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BRIEF COMMUNICATION

Serotonin syndrome presenting as febrile encephalopathy with CSF pleocytosis: a report of three cases

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Abstract Serotonin syndrome (SS) is an iatrogenic, drug-induced clinical syndrome caused by serotoninergic hyperstimulation. SS may have protean manifestations and can mimic a variety of medical conditions. Herein, we describe three cases of febrile encephalopathy who were on serotonergic agents. All three cases fulfilled Hunter's criteria for SS and responded to the removal of the offending agents and the administration of cyproheptadine. All three patients had abnormal cerebrospinal fluid (CSF) examinations (pleocytosis in three patients and increased protein in two patients) which returned to normal with therapy. We suggest that SS presenting as febrile encephalopathy may have transient CSF abnormalities. Severe SS is a medical emergency. Therefore, a trial of cyproheptadine can be given in patients fulfilling the SS criteria even in the presence of CSF abnormalities. In parallel, the patients should be investigated for other causes of febrile encephalopathy and CSF pleocytosis.

Keywords Serotonin syndrome · Serotonergic agent · Autonomic dysfunction · Clonus · Cyproheptadine

Introduction

Serotonin syndrome (SS) is an iatrogenic, drug-induced clinical syndrome characterised by a clinical triad of neuromuscular hyperactivity, autonomic hyperactivity, and altered mental status. However, the clinical symptoms may range from mild non-specific features to life-threatening conditions [1, 2]. Herein, we describe three cases of SS who presented as febrile encephalopathy and had abnormal CSF.

Case reports

Case 1

A 19-year-old male developed a sore throat, cough, and malaise. He received over-the-counter products that included cough syrup (containing dextromethorphan) and analgesics (containing tramadol). However, his condition deteriorated with the increasing body pain, the development of fever, nausea, and abdominal pain. Ondansetron was added for the gastrointestinal symptoms. His condition further deteriorated, and he developed behavioural abnormalities in the form of agitation, irritability, and restlessness, and later, he became drowsy and less communicative.

Hematologic parameters were normal except mild leucocytosis (WBC count 13,600 mm^3). Biochemical parameters were normal. Serological testing for HIV, hepatitis B virus (HBV), salmonella typhi, malarial parasite, and mycobacterium tuberculosis was negative. A magnetic resonance imaging (MRI) brain and EEG were unremarkable. CSF examinations revealed: 30 cells/μL, protein 58 mg/dL, glucose 68 mg/dL, and CSF/serum glucose ratio of 0.62.

Empirical injectable acyclovir was started. However, the patient did not respond to the treatments, and meanwhile, the CSF HSV (herpes simplex virus) antibody test came negative.

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At this point, the patient was referred to neurology department. Glasgow Coma Score (GSC) was nine. General examinations revealed diaphoresis, tachycardia, hypertension (166/104 mmHg), and fever (101.4 °F). Neurological examinations revealed mydriasis, generalised hypertonia, hyperreflexia, clonus (ankle and knee), and an extensor plantar response.

The patient fulfilled Hunter's criteria [3] for SS. Ondansetron was discontinued. Cyproheptadine was started with an initial oral dose of 12 mg, followed by 2 mg every 2 h up to 24 h. Within 12 h, the patient became communicative. Fever and clonus disappeared within 24 h. Other physical abnormalities also disappeared in 48–72 h. The patient became normal within 72 h. Cyproheptadine was continued for another 10 days. A repeat CSF was done on the 7th day of cyproheptadine administration, and it showed improvement in the parameters (cells 10 cells/μL and protein 48 mg/dL).

Case 2

A 32-year-old man had been receiving fluoxetine (40 mg/daily) for 8 weeks for depression. Tramadol/acetaminophen combination was added a few days back for the low back pain. Two days later, he developed fever, myalgia, and irritability. Later, he became confused and drowsy. He was referred to the medical emergency. Physical examination was remarkable for tachycardia, hypertension (160/100 mmHg), and fever (101.8 °F). The patient was drowsy and confused (GSC-13). Neurological examinations demonstrated meningeal signs (rigid neck), stiff lower limbs, and hyperreflexia.

Haematological and biochemical investigations were normal. MRI brain revealed no abnormality. Serological testing for HIV, mycobacterium tuberculous, malarial parasite, and enteric fever was negative. CSF examinations: 16 cells/μL, protein 60 mg/dL, CSF glucose 78 mg/dL, and CSF/serum glucose ratio of 0.69. Injectable acyclovir was started and maintained over 5 days until CSF HSV antibody was reported negative. However, his condition did not improve. At this point of time, neurological consultation was sought. We noted intermittent tremors, profuse sweating, generalized stiffness, hyperreflexia, and ankle clonus.

The patient fulfilled the Hunter's criteria for SS. Cyproheptadine was started in a similar regimen as the previous case. Within 24 h, the patient became alert and fever subsided. Clonus, rigidity, and diaphoresis also disappeared in the next 24 h. Cyproheptadine was continued for another 7 days in the dose of 8 mg three times daily. A repeat CSF examination after 5 days was normal.

Case 3

A 36-year-old man had been receiving sodium valproate for the last 2 months for migraine. A week ago, amitriptyline was added when his migraine attacks became more frequent. He was brought to the emergency department by his relative for high-grade fever and increasing confusion and agitation for 12 h.

On the admission, he was agitated and was disoriented to time, place, and person. Physical examination revealed tachycardia, hypertension (148/94 mmHg), and fever (102.8 °F).

Hematologic parameters were normal except mild leucocytosis (WBC count 12,800 mm^3). Biochemical parameters (including serum ammonia) were normal. MRI brain revealed no abnormality. CSF examinations revealed pleocytosis (16 cells/μL). EEG showed diffuse slow waves. Serological testing for HSV, HIV, HBV, mycobacterium tuberculosis, and malaria parasite was negative.

Initially, he was managed with intravenous fluids, antibiotics, and ondansetron. However, his condition worsened, and he became stuporous. In parallel, the patient developed some new physical findings, such as diaphoresis, shaking of lower limbs, rigidity of all limbs, hyperreflexia, and ankle clonus. A possibility of SS was suspected. Ondansetron was discontinued, and cyproheptadine was started in a similar regimen as the previous cases.

There was a marked improvement in the consciousness level in 24 h. Diaphoresis, stiffness, hyperreflexia, and clonus disappeared within 72 h. He became absolutely normal in 4 days after starting cyproheptadine. A repeat CSF examination (on the 5th day of the first CSF examinations) revealed no abnormality.

Discussion

A diagnosis of SS is usually made according to the Hunter Serotonin Toxicity Criteria. The Hunter criteria for SS require the presence of one of the following features or groups of features in the presence of the administration of a known serotonergic agent: (a) spontaneous clonus; (b) inducible clonus/ocular clonus with agitation or diaphoresis or rigidity with a temperature above 100.4 °F; and (c) tremor and hyperreflexia [1, 3]. There are only five symptoms that are included in Hunter criteria for SS (agitation or diaphoresis or rigidity with a temperature above 100.4 °F or tremor). However, the clinical triad of neuromuscular-hyperactivity, autonomic-hyperactivity, and altered mental status encompasses a large number of symptoms. Clonus and hyperreflexia are considered as the most important features [1, 3].

Table 1 Summary of all three patients (clinical characteristics and CSF abnormality)

	Case 1	Case 2	Case 3
Age (years)	19	32	36
Sex	M	M	M
Clinical features			
Cognitive dysfunction	Agitation, restlessness, drowsiness	Irritability, confusion, drowsiness	Agitated, disoriented
Neuromuscular abnormality	Clonus, hypertonia, hyperreflexia	Myalgia, stiffness, tremor, hyperreflexia, clonus	Tremors, rigidity, hyperreflexia, clonus
Autonomic dysfunction	Fever, tachycardia, hypertension, diaphoresis, mydriasis	Fever, tachycardia, diaphoresis	Fever, tachycardia, hypertension, diaphoresis
Serotonergic drugs causing serotonin syndrome	Dextromethorphan, tramadol, ondansetron	Fluoxetine, tramadol	Sodium valproate, amitriptyline, ondansetron
Cerebrospinal fluid examination			
Cells (cells/μL)	30	16	16
Protein (mg/dL)	58	60	41
Glucose (mg/dL)	68	78	82

All three patients fulfilled the Hunter's criteria for SS (Table 1). Immediate and sustained responses to cyproheptadine further reinforce the diagnosis of SS. Fever and altered mental status are well-recognised symptoms of SS [1, 4]. However, to the best of our literature search, there is no case mentioning CSF abnormality in such patients.

The diagnostic and therapeutic approach to a patient with febrile encephalopathy depends on the various factors [5]. The common causes of febrile encephalopathy prevalent in this region (HSV, HIV, HBV, cerebral malaria, tuberculosis, and *Salmonella typhi*) [5] were ruled out by the investigations in all cases. CSF abnormalities (pleocytosis in three patients and increased protein in two patients) are not reported in the literature in patients with SS. A possibility of some inflammatory process of the meninges or brain parenchyma was very high. Therefore, we repeated CSF in all three patients. CSF abnormalities returned to normal in two patients after 5–7 days, and there was a trend of returning to normal in another patient. A number of speculations can be done for such CSF abnormalities in these patients. All patients had normal neuroimaging. The common infective causes for such CSF abnormalities prevalent in this region were ruled out by investigations. Therefore, we speculate that CSF abnormalities in our patients could be the part of SS spectrum.

A diagnosis of SS is usually made in patients who had received serotonergic drugs in the past 5 weeks. However, a patient in febrile encephalopathy could not be in a position to give the history of serotonergic drug ingestion. As severe SS is a medical emergency, a trial of cyproheptadine should be initiated immediately. In parallel, the patients could be investigated for other causes. Most cases of SS show a marked response within 24 h.

Although clinical profiles and therapeutic responses to cyproheptadine are in favour of SS, there are many limitations. A complete evaluation for febrile encephalopathy was not done. A few febrile encephalopathies may resolve even with supportive therapies. We did not consider further investigations for CSF pleocytosis for two reasons: (1) response to cyproheptadine was immediate and (2) repeat CSF examinations (after 5–7 days) showed normal (two patients) or near normal (one patient) findings.

Pathophysiology

Serotonin syndrome results from an increase in the intrasynaptic concentration of serotonin (5-HT), especially in the brainstem and spinal cord. Various observations in experimental animals have demonstrated that stimulation of 5-HT2A receptors by specific agonists may cause hyperthermia [6] and the 5-HT2A receptor is the main receptor implicated in SS [1].

To the best of our literature search, CSF abnormalities have not been reported previously. Serotonin receptors are found throughout on cerebral meningeal circulation [7]. We speculate that stimulation of these meningeal serotonin receptors could be a reason for the CSF abnormality.

Conclusion

Serotonin syndrome presenting as febrile encephalopathy may have transient CSF abnormalities. Therefore, a trial of cyproheptadine is warranted if patients fulfil the criteria of SS even in the presence of CSF abnormalities.

Compliance with ethical standards

Conflict of interest None.

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