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SHORT COMMUNICATIONS

Severe serotonin syndrome under duloxetine in a patient with coeliac disease — Is there a connection? A case report

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Abstract
Background and objectives: Serotonin Syndrome (SS) is a rare but severe drug side effect of serotonergic substances. The various symptoms of SS are the result of excess serotonin on the central and enteric nervous system. Monotherapy with serotonin-norepinephrine reuptake inhibitors (SNRIs) like duloxetine induce the syndrome very rarely. It has been shown that patients with coeliac disease (CD) per se have significantly increased serum serotonin levels.
Methods: We report the case of a 41-year-old white male who developed an unusual severe SS under monotherapy with duloxetine. Remarkably, the patient was also diagnosed with CD shortly before.
Results: After all other possible causes have been excluded by intensive diagnostics the clinical diagnosis of a serotonergic syndrome was made.
Conclusion: To our knowledge, this case is the first report of such a severe serotonin syndrome under duloxetine monotherapy, which might be boosted trough the patient's coeliac disease. We suspect that the serotonin level of the patient could already have been significantly increased due to his CD and therefore jointly responsible for the fulminant serotonin syndrome under duloxetine.

Introduction

Serotonin Syndrome is a rare but severe drug side effect of serotonergic substances, which mostly occurs in patients who are treated with two or more serotonergic drugs that

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cause a synergistic increase in synaptic serotonin (5-HT). These drugs include monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, antibiotics, opioid analgesics, herbal products, antiemetics and also illegal substances like Methylenedioxymethamphetamine or cocaine.[1] The syndrome is very rarely induced by selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) like duloxetine and occurs mainly with co-administration of SSRIs or opioids.[2,3] The symptoms may vary from mild to life threatening. Typical signs of excess 5-HT range from tremor and diarrhea to delirium, neuromuscular rigidity and hyperthermia in life-threatening cases. The diagnosis is based on the clinical symptoms and there are no laboratory tests that can confirm or deny the diagnosis. Because the clinical manifestations of SS are highly variable, the diagnosis should be based on the Hunter Serotonin Toxicity Criteria.[4] According to the Hunter criteria, the diagnosis of SS requires the intake of an serotonergic agent and one of the following features or groups of features: spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor and hyperreflexia; or hypertonia, temperature above 38 °C and ocular or inducible clonus. It is also necessary to rule out other possibilities like dopaminergic drugs, infection, metabolic disorder, substance intoxication, or withdrawal.[4,5]

Only a few cases of SS under duloxetine have been reported.[2,3,6–8] However, in most of those cases the syndrome occurred under a combination of duloxetine with anesthetics or other SSRIs. We could only identify two cases of SS induced by duloxetine alone[3,9] and the reported symptoms were only moderate.

Serotonin is not only an important neurotransmitter in the brain but also a key modulator of gut function. There is increasing evidence of a close connection between brain and bowel[10] and the brain-gut axis has become a promising research area. There are also indications that serotonin might play a central role in various bowel diseases, which in turn are often linked to psychiatric symptoms.[11–13] Especially anxiety, depression and related mood disorders are frequently reported to be associated with gluten sensitivity and coeliac disease.[14,15] Abnormally increased 5-HT was found in a range of gastrointestinal disorders including CD, inflammatory bowel disease and irritable bowel syndrome.[12,16] Interestingly, several publications reported altered serotonin metabolism and significantly higher peak plasma 5-HT levels in coeliac patients.[17–19]

To our knowledge, this case is the first report of a severe serotonin syndrome under duloxetine alone, which might be associated with coeliac disease.

Case report

In Oct. 2017, a 41-year-old white man presented himself in the emergency room of a local hospital in Regensburg, Germany due to hyperventilation and acute disturbance of motion. He reported that about 4 h ago, after having pasta for lunch, out of complete well-being and without previous nausea, severe vomiting had suddenly occurred. He then felt dizzy, nervous and unstable on his legs. This condition was getting worse and he had finally started to hyperventilate, which is why he presented himself in the emergency room.

In the following hours after admission, the patient developed marked psychomotor restlessness, ataxia, dizziness, massive sweating and a supraventricular tachycardia with heart rates up to > 200/min and was finally admitted to the intensive care unit. After the onset of paroxysmal atrial fibrillation, several unsuccessful attempts of medication-based and electrical rhythmization had been made.

Psychomotor agitation was markedly progressive with severe excitation, spontaneous myoclonus, persistent tachycardia and development of oxygenation disorder, eventually leading to endotracheal intubation and invasive ventilation on the next morning. Striking was an extremely high demand for sedatives. In addition, the patient was treated with benzodiazepines, beta blocker, nitroglycerine and cyproheptadine. Initial hypokalaemia (2,1 mmol/l) was balanced and a pronounced increase in creatinine kinase (> 20.000 U/l) was observed. In the course also a systemic inflammatory response syndrome (without infect focus) occurred.

The extensive diagnostics (cerebrospinal fluid diagnostics, computed tomography with angiography, systematic toxicological analysis via gas chromatography with mass spectrometry for > 2000 substances, X-ray thorax, transthoracic echography, MR imaging, electroencephalography and electrocardiography and screening for neuroendocrine tumor markers) showed no evidence of infectious, ischemic, hemorrhagic or metabolic causes. In addition, intoxication with illegal substances or deliberate or accidental overdose of the antidepressant medication was excluded, due to the initial plasma levels (duloxetine: 105.00 µg/l; norm: 30.00–120.00) and anamnestic investigations.

Since the patient even showed several of the Hunter Serotonin Toxicity Criteria, the diagnosis of a serotonergic syndrome was made. The therapy was mere symptomatic as mentioned above.

After the acute symptoms had declined and the vital parameters had stabilized, the patient was extubated after 12 days and finally discharged from the intensive care unit 23 days after admission. Besides a generally reduced condition only a mild critical illness polyneuropathy remained. Both showed a clear downward trend in the further course. Mentally, the patient felt surprisingly better after the incident. Psychopathologically, the patient just showed minor depressive symptoms such as impaired concentration and slightly reduced impetus. Subsequently, the patient took outpatient psychotherapy and reached full working capacity again after several weeks. A further treatment with antidepressants was neither recommended nor desired, nor necessary.

Prehistory

In July 2017, the patient, who had no psychiatric history, was diagnosed with a moderate depression and had initially been treated with Mirtazapin (30 mg/d) on an outpatient basis. Since there was no clinical improvement after several weeks, the treating psychiatrist switched medication to duloxetine about 2 weeks prior to the reported event and increased the dosage from 30 to 60 mg/d two days before the incident. Otherwise, he did not take any further medication or nutritional supplements and was healthy except

for a coeliac disease, which was first diagnosed in June 2017 and since then has been treated dietarily. The patient had no history of substance abuse and was a strict non-smoker. The only other predisposing factor for SS that could be identified was the fact that the patient reported to drink red wine occasionally, but not prior to the reported event.

Discussion

To our knowledge, this is the first case report of such a severe serotonin syndrome under duloxetine alone. We want to raise the question if the patient's coeliac disease could have facilitated the SS. Sjolund et al. reported markedly elevated 5-HT levels in patients with newly diagnosed coeliac disease, which even exceeded the levels found in patients with carcinoid tumors.[18] Coleman et al.[17] also reported significantly higher peak plasma 5-HT levels in patients with untreated coeliac disease, especially after a gluten-rich test meal. Peak 5-HT levels also correlated significantly with postprandial dyspepsia scores.

A concept of serotonin toxicity has been postulated,[20] which considers the SS as a form of poisoning caused by progressive elevation of 5-HT. We suspect that the serotonin level of the patient could already have been significantly increased due to his just recently diagnosed coeliac disease and additionally triggered by a previous gluten-rich meal. Even if the patient has adhered to a strict gluten-free diet, it can take up to 6 months for the disease-typical changes in the mucosa to heal.[21,22] The fact that the patient stated that he had eaten pasta before the incident does not indicate an optimal therapeutical adherence. Increasing the dose of duloxetine could additionally have led to progressively increasing serotonin levels, finally crossing the toxic threshold after a gluten-rich meal just before the incident.

Of course, the coincidence between the patient's coeliac disease and the unusual severe serotonin syndrome is primarily temporal and a causal connection can not be proven through this case report. Nevertheless, we find the reported observations very remarkably and, in our view, a causal connection could theoretically be possible. We also would like to raise the question whether CD and non-coeliac gluten sensitivity could be a more noteworthy risk factor for SS under SSRI and SSNRI treatment. Especially if you consider that coeliac disease has a prevalence of about 1:400[23] in the United States and several European countries and could not only have contributed to this patients depressive episode but is generally associated with psychiatric co-morbidities which in turn lead to psychopharmacological treatment.[14,15] Therefore, patients with CD in particular should be carefully screened for SS specific symptoms. Since there are no current studies on the subject, basic research both by psychiatrists and gastroenterologists is needed.

Ethical considerations

In this publication the WHO guidelines for good clinical practice were followed. The patient has consented that his data can be published anonymously by the author.

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Conflict of interest

The authors declare no conflicts of interest.

References

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005;352(11):1112–20.
2. Gaffney Rr, Schreibman Ir. Serotonin syndrome in a patient on trazodone and duloxetine who received fentanyl following a percutaneous liver biopsy. Case Rep Gastroenterol. 2015;9(2):132–6.
3. Gelener P, Gorgulu U, Kutlu G, Ucler S, Inan LE. Serotonin syndrome due to duloxetine. Clin Neuropharmacol. 2011;34(3):127–8.
4. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM: Monthly J Assoc Phys. 2003;96(9):635–42.
5. Ables AZ, Nagubilli R. Prevention, recognition, and management of serotonin syndrome. Am Fam Phys. 2010;81(9):1139–42.
6. Takata J, Arashi T, Abe A, Arai S, Haruyama N. Serotonin syndrome triggered by postoperative administration of serotonin noradrenaline reuptake inhibitor (SNRI). JA Clin Rep. 2019;5(1):55.
7. Guo MH, Monir RL, Wright A, Holland NP. Case of serotonin syndrome initially presenting as diffuse body pain. Am J Case Rep. 2018;19:1227–31.
8. Himmighoffen H, Seifritz E, Boeker H. Serotonin syndrome after discontinuation of olanzapine in a combined treatment with duloxetine — case report. Pharmacopsychiatry. 2011;44(2):75–6.
9. Choi JS, Lee JH, Park SK, Shim BJ, Choi WK, Sang K, et al. Serotonin syndrome following duloxetine administration in a fibromyalgia patient: case report and literature review. J Rheum Dis. 2016;23(5):332–5.
10. Khan WI, Ghia JE. Gut hormones: emerging role in immune activation and inflammation. Clin Exp Immunol. 2010;161(1):19–27.
11. Lewis-Fernandez R, Lam P, Lucak S, Galfalvy H, Jackson E, Fried J, et al. An open-label pilot study of duloxetine in patients with irritable bowel syndrome and comorbid major depressive disorder. J Clin Psychopharmacol. 2016;36(6):710–5.
12. Spiller R. Serotonin and GI clinical disorders. Neuropharmacology. 2008;55(6):1072–80.
13. Challacombe DN, Wheeler EE. Are the changes of mood in children with coeliac disease due to abnormal serotonin metabolism? Nutr Health. 1987;5(3–4):145–52.
14. Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL. Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity. Psychiatr Q. 2012;83(1):91–102.
15. Zylberberg HM, Ludvigsson JF, Green PHR, Lebwohl B. Psychotropic medication use among patients with celiac disease. BMC Psychiatry. 2018;18(1):76.
16. Cleare AJ, Keating J, Ealing J, Sherwood RA. A case of coeliac disease detected via raised 5-hydroxytryptamine and 5-hydroxyindoleacetic acid. Ann Clin Biochem. 1997;34 Pt 4:440–1.
17. Coleman NS, Foley S, Dunlop SP, Wheatcroft J, Blackshaw E, Perkins AC, et al. Abnormalities of serotonin metabolism and their relation to symptoms in untreated celiac disease. Clin Gastroenterol Hepatol. 2006;4(7):874–81.

18. Sjolund K, Nobin A. Increased levels of plasma 5-hydroxytryptamine in patients with coeliac disease. Scand J Gastroenterol. 1985;20(3):304–8.
19. Enerback L, Hallert C, Norrby K. Raised 5-hydroxytryptamine concentrations in enterochromaffin cells in adult coeliac disease. J Clin Pathol. 1983;36(5):499–503.
20. Gillman PK. A review of serotonin toxicity data: implications for the mechanisms of antidepressant drug action. Biol Psychiatry. 2006;59(11):1046–51.
21. Lebwohl B, Granath F, Ekbom A, Montgomery SM, Murray JA, Rubio-Tapia A, et al. Mucosal healing and mortality in coeliac disease. Alim Pharmacol Ther. 2013;37(3):332–9.
22. Kelly CP, Bai JC, Liu E, Leffler DA. Advances in diagnosis and management of celiac disease. Gastroenterology. 2015;148(6):1175–86.
23. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol. 2012;107(10):1538–44, quiz 7, 45.