Neuroleptic malignant syndrome associated with metoclopramide in a child

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Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal complication of treatment with antipsychotic medication. NMS has also been associated with non-neuroleptic agents that block central dopamine pathways, such as metoclopramide, amoxapine and lithium. Metoclopromide has antidopaminergic properties and is a rare but well-recognized perpetrator in the development of NMS. NMS has a constellation of signs and symptoms, including hyperthermia, muscle rigidity, autonomic instability, tachycardia, tachypnea, diaphoresis, hypertension and altered mental status. We present a 2-year-old girl who developed neuroleptic malignant syndrome after metoclopromide therapy. High-dose metoclopromide was given to our patient, and it is very likely that she was dehydrated while using metoclopromide, as she developed NMS two hours after treatment. The patient was discharged on the sixth day after admission to our hospital, having been cured. In summary, NMS developed in this patient very soon after metoclopromide treatment. NMS is a life-threatening emergency; if not recognized, or left untreated, it may be fatal. Therefore, early recognition of the developing signs and symptoms, along with a thorough medical history, is of great importance.

Key words: vomiting, metoclopromide, neuroleptic malignant syndrome, children.

Neuroleptic malignant syndrome (NMS) has a constellation of signs and symptoms including hyperthermia, muscle rigidity, autonomic instability, tachycardia, tachypnea, diaphoresis, hypertension and altered mental status[1]. NMS is a rare but potentially fatal complication of treatment with antipsychotic medication, first described by Delay et al.[2] in 1968. The incidence is 0.5% to 1.4% of patients exposed to neuroleptic agents[3,4]. However, the true incidence in children is unknown. NMS has also been associated with non-neuroleptic agents that block central dopamine pathways, such as metoclopramide, amoxapine, and lithium[5]. Metoclopramide is an antiemetic drug that is used in the treatment of gastroesophageal reflux in children and against nausea and vomiting in children with gastrointestinal system infections and children who are receiving chemotherapy [6]. Common adverse drug reactions associated with metoclopramide therapy include restlessness (akathisia) and acute dystonic reactions. Rare but serious adverse drug reactions associated with metoclopramide therapy include agranulocytosis, supraventricular tachycardia, neuroleptic malignant syndrome, akathisia and tardive dyskinesia[7].

We present a 2-year-old girl who developed neuroleptic malignant syndrome after metoclopromide administration.

Case Report

A 2-year-old girl was admitted to our pediatric emergency department with fever, whole body spasms and altered mental status. The patient had vomiting and diarrhea two days before hospital admission. After an increase in vomiting and lack of feeding, she was taken to a local hospital, where she was given 10 mg of metoclopromide intramuscularly and then discharged. Two hours after arriving home, the patient had a high temperature, full-body

spasms and changes in consciousness. There had been no previous health concerns and she had not been on medication before.

The initial examination in the pediatric emergency department had these findings: body temperature, 39.6 ^{0}C; heart rate, 161/min; respiratory rate, 44/min; blood pressure, 102/71 mmHg. Her condition was unstable; she was lethargic and had tachycardia and tachypnea. There were spasms/rigidity in the whole body.

Laboratory tests showed the following results: white blood cell count, 7000/mm^3; hemoglobin, 14.5 g/dl; platelet count, 127000/mm^3; glucose, 206 mg/dl; blood urea nitrogen, 23 mg/dl; creatinine, 0.93 mg/dl; uric acid, 12.8 mg/dl; total bilirubin, 1.05 mg/dl; albumin, 4.1 g/dl; sodium, 134 mEq/L; potassium, 3 mEq/L; calcium, 9.5 mg/dl; aspartate aminotransferase, 57 U/L; alanin aminotransferase, 21 U/L; prothrombine time (PT), 18.8 seconds; activated partial thromboplastin time (aPTT), 41.4 seconds; international normalized ratio, 1.71; fibrinogen, 2.06 g/L; D-dimer, 722 ng/ml; C-reactive protein, 137 mg/L. Creatinine phosphokinase (CPK) was 486 U/L (normal values, 26-140). Neuroleptic malignant syndrome was suspected due to the patient's high fever and rigidity, the changes in her consciousness, the recent use of metoclopramide and her high creatinine phosphokinase level.

A normal saline bolus was given at 20 ml/kg and, in addition, maintenance fluid + 10% deficit ½ normal saline intravenous fluid was given. Also, one dose of biperiden at 0.04 mg/kg was given to the patient intramuscularly. The rigidity disappeared within 3 hours. The patient was given diphenhydramine in 4 doses at 5 mg/kg/day. Whole-body hypothermia was applied. Since the patient's acute phase reactants were high, she was given ceftriaxone to prevent potential sepsis. Since her PT and aPTT were also high, she was given vitamin K and fresh frozen plasma at 10 ml/kg.

Urinalysis and stool microscopy were normal. Stool was negative for adenovirus and rotavirus. Stool, urine and blood cultures were negative for bacteria.

During follow-up, the patient's laboratory results returned to normal within 3 days. The patient's symptoms and follow-up findings during the first 3 days after metoclopramide administration are shown in Fig. 1. On the first day, the patient's body temperature fell; the change in her consciousness resolved within 36 hours. There was no repetition of the rigidity. The patient's electroencephalography was normal. She was discharged in good health on the sixth day after admission to our hospital.

Discussion

We diagnosed metoclopramide-related NMS in our patient because of high fever, rigidity all over the body, a change in the level of consciousness and a high level of creatine phosphokinase. Dystonic reactions associated with metoclopramide, usually involving the face, neck and back muscles, are more often observed as local findings but do not lead to changes in consciousness. Metoclopramide-related NMS is a rarely observed side effect of this medication[7]. Delay and Deniker[2] first described neuroleptic malignant syndrome in 1968. It is related to other extrapyramidal syndromes such as akathisia, dystonia, parkinsonism and tardive dyskinesia. Metoclopromide has antidopaminergic properties and is a rare but well-recognized perpetrator in the development of NMS[8,9]. In our country, metoclopromide is often used in primary care settings as a first-choice drug for the treatment of vomiting. NMS developed in our patient after high-dose metoclopromide use.

Neuroleptic malignant syndrome can occur at any age. Silva et al.[1] reviewed the literature on NMS in children. They found 77 cases in patients ranging in age from 0.9 to 18 years, with only 10 patients younger than 10 years of age. NMS can be fatal. It develops insidiously over days. Initial signs include changes in mental status and extrapyramidal function. Sinus tachycardia or oscillation of the blood pressure is very common. Muscle rigidity that can be described as "lead pipe," hyperthermia and increased CPK are major manifestations of NMS. Myoglobinuric renal failure due to rhabdomyolysis and respiratory distress are serious complications of NMS[10]. High-dose metoclopromide was given to our patient, and it is very likely that she was dehydrated while using metoclopromide, as she developed NMS two hours after treatment.

The treatment of NMS starts with the

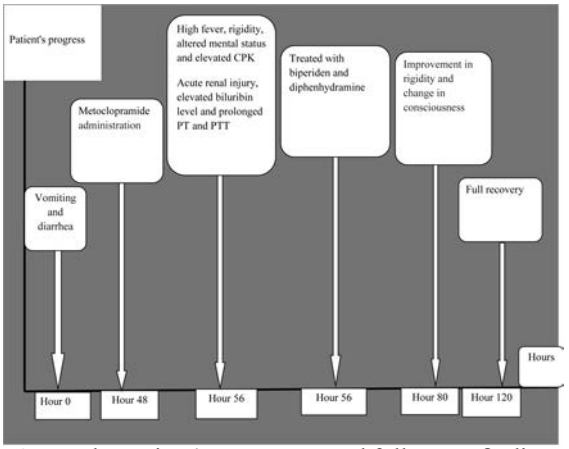

Fig. 1. The patient's symptoms and follow-up findings during the first 3 days after metoclopropamide administration.

discontinuation of neuroleptic agents as well as the initiation of supportive treatment to control hyperthermia, sustain vital functions and prevent renal failure. Medications such as amantadine, bromocriptine and levodopa have been used in the treatment of NMS. Dantrolene, which inhibits muscle contraction and heat production, has been reported as effective in 81% of patients with NMS. It has also been suggested that electroconvulsive therapy (ECT) is therapeutic[10]. We provided supportive care to our patient. Whole-body hypothermia was also applied. Mortality rates may be as high as 20-30% due to dehydration, aspiration, kidney failure and respiratory collapse[11]. Our patient had dehydration and renal failure. After treatment, she was discharged in good health on the 6th day.

In summary, NMS developed in this patient very soon after metoclopromide treatment. NMS is a life-threatening emergency; if not recognized or left untreated it may be fatal. Therefore early recognition of developing signs and symptoms, along with a thorough medical history, is of great importance. Clinicians should refrain from using metoclopromide in the treatment of vomiting in children.

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