



Available online at
ScienceDirect
www.sciencedirect.com

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



Short communication

Drug-induced enterocolitis syndrome (DIES) in a 10-year-old girl

J. Worcel^a, M. Tarelho^a, M. Baron^b, C. Ponvert^a, E. Bidat^b, G. Benoist^b, G. Lezmi^{a,c,*}

^aService de pneumologie et allergologie pédiatriques, hôpital Necker-Enfants Malades, AP-HP, Paris, France

^bService de pédiatrie générale, hôpital Ambroise Paré, AP-HP, Boulogne-Billancourt, France

^cUniversité Paris Descartes, Paris, France

ARTICLE INFO

Article history:

Received 31 January 2019

Received in revised form 30 August 2019

Accepted 11 November 2019

Available online xxx

Keywords:

Drug-induced enterocolitis syndrome

Antibiotic

Food protein-induced enterocolitis syndrome

ABSTRACT

We report the case of a child presenting with an adverse drug reaction highly suggestive of drug-induced enterocolitis syndrome (DIES) to amoxicillin (AMX). A 10-year-old girl developed repetitive vomiting and pallor without cutaneous or respiratory symptoms 2 h after AMX intake. DIES is not a well-described entity, and very few data are available in the literature. In the absence of an existing definition, the diagnosis of DIES can only be suspected and is based on its homology with food protein-induced enterocolitis (FPIES). The major criterion is the recurrence of repetitive and often incoercible vomiting occurring within 1–4 h of ingestion of the culprit food in the absence of IgE-mediated allergic classic skin and respiratory symptoms. Once the diagnosis of DIES to AMX is suspected, an open challenge with AMX should be undertaken with caution, under medical supervision in a day hospital unit because of the risk of severe recurrence. Once the diagnosis is confirmed, AMX should be contraindicated to avoid severe reactions.

© 2019 French Society of Pediatrics. Published by Elsevier Masson SAS. All rights reserved.

1. Introduction

Drug-induced enterocolitis syndrome (DIES) is a poorly described nonimmediate adverse drug reaction. In the absence of validated diagnostic criteria, the diagnosis of DIES is based on that of food protein-induced enterocolitis (FPIES). We report a highly probable case of DIES to amoxicillin (AMX) in a child.

2. Observation

A 10-year-old girl was referred for a suspected drug hypersensitivity reaction to AMX that had been administered 9 months before for acute otitis media. She had previously tolerated this beta-lactam agent. However, 2 h after intake of the first dose, she developed repetitive vomiting and pallor without cutaneous or respiratory symptoms. She was admitted to an emergency department. At initial examination, she had no fever, no dehydration, and blood pressure was normal. Symptoms resolved spontaneously without antiemetics or infusion within 2–3 h; 10 h later, she developed a watery diarrhea that resolved spontaneously within a few hours. After the reaction, she did not receive any antibiotics and she tolerated paracetamol.

Because the suspicion of DIES to AMX was low, and the index reaction was nonimmediate and nonsevere, a supervised drug provocation test (DPT) was proposed without prior skin tests (STs). The patient received 1000 mg of AMX (32 mg/kg) and, in the absence of an immediate reaction, was discharged after 1 h. At 3 h after AMX ingestion, she developed repetitive and protracted vomiting with pallor, lethargy, and abdominal pain. She received 5 mg of desloratadine and 40 mg of prednisolone, and was admitted to an emergency department because symptoms persisted. She had no fever, no dehydration, no cutaneous or respiratory involvements, and blood pressure was normal. No blood tests were performed. She was rehydrated orally, and symptoms resolved within 2 h without infusion or antiemetics. The patient developed a weak watery diarrhea 8 h later.

An allergological work-up was performed 6 weeks after the DPT, including prick tests (PTs) and intradermal tests with the soluble forms of AMX, benzyl-penicillin, and cefuroxime, as previously described [1]. Responses were negative at 15–20 min, 6–8 h, and 48–72 h. The dosage of specific IgE against AMX was not given, because an IgE mechanism was unlikely, and both the PT and intradermal tests yielded negative results in the immediate readings. In addition, their predictive values for the diagnosis of IgE-mediated reactions to drugs in children are very low. DPTs were performed with alternate drugs, including phenoxymethylpenicillin (Oracilline[®] 2,000,000 UI/day, 65,000 UI/kg/day) and cefpodoxime (Orelox[®] 250 mg/day, 8 mg/kg/day) in our day

* Corresponding author at: Service de pneumologie et allergologie pédiatriques, hôpital Necker-Enfants Malades, AP-HP, Paris, France.
E-mail address: guillaume.lezmi@aphp.fr (G. Lezmi).

hospital unit, and were prolonged at home for a total of 3 days. No reaction occurred.

3. Discussion

DIES is not a well-described entity. In the absence of an existing definition, the diagnosis of DIES is suspected and is based on its homology with FPIES. FPIES is considered to be a gastrointestinal food allergy of infancy, although it is also described in older children or adults [2]. There is also no validated biomarker for the diagnosis of FPIES, and the diagnosis is based only on the presence of typical symptoms. Symptoms depend on the frequency of food exposure. Chronic FPIES occurs when foods are consumed on a regular basis, for example, cow's milk or soy formula. Regular exposure results in non-specific symptoms including chronic diarrhea and failure to thrive, which resolve within days of elimination of the offending food. Then, after a period of avoidance, a typical acute FPIES occurs at re-exposure. For foods that are not consumed regularly, no chronic symptoms are observed, but occasional exposure results in acute FPIES. Chronic diarrhea and weight loss may have other causes than delayed food allergy, and they should be investigated. The clinical presentation of acute FPIES is typical, and recent guidelines defined criteria to improve its recognition [3]. The major criterion is the recurrence of repetitive and often incoercible vomiting in the 1–4-h period after the ingestion of the culprit food, in the absence of IgE-mediated allergic classic skin and respiratory symptoms. Three or more minor criteria are also required for the diagnosis of FPIES including lethargy, pallor, diarrhea within 24 h of ingestion, need for emergency department visit, intravenous hydration, hypotension, hypothermia, and increased neutrophil count $> 1500/\text{mm}^3$ above the baseline count. An oral food challenge (OFC) is generally not indicated for the diagnosis of FPIES if the history is convincing given the risk of recurrence of a severe reaction. However, OFC is indicated 12–18 months after the last reaction to assess the development of tolerance [2,3]. The diagnosis of FPIES during a food challenge requires the symptom of typical repetitive vomiting (major criteria) and at least two minor criteria. Acute FPIES mimics other conditions such as sepsis or gastroenteritis, but lethargy, floppiness, pallor, in the absence of fever, and a normal C-reactive protein (CRP) level may alert against a differential diagnosis [4]. In addition, acute FPIES typically completely resolves in a few hours. The clinical presentation of acute FPIES differs from IgE-mediated allergy because of its delayed onset, the absence of cutaneous or respiratory symptoms, and because allergy test results, including skin tests, and specific IgE levels are usually normal. Laboratory findings such as increased white blood cell count with neutrophilia, thrombocytosis, metabolic acidosis, and methemoglobinemia can be present in acute FPIES, but they are not specific and not mandatory for the diagnosis [3]. Acute FPIES is considered mild–moderate when vomiting is intermittent and self-resolving by oral rehydration. FPIES is severe when the patient has projectile and repetitive (≥ 4) vomiting, lethargy, pallor, dehydration, and needs intravenous fluids.

In our patient, moderate acute DIES to AMX was highly probable because:

- she had been previously sensitized
- she had a positive DPT with typical repetitive vomiting 1–4 h after ingestion of AMX
- she had three of the minor criteria, and;
- no other differential diagnoses including septic shock, metabolic disease, or surgical emergency were plausible.

The pathogenesis of FPIES and DIES is poorly understood. These entities are considered to be non-IgE-mediated allergies. Recent data showed the paucity of both humoral and cellular specific immune responses and the potential involvement of innate immunity in the pathogenesis of FPIES [5,6].

In our patient, ST results were negative in immediate and late readings, confirming the absence of both humoral and cellular sensitizations. Three cases of DIES to AMX in children [7–9] and one case to AMX/clavulanic acid in an adult have been reported in the literature [10]. To the best of our knowledge, no cases of DIES to other drugs have been reported. As in our case, DIES was diagnosed based on a positive response to DPT, in the absence of other plausible causes. DPTs with AMX or AMX/clavulanic acid were performed in all cases, but the potential cross-reactivity to phenoxymethylpenicillin and cephalosporins was not assessed. Our patient tolerated phenoxymethylpenicillin, indicating that the side chain of AMX rather than the beta-lactam ring is involved in the pathogenesis of DIES to AMX. Our patient also tolerated cefpodoxime, indicating that there was no cross-reactivity with cephalosporins. Finally, as in our case, the recurrence of more severe symptoms was observed in all patients, including dehydration and hypotension. Although the majority of children with FPIES will outgrow their disease by the age of 3–5 years (2), the prognosis of DIES is unknown.

4. Conclusion

Although rare, the diagnosis of DIES to AMX should be suspected when repetitive vomiting without skin or respiratory symptoms occurs within a few hours of drug intake, in the absence of other plausible diagnoses. A DPT with AMX should be performed with caution, under medical supervision in a day hospital unit because of the risk of severe recurrence. In the case of positive DPT results, the diagnosis is confirmed and AMX should be contraindicated to avoid severe reactions. Before being prescribed, tolerance of other penicillins and cephalosporins should be assessed.

Disclosure of interest

The authors declare that they have no competing interest.

References

- [1] Lezmi G, Alrowaishdi F, Bados-Albiero A, et al. Non-immediate-reading skin tests and prolonged challenges in non-immediate hypersensitivity to beta-lactams in children. *Pediatr Allergy Immunol* 2018;29:84–9.
- [2] Feuille E, Nowak-Węgrzyn A. Recognizing and Treating Food Protein-Induced Enterocolitis Syndrome. *Allergy* 2019;74:2019–22.
- [3] Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2017;139 [1111–26.e4].
- [4] Lee E, Barnes EH, Mehr S, et al. Differentiating acute food protein-induced enterocolitis syndrome from its mimics: a comparison of clinical features and routine laboratory biomarkers. *J Allergy Clin Immunol Pract* 2019;7 [471–8.e3].
- [5] Adel-Patient K, Lezmi G, Castelli F, et al. Deep analysis of immune response and metabolic signature in children with food protein induced enterocolitis to cow's milk. *Clin Transl Allergy* 2018;8:38.
- [6] Mehr S, Lee E, Hsu P, et al. Innate immune activation occurs in acute food protein-induced enterocolitis syndrome reactions. *J Allergy Clin Immunol* 2019;144 [600–2.e2].
- [7] Novembre E, Mori F, Barni S, et al. Drug-Induced Enterocolitis Syndrome (DIES). *Pediatr Allergy Immunol* 2014;25:415–6.
- [8] Infante S, Zapatero L. Drug-induced enterocolitis syndrome by amoxicillin. *Pediatr Allergy Immunol* 2017;28:105–6.
- [9] Van Thuijl A, Landzaat L, Liemy O, et al. Drug induced enterocolitis syndrome (DIES). *Ann Allergy Asthma Immunol* 2019;122:532–42.
- [10] 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.