



Available online at
ScienceDirect
 www.sciencedirect.com

Elsevier Masson France
EM|consulte
 www.em-consulte.com



Short communication

Drug-induced enterocolitis syndrome: A rare, severe, non-IgE-mediated immediate drug allergy. Case report and literature review



C. Eyraud^a, P. Biermé^a, M. Adam^a, C. Braun^{a,b,c,*}

^a Service de Pédiatrie, Pneumologie, Allergologie et Mucoviscidose, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Bron, France

^b Centre International de Recherche en Infectiologie, INSERM U1111, CNRS UMR 5308, UCBL1, ENS de Lyon, Lyon, France

^c Université Claude Bernard Lyon 1, Lyon, France

ARTICLE INFO

Article History:

Received 1 February 2022

Revised 29 August 2022

Accepted 11 November 2022

Available online 30 November 2022

Keywords:

Drug-induced enterocolitis syndrome

Non-IgE-mediated allergy

Food protein-induced enterocolitis syndrome

Drug hypersensitivity reaction

ABSTRACT

We report the case of a 4-year-old child who presented with vomiting, abdominal pain, and intense pallor 2 h after amoxicillin ingestion. An IgE-mediated reaction was suspected at first, which was finally diagnosed as a drug-induced enterocolitis syndrome. In this rare and poorly described non-IgE-mediated drug allergy, adrenaline is not effective. This diagnostic challenge must be known in order to administer adequate treatment, i.e., antiemetic drugs (ondansetron) and fluid challenge.

© 2022 French Society of Pediatrics. Published by Elsevier Masson SAS. All rights reserved.

1. Introduction

Drug allergies are often associated with skin eruption: urticaria in immediate, IgE-mediated allergies, which in the most severe forms are accompanied by respiratory (cough, dyspnea) and/or digestive (abdominal pain, vomiting) symptoms, and even anaphylactic shock; maculopapular exanthema, acute generalized exanthematous pustulosis, fixed drug eruption, or even erythroderma or toxic epidermal necrolysis have been reported in the most severe forms. An allergy form with isolated digestive involvement, called “drug-induced enterocolitis syndrome” (DIES), has been described in rare case reports. However, it is necessary to recognize it in order to ensure adequate management. We present a case of DIES, initially treated as an IgE-mediated allergy, in which the diagnosis was quickly rectified, allowing for appropriate treatment.

2. Case report

A 4-year-old girl was referred to the Allergology Department in Bron for suspected immediate hypersensitivity to amoxicillin (AMX). The suspicious reaction had occurred 2 years earlier. The child had been treated with antibiotics for septic arthritis of the knee: cefuroxime intravenously for 4 days, and then amoxicillin–clavulanic acid

(AMX-CLAV) orally for 17 days. On the seventh day of treatment with AMX-CLAV, a progressively extensive erythematous rash occurred followed by eyelid edema, occurred, without respiratory or digestive symptoms. Symptoms disappeared 4 h after AMX-CLAV was stopped and antihistamine was administered. As is often the case, the time between taking the drug and the onset of symptoms was not certain.

She was therefore seen at our allergology department at the age of 4 years. On her doctor's advice, she had not been given any further AMX or AMX-CLAV. She had been treated with cefpodoxime for otitis, and no reaction was noted. At this first consultation, an intradermal test (IDT) with AMX-CLAV 20 mg/mL was negative. A booster dose of 1/100 of the therapeutic dose (i.e., 0.25 mg/kg=3.5 mg) was administered and no reaction occurred during the 1-h monitoring period. The patient was seen for a challenge 2 months later with a complete dose of AMX-CLAV. The IDT was still negative. The challenge was performed with gradual doses: 1/100e (0.25 mg/kg=3.5 mg), 1/10e (2.5 mg/kg=35 mg), and the full therapeutic dose (25 mg/kg=350 mg), with a delay of 1 h between each dose. At 2 h after the full dose, the patient experienced an episode of emesis, abdominal pain, intense pallor, and tachycardia, without any other skin nor respiratory symptoms. Blood pressure was stable. An initial intramuscular injection of 150 µg adrenaline was made in combination with an IV fluid challenge (20 ml/kg of saline solution in 10 min). Emesis recurred 10 min later and persisted for more than 30 min despite a second injection of 150 µg adrenaline. The vomiting stopped after the administration of 2 mg IV ondansetron. No vomiting or other symptoms occurred during the next 24 h of monitoring.

Abbreviations: IDT, intradermal test; IV, intravenous; DIES, drug-induced enterocolitis syndrome; AMX, amoxicillin; AMX-CLAV, amoxicillin–clavulanic acid

* Corresponding author.

E-mail address: camille.braun01@chu-lyon.fr (C. Braun).

<https://doi.org/10.1016/j.arcped.2022.11.007>

0929-693X/© 2022 French Society of Pediatrics. Published by Elsevier Masson SAS. All rights reserved.

Table 1
Description of 11 other cases of DIES reported in the scientific literature until 2022^a.

Reference	Initial reaction			DPT					Alternative, cross reactivity
	Culprit drug	Culprit drug previously tolerated	History of drug reaction	Age	Symptoms	Latency between drug administration and onset of symptoms	Treatment	Biological exams	
Novembre et al. 2014 [1]	AMX	Yes	At 1 year of life, persistent vomiting 1–2 h after ingestion of AMX, next day a morbilliform rash appeared	6	Vomiting, diarrhea, pallor, lethargy, hypotension	2 h	IV hydrocortisone and saline solution	WBC 20.5 G/L (H3) and 12.8 G/L (H18) Neutrophils 16.8 G/L (H3) and 8.3 G/L (H18) pH 7.33 MetHb 1.1% Normal tryptase	n.s.
Infante et al. 2017 [2]	AMX	Yes	At 2 years of life, acute urticaria	3	Abdominal pain, vomiting, mild malaise	1st DPT: 2 h 2nd DPT: 4 h	1st DPT: methylprednisolone, dexchlorpheniramine 2nd DPT: antiemetics, hydrocortisone, saline solution	1st DPT: n.s. 2nd DPT: WBC 17.8 G/L Neutrophils 13.1 G/L Normal tryptase	Penicillin V tolerated
Garcia Rodriguez et al., 2017 [7]	AMX/CLV	Yes	Vomiting, diarrhea, malaise. A similar prior reaction with the same drug a few months earlier	60	Abdominal pain, vomiting, low oxygen saturation, hypotension, drowsiness	2 h	IM epinephrine, IV hydrocortisone and ondansetron, oxygen therapy.	Neutrophils 2.9 G/L (H1), 11.6 G/L (H5) pH 7.25 (H1), 7.35 (H5) Normal tryptase	n.s.
Van Thuijl et al. 2019 [3]	AMX	Unknown	At 2 years of age, erythematous skin reaction. At 4 years of age, repetitive vomiting and lethargy	4	Severe abdominal pain, persistent vomiting, lethargy	1.5 h	IM epinephrine (repeated after 90 min), IV hydrocortisone, ondansetron	WBC 24.0 G/L Neutrophils 19.8 G/L Normal tryptase	n.s.
Freundt Serpa et al. 2020 [8]	AMX/CLV	No	At 9 years of age, vomiting after IV infusion	18	1st DPT: Epigastric pain, dizziness, nausea and one vomit 2nd DPT: abdominal pain, profuse diarrhea, nausea and repetitive vomits, marked pallor and dizziness	1st DPT: 2.5 h 2nd DPT: 1.5 h	1st DPT: saline solution, ranitidine and ondansetron 2nd DPT: saline solution, ranitidine, ondansetron, methylprednisolone, loperamide	1st DPT: n.s. 2nd DPT: Stool ECP 77.4 (H24) and 50 (H48) $\mu\text{g/g}$ feces, normalized after 6 weeks (2 $\mu\text{g/g}$ feces)	Penicillin G and V tolerated at DPT
Worcel et al. 2020 [4]	AMX	Yes	Repetitive vomiting, pallor, diarrhea	10	Repetitive and protracted vomiting with pallor, lethargy, abdominal pain Watery Diarrhea 8 h later	3 h	Desloratadine and prednisolone	n. p	Penicillin V and cefpodoxime tolerated at DPT
Mori et al. 2021 [5]	AMX/CLV	Yes	Two years earlier, angioedema of hands and feet	6	Protracted vomiting, pallor, lethargy, dehydration	2.5 h	IV saline solution	WBC 15.3 G/L Neutrophils 13.2 G/L MethHb 0.7%	n.s.
Mori et al. 2021 [5]	AMX/CLV (DPT with AMX)	Yes	Some years earlier some episodes of persistent vomiting with streaks of blood, lethargy	14	Protracted vomiting, pallor, lethargy, abdominal pain, malaise, dehydration	2.5 h	IV ondansetron and saline solution	WBC 10.7 G/L Neutrophils 9.3 G/L Normal pH	Cefpodoxime tolerated at DPT
Mori et al. 2021 [5]	AMX	Yes	Maculopapular exanthema	9	1st DPT: vomiting 2nd DPT: protracted vomiting, pallor, lethargy, dehydration	1st DPT: 3 h 2nd DPT: 2.5 h	IV saline solution and ondansetron	n.s.	Cefuroxime tolerated at DPT

(continued on next page)

Table 1 (Continued)

Bouvette et al. 2020 [6]	Pantoprazole	Unknown	Vomiting, profuse bloody diarrhea, abdominal pain, hypotension	69	1 h	Nausea, vomiting, diarrhea, abdominal pain, high blood pressure, rapid heart rate, low blood oxygen saturation, hypovolemia	IM epinephrine, IV diphenhydramine, IV methylprednisolone, IV antiemetic, IV saline solution	WBC 14.0 G/L Neutrophils 10.5 G/L pH 7.30	n.s.
Bouvette et al. 2020 [6]	Pantoprazole	Unknown	Vomiting, profuse bloody diarrhea, abdominal pain, hypotension	69	1 h	Nausea, vomiting, diarrhea, abdominal pain, high blood pressure, rapid heart rate, low blood oxygen saturation, hypovolemia	IM epinephrine, IV diphenhydramine, IV methylprednisolone, IV antiemetic, IV saline solution	WBC 14.0 G/L Neutrophils 10.5 G/L pH 7.30	n.s.
Pascal et al. 2022 [9]	Acetaminophen (paracetamol)	No	At 10 months, asthenia, pallor, tachycardia, 4 vomits without diarrhea. Gastrointestinal symptoms at each five intakes of paracetamol	1	2 h	Repeated vomiting, marked pallor, lethargy without cutaneous or respiratory symptoms	IV saline solution, corticosteroids	Neutrophils 11.1 G/L Normal tryptase	Ibuprofen tolerated

^a Review of the published cases according to the last search of PubMed in June 2022. In gray: adults; in white: children. AMX: amoxicillin. CLV: clavulanic acid. DPT: drug provocation test. WBC: whole blood count. ECP: eosinophil cationic protein; IM: intramuscular. IV: intravenous. n.s.: not specified. MethHb: methemoglobin.

During the reaction, tryptase levels were stable: 3.2 $\mu\text{g/L}$ at the beginning of the reaction and 3.3 $\mu\text{g/L}$ 30 min later. We also learned that during the first 1/100 challenge 2 months earlier, the patient vomited at home about 4 h after taking the AMX–CLAV. This had been attributed to gastroenteritis.

In order to avoid CLAV-induced reaction, the patient was seen again in hospital for a challenge with AMX. A single dose corresponding to 1/100 of the therapeutic dose (0.25 mg/kg=3.5 mg) was administered. Abdominal pain and incoercible vomiting occurred 4 h after intake. The child was prostrated and rapidly became pale and lethargic. Blood pressure was stable. Once again, there were no respiratory symptoms or skin eruption. She was quickly treated with 2.3 mg IV ondansetron and fluid challenge (20 mL/kg of saline solution in 10 min). With this treatment, the symptoms recovered in less than 30 min.

On the basis of all these findings, we concluded on the diagnosis of AMX-induced DIES. We recommended avoiding AMX. Because cefuroxime was well tolerated, we allowed the use of cephalosporins.

3. Discussion

DIES is a rare and poorly known type of non-immediate drug hypersensitivity (HS). Only 11 cases have been reported in the literature, including seven in children (Table 1) [1–9]. Its clinical description resembles that of food protein-induced enterocolitis syndrome (FPIES) and diagnostic criteria for DIES have been proposed by Van Thuijl et al. (Table 2) [3]. In our case, the diagnosis was made on the basis of the presence of the major criterion and five minor criteria (a second episode of repetitive vomiting after ingestion of the same drug, i.e., AMX, extreme lethargy, marked pallor, need for an emergency department visit, and need for IV fluid support).

In its initial description, DIES is an acute non-IgE-mediated reaction, since symptoms occur between 1 and 4 h after ingestion of the causative drug [5]. The 1-h interval and the absence of skin and respiratory involvement distinguish it from an IgE-mediated reaction (Table 3). The absence of tryptase elevation is also a strong argument for a non-IgE-mediated reaction. This distinction is important because, as illustrated in our case, adrenaline is not effective in treating DIES. As with FPIES, acute treatment combines IV ondansetron and fluid challenge, and early management allows for rapid resolution of symptoms [5]. The use of corticosteroids could be helpful [3,7], but their efficacy in DIES is not proved. Moreover, while the majority of reported clinical cases, including our case, are antibiotic-induced DIES [5] (mainly AMX), one case of DIES due to pantoprazole, a proton pump inhibitor, has been published [6].

The pathophysiology of DIES is not known. Drawing a parallel with FPIES (whose pathophysiology is still obscure), the hypothesis is

Table 2
Diagnostic criteria of drug-induced enterocolitis syndrome (DIES) (From Van Thuijl et al. [3]).

MAJOR CRITERION	MINOR CRITERIA
Vomiting in the 1–4-h period after ingestion of the culprit drug and absence of classic IgE-mediated allergic skin or respiratory symptoms	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) Diarrhea in 24 h (usually 5–10 h) after ingested drug 7) Hypotension 8) Hypothermia

The diagnosis of DIES is made if patient meets the major criterion and at least three minor criteria.

Table 3
Differences between IgE-mediated drug allergy and drug-induced enterocolitis syndrome.

	IGE-MEDIATED DRUG ALLERGY	DRUG-INDUCED ENTEROCOLITIS SYNDROME
Mechanism	IgE-mediated mechanism	Unknown (T cell-dependent mechanism?)
Time latency	Minutes or < 1 h after exposure to drug	1–4 h after exposure to drug
Clinical symptoms		
Cutaneous signs	Urticaria, angioedema	No skin symptoms
Respiratory signs	Rhinitis, bronchospasm	No respiratory symptoms
Digestive signs	Abdominal pain, vomiting	Repeated vomiting
Most severe reaction	ANAPHYLACTIC SHOCK	HYPOVOLEMIC SHOCK
Paraclinical signs		
Laboratory finding	Tryptase elevation	No tryptase elevation <i>More studies required to confirm:</i> <i>Increase in methemoglobin [1,5]</i> <i>Increase in ECP in stool samples [8]</i>
Allergy tests	Prick and intradermal tests Drug-specific IgE	Negative skin tests and specific IgE
Treatment		
Treatment in the acute phase	Epinephrine (anaphylaxis) Antihistaminic (mild reactions)	Intravenous fluids Intravenous ondansetron <i>Systemic corticoids?</i>
Long-term treatment	Drug avoidance Desensitization if culprit antibiotic needed	Drug avoidance <i>Desensitization?</i>

ECP: eosinophil cationic protein.

that of a reaction mediated by T cells infiltrating the digestive tract [10]. Upon exposure to their specific antigen, T cells would be activated, inducing in situ lesions and fluid leakage. Some argue that innate immunity is probably involved in DIES, as illustrated by the increase in blood neutrophils in some patients [5]. This is most likely the case, as innate immunity is necessarily associated with adaptive immunity. Nevertheless, the tolerance of some treatments (such as cefpodoxime in our case) and the occurrence of a reaction only upon exposure to AMX indicates the specificity of the reaction, and thus the presence of a specific immune response. Several factors explain the lack of additional data on the pathophysiology of DIES: its rarity, the difficulty of obtaining samples of the digestive tract at the time of the reaction but also at a distance, and the absence of tests to confirm the diagnosis. Lymphocyte transformation tests could provide valuable information, such as the presence of drug-specific T cells, their activation phenotype, and the cytokines released during their

activation. This technique is used for research purposes and not much in routine practice.

The question of pathophysiology is associated with the question of an environment favoring the occurrence of a DIES. Our patient was fed with a cow’s milk protein hydrolysate at the age of 1.5 months for recurrent crying and possible abdominal pain. Cow’s milk was reintroduced after 6 months of avoidance. Although the early reintroduction test with cow’s milk, which is the gold standard test for the diagnosis of non-IgE-mediated cow’s milk allergy [10] was not performed, one can suspect an underlying digestive fragility.

4. Conclusion

Particular attention should be paid to DIES, because although the reaction appears to be “immediate” (i.e., less than 6 h after drug exposure), adrenaline is not effective and IgE is not involved. It is therefore important to remain vigilant when faced with significant vomiting within 4 h of taking a drug, and to ask for an allergy work-up at the slightest doubt.

Funding

None.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article to disclose.

References

[1] Novembre E, Mori F, Barni S, et al. Drug-induced enterocolitis syndrome (DIES). *Pediatr Allergy Immunol* 2014;25:415–6.

[2] Infante S, Zapatero L. Drug-induced enterocolitis syndrome by amoxicillin. *Pediatr Allergy Immunol* 2017;28:105–6.

[3] Van Thuijl AOJ, Landzaat LJ, Liem O, et al. Drug-induced enterocolitis syndrome (DIES): a clinical entity that deserves more awareness. *Ann Allergy Asthma Immunol* 2019;122:538–9.

[4] Worcel J, Tarelho M, Baron M, et al. Drug-induced enterocolitis syndrome (DIES) in a 10-year-old girl. *Arch Pediatr* 2020;27:51–2.

[5] Mori F, Liccioli G, Fuchs O, et al. Drug-induced enterocolitis syndrome: similarities and differences compared with food protein-induced enterocolitis syndrome. *Pediatr Allergy Immunol* 2021;32:1165–72.

[6] Bouvette G, Verreault N, Gagnon N, et al. Drug-induced enterocolitis syndrome (DIES) with pantoprazole in an adult patient. *J Allergy Clin Immunol Pract* 2020;8:3183–4.

[7] García Rodríguez R, Alfaya Arias T, Borja Segade J, et al. Drug-induced enterocolitis in an adult patient. *J Allergy Clin Immunol Pract* 2017;5:1752–3.

[8] Freundt Serpa NP, Sánchez-Morillas L, Jaqueti Moreno P, et al. Drug-induced enterocolitis syndrome due to amoxicillin-clavulanic acid with good tolerance to penicillin. *J Investig Allergol Clin Immunol* 2020;30:301–2.

[9] Pascal B, Evrard B, Merlin E, et al. Drug-induced enterocolitis syndrome with paracetamol (acetaminophen) in a 12-month-old boy. *Pediatr Allergy Immunol* 2022;33:e13755.

[10] Labrosse R, Graham F, Caubet JC. Non-IgE-mediated gastrointestinal food allergies in children: an update. *Nutrients* 2020;12:2086.