

World Journal of *Psychiatry*

World J Psychiatr 2021 April 19; 11(4): 87-152



OPINION REVIEW

- 87 Contemplative sciences: A future beyond mindfulness
Garcia-Campayo J, López del Hoyo Y, Navarro-Gil M

REVIEW

- 94 Global health disparities in vulnerable populations of psychiatric patients during the COVID-19 pandemic
Diaz A, Baweja R, Bonatakis JK, Baweja R

MINIREVIEWS

- 109 Use of technology and social media in dementia care: Current and future directions
Shu S, Woo BK

ORIGINAL ARTICLE**Retrospective Study**

- 124 Chronic serotonin syndrome: A retrospective study
Prakash S, Rathore C, Rana K, Roychowdhury D, Lodha D

META-ANALYSIS

- 133 Effectiveness of digital psychotherapeutic intervention among perinatal women: A systematic review and meta-analysis of randomized controlled trials
Lau Y, Cheng JY, Wong SH, Yen KY, Cheng LJ

ABOUT COVER

Editorial Board Member of *World Journal of Psychiatry*, Li-Ye Zou, PhD, Professor, School of Psychology, Shenzhen University, Shenzhen 518060, Guangdong Province, China. liyezou123@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Psychiatry* (WJP, *World J Psychiatr*) is to provide scholars and readers from various fields of psychiatry with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJP mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, psychoanalysis, psychosomatic medicine, etc.

INDEXING/ABSTRACTING

The WJP is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 edition of Journal Citation Reports® cites the 2019 impact factor (IF) for WJP as 3.545; IF without journal self cites: 3.545; Ranking: 46 among 155 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Jia-Hui Li; Production Department Director: Yun-Xiao Jian Wu; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Psychiatry

ISSN

ISSN 2220-3206 (online)

LAUNCH DATE

December 31, 2011

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Rajesh R Tampi

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3206/editorialboard.htm>

PUBLICATION DATE

April 19, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Retrospective Study

Chronic serotonin syndrome: A retrospective study

Sanjay Prakash, Chaturbhuj Rathore, Kaushik Rana, Diptangshu Roychowdhury, Deepali Lodha

ORCID number: Sanjay Prakash 0000-0001-7322-904X; Chaturbhuj Rathore 0000-0001-5567-1715; Kaushik Rana 0000-0002-6251-343X; Diptangshu Roychowdhury 0000-0001-6223-3123; Deepali Lodha 0000-0003-3480-9660.

Author contributions: Prakash S was involved in the conceptualization of the project, data collection, statistical analysis, supervision of the project, and writing the original draft; Rathore C was involved in the analysis and interpretation of data and writing the original draft; Rana K was involved in the analysis and interpretation of data and revising the manuscript for intellectual content; Roychowdhury D was involved in data collection and revising the manuscript for intellectual content; Lodha D was involved in data collection and revising the manuscript for intellectual content; All authors approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Sumandeep Vidyapeeth Institutional Ethics committee, Piparia, Vadodara, India (SVIEC/ON/MEDI/RP/20116).

Informed consent statement: Written informed consent was taken from all patients to publish this observation.

Sanjay Prakash, Chaturbhuj Rathore, Kaushik Rana, Department of Neurology, Smt. B.K. Shah Medical Institute and Research Centre, Sumandeep Vdyapeeth, Vadodara 391760, India

Diptangshu Roychowdhury, Department of Psychiatry, Smt. B.K. Shah Medical Institute and Research Centre, Sumandeep Vdyapeeth, Vadodara 391760, India

Deepali Lodha, Department of Medicine, Smt. B.K. Shah Medical Institute and Research Centre, Sumandeep Vdyapeeth, Vadodara 391760, India

Corresponding author: Sanjay Prakash, MD, Professor, Department of Neurology, Smt. B.K. Shah Medical Institute and Research Centre, Sumandeep Vdyapeeth, Piparia, Waghodia, Vadodara 391760, India. drprakashs@yahoo.co.in

Abstract

BACKGROUND

Serotonin syndrome (SS) is an underdiagnosed drug-induced clinical syndrome resulting from the excess intrasynaptic concentration of serotonin. Very limited information is available about chronic SS.

AIM

To evaluate the epidemiological, clinical, and other aspects of the insidious onset SS.

METHODS

We retrospectively evaluated 14 consecutive adult patients (> 18 years) who had complaints for more than 6 wk at the time of consultation and met the Hunter criteria for SS.

RESULTS

The mean age was 41.1 years (range: 21-61 years), with a male preponderance (64%). Although tremors were observed in all patients, this was a presenting complaint in only 43% of patients. Generalized body pain, insomnia, and restlessness were common presenting features (50% each). Other common clinical features were stiffness of the limbs (43%), diaphoresis (43%), gait disturbances (36%), bowel disturbances (36%), dizziness (29%), sexual dysfunctions (21%), incoordination (14%), and fatigue (14%). The mean duration of symptoms before the diagnosis of SS was 13.5 ± 5.8 wk (range: 6-24 wk). Amitriptyline was the most common drug ($n = 6$, 43%), followed by tramadol ($n = 5$, 36%) and sodium valproate ($n = 5$, 36%). All patients received cyproheptadine, a 5-hydroxytryptamine_{2A} antagonist, as treatment and noted an excellent response

Conflict-of-interest statement:

There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Clinical neurology

Country/Territory of origin: India

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 14, 2020

Peer-review started: December 14, 2020

First decision: January 18, 2021

Revised: January 21, 2021

Accepted: March 9, 2021

Article in press: March 9, 2021

Published online: April 19, 2021

P-Reviewer: Plaza MA

S-Editor: Zhang H

L-Editor: Filipodia

P-Editor: Li JH



over the course of 4-14 d.

CONCLUSION

This study represents the largest study on chronic SS. We suggest that patients receiving serotonergic drugs should be physically examined for the presence of SS upon the development of new symptoms.

Key Words: Serotonin syndrome; Serotonin toxicity; Cyproheptadine; Serotonergic agents; Serotonin; Clonus

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Chronic serotonin syndrome (SS) is an evolving concept. It may present with nonspecific symptoms such as generalized body pain, stiffness/rigidity, insomnia, restlessness, and tiredness. As misdiagnosis is common for typical cases of SS, a high level of clinical suspicion is required to identify patients with a chronic variant. A detailed drug history and thorough physical examinations are needed to detect a case of SS. Diagnosis of even mild SS is important as inadvertent use of another serotonergic agent may worsen the clinical symptoms, and sometimes it can be fatal.

Citation: Prakash S, Rathore C, Rana K, Roychowdhury D, Lodha D. Chronic serotonin syndrome: A retrospective study. *World J Psychiatr* 2021; 11(4): 124-132

URL: <https://www.wjgnet.com/2220-3206/full/v11/i4/124.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v11.i4.124>

INTRODUCTION

Serotonin syndrome (SS) is a drug-induced clinical phenomenon characterized by a triad of altered mental activity, neuromuscular hyperactivity, and autonomic disturbances. It occurs due to increased intrasynaptic concentration of 5-hydroxytryptamine (5-HT) or serotonin. Although SS is a potentially fatal condition, misdiagnosis for SS is common in clinical practice. Misdiagnosis is partly due to its protean manifestation and partly due to unfamiliarity about SS among physicians^[1]. The incidence of SS is increasing worldwide due to the widespread use of various serotonergic agents. Several new concepts about SS have emerged in recent years that further complicate clinical issues associated with SS. In earlier years, SS was commonly reported in patients with psychiatric disorders, especially from toxicology centres. The identification of a variety of serotonergic agents in the past decades has expanded the clinical scenarios where SS can be noted. Cases of SS are being reported from non-toxicological departments and clinics, including surgical departments (perioperative settings), cardiac departments, headache clinics, gynaecological clinics, and paediatric clinics. Moreover, a few drugs with serotonergic properties are not marketed as serotonergic agents (such as dextromethorphan, fentanyl, linezolid, tramadol, and methylene blue). The clinical spectrum of SS has increased dramatically in recent times, and several atypical features have been noted in patients with SS^[2]. The literature on SS is a bit biased for acute and severe cases, and there are only a few cases of SS that had insidious onset and prolonged course^[3-5].

The onset of SS is typically described in the setting of recent administration of a proserotonergic agent. The administration of proserotonergic agent means starting a drug for the first time, increasing the dose, taking an overdose (accidental or suicidal), adding other serotonergic agents, and swapping of serotonergic agents. However, SS, including severe and fatal cases, may occur even with a stable dosage. In a review of 56 cases of fatal SS, seven patients (13%) were on a stable dosage, and there was no change in the dosage of the drugs in the recent past; and all of them had insidious onset SS^[6].

The diagnosis of SS is typically made according to either the Hunter criteria or the Sternbach's criteria, and both the diagnostic criteria are primarily intended to detect acute and severe cases^[7,8]. The Hunter serotonin toxicity criteria require the presence of one of the following clinical features in the presence of serotonergic agent use: (1)

Spontaneous clonus; (2) Inducible clonus/ocular clonus with diaphoresis or agitation or rigidity, with a temperature $> 38.0^{\circ}\text{C}$; and (3) Hyperreflexia and tremor^[7]. A combination of tremor and hyperreflexia is generally noted with mild and insidious onset SS. To the best of our knowledge, no studies dedicated to insidious onset chronic SS have been conducted to date. Chronic SS is not defined in the literature. The term 'chronic' is often used when the course of the disease persists for more than 3 mo. However, in a few clinical conditions, the time limit for chronic conditions is less than 3 mo. The time limit for chronic myelitis and chronic osteomyelitis is 6 wk. Considering the seriousness of SS, we used 6 wk to define the time frame of chronic SS in this publication. Herein, to discover the different aspects of insidious onset chronic SS, we evaluated the data of the patients who met the Hunter criteria for SS and simultaneously had symptoms for more than 6 wk.

MATERIALS AND METHODS

This study was conducted as a retrospective chart review of all consecutive adult patients (≥ 18) who had 'presenting complaints' for more than 6 wk at the time of the first consultation and met the Hunter criteria for SS (Hunter criteria described above). The study included patients with a minimum of 6 wk of follow-up. The exclusion criteria included: (1) Age < 18 years; (2) A follow-up of less than 6 wk; and (3) Patients who did not give consent. Included patients were seen between February 2018 and July 2020 in the Neurology Outpatient Department of Smt. B.K. Shah Medical Institute and Research Center, Vadodara, India. Epidemiological, clinical, laboratory, management, and outcome data were collected from medical records. Our team has been working on SS for several years. Therefore, as a departmental policy, any patient fulfilling the Hunter criteria is routinely subjected to a detailed clinical history and physical examination. So, all the data were collected prospectively at the time of the first consultation. The Institutional Ethics Committee approved the study (SVIEC/ON/MEDI/RP/20116). The study was done according to the Helsinki Declaration guidelines. Written informed consent was taken from all patients to publish this observation. We used statistics with mean \pm SD for continuous variables and frequencies and percentages for dichotomous variables. Anonymized data not reported here can be obtained from the corresponding author on rational demand by any qualified researcher.

RESULTS

We identified 19 patients who met the inclusion criteria. Five patients were excluded for the following reasons: Age less than 18 years ($n = 1$ patient), follow-up less than 6 wk ($n = 2$ patients), and those who did not give consent ($n = 2$ patients). As cases of chronic SS are not well described in the literature, we are providing details of three patients. The clinical characteristics of the other 11 cases are summarized in Table 1. Epidemiological, clinical, and other characteristics of all 14 cases are summarized in Table 2.

The median age at symptom onset was 44.1 years (range: 21-61 years), with a male preponderance (64%). All patients had tremors and hyperreflexia. A combination of tremors and hyperreflexia/inducible clonus sufficed the Hunter criteria. In addition, 11 patients (78%) also fulfilled the Sternbach's criteria of SS. Generalized body pain, insomnia, and restlessness were common presenting complaints ($n = 7$ patients, 50% each). Although tremor was observed in all patients, it was part of the presenting complaints in only six patients (43%). In other patients, tremors were detected only after neurological examinations. Other common symptoms included diaphoresis ($n = 6$ patients, 43%), gait problems ($n = 5$, 36%), bowel disturbances ($n = 5$, 36%), dizziness ($n = 4$, 29%), sexual dysfunctions ($n = 3$, 21%), incoordination ($n = 2$, 14%), and fatigue ($n = 2$ patients, 14%). Besides hyperreflexia (100%), clonus ($n = 13$ patients, 93%) and rigidity/spasticity ($n = 11$ patients, 79%) were two common physical signs. Tachycardia was reported in 9 (64%) patients. Fever was not reported in any patient. The mean duration of symptoms before getting the diagnosis of SS was 13.5 ± 5.8 wk (range: 6-24 wk). While 36% of patients were on a single serotonergic agent, about 64% of patients received two serotonergic agents. There was no history of an overdose of any serotonergic agent, and all patients were on stable doses of serotonergic agents for various periods. Amitriptyline was the most common agent causing SS ($n = 6$ patients, 43%), followed by tramadol and sodium valproate ($n = 5$ patients, 36% each). We

Table 1 Details of patients with chronic serotonin syndrome

Age/sex	Details of the clinical characteristics			Serotonergic agent and its details	Investigations	Treatment and follow up
	Presenting complaint	Other symptoms and signs	Duration of illness			
49, F	Generalized body pain, fatigue, restlessness, tremors	Dizziness, insomnia, tachycardia, rigidity, clonus	6-8 wk	Valproate for 2 yr for epilepsy, sertraline added 3 mo back for depression	CK- 566 U/L	Discontinued sertraline. Cyproheptadine (4 mg bid) was started. Marked improvement in 2 d. Complete response within 5 d. No recurrence in follow-up
57, M	Irritability, disturbed sleep, slowness in gait, disturbed bowel	Tremors, sexual dysfunctions, tachycardia, rigidity, clonus	3 mo	Tramadol and amitriptyline for paraesthesia for 1 yr	Normal	Discontinued drugs. Cyproheptadine (4 mg bid) was started. Response began within 48 h. Complete response within 7 d
32, F	Headache, generalized body pain, tremors	Intermittent diaphoresis, tachycardia, rigidity, clonus	2 mo	Valproate (500 mg bid) for 6 mo for epilepsy	CK- 1283 U/L	Marked improvement by cyproheptadine (4 mg tid). Valproate changed to levetiracetam. Follow-up was uneventful
46, F	Slowness in work and gait, bladder dysfunctions, dizziness, tremors	Dizziness, sexual dysfunctions, tachycardia, rigidity, clonus	3 mo	Amitriptyline and citalopram for 1 yr for bipolar disorder	Normal	Discontinued the offending drugs. Cyproheptadine (4 mg tid) for 3 wk. Response began in 48 h. Complete response within 10
58, M	Slowness in gait, pain and stiffness in the limbs and neck, tremors	Nystagmus, tachycardia, rigidity, clonus	10-12 wk	Tramadol, and fluoxetine for 4 mo for carpal tunnel syndrome	CK-879 U/L	Cyproheptadine (4 mg tid) for 2 wk. Response began in 2 d. Complete response within 5-7 d. No recurrence in follow-up
37, F	Tremors, irritability, fatigue, muscle pain, bowel disturbances	Tachycardia, hypertension, hypertonia, clonus	8-10 wk	Amitriptyline and valproate for chronic migraine for 6 mo	Normal	Started cyproheptadine (4 mg bid). Complete response within 4-6 d. Cyproheptadine was continued as an anti-migraine drug
31, M	Gait problems, stiff legs, bowel disturbances	Tremors, spasticity, clonus, diaphoresis	9-10 wk	Paroxetine (40 mg/d) for 6 mo for depression	CK-1279 U/L	Discontinued paroxetine. Cyproheptadine (6 mg tid) for 3 wk
47, M	Insomnia, dizziness, restlessness, bowel disturbance, episodic sweating	Tremor tachycardia, rigidity, clonus, hyperreflexia	3-4 mo	Sertraline and valproate for mood disorder for 9 mo	CK-634 U/L	Discontinued both drugs. Cyproheptadine (4 mg bid) for 4 wk
42, F	Generalized body pain, stiff body, constipation	Tremors, nystagmus, rigidity, stiff neck, hyperreflexia	8-10 wk	Tramadol and amitriptyline for 3 mo for pain after radius fracture	CK-1134 U/L	Started cyproheptadine (4 mg tid). Marked response in 7 d. Cyproheptadine was continued for 6 wk
54, M	Dystonic tremor, incoordination, stiffness in legs, episodic sweating	Tremors, nystagmus, rigidity, clonus, hyperreflexia	6-8 wk	Amitriptyline and tramadol for 3 mo for cervical spondylosis	Normal	Stopped both drugs. Started cyproheptadine (4 mg tid). Complete response in 7 d. Cyproheptadine was continued for 6 wk
61, M	Tremors, stiffness, incoordination, sexual dysfunction, insomnia	Nystagmus, rigidity, clonus, hypertension	4-5 mo	Addicted to tramadol for 2 yr for neuropathic pain	Normal	Marked improvement with cyproheptadine (4 mg tid). The patient did not stop tramadol and he continued cyproheptadine

F: Female; M: Male.

found two cases each with paroxetine and sertraline. There was 1 case each with citalopram and fluoxetine. Creatine kinase levels were raised in 6 patients (43%). Cyproheptadine, a 5HT_{2A} antagonist, is the main drug used in cases of SS, and all patients received cyproheptadine. All patients showed a complete or almost complete response to cyproheptadine over 4–14 d.

Table 2 Epidemiological profiles and clinical features of 14 patients with chronic serotonin syndrome

Parameters	n (%)
Age in yr, mean \pm SD	44.1 \pm 11.6
Sex, M:F	9:5 (1.8:1)
Duration of illness in wk	13.5 \pm 5.8
Clinical characteristics	
Tremor	14 (100)
Hyperreflexia	14 (100)
Clonus	13 (93)
Spasticity-rigidity	11 (79)
Tachycardia	9 (64)
Generalized pain	7 (50)
Insomnia	7 (50)
Irritability-restlessness	7 (50)
Stiffness	6 (43)
Diaphoresis	6 (43)
Gait disturbances	5 (36)
Bowel disturbances	5 (36)
Dizziness	4 (29)
Sexual dysfunctions	3 (21)
Nystagmus	3 (21)
Hypertension	2 (14)
Incoordination	2 (14)
Fatigue	2 (14)
Fulfilments of SS criteria	
Hunter criteria	14 (100)
Sternbach's criteria	11 (78)
Serotonergic agents implicated in 14 cases	
Amitriptyline	6 (43)
Tramadol	5 (36)
Valproate	5 (36)
Paroxetine	2 (14)
Sertraline	2 (14)
Citalopram	1 (7)
Fluoxetine	1 (7)

F: Female; M: Male; SD: Standard deviation; SS: Serotonin syndrome.

Case 1

A 21-year-old male was diagnosed with a primary generalized epilepsy disorder and started taking sodium valproate (1000 mg daily) about 2 years prior. Six months ago, he developed progressively increasing tremor, irritability, bradykinesia, rigidity, and gait disturbance. When asked, the patient admitted to having irritability, disturbed sleep, and intermittent diaphoresis. Physical examinations revealed tachycardia (112 beats/min), postural tremor of both hands, rigidity in the limbs, generalized hyperreflexia, and inducible ankle clonus. Haematological and biochemical investigations (including valproate level, ceruloplasmin level, urinary copper, and

thyroid function profiles) were normal. Magnetic resonance imaging brain, electroencephalography, and cerebrospinal fluid examination revealed no abnormalities. The patient fulfilled the Hunter criteria for SS. Initially, the patient refused to discontinue valproate as he was afraid of a recurrence of seizure. Cyproheptadine was started (4 mg daily) and titrated up to 4 mg three times daily. The symptoms gradually improved, and abnormal physical examinations (tachycardia, tremor, rigidity, hyperreflexia, and clonus) returned to normal in 10-12 d. Cyproheptadine was discontinued after 3 wk. However, the symptoms gradually reappeared, which again disappeared on readministration of cyproheptadine. Later, valproate was changed to levetiracetam. There was no recurrence of the similar symptoms at 9 mo follow-up.

Case 2

A 47-year-old man had been receiving amitriptyline (25 mg daily) and tramadol (50 mg twice daily) for diabetic neuropathy for about 9 mo. About 5-6 mo ago, he developed an insidiously progressive tremor of both hands, generalized body pain associated with stiffness, and sleep disturbances. The patient also reported irritability, disturbed bowel functions, dizziness, and intermittent diaphoresis. Physical examination revealed tachycardia (104 beats/min), hand tremors, rigidity in all four limbs, hyperreflexia, and ankle clonus. Haematological and biochemical investigations were normal. Magnetic resonance imaging brain and electroencephalography revealed no abnormalities. The patient fulfilled the Hunter criteria of SS. Amitriptyline and tramadol were discontinued, and cyproheptadine was administered (4 mg thrice daily). The clinical features improved significantly over 5-6 d and disappeared in 2 wk. The symptoms did not recur in the 6-mo follow-up.

Case 3

A 36-year-old man, on paroxetine (40 mg daily) and amitriptyline (25 mg daily) for obsessive-compulsive disorder for 18 mo, developed insidiously progressive upper limbs tremor and rigidity of the lower limbs associated with gait difficulty. In parallel, he had sleep disturbances, irritability, and generalized body pain. The symptoms gradually increased in the last 4-5 mo. Physical examinations revealed tachycardia (102 beats/min), coarse postural tremor of both upper limbs, rigidity in the lower limbs, generalized hyperreflexia, and ankle and knee clonus. Biochemical parameters and neuroradiological investigations were unremarkable. The patient feared a recurrence of obsessive-compulsive disorder, so we did not attempt to discontinue paroxetine and amitriptyline. He was started on cyproheptadine (4 mg thrice daily). The patient noted an almost complete improvement in 7-8 d. Cyproheptadine was discontinued after 3 wk, but symptoms reappeared in 3-4 wk. Reintroduction of cyproheptadine provided complete cessation of the symptoms. The patient preferred to continue cyproheptadine, and paroxetine and amitriptyline as well. There was no recurrence of similar symptoms in 12 mo follow-up.

DISCUSSION

All patients met the Hunter clinical criteria of SS, and at the same time, each patient showed a positive response to cyproheptadine. Therefore, we believe that these patients had SS. There was no better alternative diagnosis for any of these 14 cases, as no biochemical or other abnormalities were found in any of the patients indicating any other pathology. The disappearance of generalized body pain, insomnia, gait problems, bowel problems, dizziness, sexual dysfunctions, incoordination, and fatigue after receiving cyproheptadine suggests that this symptom complex was the part of SS spectrum. Fever and agitation are important clinical features in both criteria of SS^[7,8]; however, none of our patients had any of these two symptoms. Patients with fever and agitation often seek immediate care in the hospital. As we included only chronic cases, fever and agitation were not the part of the symptom complex in our patients.

SS typically presents within 24 h of initiation or change in the dose of serotonergic agents, and it may evolve very rapidly, leading to death within a few hours^[1,6]. However, mild cases of SS (tremor with hyperreflexia and hypertonia) may be ignored by patients and doctors, and patients can continue to take serotonergic drugs for a longer period. Such patients may represent the chronic variant of SS. We reviewed the literature to find cases of SS having an indolent course or chronic SS. Alnwick^[3] reported a 42-year-old female patient who had been on antidepressants for a long period. She developed generalized body pain, including headaches, and received a

diagnosis of fibromyalgia. Unfortunately, she received several additional serotonergic agents over the years. A careful observation raised the possibility of SS, and the discontinuation of the offending drugs led to complete improvement. Lamberg *et al*^[4] reported a 41-year-old woman who received various serotonergic agents over the years for generalized body pain. She developed various other symptoms over the years, including aggravation of pain, hand tremors, dyskinesia, and insomnia. A detailed examination revealed the presence of clonus, hyperreflexia, and tremor, fulfilling the Hunter criteria of SS^[4]. Chechani^[9] reported a patient who had four episodes of SS over 3-4 years. In one episode, tremors persisted for 6 wk before the development of full-blown SS. Moreover, tremors and muscle pain persisted for about 2 mo, even after the withdrawal of the serotonergic agent (fluoxetine). This case highlights that tremors and myalgia may persist for a long period. Prakash *et al*^[5] reported a patient who had been on various serotonergic agents for more than 2 years after a road traffic accident. He developed various new symptoms, which were considered to be sequelae of the road traffic accident. A detailed examination suggested a possibility of SS, and discontinuation of serotonergic agents and administration of cyproheptadine led to complete resolution of the symptoms.

In the present case series, we included those patients in whom the disease started insidiously, and the duration of illness was longer (mean duration of illness-13.5 wk, range: 6-24 wk), indicating a chronic pattern. Generalized body pain, stiffness of the limbs, insomnia, dizziness, and irritability were the common presenting features. Such nonspecific symptoms are often ignored by patients, and even physicians do not take these symptoms seriously and attribute such symptoms to underlying primary disorders or associated somatic complaints or nonspecific drug-induced side effects. Several studies have reported tremors and other nonspecific symptoms as common side-effects of serotonergic agents. However, these studies are silent regarding the presence or absence of hyperreflexia and clonus. Such side effects are frequently misdiagnosed as drug-induced tremors, drug-induced parkinsonism, or extrapyramidal syndrome. Five patients in our series received sodium valproate. Sodium valproate is known to cause SS, parkinsonism, and isolated tremor. In Armon *et al*^[10] case series on valproate-induced parkinsonism, approximately 44% of patients had upper motor neuron (UMN) signs. Cognitive disturbances are also very common in valproate-induced parkinsonism. Autonomic features have also been noted in some cases of valproate-induced parkinsonism^[11]. Therefore, a subset of valproate-induced parkinsonism patients may also satisfy the Hunter criteria. In addition, most of the cases of valproate-induced parkinsonism have insidious onset and chronic course. Therefore, the possibility of chronic SS exists in a subset of patients with valproate-induced parkinsonism. Various selective serotonin reuptake inhibitors and other serotonergic agents are known to cause tremors and parkinsonism-like symptoms^[12,13]. Most of these observations did not mention anything about UMN signs. Since examination for clonus is not a regular phenomenon in clinical practice, it is possible that a subset of such patients may have hyperreflexia or inducible clonus, fulfilling the criteria of SS. So, the number of actual cases of chronic cases of SS may be much higher than the actual reported cases in the literature.

The clinical manifestations of SS depend on the degree of elevation of the intrasynaptic concentration of serotonin. The mild elevation of serotonin in the central nervous system leads to hyperreflexia, inducible clonus, tremors, anxiety, and restlessness^[2]. The most important feature in the Hunter criteria is the presence of upper motor signs (spontaneous clonus, inducible clonus, hyperreflexia, and hypertonia). Unfortunately, the Hunter criteria are silent about the UMN related symptoms or complaints. Hypertonia and other UMN signs typically induce musculoskeletal complaints, such as pain, stiffness, slowness in the movement, tiredness, and fatigue^[14]. We hypothesize that mildly elevated serotonin for a long period in the central nervous system will induce sustained UMN symptoms and signs. Persistent hypertonia or spasticity usually manifests as stiffness/rigidity, muscle pain, and functional disability. This may be a possible explanation for the presence of generalized body pain, stiffness of the limbs, gait problems, and fatigue noted in our observations and other case series. Irritability, dizziness, and insomnia may be related to mild cognitive abnormalities due to raised intrasynaptic serotonin concentration^[2].

Although SS typically develops rapidly after ingestion of serotonergic drugs, our observations suggest that a subset of patients may have mild and chronic forms. A diagnosis of SS is important even in mild and indolent form, as it is not supposed to resolve spontaneously as long as serotonergic drugs are administered. Furthermore, it may progress rapidly to death by an inadvertent increase of the dose or addition of another serotonergic agent.

Limitations

This report is a retrospective study and a possibility of unrecognized selection bias exists. We reviewed the clinical features in patients with insidious onset SS. So, these are not truly representative of typical cases of SS. Although all patients fulfilled the Hunter criteria, we cannot rule out a possibility of other causes as the full evaluation was not done on each patient.

CONCLUSION

SS is not rare in clinical practice. However, various aspects of this syndrome need to be explored. Herein, we suggest that chronic SS is not rare in clinical practice, and patients may present with non-specific clinical symptoms. We suggest that patients who are on serotonergic drugs should be physically examined for the presence of clonus and other related signs upon the development of any new symptom to rule out SS.

ARTICLE HIGHLIGHTS**Research background**

Serotonin syndrome (SS) is a life-threatening condition, and the clinical features largely depend on the degree of elevation of the intrasynaptic concentration of 5-hydroxytryptamine or serotonin. Mild elevation of serotonin levels causes mild serotonin toxicity and manifest as hyperreflexia, inducible clonus, tremors, anxiety, and restlessness. We hypothesize that mild SS may remain unnoticed for a longer duration and will manifest as insidious onset nonspecific symptoms.

Research motivation

Only very limited data are available about chronic SS. We believe that the diagnosis of chronic SS is important. Increasing the dose of a serotonergic agent or adding another serotonergic agent to a patient with chronic SS can be serious and fatal.

Research objectives

To describe the epidemiological, clinical, and other aspects of chronic SS.

Research methods

We retrospectively evaluated 14 consecutive adult patients (> 18 years) who had presenting complaints for more than 6 wk at the time of the first consultation and fulfilled the Hunter criteria of SS.

Research results

We identified 19 patients who met the inclusion criteria. Five patients were excluded for various reasons, and finally, the records of 14 cases were analysed. The mean age was 41.1 years (range: 21-61 years), with a male preponderance (64%). Generalized body pain, insomnia, and restlessness were common presenting features. The mean duration of symptoms before getting the diagnosis of SS was 13.5 ± 5.8 wk. Amitriptyline was the most common drug, followed by tramadol and sodium valproate. The response to cyproheptadine was satisfactory in all patients.

Research conclusions

Patients with chronic SS may have nonspecific symptoms. A detailed drug history and thorough physical examinations are essential to clinch the cases of chronic SS.

Research perspectives

The incidence of SS is increasing because of the widespread use of serotonergic drugs. There is a need to improve the awareness about SS among the physicians for early recognition and effective management.

REFERENCES

- 1 **Boyer EW**, Shannon M. The serotonin syndrome. *N Engl J Med* 2005; **352**: 1112-1120 [PMID: [15784664](#) DOI: [10.1056/NEJMra041867](#)]
- 2 **Buckley NA**, Dawson AH, Isbister GK. Serotonin syndrome. *BMJ* 2014; **348**: g1626 [PMID: [24554467](#) DOI: [10.1136/bmj.g1626](#)]
- 3 **Alnwick GM**. Misdiagnosis of serotonin syndrome as fibromyalgia and the role of physical therapists. *Phys Ther* 2008; **88**: 757-765 [PMID: [18420814](#) DOI: [10.2522/ptj.20060208](#)]
- 4 **Lamberg JJ**, Gordin VN. Serotonin syndrome in a patient with chronic pain polypharmacy. *Pain Med* 2014; **15**: 1429-1431 [PMID: [22925399](#) DOI: [10.1111/j.1526-4637.2012.01468.x](#)]
- 5 **Prakash S**, Rathore C. Cyproheptadine-dependent chronic serotonin syndrome. *Neurol India* 2016; **64**: 1319-1321 [PMID: [27841211](#) DOI: [10.4103/0028-3886.193796](#)]
- 6 **Prakash S**, Rathore C, Rana K, Prakash A. Fatal serotonin syndrome: a systematic review of 56 cases in the literature. *Clin Toxicol (Phila)* 2021; **59**: 89-100 [PMID: [33196298](#) DOI: [10.1080/15563650.2020.1839662](#)]
- 7 **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**: 635-642 [PMID: [12925718](#) DOI: [10.1093/qjmed/hcg109](#)]
- 8 **Sternbach H**. The serotonin syndrome. *Am J Psychiatry* 1991; **148**: 705-713 [PMID: [2035713](#) DOI: [10.1176/ajp.148.6.705](#)]
- 9 **Chechani V**. Serotonin syndrome presenting as hypotonic coma and apnea: potentially fatal complications of selective serotonin receptor inhibitor therapy. *Crit Care Med* 2002; **30**: 473-476 [PMID: [11889332](#) DOI: [10.1097/00003246-200202000-00033](#)]
- 10 **Armon C**, Shin C, Miller P, Carwile S, Brown E, Edinger JD, Paul RG. Reversible parkinsonism and cognitive impairment with chronic valproate use. *Neurology* 1996; **47**: 626-635 [PMID: [8797455](#) DOI: [10.1212/wnl.47.3.626](#)]
- 11 **Brugger F**, Bhatia KP, Besag FM. Valproate-Associated Parkinsonism: A Critical Review of the Literature. *CNS Drugs* 2016; **30**: 527-540 [PMID: [27255404](#) DOI: [10.1007/s40263-016-0341-8](#)]
- 12 **Edwards JG**, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. *Drugs* 1999; **57**: 507-533 [PMID: [10235690](#) DOI: [10.2165/00003495-199957040-00005](#)]
- 13 **Hawthorne JM**, Caley CF. Extrapyramidal Reactions Associated with Serotonergic Antidepressants. *Ann Pharmacother* 2015; **49**: 1136-1152 [PMID: [26185277](#) DOI: [10.1177/1060028015594812](#)]
- 14 **Masi AT**, Kamat S, Gajdosik R, Ahmad N, Aldag JC. Muscular hypertonicity: a suspected contributor to rheumatological manifestations observed in ambulatory practice. *Eur J Rheumatol* 2015; **2**: 66-72 [PMID: [27708929](#) DOI: [10.5152/eurjrheum.2015.0119](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

