DOI: 10.5455/bcp.20111212084626

Neuroleptic Malignant Syndrome Due to Risperidone Overdose in a Child: A Case Report

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ÖZET:

Bir çocukta risperidon aşırı dozuna bağlı gelişen nöroleptik malign sendrom: Bir olgu sunumu

Nöroleptik malign sendrom, nadir görülen ancak ölümcül olabilen, antipsikotik ilaçlara karşı gelişen idiosenkrazik bir reaksiyondur. Bu sendrom hipertermi, kas rijiditesi, akinezi, şuur değişikliği, otonomik disfonksiyon, yüksek kreatinin kinaz seviyesi, lökositoz ile karakterizedir. Bu yazıda, risperidona bağlı nöroleptik malign sendrom gelişen, 2,5 yaşındaki erkek olgu, literatürdeki en küçük olgu olması nedeniyle sunulmuştur.

Anahtar sözcükler: Nöroleptik malign sendrom, çocukluk çağı, risperidon

Klinik Psikofarmakoloji Bülteni 2012;22(1):75-8

ABSTRACT:

Neuroleptic malignant syndrome due to risperidone overdose in a child: a case report

Neuroleptic malignant syndrome is a rare, but potentially fatal idiosyncratic reaction to antipsychotic drugs that manifests itself consistently with hyperthermia, muscle rigidity, akinesia, altered mental state, autonomic instability, high creatine phosphokinase levels, and leukocytosis. We report here a case of risperidone-induced neuroleptic malignant syndrome in a 2.5-year-old boy who was given by mistake 2.5 mg risperidone instead of 0.25mg, as it is the youngest case reported in the literature.

Key words: Neuroleptic malignant syndrome, childhood, risperidone

Bulletin of Clinical Psychopharmacology 2012;22(1):75-8

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Gönderme tarihi / Date of submission: 05 Ekim 2011 / October 05, 2011

Kabul tarihi / Date of acceptance: 12 Aralık 2011 / December 12, 2011

Bağıntı beyanı:
S.S., S.S.B.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
S.S., S.S.B.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Neuroleptic malignant syndrome (NMS), the most feared complication of neuroleptic drugs, is rare, but can be fatal and requires emergency treatment (1). NMS has first been defined by Delay and Deniker in the 1960s (2). NMS develops as a result of widespread derangement or stress of the neuromuscular, autonomic, and thermoregulatory balance (3). This clinical picture can develop following the use of highly potent neuroleptics but can also follow the use of neuroleptics with low potency (4). NMS usually appears within the first 20 days after drug initiation but can appear at any stage of the treatment and even after a single dose (5).

Clinically, NMS resembles to advanced catatonia. The diagnostic features are high fever, altered consciousness, rigidity, tachycardia, labile blood pressure, diaphoresis, akinesia, and dyskinesia. The clinical picture is accompanied by high creatine phosphokinase (CPK) levels, leukocytosis, nonspecific EEG changes, dysphagia, incontinence, and aphasia (6-8). Levenson has reported 3 major and 6 minor criteria for NMS diagnosis (Table 1). The presence of 3 major criteria or 2 major and 4 minor criteria indicates NMS (9).

NMS is reported to occur twice as frequently in males and to be much more common in adults compared to children (10,11). The rare occurrence of NMS cases in childhood could be due to the less frequent neuroleptic drug use in this age group (12). However, case reports of NMS development

Table 1: Diagnostic Criteria of the Neuroleptic Malignant Syndrome

Major findings
- fever
- rigidity and other extrapyramidal symptoms
- elevated creatine phosphokinase level

Minor findings
- tachycardia
- abnormal arterial blood pressure
- tachypnea
- altered consciousness
- leukocytosis
- diaphoresis

in children and adolescents following the use of drugs such as olanzapine, quetiapine, ziprasidone, risperidone, and alimemazine have increased in recent years (4,13-17).

We present a 2.5-year-old case who developed NMS following a single dose of risperidone as it is the youngest reported case to the best of our knowledge.

CASE REPORT

A 2.5-year-old male patient was referred to our emergency room due to altered consciousness. The medical history revealed that risperidone had been started by a child psychiatry specialist at another center for hyperactivity. The child had developed flaccidity, sleepiness and absent mindedness 3 hours after receiving the first risperidone dose. The symptoms gradually increased and soon he was not able to talk. He was referred to our emergency department for further evaluation and treatment from the healthcare center he was initially taken.

The past medical and family history revealed nothing of significance and the physical examination showed that he had altered consciousness, was sleepy and was not fully cooperating. He could open his eyes with difficulty on verbal command and he could localize painful stimuli but could not talk and could only make meaningless sounds. There was decreased facial movements and mimicry when he tried to cry after painful stimuli. His Glasgow coma scale score was 12. The pupils were equal and bilateral direct and indirect pupillary reflexes were present. Nuchal rigidity could not be clearly determined due to the presence of increased muscle tonus. The cornea and gag reflexes were present. No cranial nerve pathology was observed. Muscle tonus had increased slightly in the extremities but both sides were similar on examination. Respiration was tachypneic with respiratory rate of 40 breaths/min and normal respiratory sounds. The apical heart rate was 140/min and rhythmic. Blood pressure was 90/55 mmHg. There was no organomegaly or other systemic pathology.

Questioning the mother in detail revealed that she had mistakenly administered a dose of 2.5mg risperidone instead of the prescribed 0.25 mg.

The patient's fever gradually increased (over 39°C axillary) on monitoring. Contractions increased throughout the body within hours and were most marked in the face. Facial dyskinesia was observed. Tremor and choreoathetoid movements developed in the extremities. Sinus tachycardia reaching 205/min that was not consistent with the fever developed. Intermittent tachypneic attacks continued. The patient's contractions and symptoms started to show temporary recovery when the fever started to decrease following the application of wet compresses.

Initial laboratory analysis revealed a white blood cell count of 5.500 cells/mm3. Serum electrolytes were within normal ranges and included a sodium level of 140 mEq/L; potassium, 4.6 mEq/L; and calcium 9.6 mEq/L. The blood glucose was 88 mg/dl. Renal and hepatic function test levels were also within the relevant normal range. Initial arterial venous blood gases showed a pH of 7.4; carbon dioxide tension of 29 mmHg; bicarbonate 17.6 mEq/L and, base excess, - 5.17 mmol/L. The serum creatinine phosphokinase (CPK) level was 80 U/L on admission and 256 U/L 3 hours later. Urinalysis, chest radiograph, and cranial CT revealed no significant findings.

Once the patient was diagnosed as NMS with the above sign and symptoms, supportive treatment including fluid electrolyte therapy, antipyretics, and carbidopa/ levodopa were started. However, the patient was later transferred to the intensive care unit for increasing fever and contractions and more frequent tachypneic attacks in following 12 hours. We learned that he was given IV midazolam at the ICU and discharged 2 days later following recovery.

DISCUSSION

The incidence of NMS following neuroleptic treatment increases with adolescence but it can be seen at any age (6). Edna et al. reviewed all published case reports on children and adolescents between 1973 and 2001 (18). Only one published case younger than 5 years of age has been reported, as a 3-year-old boy with NMS reported in 1973 (19). Since then, another 4-year-old boy with a history of oppositional defiant disorder, mood disorder, and XYY syndrome where the diagnosis of NMS was secondary to quetiapine therapy has been reported in 2010 (20). This case is the youngest reported case to the best of our knowledge in the literature so far . NMS develops especially following the use of highly potent neuroleptics, as in our case (17,21). One must always take the possibility of NMS development in children using highly potent neuroleptics into account as it is a rare but life-threatening condition.

The pathogenesis of NMS in risperidone treatment has not been clarified, but a disturbance of dopamine

metabolism in the brain may play an important role (22). Risperidone, a benzisoxazole-derived antipsychotic with highly effective serotonin receptor blockage and dose-related D2 receptor blockage, is not expected to cause NMS at low doses. However, numerous cases of NMS have been reported with atypical antipsychotic medications including clozapine, olanzapine, quetiapine, and risperidone in recent years (23). Nisijiama at al suggested that a disturbance of serotonin metabolism could be implicated (24).

Although high doses and long-term use of antipsychotics increase the NMS risk (5), an idiosycratic reaction independent of the dose is also reported (16). Our patient had received a single but high dose of risperidone. The mother had administered 10 times the recommended dose to the child. The syrup form of risperidone has the dose range written on the applicator but it is important for the physician to mark the dose and provide detailed information to the family to protect the child from fatal complications and ensure proper treatment, taking the family's educational level into account.

Most cases of risperidone-induced NMS have occurred within the first month of risperidone use (25). The risk increases in the first two days of antipsychotic treatment and after dose increases (1). Our case started to suffer from NMS-related flaccidity, sleepiness, absent mindedness and difficulty speaking 3 hours after risperidone use and the clinical picture got worse after 12 hours, lasting a total of 3 days.

Although the use of major and minor criteria is recommended, the NMS diagnosis is a clinical one and the differential diagnosis is very important. NMS can appear in children and adolescents with a clinical picture similar to that of adults including fever, tachycardia, and rigidity (4,16). It is reported that children suffer from tremor less often and dystonia more often than adults (4). Chung et al have reported an adolescent case where diaphoresis without high fever or rigidity was the main sign (16). Our patient was diagnosed with NMS according to the Levenson diagnostic criteria (9). He had been brought to the emergency service with altered consciousness. Tachycardia, tachypnea, hypotension, increasing fever, and muscle rigidity developed during monitoring. The CPK level was within the normal range at first but increased 3-fold within 3 hours. The serum leukocyte count was within normal limits at first. We do not know the later values of CK and leukocytes as the patient was transferred to the ICU but the CK had started to increase. The presence of 2 major (fever, rigidity and extrapyramidal symptoms) and 4 minor criteria (tachycardia, abnormal arterial blood pressure, tachypnea, and altered consciousness) from the table was accepted to be sufficient to make a diagnosis of NMS (9).

The differential diagnosis of NMS includes central nervous system (CNS) and systemic infections, CNS masses, pheochromocytoma, idiosyncratic drug reactions, malignant hyperthermia, organic phosphorus poisoning, rhabdomyolysis, and lethal catatonia (6). We did not consider any other diagnoses for our 2.5-year-old patient as the symptoms had started right after initiating antipsychotic treatment, there was nothing of significance in the personal history and there was no finding related to the other possible disorders.

The mortality rate of NMS patients without specific treatment is approximately 21% (15,26). Since NMS is a potentially fatal disease, treatment initiatives should be started immediately. The general principle of NMS treatment is to stop antipsychotic treatment and start supportive treatments (hydration, keeping fever under control, protecting the airway) after admitting the patient as a life-saving measure (27). The treatment of choice is to reverse the hypodopaminergic state by administering levodopa, bromocriptine, dantrolene, and benzodiazepine derivates as the central dopaminergic receptors are blocked in NMS. Levodopa/Carbidopa is often effective in reversing the hyperthermia (28). Dantrolene and bromocriptine are recommended for the control of muscle rigidity (29,31). Muscle relaxants such as dantrolene are effective on the muscle rigidity and high fever and decrease NMS duration (32,33). Silva et al. evaluated pediatric NMS cases and reported that anticholinergics, L-dopa and especially bromocriptine are as effective as in adults in children but dantrolene and electroconvulsive therapy are not effective in children under 18 years of age although effective in adults (4). We rapidly initiated treatment with fluids and electrolytes, antipyretic, wet compresses and carbidopa/levodopa treatment in our patient. Dantrolene was not used as it was not available at the moment. However, the patient deteriorated rapidly and was transferred to the ICU where he was given midazolam IV for treatment and recovered within two days.

In conclusion, NMS can also be seen in young children. It is essential to be careful when using neuroleptics, and to talk to the family in detail about the drug dose to be administered and potential side effects of treatment.

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