

Diagnosis of Multisystem Inflammatory Syndrome in Child (MIS-C) Case Presenting with Acute Dystonia Secondary to Use of Metoclopramide

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Abstract

Metoclopramide is a dopamine antagonist in the central nervous system and an antiemetic agent. It can cause extrapyramidal symptoms side effects such as dystonic reactions characterized by involuntary, sustained or spasmodic contractions of muscle groups, resulting in twisting, repetitive or abnormal postures. In this study, we aimed to report a pediatric patient who presented with acute dystonia due to metoclopramide use and was finally diagnosed with MIS-C.

Keywords: Acute Dystonia, Metoclopramide, Multisystem Inflammatory Syndrome in Child.

Introduction

Metoclopramide is a dopamine antagonist in the central nervous system and an antiemetic agent. Although it is recommended for adults, it is used in gastroesophageal reflux disease and acute gastroenteritis in pediatric population. It can cause extrapyramidal symptoms side effects such as dystonic reactions characterized by involuntary, sustained or spasmodic contractions of muscle groups, resulting in twisting, repetitive or abnormal postures. The incidence of acute dystonias is approximately 0.2%. It has been reported that the incidence of acute dystonias increases up to 25% with increasing dose and decreasing age. (1-3)

A growing number of reports from different countries have now described a severe inflammatory syndrome named Multisystem Inflammatory Syndrome in Children (MIS-C) with acute COVID-19 infection. To date, case series of MIS-C have described multisystem organ involvement including the gastrointestinal, mucocutaneous, respiratory and cardiac systems.(4-6) In children, COVID-19 has usually mild prognosis. Furthermore, the disease course in MIS-C can be quite severe, with many children requiring intensive care interventions. Rapid diagnosis and appropriate treatment of MIS-C are important for prognosis. The vast majority of children survive, but deaths have been reported. (5) In this study, we aimed to report a pediatric patient who

presented with acute dystonia due to metoclopramide use and was finally diagnosed with MIS-C.

Case Report

A seven-year-old previously healthy girl was admitted to the pediatric emergency department with complaints of involuntary spasm of the neck, eyes, head, upper extremities and sleepiness for five hours. It was learned that two days ago, fever and nausea started with intermittent vomiting. Due to nausea and vomiting, her family gave oral metoclopramide to her 5 mg four times, one day ago. A few hours after administration of last dose of metoclopramide, she complained of involuntary spasm.

In her past, she was close contact with her father who had COVID-19 a month ago. On physical examination, she had body temperature of 36.8°C, heart rate 75 beats/minutes, blood pressure 80/55 mmHg, respiratory rate 18/min and 97% oxygen saturation on room air. She was awake but agitated, avoided eye contact and not answered questions. The patient's head and eyes were deviated to the left, and muscle spasm was present in the left sternocleidomastoid and upper extremities. She was able to answer all the questions but had dysarthria. Both pupils were isochoric. Meningeal irritation signs were absent and deep tendon reflexes were normal. She had bilateral conjunctival

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hyperemia. The remainder of her physical examination was unremarkable. Initial laboratory tests showed blood glucose 107 mg/dL, hemoglobin of 12.3 g/dL, thrombocytopenia (82000 platelets/ μ l), 11050 leukocytes/ μ l but with only 800 lymphocytes/ μ l, hyponatremia (127 mmol/L), d-dimer 1.32 μ g/mL (Positive; 0.50 μ g/mL or greater). In addition, the C-reactive protein (CRP) level 39.5 mg/L (Positive; 5 mg/L or greater) and procalcitonin 17.7 μ g/L (Positive; 0.5 μ g/L or greater) were significantly high. Renal and liver function test results were within normal values and urinalysis was normal.

We considered that acute dystonic reaction originated from metoclopramide according to her history and physical examination findings. Therefore, biperiden was performed intramuscularly and then dystonic reaction disappeared dramatically within 30 minutes. Dystonia was not observed again, but 8 hours after biperiden injection, she developed headache and altered mental status with agitation, hallucination and confusion. Blood pressure, body temperature and saturation values were within normal ranges. Her deep tendon reflexes were normal with negative Babinski reflex bilaterally. No papilledema was noted. The remainder of physical examination was unremarkable.

Blood glucose level was within normal range. Chest radiograph, computed tomography and diffusion-weighted magnetic resonance imaging of the brain reported as normal on report. Lumbar puncture was performed for the diagnosis of encephalopathy. Cerebrospinal fluid (CSF) analysis showed leukocytes 2 cells/mm³, protein 110 mg/L and glucose 59 mg/dL with simultaneous blood glucose 105 mg/dL. The Gram stain of CSF revealed no cells or organisms. Combination therapy consisting of intravenous ceftriaxone, vancomycin and acyclovir was started for encephalopathy. The result of real-time reverse transcription quantitative polymerase chain reaction (RT-qPCR) for 2019-nCoV from nasopharyngeal swab was negative for two times. Whereas serum 2019-nCoV IgM and IgG were negative and positive, respectively.

Due to the presence of fever, mucocutaneous, neurological, gastrointestinal and hematologic systems involvement, the possibility of MIS-C associated with COVID-19 was entertained. She was treated with intravenous immunoglobulin (IVIG) 2 g/kg in a single infusion based on treatment guidelines recommended for pediatric patients with MIS-C.(4) The patient was admitted from emergency department to a tertiary center hospital for further care and management. After the negative test results of CSF for herpes virus and cytomegalovirus, empiric acyclovir was discontinued 5 days later. Blood and CSF cultures were negative after 7 days. Her neurological symptoms started to improve on the fourth day follow-up. She was discharged home 10 days later with improved symptoms and signs to follow up with outpatient clinic. Follow-up visit 2 weeks later was unremarkable.

Discussion

The inhibitory dopaminergic receptors are susceptible to blockage by metoclopramide. The potential adverse extrapyramidal effects are parkinsonism, tardive dyskinesia, akathisia, and dystonia that may be confused with seizures, tetanus, strychnine poisoning and electrolyte imbalances. Female patients, children, adults younger than 30, and patients taking high doses of metoclopramide have higher chances of developing dystonic reactions.(2, 7) About 70% of dystonic patients are female(2), which was similar to our patient, a 7-year-old female, and female gender could be a risk factor. Normal or toxic metoclopramide doses can produce side effects, which are usually seen within the first 24–72 hours of drug intake.(3, 7) In this case, dystonic reactions had occurred after 24 hours of drug intake.

Standard treatment involves discontinuation of metoclopramide and administration of injectable antihistaminic or anticholinergic drugs. Benztropine and diphenhydramine are both effective in relieving dystonic reactions.(3, 7) Symptoms usually resolve dramatically within 10 - 30 minutes of administration of parenteral anticholinergics.(8) In this case, biperiden was used to treat our patient and dystonic reaction had disappeared within 30 minutes.

Biperiden that shows atropine-like properties with its central anticholinergic effect is regularly used predominantly in the symptomatic therapy of parkinson disease and movement disorders. Biperiden causes the anticholinergic syndrome by competitive inhibition of acetylcholine at the receptor level. Central effects; It is dose dependent and is observed as altered mental status, hallucinations, recent memory loss, agitation, respiratory failure and collapse of the cardiovascular system, while its peripheral effects are; mydriasis, blurred vision, appears as dryness of mucous membranes, high fever, tachycardia, dry skin, ileus and urinary retention.(9) There is evidence that COVID-19 infection is associated with neurological symptoms and central nervous system complications. Clinical manifestations of neurological symptoms of COVID-19 include meningitis, encephalitis, encephalopathy, headaches, seizures, and peripheral nervous system manifestations, such as myelitis, neuralgia, and Guillain-Barré syndrome. In addition, reports of neurological complications in children and adolescents have been associated with MIS-C.(10) According to this literature information, the side effects of biperiden can be confused with neurological findings of MIS-C. Although the neurological findings in our case occurred after biperiden injection, our case was diagnosed as MIS-C with laboratory tests. This suggested that the neurological findings developed due to MIS-C.

Since April of 2020, there have been case reports with clinical findings are similar to incomplete Kawasaki disease, toxic shock syndrome or secondary macrophage activation

syndrome.(11, 12) On May 15th 2020, World Health Organisation (WHO) termed this condition as MIS-C. Case definition for MIS-C was reported by WHO and Centers for Disease Control and Prevention (CDC). Both definitions require fever, elevated inflammatory markers, multisystemic involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, mucocutaneous, or neurological), hematologic findings, evidence of COVID-19, or likely contact with patients with COVID-19, and no other obvious microbial cause of inflammation or infection. In CDC case definition the patient must be under 21 years old and has to be inpatient, while according to WHO case definition patient could be between 0 and 19 ages and no need to be hospitalized. (13, 14) Gastrointestinal symptoms are dominant in patients with MIS-C. Furthermore, respiratory symptoms may not be present in pediatric patients with MIS-C. And also MIS-C associated with COVID-19 infection occurs two or more weeks after acute infection. Because of these reasons, the diagnosis of MIS-C is difficult.(4) Clinical, biological features and inflammatory markers of our patient were consistent with the diagnosis of MIS-C. We diagnosed an unusual case of MIS-C in a previously healthy female child with acute dystonia secondary to use of metoclopramide.

Patients with MIS-C are treated with different regimens, mostly the use of immunomodulatory medications, including IVIG and glucocorticoids as first-tier therapy. If there is no response to these drugs, biologic agents such as anakinra, tocilizumab and infliximab are among second-line treatment options.(15) In this case, our patient was successfully treated with IVIG and improved without sequelae.

Conclusion

In conclusion, physicians working in the pediatric emergency department should prompt alertness for symptoms and signs of MIS-C, and also keep in mind that metoclopramide has the potential to cause extrapyramidal side effects in children. This case report demonstrates that drug history should be questioned in pediatric patients with acute dystonic reaction, and MIS-C should definitely be kept in mind in the etiology of vomiting and fever during the COVID-19 pandemic.

Informed consent: Informed consent was obtained from the patient's family for the publication of the case report.

References

1. Lau Moon Lin M, Robinson PD, Flank J, Sung L, Dupuis LL. The Safety of Metoclopramide in Children: A Systematic Review and Meta-Analysis. *Drug Saf.* 2016;39(7):675-87.
2. Dingli K, Morgan R, Leen C. Acute dystonic reaction caused by metoclopramide, versus tetanus. *BMJ.* 2007;334(7599):899-900.
3. Yis U, Ozdemir D, Duman M, Unal N. Metoclopramide induced dystonia in children: two case reports. *Eur J Emerg Med.* 2005;12(3):117-9.
4. Kofman AD, Sizemore EK, Detelich JF, Albrecht B, Piantadosi AL. A young adult with COVID-19 and multisystem inflammatory syndrome in children (MIS-C)-like illness: a case report. *BMC Infect Dis.* 2020;20(1):716.
5. Aldawas A, Ishfaq M. COVID-19: Multisystem Inflammatory Syndrome in Children (MIS-C). *Cureus.* 2022;14(1):e21064.
6. Çiçek G, Ayaz İO, Ünal İ, Önal Ö, Arıcı T, Yücel B, et al. Could COVID-19 cause loss of sperm motility? *Cukurova Med J.* 2021;46(2):858-60.
7. Tianyi FL, Agbor VN, Njim T. Metoclopramide induced acute dystonic reaction: a case report. *BMC Research Notes.* 2017;10(1):32.
8. Lewis K, O'Day CS. *Dystonic Reactions.* StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
9. Boran ÖF, Büyükfırat E, Elibol FE, Dolu H, Dalyan MA, Karadağ S. Biperiden intoksikasyonunda fizostigmin kullanımı: olgu sunumu. *KSU Tıp Fak Der.* 2016;11(1):20-1.
10. Bentes AA, Dos Santos Junior WR, Pessoa NL, Costa TA, Oliveira GFG, Diniz LMO, et al. Neuro-COVID-19 with or without the multisystem inflammatory syndrome (MIS-C): a single-center study : COVID-19: neurologic manifestations in children. *J Mol Neurosci.* 2023:1-9.
11. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet.* 2020;395(10237):1607-8.
12. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France:prospective observational study. *BMJ.* 2020;369:m2094.
13. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19): The CDC Health Alert Network. 2020 [16.06.2022]. Available from: <https://emergency.cdc.gov/han/2020/han00432.asp>.
14. Multisystem inflammatory syndrome in children and adolescents with COVID-19 World Health Organization (WHO). 2020; [22.06.2022]. Available from: <https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>.
15. Mahmoud S, El-Kalliny M, Kotby A, El-Ganzoury M, Fouda E, Ibrahim H. Treatment of MIS-C in children and adolescents. *Curr Pediatr Rep.* 2022;10(1):1-10.