JPPT | Case Report

Suspected Overlap Between Serotonin Syndrome and Neuroleptic Malignant Syndrome in a Child Treated With Metoclopramide?

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A 19-month-old child presented with fever and acute neurological deterioration with hypertonia, tremors, and clonus 1 day after starting metoclopramide. The clinical course of the patient was suggestive of neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS), which can both be triggered by metoclopramide. This first pediatric report of an overlap between NMS and SS associated to metoclopramide highlights the importance of considering this new entity and its consequences on treatment.

ABBREVIATIONS CK, creatine kinase; IV, intravenous; NMS, neuroleptic malignant syndrome; PO, orally; SS, serotonin syndrome

KEYWORDS child; metoclopramide; neuroleptic malignant syndrome; pediatric; serotonin syndrome

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Introduction

Neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS) are rare but potentially fatal adverse drug reactions associated with antipsychotic and antiemetic medications. Accurate estimation of NMS and SS incidence is hindered by underrecognition or underreporting. Neuroleptics are most commonly involved in NMS (incidence, 0.02%–3%),[1] while selective serotonin reuptake inhibitors are the most common trigger of SS (unknown incidence during regular use; 16% to 18% in case of overdose).[2] Antiemetics with antidopaminergic activity such as metoclopramide and domperidone are also commonly associated with NMS.[1] Prompt recognition is of paramount importance, as mortality rate is approximately 10% for SS and between 10% and 20% for NMS.[1,3]

Syndromes of SS and NMS are mainly diagnosed clinically but attenuated or incomplete presentation of both syndromes can obscure the diagnosis. Also, recent case reports describe the overlap of NMS and SS in adults, which represent a new diagnostic challenge.[4–6]

We present the evolution of a 19-month-old child after metoclopramide initiation.

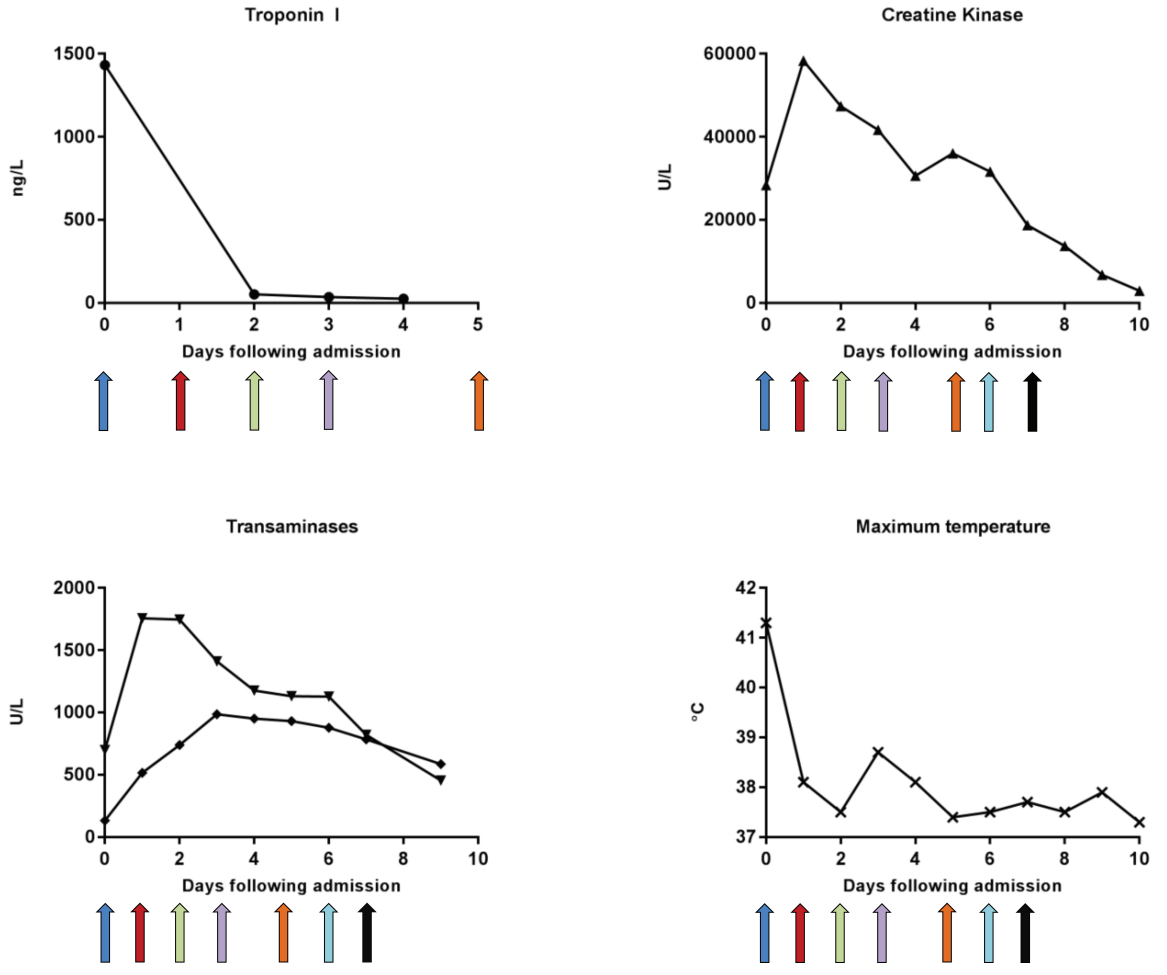
Case

A 10-kg, 19-month-old male known for severe encephalopathy and spastic quadriplegia secondary to severe birth anoxia was hospitalized for a gastrostomy change. The patient was born at 41 1/7 weeks of gestation by induced delivery with a birth weight of 3.4 kg and an Agpar score of 2-1-0. He was resuscitated and underwent cooling for 4 days. There was no prenatal drug exposure. He had global developmental delay with cortical blindness and conductive deafness. He presented severe gastroesophageal reflux disease, hypertension, and focal seizures in the neonatal period. His dysphagia, responsible for various episodes of aspiration pneumonia, motivated the treatment of hypersialorrhea with botulinum toxin and the placement of a gastrojejunostomy tube. He developed a chronic respiratory insufficiency with home oxygen thought to be due to chronic lung aspiration.

The patient was hospitalized to change his gastrojejunal tube for a gastrostomy. Two weeks after his hospital discharge, oral metoclopramide was initiated owing to poor gavage tolerance and absence of weight gain (0.1 mg/kg/dose 3 times a day). The patient received 6 doses and the parents decided to stop the medication owing to irritability and agitation that resolved within 24 hours after discontinuation. Metoclopramide was restarted 5 days later and increased to 4 times a day owing to continuing feedings tolerance. He had intermittent fever over the following 2 weeks and the parents consulted the pediatrician for fever and irritability.

Three days later, he was admitted to the hospital (day 0) with pneumonia associated with high fever (40°C), tachycardia (220 bpm), and tachypnea (45–60 breaths per minute). He also presented new onset severe spasticity, spontaneous tremors, and impaired level of consciousness. His home medications prior to admission were amoxicillin-clavulanic acid (440 mg orally [PO] twice daily), metoclopramide (1 mg PO 4 times a day), glycopyrrolate (500 mcg PO 3 times daily), ranitidine (50 mg PO twice daily), nitrazepam (1 mg PO twice daily), amlodipine (1 mg PO twice daily), and vitamin

Figure 1. Temperature, laboratory analyzes and medication therapy management within the first 10 days of hospitalization



◆ ALT, alanine aminotransferase; ▼AST, aspartate aminotransferase; Treatments initiated at Day 0: tazobactam/piperacillin, calcium gluconate, nitrazepam, cholecalciferol, ranitidine, dexmedetomidine, cefotaxime, vancomycin; Treatments initiated at Day 1: Potassium chloride; Treatments initiated at Day 2: Dexamethasone, furosemide, glycopyrrolate, dantrolene; Treatments initiated at Day 3: Levetiracetam; Treatments initiated at Day 5: Midazolam; Treatments initiated at Day 6: Propofol; Treatments initiated at Day 7: Amlodipine

D3 (400 units PO once daily). He was admitted to the pediatric intensive care unit and treated with high-dose salbutamol, oxygen, IV fluids, and empiric antibiotics (piperacillin/tazobactam and vancomycin). Myocarditis was suspected as based on highly increased troponin I (1431 ng/L on day 0) and creatine kinase (CK) (28,358 U/L on day 0 and 58,304 U/L on day 1) levels. Liver tests showed elevations of alanine aminotransferase (from 133 on day 0 to 986 on day 3) and aspartate aminotransferase (from 699 at day 0 to 1755 at day 1). Figure 1 shows the evolution of troponin I levels, CK, temperature, and liver transaminase during the first days of hospitalization and concomitant medical management.

He was intubated for respiratory failure and was treated with inotropes for a transient cardiovascular instability. Metoclopramide was discontinued. Meningitis was ruled out and viral and bacterial workups were negative. Despite being intubated, he presented several episodes of acute desaturation associated with tremors, spontaneous clonus, and important rigidity. Intravenous dantrolene (0.5 mg/kg 4 times a day incremented to 1 mg/kg 4 times a day after 24 hours) was started on day 2 with resolution of the rigidity within 24 hours but ongoing hypertonia and hyperreflexia. The CK level decreased gradually to reach normal value on day 21. Hyperhydration combined with urine alkalinization therapy with sodium bicarbonate was administered to prevent acute renal failure secondary to rhabdomyolysis. The fever resolved on day 4 of hos-

Table 1. NMS Diagnostic Criteria: Expert Panel Consensus

Criteria	Priority Score
Exposure to dopamine antagonist, or dopamine agonist withdrawal, within past 72 hours	20
Hyperthermia (>100.4°F or >38.0°C on at least 2 occasions, measured orally)	18
Rigidity	17
Mental status alteration (reduced or fluctuating level of consciousness)	13
Creatine kinase elevation (at least 4 times the upper limit of normal)	10
Sympathetic nervous system lability, defined as at least 2 of the following: Blood pressure elevation (systolic or diastolic ≥25% above baseline) Blood pressure fluctuation (≥20 mm Hg diastolic change or ≥25 mm Hg systolic change within 24 hours) Diaphoresis Urinary incontinence	10
Hypermetabolism, defined as heart rate increase (≥25% above baseline) AND respiratory rate increase (≥50% above baseline)	5
Negative workup for infectious, toxic, metabolic, or neurological causes	7
Total score	100

NMS, neuroleptic malignant syndrome

pitalization. Dantrolene was discontinued after 2 days. His condition improved and he was discharged from the pediatric intensive care unit 10 days after admission.

Discussion

Metoclopramide is an antiemetic and prokinetic, combining dopaminergic antagonist properties and serotonergic activity and can therefore trigger NMS and SS.[7] NMS is triggered by dopamine receptor antagonism that induces a temperature raise and dysautonomia in the hypothalamus and muscular rigidity and tremor in the nigrostriatal pathways.[1] Serotonin syndrome is usually triggered by an increase in serotonin level affecting temperature control and regulation of attention and behavior.[3]

Drug-induced fever is often overlooked and should be suspected when administering any at-risk drugs. Children with neurological impairment are at increased risk of infection (mainly pneumonia) and drug-induced fever due to polypharmacy and regular use of hyperthermia-triggering drugs. Therefore, in these patients, any suggestive neurological change in the presence of fever should raise concern about drug-induced fever. In our patient, the whole clinical picture suggests that metoclopramide was the causative agent: the temporal relationship between initiation and the onset of symptoms, the absence of another etiology, the fast reversal of symptoms with metoclopramide discontinuation, the positive rechallenge, and the suggestive clinical and laboratory picture. The Naranjo scale used to assess the likelihood of drug-induced reaction showed a causality score of 9, indicating a definite association between metoclopramide and the clinical picture.[8] Despite being regularly used to assess adverse drug reactions in

Table 2. Suggested Diagnostic Criteria for SS: Sternbach Criteria

Coincident with the addition of or increase in a known serotonergic agent to an established medication regimen, at least 3 of the following clinical features are present:

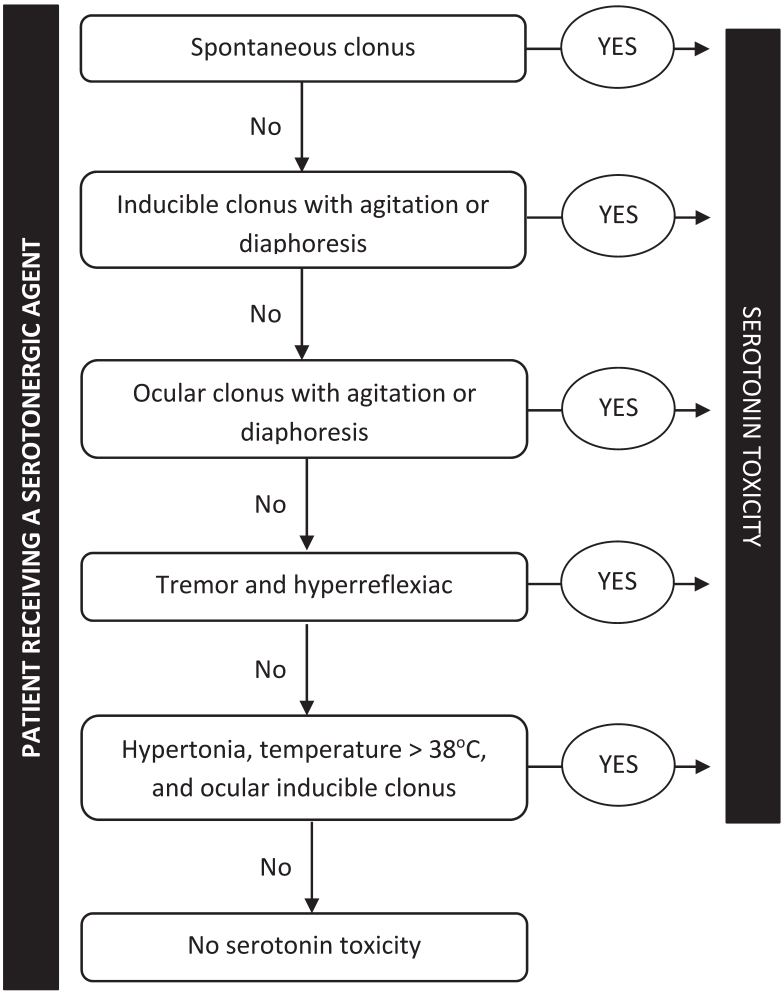
- Mental status change (confusion, hypomania)
- Agitation
- Myoclonus
- Hyperreflexia
- Diaphoresis
- Shivering
- Tremor
- Diarrhea
- Incoordination
- Fever

Other etiologies (e.g., infections, metabolic, substance abuse or withdrawal) have been ruled out.

A neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed above.

SS, serotonin syndrome

Figure 2. Hunter Serotonin Toxicity Criteria: decision rules.



children, the Naranjo scale has not been specifically validated in pediatrics, which may theoretically induce a bias in the evaluation.[9,10]

Another potential trigger of his fever was glycopyrrolate, a muscarinic antagonist, competitively inhibiting acetylcholine receptors, used to control excessive drooling in children with neurological impairment. Glycopyrrolate can induce anticholinergic syndrome, including hyperthermia and behavioral changes, and may therefore have contributed to the symptoms but cannot explain the whole clinical presentation. Indeed, creatine kinase elevation, rigidity, myoclonus, hyperreflexia, and tremor are not encountered with anticholinergic syndrome.[11–14]

Various potential risk factors for NMS development were present in our patient: his complex medical condition, the use of multiple drugs with central effect, and possibly his young age.[15,16] No personal or familial history of NMS was found and therefore genetic susceptibility is unlikely. Table 1 presents diagnostic criteria of NMS (according to the international consensus group[17]) and Table 2 presents SS diagnosis (according to Sternbach criteria). Figure 2 depicts the Hunter Serotonin Toxicity Criteria.[18,19] NMS diagnostic criteria include exposure to a known precipitating drug, suggestive clinical and laboratory markers, and the exclusion of alternative causes. Each criterion is weighted and the final score reflects the likelihood of NMS diagnosis. Despite being increasingly described in the literature,[4–6] the overlap between SS and NMS is difficult to diagnose with the current definition.[20] Indeed, the presence of a potential alternative cause decreases the likelihood of NMS and excludes the diagnosis of SS, using Sternbach criteria (but not using the Hunter criteria). Table 3 lists SS and

Table 3. NMS and SS Diagnostic Criteria Fulfilled or Not by the Patient

NMS Diagnostic[17]
Criteria fulfilled
Hyperthermia
Rigidity
Mental status alteration
Creatine kinase elevation
Blood pressure elevation
Blood pressure fluctuation
Hypermetabolism
Criteria not fulfilled
Diaphoresis
Urinary incontinence
SS Diagnostic[18]
Criteria fulfilled
Mental status change
Agitation
Myoclonus
Hyperreflexia
Tremor
Fever
Criteria not fulfilled
Diaphoresis
Shivering
Diarrhea
Incoordination

NMS, neuroleptic malignant syndrome; SS, serotonin syndrome

NMS symptoms presented by the patient and shows that he fulfilled the criteria for both. The severe hyperthermia, rigidity, and laboratory markers (very high CK and transaminase levels) were highly suggestive of NMS but can also be found in SS.[17,18] On the other hand, tremor, spontaneous clonus, and hyperreflexia are typically encountered in SS.[18]

When possible, diagnosing a specific syndrome is important as it has implications on treatment. Treatment common to both syndromes includes discontinuation of the causative drug, supportive care including temperature control by external cooling, and benzodiazepine.[3,17]

Additional treatments are more specific. Dantrolene, which may be favorable in case of severe rigidity, is the most effective drug treatment for NMS. It induces muscle relaxation by inhibiting calcium release from the sarcoplasmic reticulum and reduces hyperthermia.[17,21] Bromocriptine, a dopamine agonist, is used in NMS to reverse dopaminergic antagonism.[3] Severe cases of SS are treated with serotonin$_{2A}$ antagonists such as cyproheptadine or chlorpromazine.[3,22,23] Cyproheptadine is preferred for its more favorable adverse effect profile.[24] In case of overlap between NMS and SS, the treatment of SS remains unchanged but as bromocriptine has been associated with SS, it should ideally be avoided in the treatment of NMS.[20,21]

We found 4 cases of NMS associated with metoclopramide in pediatrics.[25,27–29] No case presents metoclopramide-related SS in children and none of the pediatric cases of NMS suggested SS as a differential diagnosis. Nevertheless, the clinical course in the cases reported by Brower et al[25] and Yaman et al[27] with hyperreflexia and the rapid onset of symptoms is very suggestive of SS. Therefore, we hypothesize that the lack of published SS cases may be due to an underrecognition of this syndrome in children. Cases of overlap between SS and NMS have been reported in adults[4–6] and recently in children.[30] Drugs involved were serotonergic antidepressants, neuroleptics, and ecstasy. Treatment included benzodiazepine, dantrolene, and cyproheptadine. To our knowledge, this is the first report of an overlap of NMS and SS in a child, associated with metoclopramide.

The clinical description of typical features of both syndromes suggests that they may coexist. Excluding SS in case of possible NMS (as in Sternbach criteria) does not take the pharmacologic action of precipitating drugs into account, as both pathways can be triggered simultaneously.

Owing to the occurrence of neurological adverse drug reaction such as extrapyramidal symptoms, metoclopramide is now contraindicated in children younger than 1 year in the European Union and in Canada and its use in children older than 1 year is only recommended as a second-line option.[31,32] This case report further highlights that metoclopramide should be used with caution in pediatrics.

Conclusion

This case report details the first case of an overlap between NMS and SS associated with the use of metoclopramide in a child. This overlap should be suspected, especially in high-risk patients with polypharmacy and neurologic comorbidities. This case highlights the importance of reporting adverse drug reactions in the pediatric population, which is often excluded from drug studies, and the need for adequate postmarketing studies and surveillance to improve safety.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent Given the nature of this study, the project was exempt from institution review board/ethics committee review, but informed consent was obtained.

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