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Concurrent Serotonin Syndrome and Hyponatremia: A Case Report and Review

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Abstract

Introduction: These days, selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed and used antidepressants. Serotonin syndrome is a potentially fatal complication with hyper-serotonergic situation. Its symptoms result from over activation of the central and peripheral receptors caused by high serotonin levels. The use of SSRIs is associated with the frequency of syndrome. Hyponatremia is one of the side effects of SSRIs, especially in elderly patients. The mechanism by which SSRIs cause hyponatremia is thought to be secondary to the development of the syndrome of inappropriate antidiuretic hormone (SIADH). Patients with hyponatremia secondary to SIADH have been reported with fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram. There are very few reports about the concurrent incidence of serotonin syndrome and hyponatremia.

Case Presentation: The patient was a 66-year-old woman with rheumatoid arthritis. She was treated with a fixed dose of fluoxetine and buspirone added with the amount of 15 mg per day. The patient was hospitalized 8 weeks with symptoms of confusion, lack of insight into time and space, inability to stand and walk, continuous involuntary tremor, uncoordinated and uncontrolled movements of arms and legs, hyperreflexia, and mydriasis. She also showed severe hyponatremia in the experiments. She was admitted to an academic general hospital in Iran on 2014. Based on the clinical findings, taking buspirone aside fluoxetine, as well as old age of the patient, she was diagnosed with serotonin syndrome. Treatment was carried out after discontinuation of fluoxetine and buspirone, restriction of fluid therapy, as well as prescription of sodium chloride 5%, cyproheptadine, and diazepam.

Conclusions: Consumers of SSRIs are at a higher risk of hyponatremia compared to those taking other antidepressants, especially if they are simultaneously treated by diuretics. Hyponatremia and SIADH need to be considered if a patient experiences disorientation receiving SSRIs. Physicians should be aware of the probability of acute hyponatremia and serotonin syndrome secondary to SSRIs in simultaneous use of fluoxetine and buspirone with diuretics. Moreover, physicians should note that serotonin toxicity is dose-dependent rather than idiosyncratic.

Keywords: Buspirone, Hyponatremia, Serotonin Reuptake Inhibitors, Serotonin Syndrome

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are considered as a first step of drug therapy in depressive disorders. Serotonin syndrome is the result of over activation of the central and peripheral serotonin receptors, in particular 5-5-HT2A and 5-HT1A receptors (1). Serotonin syndrome is caused by over stimulation of receptor 5-HT1A by SSRIs, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOI), or other serotonergic drugs.

A triad of mental, autonomic, and neurological disorders characterizes serotonin syndrome. It is a potentially fatal complication with hyper-serotonergic situation, described by confusion, agitation, myoclonus, hyperreflexia, diaphoresis, chills, tremor, diarrhea, lack of cooperation, and fever (2).

The use of SSRIs in elderly people with hyponatremia is associated with syndrome of inappropriate antidiuretic hormone (SIADH), which is defined by less than maximally diluted urine in the presence of plasma hypotonicity (< 280 mosm/kg) and hyponatremia (< 135 mEq/L) (3).

Symptoms of hyponatremia include nausea, weakness and malaise, followed by headache, lethargy, muscle cramps, disorientation, and restlessness. Concentrations lower than 120 mEq/L may result in severe situations such as seizures, coma, and respiratory arrest that cause significant morbidity (4, 5). A review article on papers published from 1966 to 2005 in the fields of hyponatremia and SSRIs found that the incidence of hyponatremia associated with SSRIs has a range of 0.5% to 32%. The risk factors for developing hyponatremia caused by SSRIs include older age, female gender, simultaneous use of diuretics, lower weight, and lower base concentrations of sodium (6-9). The mechanism by which SSRIs cause hyponatremia is still not clear (10). A proposed mechanism is SIADH induced through the release of antidiuretic hormone (ADH), the effect of sero-

tonin on the 5-HT2 and 5-HT1C receptors, or increased responsiveness of kidney to ADH (11, 12). Patients who are reported for hyponatremia secondary to SIADH have been reported with fluoxetine, paroxetine, sertraline, fluvoxamine, escitalopram, and citalopram (9, 10, 13-22). SSRIs cause SIADH by stimulating the release of AVP from the hypothalamus /neurohypophysis (23).

These SSRIs, especially in elderly patients, are strengthened due to low osmotic threshold and osmotic response curve to the sense of thirst. Large numbers of elderly patients are on thiazide diuretics and sodium depletion due to hypertension or congestive heart failure (CHF). Increased thirst leads to drinking extra water and causing water intoxication. Siah et al. (2006) studied a 69-year-old woman who suffered from hyponatremia, SIADH, hypoosmolality of blood and elevated urine osmolality, followed by fluoxetine (24). Chaudhry in 2014 reported an 83-year-old woman, who was on fixed-dose of sertraline and underwent a surgery. The patient was then treated by antiemetic drugs such as ondansetron and opioids, and the tests showed hyponatremia after 2 weeks (25).

In a review study in 2014, Choudhry found only 1 article about the concurrent incidence of serotonin syndrome and hyponatremia, which occurred in a patient with a drug overdose (25). Spigest et al. (1997) introduced a patient who experienced both serotonin syndrome and hyponatremia, after taking high doses of buspirone and citalopram simultaneously (26).

Given that concurrent serotonin syndrome and hyponatremia occurred in patients with SSRIs drug overdose in both of the 2 previous reports, in this study we will introduce a patient treated with fixed-dose of fluoxetine and buspirone who suffered from both of the 2 disorders simultaneously.

2. Case Presentation

The patient was a 66-year-old woman with a history of rheumatoid arthritis over the past 20 years. She was admitted on February 22, 2015 with symptoms such as loss of consciousness, confusion, dizziness nausea, and continued abnormal movements of mandible, which had started 5 days prior to hospitalization in the internal ward of Imam Khomeini Hospital of Sari, Iran. Neurological consultation indicated confusion, chin tremor, balance impairment, and falling down without loss of consciousness. Therefore, the patient was asked to undergo brain MRI and EEG. Moreover, an infectious disease consultation was recommended to rule out encephalitis.

Nephrology consultation due to hyponatremia (sodium 110), neurosurgery, and cardiology consultations were also requested. Psychiatric consultation was asked according to a history of psychiatric disorder and treatment with psychotropic drugs. Onset of symptoms was accompanied with nausea, vomiting, dizziness, headaches in the temporal region and falling down; and then the symptoms of delirium, fluctuations in the level of consciousness, lack of awareness of time and space, disjointed telling and talking about dead people. Symptoms would exacerbate in the evenings and severe tremor was evident in the jaw. There was no rigidity of limbs in the physical examination; however, hyperreflexia, mydriasis, sweating, clonus, inducible, (incoordination) ataxia, and tremor were identified. The patient had difficulty concentrating in mental examination and tachycardia, but was hemodynamically stable. There was no sign of alcohol poisoning.

The patient was suffering from anxiety disorder and mixed depression in axis I, while experiencing histrionic personality disorder and borderline personality disorder in axis II. She prominently used defense mechanisms such as splitting, denial, and somatization. Therefore, she had been under the supervision of a psychiatrist for the past 3 years. Fluoxetine dose had been increased from 20 mg to 30 mg, 4 months before the symptoms started. Moreover, buspirone was administrated since the past 8 weeks with an amount of 10 mg and frequency of 3 times a day.

The patient had been complaining from subjective sensation of abdominal vibrations for 4 weeks prior to treatment. Other drugs included sulfasalazine 500 mg BD, bromhexine, prednisolone 5 mg BD, captopril 25 mg BD and hydrochlorothiazide 5 mg/day, and vitamin D3 tablet once a week.

The primary sodium and potassium were 110 mEq/L and 3.5 mEq/L, respectively. Sodium was gradually increased and reached 116, 117 mEq/L, and then 138 mEq/L. 2 vials of Nacl 5% and daily serum of dextrose saline were used for treating hyponatremia and restricting hydration . There were no pathologic findings in other tests except mild leukocytosis (WBC: 14.4 $\times$ 10^3), serum glutamic oxaloacetic transaminase (SGOT; AST): 49 U/L, and serum glutamic pyruvic transaminase (SGPT; ALT): 21 U/L.

SIADH was diagnosed in the patient in the presence of cortisol, TFT, normal brain MRI, hyperosmolar urine, and euvolemia. Hyponatremia was justified due to the urine osmolality and isovolume under SIADH caused by fluoxetine. Cyproheptadine and diazepam were prescribed for the patient. Hyponatremia was improved within 5 days through the care, support measures, and fluid restriction, as well as discontinuation of serotonergic drugs and diuretics (hydrochlorothiazide). The symptoms of serotonin syndrome disappeared and the patient was discharged from the hospital after a week with good general condition, along with recommendations to her psychiatrist. In the next visit to

the psychosomatic clinic, which was made after 2 years, results of all tests such as sodium were normal for the patient and there was no history for recurrence of hyponatremia.

Written informed consent was obtained from the patient for the publication of this report.

3. Discussion

The patient in this study was simultaneously diagnosed with serotonin syndrome and hyponatremia. According to the Naranjo probability scale, fluoxetine combined with buspirone with a high probability (score 7) were considered as the cause of serotonin syndrome and acute hyponatremia (27). Serotonin syndrome is associated with the use of serotonergic drugs that affect the serotonin uptake, metabolism, synthesis, release, and activity of serotonin receptors. It can also interfere with the metabolism of P450 cytochromes, especially CYP3A4 and CYP2D6 (28). Several systematic reviews revealed that acute serotonin syndrome may be the result of drug interactions (29-33). Buspirone is an agonist for serotonin receptor (34).

SIADH diagnosis was raised for the patient in the presence of low sodium, cortisol, normal TFTs, hyperosmolar urine, euvolemia and normal brain MRI (with the exception of microvascular changes). Moreover, serotonin syndrome was diagnosed due to hyperreflexia, diaphoresis, inducible clonus in the presence of fluoxetine, and buspirone. The patient had hyperreflexia and clonus. Hyponatremia typically causes generalized cerebral edema. Focal neurological symptoms have also been reported in hyponatremia without a structural lesion, including hemiparesis, monoparesis, ataxia, nystagmus, tremor, rigidity, aphasia, and signs of unilateral corticospinal tract (35, 36).

Muscular symptoms are uncommon apart from cramps. Rigidity, tremor, myoclonus, asterixis, and corea are related to hyponatremia (37). There were severe tremors in the jaw and ataxia in this patient. Hyponatremia can cause muscle weakness along with hyporeflexia. Symptoms of muscle are more limited to cramps compared to serotonin syndrome, which is associated with hyperreflexia and clonus (38). Serotonin syndrome and acute hyponatremia can overlap in terms of clinical features, which have been proposed as a diagnostic dilemma in the patient. Both serotonin syndrome and hyponatremia may appear with lethargy confusion, difficulty in concentrating, fatigue, dizziness, forgetfulness, nausea, muscle cramps, and headaches. Both can cause ataxia, nystagmus, tremor, rigidity, aphasia, and bilateral positive Babinski reflex (39, 40). There is no specific diagnostic test for serotonin syndrome. Increased leukocyte count, total creatine kinase, and transaminase levels or decreased bicarbonate levels have also been reported (41). However, serotonin syndrome is diagnosed based on clinical findings and there are no laboratory or radiographic tests to confirm the diagnosis (42).

Diagnosis of serotonin toxicity has been proposed for patients according to both Hunter serotonin toxicity criteria and Strenbach's criteria (43). Hunter criteria is more accurate than Strenbach's criteria and focuses less on mental features. This has caused the Hunter criteria to have 84% sensitivity and 97% specificity in comparison with the gold standard for diagnosis by a medical toxicologist (44). The patient achieved a score of 4 and 2 in accordance with the Hunter serotonin toxicity criteria.

Classic features for the diagnosis of serotonin syndrome are generalized clonus (ocular, spontaneous, inducible), which are among the key implementation of Hunter serotonin toxicity criteria. They were validated and used to confirm the diagnosis of moderate or severe intoxication (45). The patient in this study was on a fixed-dose of fluoxetine for a period of 3 months, however, serotonin syndrome has been reported at therapeutic and subtherapeutic doses (25).

Adults older than 65 years appear to be most prone to develop hyponatremia caused by SSRIs, and the risk appears to increase with age (46). In general, reported adverse drug reactions occur more frequently in female patients. Hyponatremia associated with SSRIs usually occurs shortly after starting the drug. Three quarters of patients are seen within 30 days after the start of treatment. However, hyponatremia may occur late in the course of treatment with SSRIs. Ratio of spontaneous reports is identical for hyponatremia or SIADH by WHO, on any of SSRIs (47). Predisposing factors, including volume, taking diuretics, or concomitant use of other drugs that cause SIADH, may predispose an individual to hyponatremia (10). In our case, the patient was simultaneously taking hydrochlorothiazide, which could have predisposed the patient to hyponatremia.

Neurological symptoms, such as severe myoclonus and hyperreflexia are sometimes treated with benzodiazepines. For this patient, diazepam was prescribed. It is suggested to prescribe Cyproheptadine for patients in moderate and severe cases, although there are no randomized controlled trials about severe cases (47, 48). Diazepam is a GABA mimetic, which has been studied more and blunts the hyper-adrenergic symptoms of serotonin syndrome (42, 49, 50). Diazepam not only sedates the patient, but also improves mild hypertension and tachycardia, and reduces fever (1, 51).

For hyponatremia, treatment should be directly based on neurological involvements and not just based on the absolute number of serum sodium. Asymptomatic patients, who are neurologically intact, have no indication for hy-

pertonic saline regardless of serum sodium. Symptomatic hyponatremia is a medical emergency. When symptoms of encephalopathy are diagnosed, treatment should be started before performing imaging studies. Fluid restriction alone has no importance in the treatment of symptomatic hyponatremia. Symptomatic hyponatremia should be diagnosed and treated promptly, before the occurrence of a toxic event. Neurological outcomes will be good (25).

If the patient is still agitated after administration of benzodiazepines and improving vital signs, serotonin antagonists may be prescribed. More specifically, 5HT2A receptor antagonists seem to be more effective. Studies on animals have shown that high doses of both cyproheptadine and chlorpromazine due to the antagonistic effects of receptor 5- HT2A can be applied to prevent hyperthermia in serotonin syndrome. Cyproheptadine is a stronger 5HT2A receptor antagonist and is therefore more effective (1, 52).

Both serotonin syndrome and acute hyponatremia are mediated by the presence of SSRIs. Both positions have an acute onset and clinical features show overlap to a large degree, and are potentially life-threatening. High index of suspicion and less emphasis on mental features are helpful in the differential diagnosis. Hyperreflexia and clonus mostly suggest serotonin syndrome rather than acute hyponatremia. If the treatment is performed quickly, both positions have good prognosis. Clinicians should be informed that fulminant serotonin syndrome might appear in patients undergoing concomitant treatment with SSRIs and buspirone. Although, the risk of serotonin syndrome may be low on usual doses, it increases in case of overdose (53). Physicians should be aware of hyponatremia caused by SSRIs, which is a life-threatening side effect, especially in older people and adults who have risk factors for developing hyponatremia.

Routine monitoring of electrolytes may not be necessary in all patients receiving SSRIs. However, in patients taking this drug, electrolytes should be controlled, especially if unexplained symptoms such as lethargy, delirium, or nausea develop during the first few weeks of treatment (10).

Serotonin syndrome is a life-threatening potential complication. If treated early, it will have an acceptable prognosis. With the increasing number of serotonergic drugs and patients treated by polypharmacy, physicians should be aware of the possible side effect profile and interactions with this drug.

Footnotes

Authors' Contribution: Forouzan Elyasi performed primary and psychiatric evaluation, clinical interpretation and management of the case, contributed in the conception of the work, drafted the manuscript, and revised it according to the reviewers' comments. Marzieh Azizi contributed in the manuscript drafting. Both authors read and approved the final manuscript.

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