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CASE REPORT

SEROTONIN SYNDROME MIMICKING INTRATHECAL BACLOFEN WITHDRAWAL IN A PATIENT WITH HEREDITARY SPASTIC PARAPARESIS

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Context: **Serotonin syndrome is a drug-induced condition related to an increased level of serotonin in the brain, which may induce neuromuscular, autonomic and mental symptoms.**
Case report: **A 40-year-old woman with hereditary spastic paraparesis (Strumpell-Lorrain disease) with an implanted intrathecal baclofen pump for severe spasticity. Two days after starting a medication known to inhibit serotonin re-uptake (paroxetine), she developed a sudden increase in lower limb spasticity with continuous spasms, fever, tachycardia and hypertension. Intrathecal baclofen withdrawal was excluded, confirming serotonin syndrome.**
Conclusion: **Medications that inhibit serotonin re-uptake may induce serotonin syndrome, resulting in increased spasticity in patients with spinal cord lesions, and should be prescribed with caution.**

Key words: serotonin syndrome; hereditary spastic paraparesis; intrathecal baclofen; paroxetine.

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LAY ABSTRACT

Medications that inhibit serotonin re-uptake are frequently prescribed for depression. Such drugs increase the level of serotonin in the brain. An excessive level of serotonin may induce serotonin syndrome. We present here the case of a woman with hereditary spastic paraparesis who presented with a sudden increase in spasticity as a consequence of serotonin syndrome. As the patient was implanted with an intrathecal baclofen pump for spasticity management, the serotonin syndrome was mimicking a clinical picture of baclofen withdrawal. Such medications should be prescribed with caution in patients with spasticity.

In patients with a central nervous system (CNS) disease, particularly in the case of spinal cord injury (SCI) or disease, an increase in spasticity is usually caused by a medical or traumatic event. Bladder or renal infection or obstruction, constipation, skin breakdown, deep vein thrombosis and fractures are well-known possible causes of the increase in spasticity. In patients implanted with an intrathecal baclofen (ITB) pump, an ITB withdrawal induces a sudden increase in spasticity, usually associated with pruritus. We describe here a case of serotonin syndrome (SS) inducing a sudden increase in spasticity, mimicking a medical condition or ITB withdrawal.

CASE REPORT

A 40-year-old woman has been followed in our centre for an incomplete motor hereditary spastic paraparesis (Strumpell-Lorrain disease) since 1994. In 2004 she benefited from an ITB pump (Synchromed II, Medtronic, Minneapolis, MN, USA) implantation for severe lower limb spasticity that limits gait. The pump was changed in 2011 and 2018. Due to disease progression, she lost walking capacity in 2013, but remained independent in a wheelchair. She continues to benefit from ITB to control spasms, which impede transfers, activities of daily living, and work. In 2015 and 2017 she gave birth, with no complications related to the ITB pump. Her medical history is unremarkable of any other medical or surgical problems.

In October 2018 her general practitioner prescribed trazodone, 100 mg daily, for mood disturbances with

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sleep difficulties. A month later she refilled her ITB pump with no technical issues. Two days after the pump was refilled her general practitioner added paroxetine, 20 mg daily, while continuing the trazodone. Two days later she reported a sudden increase in spasticity with continuous painful spasms and clonus, leading to an emergency room visit with the suspicion of ITB withdrawal. Physical examination revealed continuous spasms in the lower limbs, an elevated temperature at 37.8°C, an increased heart rate (110 bpm) with mild hypertension (130/90 mmHg). Lumbar, abdominal, skin and orthopaedic examinations were normal. Of note, she did not report pruritus. Laboratory findings revealed no elevation of C-reactive protein, a normal white blood cell count, liver function and renal function. Urinalysis showed no haematuria or leukocyturia. Urinary culture revealed *E. coli* (> 100,000 CFU/ml), suggesting contamination of the sample. Ultrasound examination of the lower limbs and the urinary tract excluded a deep venous thrombosis, urinary lithiasis or kidney infection. Analysis of the ITB pump revealed that it was functioning normally, with a 200 µg/day administration in continuous mode and a 2,000 µg/ml baclofen concentration. Due to the high suspicion of serotonin syndrome, catheter imaging was not performed. The immediate discontinuation of paroxetine resolved the symptomatology in 2 days.

In conclusion, this patient presented with a sudden increase in spasticity with no ITB withdrawal signs or any of the classically described aggravating factors, leading to a diagnosis of serotonin syndrome.

DISCUSSION

Hereditary spastic paraparesis (HSP), also called Strumpell-Lorrain disease, is a rare neurogenetic cause of spinal cord injury due to degeneration of the corticospinal tracts (1). The key clinical finding is lower limb spastic paresis leading to gait disturbances. Initially defined by Lance as a velocity-dependent increase in the tonic stretch reflex with exaggerated tendon jerks and clonus, spasticity is a component of the spastic muscle overactivity, which includes spastic dystonia, spastic co-contraction and spasms (2). More than 80% of people with SCI and 40% of stroke patients experience spasticity (3, 4). As in other causes of CNS disease (brain injury, cerebral palsy, spinal cord traumatism, multiple sclerosis and other genetic disorders), spasticity is frequently seen in HSP, inducing functional limitations, discomfort and sleep disturbance. When spasticity increases, an aggravating factor should be considered, such as pain or discomfort triggered by a urinary tract infection, skin breakdown, deep vein thrombosis and osteo-articular disease (3). Intrathecal baclofen therapy is a highly effective treatment option for patients with spasticity resistance to oral medications. A sudden interruption of ITB delivery may result in baclofen withdrawal syndrome, characterized by a sudden increase in spasticity, pruritus, hyperthermia, autonomic dysregulation, epileptic seizures, coma, rhabdomyolysis and multiple organ failure (5). In our case, the increase in spasticity was not associated with pruritus.

Antidepressant drugs are often prescribed in patients with SCI (6). Tricyclic antidepressant agents can cause side-effects, such as urinary retention, constipation and dry mouth. Serotonin or 5-hydroxytryptamine is a natural monoamine neurotransmitter that is derived from tryptophan. It is metabolized in the liver by monoamine oxidase and it is found primarily in the gastrointestinal tract, the central nervous system (CNS) and in platelets (7). Natural serotonin in the CNS has a large range of effects on autonomic function, nociception, behaviour, mood appetite and thermoregulation. Thus, selective serotonin reuptake inhibitors (SSRIs) are considered to be the most appropriate antidepressant.

SS is a potentially life-threatening condition caused by the increase in the serotonin level in the CNS and the peripheral nervous system (7). The main clinical signs are clonus, hyperreflexia and hypertonia, which are part of spastic paresis syndrome (2). Thus, SS may be confounded with another cause of spasticity increase, including ITB withdrawal. SS is usually caused by SSRIs, such as citalopram, escitalopram, fluoxetine, paroxetine and sertraline. Monoamine oxidase inhibitors, such as phenelzine, tranylcypromine, isocarboxazid, and selegiline also inhibit serotonin metabolism and tend to produce the most severe and prolonged effects. Many other drugs also impair serotonin reuptake, including tramadol, pentazocine, metoclopramide, valproate, carbamazepine, dextromethorphan and cyclobenzaprine (7). Finally, medications such as buspirone, tryptophan, fentanyl, ergot derivatives or some dietary supplements, linezolid antibiotic methylene blue, and illicit substances (lysergic acid diethylamide (LSD), cocaine, 3,4-methylenedioxymethamphetamine, amphetamines) are direct serotonin agonists (7, 8). Thus, many drugs can cause SS, which is usually due to the interaction between several serotoninergic agents with different mechanisms of action in 85% of cases (9). Therefore, providers must be aware of existing treatment when adding new medications.

The incidence of SS in the general population is unknown. Guo et al. reported great difficulty in estimating the prevalence of SS, but revealed that 14–16% of cases of overdose of SSRIs develop symptoms of SS (10). The American Association of Poison Control Centers reported over 50,000 cases of overdose in 2016 in which SSRIs were mentioned (11). The incidence of SS in the SCI population and in spastic patients from other aetiologies (stroke, multiple sclerosis, traumatic brain injury) is unknown. In 1999, Stolp-Smith and & Wainberg reported a case of progressive exacerbation of spasticity after administration of fluoxetine and trazodone (6).

The presentation of SS is often variable, including a wide range of manifestations, from mild cases that may go

Table I. Hunter classification with prevalence of symptoms in serotonin syndrome (SS)

Hunter criteria symptoms of SS, %	
Clonus	34
Tremor	58.5
Agitation or Diaphoresis	53.2
Hyperreflexia	56.5
Hypertonia	45.4
Hyperthermia	59.7
Other manifestations, %	
Altered mental status	63.9
Autonomic instability	75.8–85.1
Diarrhoea	15.1
Mydriasis	34.1
Diaphoresis	53.2
Pain	
Flushing	
Trismus	

unnoticed to severe or even lethal instances. The diagnosis of SS remains challenging, since it can only be made on clinical grounds, leading to under-diagnosis. There is no objective diagnostic test. The clinical manifestations usually appear in the first 24 h and are non-specific without singular laboratory tests or pathognomonic clinical findings. The diagnosis must be as prompt as possible, as autonomic instability can be life-threatening.

The Hunter classification (**Table I**) is thought to be the best diagnostic assessment tool, with a reported sensitivity of 84% and specificity of 97% (12). The prevalence of symptoms ranged from 34% for clonus to 59.7% for hyperthermia.

To fulfil the Hunter criteria, a patient must have taken a serotonergic agent and must meet one of the following conditions: spontaneous clonus, inducible clonus *plus* agitation or diaphoresis, ocular clonus *plus* agitation or diaphoresis, tremor *plus* hyperreflexia and/or hypertonia *plus* temperature above 38ºC plus ocular clonus or inducible clonus (Table I).

Other classifications (Sternbach, Radomski and Dunkley) are also described (9, 12, 13) (**Table II**).

Fortunately, reported cases of SS requiring hospitalization or causing death are rare (14). The first step of treatment is to stop all serotonergic agents (or decrease the dose) and, if clinically necessary, add supportive measures or, in more severe cases, administer anti-serotonergic agents (11, 15).

Neuroleptic malignant syndrome (NMS) is often confused with SS. NMS is classically associated with fever, stiffness, creatinine phosphokinase elevation and autonomic dysfunction as the main criteria (16). Neuroleptic malignant syndrome results from exposure to antipsychotic drugs, which block dopamine receptors or deplete dopamine, such as anti-parkinsonian drugs, and usually appears within 24–72 h after initiation of the drugs. However, in this case, the patient did not take any of this class of drugs.

In conclusion, the presentation of SS is often variable and this probably leads to under-diagnosis. All care providers should take a detailed medication history before adding additional medication, due to the range of medications that may cause SS. In patients with SCI who present with an increase in spasticity, other diagnoses should be excluded, such as urinary tract infection, urinary obstruction, constipation, skin breakdown, deep vein thrombosis, fracture and baclofen withdrawal.

Table II. Sternbach, Randomski and Dunkley diagnostic criteria for serotonin syndrome (SS)

Varying diagnostic criteria for SS		
Sternbach (9) (1991)	Radomski et al. (13) (2000)	Dunkley et al. (12) (2003)
1. Required serotonin agent started or increased 2. At least 3 of the following features are present: • Agitation (restlessness) • Diaphoresis • Diarrhoea • Hyperreflexia • Incoordination (ataxia) • Confusion • Hypomania • Myoclonus • Shivering • Tremor 3. Other cause ruled out 4. A neuroleptic had not been started or increased in dosage	1. Required serotonin agent started or increased 2. Presence of 4 of the following major symptoms or 3 major and 2 of the following minor symptoms: *Major symptoms:* • Diaphoresis • Elevated mood • Fever • Hyperreflexia • Impaired consciousness • Myoclonus • Rigidity • Semi-coma/coma • Shivering • Tremor *Minor symptoms:* • Akathisia • Diarrhoea • Dilated pupils • Hypertension or hypotension • Incoordination • Insomnia • Restlessness • Tachycardia • Tachypnea or dyspnoea 3. Symptoms not related to pre-existing psychiatric disorder or other process	Presence of one of following conditions suggest SS: • Spontaneous clonus • Inducible clonus PLUS agitation or diaphoresis • Ocular clonus PLUS agitation or diaphoresis • Tremor PLUS hyperreflexia • Hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus

The decision to use medications that inhibit serotonin recapture should be taken with caution.

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REFERENCES

1. Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. Lancet Neurology 2008; 7: 1127–1138.
2. Yelnik AP, Simon O, Paratte B, Gracies JM. How to clinically assess and treat muscle overactivity in spastic paresis. J Rehabil Med 2010; 42: 801–807.
3. Haisma J, van der Woude LH, Stam HJ, Bergen MP, Sluis TA, et al. Complications following spinal cord injury: occurrence and risk factors in a longitudinal study during and after inpatient rehabilitation. J Rehabil Med 2007; 39: 393–398.
4. Wissel J, Verrier M, Simpson DM, Charles D, Guinto P, Papapetropoulos S, et al. Post-stroke spasticity: predictors of early development and considerations for therapeutic intervention. PM R 2015; 7: 60–67.
5. Brabec K, Stetkarova I, Vasko P, Mencl L. Intrathecal baclofen in spinal spasticity: frequency and severity of withdrawal syndrome. Pain Physician 2015; 18: 633–641.
6. Stolp-Smith K, Wainberg M. Antidepressant exacerbation of spasticity. Arch Phys Med Rehabil 1999; 80: 339–342.
7. Simon LV, Keenaghan M. Serotonin syndrome. StatPearls Publishing; Treasure Island 2019.
8. Werneke U, Jamshidi F, Taylor DM, Ott M. Conundrums in neurology: diagnosing serotonin syndrome – a meta-analysis of cases. BMC Neurol 2016; 16: 97.
9. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991; 148: 705–713.
10. Guo M, Monir R, Wright A, Holland N. Case of serotonin syndrome initially presenting as diffuse body pain. Am J Case Rep 2018; 19: 1227–1231.
11. Bruggeman C, O'Day CS. Selective serotonin reuptake inhibitor (SSRI) toxicity. StatPearls Publishing; Treasure Island 2018 (updated 2018 Nov 28).
12. 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 2003; 96: 635–642.
13. Radomski JW, Dursun S, Reveley MA, Kutcher SP. An exploratory approach to the serotonin syndrome: an update of clinical phenomenology and revised diagnostic criteria. Medical Hypotheses 2000; 55 : 218–224.
14. Foong AL, Grindrod KA, Patel T, Kellar J. Demystifying serotonin syndrome (or serotonin toxicity). Can Fam Physician 2018; 64: 720–727.
15. Lappin RI, Auchincloss E. Treatment of the serotonin syndrome with cyproheptadine. N Engl J Med 1994; 331: 1021–1022.
16. Fernández M, Lago L, Alonso MG, Guede A, Benavente JL, Olivares JM. Serotonin syndrome versus neuroleptic malignant syndrome: a case report. Actas Españolas de Psiquiatría 2018; 46: 68–74.