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UNDERSTANDING DRUG-INDUCED ENTEROCOLITIS

Catarina Maria Queirós Fraga, Ana Rita Barroca Macedo, Ana Carolina Coelho de Castro, Georgeta Maria Costa Alves de Oliveira.

Pediatrics Department of Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Oporto, Portugal.

ABSTRACT

Drug-induced enterocolitis syndrome (DIES) is a rare but potentially fatal non-IgE-mediated hypersensitivity reaction triggered by drugs. It often presents with gastrointestinal symptoms similar to those of food protein-induced enterocolitis syndrome (FPIES). The authors report the case of a 10-year-old girl who suffered from severe vomiting and diarrhoea after taking amoxicillin-clavulanic acid. A hospital-based oral drug challenge with amoxicillin replicated her symptoms, confirming DIES diagnosis. Supportive measures led to positive outcomes. We discuss the diagnostic criteria, management strategies and the importance of greater awareness in identifying cases of DIES. Despite its rarity, we advocate for hospital-based oral challenges when DIES is suspected, facilitating prompt diagnosis and management of potentially severe reactions

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A 10-year-old female child of European origin, with no relevant past history, namely atopic disease and a complete national vaccination program, was referred by the attending paediatrician to the Paediatric Immunology and Allergology clinic due to a suspected allergy to the combination of amoxicillin-clavulanic acid. In the episode that led to suspicion, she experienced uncontrollable vomiting and profuse diarrhoea one hour after taking 1200 mg of the drug in formulation 14:1, prescribed to treat acute otitis.

Upon reviewing the patient's medical history, the caregivers reported five other episodes of copious vomiting and diarrhoea beginning at the age of two, consistently following the administration of amoxicillin or amoxicillin-clavulanic acid. Following these occurrences, they sought urgent medical attention at private healthcare facilities, attributing the symptoms to the side effects of the medication. During three out of five of these episodes, the patient required hospitalization due to oral intolerance, completing the antibiotic regimen via intravenous administration.

About a month after the referral and seven months after the episode, she was proposed for a direct (without preceding skin tests) oral drug challenge. To avoid any potential adverse gastrointestinal reaction due to clavulanate, only amoxicillin was used instead of amoxicillin-clavulanate. Therefore, the challenge involved a full standard dose of 45 mg/kg of amoxicillin, without grading, corresponding to a total daily dose of 90 mg/kg.

At the beginning of the challenge, the patient's vital signs were normal, with a temperature of 36.7°C, blood pressure within the 50th percentile range and heart rate of 120 beats per minute. Two and a half hours after taking the amoxicillin, she experienced lethargy and pallor followed by nausea and three episodes of profuse vomiting. She had no skin rashes or respiratory symptoms. Her blood pressure and heart rate maintained above the 5th percentile. We administered 4 mg of intravenous ondansetron and a normal saline bolus of 10 mL/kg with progressive recovery. Three hours after the beginning of the challenge, she had colicky abdominal pain followed by two large, foul-smelling bowel movements of soft to liquid consistency, with no visible blood or mucus. No complementary study was performed. The patient was discharged after four hours of hospital surveillance, with complete clinical recovery, good oral tolerance and no further diarrhoeal episodes. Written information was provided to advise future amoxicillin avoidance, as well as an allergy action plan in case of an accidental administration.

Address for Correspondance: Catarina Maria Queirós Fraga, Rua Eduardo Torres 4464-513 Senhora da Hora.

Email: catarinafragapediatra@gmail.com

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Discussion

In 2014, in a letter to the editor, an Italian work group described a case of food protein-induced enterocolitis syndrome-like (FPIES-like) caused by medicines in a 6-year-old child. The patient presented with vomiting, diarrhoea, pallor and lethargy after taking amoxicillin, accompanied by hypotension, tachycardia and tachypnoea, requiring intravenous fluid therapy and corticosteroids, gradually returning to baseline within two hours. At the time, researchers realised that there could be a similar entity to FPIES, what they called drug-induced enterocolitis syndrome (DIES).[1]

DIES is a non-IgE-mediated hypersensitivity reaction triggered by drugs. It is characterised by the appearance of gastrointestinal symptoms within 1 to 4 hours after the intake, sometimes along with autonomic symptoms, similar to FPIES. It's a rare syndrome that can be life-threatening.[2] However, despite its potential severity, its awareness is scarce.[2,3] Although, to date, all the paediatric patients described have recovered completely.[4]

The incidence of DIES is unknown, probably due to its underdiagnosis. Until the first semester of 2023, less

than a dozen cases in children have been described in the literature. The drugs most frequently involved were amoxicillin, amoxicillin/clavulanate and paracetamol.[2] The frequency of DIES with these agents seems to be related to the fact that they are widely prescribed in this age group. For this reason, the occurrence of this syndrome associated with drugs seems likely.[4]

Since few cases have been described, it is not possible to assess whether this entity is transitory or persistent.[4] Unlike FPIES, DIES seems to occur in people who have previously tolerated the drug.[2]

The pathophysiology of DIES is unknown, but it is postulated that the interaction of drug metabolites or the drug-protein complex with the epithelium of the gastrointestinal tract causes an increase in the permeability of this barrier, increasing the penetration of drug antigens into the lamina propria and culminating in the activation of the local inflammatory response. It is also thought that factors such as age, gender, drug dose, exposure time and intestinal microbiota can shape the gastrointestinal pathological response to drugs.[2]

Though the diagnostic criteria have not yet been perfectly established, it is accepted that DIES can be considered when there is a recurrence of repetitive and often incoherent vomiting within 1-4 hours of the drug intake, in the absence of classic IgE-mediated allergic skin and respiratory symptoms. Also, when more than three of the following are present, the diagnosis may be considered: a second episode of vomiting after ingesting the same drug; a repetitive episode of vomiting after ingesting a different drug; lethargy; marked pallor; diarrhoea within 24 hours of ingestion (usually 5-10 h); the need for a visit to the emergency department; intravenous hydration; hypotension; hypothermia; and an increase in the neutrophil count >1500/mm^3 compared to the baseline count.[2,5] Although the diagnosis is clinical, the oral drug challenge confirms or excludes the diagnosis.[4]

Oral drug challenge, also known as drug provocation tests (DPT) are widely considered to be the gold standard diagnostic test for assessing drug allergy.[6] However, there is no agreement on how to conduct DPT in children. Some experts suggest using DPTs with increasing doses for immediate reactions[7], while most studies report delayed reactions appearing hours or days after the patient has taken the full drug dose.[7,8] This indicates that a single-dose DPT can be as safe as a multi-step approach, eliminating the need for multiple or extended hospitalization.[8] Therefore, we decided to follow the single-stage DPT strategy and administered a full dose of amoxicillin to our patient. Our patient presented three episodes of profuse vomiting two and a half hours after the challenge in the absence of skin or respiratory symptoms (major criterion), lethargy, marked pallor, abdominal pain and diarrhoea, in addition to the previous episodes of vomiting after taking amoxiclavulanate, which makes this a seventh episode (four minor criteria). There are no described laboratory markers specific to DIES. However, some possible findings described to date are leukocytosis with a predominance of neutrophils and an increase in methemoglobin. These findings can support the diagnosis. Tryptase levels are usually normal. Specific IgEs, prick tests and intradermal tests are also negative.[2] In the case described, no additional tests were conducted, considering that the oral drug challenge was positive.

In line with the advocate for FPIES, for DIES and in the case described above the treatment was supportive, with intravenous administration of ondansetron and normal saline, with a good clinical response.[4] In DIES and FPIEs, corticosteroids can be used in patients with severe symptoms, although their effectiveness has not been proven.[2] On the other hand, the administration of adrenaline is not recommended, although it can be used as an adjunct to fluid therapy in the approach to hypotension.[1,2,4]

Conclusion

Despite the low frequency of DIES, the authors would like to raise awareness of the diagnosis of DIES when approaching vomiting and diarrhoea after medicine intake. They also highlight that oral drug challenges, in case of late reactions, should be performed in a hospital environment, especially in cases of moderate to severe clinical reactions, such as the case described above.

Compliance with Ethical Standards
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