Serotonin syndrome presenting as pulmonary edema

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ABSTRACT

Serotonin syndrome (SS) is a potentially life-threatening condition resulting from excessive central and peripheral serotonergic activity. Clinically, it is a triad of mental-status changes, neuromuscular abnormalities, and autonomic disturbances. It can be caused by intentional self-poisoning, overdose, or inadvertent drug interactions. We report the case of a 58-year-old male with type 2 diabetes mellitus and obsessive compulsive disorder who developed pulmonary edema as a possible complication of SS. SS was caused by a combination of three specific serotonin re-uptake inhibitors (fluoxetine, fluvoxamine, and sertraline), linezolid, and fentanyl. The hospital course was further complicated by difficult weaning from the ventilator. SS was identified and successfully treated with cyproheptadine and lorazepam. The case highlights the importance of effective consultation-liaison and prompt recognition of SS as the presentation may be complex in the presence of co-morbid medical illness.

KEY WORDS: Fentanyl, linezolid, serotonergic drugs, serotonin syndrome

Introduction

Serotonin syndrome (SS) is a potentially life-threatening adverse drug reaction resulting from therapeutic drug use, intentional self-poisoning, or inadvertent interactions between drugs leading to excessive serotonergic activity in the central nervous system and the peripheral serotonergic receptors. It is a clinical triad of mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities. There are definite criteria for the diagnosis of SS based on clinical signs and symptoms that help in prompt recognition and treatment. We present here a case of SS that presented with pulmonary edema (PE) in a patient suffering from type 2 diabetes mellitus (DM-2) and obsessive compulsive disorder (OCD).

Case Report

A 58-year-old male had a 30-year history of both DM-2 (on oral hypoglycemic drugs) and OCD. He had been on 60 mg fluoxetine for OCD since 10 years. Sertraline 100 mg was added 6 weeks back and fluvoxamine, 100 mg, 4 weeks back, for recent exacerbation of OCD. On presentation, he had headache, dizziness, anorexia, diarrhea, and vomiting. He was diagnosed with diabetic autonomic dysfunction and gastropathy and prescribed domperidone and fludrocortisone. A week later, he developed mild dyspnea. Physical examination revealed tachycardia (112 beat/min) and high blood pressure (BP) of 166/90 mmHg. Chest X-ray showed pulmonary congestion. Electrocardiogram, complete blood count, serum electrolytes, and liver function tests were normal. Serum creatinine was 1.6 mg/dl. A renal Doppler study ruled out renal artery stenosis. The two-dimensional echocardiogram showed an ejection fraction of 50% with concentric left ventricular hypertrophy and mild diastolic dysfunction. He was prescribed torsemide and clonidine; without much improvement. The following day, he was hospitalized with PE and hypertensive crisis (BP 210/110 mmHg), requiring bilevel positive pressure ventilation, nitroglycerin infusion, and intravenous furosemide. He also developed altered mental-status and had to be intubated and mechanically ventilated. Sedation and analgesia were maintained with an infusion containing fentanyl and midazolam. He was also put on antibiotics (including linezolid 600 mg...
intravenously every 12 h) to prevent secondary infection. His psychiatric medications were withheld. His BP stabilized to 130/80 mmHg. PE gradually showed signs of improvement, and it was decided to taper the fentanyl-midazolam drip and extubate the patient. However, on tapering, he developed agitation, involuntary jerky movement of the body (especially lower limbs), diaphoresis, and BP of 230/120 mmHg. This made it difficult to get the patient off the ventilator. A work up for secondary hypertension ruled out pheochromocytoma. Coronary angiography revealed double vessel disease necessitating only medical management. A computed tomography scan of the thorax showed bilateral pulmonary venous congestion with bilateral pleural effusion.

A neurology opinion was sought for agitation and involuntary movements. Involuntary movement of the limbs was considered as spontaneous clonus, as these movements got aggravated while eliciting ankle and knee clonus. The presence of hyperreflexia, rigidity, and diaphoresis were also confirmed. The patient fulfilled the Hunter’s criteria for SS. Linezolid and fentanyl were stopped. His psychiatric medications were already withheld. Cyproheptadine, known to have antiserotonergic property, was initiated with a loading dose of 12 mg followed by 2 mg every 2 h crushed and delivered via a nasogastric tube. After 8 h of initiation of cyproheptadine, midazolam drip was tapered off successfully without any further episodes of altered mental-status, diaphoresis, or involuntary jerky movement. Clinical features suggestive of PE disappeared completely. BP returned to normal. Cyproheptadine was discontinued after 3 days and further occurrences of mild agitation and hypertension were treated with intravenous lorazepam as needed. The patient was extubated, his delirium cleared in 5 days, and he was deemed stable to be discharged. In the next 3 years of follow-up, he did not get a similar problem. BP remained under control without any antihypertensive agent.

Discussion

This case fulfilled the Hunter’s criteria for SS. Response to cyproheptadine further reconfirms the diagnosis. SS is caused due to excessive serotonergic activity; and in this case, it seems likely that it was caused due to concurrent administration of drugs that increased serotonergic activity (fluoxetine, sertraline, fluvoxamine, linezolid, and fentanyl), rather than any single drug alone. For each of the serotonergic drugs, the causation of SS was assessed as “probable/likely” by the World Health Organization Uppsala Monitoring Center criteria for case causality assessment and as “probable” level of causality based on Naranjo’s algorithm, with a score of eight. SS was considered as severe, at level five, as per the modified Hartwig and Siegel severity assessment scale.

SS is an under-diagnosed condition as most physicians (up to 85%) are unaware of this syndrome. Diagnosis is also difficult because of its protean manifestations, which mimic a variety of medical conditions ranging from barely perceptible to life-threatening disease. Physicians may dismiss mild symptoms of SS as unrelated to drug therapy. However, a diagnosis of mild form is very important as escalating the previously used serotonergic drugs, or addition of new serotonergic drugs may lead to a life-threatening condition.

The initial symptoms of headache, dizziness, anorexia, vomiting, and diarrhea after the recent addition of serotonergic drugs, were probably the manifestations of mild SS. These symptoms are described as the presenting features of SS in the literature. He further developed hypertensive crisis and PE. After hospitalization, he received two more serotonergic drugs (fentanyl and then linezolid) that led to the further aggravation of symptoms.

This case is also atypical for the presence of PE. The common causes of PE (such as left ventricular failure and bilateral renal artery stenosis) were ruled out. We speculate that our patient developed PE secondary to SS. There was a temporal relation in the development of PE (with other clinical features of SS) and initiation of serotonergic drugs. Although there was some improvement with symptomatic management, complete response in PE was noted only after the initiation of cyproheptadine. No recurrence of symptoms in the next 3 years suggests a monophasic type of illness and favors that PE was part of the SS symptom complex.

To the best of our literature search, PE is not reported in any patient with SS; although there are a few case reports where PE was observed as a side effect of serotonergic agents. Edriss and Pfarr have reported a case in which citalopram overdose precipitated a noncardiogenic PE. A combination of antidepressant drugs and fentanyl causing PE has also been reported by Rim et al. However, these case reports are silent regarding the presence of physical findings required for SS.

The pathophysiology of SS is related to the type of receptors involved. The 5-HT2A is the key receptor implicated in serotonin toxicity. 5-HT1A receptor and other neurotransmitters may also contribute substantially to the development of SS. To the best of our knowledge, this case is also atypical for the presence of PE. The pathophysiology of SS is related to the type of receptors involved. The 5-HT2A is the key receptor implicated in serotonin toxicity. 5-HT1A receptor and other neurotransmitters may also contribute substantially to the development of SS. To the best of our knowledge, this case is also atypical for the presence of PE. The pathophysiology of SS is related to the type of receptors involved. The 5-HT2A is the key receptor implicated in serotonin toxicity. 5-HT1A receptor and other neurotransmitters may also contribute substantially to the development of SS. This may indicate that the hypertensive surge was a part of the SS due to autonomic instability. In addition, serotonin receptors are found throughout the lung parenchyma and pulmonary vasculature. SS may alter the fluid equilibrium across the microvascular membranes via a change in the capillary pressure. Thus, SS may have caused PE in our patient due to hypertensive surges and a serotonergic mechanism at the alveolar level.

Conclusion

SS is an underdiagnosed condition, partly due to unfamiliarity of SS among physicians and partly because of its protean manifestations. The initial mild presentation may be missed, and the inadvertent addition of serotonergic agents may lead to a life-threatening condition. Hence, while the serotonergic drugs are widely being prescribed, one must be watchful of this iatrogenic and potentially life-threatening syndrome.

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Conflicts of Interest

There are no conflicts of interest.

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