# Serotonin Syndrome: A Case Report

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*Serotonin syndrome is a rare but potentially fatal complication of drugs that have effects on central nervous system serotonin. It is characterized by sudden onset of altered mental status, increased neuromuscular activity and autonomic instability. The author reports a child with suprasellar region tumor who presented with depression and obsessive-compulsive disorder and received a combination of sertaline (selective serotonin reuptake inhibitor) and clomipramine (tricyclic antidepressant). Symptoms of serotonin syndrome occurred within 24 hours after increasing the dose of sertaline. The patient's symptoms resolved rapidly with discontinuation of the offending drugs and supportive care.*

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Serotonin syndrome (SS) is an iatrogenic and potentially fatal disorder[1]. It is characterized by altered mental status, abnormal neuromuscular activity and autonomic dysfunction[2]. SS is often reported in patients taking two or more drugs that increase central nervous system serotonin[1-3]. With the increased use of serotonergic active agents treating patients with various psychiatric disorders, and according to the diagnostic criteria of SS proposed by Sternbach[2], SS can be increasingly recognized[4]. Since SS may be fatal, early recognition of this syndrome and termination of the offending medications are important. The author reports a case of SS in a child with a suprasellar region tumor taking a combination of selective serotonin reuptake inhibitor (SSRI) and tricyclic antidepressant (TCA).

**Case Report**

A 12-year-old boy was transferred to Chiang Mai University Hospital with a 1-day history of fever and altered mental status. Six weeks before admission, he presented to a private psychiatrist with a 6-month history of mood lability and aggression with obsessive-compulsive symptoms. He was diagnosed as having depression and obsessive-compulsive disorder. He was placed on sertraline at 25 mg/d, amitryptyline at 10 mg/d, and alprazolam at 0.25 mg for insomnia. Five weeks later, he was admitted to a local hospital with worsening symptoms. Amitryptyline and alprazolam were discontinued and he was started on clomipramine at 25 mg/d. One day prior to admission to the hospital, sertaline was increased from 25 to 50 mg/d. On that day he developed high fever in the range of 39- 39.5°C, and altered mental status. He was then transferred to the hospital.

On arrival at the emergency room, his body temperature was 38.9°C, pulse 100 beats/min, blood pressure 128/77 mm Hg and respiratory rate 30 breaths/min. Examination of the cardiovascular, respiratory and alimentary system were unremarkable. Neurological examination revealed a stuporous boy with closed eyes who moaned or withdrew his extremities only with painful stimulation. His pupils were 6 mm in diameter and reacted to light bilaterally. Other cranial nerve examinations were unremarkable. He moved all 4 extremities with painful stimuli. Rigidity of the lower extremities was greater than the upper ones, and hyperreflexia of the lower extremities as well as sustained ankle clonus and Babinski reflexes were noted. There were no signs of meningeal irritation.

Initial laboratory findings were hemoglobin of 7.7 gm/dL, white blood cell count of 13,200/cumm with 49% neutrophil, 40% lymphocyte, and 5% eosinophils. Blood urea nitrogen was 32 mg%, creatinine 1.9 mg%, Na 176 mEq/L, K 3.1 mEq/L, Cl 136 mEq/L, and bicarbonate 26 mEq/L. Urine analysis revealed specific

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gravity of 1.005 with no cell, proteinuria nor glucosuria. Urine heme was positive. Computed tomography of the brain showed hyperdensity mass at the suprasellar region. Cerebrospinal fluid examination revealed 1 white blood cell, protein 98 mg% and glucose 112 mg%. Serum CPK was 8,598 U/L (normal 0-195). Urine drug screening tests were positive for benzodiazepine, tricyclic antidepressant and negative for phenothiazine and butyrophenones.

Fluctuation of blood pressure between 140/70 to 100/50 mmHg was observed during admission. The patient's condition deteriorated after admission. He was intubated and received respiratory support. A diagnosis of serotonin syndrome was made. All medications from the outside hospital were withdrawn. Intravenous diazepam 10 mg was given once to control rigidity. Supportive treatment included intravenous fluid, respiratory support, and careful monitoring of urine output and serum sodium, along with tepid sponge and acetaminophen for fever. Hypernatremia was treated accordingly. On the following day, he was extubated, his consciousness improved and a resolution of hyperthermia was observed. Rigidity of the lower extremities gradually improved and disappeared within 1 week. After all symptoms subsided, an endocrinologic test revealed central diabetes inspidus. Hypernatremia and polyurea improved after desmopressin treatment. Serum CPK was in the normal range in the second week after admission.

A magnetic resonance image of the brain showed a heterogenous intensity mass at the suprasellar region. A tumor biopsy revealed germinoma. Irradiation of the head and spine was given as adjunctive therapy.

**Discussion**

The presented case report had complex symptoms and signs due to the patient's underlying brain tumor, metabolic disturbances and drug ingestion. His initial presenting symptoms were mood lability, aggression and obsessive-compulsive behaviors. It was difficult to determine whether they were caused by suprasellar germinoma or not, although in rare instances, a tumor in this region may cause similar symptoms[5]. While hypernatremia could had caused altered mental status in this patient, many neurological signs such as hyperthermia, pupillary dilatation, and limb rigidity, could not be simply explained. Hypernatremia and polyurea are best explained by central diabetes inspidus secondary to suprasellar tumor. With the clinical symptoms of altered mental status, rigidity, autonomic disturbance, and history of taking a combination of TCA and SSRI in the absence of other identifiable causes, this patient most likely suffered from SS. His clinical symptoms reached the diagnostic criteria of SS, as proposed by Sternbach[2].

SS was first described in animals and later in humans[2]. The triad features of SS are mental status changes, neuromuscular abnormality and autonomic instability[2,4]. Mental status change is usually the initial presenting symptom[1,4]. Confusion and disorientation are the most common. However, some patients may present with agitation, lethargy or coma[4]. Myoclonus, hyperreflexia, muscle rigidity, restlessness and tremor are common neuromuscular changes. Symptoms of autonomic instability include hyperthermia, diaphoresis, tachycardia, hypertension, nausea/vomiting and dilated pupils[1,4]. Symptoms typically occur within hours, and in most cases (75%) less than 24 hours, after initiation, and dose increment of the offending serotonergic drugs[1,3,4]. Most cases develop this syndrome when 2 or more serotonergic drugs are used in combination[1,4], although cases with monotherapy do occur[6-8]. Many patients may have symptoms after adding a new serotonergic drug to regimens that already had serotonin-enhancing effects, or prematurely adding new serotonergic drugs after discontinuing serotomimetic drugs that have a long half-life[3]. Over 90% of cases, in which drug levels of serotonergic drugs can be obtained, are in acceptable therapeutic ranges[1]. However, intoxication with serotonergic drugs producing SS was also reported[6,7].

Laboratory findings in SS are not diagnostic[1,4]. Elevation of creatine kinase, total white blood cell counts, and transaminase and decrease in bicarbonate level are non-specific to SS and most likely secondary to complications[1,4]. In severe cases, disseminated intravascular coagulation, rhabdomyolysis, renal failure, cardiac arrhythmia, and adult respiratory distress syndrome may occur[1,3,4].

Diagnosis of SS is based on clinical symptoms and signs with the exclusion of other conditions such as infection, metabolic disturbances, and substance abuse or withdrawal[1,2,4]. Diagnostic criteria of SS, as proposed by Sternbach, is based on clinical manifestations[2]. However, mild cases of SS may not have the clinical symptoms to fulfill this criteria and they could be missed[3].

The incidence of SS is unknown[2]. Patients with certain medical problems that demonstrate a decrease in MAO-A activity and in metabolize sero-

tonin, such as hypertension, artherosclerosis, hypercholesterolemia, and connective tissue diseases, may have a higher risk in developing SS[9]. In addition, 7% of the population show a slow metabolism in some SSRIs, thus putting these patients at a higher risk of SS[9].

Agents that could cause SS are those that: increase serotonin synthesis (L-tryptophan), decrease serotonin metabolism (MAOIs), inhibit serotonin uptake (SSRIs, TCA), increase serotonin release (amphetamine, cocaine, reserpine), serotonin receptor agonist (buspirone, lithium) and dopamine agonist (levodopa, bromocriptine)[1,4]. Previous reviews have had an extensive list of medications that could cause SS[1-4]. Some combinations may notably increase the risk of SS: SSRIs in combination with monoamine oxidase inhibitors (MAOIs), TCA and trazodone; MAOIs in combination with TCA and meperidine[1,4].

SS has clinical symptoms that overlap with neuroleptic malignant syndrome (NMS) in several aspects such as mental status change, autonomic dysfunctions and fever[1,3,4]. In SS, symptoms most often develop within 24 hours of initiation, or the increase or adding of new serotonergic drugs. In NMS, symptoms usually occur within 2 weeks after using neuroleptic drugs, while they occur within 24 hours in only 16% after starting or changing neuroleptic drug medications[10]. In addition, myoclonus, hyperreflexia, bowel hyperactivity and pupillary dilatation are commonly found in SS, while rigidity is more common in NMS[1,10].

The pathogenesis of SS in not well understood. SS is thought to result from overstimulation of the serotonin receptor 1A (5-HT1A) and possibly 5-HT2A[9,11]. Stimulation of 5-HT1A results in myoclonus, hyperreflexia, increase in respiratory rate, change in peripheral vasomotor tone and mental status changes. These clinical symptoms are similar to those in patients with SS[9,11]. Other neurotransmitters may be involved in the pathogenesis of SS such as such as cholinergic, dopaminergic, noradrenergic and GABA system[11].

Symptoms of SS are usually self-limited with the discontinuation of serotonergic drugs and supportive care[1-4]. However, pharmacologic therapy may be needed in acute management of SS. Specific treatment has not been systemically studied[4]. Control of muscle rigidity generally resolves hyperthermia. Benzodiazepines are commonly used to control myoclonus and rigidity[1,3]. Other medications used to control rigidity are diphenhydramine, benztropine or nondepolarizing muscle relaxant, which may be used in severe cases[3]. Dantrolene may also be used to control severe cases. Cyproheptadine, methysergide, and propanolol have antiserotonin activities and they have been reported as effective and may shorten the duration of the symptoms[1,3,4]. Supportive care includes intravenous fluids, antipyretics, and cooling. Cardiac arrhythmia, rhabdomyolysis, renal failure or respiratory failure should be treated accordingly. Up to 40% of the patients may require intensive care and 25% need respiratory support[1].

Symptoms of SS are generally resolved within 24 hours after discontinuation of serotonergic drugs in 60-70% of the patients[1,4]. Without complications, all symptoms rarely last for more than 72-96 hours[1]. Duration and severity of the symptoms may be related to the strength, higher dose and half-life of the serotonergic drugs. Deaths occur in 2.4-12% of the patients[4].

Limited information is available on the rechallenge in patients with serotonin syndrome. Although some patients may not develop the syndrome after rechallenging with a lower dose of the offending drug[3], it seems best to avoid all SSRIs and possibly all serotonergic medications. If necessary, avoiding combinations, decreasing the dose, or using a low potency of serotonergic drugs may be appropriate[1].

**Conclusion**

With the increased use of serotonergic drugs for various psychiatric problems, the prevalence of SS may be increasing. Since the clinical symptoms vary and no pathognomonic laboratory findings are found in SS, the diagnosis of SS relies on strong clinical suspicion and exclusion of the other medical and psychiatric problems. Although most cases of SS are benign, deaths from this syndrome do occur. Thus, pediatricians as well as generalists should be aware and diagnose this syndrome early. Prompt recognition, identification, removal of the offending drugs and supportive care are crucial in the management of SS.

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## *Serotonin syndrome: รายงานผู้ป่วย 1 ราย*

***สุรชัย ลิขสิทธิ์วัฒนกุล***

*กลุ่มอาการแทรกซ้อนจากยาซีโรโทนิน หรือ serotonin syndrome เป็นผลข้างเคียงจากการใช้ยาที่มีฤทธิ์ต่อ serotonin ในระบบประสาทส่วนกลาง ภาวะนี้พบได้น้อยมากแต่มีความรุนแรงและผู้ป่วยอาจจะเสียชีวิตจากภาวะแทรกซ้อนนี้ได้ อาการสำคัญของภาวะนี้คือ มีการเปลี่ยนแปลงของสติสัมปชัญญะ อาการหดเกร็งของกล้ามเนื้อลาย ระบบประสาทเสรีทำงานผิดปกติ ในรายงานฉบับนี้เสนอผู้ป่วยเด็ก 1 รายที่มีอาการซึมเศร้า ย้ำคิดย้ำทำ ซึ่งได้รับการรักษาด้วย sertaline (ยาในกลุ่ม selective serotonin reuptake inhibitor) และ clomipramine (ยาในกลุ่ม tricyclic antidepressant) และมีอาการแทรกซ้อนจากยาซีโรโทนินนี้หลังจากเพิ่มขนาดยา sertaline ภายใน 1 วัน จากการตรวจทางห้องปฏิบัติการเพิ่มเติมพบว่าผู้ป่วยไม่มีการติดเชื้อในระบบประสาท แต่พบว่ามีก้อนเนื้องอกในสมอง (germinoma) การรักษาประกอบด้วย การหยุดยาที่ทำให้เกิดภาวะนี้และการรักษาแบบประคับประคองซึ่งได้ผลดี*