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REVIEW

The Serotonin Syndrome – a narrative review

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Abstract

Serotonin syndrome is a potentially life-threatening condition caused by overstimulation of the serotonin receptors. Overstimulation may be the result of an overdose of serotonergic medication, but can also be caused by a combination of two or more serotonergic drugs administered in a therapeutic dose. Serotonergic drugs are frequently prescribed by general practitioners and medical specialists; however, the serotonin syndrome is not well recognised. Classical signs of the serotonin syndrome include mental status changes, autonomic hyperactivity and neuromuscular abnormalities. The presentation is highly variable and ranges from benign to life-threatening. Increasing of dose or addition of another serotonergic substance in case of unrecognised benign serotonin syndrome may lead to a rapid deterioration, multi-organ failure and death. We recently encountered a fatal case of serotonin syndrome and would like to present a brief review of literature to heighten awareness of this condition.

Introduction

Serotonin syndrome is a potentially life-threatening condition caused by overstimulation of serotonin receptors.[1-11] Overstimulation may be the result of an overdose of serotonergic medication, but can also be caused by a combination of two or more serotonergic drugs administered in a therapeutic dose.[1,2,4] Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, tryptophan, tramadol, lithium and amphetamines.[1,2,4] These drugs are frequently prescribed by general practitioners and medical specialists.[2,11] Classical signs of the serotonin syndrome include changes in mental status, autonomic hyperactivity and neuromuscular abnormalities. The presentation is, however, highly variable and ranges from benign to life-threatening.[1,11] The serotonin syndrome is not well recognised by physicians.[2,3,8,11] We recently encountered a fatal case of serotonin syndrome and would like to present a brief review of literature to heighten awareness of this condition.

Case history

A 55-year-old woman with a history of anxiety, panic disorders and chronic depression was found in a disordered state at her home. She admitted to have taken a total of 4600 mg sertraline, 65 mg olanzapine, 180 mg lorazepam, 200 mg nifedipine and 10 g paracetamol the previous night. She was admitted to the emergency room.

In the emergency room the patient was tachypnoeic, tachycardic, had an undetectably low blood pressure and was hypothermic (33.9 °C). Neurological examination revealed hyperreflexia and hypertonia, which was more prominent in the lower than the upper extremities, and a Glasgow coma score (GCS) of 14.

Blood tests showed a metabolic acidosis with an increased lactate and creatine kinase (> 33,000 U/l). Full lab results on admission are shown in *table 1*. The ECG showed sinus tachycardia (101 beats/min), without any other abnormalities.

The patient was admitted to the intensive care unit. She received haemodynamic support through volume resuscitation and rewarming. Additionally, she was started on inotropics and vasopressors and was given bicarbonate to compensate for the metabolic acidosis. The stomach was rinsed and acetylcysteine was added as an antidote for the paracetamol. Lastly, she received empiric antibiotic treatment with cefotaxime and clindamycin due to suspicion of aspiration pneumonia.

During the evening a rapid clinical deterioration occurred. The patient became somnolent with a GCS of <8 and suffered from hypoxic respiratory failure despite 15 litres of oxygen. She was intubated and mechanically ventilated. Shock persisted despite aggressive fluid resuscitation and high-dose inotropics and vasopressors. Transthoracic echocardiography showed a

Table 1. Lab results on admission

Arterial blood gas		Reference values
Ionized calcium (mmol/L)	1,36	1,15 – 1,29
Lactate (mmol/L)	14,5	0,5 – 1,7
pH	7,02	7,35 – 7,45
pCO2 (kPa)	3,6	4,5 – 6,0
pO2 (kPa)	14,5	9,5 – 13,0
HCO3 (mmol/L)	6,5	22,0 – 26,0
Base excess (mmol/L)	-24,8	-2,0 – 2,0
SpO2 (%)	96	92 – 99

Full blood count		Reference values
Hemoglobin (mmol/L)	9,7	7,5 – 10
Hematocrit (L/L)	0,50	0,36 – 0,46
Mean corpuscular volume (fL)	91	80 – 100
White blood cells (/nL)	6,7	4,0 – 11,0
Platlets (/nL)	438	150 – 400
Coagulation tests		**Reference values**
APTT (s)	36	25 – 35
PT (s)	14	10 – 15
D dimer (ug/ml)	6,61	0,10 – 0,50
Metabolic panel		**Reference values**
Urea (mmol/L)	10,9	2,5 – 6,4
Creatinine (umol/L)	136	50 – 90
Natrium (mmol/L)	134	135 – 145
Potassium (mmol/L)	4.3	3,5 – 4,7
Chloride (mmol/L)	103	97 – 107
Aniongap	29,5	0 – 10
Calcium (mmol/L)	2,7	2,20 – 2,65
Phosphate (mmol/L)	3,70	0,80 – 1,40
Gamma GT (IU/L)	102	0 – 40
Alkaline phosphatase (IU/L)	131	0 – 120
ASAT (IU/L)	976	0 – 30
ALAT (IU/L)	641	0 – 35
Creatine Kinase (IU/L)	33.861	0 – 145
Troponine-i (ug/L)	<0,045	0,00 – 0,045
Albumin (g/L)	37	35 – 50
Magnesium (mmol/L)	1,18	0,70 – 1,10
Bilirubin (umol/L)	5	0 – 17
CRP (mg/L)	75	0 – 5
TSH (mU/L)	2,4	0,4 – 4
FT4 (pmol/L)	24,7	10 – 24
Toxicology tests		**Reference values**
Acetaminophen (mg/L)	15	10 -20
Sertarline (ug/L)	1977	50 – 300
Ethanol (0/00)	<0,1	0

moderately reduced left ventricular function with hypokinesia of the anterior wall. Acute kidney failure occurred and was treated with dialysis.

At this point, we suspected the serotonin syndrome. The hypothermia did not fit the pathology and was attributed to her laying on the cold floor. Due to a combined intoxication with benzodiazepines, the classical clinical signs of serotonin syndrome were obscured. We consulted the hospital pharmacist and the National Poisons Information Centre; administration of the antidote cyproheptadine was advised but unfortunately cyproheptadine was not available as it was recalled several years ago. The patient was treated with maximal supportive therapy, but developed severe multi-organ failure including ARDS, refractory shock, kidney failure and liver failure.
The patient died within 24 hours of ICU admission.

Pathophysiology

Serotonin syndrome is the consequence of overstimulation of the central and peripheral serotonin receptors by serotonergic

Table 2. Serotonergic drugs[1,2]

Serotonergic agent	
Pyschotropics	Selective serotonin reuptake inhibitors (SSRIs)
	Serotonin-norepinephrine reuptake inhibitors (SNRIs)
	Norepinephrine-dopamine reuptake inhibitors (NDRIs)
	Tricyclic antidepressants (TCAs)
	Monoamine oxidase inhibitors (MAOIs)
	Lithium
	L-Dopa
	Buspirone
	Mirtazapine
Anti-epileptics	Valproate
	Carbamazepine
Antimigraine agents	Triptans
Anti-emetics	Ondansetron
	Metoclopramide
	Granisetron
Analgesics	Tramadol
	Fentanyl
	Pethidine
Recreational drugs	Amphetamine
	Cocaine
	MDMA
	LSD
Other drugs	Linezolid
	Methylene blue
	Dextromethorphan ('cough syrup')
	Ritonavir
Dietary supplements	Tryptophan
	St. John's wort
	Ginseng

substances.[1-11] Serotonin (5-hydroxytryptamine or 5-HT) is derived from L-tryptophan and released into the synaptic cleft where it can bind to several serotonin receptors.[2,11] In the central nervous system these receptors are found primarily in the raphe nuclei in the brain stem.[2] They modulate affective behaviour, thermoregulation, wakefulness, emesis, migraine, food intake, sexual behaviour, nociception and motor tone. Peripheral serotonin receptors influence gastrointestinal motility, bronchoconstriction, vasoconstriction and platelet aggregation.[2,3,8] There are seven serotonin receptors of which overstimulation of the 5-HT_{1A} and 5-HT_{2A} receptors are most associated with the serotonin syndrome.[2,3,8,11]

Eventually serotonin is degraded by monoamine oxidase to 5-hydroxyindole acetic acid which is excreted in urine.[11]

Serotonergic substances cause overstimulation by increasing the production or secretion of serotonin; inhibiting serotonin re-uptake between the synapses; inhibiting the breakdown of serotonin; or increasing sensitivity of the serotonin receptors.[1,2,4] Commonly used serotonergic drugs are psychotropics, antiepileptics, antiemetics and analgesics. Furthermore, several types of recreational drugs stimulate the serotonin receptors *(table 2)*.[1,2,4] Lastly, addition of drugs that inhibit the cytochrome isoforms CYP2D6 and CYP3A4 to an SSRI regimen can cause serotonin syndrome as these enzymes metabolise SSRIs.[2]

Excessive levels of serotonin lead to a wide range of symptoms including cognitive, autonomic, and somatic effects, which is termed the serotonin syndrome. Symptoms may range from barely perceptible to life-threatening.[1-9, 11]

Epidemiology

The exact incidence of serotonin syndrome is unknown, as it is often not recognised. In mild cases, symptoms are often attributed to other origins.[2,11] However, the use of serotonergic medication is not infrequent and combination therapies with the use of multiple serotonergic substances has increased over the past years. In the Netherlands, SSRIs are used by 31 per 1000 patients.[12] Literature reports an incidence of 14-18% in patients who have taken an overdose of SSRIs.[2,4] The estimated mortality is 0.2-1.3%.[4] For severe cases of the serotonin syndrome, this number has been estimated at 2-12%.[3] MAOIs are specifically associated with severe serotonin syndrome. Life-threatening serotonin syndrome may occur in 50% of patients who have ingested a combination of MAOIs and (S)SRI.[1,11]

Presentation & Diagnosis

Serotonin syndrome is a clinical diagnosis with no laboratory test for confirmation.[1,2,8] The gold standard is a diagnosis by a medical toxicologist.[2,8] Symptom observation and the patient's medical history are essential. Classically, patients present with a triad of symptoms involving a change in mental status, autonomic hyperactivity and neuromuscular impairment *(table 3)*.[1-11] However, the presentation is highly variable and may range from benign to life-threatening.[1-5, 7-11] Mental status change may manifest as agitation, anxiety, confusion, restlessness and in severe cases in loss of consciousness.[1-4] The most important autonomic symptoms are hyperthermia, hyperreactivity of the gastrointestinal tract and hypertension.[1-4] Conversely, a combined drug intoxication with antipsychotics or benzodiazepines can lead to severe hypotension, as was observed in our patient.[1,2] Neuromuscular impairments that may arise are hypertonia/rigidity, spontaneous myoclonus or ocular clonus, bilateral Babinski's sign or hyperreflexia. Typically, hyperreflexia is more pronounced in the lower extremities, which was also found on physical examination of our patient.[1-4] Severe symptoms of the serotonin syndrome are a fluctuating blood pressure, rhabdomyolysis, disseminated intravascular coagulopathy, tonic-clonic seizures, kidney failure, liver failure, acute respiratory distress syndrome (ARDS), respiratory arrest and arrhythmias including ventricular tachycardia.[2,4] Multi-

Table 3. Signs and symptoms of serotonin syndrome[1,4]

Cognitive changes	Confusion and delirium
	Agitation
	Restlessness
	Anxiety
	Altered level of consciousness or coma*
Autonomic changes	Erythema
	Dry mucous membranes
	Perspiration
	Tachycardia
	Ventricular tachycardia*
	Hypertension
	Quickly alternating hypotension and hypertension*
	Hyperthermia > 38 °C of > 41 °C *
	Tachypnoea
	Mydriasis
	Gastrointestinal hyperactivity: vomiting, diarrhoea
Neuromuscular changes	Spontaneous myoclonus**
	Ocular clonus
	Hyperreflexia**
	Hypertonia
	Ataxia
	Tremor**
	Babinski's sign
	Rhabdomyolysis *
	Tonic-clonic seizures*
Other signs and symptoms	Metabolic acidosis*
	Acute kidney injury*
	Acute liver failure*
	Diffuse intravascular coagulation*

*Sign/ symptom of severe serotonin syndrome;
**Usually greater in lower extremities.

organ failure caused by the serotonin syndrome ultimately resulted in the death of our patient.
Typically, the symptoms emerge within 24 hours after an increase in dosage, addition of a new serotonergic drug, or overdose.[1,2,11] In 60% of patients clinical manifestations develop within six hours.[2,11] However, in mild cases the classic triad may not always occur, and patients may more often present with chronic complaints.4 Recognising the triad of symptoms in a combined drug intoxication can also be difficult, as these can be masked or antagonised by other medications.[1,2] Tests to exclude other causes of symptoms may be ordered.[2]

To assist the physician in diagnosing the serotonin syndrome, several diagnostic criteria have been developed. The first criteria were introduced in 1991 by Harvey Sternbarch.[5] However, when strictly applied these criteria potentially rule out early, mild or subacute cases of serotonin syndrome. Therefore, the Hunter Serotonin Toxicity criteria have replaced the original criteria by Sternbarch due to a higher sensitivity (84%) and specificity (97%).[7]
Laboratory blood tests are only indicated when there is reasonable doubt about whether the patient has ingested serotonergic drugs.[2] In our patient serum levels of sertraline over six times the upper limit were found (1977 µg/l).

Differential diagnosis
The differential diagnosis of serotonin syndrome includes central nervous system (CNS) infections, anticholinergic poisoning, sympathomimetic toxicity, heatstroke, thyrotoxicosis, malignant hyperthermia, a worsening underlying psychiatric condition and neuroleptic malignant syndrome.[1,2,4,10] Most of these conditions can be readily distinguished from the serotonin syndrome on the basis of medical history and clinical grounds.[1,2,4,9,10] In our patient CNS infections were deemed unlikely based on medical history and the absence of fever, headache or meningism. Thyroid levels were normal excluding thyrotoxicosis.

The condition most often confused with serotonin syndrome is neuroleptic malignant syndrome.[1-4,9,10] In both conditions symptoms of hyperthermia, hypertension, tachycardia and rigidity are seen.[1,2,9,10] However, they are actually very different conditions with different underlying dysfunction and a different time course.[1,2,4,9,10] Serotonin syndrome is caused by excessive serotonergic stimulation due to serotonergic drugs and has a rapid onset (within 24 hours after drug administration).[1,2,4,9,10] Neuroleptic malignant syndrome is an idiopathic drug reaction to dopamine antagonists, defined by a slow onset of several days.[1,2,9,10] Features that are classically present in neuroleptic malignant syndrome and that are useful for differentiating the two are bradykinesia and extrapyramidal 'lead pipe' rigidity, whereas serotonin syndrome causes hyperkinesia and clonus.[1,2,9,10] Even though our patient ingested 65 mg olanzapine, a dopamine antagonist, neuroleptic malignant syndrome seemed unlikely as there was a rapid onset of symptoms and hyperkinesia was present opposed to bradykinesia and lead pipe rigidity.

An in-depth history is extremely important in signalling the differences between the conditions.[2,4,9,10] Culprit agents are often very useful in distinguishing syndromes.[9,10] However, both syndromes can occur at the same time in case of polypharmacy.[9]

Additionally, although there is no laboratory test to identify neuroleptic malignant syndrome, or serotonin syndrome, using laboratory values to distinguish between the two has been proposed. In > 75% of patients with neuroleptic malignant syndrome high creatine kinase levels, electrolyte disturbances (especially hypocalcaemia), low iron levels, leucocytosis and proteinuria are seen. However, most of these are attributable to rhabdomyolysis, which can also be seen in severe cases of serotonin syndrome.[9,10] In our patients rhabdomyolysis was present without normal leukocyte and calcium levels on admission. Iron levels and proteinuria were not tested.

The correct diagnosis is indispensable to initiate the right treatment. For example, bromocriptine is recommended in neuroleptic malignant syndrome but has been shown to worsen serotonin syndrome as it stimulates 5-HT1A.[2,8,9,11] Also neuroleptics have been suggested in the treatment of serotonin syndrome but can potentially worsen neuroleptic malignant syndrome.[2,9]

Management

The management of serotonin syndrome includes immediate discontinuation of the serotonergic drugs and starting supportive therapy.[1-4,6,8,11] The intensity of the therapy depends on the severity of the illness.[2-4,11] Supportive therapy aims to control agitation, and treat hyperthermia and autonomic instability.[1,2,8,11]
Control of agitation with benzodiazepines is essential in the management of the serotonin syndrome regardless of its severity as it has been proven to reduce mortality.[2] Physical restraints should be used with caution, since they may contribute to mortality by enforcing isometric muscle contractions that are associated with severe lactic acidosis and hyperthermia.[2,8,12]

As hyperthermia is caused by excessive muscle activity it is most effectively managed by reducing muscle activity through sedation or in severe cases (> 41.1 °C) by inducing paralysis with non-depolarising muscle relaxants.[1,2] When paralysis is indicated the patient must also be intubated and mechanically ventilated.[1,2] Additionally, cooling can be used to further reduce body temperature.[1-3] Antipyretics are not indicated as the hyperthermia does not result from an alteration in the hypothalamic set point.[11]

Autonomic instability can result in severe hypertension, hypotension or a rapid fluctuation between hypertension and hypotension.[1,2] Therefore, short-acting antihypertensive agents are preferred in case of hypertension (e.g. esmolol).[1,2] For the treatment of hypotension direct-acting sympathomimetic amines must be used (e.g. norepinephrine, phenylephrine and epinephrine) as indirect acting agents such as dopamine may lead to unpredictable haemodynamic responses.[2] Normally, indirect agents are metabolised to (nor)epinephrine and the intracellular concentration of the metabolites is controlled by monoamine oxidase.[2] When monoamine oxidase is inhibited the amount of (nor)epinephrine produced is not controlled.[2]

In addition to the mentioned supportive measures, the use of 5-HT_{2A} antagonists must be considered in severe cases of serotonin syndrome.[1-4,11] Present recommendations include treatment with the non-selective serotonin receptor-antagonist cyproheptadine when supportive therapy is not sufficiently effective.[1] A dosage of 12-32 mg within 24 hours should bind 85-95% of the serotonin receptors.[2,11] However, the clinical effectivity of cyproheptadine in serotonin syndrome has not been proven. If charcoal has already been administered another 5-HT_{2A} antagonist, chlorpromazine, should be considered as this can be administered intravenously.[2,11] However, it must be kept in mind that chlorpromazine can worsen hypotension.[11]

Usually, improvement of the clinical situation will emerge within 24 hours after the termination of serotonergic drugs. For SSRIs with a long half-life this could take longer. During this period supportive therapy is necessary to reduce morbidity and mortality.[1-4,11]

Mortality is mainly the result of late recognition of serotonin syndrome as the patient has already developed multi-organ failure.[8] Arrhythmias and respiratory failure are main causes of death. Arrhythmias are either the result of autonomic dysfunction or of hyperkalaemia caused by renal failure due to rhabdomyolysis.[11] Respiratory failure is due to ARDS or acute respiratory arrest.[1] Our patient developed irreversible multi-organ failure including rhabdomyolysis, autonomic dysfunction, ARDS and acute liver failure.

Discussion

Serotonin syndrome is a potentially life-threatening condition which is often not recognised.[2,3,8,11] Conversely, serotonergic drugs causing the syndrome are frequently prescribed by general practitioners and medical specialists.[13] Probably most cases of serotonin syndrome are mild and go unnoticed by physicians.[2,3,8,11] It is, however, important to recognise even mild cases of serotonin syndrome as this may prevent a life-threatening situation.[2] For example, if mild symptoms of serotonin syndrome are overlooked by a physician he may decide to increase the dose of the causative agent or add a drug with serotonergic effects leading to severe serotonin syndrome. Severe serotonin syndrome is mainly seen in patients using MAOIs in combination with other serotonergic drugs.[1,11] Therefore, awareness of symptoms of serotonin syndrome is highly important in this patient category.

In conclusion, serotonin syndrome is a potentially life-threatening condition but it is also preventable. Therefore, prudence of the serotonin syndrome in case of non-specific cognitive, neuromuscular and/or autonomic dysfunction is highly important.

Disclosures

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