

Serotonin Syndrome after Clomipramine Overdose in a Child

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Serotonin syndrome (SS) is a potentially life-threatening condition associated with increased serotonergic activity in central nervous system and may occur during the use of serotonergic drugs. Although increasing frequency of serotonergic drug use in children, pediatricians, emergency medicine and pediatric intensive care specialists have not enough knowledge and experience about SS that is a potentially life-threatening condition. A 12-year-old girl patient was admitted to our emergency room with the history of involuntary contractions on her extremities and alteration of consciousness. Her physical examination showed agitation, hyperthermia, dilated pupils, tremor, increased deep tendon reflexes, positive spontaneous clonus, agitation, flushed skin and diaphoresis, excessive perspiration, and continuous horizontal ocular movements. The patient diagnosed as SS by clinical history, physical and laboratory findings. In this paper, we will discuss SS occurred in a 12-year-old girl after concurrent clomipramine and risperidone use.

KEY WORDS: Child; Clomipramine; Serotonin syndrome; Risperidone; Early diagnosis.

INTRODUCTION

Serotonin syndrome (SS) is a potentially life-threatening condition associated with increased serotonergic activity in central nervous system. SS may occur during the use of serotonergic drugs. Clinical findings include mental state alterations, autonomic hyperactivity and neuromuscular excitability.¹⁾ Neuroleptic malignant syndrome, anticholinergic toxicity, malignant hyperthermia, sympathomimetic agent intoxications, central nervous system infections should be considered in differential diagnosis.^{1,2)} Although there are limited numbers of pediatric case reports concerning SS,³⁻⁹⁾ making the diagnosis of SS is more difficult in children. In this paper, we will discuss SS occurred in a 12-year-old girl after concurrent clomipramine and risperidone use.

CASE

A 12-year-old girl was admitted to emergency room

with the history of involuntary contractions on her extremities and alteration of consciousness. The diagnosis of epilepsy and status epilepticus was made based on her clinical history at onset. The case was hospitalized to pediatric intensive care unit. Heart rate was 140 pulses/minute, her body temperature was 39.5°C, oxygen saturation was 99% and blood pressure was 120/60 mmHg. Her physical examination showed agitation, hyperthermia, dilated pupils, tremor, increased deep tendon reflexes, positive spontaneous clonus, agitation, flushed skin and diaphoresis, excessive perspiration, and continuous horizontal ocular movements. There were no meningeal irritation signs. We suspect the diagnosis of epilepsy and status epilepticus because of incompatible physical signs and symptoms. Detailed clinical history was retaken and physical examination was repeated. Repeated examination showed that nail biting and clues of self-injury behavior. We learned that she has been living with her stepmother and irregularly receiving risperidone for a week prescribed by psychiatry clinic. She had behavioral problems such as stealing money, lying, and escaping from home and school. She had taken nine pills of 75 mg clomipramine tablets for suicidal attempt, which were belonging to her stepmother, in one day. Her abnormal blood chemistry test results were high creatinine kinase and myoglobin levels (creatinine kinase 2,823 U/L [0-145 U/L];

Received: October 27, 2015 / **Revised:** December 24, 2015

Accepted: January 19, 2016

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myoglobin 112 ng/ml [0-7 ng/ml]). Urea, creatinine, Na, K, aspartate transaminase, alanine transaminase, complete blood count, prothrombin time, activated partial thromboplastin time, electroencephalography and brain computed tomography results were normal. The patient has diagnosed as SS. Clomipramine was discontinued, oral diazepam and intravenous hydration was started. Clinical symptoms of the patient disappeared in 24 hours. Two days later, creatinine kinase level regressed to 755 U/L and myoglobin level regressed to 15 ng/ml. The patient was consulted to child and adolescent psychiatry clinic as she had suicidal attempt and thoughts of self-injury. The patient's physical examination and laboratory test results returned to the normal ranges four days later and she was discharged from the hospital under the supervision of child and adolescent psychiatry clinic.

DISCUSSION

Serotonin is one of the most important neurotransmitters affecting mental health.¹⁰⁾ SS is result from serotonergic overstimulation of serotonin receptors. The frequency of serotonergic drug use in pediatric age group is increasing. Serotonergic drugs may use in treatment of many pediatric, psychiatric and neurologic conditions such as migraine, depression, anxiety disorder and obsessive-compulsive disorders. Serotonin is a neurotransmitter produced by presynaptic neurons. There are central and peripheral serotonin receptors. Central serotonin receptors are involved in behavior, mood, sleep-wakefulness cycles, muscular tone and thermoregulation; on the other hand peripheral receptors are involved in gastrointestinal mobility and vascular tone.¹¹⁾ Clinical findings of SS are related to central and peripheral receptors. Although increasing frequency of serotonergic drug use in children, pediatricians, emergency medicine and pediatric intensive care specialists have not enough knowledge and experience about SS that is a potentially life-threatening condition. Making the diagnosis of SS in children is more difficult than adults.¹²⁾ Manifestations may be falsely attributed to another cause in mild cases. On the other hand, children may not be able to communicate enough about symptoms; adolescents may be reluctant to disclose use of psychiatric drugs. There is no mandatory laboratory test or diagnostic method in diagnosis of SS. Diagnosis is mainly based on clinical history and physical findings. In our case, both clinical history and physical examination supported the diagnosis of SS. In the literature, there are three different diagnostic criteria systems for the diagnosis of

SS published by Sternbach,¹²⁾ Radomski *et al.*¹³⁾ and Hunter.¹⁴⁾ The present case meets overall diagnostic criteria defined by three researchers.

The highest risk for the development of SS is using monoaminoxidase inhibitors, which suppress serotonin metabolism, together with these drugs.¹⁵⁾ Herein, we report a 12-year-old girl with SS, which developed during concurrent irregular use of risperidone and clomipramine. Clomipramine, which is a member of tricyclic antidepressant group, is a noradrenalin and serotonin reuptake inhibitor. Risperidone is one of the atypical antipsychotics and the antagonist of dopamine D₂, serotonin 5HT_{2A} and 5HT_{2C} receptors. It is used in patients with behavioral disorder which is usually administrated in doses ranging from 1 to 4 mg/day.^{16,17)} The interaction of these drugs may be facilitated SS in the present case which 2D6 isoenzyme might have been overloaded producing thus a state of serotonin toxicity. More specifically, co-administration of risperidone might have enhanced the plasma concentration of clomipramine.¹⁷⁾ There are limited numbers of pediatric case reports in the literature.

Some of these include three cases due to sertraline use,³⁻⁵⁾ a case due to fluvoxamine use⁶⁾ and a case due to fluoxetine use,⁷⁾ which are antidepressant agents. Grenha *et al.*⁸⁾ defined SS due to concurrent use of sertraline and risperidone in a pediatric case. However, There is no SS case report due to concurrent use of risperidone and clomipramine in literature.

In the treatment of SS, first all of serotonergic drugs must be discontinued and supportive treatment should be started. Most of the patients improve within 24 hours following discontinuation of serotonergic drug.¹¹⁾ Benzodiazepine, cyproheptadine and chlorpromazine are the drugs most commonly used in the treatment of SS. Benzodiazepines are used for muscle rigidity, seizure-like movement disorders and agitations of the patients.¹⁸⁾ The symptoms of the present case, which was monitored in intensive care unit, regressed with fluid replacement and benzodiazepine within 24 hours as described in literature.

In conclusion, SS is a rare condition with high mortality. It should be diagnosed promptly and requires serious monitoring. In the present case, concurrent use of risperidone and high-dose clomipramine use caused SS. To our knowledge, this case is the first reported SS case due to concurrent clomipramine and risperidone use in literature. It is important to warn the parents of children that are using these drugs in terms of dose and symptoms. In addition, SS should be kept in mind for adolescents receiving antidepressant therapy, as they usually attempt

suicide with their drugs. We also presented the case to emphasize that detailed anamnesis and physical examination, which could save the patient's life.

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