Treatment of Serotonin Syndrome

70

Stewart A. Factor

Case

A 25-year-old man was seen in hospital consultation because of 1–2 days of increased anxiety, associated confusion, and a movement disorder. He had a medical history of depression and anxiety and had been admitted with a traumatic back injury after falling 5 feet from a ladder. He had been treated with mirtazapine 30 mg/night and fluoxetine 20 mg/day for the psychiatric issues. Upon admission he had an MRI of the lumbar spine which demonstrated a compression fraction at L5. He was treated with intravenous fentanyl 100 mcg/hr. Within 8 h he developed increased anxiety and confusion. On examination he was febrile at 102° F and was diaphoretic. He was awake but kept his eyes closed and was lethargic and disoriented to place and time. Key findings included motor impersistence with tongue protrusion, tongue tremor, and multifocal myoclonus involving the neck, face, and extremities. It increased when the patient held his arms in front of him and further with finger to nose; he had asterixis (negative myoclonus) and a fine postural tremor. He had normal muscle tone and no bradykinesia. He had no ataxia. Reflexes were brisk with patella and ankle clonus but downgoing toes. He could not walk. Abnormal labs included white blood count of 12.7×10^3/mcL (normal 4.2–9.1) and creatine kinase of 445 units/L (normal 49–397). Computerized tomography brain scan was normal.

He was treated with removal of the fentanyl and mirtazapine, IV fluids, acetaminophen, and clonazepam 0.5 mg q 8h PRN anxiety. He only received one dose over 2 days, but the syndrome resolved by then including the fever, confusion, and movement disorder. No other treatment was necessary, and he recovered fully.

S. A. Factor
Vance Lanier Chair of Neurology, Department of Neurology, Jean and Paul Amos Parkinson's Disease and Movement Disorder Program, Emory University, Atlanta, GA, USA
e-mail: sfactor@emory.edu

Discussion

Historically, serotonin syndrome was reported to occur with the combination of therapeutic doses of tricyclics or SSRIs (>SNRIs) and nonselective monoamine oxidase inhibitors (MAOI). However, other drugs such as fentanyl, tramadol, methylphenidate, methylene blue, ondansetron, valproate, linezolid, dextromethorphan, meperidine, cyclobenzaprine, and ecstasy have also been reported to cause serotonin syndrome when used with SSRIs or SNRIs as seen in the case report. In fact the most common combination in the literature is paroxetine and tramadol. It is also possible that high doses of a single serotonergic drug can cause serotonin syndrome. The occurrence relates to excessive stimulation of the 5HT1 and 5HT2 receptors and secondary inhibition of DA neurons in the SNc.

The serotonin syndrome generally develops over hours to days after initiation of the second drug or an increase in the dose. The clinical features are in several realms including motor, mental, and autonomic. The most prominent motor signs are myoclonus and hyperreflexia (clonus) but also include tremor, dystonia, rigidity, as well as extensor plantar reflexes. The mental features are confusion, agitation, disorientation, and restlessness. Autonomic instability includes fever, nausea, diarrhea, flushing, diaphoresis, rigors, tachycardia, tachypnea, BP change, and pupillary dilatation. In severe cases high fever, seizures, oculogyric crisis, and opisthotonus are seen. Laboratory changes include elevated creatine kinase, leukocytosis, metabolic acidosis, and possible rhabdomyolysis. Reported mortality rates range from 2.4% to 12% with death occurring because of DIC, myoglobinuria with renal failure, and cardiac arrhythmias.

The serotonin syndrome may appear to be clinically similar, if not identical, to neuroleptic malignant syndrome. Diagnosis will depend on the drug combination that triggered the event. The differential can be particularly complicated when the patient is treated with antidepressants and an atypical antipsychotic, especially one with serotonergic

S. G. Reich, S. A. Factor (eds.), *Therapy of Movement Disorders*, Current Clinical Neurology,
https://doi.org/10.1007/978-3-319-97897-0_70

properties. Some in the literature have labeled such cases neuroleptic malignant syndrome and others serotonin syndrome. Since there are no diagnostic markers for either disorder, the therapeutic approach should be the same. Other disorders in the differential include anticholinergic toxicity, acute dystonic reaction, acute encephalitis or meningitis, catatonia, heat stroke, sympathomimetic intoxication, cocaine, methamphetamine, and PCP intoxication.

Two sets of diagnostic criteria have been developed for the serotonin syndrome. The Sternbach criteria published in 1991 include (1) a recent increase or addition of known serotonergic agent to an established regimen and (2) at least three of the following: mental status change, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, fever, and (3) other etiologies ruled out.

The Hunter Criteria, published in 2003, include clonus as a prime feature. They include any of the following findings: spontaneous clonus, inducible clonus with agitation and or diaphoresis, ocular clonus plus agitation or diaphoresis, tremor plus hyperreflexia, and hypertonia plus hyperpyrexia plus ocular clonus or inducible clonus.

The key to the treatment of serotonin syndrome is recognition. Once recognized, the principal treatment step involves withdrawal of the causative agent(s), and generally the syndrome will resolve over hours to days, as seen in this case. Patients should be closely observed until resolution and supportive measures that may be required include antipyretics and intravenous fluids. On rare occasions patients will require treatment for myoclonus with clonazepam at doses up to 0.5 mg TID or lorazepam 0.5 TID, but these can worsen mental status changes. As with most drug-induced movement disorders, there is a propensity for physicians to try anticholinergics, but they have limited use in this scenario and can add to mental status dysfunction as well. Antiserotonergic medications such as cyproheptadine (4–20 mg per day), methysergide (4–8 mg daily), or propranolol (up to 120 mg per day) may be helpful but should only be used short term. I have not seen the need to use these drugs in the cases I have seen. In severe cases treatment of seizures, arrhythmias, coagulopathy, and rigidity may be necessary. To prevent a recurrence, high dosages or combinations of serotonergic medications should be avoided.

Suggested Reading

Bodner RA, Lynch T, Lewis L, Kahn D. Serotonin syndrome. Neurology. 1995;45:219–23.

Abadie D, Rousseau V, Logerot S, Cottin J, Montastruc J-L, Montastruc F. Analysis of Cases Registered in the French Pharmacovigilance Database. J Clin Psychopharmacol. 2015;35:382–8.

Nordstrom K, Vilke GM, Wilson MP. Psychiatric emergencies for clinicians: Emergency department management of serotonin syndrome. J Emerg Med. 2016;50:89–91.

Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. Q J Med. 2003;96:635–42.

Sternbach H. The serotonin syndrome. Am J Psychiatry. 1991;148:705–13.