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Original Research

Drug Allergy in Children: What is the Actual Frequency of Drug Allergies?

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Abstract

Objectives: Drug hypersensitivity reactions are immunologically mediated reactions resulting in the production of drug-specific antibodies and/or T-cells and constituting only <15% of all drug reactions. Based on the clinical observations, both patients and their parents refer to any undesirable drug reactions as drug allergy, regardless of whether the underlying mechanism is immunological or not. After allergy examinations, only a small percentage of the patients who were reported positive for drug reactions based on their clinical history are actually confirmed to have hypersensitivity. This study aims to determine the actual frequency of drug allergies in children, the drugs that cause the most common allergies in patients with a complaint of drug allergy and evaluate the accompanying demographic and clinical features.

Methods: The study evaluated data from a total of 266 patients (ages of 0–18) with suspected drug allergy during a 3-year period. Twenty-four patients with doctor-diagnosed drug-related anaphylaxis and 85 patients who did not accept diagnostic tests were excluded from the study and the study continued with a total of 157 patients. The allergy work-up consisted of in vivo and in vitro tests, in accordance with the recommendations of the ENDA/EAACI guidelines.

Results: Data from a group of 157 patients (M [54.6%]; F [45.4%]) were retrospectively analyzed. Beta-lactams (BLs) were the most common drugs involved in the reported clinical history followed by non-steroidal antiinflammatory drugs (NSAIDs). Allergic reactions occurred on the median 1st day (min: 1-max: 8) after drug intake and were most frequently observed as urticaria (55.3%). Immediate reactions (IRs) were observed in 53.5% and non-IRs in 46.5% of the patients.

Conclusion: Our data demonstrated that only 15.5% of patients confirmed to be positive to allergy during testing which is in line with the data in the literature. An allergy work-up is mandatory for excluding suspected hypersensitivity.

Keywords: Allergy tests, drug hypersensitivity reaction, epidemiology, pediatrics

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Drug hypersensitivity reactions (DHRs) are immunologically mediated reactions resulting in the production of drug-specific antibodies and/or T-cells and constituting only <15% of all drug reactions.[1,2] Based on the clinical observations, both patients and their patients refer to any undesirable drug reactions as drug allergy, regardless of whether the underlying mechanism is immunological or not. A cross-sectional studies revealed that the drug allergies reported by families in children ranged from 2.5% to 10%.[3] A systematic review of 17 prospective studies shows that drug reactions in children were responsible for 2.09% of emergency applications, 1.46% of outpatient ap-

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plications, and 9.53% of inpatients.[4] Data on the incidence of drug allergies and drug reactions in children in Turkey are limited, although drug allergies are frequently 2.8% reported by parents in 6-–9-year-old children.[5] Despite this rate of reported cases by parents, the actual frequency of drug allergies confirmed by diagnostic tests is much lower. In France, the prevalence of drug allergy reported by their parents among 1426 children was 4.6% (n=67); however, skin and provocation tests ultimately diagnosed only three of them (0, 21%) as genuinely allergic to the culprit drug.[6] Tugcu et al. demonstrated that only 17.7% of the patients, who initially applied with the complaint of drug allergy, were actually diagnosed with drug allergy by the confirmation of the diagnostic test results.[1]

Diagnosis of suspicious DHRs brings both an economic burden for the country and a psychological burden for the patient.[1] Therefore, the diagnosis must be confirmed by performing diagnostic tests. Detailed history and physical examination of patient are the first step in suspected drug allergy, but it is not sufficient for diagnosis. Hence, allergic evaluation is required for the diagnosis of drug allergy. Although skin tests are widely used in allergic evaluations, these tests have only been validated for some drugs such as beta-lactam antibiotics and local anesthetics. As a result, drug provocation tests (DPTs) are accepted as the gold standard for the diagnosis of drug allergy. The contribution of skin tests for the diagnosis of DHRs in children is very low and with some exceptions DPT are safe procedures.

This study aims to determine the actual frequency of drug allergies in children, the drugs that cause the most common allergies in patients with a complaint of drug allergy and evaluate the accompanying demographic and clinical features.

Methods

Patients

In Pediatric Allergy Clinic of the İstanbul Prof. Dr. Cemil Tascioglu City Hospital, between 2017 and 2020, a total of 266 patients (ages of 0–18) with suspected drug allergy were retrospectively analyzed. Twenty-four patients with doctor-diagnosed drug-related anaphylaxis and 85 patients who did not accept diagnostic tests were excluded from the study and the study continued with a total of 157 patients. Demographic characteristics of the patients (age, gender, additional allergic disease, and presence of drug allergy in the family), reaction type observed after contact with the suspected drug (anaphylaxis, urticaria, macular rash, and angioedema), responsible drug, time between drug intake and drug reaction, the day the reaction developed, laboratory tests (Ig-E, percentage of eosinophils) and diagnostic test results for drug allergy (drug skin prick test, intradermal test [IDT], drug patch test, and drug specific Ig-E values if available and DPT results) were collected from patient data files. Those with any concomitant allergic disease were considered atopic.

In accordance with the information obtained from the parents of the patients, if the reaction was observed within the 1st h after the use of the drug, the drug reaction was classified as "immediate reaction," if it was observed after the 1st h, "non-immediate reaction."[7]

Patients with doctor-diagnosed anaphylaxis were accepted in the group with drug allergy and no diagnostic tests were performed. Adrenaline auto injectors were prescribed to these patients and drug allergy tests were performed for safe drug selection that was not in the cross-reactivity.

Diagnostic Tests

The presence of penicillin V and G specific IgE was investigated by ImmunoCAP method in patients with a history of reaction with beta-lactam (BLs) antibiotics and values above 0.35 kUA/L are accepted as positive.

Skin tests

Patients who applied to our clinic with a suspicion of drug allergy were tested with the culpid drug at least 4 weeks after the suspected drug reaction, as recommended by ENDA.[8,9] Skin prick tests (SPTs) were applied to the palmar side of the forearm. SPTs were performed with the culprit drug, histamine was used as positive control, and 0.9% sterile saline as a negative control. If the skin prick test with the culpid drug was negative, IDT was applied with certain diluted forms, paying attention to the maximum non-irritant concentration of the drug according to the previously determined test protocol. If no positive response was obtained 15–20 min after the IDT dose, the test was continued with increasing concentrations until the pre-determined non-irritant skin test concentration was reached. An erythema diameter of ≥3 mm to negative control was accepted as a positive test. A wheal of at least 3 mm or greater in diameter compared to negative control with saline was considered as a positive test. If a positive response was obtained at any concentration, the test was terminated. Delayed reading of the IDT was done 72–96 h after the test.

Patch tests were applied for the antibiotic (penicillin G, penicillin V, ampicilin, clarithromycin, cefotaxime, cefuroxime, cefixime, amoxicillinthrihydrate, potassium clavunate, and cotrimaxozole) or NSAID (ibuprofen, ketoprofen, acetominophen, and diclofenac sodium) groups according to the culprit drug to the patients who represented delayed type reactions based on the related culpit drug. The test was evaluated after 48 and 96 h.

DPT

DPT was performed with full anaphylaxis back-up under strict hospital surveillance on patients with negative skin tests or who have had a reaction with a drug that does not have an intravenous form suitable for skin testing. DPTs were start by administering at 1/10th or 1/100th dose of the treatment dose as recommended for each drug and continued until the daily treatment dose was reached. The test was terminated when the treatment dose was reached or when a positive reaction was observed. Moreover, patients with positive DPTs were treated accordingly and monitored until the symptoms disappeared. The patients who could use the last dose of the drug without any problem were kept under observation for at least 2 h. DPT was considered negative in patients who did not develop any symptoms. In terms of late reaction, patients were advised to use culprit drug at home for another 5 days and the patients were called for control. Patients who had positive DPT results with the suspected (culprit) drug and positive IDT and/or patch tests with the suspected drug, but whose family did not accept DPT were considered as drug allergy. DPT was not performed in patients with anaphylaxis and a history of severe cutaneous reactions.

Written consent was obtained from families before all diagnostic tests.

Statistical Analysis

After the data obtained from the research were coded, they were transferred to the computer in SPSS (Version 22 for Windows, SPSS Inc, Chicago, IL, USA) package program and analyzed. The suitability of continuous variables to normal distribution was evaluated with the "Kolmogorov–Smirnov Test" and expressed as median (minimum and maximum value) since they are not parametric. Frequency data were expressed in numbers and percentages (%). "Pearson's Chi-square Test" and "Fisher's ExactTest" were used in comparison of frequency data. "Mann–Whitney U-Test" was used for intergroup comparisons of continuous variables. Statistical significance level was accepted as $p<0.05$ for all tests.

Results

Among 157 patients included in the study, 58.6% were male and 41.4% were female. The median age was 5 (min: 0-max: 16) years and the mean age was 5.9±3.8 years. The median age of girls was 6.0 (1–16) years and that of boys was 5.0 (0–15) years, and there was no significant age difference between the genders (p=0.41). There was no known history of drug allergies in 153 (97.5%) of the patients. It was determined that 103 (65.6%) of the patients had never used the drug in question before, while 52 (33.1%) patients had a history of using the same drug. Twenty-seven patients (17.2%) had a family history of drug allergies, while 130 (82.8%) did not have. The serum and blood measurements of the patients showed a median value of 74.8 (1.9–1391.0) KU/L for total IgE level and the median value of 2.9% (0.0–13.0) for eosinophils according to the clinical history of the patients. While 82.2% of the patients (129 children) had a single drug allergy, 17.8% (28) had multiple drug allergies. Immediate type reactions were observed in 53.5% and late type reactions in 46.5% of the patients. The number of patients who were positive in any of the tests performed on 157 patients included in the study was determined as 25 (15.5%) (Fig. 1). According to the test results, 15 patients were positive for BLs antibiotics, five patients for non-BLs antibiotics, four patients for paracetamol, and one patient for NSAIDs.

A total of 237 drug allergy cases were observed in the study with BLs antibiotics (61.6%) being the most prominent group followed by non-BLs antibiotics (19%), NSAIDs (11.8%), paresetamol (5.9%), and other drugs (1%). The less prominent group was anesthetic substances causing allergy only in one patient (0.4%) (Fig. 2). Allergic reactions

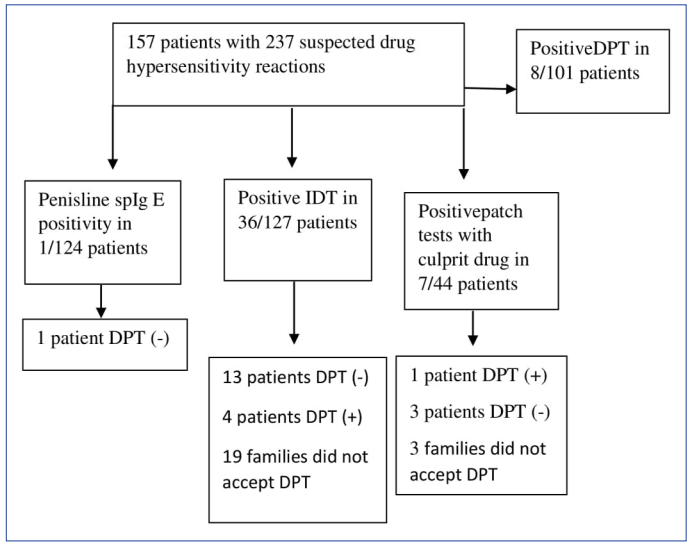

Figure 1. Drug allergy test results of the study group.

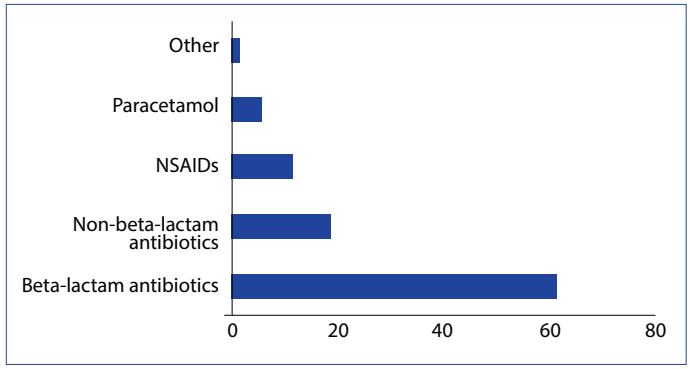

Figure 2. Distribution of suspicious drugs in patients presenting with drug allergy reaction.

occurred on the median 1st day (min: 1-max: 8) after drug intake and were most frequently observed as urticaria (55.3%) (Fig. 3).

There was no statistically significant difference in terms of demographic, clinical, and laboratory characterics between the patients diagnosed as positive and negative (Table 1).

Discussion

In our study, 157 patients with 237 suspected DHRs were evaluated retrospectively in accordance with the ENDA guideline, and 15.5% of them were diagnosed with drug allergy. In the study of Piccorossi et al., the frequency of patients diagnosed with drug allergy was 9.1%.[10] In our country, in a study by Tugcu et al., the frequency of patients diagnosed with drug allergy was found to be 17.7%.[1] In France, parentally-reported drug allergy prevalance among 1426 children was %4.6 (n=67); however, skin and provacation tests ultimately diagnosed only three of them (4.5%) were diagnosed as genuinely allergic to the culprit drug.[6] In the study of Arikoglu et al., the rate of patients whose diagnosis of drug allergy was confirmed was reported to be 27.2%.[11] Ozhan et al. reported that when a total of 27 DPTs were applied, nine of which were with culprit drugs, 4 (44.4%) of the tests performed with the culprit drugs were positive, and 25% of the provocation tests performed with the culprit drugs had a reaction compatible with the story.[12] In another study performed by Gomes et al., drug allergy was confirmed by DPT in 19% of the patients who were thought to develop allergic reactions with beta-lactam antibiotics, and the diagnosis of 8–17% of the patients with negative drug provocation test was confirmed by DPT in another study.[13] The results of our study fit to the previously reported study results. Antibiotics are the most frequent cause of DHRs in childhood in the literature. BLs antibiotics are the most frequently accused antibiotics.[1,11-14] It has been reported that NSAIDs and antiepileptics are responsible for DHRs following antibiotics.[11,14] In our study group, it was found that beta-lactam antibiotics (61.6%) most fre-

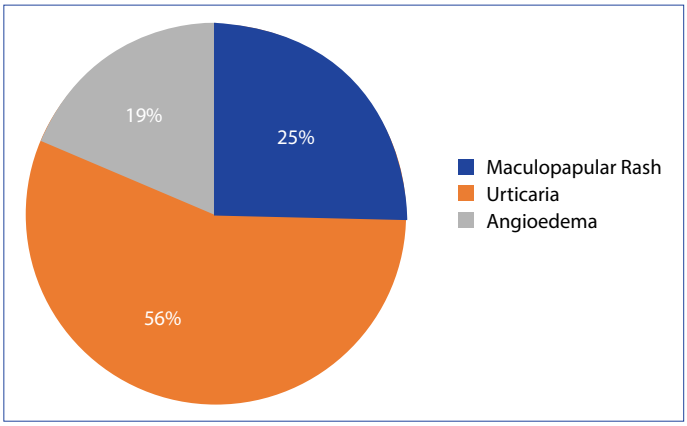

Figure 3. Types of drug reactions.

Table 1. Distribution of patients with suspicious drug allergy according to some characteristics

Variables	Drug allergy test (+) n=25	Drug allergy test (–) n=132	p
Age (years) median (min-max)	5 (1–14)	5 (0–16)	0.82
Gender			
Male	20 (80.0)	72 (54.5)	0.018
Female	5 (20.0)	60 (45.5)	
Multiple drug allergy			
No	18 (72.0)	111 (84.1)	0.14
Yes	7 (28.0)	21 (15.9)	
A history of drug allergies			
Yes	0 (0.0)	4 (3.0)	0.37
No	25 (100.0)	128 (97.0)	
Family history of drug allergies			
Yes	5 (20.0)	22 (16.7)	0.68
No	20 (80.0)	110 (83.3)	
A previous history of using the same medicine			
Yes	8 (33.3)	44 (33.6)	0.98
No	16 (66.7)	87 (66.4)	
Reaction type			
Early	9 (36.0)	75 (56.8)	0.056
Late	16 (64.0)	57 (43.2)	
Total serum IgE level (KU/L) median (min-max)	93.0 (11.4–823.0)	69.6 (1.9–1391)	0.30
Eosinophil value (%) median (min-max)	3.0 (0.9–9.9)	2.8 (0.0–13.0)	0.66

quently caused allergies in a total of 237 suspected drug allergy reactions. In a study conducted by Arikoglu et al., beta-lactam antibiotics with a rate of 30.1% were found in the first place among the suspected drug groups causing drug allergy.[11] The beta-lactam antibiotics taking the first place may be due to the fact that they are among the most commonly prescribed antibiotics in childhood. In the literature, ampicillin-sulbactam, amoxicillin-clavulonate, and cefaclor are reported as the most frequently preferred antibiotics by physicians and parents in childhood.[15-18] However, to obtain more accurate data, it is necessary to evaluate drug reactions under the conditions of equal number of prescriptions for all kinds of drugs.

Although drug allergy reactions were reported more frequently in women than men in the literature,[14] in our study among the 157 patients, 58.6% were male and 41.4% were female. In a study conducted with 4460 patients in Spain, it was reported that the drug allergy frequency rate was more common in women with a rate of 64.5%.[19] Similar to our results, Piccorossi et al. also reported that 54.6% of drug allergy cases in their study were observed in males.[10] In our country, one study conducted at Hacettepe University demonstrated drug allergy frequency being higher in males (51%),[1] while another study from Cukurova University showing higher frequency in females (51.3%).[12] Furthermore, in Singapore, male dominance is observed in the study of Kidon et al.[20] In our study, the median age of the girls was 6.0 (1–16) years and that of the boys was 5.0 (0–15) years, and there was no significant age difference between the genders (p=0.41). In the study of Ozhan et al.[12] at Çukurova University, the mean age was 8.94±4.62 (min: 1-max: 17) years; the mean age was found to be 10.1 years in the study of Piccorossi et al.,[10] and 7.5 (5.31–11) years in the study of Tugcu et al.[1] In a similar study conducted by Temple et al., the mean age was found to be 9.6 years, and this value was found to be 7 years in the study of Le et al.[21,22] In addition, in a multi-center prospective cohort study conducted by Rashed et al., the mean age was found to be 2 years.[23] Although different results were obtained in various studies, it is seen that the frequency of drug allergy increases with age. The reason for this may be that the drug allergy reactions presenting in the early age group are not real drug allergy reactions, since viral infections and maculopapular rash (MPR) complaints due to viral infections are more common at early ages. Again, if the patient is previously sensitized with a certain drug and then encounters again, the development of a drug reaction may support the hypothesis that the frequency increases with age.

DHRs can be seen in a wide range from urticaria to anaphylaxis and/or macular rash to severe skin reactions can affect many different systems in the body. In the literature, the most frequently affected organ is the skin, followed by the gastrointestinal and respiratory system.[1,10,12,24,25]

Skin findings are mostly seen as MPR.[1,10,12,24,25] In our study, patients who presented skin findings were in the first place; the most common symptom was urticaria (56%). In the study of Kont Ozhan et al., the skin is the most commonly involved organ with a rate of 78.16%, urticaria is the most common symptom, and its frequency was found to be 40.2%.[12] In the study conducted by Rebelo Gomes et al., the most frequent involvement is seen in the skin with a rate of 62%, followed by gastrointestinal system (GIS) symptoms with a rate of 26% and respiratory system symptoms with a rate of 20%.[6] However, in our study, gastrointestinal symptoms were found less frequently. In general, we thought that this rate might have been found low in our study, due to the patients' relatives not being able to associate the relation between GIS symptoms and DHRs. Clinically, DHRs are classified as immediate reactions (IRs) (appearing 1 h after drug intake) or non-immediate/delayed reactions (appearing >1 h after drug intake) depending on their onset during treatment.[26-28] Immediate DHRs are possibly induced by an IgE-mediated mechanism and occur within 1 h after the last drug administration.[29] Typically, they occur within the 1st h following the first administration of a new course of treatment. They usually manifest as isolated symptoms such as urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), or as anaphylaxis or anaphylactic shock. In certain guidelines, when DHR symptoms are systemic, non-IgE-dependent, and mimicking anaphylaxis, they are designated as "anaphylactoid" reactions.[30] Non-immediate DHRs may occur any time as from 1 h after the initial drug administration. They commonly ocur after many days of treatment and are often associated with a delayed T-cell-dependent type of allergic mechanism.[2] Maculopapular exanthemas and delayed urticaria are the most common clinical presentations of nonimmediate DHRs.[2] Although artificial, this classification is very important in clinical practice for workup planning. In any case, a precise description of the morphology and chronology of the reaction is mandatory. However, there are still limitations, because other factors such as the route of administration, the role of drug metabolites, and the presence of cofactors or coprescribed drugs may accelerate or slow down the onset or progression of a reaction.[29] Mechanistically, drugs are capable of inducing all of the types of immunological reactions described by Gell and Coombs,[31] but the most common are IgE-and T-cell-mediated reactions. Type I reactions are responsible for immediate reactions, whereas Type II-III-IV hypersensitivity mechanisms are responsible for non-immediate reactions. In the study of Kont Ozhan et al., reactions were observed in the first 1 h in

55.4% of the patients, and between 1 and 6 h in 44.6%.[12] In a study evaluating beta-lactam allergies, the frequency of IRs was reported as 24.2% and non-IRs as 75.8%.[32] In our study, it was observed that allergy conditions appeared on the median 1st day (min: 1-max: 8) after drug intake, and 53.5% of the patients had immediate type reactions and 46.5% of them had non-immediate type reactions.

There are different results in studies that reveal the relationship between atopy and drug allergy reactions.[33-35] While the atopic person creates an increased risk for radiocontrast material allergy, it also causes the reactions with other drugs to be more severe.[33-35] However, in our study, 153 (97.5%) of the patients did not have a previously known drug allergy history. Atopic disease is not generally considered as a risk factor the development of DHRs. However, asthma appears to be a risk factor for severe reactions[33] to any medication and a significant risk factor in adverse reactions to NSAIDs.[36] In our study, the relationship between atopy and drug allergy frequency could not be revealed due to insufficient data.

Our study demonstrates that demographic features, atopy, history of allergic disease, and family history of allergic disease or drug allergy are not risk factors for the diagnosis of drug allergy reaction. There are also some studies in the literature on the effect of genetic factors ((IL-10 promoters, IL-4Rα, and FcεRßgenespolimorphism)[37,38] on drug allergy reactions. In a study conducted by Faitelson et al., asthma in children with amoxicillin allergies, a family history of drug allergy, advanced age, and angioedema findings were associated with amoxicillin reaction.[39] In a recent study, advanced age and IRs were reported as risk factors for beta-lactam allergy.[40] The limitation of our study is that genetic factors could not be investigated due to the lack of patients' genetic information as well as diagnostic too required for that kind of investigation.

Conclusion

Drug allergy was confirmed in only 15.5% of the patients who applied with suspected DHRs complaints in our study. Considering the actual frequency of the DHR being much lower than initially suspected cases determined in our study, it is clear that diagnosing drug allergy based on the anamnesis taken only by the parents' statement causes misdiagnosis in many patients as well as the use of more expensive drugs with less effectiveness or more side effects in treatment. For this reason, a detailed anamnesis should be taken and a physical examination should be performed for a correct diagnosis, and then, appropriate diagnostic tests should be applied. It should be kept in mind that the gold standard test for the diagnosis of drug allergy is the drug provocation test if there is no contraindication.[24,41]

It should also be noted that direct provocation test can be performed in low-risk patients, especially in children, without the need for allergic evaluation such as skin testing.[42]

Disclosures

Ethics Committee Approval: This study was approved by ethics committee of İstanbul Prof. Dr. Cemil Tascioglu City Hospital. 20/10/2020-399.

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Conflict of Interest: None declared.

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