The Serotonin Syndrome: Initial Misdiagnosis

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ABSTRACT: **Background:** The selective serotonin reuptake inhibitors are major drugs used in psychiatry today. While serotonin syndrome has become more frequent in an overdose situation and when an interacting drug is given, the toxicity of SSIRs is less than that of most other psychiatric drugs. Although the characteristics of toxicity are defined, it seems that physicians are not aware of the phenomenon.

Objectives: To investigate patients with serotonin syndrome who were initially misdiagnosed.

Methods: We conducted a retrospective chart review of seven patients admitted in the last 2 years with mild to severe serotonin syndrome who were initially diagnosed as having other diseases.

Results: Most patients (5/7) were initially diagnosed with exacerbation of their psychiatric disorder. Gastroenteritis was diagnosed in two patients. One patient was suspected of having a metastatic lesion in the brain, and severe drug overdose was diagnosed in one patient. They all recovered after withholding the culprit drugs.

Conclusions: This report is an addition to the growing literature on misdiagnosis of psychiatric patients. Serotonin toxicity should be considered in patients in whom the combination of mental changes, neuromuscular abnormalities and autonomic hyperactivity are features of acute disease.

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The serotonin syndrome is a triad of altered mental status, autonomic instability and neuromuscular hyperactivity [1]. Mental status changes range from confusion, agitation, anxiety, delirium and hallucinations to drowsiness and coma. The neuromuscular features are myoclonus, hyperreflexia, muscle rigidity, tremor and even severe shivering. Autonomic instability usually includes hyperthermia, diaphoresis, sinus tachycardia, hypertension or hypotension, flushing of the skin, and diarrhea. Life-threatening acute complications include coma, seizures, rhabdomyolysis and disseminated intravascular coagulation. The incidence of the syndrome is increasing due to the common use of selective serotonin reuptake inhibitors. Since physicians are largely unaware of serotonin syndrome, it is quite difficult to evaluate its real incidence. It has been estimated that the syndrome occurs in 14% of persons who overdose on SSRI drugs [2].

It is not surprising that many patients with the clinical syndrome are initially diagnosed erroneously. There is an ongoing debate on the specific criteria for diagnosis of the syndrome. The Sternbach criteria comprise 10 clinical features that are non-specific [3], and attempts have been made to produce more specific criteria. The Hunter serotonin toxicity criteria can be used to determine whether a patient taking an overdose has significant serotonin toxicity [4]. The appearance of clonus, hyperreflexia and muscular hypertonicity distinguishes serotonin toxicity from other syndromes in the differential diagnosis. These syndromes comprise mainly neuroleptic malignant syndrome, anticholinergic delirium, and malignant hyperthermia. No laboratory test for diagnosis exists, and only the combination of signs on physical examination and the patient's drug history can lead to diagnosis. Since physicians in the emergency room may be less vigilant due to stress and pressure, a syndrome whose diagnostic procedure is a thorough drug history together with a meticulous physical examination could be missed.

In the last 2 years we have treated seven patients with overt serotonin syndrome who initially were evaluated and treated for other diagnoses.

PATIENTS AND METHODS

We retrospectively examined the charts of seven patients who were admitted to our internal medicine ward and were eventually diagnosed with serotonin syndrome. The characteristics of the patients and the criteria for diagnosis of serotonin syndrome were evaluated.

The initial diagnosis made in the emergency room, in the wards in which the patients were hospitalized, and by the first resident who admitted the patients from the ER was confirmed. Once patients were diagnosed as having the serotonin syndrome the culprit drugs were withheld.

SSIR = selective serotonin reuptake inhibitors

ER = Emergency Room

Table 1. Signs on physical examination, interacting drugs and initial diagnosis of the patients

Patient no.	Age (yrs)	Consciousness	Temperature	Diaphoresis	Diarrhea	Blood pressure	Tachycardia
1	50	Somnolent	Hyperthermia	+	+	Hypotension	+
2	40	Coma	39.5°C	+	+	Hypotension	+
3	42	Awake	Normal	+	Slight	Normal	+
4	64	Awake	Normal	+	–	Normal	+
5	19	Awake	37.5°C	–	–	Hypotensive	+
6	74	Awake	38°C	+	+	Normal	+
7	20	Somnolent	Normal	+	+	Hypotensive	+

RESULTS

The characteristics of the patients and their initial diagnosis are shown in Table 1. All the patients were women and their ages ranged from 19 to 74. They were taking serotoninergic drugs for anxiety or depression. They all met the Hunter criteria. The diagnosis was based on the following features: spontaneous clonus in one patient, inducible clonus and diaphoresis in six patients, tremor and hyperreflexia in one, and ocular clonus and diaphoresis in two. All patients also had other manifestations of the serotonin syndrome, which are shown in Table 1.

PATIENT 1

A 50 year old woman attempted suicide by jumping from the fourth floor of a building. She was known to suffer from severe depression and multiple drugs had been prescribed. Three weeks before the suicide attempt she stopped all medications. She was admitted with polytrauma due to the fall. She had to undergo splenectomy, bilateral chest tube insertion for a flail chest, and multiple orthopedic operations. During her stay in the intensive care unit she was unconscious and was mechanically ventilated. When she regained consciousness she required opiates. On referral to the surgical department intravenous morphine was changed to a fentanyl patch. The psychiatrist instituted citalopram for major depression. After 2 days of concomitant treatment she exhibited severe tremor, myoclonic jerks, hypotension, hyperthermia of 40°C, tachycardia, mydriasis, eye clonus, and hyperreflexia with prominent clonus. She also had diaphoresis and diarrhea. The nurses suspected that she suffered convulsions and the neurologist prescribed intravenous dilantin, and when no benefit was evident phenobarbital was instituted. The psychiatrist increased the dose of citalopram since he believed her to be in severe anxiety. The patient was transferred to the medicine ward where the SSRI and opiates were stopped, with prompt resolution of the syndrome.

PATIENT 2

A 40 year old woman who was severely depressed was treated with multiple drugs and even electroconvulsive therapy. Two months prior to admission she was given Nardil® (phenelzin) and was warned against taking an SSRI. Her condition seemed to be improving until she was found convulsing and needed intubation. On admission she was unconscious, diaphoretic, hypotensive, with high fever (39.5°C), tachycardic, with rigidity specifically in the lower limbs but the upper limbs were also involved, and hyperreflexia with clonus. She also exhibited mydriasis with "ping pong eyes" (eye clonus). She was admitted to the ICU with the presumptive diagnosis of drug overdose. Laboratory results were remarkable for high creatine phosphokinase concentration of 1500 U/L. Urine toxicological screen was negative. Her family (and later on the patient) denied using an SSRI and denied phenelzin overdose, but we decided to measure urinary and gastric secretions for SSRI (fluoxetine), which was positive. She regained consciousness and was discharged after a week. A month later she admitted to taking fluoxetine.

PATIENT 3

A 42 year old woman was admitted because of vomiting, two episodes of soft stools, and headaches. She was known to be in remission after treatment for breast cancer. She had been on tamoxifen for the last 2 years without any sign of recurrence. Venlafexine treatment reduced her anxiety. A day before admission she started vomiting and took metoclopramide. In the ER the physician found her vomiting and anxious, and a brain computed tomography scan showed a frontal lesion. She was treated with intravenous fluids and IV metoclopramide and was admitted with the presumptive diagnosis of metastatic disease and severe anxiety. Her physical examination showed severe tremor, bilateral myoclonic jerks, hyperreflexia, clonus, and intermittent diaphoresis. Serotonin syndrome was diagnosed, and venlafexine and metoclopramide were discontinued. Her condition improved within 24 hours. The brain CT lesion was a cavernoma, which showed no changes from a CT scan 4 years previously.

PATIENT 4

A 64 year old woman with metastatic breast carcinoma to bone was admitted for anxiety and general deterioration. She

ICU = intensive care unit

Mydriasis	Hyperreflexia/Clonus	Rigidity /Tremor	CPK N<140 U/L	Interacting drug	Initial diagnosis
+	+/+	+/+	–	Fentanyl	Epilepsy and severe anxiety
+	+/+	+/+	1500	Phenelzine	Drug overdose
–	+/+	-/+	–	Metoclopramide	Metastatic breast cancer and anxiety
–	+/+	+/-	–	Fentanyl	Anxiety and general deterioration
–	+/+	+/+	420	Metoclopramide	Gastroenteritis
–	+/+	+/+	–	No interacting drug.(clomipramine)	Urinary tract infection, gastroenteritis and anxiety
+	+/+	Slight/+	–	No interacting drug (paroxetine)	Anxiety state

suffered from severe pain and was treated with a fentanyl patch. Two days prior to admission she started taking paroxetine. On admission she was sweating; the size of her pupils was normal (even though fentanyl dose was increased). Spasticity of both legs and hyperreflexia with clonus were noted. There was no sign of any sensory or motor deficit and a CT scan and magnetic resonance imaging of the spine ruled out compression. Paroxetine was stopped (we could not stop fentanyl treatment due to the severe pain) and the clinical picture improved after 2 days.

PATIENT 5

A 19 year old girl was admitted to the ER because of excessive vomiting. She had been taking fluoxetine due to anxiety for 5 months. A day prior to her admission she experienced abdominal pain and vomiting with diarrhea and she started taking metoclopramide. In the ER she was found to have a marked tremor and seemed very anxious. Acute gastroenteritis was suspected and she was admitted to the internal medicine ward. On admission she looked dehydrated and had a low grade fever of 37.5°C. Severe tremor, myoclonic jerks with prominent hyperreflexia and clonus were noted. CPK measured 420 U/L. Metoclopramide and fluoxetine were discontinued and her situation improved within 24 hours.

PATIENT 6

A 74 year old depressed woman was admitted to the internal medicine ward due to diarrhea, low grade fever and severe sweating. One month prior to admission she started taking venlafexine. Two weeks before admission the drug was stopped for an unknown reason and clomipramine (75 mg) was started. Soon after, she began to complain of watery diarrhea, hot flushes, diaphoresis and increase in tremor. She was admitted for suspected gastroenteritis and possible sepsis. On physical examination she appeared anxious and dehydrated. Temperature was 38°C; and bilateral tremor, hyperreflexia in the lower limbs, clonus, and mydriasis were observed. She had bouts of diaphoresis and diarrhea. After being evaluated for a gastrointestinal disorder that included stool and blood cultures (they were negative), an abdominal CT was performed, which was normal. Serotonin syndrome was diagnosed and the clomipramine was stopped. Her condition began to improve within 36 hours.

PATIENT 7

A 20 year old female started treatment with paroxetine (20 mg) due to severe panic attacks. Since starting the drug she had intermittent bouts of diarrhea, sweating, weakness, and mild somnolence. These complaints were attributed to the psychiatric disease. Doses of paroxetine were increased without any clear response. The patient observed an increase in the size of her pupils but did not mention it to her physician or psychiatrist. Her treatment continued without any change for 2 years. Since she had attention deficit disorder, Ritalin® was started and on days of the combined treatment, symptoms seemed to subside and the mild somnolence disappeared. Ten days prior to her admission she stopped treatment with Ritalin and after one day the symptoms were aggravated, especially the somnolence. Diarrhea persisted, as did the diaphoresis. She lost 3 kg in weight. She was referred due to exacerbation of the psychiatric disease. On admission she was somnolent with sunset eyes. Her blood pressure was 90/70 and pulse 125/minute. She had mydriasis, slight muscle rigidity especially in the lower limbs, hyperreflexia, clonus and myoclonus. Paroxetine was stopped and in 2 days all symptoms disappeared.

DISCUSSION

Serotonin syndrome usually manifests as a triad of neuromuscular abnormalities, autonomic hyperactivity, and mental status changes [1]. This syndrome can be mild, moderate, or even severe, necessitating admission to the ICU.

The diagnosis of the syndrome is based on Sternbach's criteria [3], but other modified criteria are also used since they are more specific, especially for mild cases. We use the simplified Hunter criteria [4]. Although the criteria are defined, the syndrome seems to be under-diagnosed.

CPK = creatine phosphokinase

Most patients with serotonin syndrome have a mild and at times indistinguishable syndrome. Their symptoms are often attributed to the underlying disease [5]. It seems from the group of patients presented here that physicians are unaware of the triad of symptoms and hence fail to diagnose the syndrome.

In our group of patients the drug interactions causing the syndrome were: SSRIs interacting with opiates, metoclopramide, and phenelzin. There was one case with monotherapy of clomipramine, which acts as a SSRI, and one case of long-term treatment with paroxetine where most symptoms were masked by methylphenindate, but once this medication was stopped the syndrome became overt [6]. These interactions are not common but they are predictable.

Phenelzin and SSRI combination is actually contraindicated [7]. The patient knowingly used this combination, and only because we tested urine and gastric secretions was the culprit drug (fluoxetine), which had caused the severe and almost fatal syndrome, detected.

The combination of SSRIs and fentanyl has been shown to cause this syndrome. Fentanyl is an agonist to the 5HT1A receptor, increasing serotonin flux. It has also been shown that fentanyl decreases serotonin reuptake [8-10]. Metoclopramide has been reported to interact with SSRIs and induce the syndrome [11].

There are a few case reports in the literature on serotonin syndrome as a result of clomipramine [12,13]. Common side effects after SSRI initiation are gastrointestinal symptoms like nausea, epigastric pain and diarrhea. These symptoms are usually transient and respond to lowering the dose or taking the drug with meals. These symptoms should not be mistaken for the serotonin syndrome.

Although the cases presented here depict classical manifestations of serotonin syndrome the diagnosis was missed. Why do doctors misdiagnose this entity? Patients who have mild manifestations are usually missed as they themselves attribute their symptoms to the anxiety state for which the drug was given. Some patients identify the drug as causing the syndrome and stop taking it. When a patient is admitted with the severe syndrome, which is a combination of hemodynamic and neurological deficits, an investigation for acute and life-endangering diseases is performed. Until these diseases are ruled out the syndrome is rarely in the differential diagnosis.

Alteration of mental status secondary to medical illness may occasionally be incorrectly attributed to a psychiatric problem. Reevs et al. [14] described 64 patients with unrecognized medical emergencies inappropriately admitted to psychiatric units from emergency departments, and the causes for misdiagnoses were evaluated. The diagnoses most often missed included severe intoxication with alcohol or other illicit substances (34.4%). Common causes of misdiagnosis included inadequate physical examination (43.8%) and failure to obtain available history (34.4%). In another study [15] demonstrating deficiency in evaluating psychiatric patients in the emergency department, the authors concluded that process deficiencies in the medical history and physical examination accounted for the vast majority of missed acute medical conditions. The seven patients presented here are no different. What is common to most of our patients is the lack of an appropriate physical examination and a thorough drug history.

We conclude that although it is crucial to rule out other illnesses, it is of utmost importance to be able to diagnose the syndrome of serotonin toxicity and withhold the culprit drugs promptly. Educational programs should be initiated to enhance awareness of serotonin toxicity.

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