Original Article

Refining the Clinical Features of Serotonin Syndrome: A Prospective Observational Study of 45 Patients

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Abstract

Introduction: Serotonin syndrome (SS) is a drug-induced clinical syndrome that results from the excess intrasynaptic concentration of serotonin. Prospective observations are limited for SS. **Methods:** We prospectively recruited 45 consecutive adult patients (>18 years) fulfilling the Hunter's criteria for SS. All patients were subjected to a detailed clinical history and examinations. Patients were subjected to appropriate investigations to find out the other causes. The causation of SS to serotonergic drugs was assessed according to Naranjo adverse drug reaction probability scale. **Results:** The mean age was 37.3 years (range: 18–59 years). Sixty-two percent of patients were male. There were 15 different underlying clinical syndromes for which serotonergic drugs were started. Psychiatry conditions (36%) and cough/respiratory tract infection (16%) were the two most common clinical conditions for starting serotonergic drugs. We noted 49 different symptoms and physical signs. Overall, tremor (78%) and dizziness (47%) were the two most common symptoms. Headache (16%) and dizziness (16%) were the two most common initial (or first) symptoms. However, gait difficulty and febrile encephalopathy were the two most common reasons to visit the hospital. We noted 18 different drugs causing SS. Thirty-eight percent of patients received single serotonergic agent antidepressants, pain medicines and cough syrups were other important drugs causing SS. **Conclusions:** This study represents the largest clinic-based study on SS. SS is not rare in clinical practice. However, various aspects of this syndrome are still to be determined. All patients on serotonergic drugs should be physically examined for the presence of SS on the development of any new symptom.

Keywords: Antidepressant, cyproheptadine, serotonin, serotonin syndrome, selective serotonin reuptake inhibitors

Introduction

Serotonin syndrome (SS) is an iatrogenic, drug-induced constellation of various clinical features. It is classically defined as a clinical triad of neuromuscular hyperactivity, autonomic hyperactivity, and altered mental status. SS is highly underdiagnosed clinical syndrome as up to 85% physicians may not be aware of this syndrome.[1] The literature is biased for severe cases of SS. The literature is sparse regarding the clinical presentations and evolution of SS. Recognition of even mild SS in the early stage is important as patient may develop life-threatening SS because of the inadvertent increase in the dose of the causative agent or the addition of another proserotonergic agent.[2]

There has been a reported increase in the incidence of SS because of the widespread use of selective serotonin reuptake inhibitors (SSRIs) and other proserotonergic agents.[1] Our team have reported a number of cases of SS earlier,[2-7] and we think that it is not that rare in the clinical practice. The clinical triad of neuromuscular hyperactivity, autonomic hyperactivity, and altered mental status of SS includes a number of symptoms and signs. However, the diagnostic criteria of SS include only a few clinical features.[8] The Hunter diagnostic criteria require the presence of one of the following in the presence of the intake of a known serotonergic agent: (a) tremor and hyperreflexia, (b) spontaneous clonus, and (c) inducible clonus/ocular clonus with diaphoresis or agitation or rigidity with a temperature above 100.4°F. Hence, a diagnosis of SS is made on the presence of only a few symptoms (fever, agitation, and diaphoresis) and signs (tremor, rigidity, hyperreflexia, and clonus). The presence of isolated "spontaneous clonus" suffices the diagnosis of SS. Hunter's diagnostic criteria are useful in well-established/severe cases of SS. However, it does not provide an overall picture of SS. In this study, we planned to do a prospective observation on SS patients to find out the evolution of SS so that such cases can be diagnosed in early stage.

Materials and Methods

This prospective observational study was done in a neurology department of a large tertiary hospital between September 2015 and May 2018. The Institutional Ethic Committee approved the study protocol (SVRC/ON/MEDI/FP/15028). Subjects were

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registered only after obtaining a written informed consent. In patients with cognitive impairment, consents were taken from the nearest relative.

Inclusion criteria

The inclusion criteria for the cases were as follows: (i) age >18 years, (ii) patients fulfilling the criteria of Hunter's SS criteria, and (iii) a minimum follow-up of 4 weeks. The Hunter criteria for SS include following in the presence of serotonergic agents' ingestion in the past 5 weeks: (i) hyperreflexia with tremor, (ii) spontaneous clonus, (iii) inducible clonus with agitation or diaphoresis or temperature >38°C and rigidity, and (iv) ocular clonus with agitation or diaphoresis or temperature >38°C and rigidity.[8] A diagnosis of spontaneous clonus was made when spontaneous involuntary rhythmic movements of the limbs got intensified while stretching the tendons to elicit clonus.[7,9] Spontaneous clonus is often triggered by minor movements or vibration.[9] Ocular clonus was defined as abnormal involuntary of eyeball in any direction, classically triggered by rapid eye movement.[9]

Exclusion criteria

The exclusion criteria include (i) age <18 years, (ii) patients having a history chronic disorders such as diabetes and hypertension to avoid the possible confounders, (iii) patients having obvious alternative diagnosis, and (iv) patients not having significant improvement with the therapy.

Clinical assessment

All patients fulfilling the inclusion criteria were subjected to a detailed clinical history and examination. Face-to-face interviews were conducted using a structured questionnaire. Patients with cognitive impairment were interviewed once they recovered from the present illness. All patients underwent a detailed physical examination. The questionnaires included the following details: demographic characteristics, duration of illness, history of taking serotonergic agents, reasons to start serotonergic drugs, first new symptom after the start of serotonergic drugs, presenting symptom (reason to consult in the neurology department), symptom pertinent to autonomic feature, symptoms pertinent to abnormal mental status, symptoms pertinent to neuromuscular abnormalities, and miscellaneous (fever, breathlessness seizure generalized pain, headache, pain at any other sites, paresthesia, vertigo, and pain abdomen). The questionnaires also include all the drugs patients received in the last 5 weeks. All patients were examined in detail with a special focus on autonomic features, cognition, and neuromuscular abnormalities.

Laboratory investigations

Routine biochemical investigations, including a complete hemogram, erythrocyte sedimentation rate, blood sugar, liver function tests, kidney function tests, electrolytes, and electrocardiography, were done in all patients. Other specific investigations were done according to the presenting symptoms or provisional or differential diagnosis. All patients with abnormal mental status were subjected to magnetic resonance imaging (MRI) brain and cerebrospinal fluid (CSF) analyses.

Determination of causation

The causation of SS to serotonergic drugs was assessed according to Naranjo adverse drug reaction (ADR) probability scale.[10] The ADR probability categories are as follows: definite if the overall score is 9 or greater, probable for a score of 5–8, possible for 1–4, and doubtful if the score is 0. One of the points in this scale is "did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?" Although there is no controlled study, available evidences suggest that SS responds to serotonin antagonists at least partly in most cases.[7] To minimize the misdiagnosis of SS, we excluded all such cases who did not show a significant response to serotonin antagonists.

Determination of severity

The severity of SS was determined as per the modified Hartwig and Siegel severity assessment scale.[11] The severity scale is as follows: severe if the level is 5 or greater, moderate for level 3–4, and mild for level 1–2.

Treatment

Treatment was not standardized as there is no evidence-based treatment regimen for patients with SS. Treatment was individualized and it included (i) removal of offending agents, (ii) administration of 5-HT 2A antagonists (cyproheptadine), and (iii) symptomatic managements.

Biostatistics

Data are presented as a percentage or as an arithmetic mean with standard deviation (SD).

Results

Sixty-one patients who had symptoms meeting Hunter's diagnostic criteria of SS were evaluated. Sixteen patients were excluded for the following reasons: (i) a possibility of other diagnosis – 8 patients (tuberculosis meningitis – 3 patients, hypoxic brain damage – 2 patients, central pontine myelinolysis – 1 patient, Wernicke's encephalopathy – 1 patient, and hypertensive encephalopathy – 1 patient), (ii) age < 18 years – 1 patient, (iii) incomplete follow-up – 2 patients, (iv) incomplete investigation – 2 patients, (v) a history of associated chronic disorders – 3 (diabetes – 1, hypertension – 1, and hypothyroidism – 1 patient). Finally, 45 patients were included for the analyses. Table 1 summarizes the symptoms of all 45 patients. The median age of the cases was 37.3 years (range: 18–59), and 28 (62%) were male.

Clinical features

We divided the clinical features in the five broad groups: (i) symptoms or disease for which serotonergic drugs were started, (ii) first or initial new symptom after the administration of serotonergic drugs, (iii) reasons to consult (chief or presenting complains), (iv) other associated symptoms, and (v) clinical signs detected on physical examinations.

Underlying syndromes or background disease for starting serotonergic agents

The reasons for starting serotonergic agents are shown in Table 2. We noted 15 different clinical syndromes for which serotonergic drugs were started. Psychiatry conditions were the most common group and were noted in 36% patients. Cough/respiratory tract infection, migraine, low back pain, and neck pain/cervical spondylosis were other common indications to receive serotonergic drugs. Some patients had two comorbid conditions for which they received two or more serotonergic agents.

Clinical features pertinent to serotonin syndrome

Overall, 49 separate symptoms and physical signs were identified. There were >30 symptoms related to SS [Table 3]. Tremor (78%) and dizziness (47%) were the two most common symptoms. Other common symptoms were headache, insomnia, agitation, gait difficulty, diaphoresis, generalized body pain, nausea-vomiting, fever, dysarthria, myoclonus, and sexual dysfunctions.

First or initial clinical symptoms

We analyzed the patients to find out the evolution of all clinical features. Patients recognized 18 different symptoms in the initial stage of SS [Table 3]. Headache (16%) and dizziness (16%) were the two most common initial (or first) symptoms. Other common initial symptoms were fever, insomnia, agitation, tremor, and sexual dysfunctions. A few patients also noted lower limb pain, generalized body pain, neck pain, abdominal pain, somnolence, dystonia, slowness in work, palpitation, diarrhea, dysarthria, and gait problem in very early stage of SS.

Presenting or chief complaint at the time presentation

Patients visited the department for 18 different symptoms. Difficulty in walking (29%) was the most common reason to visit the clinic. Fever, impaired consciousness, agitation, dizziness, slowness in work, tremor, generalized body pain, bladder symptoms, and dystonia were other common presenting complaints. A few other chief complaints were diaphoresis, dysarthria, abdominal pain, neck pain, visual blurring, and syncope.

Physical examinations

It is summarized in Table 4. Hyperreflexia was noted in all 45 patients. Tachycardia (82%), inducible clonus (82%), hypertonia/rigidity in limbs (64%), and new-onset hypertension (49%) were some other common physical abnormalities. Incoordination and nystagmus were noted in one-third of cases. Other physical signs included increased bowel sound, neck rigidity, extensor planter, mydriasis, orthostatic hypotension, hypotension, skin rashes, crackles in lungs, pedal edema, disc edema, spontaneous clonus, and ocular clonus.

Interrelation among clinical features

Of the ten patients with fever, seven subjects had impaired consciousness and two patients had agitation. One patient with fever reported severe headaches. Orthostatic hypotension was noted in five patients (11%). All patients with orthostatic hypotension had dizziness, and we found episode or aggravation of dizziness with a physical demonstration of orthostatic hypotension.

Aggravation of the previous syndrome

One patient received a combination of amitriptyline with valproate for chronic migraine. However, there was an increase in headache severity and patients developed other symptoms pertinent to a diagnosis of SS. Another patient received paroxetine for depression. However, he developed insomnia and agitation. Initially, it was considered as a part of his previous syndrome. However, later, he was diagnosed as a case of SS.

Severity of serotonin syndrome

It was determined according to modified Hartwig's Severity Assessment Scale [Supplementary File - Table S1]. SS was moderate in intensity in 35 (78%) patients, whereas severe intensity was noted in 10 (22%) patients. All patients with severe intensity had been receiving two or more serotonergic drugs. Agitation or impaired consciousness was noted in all ten patients with severe SS. Diaphoresis was also noted in all severe SS. Eight out of ten severe SS had fever.

Causal association of serotonin syndrome with serotonergic drugs

We determined the association of serotonergic drugs to SS according to Naranjo Algorithm score [Supplementary File - Table S2]. The level of causation was "possible" for 27 patients (60%) and "probable" for 18 patients (40%). Table 5 summarizes the different types of serotonergic agents noted in these 45 patients. We noted 17 different drugs. The interrelation of the development of SS to serotonergic drugs' administration was analyzed [Supplementary File - Table S3].

Seventeen (38%) patients received single serotonergic agent. Other 28 (62%) patients received two or more serotonergic agents. Twenty-seven (60%) patients noted symptoms just after the initiation of serotonergic drugs. Ten (22%) patients had SS after the increment of previously used drugs. Seven (16%) patients noted symptoms on the addition of second or third serotonergic agent. One patient developed SS on swapping the preexisting drug to other serotonergic drugs. All patients received only therapeutic doses of serotonergic drugs. None of the patients took an overdose. Six patients (13%) (All severe SS) reported within 24 h of the drugs' initiation/increment or addition of the second drug. Twenty-three patients reported within 2–7 days. All other patients (16 patients) reported after 1 week of the drug initiation or modification in it.

Investigations

All patients were subjected to routine biochemical investigations [Supplementary File - Table S4]. Leukocytosis was noted in 7 (16%) patients. Five of these patients had fever. Overall, 50% of patients with fever reported leukocytosis. Leukocytosis returned within the normal range

Table 1: Clinical summary of 45 patients with serotonin syndrome

Case number	Age	Male/female	First symptoms	Chief complains	Other clinical features	Serotonergic agents and its details
1	35	Female	Dizziness	Tremor	Insomnia, diarrhea, fatigue, palpitation, visual blurring	Cough syrup (dextromethorphan and chlorpheniramine)
2	18	Female	Lower limb pain	Gait problem	Tremor, GBP, headache, nausea, myoclonus, dysarthria, abdominal pain	Paroxetine for anxiety
3	39	Male	Fever	Fever, agitation	Headache, myoclonus, nausea, diaphoresis, shivering	Lithium and paroxetine for bipolar disorder
4	31	Male	Headache	Increased headache, gait problem	Tremor, GBP, insomnia, dysarthria	Amitriptyline with valproate for chronic migraine
5	26	Male	Headache	Dizziness	Tremor, insomnia, nausea, sexual dysfunctions, fatigue, constipation, abdominal pain	Cough syrup (dextromethorphan and chlorpheniramine)
6	26	Male	Dysarthria	Dysarthria, gait problem	Tremor, GBP, urinary problems	Duloxetine for low back pain
7	43	Male	Dizziness	Dizziness, syncope	Tremor, diarrhea, visual blurring	Cough syrup (dextromethorphan and chlorpheniramine)
8	35	Male	Headache	Generalized pain, slowness in work	Tremor, nausea, myoclonus, fatigue, constipation, abdominal pain	Fluoxetine and tramadol for low back pain
9	43	Female	Insomnia	Agitation	Tremor, GBP, urinary problems, palpitation	Nortriptyline and tramadol for carpal tunnel syndrome
10	57	Female	Generalized pain	Gait problem, generalized pain	Tremor, dysarthria, insomnia	Tramadol and sertraline for neck pain
11	54	Male	Dystonia	Dystonia	Tremor, GBP, insomnia, headache, nausea, sexual dysfunctions	Herbal product for osteoarthritis
12	32	Female	Dizziness	Dystonia/chorea	Tremor, GBP, somnolence	Sertraline for depression
13	30	Male	Fever, Agitation	Fever, impaired consciousness	Headache, myoclonus, diaphoresis, dysarthria, dyspnea, shivering	Dothiepin with valproate Chronic migraine
14	54	Male	Fever	Fever, impaired consciousness	Headache, agitation, diaphoresis dyspnea, shivering	Cough syrup (dextromethorphan) ondansetron added for nausea
15	19	Male	Headache	Dystonia	Tremor, GBP, fatigue, insomnia, abdominal pain	Fluoxetine for depression
16	28	Male	Headache	Lower limb pain/ stiffness	Tremor, nausea, constipation	Sertraline for low back pain
17	25	Female	Dizziness	Gait problem, slowness in work	Tremor, sexual dysfunctions, dysarthria	Dothiepin with valproate for chronic migraine
18	44	Male	Fever	Fever, impaired consciousness	Agitation, myoclonus, diaphoresis, dyspnea, shivering	Nortriptyline and fluoxetine for neck pain and cervical radiculopathy
19	47	Male	Dizziness	Urinary problems	Tremor, sexual dysfunctions, palpitation, visual blurring	Venlafaxine for depression
20	53	Female	Dizziness	Dizziness, Visual blurring	Tremor, GBP	Tramadol for osteoarthritis
21	41	Female	Tremor	Dizziness, tremor	Diarrhea, somnolence, visual blurring	Amitriptyline and ondansetron for abdominal pain/irritable bowel syndrome
22	25	Male	Abdominal pain	Abdominal pain, agitation	Tremor, headache, nausea	Carbamazepine for trigeminal neuralgia Nortriptyline was added
23	52	Male	Insomnia	Agitation	Tremor dizziness, diaphoresis, flushing, palpitation	Paroxetine for depression
24	21	Male	Sexual dysfunction	Gait problem, slowness in work	Tremor, dizziness, diarrhea	Fluoxetine and tramadol for radiculopathy
25	49	Male	Sexual dysfunction	Urinary problems, gait problem	Tremor, insomnia, dizziness, diarrhea, diaphoresis, palpitation	Fluoxetine for depression

Contd...

Table 1: Contd...

Case number	Age	Male/female	First symptoms	Chief complains	Other clinical features	Serotonergic agents and its details
26	42	Male	Headache	Fever, impaired consciousness	Agitation, nausea, diaphoresis, dysarthria, dyspnea, shivering	Fluoxetine and tramadol back pain
27	19	Female	Palpitation, dizziness	Insomnia, dizziness	Tremor, fatigue	Amitriptyline for tension-type headache
28	59	Female	Headache	Fever with headache	Dizziness, nausea, myoclonus, diaphoresis, dysarthria, shivering	Amitriptyline and tramadol for neck pain/cervical spondylosis
29	25	Female	Insomnia	Fever, impaired consciousness	Agitation, diaphoresis, dyspnea	Paroxetine and tramadol for depression and back pain Ondansetron was added for nausea/abdominal discomfort
30	29	Male	Somnolence, slowness in work	Dizziness, headache and neck pain	Tremor, GBP, nausea, fatigue, urinary problems	Cough syrup (codeine and chlorpheniramine)
31	30	Female	Gait problem	Gait problem, slowness in work	Tremor, sexual dysfunctions, myoclonus	Paroxetine for depression with anxiety
32	34	Female	Fever	Fever, impaired consciousness	Agitation, nausea, diaphoresis, dysarthria, dyspnea, shivering	Sertraline for depression Ondansetron added for nausea-vomiting
33	37	Male	Neck pain	Headache, generalized pain	Tremor, dizziness, gait problems	Cough syrup codeine and chlorpheniramine
34	42	Male	Sexual dysfunction	Gait problem	Tremor, GBP, diarrhea	Sertraline and valproate for chronic migraine
35	54	Female	Diarrhea	Gait problem	Tremor, dizziness, fatigue, abdominal pain	Duloxetine and tramadol for radiculopathy
36	35	Male	Insomnia	Agitation	Tremor, diaphoresis	Valproate for epilepsy
37	46	Male	Lower limb pain	Urinary problems	Tremor, dizziness, diarrhea, sexual dysfunctions	Amitriptyline and valproate for migraine
38	42	Male	Lower limb pain/stiff	Gait problem	Tremor, constipation, abdominal pain	Lithium for bipolar, tramadol was added for neck pain
39	46	Female	Tremor	Insomnia	Dizziness, constipation, visual blurring	Venlafaxine for depression
40	21	Female	Tremor	Tremor	Dizziness, fatigue, somnolence	Escitalopram for depression
41	24	Male	Agitation	Fever, agitation	Headache, nausea, diaphoresis, dysarthria, flushing	Sertraline for depression Tramadol was added for ankle trauma
42	26	Female	Fever	Fever, impaired consciousness	Agitation, myoclonus, diaphoresis, dyspnea, shivering, dystonia	Fluoxetine for depression Cough syrup (codeine) was added for URTI
43	54	Male	Sexual dysfunction	Gait problem, slowness in work	Tremor, insomnia, dizziness, diarrhea, myoclonus, urinary problems	Amitriptyline and tramadol for depression and neck pain
44	49	Male	Tremor agitation	Gait problem, diaphoresis	Dizziness, shivering, myoclonus	Amitriptyline and tramadol for cluster headache Switched to lithium
45	37	Male	Insomnia	Insomnia, agitation	Tremor	Valproate, amitriptyline, for chronic migraine

GBP=Generalized body pain, URTI=Upper respiratory tract infection

in 5–14 days duration. HyperCKemia was noted in six patients. Electromyography studies in these patients were nonspecific. Elevated CPK turned to normal level in all patients in 3 months. MRI brain and/or spine was done in 29 cases. None of them had any significant abnormality.

All patients with fever and altered behavior were subjected to CSF analyses (10 patients). CSF pleocytosis was noted in five patients. Four patients had increased protein. Two patients had both increased protein and CSF pleocytosis together. CSF abnormalities returned to baseline in 2–4-week duration. MRI brain did not reveal any abnormality in these patients. Serological testing for herpes simplex virus, human immunodeficiency virus, hepatitis B virus, *Mycobacterium tuberculosis*, malarial parasite, and enteric fever were negative in all these patients.

Table 2: Underlying clinical syndrome to start serotonergic agents

Clinical scenario	Number of patients, *n* (%)
Depression/anxiety	16 (36)
Cough/URTI	7 (16)
Migraine	6 (13)
Low back pain	5 (11)
Neck pain/cervical spondylosis	5 (11)
Radiculopathy	3 (7)
Nausea/vomiting	3 (7)
Osteoarthritis	2 (4)
Ankle sprain/trauma	1 (2)
Tension-type headache	1 (2)
Trigeminal neuralgia	1 (2)
Cluster headache	1 (2)
Epilepsy	1 (2)
Carpal tunnel syndrome	1 (2)
Irritable bowel syndrome	1 (2)

A few patients had two or more co-morbid conditions for receiving serotonergic agents. URTI=Upper respiratory tract infection

Management and follow-up

As there are no guidelines for the management in patients with SS, treatments were not standardized. All severe cases were admitted to the Intensive Care Unit. Four "moderately severe" cases were also admitted in the department. All other cases were managed as outpatients. All patients were followed up for at least 4 weeks.

Severe serotonin syndrome (ten patients)

All cases received 12 mg loading dose of cyproheptadine. It was continued as 2 mg every 2 h till autonomic instability (i.e., heart rate, blood pressure, and diaphoresis) persisted. Blood pressure and heart rate subsided within 24 h in six patients. It took 48–72 h in other four patients. Thereafter, patients were put on the dose of 8 mg 6 hourly till other clinical features persisted. The drug was withdrawn gradually (about 20%–25% every day). If patients showed any relapse or increase in the symptoms on tapering of the drug, it was further escalated to the previous doses. The average duration of cyproheptadine was 14 days (range: 8–25 days). Besides cyproheptadine, all patients received some sort of symptomatic management. Symptomatic management was individualized, depending on the associated symptoms and signs. Two cases with febrile encephalopathy with CSF abnormalities received empirical intravenous acyclovir. However, it had been stopped in a few days once viral markers came negative.

Moderate serotonin syndrome (35 patients)

Initial dose for all patients was 4 mg every 8 hourly. Depending on the initial response (within 24–72 h), it was titrated up to 8 mg 6 hourly. The drug was continued till clinical features persisted. Thereafter, the drug was tapered off gradually (about 20%–25% every day). The average dose of cyproheptadine was 17 mg/day (range: 12–24 mg/day). The duration of treatment varied from 5 to 30 days (average: 12 days; SD ± 4.5)

Table 3: Prevalence of different clinical symptoms in 45 patients with serotonin syndrome

Clinical feature	Total number of patients, *n* (%)	As a first or initial symptom, *n* (%)	As a chief symptom, *n* (%)
Tremor	35 (78)	4 (9)	3 (7)
Dizziness	21 (47)	7 (16)	6 (13)
Headache	16 (36)	7 (16)	4 (9)
Insomnia	15 (33)	5 (11)	3 (7)
Agitation	15 (33)	3 (9)	7 (16)
Gait problem	14 (31)	1 (2)	13 (29)
Diaphoresis	14 (31)	0	1 (2)
General body pain	13 (29)	1 (2)	3 (7)
Nausea/vomiting	12 (27)	0	0
Fever	10 (22)	6 (13)	10 (22)
Dysarthria	10 (22)	1 (2)	1 (2)
Myoclonus	10 (22)	0	0
Sexual dysfunctions	10 (22)	4 (9)	0
Diarrhea	9 (20)	1 (2)	0
Shivering	9 (20)	0	0
Fatigue	8 (18)	0	0
Impaired consciousness	7 (16)	0	7 (16)
Dyspnea	7 (16)	0	0
Abdominal pain	7 (16)	1 (2)	1 (2)
Bladder symptoms	7 (16)	0	3 (7)
Palpitation	6 (13)	1 (2)	0
Visual blurring	6 (13)	0	1 (2)
Slowness in work	6 (13)	1 (2)	5 (11)
Constipation	5 (11)	0	0
Somnolence	4 (9)	1 (2)	0
Dystonia/chorea	4 (9)	1 (2)	3 (7)
Lower limb pain	4 (9)	3 (4)	1 (2)
Hot flushing	2 (4)	0	0
Neck pain	2 (4)	1 (2)	1 (2)
Syncope	1 (2)	0	1 (2)

Discussion

The incidence of SS is largely unknown because of various reasons. A few retrospective observations have been done from the database of drug toxicity reports. Dunkley *et al*. reviewed 2222 cases from a dataset (collected over 15 years) with serotonergic drugs' poisoning (overdose).[8] Abadie *et al*. noted 125 cases of SS in the French Pharmacovigilance Database recorded over 28 years.[12] A few retrospective observations have evaluated the incidence of SS after SSRIs overdose. The SS was noted in about 19% cases who took overdose of SSRIs. It was about 29% for venlafaxine overdose.[13] The incidence of SS in patients on SSRI monotherapy on therapeutic drug dosing was 0.5–0.9 cases per 1000 patient-months in one postmarketing surveillance study.[14] To the best of our literature

Table 4: Prevalence of various physical signs in 45 patients with serotonin syndrome

Physical examinations	Number of patients, *n* (%)
Hyperreflexia	45 (100)
Tachycardia	37 (82)
Inducible clonus	37 (82)
Hypertonia/rigidity of limbs	29 (64)
New onset hypertension	22 (49)
Nystagmus	15 (33)
Incoordination	15 (33)
Increased bowel sound	13 (29)
Neck rigidity	12 (27)
Extensor planter	11 (24)
Mydriasis	6 (13)
Orthostatic hypotension	5 (11)
Hypotension	3 (7)
Skin rashes	3 (7)
Crackles in lungs	2 (4)
Pedal edema	2 (4)
Disc edema	1 (2)
Spontaneous clonus	1 (2)
Ocular clonus	1 (2)

Table 5: Serotonergic drugs used in 45 patients

Name of the drugs	Number of patients, *n* (%)
Tramadol	13 (29)
Amitriptyline	8 (18)
Valproate	7 (16)
Fluoxetine	7 (16)
Sertraline	6 (13)
Paroxetine	5 (11)
Chlorpheniramine	5 (11)
Dextromethorphan	4 (11)
Ondansetron	4 (9)
Codeine	3 (7)
Nortriptyline	3 (7)
Lithium	3 (7)
Dothiepin	2 (4)
Venlafaxine	2 (4)
Escitalopram	1 (2)
Duloxetine	1 (2)
Carbamazepine	1 (2)
Herbal product	1 (2)

search, this is the first clinic-based prospective observation in patients with SS.

Serotonergic agents

SS is classically described in patients with psychiatry disorders receiving SSRIs or other serotonergic agents. However, we noted 14 more underlying clinical conditions where serotonergic drugs led to SS. Cough, migraine, neck pain, and back pain were other common indications for starting serotonergic agents. Our observations expanded the underlying conditions where patients can develop SS. We noted 18 different types of serotonergic agents. All drugs are known for their serotonergic properties. Ten out of 18 were antidepressants. However, tramadol was the most common agent in our observation. In Abadie *et al*. observation, tramadol was the third most common encountered drugs.[12] Tramadol is frequently advised for various painful conditions. It is also available as over-the-counter product in this part of the world.

Seventeen (38%) patients had been on single serotonergic agent. It was comparable to the recent observation done on French Pharmacovigilance Database. In this database analyses, 40.8% patients were on a single serotonergic agent, and majorities (93%) were on the therapeutic dose.[12] There is a common belief that a single serotonergic agent usually causes mild SS.[9] One patient had severe SS, whereas other 16 patients developed moderately severe SS. In French pharmacovigilance database analyses, 69% patients on single serotonergic agent had serious/severe SS. Hence, our observation and French database analyses suggest that a single serotonergic agent in therapeutic dose may cause moderate-to-severe SS.

Various review on SS suggests that it develops within 24 h of the initiation or change of the drug or addition of the new drug.[15] Only 13% in our series visited to the hospital within 24 h. This may be because of a large number of moderate cases in our observations. Nearly 36% of patients reported after 1 week of the drug initiation or modification. It was comparable to the observation seen in French pharmacovigilance database analyses. About 38% patients in this database analyses developed SS after 1 week.[12]

Clinical features

The clinical triad of SS, mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities encompasses a wide range of clinical symptoms and physical signs. Moreover, it develops over some preexisting syndrome (for which patients had been taking serotonergic drugs). Hence, it may be difficult to differentiate SS from underlying disease. It may be difficult to identify at what time exactly patient developed new symptoms pertinent to SS. Moreover, some features related to SS may mimic underlying syndrome for which serotonergic drugs have been prescribed.

The clinical features related to SS in the literature are mainly derived from the severe cases developing from the drug overdose or emerging from multiple serotonergic drugs' ingestion. The literature is almost silent regarding the evolution of clinical features in SS. We noted more than thirty different symptoms. Gait problems were the most common reason to consult the physicians. Fever with agitation or altered behavior was the second most common reason. Patients with gait abnormality showed a mixed picture of pyramidal dysfunctions (hypertonia, brisk reflex, and clonus), cerebellar abnormalities (tremor, incoordination, etc.), and parkinsonism (rigidity, bradykinesia, etc.). Febrile encephalopathy is the well-known clinical syndrome with SS. Overall, 22% patients had fever. It was the initial symptom in 13% patients. One interesting observation was CSF

pleocytosis (5 patients) and increased CSF protein (4 patients). We have reported three similar cases earlier and speculated a possible pathogenesis for it.[6] Febrile encephalopathy has a number of differential diagnosis. A number of investigations are required to confirm or to exclude a particular diagnosis. However, a severe case of SS is a medical emergency. A trial of cyproheptadine should be administered straightaway on the suspicion of SS. In parallel, the patients should be subjected to other appropriate investigations.

Dizziness and headache were two most common initial symptoms. Overall, headache was noted in 36% patients and it was the presenting feature in 9% of cases. There are various case reports where headache was one of the accompanying features of SS.[2,3,16] Headache, as side effects, has been reported by various serotonergic drugs.[17] In one patient, migraine headache got aggravated by amitriptyline and valproate. A similar case was noted in one patient of Richard *et al*.'s series. Patients showed worsening of his headaches after the administration of an antidepressant.[18] Available evidence suggests that serotonin (5-HT) has a dual role in the pain-modulating system. Chronic 5-HT deficit may be the biochemical basis of migraine. However, an intermittent release of serotonin at higher concentration may induce headache attack by binding to 5-HT2A receptors.[19]

Generalized body pain was the chief complaint in 7% of patients. Generalized body pain was one of the accompanying features in some case reports in the literature.[2,16] Alnwick reported a patient who had been on antidepressants for years. Over the years, the patient developed chronic headache and generalized pain. Physical examination confirmed SS.[20]

Dizziness was noted in 47% patients, and it was the presenting features in 13% of cases. Dizziness is a common side effect of serotonergic agents.[17] It has also been noted as one of the features of SS. It was present in 12.5% cases in Radomski *et al*.'s review. Kaneda *et al*. reported dizziness in 16% of patients.[21] Dizziness is very nonspecific symptoms and may have a number of pathophysiological reasons for it. We noted orthostatic hypotension in five patients (out of 21 dizzy patients). Another three patients had newly (first time) detected hypertension. We suggest that dizziness in SS may be related to autonomic instability in a subset of patients.

Tremor was the most common symptom in our observation. The prevalence of tremor was 58.5% in Werneke *et al*. review.[15] However, patients may not be aware of the presence of tremor. Only 7% of patients in our observation came with the complained of tremor. Patients should be checked for the presence of tremor if patients on serotonergic drugs develop any new symptoms.

Insomnia is a common side effects of most of the serotonergic drugs.[17] It was noted in about 10% of cases of SS. It was one of the initial symptoms in 11% patients of our patients.

Serotonin affects gastrointestinal motility and peristaltic reflex.[22] Gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation, abdominal pain, increased bowel sound, etc.) are not uncommon in SS.[15,16] Diarrhea was noted in 15% of patients in Werneke *et al*. meta-analyses. Abdominal pain/cramps have been reported in various case reports.[16] About one-fourth of our patients had nausea and/or vomiting. 16% of patients noted abdominal pain. Abdominal pain was one of the prominent symptoms in one patient.

5-HT_{2A} receptors are located in Onuf's nucleus, and it controls voiding functions.[23] Therefore, bladder symptoms (retention, urgency, dysynergia, incontinence, etc.) may be associated with SS. Various case reports have reported different bladder symptoms. It was noted in 16% of patients, and 7% patients had bladder symptoms as chief complains.

It is suggested that higher serotonin levels reduce sexual function and sexual dysfunctions are one of the common side effects of serotonergic agents.[24] However, the literature is silent if it is the part of SS. We noted some form of sexual dysfunctions in 22% of patients and it was one of the initial symptoms in 9% patients. Cyproheptadine is frequently used as a treatment modality for SSRIs induced sexual dysfunctions. Therefore, we speculate that sexual dysfunctions in a subset of patients may be the part of SS.

Tachycardia and hypertension are very common physical findings. In a meta-analysis by Werneke *et al*., tachycardia/bradycardia was noted in 85% of patients.[15] Hypertension or hypotension was noted in 76% of cases.[15] One newly detected hypertensive patient was referred to neurology department for the evaluation of tremor. After detailed history and examination, we noted SS. Blood pressure responded by the discontinuation of SSRI and after administration of cyproheptadine.

Two patients had marked pedal edema that subsided by therapy with cyproheptadine. Two other patients also had crackles in the lungs. It also responded to therapy of SS. Shah and Jain reported a case of SS where pulmonary edema was the prominent feature.[25] It has been suggested that SS may alter the fluid equilibrium across the microvascular membranes through autonomic instability.[26] It may be the reason for pedal edema and crackles in the lungs.

Pathophysiology

SS mainly results from an increase in the intrasynaptic concentration of serotonin, especially in the brainstem and spinal cord. The 5-HT_{2A} and 5-HT_{1A} are the main receptors implicated in the development of serotonin toxicity.[1] Serotonergic neurons in the CNS modulate wakefulness, behavior, sexual behavior, thermoregulation, muscular tone, nociception and voiding functions. In parallel to central 5-HT effects, peripheral 5-HT receptors also implicated in SS. Peripheral serotonin receptors modulate vascular tone and gastrointestinal motility.[1] Besides serotonin, some other neurotransmitters (noradrenaline, dopamine, N-methyl-D-aspartate receptor antagonist, and gamma-aminobutyric acid) may play a role in the generation of SS. Therefore, a large number of symptoms can be present in SS. Each and every drug has a different affinity for different neurotransmitters and receptors. The development of clinical

features of SS depends on the net effects of stimulation of different receptors by different neurotransmitters. It may be a reason for the variability in symptom complex of SS in different patients.

Various drugs may increase the intrasynaptic serotonin in brainstem and spinal cord by increased production, increased release, or decreased breakdown.[27] Studies have demonstrated increased serotonin levels in brain after various antiepileptic ingestion (including sodium valproate and carbamazepine).[4,28] Inhibition of cytochrome P450 enzymes by certain drugs also decrease the metabolism of certain serotonergic drugs (such as tramadol).[29] Carbamazepine also inhibits the cytochrome P450 enzymes.

Limitations

There are a number of difficulties in doing a study in SS-like disease entity. They have protean manifestations, and there are no biochemical markers for diagnosis. Clinical syndromes have a number of differential diagnosis. Moreover, SS develops over some preexisting disease. Hence, differentiation of drug-induced SS with preexisting illness may be difficult. On occasions, you have to start drug on the emergency basis without getting investigations. These all make the study somewhat difficult. Although we tried our best to rule out other secondary causes, we cannot rule out completely a possibility of other disorder. However, the authors are confident that the patients included in this study had a definite SS as all patients fulfilled the Hunter's criteria and there were no better alternative diagnoses. Management was not standardized. A possibility of placebo response can also be not ruled out as spontaneous remission may occur in a few cases.

The study was done in an adult tertiary neurology outpatient clinic. Therefore, our observations cannot be generalized as our sample of patients may not truly represent patients with SS.

Conclusions

SS is not that rare in clinical practice. However, various aspects of this syndrome are still to be determined. SS is classically described in patients with psychiatry disorders. Our observation expanded the underlying disorders where patients can develop SS. SS typically develops within 24–48 h after the drug administration. However, a substantial number of patients report after 1 week of drug initiation or modification. An SS can be mistaken for the underlying illness itself, all patients on serotonergic drugs should be physically examined for the presence of SS on the development of any new symptom.

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Conflicts of interest

There are no conflicts of interest.

References

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112-20.
2. Prakash S, Patel V, Kakked S, Patel I, Yadav R. Mild serotonin syndrome: A report of 12 cases. Ann Indian Acad Neurol 2015;18:226-30.
3. Prakash S, Belani P, Trivedi A. Headache as a presenting feature in patients with serotonin syndrome: A case series. Cephalalgia 2014;34:148-53.
4. Prakash S, Adroja B, Parekh H. Serotonin syndrome in patients with headache disorders. BMJ Case Rep 2017;2017. pii: bcr-2017-221383.
5. Prakash S, Rathore C. Serotonin syndrome presenting as surgical emergency: A report of two cases. Indian J Crit Care Med 2016;20:120-2.
6. Prakash S, Makwana P, Rathore C, Dave A. Serotonin syndrome presenting as febrile encephalopathy with CSF pleocytosis: A report of three cases. Neurol Sci 2016;37:1561-4.
7. Prakash S, Rathore C. Cyproheptadine-dependent chronic serotonin syndrome. Neurol India 2016;64:1319-21.
8. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The hunter serotonin toxicity criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. QJM 2003;96:635-42.
9. Buckley NA, Dawson AH, Isbister GK. Serotonin syndrome. BMJ 2014;348:g1626.
10. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
11. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49:2229-32.
12. Abadie D, Rousseau V, Logerot S, Cottin J, Montastruc JL, Montastruc F, *et al.* Serotonin syndrome: Analysis of cases registered in the French pharmacovigilance database. J Clin Psychopharmacol 2015;35:382-8.
13. Whyte IM, Dawson AH, Buckley NA. Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. QJM 2003;96:369-74.
14. Mackay FJ, Dunn NR, Mann RD. Antidepressants and the serotonin syndrome in general practice. Br J Gen Pract 1999;49:871-4.
15. Werneke U, Jamshidi F, Taylor DM, Ott M. Conundrums in neurology: Diagnosing serotonin syndrome – A meta-analysis of cases. BMC Neurol 2016;16:97.
16. Radomski JW, Dursun SM, Reveley MA, Kutcher SP. An exploratory approach to the serotonin syndrome: An update of clinical phenomenology and revised diagnostic criteria. Med Hypotheses 2000;55:218-24.
17. Ferguson JM. SSRI antidepressant medications: Adverse effects and tolerability. Prim Care Companion J Clin Psychiatry 2001;3:22-7.
18. Richard IH, Kurlan R, Tanner C, Factor S, Hubble J, Suchowersky O, *et al.* Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Parkinson study group. Neurology 1997;48:1070-7.
19. Sommer C. Serotonin in pain and pain control. In: Muller C, Jacobs B, editors. Handbook of Behavioral Neurobiology of Serotonin. London, Burlington, San Diego: Academic Press; 2010. p. 457-71.
20. Alnwick GM. Misdiagnosis of serotonin syndrome as fibromyalgia and the role of physical therapists. Phys Ther 2008;88:757-65.
21. Kaneda Y, Ishimoto Y, Ohmori T. Mild serotonin syndrome on fluvoxamine. Int J Neurosci 2001;109:165-72.
22. Sikander A, Rana SV, Prasad KK. Role of serotonin in gastrointestinal motility and irritable bowel syndrome. Clin Chim Acta 2009;403:47-55.
23. Lychkova AE, Pavone LM. Role of serotonin receptors in regulation of contractile activity of urinary bladder in rabbits. Urology 2013;81:696.e13-8.
24. Montejo-González AL, Llorca G, Izquierdo JA, Ledesma A, Bousoño M, Calcedo *et al.* SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. J Sex Marital Ther 1997;23:176-94.
25. Shah ND, Jain AB. Serotonin syndrome presenting as pulmonary edema. Indian J Pharmacol 2016;48:93-5.
26. Mikulski Z, Zaslona Z, Cakarova L, Hartmann P, Wilhelm J, Tecott LH, *et al.* Serotonin activates murine alveolar macrophages through 5-HT2C receptors. Am J Physiol Lung Cell Mol Physiol 2010;299:L272-80.
27. Gillman PK. A review of serotonin toxicity data: Implications for the mechanisms of antidepressant drug action. Biol Psychiatry 2006;59:1046-51.
28. Dailey JW, Reith ME, Steidley KR, Milbrandt JC, Jobe PC. Carbamazepine-induced release of serotonin from rat hippocampus *in vitro*. Epilepsia 1998;39:1054-63.
29. Ogu CC, Maxa JL. Drug interactions due to cytochrome P450. Proc (Bayl Univ Med Cent) 2000;13:421-3.

Supplementary File

Table S1: Severity of serotonin syndrome according to Hartwig's Severity Assessment Scale

Level	Number of patient, *n* (%)	Severity
1-2	0	Mild
3	14 (31)	Moderate
4	21 (47)	Moderate
5	10 (22)	Severe
6-7	0	Severe

Table S2: Causal association of serotonin syndrome with serotonergic drugs according to Naranjo Algorithm

Score (Naranjo algorithm)	Number of patients, *n* (%)	Level of causation
0	0	Doubtful
1	0	Possible
2	1 (2)	Possible
3	3 (7)	Possible
4	23 (51)	Possible
5	7 (16)	Probable
6	5 (11)	Probable
7	6 (13)	Probable
8	0	Probable
9	0	Definite

Table S3: Drug relation with the onset of serotonin syndrome

	Number of patients, *n* (%)
Number of serotonergic drug used in the last 5 weeks	
Single serotonergic drug	17 (38)
Two or more serotonergic drugs	28 (62)
Temporal relation between drug ingestion and SS development	
Start of serotonergic drugs	27 (60)
Increment of serotonergic drugs	10 (22)
Addition of new serotonergic drug	7 (16)
Swap of serotonergic drugs	1 (2)

SS=Serotonin syndrome

Table S4: Laboratory investigations in 45 patients in serotonin syndrome (only abnormalities are shown)

Investigations	Number of patients, *n* (%)	Remarks
Leukocytosis	7 (16)	Range 11,900-15,400/mm^3
Increased CPK	6 (13)	844-2100 U/L
Hypernatremia	1 (4)	154 mmol/L
Hyponatremia	1 (4)	125 mmol/L
CSF analyses (10 patients)		
Increased cell	5	15-90 cells/mm^3
Increased protein	4	54-68 mg/dL
Decreased glucose	0	
Abnormal EEG		
Slow wave	6	Diffuse slowing
Epileptiform discharge	0	

CPK=Creatine phosphokinase, EEG=Electroencephalography, CSF=Cerebrospinal fluid