CASE REPORT

Serotonin Syndrome: a Case Report From India

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Abstract

Objective: To report a case of serotonin syndrome, with episodic worsening course, which responded to treatment with cyproheptadine. Case Report: A 56 year old male, was diagnosed as a case of bipolar affective disorder, hypertension and generalized seizure disorder. While receiving a combination of lithium carbonate 750 mg/d, amlodipine 10 mg/d, phenytoin 300mg/d, sertraline 100 mg/d, trazodone 100mg/d, and escitalopram 10mg/d for 1 week presented with abrupt onset symptoms of 4 days duration, episodic in nature, characterized by confusion, perseveration, shivering, coarse tremors of extremities, perioral and tongue tremors; marked diaphoresis, rigidity, dysarthria, ataxia, occurring once in a day, during the evening hours lasting for few hours. On examination patient was found to have tachycardia (120/min), tachypnea (24/min), malignant hypertension (230/130 mmHg), marked diaphoresis, generalized tremors, cold extremities, marked rigidity in all four limbs, hyperreflexia, bilateral patellar clonus and dysarthria. He was treated with supportive therapy in the form of monitoring of vitals and fluid balance along with cyproheptadine. Conclusion: In most cases of serotonin syndrome the initial symptoms are of mild intensity and are missed. The initial symptoms can run an episodic course and high index of suspicion is required for accurate diagnosis as prompt discontinuation of the causative agents can have profound impact on the clinical course and outcome of this particular toxic syndrome (German J Psychiatry 2007; 10: 100-102).

Keywords: serotonin syndrome, selective serotonin reuptake inhibitors

Introduction

Over the years there is increase in the rate of prescription of selective serotonin reuptake inhibitors (SSRIs), but the alarming thing is the fact that there is also increase in the prescription rate of combination of medication - SSRI and another psychotropics or a SSRI with other medications (DeBattista et al, 1998). Due to use of multiple medications, many a time patients develop many life threatening complications, either because of pharmacokinetic or pharmacodynamic interactions. Serotonin syndrome (SS) is one of such potentially life threatening complication which usually results from use of more than one proserotonergic agent (Boyer & Shannon, 2005). Many case reports and case series have reported this complication from various parts of the world and many drugs have been implicated (Gillman, 2006). Drugs like cyproheptadine, chlorpromazine, dantrolene, benzodiazepines, methysergide, propranolol etc. have been found to be useful in reversing SS (Boyer & Shannon, 2005).

In many reports it has been mentioned that many a times the patients presenting with mild to moderate SS are missed because of lack of suspicion (Boyer & Shannon, 2005). However, in our literature search we could not find any report suggesting that SS can run an episodic course, with
Case Report

Mr. S, 56 years old, belonging to middle socioeconomic status, urban background, was diagnosed as a case of bipolar affective disorder (duration – 28 years), essential hypertension (duration – 3 years) and generalized seizure disorder (duration – 6 months) and was on combination of lithium carbonate 750 mg/d, amlodipine 10 mg/d, phenytoin 300mg/d for last 6 months. About 5 weeks prior to the presentation, he developed moderate depression without somatic symptoms (as per ICD-10) for which he was started on sertraline 100 mg/d and trazodone 100mg/d in addition to the above medications. Even after continuing on the above combination for about 3 weeks, patient did not perceive any significant improvement. Due to lack of improvement he consulted another psychiatrist, who started escitalopram 10mg/d along with the above regimen. After taking the combination of the above medications for 1 week he presented to the emergency department of our hospital with abrupt onset symptoms of 4 days duration, episodic in nature, characterized by confusion, disorientation to time and place, perseveration, shivering, coarse tremors of extremities, perioral and tongue tremors; marked diaphoresis, rigidity, dysarthria, ataxia lasting for 1-2 hrs initially, occurring once in a day, during the evening hours with spontaneous improvement for the first two days. On the 3rd day the episode was much more severe and lasted for 3 to 4 hours, he was brought to the emergency department and was managed with benzodiazepines, with the possibilities of panic attack and recurrence of seizure. On the day of presentation, the episode started in the late afternoon and much more intense. On examination patient was found to have tachycardia (120/min), tachypnea (24/min), malignant hypertension (230/130 mmHg), marked diaphoresis, generalized tremors, cold extremities, marked rigidity in all four limbs (Lower limbs >Upper limbs), hyperreflexia, bilateral patellar clonus and dysarthria. There was no history of fever, headache, vomiting, head injury, substance abuse, any other drug intake, loss of consciousness, diarrhea, generalized seizures and poor compliance with the medication during or prior to development of episodes. Diagnostic possibilities of serotonin syndrome and neuroleptic malignant syndrome (NMS) were considered, all his medications were stopped and he was investigated. His hemogram, renal function tests, liver function tests, electrocardiogram, arterial blood gas analysis, random blood glucose levels, noncontrast computerized tomography of brain did not reveal any abnormality. His serum creatinine phosphokinase (CPK) level was 836 IU/L. He was immediately started on supportive management. Because of high index of suspicion, lack of history of receiving any antipsychotics or antiemetics and characteristic constellation of signs and symptoms diagnosis of serotonin syndrome was given precedence over NMS and he was given cyproheptadine 4 mg stat, metoprolol 50mg through nasogastric tube along with continuous infusion of nitroglycerin. After 2 hours of administration of cyproheptadine, patient showed significant improvement in all the symptoms which was maintained for next 8 hours, after which he had recurrence of the symptoms of milder intensity which again responded to cyproheptadine 4 mg stat. Following which he was started on cyproheptadine 2 mg thrice daily along with the lorazepam 2 mg thrice daily, phenytoin 300 mg/day, amlodipine 10 mg/d, atenolol 50 mg/day. He was continued on the above regimen for next 4 days without any recurrence in his symptoms. After this he was found to be hypomanic, for which he was started on divalproex sodium, which was gradually built up to 1000mg/d along with antihypertensives and phenytoin was stopped. His hypomanic symptoms responded to the above regimen.

Discussion

Despite an increase in awareness about SS in recent years, it is under-diagnosed, both in routine clinical and emergency setting. SS should be suspected in a subject who has recently taken a drug that can disrupt serotonin balance and has sudden onset of autonomic, cognitive, and neuromuscular symptoms in the absence of metabolic and infectious causes for the clinical constellation. The mental status changes include anxiety, agitation, confusion, restlessness, hypomania, and frank disorientation. Thought processes may seem purposeful at times, or confused and agitated at other times. The neuromuscular findings include tremor, clonus, hyperreflexia, diaphoresis, and shivering. A peculiar clinical finding is that the lower extremities tend to be more affected than the upper extremities, displaying strikingly increased tone and deep tendon reflexes. The autonomic symptoms may comprise of hyperthermia, tachycardia, hypertension, and mydriasis (Boyer & Shannon, 2005). Our case displayed most of these signs and symptoms at presentation. The case was missed at the initial presentation to emergency a day prior to the diagnosis. This highlights the fact that a proper history of medication intake (both prescribed and unprescribed) and high index of suspicion is required for accurate diagnosis as prompt discontinuation of the causative agents can have profound impact on the clinical course and outcome of this particular toxic syndrome.

Besides the infectious and metabolic causes, one of the most important differential diagnoses is neuroleptic malignant syndrome (NMS). It is usually distinguished on the basis of history of intake of a neuroleptic or antiemetics agent (metoclopramide) and presence of characteristic “lead pipe rigidity”. Raised creatinine phospho-kinase enzyme levels may not be a very good index of distinguishing the 2 syndromes as in some cases of SS, life-threatening hyperthermia and rhabdomyolysis may develop if muscular hyperactivity is not quickly controlled in time (Boyer & Shannon, 2005), as seen in our case.

Although it has been reported in the past that, many a times SS is missed in the initial stages because of mild symptoms,
none of the previous reports in literature mentions that these mild symptoms run an episodic course.

In most reports SS has been reported in cases receiving more than one serotonergic agent, same was true in our case too. It has been suggested that the clinical symptoms of serotonin syndrome are a result of overstimulation of central and peripheral serotonin receptors, specifically 5-HT1A and 5-HT2. In our case the subject was on 4 medications acting on this system. Lithium has been reported to enhance serotonergic activity either through increased biosynthesis of serotonin or by receptor adaptation (Lenox et al, 1995). Trazodone itself is a 5-HT2A antagonist but its predominant metabolite is a 5-HT2A agonists. Both sertraline and escitalopram are reuptake inhibitors. All contributing to the overstimulation of 5-HT1A and 5-HT2 receptors. However, another interesting finding in our case was that the index case didn’t have any symptoms of SS while on lithium, sertraline and trazodone, and his symptoms started after addition of escitalopram, which provides credence to the notion that SS may be a syndrome with “dose-effect” relationship (Gillman, 1998).

Other important factors which could have led to SS in the index case are drug interactions with polypharmacy. Although the use of combination of sertraline and phenytoin is reported to cause decrease in sertraline levels, other combinations in the index case can be responsible for increase in serotonergic activity and neurotoxicity. Use of lithium along with SSRIs has been reported to increase the serotonin effects. Similarly use of sertraline along with trazodone causes increase in the trazodone levels due to release of trazodone from plasma protein binding sites and ultimately leads to increased seratonergic activity at the receptor level. Combination of lithium and phenytoin has been reported to cause increased neurotoxicity (Psychopharmacology drug interaction calculator, German Journal of Psychiatry).

Many case reports have reported successful treatment of SS with cyproheptadine (Boyer & Shannon, 2005), and with adequate doses, it has been reported that cyproheptadine can reverse the whole clinical picture in 1 to 2 hours, as seen in our case.

Our case highlights the fact that serotonin syndrome can have an episodic course with initial episodes of milder intensity. It follows a “dose-effect” relationship. In the era of increasing consumerism and doctor shopping, clinicians should take a proper history of medication intake by the subjects before prescribing newer agents. At the same time clinicians using multiple medications should be aware of this entity and should avoid combining medications having pharmacodynamic and pharmacokinetic interactions.

**References**