CASE REPORT

Serotonin syndrome triggered by an exacerbation of multiple sclerosis?

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Abstract - We present a possible diagnosis of serotonin syndrome in a patient previously diagnosed with multiple sclerosis (MS) and depression. The patient developed severe serotonin toxicity while she was being treated with a selective serotonin reuptake inhibitor (SSRI) in a decreasing dose schedule. We present a hypothesis which could explain this effect in patients with MS.

Keywords: serotonin syndrome, multiple sclerosis

Introduction

The serotonin syndrome is classically described as the triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. These clinical findings are the result of increased serotonergic activity in the central nervous system [1,2]. The diagnosis is made solely on clinical grounds, and symptoms may vary from mild, hardly bothering the patient, to life-threatening, demanding immediate medical treatment. Mild cases of serotonin syndrome are often missed by clinicians, while early recognition is important to start treatment before symptoms exacerbate [3,4].

Case Report

A 25-year-old woman was found unconscious in her room. She had a history of relapsing remitting multiple sclerosis (MS), and depression. Her medication was citalopram (5 mg/day) in a decreasing dose schedule. In the ambulance, she developed seizures which were treated with midazolam (5 mg).

On arrival in the Emergency Room (ER), her Glasgow Coma Score (GCS) was 3. Neurological examination showed slow horizontal eye movements, bilateral mydriasis, diffuse tremor, and hyperreflexia in all extremities. The patient’s vital functions were: blood pressure 110/40 mm Hg, heart rate 90 beats/min, central temperature 37,0 °C, and peripheral oxygen saturation 100% with oxygen at 15 l/min via a non-rebreathing mask.

Laboratory investigation of blood drawn immediately after admission showed no abnormalities except for respiratory acidosis (pH 7,18; pCO₂ 8,5 kPa). Serum toxicology screening showed the citalopram level was not elevated, and no other drugs were present. A CT scan of the brain showed diffuse lesions of the white matter, but no signs of bleeding or infarction. A lumbar puncture showed no abnormalities.

After 15 minutes, the patient suddenly developed myoclonus in all extremities, which was successfully treated with clonazepam (1 mg). A diagnosis of de novo epilepsy in MS was suspected, and treatment with diphantine (750 mg, 15 mg/kg) was started. The patient was intubated after induction with propofol and rocuronium and transferred to the Intensive Care Unit (ICU).

In the ICU, the sedation was stopped to evaluate the level of consciousness. The patient remained comatose (GCS 3) but developed extreme shivering, which was treated with pethidine (25 mg). After fifteen minutes she gradually began to develop hypertension and tachycardia (blood pressure 155/95 mm Hg, heart rate 110 beats/min), and her central temperature rose rapidly from 37,5 to 38,5 °C (Figure 1). At that time, serotonin syndrome was suspected, with a differential diagnose of intoxication, meningitis or encephalitis, malignant hyperthermia, neuroleptic malignant syndrome, catatonia and de novo epilepsy. Active cooling measures with ice bags and cold fluids were started, and the patient was deeply sedated with high doses of midazolam and propofol until the shivering disappeared. Dantrolene (1 mg/kg) was given, followed by a second dose 30 minutes later. Cyproheptadine was not directly available.

Despite deep sedation and active cooling measures, her blood pressure, heart rate and central temperature remained elevated (blood pressure 160/95 mm Hg, heart rate 110 beats/min, central temperature 38,5 °C). After 2 hours, they gradually decreased to normal values, and the active cooling measures were stopped (Figure 1).

After 24 hours of stable vital functions and central temperature the sedation was stopped, and the patient was extubated one day later. She had hemiplegia and revealed that she had been suffering from weakness in her right extremities and hyperesthesia in the left side of her face in the days before admission. A second CT scan of the brain on day 7 showed the same diffuse lesions of the white matter, but again no signs of bleeding or infarction. An exacerbation of MS was diagnosed by the neurologist, and treated with steroids. Symptoms resolved completely over the following weeks, and the patient was discharged from the hospital after 21 days.

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Discussion

The serotonin syndrome results from therapeutic medication use, intentional self-poisoning, or inadvertent drug interactions [1,2]. The clinical features of serotonin syndrome are depicted in Table 1 [1]. The transition point at which serotonergic signs become the toxic reaction known as the ‘serotonin syndrome’ remains questionable. Therefore, cases with mild serotonergic signs are frequently missed and several sets of diagnostic criteria have been developed to define features that relate solely to serotonin toxicity. The most accurate are the Hunter Criteria Decision Rules [5]. To fulfill the Hunter Criteria, a patient must have taken a serotonergic agent and have one of the following symptoms:
- spontaneous clonus
- inducible clonus plus agitation or diaphoresis
- ocular clonus (slow continuous lateral eye movements) plus agitation or diaphoresis
- tremor and hyperreflexia
- hypotonia
- temperature above 38 °C plus ocular clonus or inducible clonus

The Hunter Criteria were validated in the setting of a toxicology service, by comparing the criteria with the diagnosis made by a medical toxicologist. This results in a sensitivity of 84%, and a specificity of 97% [5]. Yet, the Hunter Criteria diagnose serotonin toxicity, not serotonin syndrome. Serotonin syndrome remains a clinical diagnosis. Based on the Hunter Criteria, we can only state that our patient displayed severe serotonin toxicity. We cannot prove the diagnosis serotonin syndrome, despite the presence of many serotonergic signs.

The treatment of life-threatening serotonergic symptoms involves aggressive treatment of autonomic instability. Patients with hyperthermia often require deep sedation with benzodiazepines, paralysis and endotracheal intubation. In our patient, endotracheal intubation was already necessary in the ER, to keep the airway patent and to treat respiratory acidosis. Control of hypertension, tachycardia, and hyperthermia was accomplished by the administration of high doses of midazolam and propofol, and by applying active cooling measures.

Cyproheptadine is an antihistaminic and antiserotonergic agent, which acts by antagonizing 5-HT2 receptors and by blocking calcium channels [6]. It is the recommended antidote for serotonin if benzodiazepines and supportive care fail to correct vital signs, but randomized controlled trial evidence is lacking. The initial dose is 12 mg; after this, 2 mg can be added every two hours [7]. Unfortunately, cyproheptadine only became available two hours after serotonin syndrome was diagnosed. Symptoms were gradually resolving by that time, and we decided not to give it. Nevertheless, initially high doses of benzodiazepines failed to correct autonomic instability, therefore, we decided to give dantrolene. In a case series dantrolene has been reported to improve symptoms of serotonin syndrome, but has also been implicated in the development of serotonin toxicity and is not generally recommended [6].

Obviously, all drugs with serotonergic potency are contraindi-
cate in serotonin syndrome, since it is a clear dose-related phenomenon [8]. The administration of pethidine is therefore likely to have caused further deterioration in the condition of our patient, although severe serotonin toxicity due to a combination of pethidine with SSRIs is not frequently reported [9,10]. Unfortunately, we diagnosed serotonin toxicity only after symptoms aggravated in the ICU. We overlooked the mild serotonergic symptoms present in the ER, and falsely diagnosed them as seizures in de novo epilepsy.

The presence of severe serotonin toxicity and an exacerbation of MS during treatment with SSRIs in a decreasing dose schedule is conflicting. Intrigued by this concurrence, we searched for an explanation and present the following hypothesis: Patients with MS are serotonergically depleted, and possibly adapted to low serotonin levels [11-13]. Our patient was being treated with an SSRI in a decreasing dose schedule, which may also contribute to this effect. In contrast, elevated serotonin levels have been measured during exacerbations [14]. As our patient was diagnosed with an exacerbation of MS, we theorize that she developed serotonin syndrome due to temporary elevated serotonin levels while adapted to low serotonin levels. This effect has not been described before.

**Summary**

Serotonin syndrome is a dangerous clinical entity requiring urgent medical treatment, while the diagnosis is difficult and frequently missed by clinicians. In our case, an exacerbation of multiple sclerosis possibly triggered the serotonin syndrome.

**References**