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LETTER TO THE EDITOR

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An Unrecognized Reaction: A Case of Cefuroxime-Induced Drug-Induced Enterocolitis Syndrome in a 7-Year-Old Child

Murat OZER

Department of Pediatric Immunology and Allergy, Ordu Training and Research Hospital, Ordu, Türkiye

Corresponding Author: Murat Ozer ✉ drmuratozer@yahoo.com

Dear Editor,

Drug-Induced Enterocolitis Syndrome (DIES) is an increasingly recognized but still underreported non-IgE-mediated hypersensitivity reaction, most commonly triggered by beta-lactam antibiotics. Clinically, it resembles Food Protein-Induced Enterocolitis Syndrome (FPIES), presenting with delayed gastrointestinal symptoms such as repetitive vomiting, lethargy, diarrhea, and hypotension within 1 to 4 hours after drug ingestion. However, due to the absence of specific biomarkers and the lack of standardized diagnostic criteria, diagnosing DIES remains challenging. Although its exact immunopathogenesis has not been fully elucidated, a T-cell-mediated response involving neutrophilic inflammation and cytokine release is suspected (1, 2). The limited number of reported cases has contributed to low awareness among healthcare professionals, often resulting in misdiagnosis or delayed intervention. In this report, we present a 7-year-old boy who developed DIES following oral administration of cefuroxime and describe in detail the clinical evaluation and management. To our knowledge, this is the first reported case of DIES associated with cefuroxime in the literature.

Our patient presented 5 months ago with complaints of nausea and vomiting approximately two hours after taking oral cefuroxime, followed by subsequent altered consciousness. Emergency department evaluation revealed acidosis in the blood gas. Intravenous (IV) hydration and ondansetron treatment were administered, leading to symptom resolution. Serum tryptase levels measured at the initial emergency department visit were within normal limits. Subsequently, in our clinic, to exclude suspected drug allergy, skin prick test (SPT) and intradermal test (IDT) were performed, with both early and late readings showing negative results. A patch test with cefuroxime was conducted, yielding negative results. The patient underwent an oral provocation test with cefuroxime, administered in incremental doses (10%, 40%, 50% of the maximum single dose) at 30-minute intervals. Approximately 1.5 hours after the final dose, the patient developed nausea and recurrent vomiting, followed by hypotension (blood pressure decreased from a baseline of 110/70 mmHg to 80/60 mmHg) and lethargy. Notably, there were no cutaneous or respiratory manifestations. IV fluid therapy with 0.9% NaCl and IV ondansetron were administered. Venous blood gas analysis revealed mild metabolic acidosis (pH 7.26; bicarbonate 18 mmol/L), and complete blood count showed neutrophil-dominant leukocytosis (leukocyte count: 18,200/μL; neutrophils: 70%). Serum tryptase level remained within normal limits (3.2 ng/mL). The patient was discharged 1.5 days later, after normalization of vital signs and improvement in oral intake.

ORCID Murat Ozer / 0000-0002-4832-7489

Table I: Diagnostic Criteria for Patients Presenting with Possible DIES

Major criteria
1. Vomiting in the 1- to 4-h period after ingestion of the suspected drug and absence of classic IgE-mediated allergic skin or respiratory symptoms
Minor criteria
1. A second episode of repetitive vomiting after ingestion of the same drug
2. Repetitive vomiting episode 1-4 h after ingestion of a different drug
3. Extreme lethargy
4. Marked pallor
5. Need for emergency department visit
6. Need for intravenous fluid support
7. Diarrhea in 24 h (usually 5-10 hours) after ingested drug
8. Hypothermia
9. Hypotension
DIES: Drug-induced enterocolitis syndrome
DIES is diagnosed when the patient fulfills the major criterion along with at least three minor criteria. In cases where only a single episode has occurred, a diagnostic oral provocation test is strongly recommended to confirm the diagnosis.
Adapted from: Van Thuijl A, et al. (4)

Similar to cases reported in the literature, our patient's clinical findings resemble those of FPIES. Nonetheless, DIES presents important distinctions, such as prior tolerance to the implicated drugs, longer reaction duration, and the lack of defined diagnostic biomarkers. As in our case, DIES is generally characterized by delayed symptom onset, recurrent vomiting, lethargy, and neutrophil-dominant leukocytosis (3-5). Prior studies have also indicated methemoglobin elevation in severe cases, though this was not detected in our patient (1).

The diagnostic criteria for DIES were first defined in 2019, based on reaction timing, clinical findings, and laboratory results (Table I) (4, 6). In the second month following the patient's discharge, repeat allergic evaluation was performed, with negative results for SPT and IDT. Subsequently, three doses of cefuroxime were administered intravenously, and no reaction developed. This finding suggests that the drug only triggered a reaction when taken orally.

DIES has a distinct mechanism compared to Type A drug reactions. Type A reactions are usually dose-dependent and predictable based on pharmacological properties, whereas DIES is a non-IgE-mediated, idiosyncratic reaction developing through specific immunological mechanisms (7). Unlike Type A drug reactions, which are dose-dependent and related to the pharmacological properties of the drug, DIES is a non-IgE-mediated hypersensitivity reaction that occurs only in susceptible individuals and is characterized by gastrointestinal inflammation, a neutrophil-dominant immune response, and possible cytokine release. Type A reactions generally do not show significant systemic involvement and are associated with expected side effects; in contrast, DIES can lead to severe dehydration, hypotension, and shock. Therefore, it is very important to distinguish DIES from Type A reactions in order to provide appropriate treatment. Due to the very low number of cases reported worldwide, some cases may have been misdiagnosed as Type A drug reactions, suggesting that the true incidence of DIES may be higher than currently known (4,7).

DIES is an uncommon, non-IgE-mediated hypersensitivity reaction with few published pediatric cases. Most have been linked to amoxicillin or its combination with clavulanic acid (1). Yet, the reaction is not exclusive to these agents. Reports of DIES after paracetamol (8) and pantoprazole (9) use illustrate that non-antibiotic drugs can also provoke this syndrome.

Van Thuijl et al. highlighted that DIES should be included among the differential diagnoses of drug-induced reactions, documenting several cases caused by different medications (4). Our report describes, to the best of our knowledge, the first pediatric case of DIES triggered by cefuroxime. Previously, all three pediatric DIES cases reported from Türkiye involved amoxicillin-clavulanic acid (10,11). Thus, our observation expands the range of implicated agents and emphasizes that DIES should be considered in children who develop delayed gastrointestinal symptoms after drug exposure, particularly in the absence of typical IgE-mediated features.

This is the first reported case of cefuroxime-induced DIES and highlights the need for awareness of this distinct clinical entity. Most previously reported cases have implicated amoxicillin-clavulanic acid as the causative agent. In this context, our case represents the first reported instance of DIES associated with cefuroxime, contributing valuable insights to the literature. Further investigations are needed to clarify the underlying mechanisms, establish clearer diagnostic criteria, and define the long-term outcomes of DIES. Considering the diagnostic difficulties and limited clinical awareness surrounding this entity, we believe that our report will help raise recognition and support more accurate management of affected patients.

Sincerely,

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