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Case Report

Metoclopramide-induced rapid-onset psychosis in a child with methylphenidate use: a case report

Gökçen İlçioğlu Ekici[1], Gülser Şenses Dinç[2], Ayşegül Neşe Çıtak Kurt[3]

[1]Department of Child and Adolescent Psychiatry, Ankara Bilkent City Hospital, Ankara Yildirim Beyazit University Faculty of Medicine, Ankara; [2]Department of Child and Adolescent Psychiatry, Ankara Bilkent City Hospital, University of Health Sciences, Ankara; [3]Department of Pediatric Neurology, Ankara Bilkent City Hospital, Ankara Yildirim Beyazit University Faculty of Medicine, Ankara, Türkiye.

ABSTRACT

Background. Metoclopramide, a dopamine antagonist employed for its antiemetic effects, can precipitate neuropsychiatric adverse effects, including extrapyramidal symptoms and, in a few instances, acute psychosis. Although there have been reports of metoclopramide-induced psychosis in elderly individuals, there is no documentation of such incidents in children as far as we are aware.

Case presentation. This case report describes an 11-year-old girl with a history of mild intellectual disability and attention deficit hyperactivity disorder, managed with 10 mg of methylphenidate daily. She presented to the emergency department with acute gastrointestinal symptoms and was administered two tablets of metoclopramide alongside her regular dose of methylphenidate. Subsequently, she developed psychotic symptoms, disorganized behavior, and agitation. An extensive medical evaluation ruled out other organic pathologies, leading to a diagnosis of rapid-onset psychosis induced by metoclopramide. The psychotic episode, which lasted approximately two weeks, resolved with low-dose antipsychotic treatment.

Conclusions. Children, especially those with neurodevelopmental disorders, are more susceptible to a wide range of side effects. Therefore, this report highlights the necessity for careful pharmacological management. Additionally, this case represents a significant contribution to the scientific literature by being the first to document metoclopramide-induced acute psychosis in children to the best of our knowledge.

Key words: metoclopramide, acute psychosis, children, adverse drug reactions.

Children with comorbid conditions such as attention deficit hyperactivity disorder (ADHD) and mild intellectual disability often require multidrug regimens to manage their symptoms.[1] Methylphenidate, a central nervous system stimulant, is a common pharmacological treatment for ADHD[2], and is used effectively for both children with intellectual impairment and typically developing children.[2,3] Although the side effects of methylphenidate are typically transient, dose-dependent, and generally regarded as minor from a clinical standpoint[4], there is a risk of developing psychosis, albeit rarely.[5]

Metoclopramide is a dopamine receptor (D2) antagonist frequently prescribed for its antiemetic properties.[6] Although effective, metoclopramide is associated with a range of neuropsychiatric side effects, including extrapyramidal symptoms (EPS)[7,8], mood dysregulation, increased anxiety[9,10], and, in rare cases, psychotic reactions.[11]

✉ Gökçen İlçioğlu Ekici ▪ gokcen90ilcioglu@gmail.com

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Methylphenidate functions by inhibiting the dopamine transporter, consequently increase the extracellular levels of dopamine.[12,13] In contrast, antipsychotic agents (including dopamine receptor blockers such as metoclopramide) exert an opposing influence on the dopaminergic system. This divergence in their mechanisms of action can lead to potential pharmacodynamic antagonism.[14] The stimulant properties of methylphenidate may counterbalance[15] or interfere with the effects of dopamine antagonists, potentially exacerbating psychiatric symptoms or precipitating new ones in certain individuals.[16]

Acute-onset psychosis, also known as supersensitivity psychosis, is a condition caused by the sensitization of dopamine receptors due to prolonged blockade by long-term antipsychotic use.[17] Past research has shown that psychosis following metoclopramide use has been documented in two elderly patients with no prior psychiatric history.[11] However, to our knowledge, metoclopramide-induced rapid-onset psychosis has not been previously reported in the pediatric population.

We present the case of an 11-year-old girl with a background of mild intellectual disability and ADHD managed with methylphenidate, who developed rapid-onset psychosis following the administration of metoclopramide for acute gastrointestinal symptoms.

Case Presentation

The case in an 11-year-old girl followed-up at another center for two years prior, with diagnoses of ADHD and mild intellectual disability. She was also on a medical regimen of 10 mg/day of methylphenidate. The patient presented to the emergency department with complaints of high fever, nausea, and vomiting. Due to her nausea and vomiting, she was prescribed 10 mg of metoclopramide tablets. On the same day, she took two metoclopramide tablets along with 10 mg of methylphenidate. By the evening, she started exhibiting restlessness and agitation. She was talking to herself nonsensically. Upon returning to the emergency department, she was given intravenous hydration. Although her symptoms eased somewhat on the following day, her nonsensical speech and behavioral problems persisted. She refused to eat, and her sleep patterns became irregular. On the fourth day of persistent symptoms, the patient was brought to our clinic and admitted to the general pediatric ward.

The patient's birth history was unremarkable, and she had no previous history of seizures. There was consanguinity between the parents, who were second-degree cousins, but had no known neurological diseases in the family.

Upon initial psychiatric examination, she was conscious, oriented and cooperative. However, her affect was blunted, and she gave nonsensical answers to questions. Her associations were disorganized. Echolalia was observed during the interview, along with auditory and visual hallucinations. Her psychomotor activity was within normal limits. For the psychotic symptoms, haloperidol was initiated at a dose of 0.6 mg/day.

Given the sudden onset of her psychotic symptoms and her young age, consultations with the neurology and infectious diseases departments were requested to explore potential underlying organic causes. The primary differential diagnoses included encephalitis, delirium, and psychosis. The infectious diseases department initiated ceftriaxone and acyclovir treatments due to the possibility of encephalitis.

The initial blood test results for the patient indicated a glucose level of 88 mg/dL. Electrolytes were within the normal range: Na 138 mEq/L, K 4.1 mEq/L, Cl 108 mEq/L, Ca 9.2 mg/dL, Mg 2.1 mg/dL, and P 4.4 mg/dL. Renal function tests revealed normal results with uric acid at 4.3 mg/dL, urea at 28 mg/dL, and creatinine at 0.45 mg/dL. Her liver function tests were also all within the normal range. Specifically, total protein was measured at 71 g/L, albumin at 45

g/L, with aspartate aminotransferase (AST) at 18 U/L, alanine aminotransferase (ALT) at 13 U/L, alkaline phosphatase (ALP) at 179 U/L, and gamma-glutamyl transferase (GGT) at 16 U/L. Additionally, lactate dehydrogenase (LDH) was 269 U/L, total bilirubin 0.55 mg/dL, and direct bilirubin 0.2 mg/dL. The patient's C-reactive protein (CRP) level was below 0.5 mg/L.

The following day, she displayed increased restlessness and excessive activity, engaging in self-harming behaviors. Additionally, her previous symptoms persisted. Cranial and diffusion magnetic resonance imaging (MRI) and electroencephalogram (EEG) results were normal, and cerebrospinal fluid (CSF) analysis showed normal results. The haloperidol dose was revised to 1 mg/day.

On the third day of hospitalization, the patient was re-evaluated and found to have a decrease in visual and auditory hallucinations, improved sleep and appetite, but increased agitation. She had a blank look and avoided eye contact, exhibiting disorganized behaviors such as urinating on the side of the bed. The haloperidol dose was reduced to 0.6 mg/day.

On the fourth day, she had bilateral rigidity in the extremities and upward eye movement, defined as a haloperidol-induced EPS side effect. Haloperidol was discontinued, and biperiden 2.5 mg was administered intramuscularly, resulting in relief of joint stiffness.

By the fifth day, her overall condition had worsened. She responded incoherently to questions, and her emotional expression was dull. Nevertheless, the occurrence of hallucinations and disordered behaviors had markedly diminished. She engaged in sporadic soliloquies. Due to the substantial risk of EPS, it was deemed essential to start antipsychotic medication at an exceedingly low dose (quetiapine 6.25 mg twice daily). Two days later, she was partially responsive to questions but unable to sustain a conversation. Disorganized speech and behaviors had ceased, and there was no agitation or aggression. No side effects related to the medication were observed. Given the perceived benefit of treatment, the quetiapine dose was increased to 25 mg/day, divided into two doses.

Approximately 11 days after admission, the patient was thoroughly evaluated by multiple departments. CSF and blood cultures, as well as the viral meningitis panel, tests for thyroid autoantibodies, paraneoplastic indicators, limbic encephalitis panel, and viral markers, all yielded negative results. Additionally, other rheumatological factors, including anti-nuclear antibodies, anti-double-stranded DNA antibodies, extractable nuclear antigen profile, complement 3, and complement 4, were also found to be within normal limits. In addition, the patient's amino acid plasma panel and hereditary metabolic screening were also normal. Her symptoms entirely disappeared, and she regained her previous level of functioning.

In this case, comprehensive investigations and evaluations excluded infection, electrolyte imbalance, substance intoxication, excessive or prolonged use of any medication, or any other organic pathology as potential causes. Apart from changes in the patient's condition in response to antipsychotic treatment, no fluctuations in consciousness were observed, and orientation remained intact throughout this process. These findings ruled out delirium and led to the conclusion that the patient's presentation was most consistent with rapid-onset psychosis induced by metoclopramide.

The patient was discharged the following day. During a follow-up visit one week after discharge, the patient's associations were organized and goal-directed, and her affect was appropriate. She could attend school but appeared tired and sluggish during the day. This sedation was considered a side effect of quetiapine, and due to the complete resolution of symptoms, the dose was reduced to 12.5 mg/day. At her one-month follow-up, with no active symptoms or complaints, quetiapine medication was terminated.

The family provided a written consent form for this publication.

Discussion

This case study delves into the rare and remarkable occurrence of rapid-onset psychosis induced by metoclopramide, representing the first reported case of its kind in the pediatric population. The convergence of several factors appears to have facilitated the manifestation of such an atypical condition, particularly in a child. Firstly, the presence of mild intellectual disability and ADHD may have significantly contributed to the patient's susceptibility to this adverse reaction since individuals with neurodevelopmental disorders are at an increased risk of developing other mental health conditions, including psychosis.[18,19] This heightened vulnerability is partly due to the complex interplay between their underlying genetic, neurobiological abnormalities, and environmental stressors.[20,21] Furthermore, these individuals often require pharmacological interventions that can exacerbate or precipitate neuropsychiatric symptoms. Studies have shown that adverse drug reactions are more common in this population, necessitating careful management and monitoring of their pharmacotherapy regimens to mitigate potential risks.[22,23] Additionally, it is worth noting that the two other cases who developed psychosis after the administration of metoclopramide were of elderly age and had already suffered from a cerebrovascular event around 5-10 years earlier.[11] Therefore, each of these cases appear to exhibit some kind of neurological vulnerability, albeit in a distinct manner.

Another potential reason might be the use of a higher-than-usual dosage of metoclopramide. In our case, administering 20 mg of metoclopramide at short intervals on the same day might have increased dopamine receptor blockage, which in turn could have triggered dopamine supersensitivity. Certain factors, including the rapidity of drug withdrawal and the higher dosages, may contribute to the severity of hypersensitivity psychosis.[17,24] Although dopamine supersensitivity is typically observed following prolonged use of antipsychotic medication, literature reports indicate that it can also occur in individuals without a prior history of psychosis, particularly after discontinuation of short half-life drugs like metoclopramide.[17]

The final trigger for the patient's psychosis was probably the concomitant use of methylphenidate. Psychostimulants have been associated with psychotic symptoms in children with ADHD.[25,26] In light of the considerations explained above, their concurrent use with other medications like metoclopramide can further elevate this risk. Despite their divergent pharmacological mechanisms, stimulants and antipsychotics are frequently co-prescribed in clinical practice.[27] Nonetheless, the literature highlights that prolonged administration, abrupt cessation, or even acute exposure to dopamine-enhancing agents may precipitate complex drug interactions and adverse effects.[16,27]

To conclude, this case underscores the potential for serious neuropsychiatric reactions in children, particularly those with underlying neurodevelopmental disorders and concurrent psychostimulant use. It emphasizes the necessity for meticulous pharmacological management in such vulnerable populations.

Ethical approval

A written consent form was obtained from the family for this publication.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: GIE; data collection: GIE. analysis and interpretation of results: GIE, GSD, ANCK; draft manuscript preparation: GIE. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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