glucose of 95 mg/dl, normal electrolytes, normal blood gas with normal carbon monoxide levels, normal thyroid studies, and negative urine and serum drug screens. CT scan of the brain without contrast was normal and did not reveal any intracranial masses or hemorrhage. His serum creatine phosphokinase (CPK) was within normal limits, and his urine myoglobin was negative. We decided to withhold the lumbar puncture in view of very short duration of symptoms and lack of meningeal signs. In view of his persistent agitation, he was given a dose of lorazepam. A diagnosis of serotonin syndrome (SS) was made based on history of intake of fluoxetine and clinical signs, which included presence of inducible clonus and agitation. The child was admitted to the hospital for supportive care in the form of intravenous hydration and lorazepam for control of his agitation. His fluoxetine was also discontinued. Two days later a urine comprehensive drug screen came back positive for dextromethorphan. The uncle concurred that he was indeed missing a cough syrup bottle from his home. The child was back to his baseline mental status and had a normal neurological exam by 24 h, and was discharged home later for follow-up with a psychiatrist.

Introduction

Serotonin syndrome is a potentially life-threatening adverse drug reaction that results from therapeutic drug use, usually of selective serotonin reuptake inhibitors (SSRIs), intentional excessive use or interactions between various drugs. It is not an idiopathic reaction and occurs due to excess serotonin activity in the brain and periphery. The serotonin syndrome was first described in 1959 in a patient with tuberculosis who received meperidine and died [1]. The syndrome received its current name in 1982 [2]. The significance of serotonin syndrome was brought to attention in 1984 when Libby Zion, an 18-year-old college student, presented to a New York hospital with fever, agitation and confusion. The child was on phenelzine, a monoamine-oxidase inhibitor (MAOI) antidepressant. She was given meperidine in the hospital for agitation. She became increasingly agitated and hyperpyrexic with a temperature of 41.6°C and died 6 h later.

Epidemiology

Serotonin syndrome has been reported in all age groups. There has been a reported increase in its incidence because of the increasing use of proserotonergic agents over the last few years [3]. In 2004, the Toxic Exposure Surveillance System (TESS) reported 48,204 exposures from SSRIs that resulted in moderate or major outcomes in 8,187 patients, including 103 deaths [4]. The serotonin syndrome has been reported to occur in approximately 15% of persons who overdose SSRIs [5]. The true incidence is difficult to assess because of lack of awareness of this clinical entity amongst physicians, and indeed one survey found that 85 % of physicians were unaware of this syndrome [6].

Pathophysiology

Serotonin is produced by decarboxylation and hydroxylation of L-tryptophan. Its effects are regulated by reuptake mechanisms, feedback loops and enzymes (Fig. 1) [7]. In the central nervous system, it modulates attention, behavior, motor tone, temperature and pain. In the periphery, it regulates vascular tone and gastric motility. These effects of serotonin are mediated through its effects on 5-HT_1 to 5-HT_7 receptors, which have further subgroups like 5-HT_{1A}, 5-HT_{1B}, etc.

No single receptor appears to be solely responsible for the serotonin syndrome. Stimulation of postsynaptic $5HT_{1A}$ and $5HT_{2A}$ receptors has been mainly implicated in the development of the syndrome. A large number of drugs and drug combinations are associated with the syndrome (Table 1) [8]. As mentioned in the table, interaction with dextromethorphan has been implicated in the causation of this syndrome, as was seen in our patient. Classically, ingestion of two drugs simultaneously has caused the syndrome, but it can occur with initiation of a single drug or increasing dose of SSRI in a sensitive patient [9]. Administration of serotonergic agents within 5 weeks after the discontinuation of SSRIs has also produced this syndrome [10].

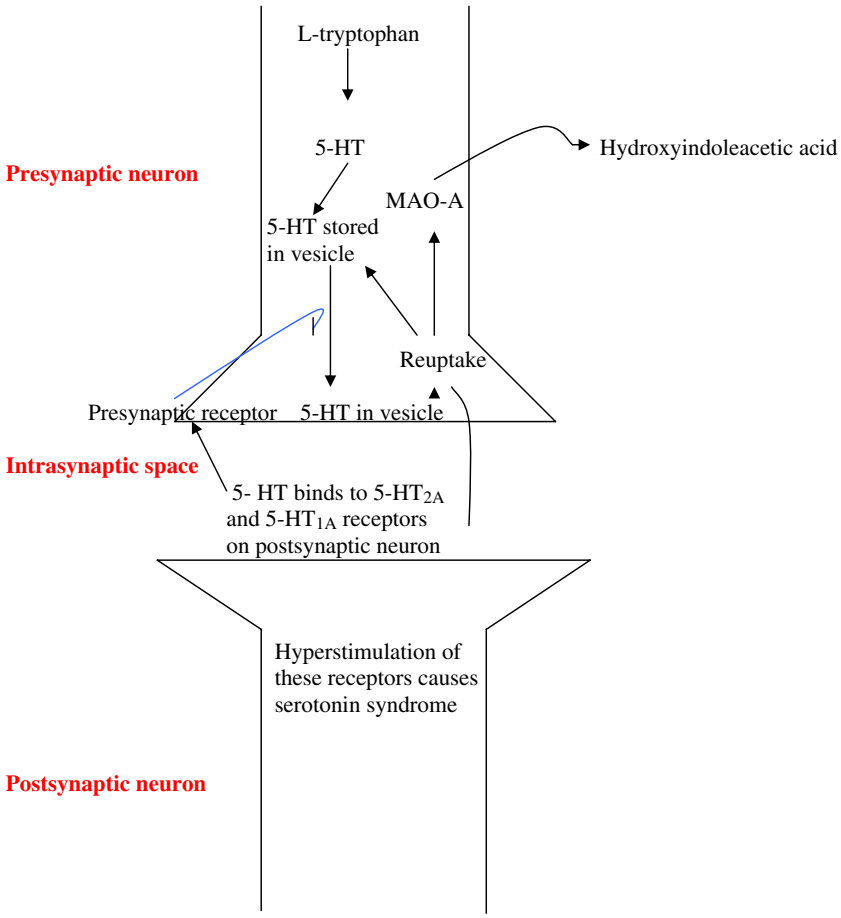

Fig. 1 Pathophysiology of serotonin syndrome

Clinical manifestations

SS presents with a classical triad comprised of mental status changes, autonomic hyperactivity and neuromuscular manifestations (Table 2). The onset of symptoms is usually rapid, within minutes to hours after the ingestion. The manifestations may vary from mild to severe. The patient with mild syndrome may have only tachycardia and some autonomic symptoms such as mydriasis, diaphoresis and neurological findings such as hyperreflexia. In severe cases there might be severe hypertension, agitation, delirium and hypertonia. The core temperature has been recorded as high as 41°C in severe cases. The neuromuscular features of clonus and hyperreflexia are highly diagnostic for serotonin syndrome, and their presence in the setting of serotonergic drugs establishes the diagnosis. Clinicians should remember that muscle rigidity could sometimes mask these signs. No laboratory tests confirm the diagnosis of SS. CPK and myoglobin are done to assess the muscle breakdown, secondary to the muscular activity, and rigidity that is seen with this syndrome. Drug screens may help in the detection of co-ingestions that precipitated the syndrome. Measurement of serum serotonin levels has not been shown to be helpful. Sternbach reviewed

Table 1 Drug interactions implicated in serotonin syndrome

Antidepressants:	Monoamine oxidase inhibitors (MAOIs), TCAs, SSRIs, bupropion
Opioids:	Tramadol, pethidine, meperidine
CNS stimulants:	Phentermine, diethylpropion, amphetamines, methylphenidate, methamphetamine, cocaine
5-HT_1 agonists:	Triptans
Phenethylamines:	MDMA, amphetamines, methylphenidate, methamphetamine
Indoles:	Psilocybin, LSD
Others:	Tryptophan, montelukast, buspirone, lithium, linezolid, dextromethorphan, 5-Hydroxytryptophan, chlorpheniramine
Herbs:	St John's wort, yohimbe

Table 2 Clinical manifestations of serotonin syndrome

Autonomic	Hyperthermia, hypertension, tachycardia, sweating, mydriasis flushing
Cognitive	Agitation, confusion, hyperactivity, hypomania
Neuromuscular	Hyperreflexia, hypertonia, clonus, tremor (more prominent in lower limbs)

Table 3 Sternbach criteria for serotonin syndrome

Recent addition or increase in a serotonergic agent
Absence of other possible etiologies like infections, etc.
No recent addition or increase of neuroleptic agent
Three of the following symptoms:
Alteration in mental status (confusion, hypomania)
Agitation
Myoclonus
Hyperreflexia
Sweating
Shivering
Tremor
Diarrhea
Incoordination
Fever

38 cases from 10 case reports and 2 case series published in the literature, from which he derived diagnostic criteria for serotonin syndrome (Table 3) [11]. A significant problem with Sternbach's criteria was the inclusion of four criteria that relate to mental status, i.e., confusion, hypomania, restlessness and incoordination. Because only three were required for the diagnosis of serotonin syndrome, someone with an anticholinergic syndrome would also meet the clinical criteria. Ataxia or incoordination is also not seen in serotonin toxicity since there is no cerebellar involvement. Hunter et al. have described clinical criteria for the diagnosis of this syndrome, which are 84% sensitive and 97% specific for the diagnosis of serotonin syndrome (Fig. 2) [12]. These are currently used to make a diagnosis of serotonin syndrome. Our patient was on a serotonergic agent (fluoxetine) and had inducible clonus with agitation satisfying the Hunter criteria for serotonin syndrome.

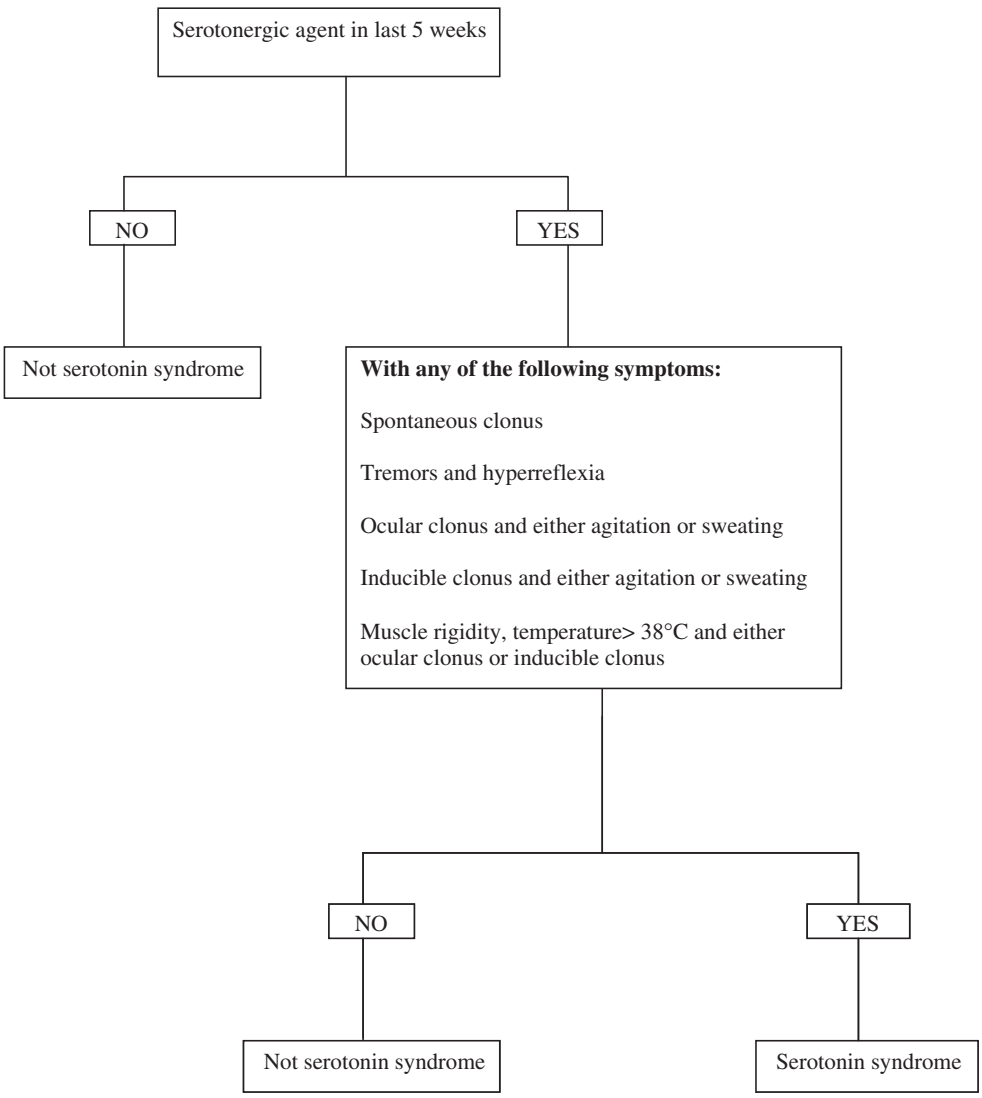

Fig. 2 Diagnostic criteria for serotonin syndrome (based on Hunter's criteria)

Differential diagnosis

Differential diagnosis includes various toxidromes such as anticholenergic syndrome, sympathomimetic syndrome, neuroleptic malignant syndrome and malignant hyperthermia [13]. Patients with anticholenergic syndrome have normal reflexes, dry, hot skin and absence of bowel sounds. There are no neuromuscular abnormalities as seen in SS. In sympathomimetic syndrome, there might be tachycardia, hypertension, agitation and delirium, but no neuromuscular abnormalities are seen. Malignant hyperthermia, caused by inhalational anesthesia and succinylcholine, is characterized by hypertonicity, hyperthermia and metabolic acidosis. The skin is mottled, and there is rigor mortis like rigidity and hyporeflexia. Neuroleptic malignant syndrome is caused by dopamine antagonists and is characterized by slow onset, bradykinesia, lead pipe rigidity, hyperthermia and fluctuating consciousness. The signs and symptoms usually evolve over several days. Other differential diagnoses include alcohol and benzodiazepine withdrawal, salicylate toxicity, central nervous system disorders such as meningoencephalitis, trauma, tumors, systemic disorders like systemic lupus erythematosus, endocrine disorders like hyperthyroidism and pheochromocytoma.

Treatment

Most cases of SS resolve within 24 h of cessation of serotonergic medications. Supportive care is recommended and involves use of intravenous fluids, cooling measures and correction of vital signs. The intensity of therapy depends on the severity of illness. In mild cases, supportive care and administration of benzodiazepines to control the agitation are adequate. In moderate and severe cases, administration of 5-HT_{2A} antagonists is found to be useful [14]. Cyproheptadine and chlorpromazine have been found to be useful. Experience with use of cyproheptadine in humans for the treatment of serotonin syndrome is limited. Isolated cases of treatment with cyproheptadine have been reported with no major adverse effects [3]. Chlorpromazine has also been reported to be effective in management of serotonin syndrome [16], its advantage being that it can be administered intramuscularly. It may produce hypotension, dystonic reactions and neuroleptic malignant syndrome. Atypical antipsychotics such as olanzapine have also been used, but their efficacy has not been determined. Control of hyperthermia may warrant neuromuscular paralysis and intubation. Control of autonomic instability involves stabilization of blood pressure and pulse. Use of short-acting agents such as esmolol and nitroprusside is helpful [15].

Pitfalls

SS occurs with increasing frequency, and most cases resolve with prompt recognition and supportive care. There is no role of antipyretic agents since the increase in temperature is due to muscular activity. Physical restraints are ill advised since they can worsen hyperthermia and lactic acidosis. Certain pharmacologic agents, such as cyproheptadine and chlorpromazine, may have a limited role in management, but their efficacy has not been proven in clinical trials. These agents, especially chlorpromazine, might have more side effects if used injudiciously. Failure to comprehend the adverse pharmacological effects of therapy can lead to more adverse outcomes.

In conclusion, prevention, early recognition of the clinical presentation, identification and removal of the offending agent and supportive care still remain the mainstays of the treatment of serotonin syndrome.

Conflicts of interest None.

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