



Exanthematous reactions to drugs in children

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Purpose of review

The true exanthematous reactions to drugs in children are rare and overdiagnosed. Drugs may cause exanthema either due to inducing an immune response or because of their interaction with viruses, if drugs are taken in the course of a viral infection. Also, viral infections are very often in children and they can provoke an exanthema which is difficult to differentiate from exanthematous reactions to drugs. Consequently, the majority of children are incorrectly labeled as 'allergic'.

Recent findings

The correct diagnosis of exanthematous drug reactions in children is still an important and hot topic. Most information about the approach and management of drug hypersensitivity in children is applied from available guidelines and consensus statement for adults. Recently, a systematic clinical approach for timely differential diagnosis and management of rashes in children who present a cutaneous exanthema while receiving a drug, is proposed.

Summary

It is important to consider the detailed clinical history of appearing and developing exanthematous drug reaction, as well as physical examination which includes the description and the distribution of exanthema and at the end making the appropriate diagnosis. Thus, it could reduce overdiagnosis and promote appropriate procedures, that will prevent the overlabeling of drug hypersensitivity in children.

Keywords

children, drug hypersensitivity, makulopapular exanthema

INTRODUCTION

Drug hypersensitivity reactions (DHRs) are adverse effects of drugs in which the immune system is involved. According to underlying immunological mechanisms, DHRs have been classified into allergic (the hapten hypothesis), pharmacologic interaction (p-i concept) and nonallergic hypersensitivity. Allergic reactions can be mediated by immunoglobulin E (IgE) and immunoglobulin G (IgG) antibodies or by T cells [1]. According to the type of reactions, these reactions can be immediate or nonimmediate [2]. In p-i concept, the drug can bind (via non-covalent bonds) directly to immune receptor proteins (human leukocyte antigen [HLA] and T-cell receptor [TCR]). These reactions are T-cell-mediated. In nonallergic hypersensitivity reactions, the drugs bind directly to the receptors or interact with enzymes or effector cells. These reactions are considered immediate [1,3^{***},4^{***}].

According to timing between the start of treatment until symptoms appear DHRs have been classified into immediate and delayed reactions. Immediate reactions usually appear within 1 h although this time interval can be extended to 6 h. Delayed reactions appear mostly after days

(from 3 to >12 days), but symptoms may already appear on the first day in re-exposures, even within hours of exposure reaction may appear [1].

Gell and Coombs classification (type I to type IV) links the clinical phenotype to the immune mechanisms [1].

NONIMMEDIATE DRUG REACTIONS

Clinical manifestations of delayed or nonimmediate reactions (NIRs) range from benign rashes (maculopapular exanthems [MPE], urticarial exanthema) to potentially life-threatening severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN),

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KEY POINTS

- Maculopapular exanthems is the most common manifestation of benign nonimmediate reactions.
- Viral infections can provoke an exanthema which is difficult to differentiate from exanthematous reactions to drugs in children in the acute phase.
- For an accurate diagnosis, a rational approach is required which include the detailed clinical history of exanthema, physical examination and allergy work-up.

drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) [4¹¹].

Exanthem is defined as an acute eruptive, widespread distribution of multiple small, round to oval erythematous macules and/or papules with different degrees of confluence. The morphology of exanthema, presence of cellular infiltrate and its duration (several days) contrasts with other entities [5¹¹,6¹¹].

MACULOPAPULAR EXANTHEMS

MPE are the most common manifestation of NIRs (Gell and Coombs type IVc). They primarily appear with erythematous macules and infiltrated papules from 1 to 5 mm in diameter, with different degree of confluence, which often involve face, neck, or upper trunk and the proximal extremities in a symmetric distribution. Pruritus and mild fever also could be accompanied by MPE. Mucous membranes are normally not involved. When the drug is taken for the first time MPE appear mostly 7–12 days of treatment, but not rarely after therapy was already stopped. However, when the drug is taken for a second time the initial symptoms already may appear within few hours and develop into a typical exanthem after 1 or 2 days. The duration of MPE is up to 2 weeks after the last drug intake. With resolution, lesions may become brownish and desquamation may occur [5¹¹,6¹¹,7,8]. The most common implicated drugs include β -lactams (BL), macrolides, sulfonamides, aminoglycosides, antiepileptics, antineoplastics, and antituberculosis drugs [7,9,10]. Drug-induced MPE develops in 5–10% of children with a concomitant viral infection. Children who are infected with Epstein–Barr virus (EBV), human herpesvirus 6 (HHV-6), and cytomegalovirus (CMV) are at increased risk of appearing MPE [6¹¹,7,11]. Until recently, it has not been clearly understood whether sensitization to antibiotics, EBV itself or transient loss of drug tolerance due

to the virus, is responsible for the development of MPE following amoxicillin intake in patients with infectious mononucleosis (IM). Proposed mechanism of drug-induced MPE in a patient with IM is that the viral load and the increasing numbers of activated CD8⁺ T lymphocytes lead to a rise in the levels and activity of interferon- γ (IFN- γ) and interleukin-2 (IL-2). Consequently, the activity of Th2 cells is inhibited, which leads to the suppressed release of the characteristic Th2 cell cytokines IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. Appropriate IL-10 activity has been shown to be required to maintain immune tolerance and limit the immune response to certain antigens. A crucial factor in the susceptibility to drug-induced MPE seen in IM is suppression of IL-10 activity, which is accompanied by an increase in activated Th1 cells, which are contributor to the development of NIR. Consequently, the antibiotic molecules in the context of EBV-mediated immune changes set the stage for a hypersensitivity reaction, with the presentation of MPE [6¹¹,12–14].

In a study by Caubet *et al.* [15] based on 88 children developing a nonimmediate exanthema during a BL treatment, it has been shown that the majority of children with a negative oral drug provocation test (DPT) tested positive for a viral infection (enteroviruses and herpes viruses). Atanaskovic-Markovic *et al.* [16¹¹] have shown similar results, when testing revealed that MPE that developed during BL treatment were of infective origin (mostly *Mycoplasma pneumoniae*).

URTICARIAL EXANTHEMA

Delayed appearing urticaria and MPE are the most common manifestations of NIRs reported by patients [16¹¹,17¹¹,18,19]. Nonimmediate urticaria, urticarial exanthema (UE) and delayed appearing urticaria are different names of the same entity. UE was defined as larger erythematous areas elevated from the skin, accompanied or not by angioedema and persisting for several days. Symptoms had to have occurred at least several hours after drug intake and usually within an interval of 24–48 h [20,21]. The underlying immunological mechanisms involved in UE are not completely understood. In UE, lymphocytes and other inflammatory cells are recruited to the skin and are able to secrete histamine-releasing factors that induce mast cell degranulation [17¹¹]. Padial *et al.* [17¹¹], comparing the results of MPE vs. UE, have found a greater presence of CD41 cells with a higher expression of cutaneous lymphocyte associated antigen and major histocompatibility complex II cell surface receptor in the MPE.

The most common implicated drugs include BL (particularly amoxicillin, amoxicillin + clavulanic acid), macrolides, antiepileptics, and antituberculosis drugs [9,18].

In the last few years, differences had been found between position papers and documents on drug allergy, particularly the definition of delayed urticaria [1,3²²,5²²,9,15,17²²,19–21,22²²]. Therefore, some authors asked the question: does delayed urticaria induced by drug allergy exist? [23]

DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

The exanthema in DRESS usually appears 2–8 weeks after the start of therapy and is maculopapular but without erosions in the mucosa. Erythematous central facial swelling is typical. Fever, malaise, lymphadenopathy, eosinophilia, and involvement of many organs are usually present. In the peripheral blood, except eosinophilia, leukocytosis, and atypical lymphocytes are often found. DRESS starts with unspecific prodromal symptoms such as asthenia, pruritus and fever (38–40°C). Fever can precede by several weeks the MPE. MPE is starting on the face (frequently peri-orbitally) and upper trunk, then expanding quickly downward and developing a violaceous hue. The liver is the most frequently affected organ (hepatitis with an elevation of liver enzymes), but renal failure, pneumonitis, myocarditis, meningitis or encephalitis, gastroenteritis, thyroid or pancreatic dysfunction can also occur. Reactivation of HHV-6 or EBV or CMV infection is present. Individuals with specific HLA haplotypes are predisposed to develop DRESS. The most common implicated drugs include antiepileptics, allopurinol, sulfonamides, BL and dapsone [5²²,6²²,8,24–26]. The pathophysiology is thought to be a T-cell-mediated hypersensitivity reaction type IVb (Coombs and Gell classification) with increased IL-5 expression and increased eosinophil number and their activation and recruitment to the affected tissues [3²²,8]. Activated T cells produce large amount of tumor necrosis factor α , IL-2, and IFN- γ , responsible mediators of the ‘cytokine storm’, and subject to typical symptoms of DRESS. It has also been demonstrated that the increased ILC2 (type 2 innate lymphoid cells) with a high expression of IL-33 and soluble suppression of tumorigenicity two peptides, are important in skin inflammation [3²²,27]. It has also been shown that amoxicillin acts directly on herpesvirus replication, producing a flare in patients with DRESS. This situation resulted in a transient state of immunosuppression and extensive nonspecific immune system feedback, leading to a failure of tolerance to other drugs also, in particular anticonvulsants [6²²].

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

In AGEP, the exanthema is pustular (sterile, non-follicular, smaller than 5 mm in diameter), located in intertriginous areas and the trunk and accompanied by fever and edema. It may start on the third or fifth day of antibiotic therapy. In the peripheral blood leukocytosis with neutrophilia and sometimes mild eosinophilia are found. Internal organ involvement is usually absent. Resolution of the exanthema is associated with typical postpustular desquamation. Full recovery is usually expected within 1–2 weeks after withdrawal of the drug. The most common involved antibiotics are aminopenicillins, cefixime, clindamycin, vancomycin and macrolides [5²²,6²²,8,28]. AGEP is considered to be a type IVd hypersensitivity reaction (Coombs and Gell classification). Drug-specific T cells produce large amounts of chemokines C-X-C motif chemokine ligand 8/IL-8, which play a central role in the formation of pustules by recruitment of neutrophils. High levels of IL-17, IL-22, and GM-CSF (granulocyte-macrophage colony-stimulating factor) may also have some role in the strong neutrophilic activity [28,29].

DIAGNOSIS OF NIRS

If a child takes a drug during a viral infection, an exanthema can appear, which is often labeled as a drug allergy in 10% of cases. In the majority of cases, the distinction between virus-induced and drug-induced exanthema during the acute phase is not possible. It is also difficult to identify the cause of exanthema if one or several different drugs are taken during the infection.

For an accurate diagnosis, a rational approach is required, which is recommended by Tsaouri and Atanaskovic-Markovic [6²²]. The first part should be a detailed clinical history of exanthema which includes: prodromal symptoms, a chronology of the exanthema development, in comparison with the drug exposure timeline and presence of pruritus. It must be also considered fever to be present/not present in the early symptoms of exanthema. The second mandatory part should be physical examination which includes: morphological pattern of the exanthema, body areas affected and if possible take a photo of the exanthema. The third part should be a diagnostic process, which includes: serology testing or detecting of the virus by polymerase chain reaction (PCR) in the acute phase. Also, we should not forget that concomitant acute infections do not totally exclude DHRs. Diagnostic workup should be performed for a minimum of 4–6 weeks after the complete resolution of all clinical symptoms, to avoid both false positive and false

negative and flare-ups of systemic reactions as well [4[■],6[■]].

In children with isolated benign exanthema (MPE or UE), appeared during antibiotic treatment, skin tests are of limited diagnostic value and direct DPT is suggested by the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) for the management of drug hypersensitivity in children [30]. In 2020 according to an EAACI position paper, DPT with culprit BL should be performed as, one-tenth of the maximum single unit dose should be given in the first place and, if tolerated, a full dose 1–7 days after, depending on the time interval of the index reaction [22[■]]. The optimal (incremental or full) doses and intervals between the doses are controversial, as consensus is lacking. There is an ongoing debate in drug allergy in children, as to whether one-day DPT is sensitive enough vs. several-day DPT [4[■]]. Shorter protocols are more efficient and have fewer adverse effects, longer protocols may increase the sensitivity of DPT up to 15% [31[■],32]. It should be taken into consideration that prolonged DPT can account for new sensitization. Also, prolonged exposure to antibiotics could lead to microbial resistance and disturbances of the gut microbiota and healthy children are exposed to an unnecessary course of antibiotics [4[■]]. However, DPT remains the gold standard and is important in the management of children with a suspicion of drug allergy.

In the diagnosis of AGEP and DRESS, patch tests are useful. Intradermal tests are potentially useful in AGEP, and their safety is unknown in DRESS. DPTs are contraindicated both in AGEP and DRESS. Skin biopsy should be performed, it can be helpful, although it is not indicated in all cases of AGEP and DRESS [4[■],33,34].

In-vitro test, such as IFN γ producing cells determination by enzyme-linked immunospot assay (ELISpot), in combination with patch tests has demonstrated a potential utility in drug-induced SCARs [3[■],35]. The sensitivity and specificity of the lymphocyte transformation test (LTT) is still unsatisfactory. The LTT can help identify causes of SCARs, when DPT is strongly contraindicated. SCARs in 54 children were recently investigated, and LTT sensitivity towards BL or carbamazepine was reported up to 80% [36[■]], although a study on adults revealed lower sensitivity (25–75%), and the performance of LTT is influenced by the culprit drug and the type of reaction [37].

CONCLUSIONS

MPE is one of the most common reasons for visiting a pediatrician. In the majority of cases, the

distinction between virus-induced and drug-induced MPE during the acute phase is not possible. Consequently, it is important to consider the detailed clinical history of appearing and developing MPE, as well as a physical examination which includes the description and the distribution of MPE and at the end making the appropriate diagnosis. Thus, it could reduce overdiagnosis and promote appropriate procedures, that will prevent the over-labeling of drug hypersensitivity in children.

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Conflicts of interest

There are no conflicts of interest.

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