Original Article

Cyproheptadine in serotonin syndrome: A retrospective study

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Abstract

Objective: Serotonin syndrome (SS) is an iatrogenic life-threatening condition caused by serotonergic agents. The treatment for SS involves the administration of a serotonin antagonist (cyproheptadine). However, the dosing schedule for cyproheptadine is not uniform in the literature. **Methods:** We retrospectively evaluated 23 adult patients (>18 years) admitted to the Neurology Department and met the Hunter criteria for SS. **Results:** The mean age was 35.2 years, and 52% were female. Ten patients were managed in the intensive care unit (ICU), whereas thirteen patients were admitted to the ward. Hyperreflexia was the most common clinical feature (100%), followed by clonus (91%), tachycardia (83%), and tremor (83%). Other common clinical features were rigidity (65%), increased bowel sound (61%), diaphoresis (48%), fever (43%), hypertension (39%), and myoclonus (30%). All but one patient received two or more serotonergic drugs. Tramadol was the most common serotonergic agent (39%), followed by sodium valproate (21%), and amitriptyline (21%). Cyproheptadine was administered to all patients. All patients admitted in the ICU received a loading dose of 12 mg followed by 2 mg every 2 h for at least 24 h. All patients admitted to the ward were given 4 mg of cyproheptadine three times each day. Every patient showed at least some response to cyproheptadine within 24 h. The total doses of cyproheptadine and the length of treatment differed between patients. **Conclusion:** Any response to cyproheptadine at a therapeutic dose within 24 h, even a partial one, could be a diagnostic indicator of the existence of SS.

Keywords: Cyproheptadine, serotonin, serotonin syndrome, serotonin toxicity

Introduction

Serotonin syndrome (SS) is an iatrogenic, drug-induced, potentially life-threatening clinical condition characterized by an altered mental state, neuromuscular hyperactivity, and autonomic hyperactivity.[1,2] The incidence of SS is rising globally as a result of the pervasive and expanding usage of serotonergic drugs in clinical practice. Historically, the majority of SS reports were published from toxicology centers, primarily in patients with mental disorders. However, a number of new clinical settings have been identified, and cases are now being reported from nontoxicological centers such as perioperative settings, neurology clinics, cardiac settings, gynecological settings, and pediatric clinics.[3] Antidepressants are the most common drugs implicated in the generation of SS. However, several new drugs, including over-the-counter medications, have been discovered to have serotonergic properties. SS cases have been documented in both intensive care units and outpatient clinics across all departments. Therefore, physicians should be familiar with SS.

SS is a highly underdiagnosed clinical condition, and awareness about this syndrome is extremely low among medical professionals.[4] SS is typically diagnosed according to either Hunter criteria or Sternbach's criteria.[5,6] The criteria is based

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on the demonstration of specific clinical features. However, the differential diagnosis of SS includes a wide range of clinical syndromes such as neuroleptic malignant syndrome (NMS), catatonia, anticholinergic toxicity, malignant hyperthermia, sympathomimetic agent intoxication, thyroid storm, acute extrapyramidal syndromes, encephalitis, and meningitis.[1] Therefore, a thorough history and physical examination are crucial. Treatment for SS consists of *1*) withholding serotonergic medications, *2*) supportive care, *3*) sedating the patient with benzodiazepines, and *4*) administration of serotonin antagonists (cyproheptadine). However, there is no agreement on the use of cyproheptadine in the treatment of SS. The dosing schedule of cyproheptadine is not uniform, and it varies considerably across published studies.[7-9]

Methods

This retrospective study comprises all consecutive adult patients (>18) who were hospitalized with a diagnosis of SS. Included individuals were seen in the neurology department of a tertiary hospital between September 2020 and February 2023. Inclusion criteria include *1*) age: >18 years; *2*) patients fulfilling the criteria for SS; and *3*) patients who were admitted to the hospital for the management of SS. Exclusion criteria were *1*) age: <18 years; *2*) patients who were managed without getting admitted to the hospital; *3*) patients with a history of chronic illnesses like diabetes and hypertension to prevent potential confounders; and *4*) patients who refused to give consent. The primary objective was to observe the effects of cyproheptadine on clinical characteristics over time. Therefore, the patients who were managed without getting admitted to the hospital were excluded from the study. The institutional ethics committee approved the study. The study was carried out in accordance with the Helsinki Declaration guidelines. All patients gave consent for the publication of this observation. Our group has been working on SS for a number of years. So, as a departmental policy, all patients who satisfy the Hunter criteria for SS are routinely subjected to a thorough clinical history and physical examination during their hospital stay. So, all of the data presented here were gathered prospectively. Cyproheptadine is considered an antidote for SS. There is, however, no consensus on the use of cyproheptadine in the management of SS. However, the dosing regimen for cyproheptadine is not standardized and varies substantially between published case reports. According to reports, SS patients may need 12 to 32 mg of cyproheptadine per day.[1] For severe SS, admitted to the ICU, we followed the treatment regimen as described by Boyer *et al.*[1] They recommend a loading dose of 12 mg, followed by 2 mg every 2 h if symptoms continue. It was followed by a maintenance dose of 8 mg of cyproheptadine every 6 h. This regimen of cyproheptadine was administered to all patients admitted to the ICU, in addition to other supportive treatments. The patients who were stable and were admitted to the ward received 4 mg of cyproheptadine three times daily (tid) as an initial dose. This dose was titrated based on the patient's response to cyproheptadine.

Results

We identified 38 patients who met the Hunter criteria for SS. Fifteen patients were excluded from the study for the following reasons: age less than 18 years (n = 2 patients), patients treated without hospitalization (n = 6 patients), a history of associated chronic illness = 5 (hypertension = 2, diabetes = 2, and multiple sclerosis = 1 patient), and patients who did not give consent (n = 2 patients). Finally, 23 cases were included in the analysis. Table 1 provides an overview of the clinical characteristics and other aspects of all 23 patients. The mean age was 35.2 years (range: 23–59 years), and 52% were female. Ten patients were managed in the ICU, whereas 13 patients were admitted to the ward.

Hyperreflexia was the most common clinical feature (n = 23, 100%), followed by clonus (n = 21, 91%), tachycardia (n = 19, 83%), and tremor (n = 19, 83%). Other common clinical features were rigidity or spasticity (n = 15, 65%), increased bowel sound (n = 14, 61%), diaphoresis (n = 11, 48%), fever (n = 10, 43%), hypertension (n = 9, 39%), and myoclonus (n = 7, 30%). Other clinical features were insomnia (n = 6, 26%), dizziness (n = 5, 22%), ataxia (n = 4, 17%), nausea-vomiting (n = 4, 17%), generalized body pain (n = 4, 17%), headache (n = 4, 17%), and incoordination (n = 3, 13%). All patients admitted to the ICU had a fever, abnormal mental status (agitation or irritability, drowsiness, stupor, and coma), and diaphoresis. Acute febrile encephalopathy was a syndromic diagnosis for all patients admitted to the ICU. Patients admitted to the ward had a variety of syndromic diagnoses, including dizziness, insomnia, ataxia, incoordination, generalized body pain, and headaches. All of the ICU patients had symptoms for 4 to 10 days before they were admitted. The duration of illness for the ward patients was somewhat prolonged, ranging from 1 to 4 weeks.

All but one patient received two or more serotonergic drugs. Eleven patients (48%) received two serotonergic drugs, whereas nine patients (39%) got three. Tramadol was the most common drug that caused SS (n = 9, 39%), followed by sodium valproate (n = 5, 21%), amitriptyline (n = 5, 21%), sertraline (n = 4, 17%), nortriptyline (n = 4, 17%), pregabalin (n = 4, 17%), and ondansetron (n = 4, 17%). Other drugs were escitalopram (n = 3, 13%), gabapentin (n = 3, 13%), linezolid (n = 3, 13%), dextromethorphan (n = 3, 13%), lithium (n = 2, 9%), fluoxetine (n = 2, 9%), chlorpheniramine (n = 2, 9%), venlafaxine (n = 2, 9%), paroxetine (n = 1, 4%), and topiramate (n = 1, 4%). Every patient received only therapeutic doses of serotonergic medications. There were no overdoses among the patients. All patients were subjected to a number of investigations. Leukocytosis was noted in 13 (57%) patients. All 10 patients admitted to the ICU had leukocytosis. Nine patients had raised creatine phosphokinase (CPK).

The dosage schedule and effects of cyproheptadine on each patient are described in Table 2. All 10 patients who were brought to the ICU received the identical initial dosage

Table 1: Details of patients with serotonin syndrome

Age/ Sex	Clinical settings	Details of the clinical characteristics			Serotonergic agent and its details	Investigations
		Presenting complaint	Other symptoms and signs	Duration of illness		
35 M	ICU	Altered behavior leading to coma	Fever, diaphoresis, tachycardia, hypertension, rigidity, clonus, myoclonus hyperreflexia, increased bowel sound	5 days	Lithium and sertraline for chronic depression. Dose of sertraline was increased 2 wk back	Leukocytosis, raised CPK
32 F	ICU	Agitation, fever, vomiting	Tachycardia, tremor, myoclonus, diaphoresis, rigidity, hyperreflexia, clonus, bowel sound	7 days	Valproate for seizure (2 years), tramadol for pain (3 wk), and linezolid after admission.	Leukocytosis
24 M	ICU	Fever, altered behavior, myoclonus, tremulousness,	Tachycardia, diaphoresis, hypertension, rigidity, hyperreflexia, clonus, increased bowel sound.	5–6 days	Dextromethorphan and chlorpheniramine for cough. Linezolid and ondansetron for fever	Leukocytosis, raised CPK
44 M	ICU	Agitation, fever, diaphoresis shivering, ataxia,	Tachycardia, tremor, nystagmus, mydriasis, hyperreflexia, clonus, increased bowel sound	7–10 days	Escitalopram, pregabaline, tramadol for fibromyalgia (8 wk)	Leukocytosis, raised CPK
23 M	ICU	Fever, tremulousness, agitation	Tachycardia, diaphoresis hypertension, rigidity hyperreflexia, clonus, increased bowel sound	4–6 days	Amitriptyline, sertraline, tramadol for posttraumatic pain (2 wk)	Leukocytosis, raised CPK
39 M	ICU	Fever, agitation, myoclonus, tremulousness	Tachycardia, diaphoresis, hypertension, clonus hyperreflexia, bowel sound	5–6 days	Valproate and lithium for cluster headache (3 wk)	Leukocytosis,
49 F	ICU	Fever, stupor, myoclonus, diaphoresis	Tachycardia, hypertension, rigidity, hyperreflexia, clonus, bowel sound	8–10 days	Linezolid, ondansetron, dextromethorphan for fever and cough (2 wk)	Leukocytosis, raised CPK
26 M	ICU	Irritability, fever, diaphoresis, tremulousness,	Tachycardia, rigidity, hyperreflexia, clonus, increased bowel sound	9–10 days	Escitalopram and Venlafaxine for depression (6 wk)	Leukocytosis
37 F	ICU	Fever, nausea, vomiting, drowsiness, diaphoresis	Tachycardia, hypertension, hyperreflexia, clonus, rigidity, myoclonus, increased bowel sound	4–5 days	Cough syrup (chlorpheniramine and dextromethorphan), tramadol for pain (6–7 days)	Leukocytosis
46 M	ICU	Fever, drowsiness, tremulousness, diaphoresis	Tachycardia, hyperreflexia, clonus, myoclonus, rigidity, increased bowel sound	6–7 days	Pregabaline, tramadol nortriptyline for cervical spondylosis, ondansetron	Leukocytosis, raised CPK
34 F	Ward	Dizziness, fatigue, restlessness, insomnia,	Tremor, hyperreflexia, rigidity, clonus, increased bowel sound	10–12 days	Amitriptyline and paroxetine for depression for 6 wk	
59 M	Ward	Gait problems, tremor, insomnia	Tachycardia, rigidity, hyperreflexia, clonus, increased bowel sound	1–2 wk	Pregabalin and amitriptyline for back pain (4 wk)	raised CPK
36 F	Ward	Generalized body pain, tremor	tachycardia, hypertension, rigidity, hyperreflexia, clonus,	3–4 wk	Topiramate and amitriptyline for migraine (2 months)	Leukocytosis
26 F	Ward	Headache, insomnia, dizziness,	Tachycardia, tremor, rigidity, hyperreflexia, clonus (ill-sustained).	2 wk	Tramadol, gabapentin for carpal tunnel syndrome (for 4 wk)	
33 F	Ward	Dizziness, fatigue, insomnia, tremor, irritability	Tachycardia, hypertension, hyperreflexia, clonus, rigidity, diaphoresis	1–2 wk	Amitriptyline, sertraline for depression. tension-type headache (6 wk)	Leukocytosis
27 M	Ward	Tremor, ataxia, incoordination	Tachycardia, rigidity, hyperreflexia, clonus	2 wk	Gabapentin, nortriptyline, tramadol for back pain (3 wk)	raised CPK
29 F	Ward	Dizziness, body pain, irritability	Tremor, tachycardia, hypertension, hyperreflexia	7–8 days	Valproate and ondansetron for mood disorder (6–7 wk)	
42 M	Ward	Tremors, ataxia, incoordination	Tachycardia, hyperreflexia, clonus	10–12 days	Venlafaxine and fluoxetine for mood disposer (8 wk)	
45 M	Ward	Tremor, insomnia headache, nausea, vomiting	Tachycardia, hyperreflexia, clonus, increased bowel sound	2–3 wk	Gabapentin, nortriptyline, tramadol for back pain and radiculopathy (8 wk)	
32 F	Ward	Diffuse body pain, vertigo, ataxia	Tremors, hyperreflexia, clonus, incoordination	2–3 wk	Valproate and escitalopram for migraine (4 wk)	raised CPK
32 F	Ward	Anxiety, headache insomnia	Tremors, spasticity, hyperreflexia, clonus	2 wk	Pregabaline, nortriptyline, tramadol for back pain (5 wk)	
24 F	Ward	Headache, nausea, vomiting, dizziness	Tachycardia, hyperreflexia, clonus, increased bowel sound.	10–12 days	Valproate for epilepsy. Sertraline added for depression 2 wk back	Leukocytosis
37 F	Ward	Headache, diffuse body pain	Tremor, hyperreflexia,	3 wk	Fluoxetine for chronic depression for 8 wk	

CPK, creatine phosphokinase; F, female; ICU, intensive care unit; M, male; wk, weeks

Table 2: Treatment with cyproheptadine in patients with serotonin syndrome

Initial Dose (first 24 h)	Clinical Response within 24 h	Dose of Cyproheptadine and Clinical Response after 24 h
12 mg loading dose, 2 mg 2 hourly	Diaphoresis, clonus, hypertension subsided. Fever, rigidity reduced	8 mg qid for next 2 days. Reduction of dose (4 mg tid) led aggravation of symptoms. Restarted (8 mg qid). Complete improvement in 10 days. Gradually tapered over 2 wk
12 mg loading dose, 2 mg 2 hourly	Clonus disappeared. Agitation, fever, rigidity improved	8 mg qid for next 24 h. Reduction of dose (4 mg qid) led aggravation of symptoms. Restarted (8 mg qid). Complete response in 8 days. Gradually tapered over 2 wk
12 mg loading dose, 2 mg 2 hourly	Clonus, myoclonus, rigidity, tremulousness improved	8 mg qid for next 4 days. Further Improvement in next 2 days, bowel sound decreased, diaphoresis-subsided. Fever and behavioral abnormally persisted (little bit improved). Change in antibiotic led improvement in 2 wk
12 mg loading dose, 2 mg 2 hourly	Fever, diaphoresis, hypertension, rigidity, clonus improved	8 mg qid for next 48 h. Improvement continued. Reduction of dose (4 mg qid) led aggravation of symptoms. Restarted (8 mg qid). Complete response in 10 days. Gradually tapered over 2–3 wk. Aggravation by while tapering was noted
12 mg loading dose, 2 mg 2 hourly	Fever, diaphoresis, rigidity clonus improved	8 mg qid for next 5 days. Gradual improvement continued. Reduction of dose (4 mg qid) after 5 days. Complete response in 12 days. Drug was gradually tapered over 2–3 wk
12 mg loading dose, 2 mg 2 hourly	Fever, agitation, clonus, myoclonus, diaphoresis improved	8 mg qid for next 2 days. Improvement continued. Reduction of dose (4 mg qid) led aggravation of symptoms. Restarted (8 mg qid). Complete response in 7 days. Gradually tapered over 2 wk
12 mg loading dose, 2 mg 2 hourly	Fever, mental status, clonus myoclonus, diaphoresis improved	8 mg qid for next 4 days. Gradual improvement continued. Reduction of dose (4 mg qid) after 4 days. Complete response in 10 days. Drug was gradually tapered over 2 wk
12 mg loading dose, 2 mg 2 hourly	Irritability, fever, rigidity, clonus improved	8 mg qid for next 3 days. Gradual improvement continued. Reduction of dose (4 mg qid) after 3 days. Complete response in 7–8 days. Drug was gradually tapered over 10 days
12 mg loading dose, 2 mg 2 hourly	Clonus disappeared Fever, mental status, diaphoresis improved	8 mg qid for next 5 days. Further Improvement in next 2–3 days. No complete improvement. Fever and irritability persisted (little bit improved). Change in antibiotic led to improvement in 2 wk
12 mg loading dose, 2 mg 2 hourly	Clonus disappeared Fever, drowsiness improved	8 mg qid for next 1 day. Reduction of dose (4 mg qid) led aggravation of symptoms. Restarted (8 mg qid). Complete improvement in 5 days. Gradually tapered over 15 days
4 mg tid	Clonus disappeared Restlessness, rigidity improved	Dose was reduced to 2 mg tid due to sedation. Aggravation of symptoms. Again escalated to 4 mg tid. Complete improvement in 7 days. Drug was continued for another 10 days
4 mg tid	Clonus reduced, Gait improved	Dose was escalated to 8 mg tid. Marked improvement in 3 days. Complete improvement in 10 days
4 mg tid	Rigidity, clonus subsided	Skipped the drug for 1 day due to sedation. Aggravation of symptoms. Restarted at 2 mg tid. Complete response in 7 days. Withdrawal of drug again led to reappearance of symptoms. Reinstitution of drug again provided complete improvement. Drug was continued for 2 wk
4 mg tid	Clonus, rigidity disappeared	4 mg tid for next 7 days. All symptoms disappeared in 5 days. Drug was continued for 7 more days (2 mg tid)
4 mg tid	Rigidity, clonus subsided Dizziness, fatigue improved	4 mg tid for next 7 days. Marked improvement in 7 days. Reduction of dose (2 mg tid) led to reappearance of symptoms. Dose was escalated (4 mg tid). Symptoms again subsided. Continued for 4 wk
4 mg tid	Rigidity, clonus, incoordination improved	4 mg tid for next 3 wk. Gradual improvement continued. Complete improvement in 3 wk. Skipping the drug led to reappearance of the symptoms
4 mg tid	Dizziness, irritability, hypertension improved	4 mg tid for next 7 days. Improvement continued. Complete response in 2 wk. Drug was gradually tapered over 2 wk
4 mg tid	Clonus disappeared Incoordination improved	Dose was reduced to 2 mg qid due to sedation. Aggravation of symptoms. Escalated to 4 mg tid after 3 days. Complete improvement in 4 days. Drugs was continued for 14 days
4 mg tid	Clonus disappeared headache, nausea, vomiting improved	Dose was reduced to 2 mg qid due to sedation. Gradual improvement continued. Complete improvement in 8 days
4 mg tid	Clonus disappeared Vertigo, incoordination, ataxia improved	4 mg tid continued. Complete improvement in 2 wk. Drug was gradually tapered over 2 wk
4 mg tid	Clonus disappeared Headache improved	4 mg tid continued. Complete improvement in 5 days. Drug was gradually tapered over 2 wk

Contd...

Table 2: Contd...

Initial Dose (first 24 h)	Clinical Response within 24 h	Dose of Cyproheptadine and Clinical Response after 24 h
4 mg tid	Clonus disappeared Headache, dizziness, nausea improved	4 mg tid continued. Complete improvement in 7 days. Drug was gradually tapered over 2 wk
4 mg tid	Headache, body pain improved	Dose was reduced to 2 mg qid due to sedation. Gradual improvement continued. Complete improvement in 6 days

qid- four times daily; tid- three times daily; wk- weeks

regimen, which consisted of a loading dose of 12 mg followed by 2 mg every 2 h for at least 24 h. Those admitted to the ward had a lower initial dose. All patients admitted to the ward were given 4 mg of cyproheptadine three times each day. Every patient showed at least some response to cyproheptadine within 24 h. In fact, the response was noted in almost all clinical features. However, the most notable response was noted in the clonus. Clonus was noted in 21 patients (out of 23) at the time of admission. There was no clonus in 11 patients after 24 h of cyproheptadine administration. In another 10 patients, the clonus was markedly reduced. After 24 h of cyproheptadine administration, clonus disappeared in 11 patients and diminished in 10 more. Rigidity or spasticity (noted in 15 patients) disappeared or subsided in 11 patients. The degree of fever and diaphoresis decreased in all ICU patients within 24 h. Out of the 10 patients with mental abnormalities, six showed improvement in their mental state within 24 h after cyproheptadine administration. After 24–36 h, the dose of cyproheptadine was changed from 2 mg every 2 h to 8 mg every 6 h in all ICU patients. This dose was administered for 1 to 5 days, depending on the improvement of the patient's clinical conditions. Thereafter, the dose was reduced to 4 mg every 6 h. Nonetheless, there has been a worsening of the symptoms in 7 patients out of 10. The previous dose was reinstituted, and the same dose was given for another 5 to 14 days. After complete improvement, cyprohepatadine was gradually withdrawn over 2 weeks. Two ICU patients, although they showed marked responses in the early stages, did not show complete responses. Both patients had an associated respiratory tract infection. We believe that these patients had two syndromes during their hospital stay (serotonin syndrome and respiratory tract infection).

Although the ward patients received a lower daily dose of cyproheptadine (4 mg tid), every patient had some improvement within 24 h. Improvement in clonus was noted in all patients within 24 h. Depending on the resolution of symptoms and the development of cyproheptadine-induced sedation, each patient's treatment duration varied. The dosage of cyproheptadine was reduced from 4 mg tid to 2 mg tid in five ward patients due to the development of sedation. Reduction of the dose led to aggravation of symptoms in all five patients. Three patients resumed their previous dose, whereas two continued to take a reduced dose. One patient need an escalation of the dose as improvement stopped after 2–3 days. The duration of treatment for the ward patients varied from 2 weeks to 4 weeks.

Discussion

The primary objective of the study was to observe the effect of cyproheptadine in addition to detailing its clinical characteristics. The true incidence of SS is largely unknown for a variety of reasons. Nonetheless, it appears that it is not uncommon in clinical practice. Dunkley *et al.*[5] reviewed 473 cases with a single-agent selective serotonin reuptake inhibitors (SSRIs) overdose. Overall, 73 patients (15.4%) had SS. Similarly, 10.3% (14/136) of the patients developed SS following a noncyclic antidepressant overdose.[10] In the Whyte *et al.* study,[11] SS developed in 29% of venlafaxine overdose patients and 19% of SSRI overdose cases. In one postmarketing survey, the incidence of SS was 0.5–0.9 cases per 1000 patient months in patients receiving SSRI monotherapy at a therapeutic dose.[12] In a cross-sectional study of older adults receiving antidepressants, 25.2% (60/238) were found to have SS. In one cross-sectional study, 7.8% (24/309) of the patients met the criteria for SS in an ICU setting.[13]

The majority of earlier case studies on SS were restricted to patients with psychiatric disorders. Lately, a number of nonpsychiatric medicines have been found to have serotonergic properties, and they include antiepileptic drugs, analgesics, antitussive agents, antiemetic agents, antimigraine drugs, and herbal products. Therefore, nowadays several cases of SS are being reported from nontoxicology centers.[3] We are reporting 23 cases of SS observed in the neurology department. We identified a wide variety of drugs associated with the onset of SS, including SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antiepileptic, antitussive agents, antiemetic, analgesic, antibiotic, and gabapentinoids. Most of the initial cases reported in the literature were linked to serotonergic drug overdose or poisoning. Nowadays, cases of SS are being reported from the therapeutic doses of serotonergic medications.[14] There was no overdose or poisoning of any serotonergic medicines in any of our patients, and all of our cases were on therapeutic doses of serotonergic medicines.

Cognitive impairments in SS vary from mild irritability to coma. Neuromuscular dysfunctions range from hyperreflexia to severe rigidity or spontaneous clonus. Autonomic hyperactivity vary from mild nausea to hyperthermia.[15] Untreated or severe SS may cause a number of complications, including multiorgan failure. The Hunter criteria for SS, however, only lists seven characteristics, including fever, agitation, diaphoresis, rigidity-spasticity, tremor, hyperreflexia, and clonus (induced,

spontaneous, and ocular).[5] The most common symptoms of SS are probably hyperreflexia, clonus, tachycardia, and tremor.[3,14] The central features of SS, according to the Hunter criteria, are hyperreflexia and clonus (including ocular clonus). The enterochromaffin cells of the gastrointestinal tract store almost 95% of the body's serotonin, which controls a number of gastrointestinal processes.[16] Therefore, gastrointestinal features (nausea, vomiting, diarrhea, and increased bowel sounds) are common in SS. Although gastrointestinal symptoms are not included in the Hunter criteria, diarrhea is one of the symptoms listed in Sternbach's criteria for SS.[6] Gastrointestinal features, particularly increased bowel sounds, may be an important diagnostic point favoring a diagnosis of SS over other similar conditions, such as NM.[17]

Dunkley *et al*.[5] made the first reference to the ocular clonus when they proposed the Hunter criteria. They did not, however, provide any information about ocular clonus, including a definition. There are just a few case reports of SS that mention the presence of ocular clonus in patients with SS. Even these case reports did not define the ocular clonus. The literature is silent on whether ocular clonus of SS differs from opsoclonus. A video of ocular movement in a patient with SS was uploaded in NEJM, and the author reported it as "ocular flutter."[18] There is a need to define the place of ocular clonus in the diagnostic criteria for SS.

SS develops over some preexisting disorder (for which serotonergic agents have been started). SS and preexisting syndrome disorders may progress and produce a myriad of complications. So, a patient may not have isolated SS, but rather it may be superimposed on a preexisting illness. Therefore, SS is called "Syndrome on Syndrome."[19] Our two patients had SS over preexisting illnesses during their hospital stay. A correct diagnosis of both diseases at the same time is crucial since the two diseases may require different treatments. Such patients may show only partial response to cyproheptadine. A proper history is required to find out the possibility of a preexisting disorder with SS.

As SS is a potentially life-threatening condition, a proper treatment is crucial. Depending on the severity of the symptoms, treatment may differ. Moderate and severe SS may necessitate immediate and aggressive therapy. Patients may require serotonin antagonists in addition to discontinuing serotonergic medications and symptomatic therapy. Cyproheptadine is one of the best serotonin antagonists, and it is considered an antidote in SS. However, its efficacy in SS has not been rigorously proven. The majority of the data is derived from case reports, and these reports show varying responses to cyproheptadine. The variability in response could be attributed to varied dosages and a delay in the initiation of the drug.[20]

Nguyen *et al*.[7] reviewed the effects of cyproheptadine in 288 patients with probable SS. A total of 68 patients received cyproheptadine. They compared it with a control group that did not get cyproheptadine. They did not find any differences between the groups. Unfortunately, there were several limitations in the study. The details of the cyproheptadine dose was available for only 44% of patients (30 of 68). The average initial dose was 7.1 mg (range: 1 to 12.5 mg). They provided no information regarding the maintenance dose. It will not be rational to draw any conclusions from this study. They suggested that the lack of effects could be attributed to a lower-than-required dose. Graudins *et al*.[8] reported five patients with moderate SS who received cyproheptadine. Four patients received an initial dose of 8 mg, whereas one patient received 4 mg. Three experienced complete resolution of symptoms within 2 h of treatment. Two additional patients had a residual tremor or hyperreflexia following the initial dose, which resolved after receiving a second dose. In a retrospective study, Frye *et al*.[9] evaluated the effects of cyproheptadine on 28 SS patients. Cyproheptadine regimens varied greatly in these patients. In 25 cases, the initial dose was at least 12 mg or higher. The cumulative dose varied from 12 mg to 116 mg. With the exception of one patient, the clinical symptoms resolved within 48 h. The duration of treatment varied from 1 day to 7 days.

One study found that 30 mg of cyproheptadine is needed to block 85%–95% of brain 5-HT2A receptors. Therefore, a few authors recommend a higher initial dose (12 to 32 mg) in the first 24 h for the treatment of moderate to severe SS. It could be the reason for the excellent result in the Frye *et al*. study and the poor outcome in the Nguyen *et al*. study. We also used a higher dose, and all patients responded favorably. In light of this, at least some response to cyprohepatadine at a therapeutic dose within 24 h may serve as a diagnostic sign for the presence of SS. It can be included in the diagnostic criteria of SS. One thing that was unusual in our study was that these patients needed a longer duration of treatment with cyproheptadine.

The patients with poisoning or intentional overdose may have a relatively acute onset and severe symptoms. The diagnosis of such cases may be overt because of the circumstances. The onset of symptoms in patients who develop SS as a result of therapeutic doses may be gradual. Because of the insidious onset and nonspecific symptoms, patients may continue to take serotonergic drugs despite having SS. A few studies have found that chronic use of SSRIs can cause cortical hyperexcitability.[21] Another study demonstrated increased dendritic arborization of cortical cells by chronic fluoxetine administration.[22] Therefore, chronic treatment with SSRIs may cause persistent hyperexcitable states. These may be the reasons for the longer treatment in a subset of patients in our series.

The medications that cause SS differ depending on the clinics. In psychiatry clinic, it is mainly SSRI. In various clinical settings, tramadol is emerging as a significant medication producing SS.[3,23]

There are various limitations to our study. This is a retrospective case series from a single center, observed by neurologists. So, it cannot be generalized. There can be several biases in this study. We did not find any SS due to overdose. Even though all cases in our cohort met the Hunter criteria, we could not exclude the

possibility of all causes of SS-like illness for several reasons. Despite these limitations, our cases indicate that different patients with SS may require a varied cyproheptadine dosage regimen. Multicenter prospective studies from different clinical settings are required to determine the optimal dosing regimen.

Ethical policy and Institutional Review board statement

The institutional ethics committee approved the study (SVIEC/ON/MEDI/RP/23/April/5Y). The study was carried out in accordance with the Helsinki Declaration guidelines.

Patient declaration of consent statement

All patients gave consent for the publication of this observation. There is no image of any patients.

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Conflicts of interest

There are no conflicts of interest.

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