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CASE REPORT Open Access

Serotonin syndrome: a rare undiagnosed cause of hyperpyrexia

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Abstract

Serotonin syndrome (SS) is a rare but potentially life-threatening condition, and it is caused byincreasing serotonergic activities. It is an underdiagnosed and under-reportedcondition. Clinical manifestations can range from mild to moderate to severesymptoms. The intensity of symptoms reflects the degree of serotonin toxicity, andmild serotonin syndrome is easily overlooked by physicians.

Severe serotonintoxicity typically occurs to a combination of serotonergic agents.

Herein, we describe acase of severe serotonin toxicity in a 38-year-old Egyptian male with a historyof generalized anxiety disorder and depression. With increased depressivesymptoms, he received 20 mg of fluoxetine daily, and the symptomsdeveloped 1 month after starting fluoxetine, which is the uncommon onsetof presentation. The patient was already on tramadol for chronic low backache. Theaim is to increase awareness of the syndrome among physicians andneuropsychiatrists.

Keywords Serotonin syndrome, Serotonin toxicity, Hyperpyrexia, Fluoxetine, Tramadol

Background

A 38-year-old male was presented to the emergency departmentof Embaba Fever Hospital (Giza, Egypt) in an acute confusional state associatedwith hyperpyrexia and severe agitation, and he is known to have had a psychicdepression for which he had been prescribed fluoxetine 20 mg once daily. Hehad a history of chronic low back pain for which he was receiving tramadol. Thesymptoms started 1 month after fluoxetine treatment, and he was observedto have myoclonic jerks, marked tremors, and inducible patellar and ankle clonus. According to the presence of hyperpyrexia,inducible clonus, marked tremors, severe agitation, and a history ofconcurrently using two serotonergic medications (fluoxetine and tramadol), a diagnosis of serotonin syndrome was made.

The purpose is to highlight theclinical manifestation of serotonin syndrome in its severest form and also toalert emergency physicians and neuropsychiatrists to be aware of the syndromeeven in mild cases as they are likely to be missed as the patient on aserotonergic agent presents with only tremors and hyperreflexia. Every patientwith mild SS is a potential candidate for developing life-threatening severeserotonin syndrome [1].

Case presentation

A 38-year-old male wasreferred from a private hospital to the emergency department of Embaba FeverHospital (Giza, Egypt), with an ambulance he was referred in a delirious stateand severe agitation. There was no history of head trauma, and he convulsedonce in the ER. He is on regular use of tramadol because of chronic lowbackache. He had suffered an attack of depression and anxiety 1 monthbefore admission, for which he received fluoxetine 20 mg single daily dose.

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Examination

The temperature on admission was 41 °C for which he had been managed in the ER as non-exertional heat hyperpyrexia. He was admitted to the intensive care unit, sedated, intubated, and mechanically ventilated. The patient was tremulous. Restless with marked spasticity in both lower limbs to the degree that both knee joints appeared to be locked, he had hyperreflexia and induced clonus in both ankles and patellae.

Investigation

Complete blood count, Biochemical investigation, Arterial blood gases, and CSF analysis are shown in table 1.

Chest X-ray: normal

The patient was diagnosed clinically with serotonin syndrome according to Hunter's toxicity criteria [2] after the exclusion of other causes in the differential diagnosis.

Discussion

Serotonin syndrome is an under-reported and underdiagnosed condition [1]. The diagnosis of SS is easily missed as many physicians (up to 85%) might not be aware of this syndrome as a clinical entity and hence the importance of this case to increase its awareness [3, 4].

The assessment of serotonin syndrome requires determining first whether the clinical features are consistent with serotonin toxicity, and second the severity of the toxicity, the clinical assessment should include observation for myoclonus jerks, diaphoresis, ocular clonus (slow continuous horizontal eye movements), and agitation. The presence of hyperreflexia with tremors is suggestive of SS if the patient has taken serotonergic agents in the past 5 weeks [5]. Tremor is a well-known recognized symptom of SS. Severe SS may develop after the addition of the second serotonergic drug in patients who already have some mild SS because of the first serotonergic drug [6–8]. The onset of mild SS may have an indolent course or symptoms may go unnoticed by patients [5], while the onset of severe serotonin toxicity usually rapidly follows the administration of the offending agent [4]. Unlike this patient, symptoms' onset may be rapid and may occur within minutes [3], mostly within 24 h of taking a serotonergic agent, with an estimated 60% of patients experiencing symptoms within 6 h [9, 10]. However approximately 7% of patients may experience delayed symptoms up to 6 weeks after the initial dose [9], like this patient.

Severe serotonin toxicity typically occurs to a combination of serotonergic agents, examination findings can include hyperthermia, agitation, ocular clonus, tremors, akathisia, deep tendon hyperreflexia, inducible or spontaneous clonus, muscle rigidity, dilated pupils, dry mucous membranes, increased bowel sounds, flushed skin and diaphoresis, neuromuscular finding are typically more pronounced in the lower extremities, Hunter's Criteria is a measure commonly used to diagnose serotonin syndrome.

Table 1 Complete blood count, biochemical investigation, arterial blood gases and CSF analysis

Test	Result	Unit	Reference range
Complete blood count			
Hemoglobin	8	g/dl	11–16
Red blood cells	3.681.000	million u/l	3.8–5.4
Platelets	262.000	u/l	150–540
TLC	21.900	u/l	4–11
Neutrophils	78.4	%	40–60
Lymphocytes	7.5	%	20–40
MCV	66.8	Fl	78–96
MCH	21.7	Pg	26–32
Chemistry			
Serum sodium	136	meq/l	135–145
Serum potassium	3.7	mmol/l	3.5–5
Serum calcium	8.9	mg/dl	9–11
Ionized calcium	1.1	mmol/l	1.2–1.4
Random blood sugar	135	mg/dl	74–106
ALT	23	u/l	14–63
AST	113	u/l	15–37
Alkaline phosphatase	88	u/l	44–147
Total bilirubin	0.3	mg/dl	0.20–1.00
Total protein	6.3	gm/dl	6–8.3
Serum albumin	3.2	gm/dl	3.4–5.4
Creatine kinase (CK)	12,620	IU/L	2–=30
Serum urea	39	mg/dl	17–49
Serum creatinine	1.5	mg/dl	0.7–1.3
Serum urea (second day)	60	mg/dl	17–49
Serum creatinine (second day)	2.5	mg/dl	0.7–1.3
Arterial blood gases:			
PH	7.25		7.35–7.45
PCO2	30	mmHg	35–45
PCO2	18	mEq/l	22–26
HCO3	55	mmHg	75–100
CSF analysis			
Aspect	Clear		Clear
Color	Colorless		Colorless
Sugar	59	mg/dl	50–80 mg/dl
Protein	30	mg/dl	15–45 mg/dl
Cells	No cells		0–5
Gram stain	No organism		No organism
Zeil Nelsen stain	No organism		No organism
CSF culture	No growth		No growth

There is no specific test for serotonin syndrome and measurement of serotonin levels has not been shown to be helpful [11]. Laboratory abnormalities are non-specific but include elevated creatine phosphokinase, leukocytosis, transaminitis, and low serum bicarbonate [12].

The differential diagnosis includes anxiety, neuroleptic malignant syndrome (NMS), anticholinergic toxicity, malignant hyperthermia, sympathomimetic intoxication, encephalitis, and serotonin syndrome is often misdiagnosed with NMS [13].

NMS is distinguished on the basis of history, examination findings, and clinical course. NMS develops over days to weeks, whereas serotonin syndrome mostly develops over 24 h [14]. Approximately 7% of patients with serotonin syndrome may experience delayed symptoms like this patient (serotonin syndrome is characterized by neuromuscular hyperactivity (tremors, hyperreflexia, myoclonus), while NMS develops sluggish neuromuscular response (rigidity, hyporeflexia). Anticholinergic toxicity classically presents with hyperthermia and agitation, altered mental status, mydriasis, dry mucous membranes, urinary retention, and decreased bowel sounds but the muscular tone and reflexes are normal, malignant hyperthermia occurs in susceptible individuals exposed to halogenated volatile anesthetics and depolarizing muscle relaxants (e.g., succinylcholine) [15]. Serotonin syndrome is distinguished from other causes of agitated delirium on the basis of neuromuscular findings, whereas patients with serotonin syndrome show signs of neuromuscular activation, patients with sympathomimetic activity or infections of the CNS lack these findings [6].

The Hunter serotonin toxicity criteria decision rules in the presence of a serotonergic agent are the following:

1 If spontaneous clonus = yes, then serotonin toxicity = yes
2 If inducible clonus = yes, and agitation = yes or diaphoresis = yes, then serotonin toxicity = yes
3 If ocular clonus = yes and agitation = yes or diaphoresis = yes, then serotonin toxicity = yes
4 If tremor = yes, and hyperreflexia = yes, then serotonin toxicity = yes
5 If hypertonia = yes, and temperature > 38 °C, and ocular clonus = yes, or inducible clonus = yes, then serotonin toxicity = yes

According to the presence of Hunter's criteria [2] for serotonin toxicity, (hyperthermia, marked agitation, hyperreflexia, muscle rigidity, inducible clonus, and the medical history of combined serotonergic drug intake), the diagnosis of serotonin syndrome was made, and both the analgesic medicine tramadol and the selective serotonin reuptake inhibitor 'fluoxetine' inhibit serotonin reuptake, thus increasing serotonin activity and causing serotonin toxicity. There is no specific antidote for serotonin toxicity. Although cyproheptadine is considered a drug of choice for SS, cyproheptadine is an antihistamine with antimuscarinic properties [16, 17]. To date, there are no specific treatment guidelines for the treatment of serotonin syndrome; the most important course of treatment is to discontinue the offending drugs [1, 3–5]. It should be noted that linezolid is a reversible, non-selective monoamine oxidase inhibitor. Serotonin syndrome with linezolid plus either an SSRI or venlafaxine is a progressive process. When recognized, however, serotonin syndrome is readily reversible on discontinuation or a decrease of the dosage of serotonergic agents, if the clinical situation warrants the use of linezolid in a patient receiving an SSRI, linezolid may be used concomitantly with SSRI with careful monitoring for signs and symptoms of serotonin syndrome [18].

The patient was sedated and mechanically ventilated based on the hypoxemia and severe metabolic acidosis, and the management included treatment of hyperthermia, IV fluids, muscle relaxants, and cyproheptadine 8 mg initial dose by the Ryle tube, followed by 2 mg every 2 h with no physical restraint in order not to increase hyperthermia. Evaporative and convective cooling is the method used most often to treat non-exertional (classic) heat stroke because it is effective, non-invasive, and easily performed; and does not interfere with other aspects of patient care, hyperpyrexia was managed by placing the patient in an air-conditioned room with a current airway (fan) behind the bed with the removal of restrictive clothing and spraying water on the body, alternating with soaked sheets and placing ice packs in the axillae and groins. Rapid cooling is a key determinant of a favorable outcome. When used to treat older adult patients with non-exertional heat stroke, evaporative and convective cooling is associated with decreased morbidity and mortality [19–21].

Special beds called body cooling units have been made for this purpose [20]. In spite of every effort that was done to save the life of the patient, he was ultimately arrested and failed all trials for his resuscitation.

Conclusion

Serotonin syndrome is a rare cause of hyperpyrexia, it should be suspected in all patients receiving serotonergic medicine, a single serotonergic agent usually causes mild or moderate serotonin toxicity while severe serotonin syndrome may develop after the addition of a second serotonergic drug.

Early diagnosis of mild serotonin syndrome prevents the development of severe life-threatening serotonin syndrome so it is suggested that every patient on the

serotonergic drug should be examined for the presence of hyperreflexia, tremor, and clonus.

Abbreviations

SS	Serotonin syndrome
NMS	Neuroleptic malignant syndrome
CSF	Cerebrospinal fluid
ER	Emergency room
CK	Creatine kinase

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Authors' contributions
AS collected the patient data and wrote the manuscript. Hamdy Ibrahim was the major contributor in writing the manuscript. All authors read and approved the final manuscript.

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