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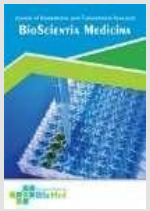

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Metoclopramide-Induced Extrapyramidal Syndrome in a Child: Diagnostic Challenges and Management

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A B S T R A C T

Background: Metoclopramide, a dopamine D2 receptor antagonist, is used for its antiemetic and prokinetic properties. However, its use in pediatric populations is restricted due to a significant risk of neurological adverse effects, particularly acute extrapyramidal symptoms (EPS). These reactions, including acute dystonia, are more frequent in children compared to adults, posing diagnostic and management challenges. **Case presentation:** We report the case of a 10-year-old girl who presented with acute torticollis and oculogyric crisis following the administration of metoclopramide syrup for fever and vomiting. The symptoms developed approximately one day after initiating the medication. Physical examination and basic laboratory results were otherwise largely unremarkable, apart from elevated white blood cells suggestive of an underlying infection. A diagnosis of metoclopramide-induced acute extrapyramidal syndrome was made. **Conclusion:** The patient experienced rapid resolution of symptoms within 30 minutes following the administration of intravenous diphenhydramine. Metoclopramide was discontinued, and she was discharged without symptom recurrence. This case underscores the importance of recognizing metoclopramide-induced EPS in children, the diagnostic difficulties posed by its varied presentation potentially mimicking other serious neurological conditions, and the effectiveness of prompt management with anticholinergic agents like diphenhydramine. Clinicians must maintain a high index of suspicion, adhere to restrictive prescribing guidelines for metoclopramide in pediatrics, and consider safer antiemetic alternatives.

1. Introduction

Metoclopramide is a pharmaceutical agent widely employed in clinical settings due to its combined antiemetic and prokinetic actions. The drug's therapeutic effects are primarily mediated through the blockade of dopamine D2 receptors. This blockade occurs both centrally at the chemoreceptor trigger zone (CTZ) within the area postrema of the medulla oblongata and peripherally within the gastrointestinal tract. In addition to dopamine D2 receptor antagonism, metoclopramide also exerts effects through the antagonism of serotonin 5-HT3 receptors and agonism of 5-HT4 receptors. The composite action of these mechanisms results in the inhibition of the vomiting reflex, the acceleration of gastric emptying, and an increase in the resting tone of the lower esophageal sphincter. The onset of action of metoclopramide is relatively rapid. Following intravenous administration, the effects are typically observed within 1 to 3 minutes, while oral intake leads to effects within 15 to 20 minutes. The drug undergoes metabolism in the liver, primarily via the cytochrome P450 enzyme CYP2D6. Excretion of metoclopramide and its metabolites occurs mainly through the urine, with a half-life ranging from approximately 2.5 to 6 hours. While metoclopramide has demonstrated efficacy in managing nausea and vomiting associated with various conditions, its use, particularly in the

pediatric population, has been significantly limited. This curtailment is attributed to the substantial risk of neurological adverse drug reactions, collectively termed extrapyramidal symptoms (EPS).[1-3]

The clinical manifestations of metoclopramide-induced EPS encompass a range of neurological disturbances. These include acute dystonic reactions, which represent the most frequent form of EPS observed in children, akathisia, drug-induced parkinsonism, tardive dyskinesia (TD), and, in rare instances, the potentially life-threatening neuroleptic malignant syndrome (NMS). Acute dystonia is characterized by the abrupt onset of involuntary muscle contractions. These contractions can affect various anatomical regions, including the face, leading to grimacing or trismus; the neck, resulting in torticollis or retrocollis; the trunk, causing opisthotonus; and the extremities. A distinctive feature of acute dystonia is the oculogyric crisis, marked by the forced, sustained upward deviation of the eyes. Akathisia is another form of EPS that manifests as both subjective and objective restlessness. It is characterized by the inability to remain still and can be challenging to diagnose accurately. Tardive dyskinesia involves involuntary, repetitive movements, often choreoathetoid in nature. These movements typically affect the orofacial region and the extremities. Tardive dyskinesia carries the risk of irreversibility, particularly with chronic use and in older adults. Neuroleptic malignant syndrome is a medical emergency. It is characterized by hyperthermia, muscle rigidity, autonomic dysfunction, and altered mental status. Children and adolescents exhibit a significantly higher susceptibility to metoclopramide-induced EPS compared to adults. Incidence rates in pediatric populations have been reported to vary widely, with some studies indicating rates as high as 25%. These reactions can occur even following a single dose or within the therapeutic dosage range. The onset of symptoms typically occurs within 24 to 72 hours of drug initiation or an increase in dosage.[4-6]

Several factors are believed to contribute to the increased vulnerability of younger patients to metoclopramide-induced EPS. These include the relative immaturity of the blood-brain barrier, which may allow for greater drug penetration into the central nervous system (CNS). Additionally, the developing nigrostriatal dopamine pathways in the basal ganglia may exhibit heightened sensitivity to D2 receptor blockade. Some reports also suggest a higher incidence of these reactions in females, potentially due to hormonal influences on dopamine systems. In response to these risks, regulatory agencies worldwide have implemented substantial restrictions on the use of metoclopramide in the pediatric population. The European Medicines Agency (EMA) has issued recommendations advising against its use in children under one year of age. For older children (1-18 years), the EMA recommends limiting its use to second-line therapy for specific conditions, such as the prevention of delayed chemotherapy-induced nausea and vomiting (CINV) or the treatment of established post-operative nausea and vomiting (PONV), with a maximum treatment duration of five days. Similarly, the US Food and Drug Administration (FDA) advises caution regarding the use of metoclopramide in pediatric patients. The FDA states that safety and effectiveness have not been established in this population, except for facilitating small bowel intubation, and includes boxed warnings about the risk of tardive dyskinesia. Furthermore, the FDA emphasizes the need for precise dosing of oral liquid formulations to avoid overdose and recommends slow intravenous administration (over at least 3 minutes) to minimize the risk of acute reactions. Despite these warnings and restrictions, metoclopramide continues to be prescribed off-label for common conditions in pediatric settings, such as acute gastroenteritis. This off-label use contributes to the ongoing reports of EPS in children. The clinical presentation of acute dystonia can be dramatic and distressing, often mimicking serious neurological emergencies. These emergencies may include seizures, meningitis, encephalitis, or electrolyte disturbances like tetany. The potential for

misdiagnosis underscores the importance of maintaining a high level of suspicion for drug-induced movement disorders in any child presenting with the acute onset of abnormal movements or postures. A meticulous medication history is crucial in these cases. This report details the case of a 10-year-old girl who developed acute EPS, specifically torticollis and oculogyric crisis, following the administration of metoclopramide for symptoms associated with a febrile illness.[7-10] The aims of this report are to describe the clinical presentation, discuss the diagnostic considerations, document the successful management, and reinforce the importance of adhering to current safety guidelines concerning the use of metoclopramide in the pediatric population.

2. Case Presentation

This case presentation details the clinical findings of a 10-year-old female patient who presented with a constellation of symptoms that ultimately led to a diagnosis of metoclopramide-induced acute extrapyramidal syndrome (EPS), specifically manifesting as acute dystonic reaction involving torticollis and oculogyric crisis. The following sections provide a comprehensive summary of her demographics, anamnesis, physical examination, laboratory findings, imaging findings, and the final clinical diagnosis. The patient was a 10-year-old female. In the context of metoclopramide-induced EPS, pediatric patients, particularly females, have been observed to exhibit a higher propensity for developing these reactions compared to the adult population. The immaturity of the blood-brain barrier and the developing dopaminergic systems in children are contributing physiological factors. Hormonal influences may also play a role in the gender disparity observed in some studies. The patient's ethnicity and location are specified as Indonesian. This information, while not always directly causative, can be relevant in epidemiological contexts, considering potential genetic predispositions or environmental factors that might influence disease prevalence or presentation. However, in this specific case, the primary focus remains on the drug-induced etiology of the patient's symptoms. The patient's chief complaints at the time of presentation were intermittent fever of 4 days' duration, accompanied by nausea and vomiting, and the acute onset of neck stiffness and upward eye deviation. The neck stiffness and upward eye deviation had manifested approximately 30 minutes prior to her arrival at the emergency department (ED). The presence of intermittent fever for 4 days suggests an underlying systemic process, most likely an infection. Fever is a common physiological response to a variety of pathological insults, including viral, bacterial, or parasitic infections. The duration of the fever is important as it provides insights into the temporal course of the illness. The associated symptoms of nausea and vomiting are also common manifestations of systemic illnesses, particularly those affecting the gastrointestinal tract or those that trigger the chemoreceptor trigger zone in the brain. Nausea and vomiting can lead to dehydration and electrolyte imbalances, necessitating careful assessment and management. The acute onset of neck stiffness (torticollis) and upward eye deviation (oculogyric crisis) is the most striking aspect of the patient's presentation. These symptoms developed abruptly and close to the time of presentation, indicating a rapid onset of a neurological disturbance. Torticollis is characterized by involuntary contraction of the neck muscles, leading to a twisting or tilting of the head. Oculogyric crisis involves the involuntary, sustained upward deviation of the eyes. These are classic signs of acute dystonia, a type of extrapyramidal symptom. The patient's history of present illness reveals that her symptoms of fever and vomiting had been ongoing for 4 days prior to presentation. She had been treated with metoclopramide syrup for 1 day prior to admission. The dosage of metoclopramide was 5 mL, administered three times a day. Assuming a standard concentration of 5 mg/5 mL, this translates to a daily dose of 15 mg. Based on the patient’s estimated weight of 35 kg, the metoclopramide dosage was approximately 0.43 mg/kg/day. The temporal relationship between the initiation of metoclopramide

treatment and the onset of acute neurological symptoms (neck stiffness and eye deviation) is critically important. The fact that these symptoms began approximately 30 minutes before the patient arrived at the ED strongly suggests a drug-induced etiology, specifically pointing to metoclopramide as the causative agent. It is essential to note that even doses within the recommended range can trigger EPS in susceptible individuals, particularly children. The history also indicates that the patient's symptoms of fever and vomiting began 4 days prior to the acute neurological symptoms and were treated with metoclopramide for only one day before presentation. This timeline helps to establish the sequence of events and reinforces the likelihood of a drug-related adverse reaction. The patient's past medical history is significant for the absence of any known seizures, movement disorders, or drug allergies. The lack of a history of seizures or movement disorders is crucial in the differential diagnosis, as it helps to rule out preexisting neurological conditions that could mimic or contribute to the presenting symptoms. The absence of drug allergies is also important for guiding treatment decisions, particularly in the selection of medications to manage the acute dystonic reaction. The patient's family history is unremarkable, with no family history of seizures or movement disorders mentioned. A negative family history for similar neurological conditions further supports the likelihood of an acquired condition rather than an inherited one. Other relevant history includes the absence of head trauma or toxin exposure. This is important to exclude traumatic brain injury or toxicological causes as potential explanations for the acute neurological symptoms. Head trauma can cause a variety of neurological sequelae, including movement disorders, while exposure to certain toxins can also induce dystonia. The absence of these factors strengthens the association between metoclopramide administration and the observed EPS. Upon admission, the patient's vital signs were recorded. Her temperature was 37.8°C, indicating a mild elevation consistent with the reported fever. A heart rate of 98 beats per minute is within the upper range of normal for a child of this age, potentially reflecting the fever or anxiety associated with her symptoms. The respiratory rate was 20 breaths per minute, which is also within the normal range. The blood pressure was 105/70 mmHg, which is appropriate for her age. The oxygen saturation was 99% on room air, indicating adequate respiratory function. The patient's general appearance was described as anxious but conscious, alert, oriented, and cooperative. She exhibited no acute distress between episodes of neurological symptoms. This is important because it suggests that her level of consciousness and cognitive function were intact, helping to differentiate the episodes from conditions involving altered mental status, such as seizures or encephalitis. The anxiety is understandable, given the distressing nature of the involuntary movements she was experiencing. The neurological examination was conducted both during and between the episodes of acute symptoms. During the episodes, the patient exhibited marked torticollis, characterized by involuntary twisting of the neck, and oculogyric crisis, involving sustained upward eye deviation. These are the hallmark signs of acute dystonia. Between the episodes, or at baseline, the neurological examination revealed normal findings. Her mental status was normal, with a Glasgow Coma Scale (GCS) score of 15/15, indicating full consciousness. Cranial nerves II-XII were intact, with pupils being equal and reactive to light, and baseline extraocular movements were full and normal. Motor strength, tone, and bulk were normal. Sensory function was intact. Reflexes were normal, including deep tendon reflexes and plantar responses (flexor). Coordination was normal, as assessed by finger-to-nose and heel-to-shin tests. Meningeal signs, including Kernig's and Brudzinski's signs, were negative, ruling out meningeal irritation. The examination of other systems, including cardiovascular, respiratory, and abdominal systems, was unremarkable. This is important to rule out other potential causes of the patient's symptoms and to assess for any systemic involvement of her underlying

illness. The laboratory findings included a complete blood count (CBC) and serum biochemistry. The complete blood count showed an elevated white blood cell (WBC) count of 12.9 x 10^3/L. The normal range for WBC count varies with age, but this elevation suggests an inflammatory or infectious process, which aligns with the patient's history of fever. The body's immune system responds to infection or inflammation by increasing the production and release of white blood cells. The hemoglobin level was 12.8 g/dL, and the platelet count was 365 x 10^3/L. Both of these values are within normal limits. This is important to rule out anemia or thrombocytopenia as contributing factors to the patient's condition. The serum biochemistry results showed that electrolytes (Na+, K+, Cl-, Ca++, Mg++) and glucose levels were within normal limits. This is essential to exclude metabolic disturbances that can sometimes mimic or exacerbate neurological symptoms. Electrolyte imbalances, such as hypocalcemia or hypomagnesemia, can cause muscle spasms and neurological dysfunction. Normal glucose levels rule out hypoglycemia or hyperglycemia as the cause of the patient's symptoms. Liver function tests (ALT, AST, Bilirubin) and renal function tests were also within normal limits, indicating that these organ systems were functioning properly. Abnormal liver or kidney function could affect drug metabolism and excretion, potentially influencing the severity or duration of drug-induced side effects. No specific neuroimaging studies, such as a CT head or MRI brain, were performed. This decision was based on the clinical picture and the patient's response to treatment, which strongly indicated a drug-induced reaction. Neuroimaging is typically indicated when there is suspicion of structural brain abnormalities, such as tumors, hemorrhage, or infarction. In this case, the acute onset of symptoms following metoclopramide administration, the characteristic nature of the dystonic movements, and the rapid resolution of symptoms with diphenhydramine strongly supported the diagnosis of drug-induced EPS, making neuroimaging less critical for immediate management. However, in cases with atypical presentations or lack of response to initial treatment, neuroimaging might be warranted to rule out other neurological conditions. The final clinical diagnosis was metoclopramide-induced acute extrapyramidal syndrome (EPS), specifically presenting as an acute dystonic reaction with torticollis and oculogyric crisis. This diagnosis was established based on the temporal relationship between the administration of metoclopramide and the onset of the characteristic neurological symptoms. The rapid and dramatic improvement of symptoms following the administration of diphenhydramine further supported this diagnosis. The absence of other significant findings in the patient's history, physical examination, and laboratory tests also contributed to the conclusion that the EPS was drug-induced. It is critical to recognize drug-induced movement disorders, as prompt discontinuation of the offending agent and appropriate treatment can lead to complete resolution of symptoms and prevent long-term complications (Table 1).

This section describes the medical interventions and subsequent monitoring applied to a 10-year-old female patient who presented with metoclopramide-induced acute extrapyramidal syndrome (EPS), specifically acute dystonic reaction. The patient's management was divided into distinct phases, each with specific objectives and actions, aimed at resolving the acute episode, addressing the underlying condition, and preventing recurrence. The initial phase of the patient's care took place in the Emergency Department, where the primary objectives were to establish a definitive diagnosis, discontinue the offending medication, reverse the acute dystonic reaction, and provide supportive care. The first critical step was Assessment & Diagnosis. Clinical assessment played a pivotal role in identifying the acute symptoms of torticollis and oculogyric crisis. A detailed history, including the recent administration of metoclopramide, was crucial in establishing the likely etiology of these symptoms. The temporal relationship between the drug administration and the onset of the neurological signs strongly suggested a

drug-induced etiology. The diagnosis of Metoclopramide-Induced Acute EPS was established based on these findings. Following the diagnosis, Drug Discontinuation was implemented immediately. This involved the cessation of any further administration of metoclopramide. Prompt discontinuation of the offending agent is a fundamental principle in the management of any drug-induced adverse reaction. This action aims to prevent further accumulation of the drug and mitigate the ongoing effects on the patient's neurological system. Pharmacological Intervention was then initiated to directly address the acute dystonic reaction. Intravenous (IV) diphenhydramine was administered. The dose was 36 mg (approximately 1 mg/kg) diluted in 50 mL of 0.9% NaCl. The infusion was administered over a period of 30 minutes. Diphenhydramine, an antihistamine with significant anticholinergic properties, is commonly used to counteract the dopamine-acetylcholine imbalance in the basal ganglia that is characteristic of acute dystonia. The rationale for its use lies in its ability to block muscarinic acetylcholine receptors, thereby alleviating the excessive cholinergic activity that precipitates the muscle contractions and abnormal movements seen in dystonic reactions. Simultaneously, Supportive Care was provided. This involved the establishment of intravenous (IV) access and the administration of intravenous fluids. 0.9% NaCl was administered at a maintenance rate of 42 mL/hour. The purpose of IV fluid therapy was to maintain adequate hydration, especially considering the patient's history of vomiting, and to ensure a route for the administration of medications. The patient experienced Rapid and complete resolution of torticollis and oculogyric crisis within 30 minutes of completing the diphenhydramine infusion. The patient also reported feeling better. This positive response to diphenhydramine not only confirmed the diagnosis of acute dystonia but also demonstrated the effectiveness of this treatment modality in reversing the acute symptoms. The patient remained hemodynamically stable throughout the ED management phase. Following the stabilization of the patient's acute symptoms in the ED, she was admitted to the pediatric ward for further observation and management of her underlying condition. This phase focused on continued monitoring, supportive care, and observation for any recurrence of EPS. Admission & Observation involved transferring the patient to the pediatric ward. The rationale for admission was to allow for close monitoring of the patient for any potential recurrence of the extrapyramidal symptoms and to address the underlying febrile illness that had initially prompted the metoclopramide administration. Continued Supportive Care was provided, including ongoing IV fluids as needed. Antipyretics were administered as needed for the fever. Monitoring of oral intake and hydration status was also conducted. The management of the initial fever and vomiting was addressed during this phase. Monitoring for EPS Recurrence was a critical component of the inpatient management. Close observation was maintained for any return of neck stiffness, abnormal eye movements, or other neurological signs. This was essential to ensure the complete and sustained resolution of the acute dystonia and to detect any delayed or recurrent manifestations of EPS. During the hospitalization, the patient’s fever and vomiting gradually resolved. The patient remained well-hydrated, and no further episodes of dystonia or other EPS were noted throughout the entire hospitalization period. This indicated that the initial treatment in the ED was effective and that there was no recurrence of the drug-induced reaction. The patient's condition continued to improve, and she was deemed suitable for discharge on the third day of hospitalization. This phase involved assessing the patient's readiness for discharge, providing education and counseling to the patient's family, and ensuring appropriate follow-up arrangements. Discharge Readiness Assessment was conducted to ensure the patient met the criteria for safe discharge home. The patient was clinically stable, and there was a resolution of the presenting EPS. The initial febrile illness symptoms had also resolved, and the patient was tolerating oral intake. Patient & Family Education / Counseling was provided. This included

a detailed explanation to the parents regarding the adverse drug reaction. Clear instructions were given to avoid metoclopramide in the future. The rationale for this education was to prevent future exposure and reactions and to empower the family to make informed decisions about the patient's care. The parents verbalized understanding of the reaction and the need to avoid metoclopramide. No specific medications were prescribed related to the EPS at discharge, as it had fully resolved. Any medications for other conditions were prescribed as appropriate. The acute dystonia had resolved, and there was no indication for ongoing anticholinergic therapy. The patient was discharged home. The final phase of the patient's care involved arrangements for post-discharge monitoring and long-term prevention of recurrent EPS. The family was instructed to monitor for any recurrence of symptoms after discharge. They were advised to seek medical attention if any concerning symptoms reappeared. Follow-up contact confirmed no recurrence of symptoms after discharge. The adverse drug reaction was prominently documented in all the patients' medical records. It was considered to recommend a medical alert bracelet or information card. The rationale for this was to prevent accidental re-exposure by other healthcare providers in the future. Documentation of the adverse drug reaction was completed (Table 2).

Table 1. Summary of patient's clinical findings.

Category	Parameter	Details
Demographics	Age	10 years
	Gender	Female
	Ethnicity / Location	Indonesian
Anamnesis (History)	Chief Complaints	- Intermittent fever (4 days)
		- Nausea and vomiting (4 days)
		- Acute onset neck stiffness (approx. 30 mins prior to ED)
		- Acute onset upward eye deviation (approx. 30 mins prior to ED)
	History of Present Illness	Symptoms of fever and vomiting for 4 days, treated with Metoclopramide starting 1 day prior. Acute neurological symptoms (neck stiffness, eye deviation) began ~30 mins before ED arrival, recurring in ED. Patient remained conscious.
	Medication History	Metoclopramide syrup 5 mL (assumed 5mg/5mL), three times daily. Started 1 day prior to admission. (Approx. dose: 15 mg/day or ~0.43 mg/kg/day based on estimated weight of 35kg). No other recent new medications.
	Past Medical History	No history of seizures, known movement disorders, or drug allergies.
	Family History	No family history of seizure or movement disorders mentioned.
	Other Relevant History	No history of head trauma or toxin exposure mentioned.
Physical examination	Vital Signs (on Admission)	- Temperature: 37.8°C
		- Heart Rate: 98 bpm
		- Respiratory Rate: 20 bpm
		- Blood Pressure: 105/70 mmHg
		- Oxygen Saturation: 99% on room air
	General Appearance	Anxious but conscious, alert, oriented, cooperative. No acute distress between episodes.
	Neurological Examination	**During Episodes:** Marked torticollis (involuntary neck twisting); Oculogyric crisis (sustained upward eye deviation).
		Between Episodes / Baseline: Mental Status: Normal, GCS 15/15; Cranial Nerves: II-XII intact, pupils equal/reactive, extraocular movements full (baseline); Motor: Normal strength, tone, bulk; Sensory: Intact; Reflexes: Normal deep tendon reflexes, plantar responses flexor; Coordination: Normal finger-nose, heel-shin; Meningeal Signs: Negative (Kernig's, Brudzinski's).
	Other Systems	Examination unremarkable (cardiovascular, respiratory, abdominal systems examined).
Laboratory findings	Complete Blood Count (CBC)	- White Blood Cells (WBC): 12.9 × 10^3/L (Elevated)
		- Hemoglobin (Hb): 12.8 g/dL (Normal)
		- Platelets: 365 × 10^3/L (Normal)
	Serum Biochemistry	- Electrolytes (Na+, K+, Cl-, Ca++, Mg++): Within normal limits
		- Glucose: Within normal limits
		- Renal Function (BUN, Creatinine): Within normal limits
		- Liver Function (ALT, AST, Bilirubin): Within normal limits
Imaging findings	Relevant Imaging	No specific neuroimaging (such as CT Head, MRI Brain) was performed, as the clinical picture and response to treatment strongly indicated a drug-induced reaction.
Clinical diagnosis	Final Diagnosis	Metoclopramide-Induced Acute Extrapyramidal Syndrome (EPS), specifically presenting as an Acute Dystonic Reaction (Torticollis and Oculogyric Crisis).

Table 2. Patient treatment procedures and follow-up (Revised).

Phase	Procedure / Treatment	Details / Rationale	Outcome / Response	Follow-up plan
Emergency Department (ED) Management	**Assessment & Diagnosis**	Clinical assessment confirming acute dystonia (torticollis, oculogyric crisis). Identification of metoclopramide as the likely causative agent via medication history.	Diagnosis: Metoclopramide-Induced Acute EPS established.	Proceed to immediate treatment.
	Drug Discontinuation	Immediate cessation of any further metoclopramide administration.	Essential first step in managing drug-induced EPS.	Metoclopramide stopped.
	Pharmacological Intervention	Intravenous (IV) Diphenhydramine infusion.	Dose: 36 mg (approx. 1 mg/kg) diluted in 50 mL 0.9% NaCl. Administration: Infused over 30 minutes. Rationale: Anticholinergic effect counteracts dopamine blockade.	Rapid and complete resolution of torticollis and oculogyric crisis within 30 minutes of completing the infusion. Patient reported feeling better.
	Supportive Care	IV fluid therapy initiated.	0.9% NaCl administered at a maintenance rate of 42 mL/hour. Rationale: Maintain hydration, ensure IV access.	Patient remained hemodynamically stable.
Hospitalization (Day 1 - Day 3)	**Admission & Observation**	Admitted to the pediatric ward.	Rationale: Monitor for potential symptom recurrence, manage underlying febrile illness.	Transfer to ward successful.
	Continued Supportive Care	Ongoing IV fluids as needed. Management of initial fever and vomiting symptoms.	Antipyretics administered as needed for fever. Monitoring of oral intake and hydration status.	Fever and vomiting gradually resolved. Patient remained well-hydrated.
	Monitoring for EPS Recurrence	Close observation for any return of neck stiffness, abnormal eye movements, or other neurological signs.	Rationale: Ensure complete and sustained resolution after initial treatment.	No further episodes of dystonia or other EPS noted during the entire hospitalization period.
Discharge (Day 3)	**Discharge Readiness Assessment**	Patient clinically stable. Resolution of presenting EPS. Resolution of initial febrile illness symptoms. Tolerating oral intake.	Met criteria for safe discharge home.	Patient stable and asymptomatic.
	Patient & Family Education / Counseling	Detailed explanation provided to parents regarding the adverse drug reaction. Clear instructions given to avoid metoclopramide in the future.	Rationale: Prevent future exposure and reactions, empower family.	Parents verbalized understanding of the reaction and the need to avoid metoclopramide.
	Discharge Medications	No specific medications prescribed related to the EPS at discharge, as it had fully resolved. Any medications for other conditions as appropriate.	Rationale: Acute dystonia resolved, no indication for ongoing anticholinergic therapy.	Patient discharged home.
Post-Discharge Follow-up	**Short-term Monitoring**	Family instructed to monitor for any recurrence of symptoms after discharge.	Advised to seek medical attention if any concerning symptoms reappeared.	Follow-up contact confirmed no recurrence of symptoms after discharge.
	Long-term Prevention	Ensure adverse reaction is prominently documented in all medical records. Consider recommending a medical alert bracelet/information card.	Rationale: Prevent accidental re-exposure by other healthcare providers in the future.	Documentation completed.

3. Discussion

The fundamental pathophysiology underpinning metoclopramide-induced EPS is intricately linked to the drug's potent antagonistic activity at dopamine D2 receptors. These receptors are densely concentrated within the basal ganglia, a group of interconnected nuclei located deep within the brain that plays a pivotal role in the regulation of motor control, posture, and muscle tone. Within the basal ganglia, a delicate equilibrium exists between the neurotransmitters dopamine and acetylcholine. Dopamine, acting via D2 receptors, generally exerts an inhibitory influence on

motor activity, while acetylcholine has an excitatory effect. Metoclopramide, by effectively blocking dopamine's action at the D2 receptors, disrupts this finely tuned balance. This disruption leads to a relative preponderance of cholinergic activity, meaning there is an excess of acetylcholine signaling compared to dopamine signaling. It is this relative cholinergic excess that is believed to be the primary driver of the dystonic muscle contractions and other extrapyramidal symptoms observed in cases of metoclopramide-induced reactions. The nigrostriatal pathway, a specific dopaminergic tract within the basal ganglia, is particularly implicated in the genesis of these movement disorders. This pathway is crucial for the smooth initiation and execution of voluntary movements, and its disruption by dopamine blockade manifests as the characteristic symptoms of EPS. The precise mechanisms by which this neurotransmitter imbalance translates into the diverse clinical manifestations of EPS are complex and not fully elucidated. However, it is thought that the relative cholinergic excess leads to abnormal firing patterns of neurons within the basal ganglia. These aberrant signals are then transmitted to other brain regions involved in motor control, ultimately resulting in the involuntary muscle contractions, rigidity, and abnormal movements that characterize dystonia, parkinsonism, and other EPS. In acute dystonia, such as that observed in the presented case, the excessive cholinergic activity likely triggers sustained muscle contractions in specific muscle groups, leading to the characteristic twisting postures like torticollis or the fixed gaze deviation of oculogyric crisis. The variability in the clinical presentation of EPS, encompassing dystonia, akathisia, parkinsonism, and tardive dyskinesia, likely reflects the differential involvement of various subregions within the basal ganglia and the complex interplay of other neurotransmitter systems.[11,12]

A particularly concerning aspect of metoclopramide's use, as highlighted by this case and numerous other reports, is the heightened susceptibility of children and adolescents to developing EPS compared to the adult population. Several key physiological and developmental factors are thought to contribute to this increased vulnerability. One important factor is the relative immaturity of the blood-brain barrier (BBB) in children. The BBB is a highly selective semipermeable membrane that separates the circulating blood from the brain extracellular fluid, preventing potentially harmful substances from reaching the central nervous system. In young children, the BBB is not fully developed and may exhibit increased permeability compared to adults. This increased permeability can allow a greater amount of metoclopramide to cross the BBB and enter the brain, leading to higher drug concentrations within the CNS and consequently increasing the risk of D2 receptor blockade in the basal ganglia. Another crucial consideration is the ongoing development of the dopaminergic systems in the pediatric brain. The nigrostriatal dopamine pathways, which are critical for motor control, are still maturing throughout childhood and adolescence. These developing pathways may exhibit increased sensitivity to the effects of dopamine receptor antagonists like metoclopramide. This heightened sensitivity can result in a more pronounced disruption of the dopamine-acetylcholine balance, even at relatively low doses of the drug, predisposing children to a higher risk of EPS. Furthermore, children may possess a higher density of dopamine receptors in certain brain regions compared to adults. A greater number of available D2 receptors provides more targets for metoclopramide to bind to, potentially amplifying its effects on motor control and increasing the likelihood of EPS. It is also important to acknowledge that the pharmacokinetics of metoclopramide, including its metabolism and elimination, may differ between children and adults. Variations in hepatic enzyme activity, particularly CYP2D6, which is the primary enzyme responsible for metoclopramide metabolism, can influence drug levels in the body. These pharmacokinetic differences can contribute to interindividual variability in drug response and the risk of adverse effects. Finally, while

not fully understood, hormonal influences may also play a role in the observed gender differences in susceptibility to metoclopramide-induced EPS. Some studies suggest a higher incidence of these reactions in females, as was the case in our patient. Fluctuations in estrogen and other hormones can modulate dopamine receptor function and sensitivity, potentially contributing to the increased risk in females.[13-15]

While the risk of metoclopramide-induced EPS is generally associated with higher doses and prolonged use, it is crucial to recognize that these reactions can occur even at therapeutic doses and following relatively short durations of treatment. This case vividly illustrates this point, as the patient developed significant EPS after receiving metoclopramide at a dose of approximately 0.43 mg/kg/day for only one day. Although this dose is within the generally recommended pediatric range (up to 0.5 mg/kg/day), it was sufficient to trigger a pronounced dystonic reaction in this particular patient. This observation underscores the concept of "idiosyncratic" drug reactions. Idiosyncratic reactions are adverse drug events that are not predictable based on the known pharmacological properties of the drug and do not typically exhibit a clear dose-response relationship. These reactions are thought to arise from a complex interplay of individual patient factors, including genetic predispositions, variations in drug metabolism, and individual differences in receptor sensitivity. In the context of metoclopramide-induced EPS, some individuals may possess a heightened sensitivity to the drug's D2 receptor blockade, making them more prone to developing EPS even at lower doses. Genetic polymorphisms in the CYP2D6 enzyme, for instance, can lead to variations in metoclopramide metabolism, with some individuals being "poor metabolizers" and experiencing higher drug levels than expected. The unpredictability of these idiosyncratic reactions highlights the importance of careful patient monitoring and a high index of suspicion for EPS in any child receiving metoclopramide, regardless of the dose or duration of treatment. Clinicians should be vigilant for the early signs of dystonia, akathisia, parkinsonism, and other EPS, and should be prepared to promptly discontinue the drug and initiate appropriate treatment if these reactions occur.[16,17]

The clinical presentation of metoclopramide-induced EPS, particularly acute dystonia, can be dramatic and alarming, often posing significant challenges in differential diagnosis. The sudden onset of involuntary muscle contractions, abnormal postures, and bizarre movements can mimic a variety of other neurological conditions, some of which are potentially life-threatening. In this case, the patient presented with acute torticollis and oculogyric crisis, which are classic manifestations of acute dystonia. Torticollis involves involuntary twisting or tilting of the neck, while oculogyric crisis is characterized by sustained upward deviation of the eyes. These symptoms developed rapidly and were quite distressing to the patient. However, it is essential to recognize that acute dystonia can manifest in a variety of ways, affecting different muscle groups and producing a range of abnormal movements. The differential diagnosis of acute dystonia in children is broad and includes several important neurological conditions. Seizures are a critical consideration, as some seizure types can involve abnormal muscle contractions and eye movements. However, seizures are typically associated with altered consciousness, postictal confusion, and other features that were not present in this case. Meningitis and encephalitis, infections of the brain and meninges, can also cause neurological symptoms, but they are usually accompanied by fever, headache, stiff neck, and altered mental status. Tetanus, a bacterial infection affecting the nervous system, can lead to muscle rigidity and spasms, but it has a distinct clinical presentation and is often associated with a history of puncture wound. Electrolyte abnormalities, such as hypocalcemia and hypomagnesemia, can also cause muscle contractions and abnormal movements, but they are typically accompanied by other systemic signs and abnormalities in laboratory tests. Poisoning

with certain substances, such as strychnine, can induce severe muscle spasms, but this was ruled out by the patient's history. Finally, it is important to consider non-organic causes, such as conversion disorder (functional neurological disorder), although the acute onset and characteristic features of dystonia in this case strongly suggested an organic etiology. The key to accurately diagnosing metoclopramide-induced EPS lies in a careful and systematic approach to patient evaluation. A detailed medical history is paramount, with a particular focus on recent medication use. Clinicians must specifically inquire about the use of metoclopramide or other dopamine antagonists, including antipsychotics, antiemetics, and certain gastrointestinal motility agents. The temporal relationship between the initiation of the offending drug and the onset of symptoms is crucial. In this case, the symptoms developed shortly after the patient started metoclopramide, strongly suggesting a drug-induced reaction. The physical examination should focus on characterizing the nature of the abnormal movements, assessing the patient's neurological status, and looking for any signs of other underlying conditions. The characteristic features of dystonia, such as sustained muscle contractions, twisting movements, and abnormal postures, should be carefully documented. It is also important to assess the patient's level of consciousness, cognitive function, and cranial nerve function. Laboratory tests and imaging studies may be necessary to rule out other conditions in the differential diagnosis. However, in cases where the clinical presentation is typical and there is a clear temporal relationship with metoclopramide exposure, extensive investigations may not be required.[18-20]

4. Conclusion

This case report elucidates a significant instance of metoclopramide-induced acute extrapyramidal syndrome (EPS) in a 10-year-old girl, manifesting as acute torticollis and oculogyric crisis, which occurred following the administration of the drug for fever and vomiting. The prompt recognition of the drug-induced etiology was crucial, leading to the immediate discontinuation of metoclopramide and the administration of intravenous diphenhydramine. The patient's symptoms resolved rapidly following this intervention, underscoring the effectiveness of anticholinergic agents in reversing acute dystonic reactions. The case highlights the diagnostic challenges associated with metoclopramide-induced EPS, as its varied clinical presentations can mimic other neurological conditions. It emphasizes the necessity of a meticulous drug history in any child presenting with acute-onset abnormal movements or postures. Furthermore, this report reinforces the importance of adhering to established guidelines that restrict the use of metoclopramide in pediatric populations due to the heightened risk of EPS. While metoclopramide can be a valuable therapeutic agent, its use in children necessitates careful consideration of the risk-benefit ratio and the availability of safer alternatives. Increased awareness among clinicians regarding this potential adverse effect is essential to ensure timely diagnosis, appropriate management, and the prevention of long-term complications.

5. References

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