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RESEARCH ARTICLE

Retrospective Examınatıon of Children with Beta Lactam-Drug Allergy: A Single-Center Experience

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ABSTRACT

Objective: The occurrence of drug reactions due to IgE or T-cell-mediated hypersensitivity reactions is referred to as drug allergy. Beta-lactam antibiotic (BLA) is the most common cause of drug allergy. In our study, we aimed to determine the true frequency of allergy in patients who presented to the children's immunology and allergy polyclinic on suspicion of BLA allergy and performed drug provocation test (DPT) and to evaluate the clinical, demographic, and laboratory characteristics of these patients.

Methods: Between 2017 and 2023, 141 patients (75 immediate reaction and 66 non immediate reaction) aged 0-18 years who applied to our hospital's pediatric immunology and allergy outpatient clinic with suspicion of BLA allergy and underwent DPT were included. Retrospective records from the last 6 years were examined from hospital data; age (month), sex, history of concomitant chronic diseases, history of additional allergic diseases, history of drug allergies in the family, type of reaction, serum total IgE, percentage of eosinophils (%), history of BLA use (penicillin V, penicillin G, ampicillin, amoxicillin etc.), specific IgE values, and drug intradermal test (IDT) results were recorded.

Results: In our study, 141 patients aged between 0 and 18 years were evaluated. 33 (23.4%) of them were IDT-positive. DPT was not performed because 24 patients did not have family permission and 9 patients experienced anaphylaxis. In our study, the BLA allergy rate determined by and/or skin tests was 26.9%, whereas the frequency of BLA allergy confirmed by DPT was 5.6%.

Conclusions: Beta lactam antibiotics are widely used worldwide and are the most common cause of drug-induced allergic reactions. Diagnosing a drug allergy thought to be associated with BLA based on history alone leads to the unnecessary use of broad-spectrum antibiotics and, consequently, to the development of antibiotic resistance. The patients should be referred to the child allergy department to be able to be definitively diagnosed for patients with suspected BLA drug allergy. Thus, we hope that unnecessary broad-spectrum antibiotics will be prescribed and that the use of expensive drugs will be prevented.

Keywords: Child, drug allergy, beta-lactam, penicillin, cephalosporin

INTRODUCTION

The occurrence of drug reactions mediated by hypersensitivity reactions via IgE or T cells is referred to as drug allergy (1). Beta-lactam antibiotics (BLA), which are widely used worldwide, are the most common cause of drug-induced allergic reactions (2). Maculopapular rashes and acute urticaria caused by viral infections in children are highly evaluated as allergic reactions to antibiotics used in the same period. Although allergic reactions to BLA drugs are reported in approximately 10% of the population, approximately 90% of patients can tolerate the drug after proper evaluation and diagnostic tests (3). For this reason, diagnosing a BLA allergy based solely on the story may lead patients to receive less effective, more broad-spectrum, or more expensive treatment (4).

The first step in diagnosing drug allergies in suspected cases is a detailed medical history (5). In accordance with the patient's condition, in vitro tests, intradermal tests (IDT), and the gold standard drug provocation test (DPT) should be performed (6).

This study aimed to determine the true frequency of BLA allergies in patients presenting with a pre-diagnosis of drug allergy at the Children's Allergy Clinic of Prof. Dr. Cemil Taşcıoğlu City Hospital and to retrospectively evaluate the clinical, demographic, and laboratory characteristics.

MATERIALS AND METHODS

Patient group

From January 2017 to January 2023, patients aged 0-18 years who were admitted to the Children's Allergy Clinic at Prof. Dr.

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Cemil Taşcıoğlu City Hospital, University of Health Sciences, with suspected allergies and who underwent diagnostic tests were included in the study. Patients' age (in months), gender, history of concomitant chronic diseases, history of additional allergic diseases, family history of drug allergies, type of admission reaction (immediate reactions: urticaria, anaphylaxis, angioedema, bronchospasm; non immediate reactions: maculopapular rash, fixed drug reaction, and others), BLA drug group (including penicillin V, penicillin G, ampicillin, amoxicillin, etc.), serum total IgE levels, eosinophil percentage (%), specific IgE values, IDT, DPT, and drug patch test results were recorded. Drug allergies other than BLA and those with missing data were not included in the study.

Patients were not asked for any additional examinations, nor was any questionnaire administered reactions occurring within the first hour after drug use classified as "immediate reactions," while those occurring after one hour were classified as 'non immediate reactions'(7).

Patients who experienced anaphylaxis following drug use were placed in the drug allergy group, and no diagnostic tests were performed for these patients.These patients were prescribed adrenaline auto-injectors and were given drug allergy tests for safe drug selection.

In vivo test

Specific IgE levels for penicillin V, penicillin G, amoxicillin, and ampicillin were assessed in all patients using the ImmunoCAP method, with values >0.35 kUA/L considered positive.

Skin tests

Patients suspected of having a drug allergy were tested with the suspected drug at least 4 weeks after the drug reaction, as recommended by the European Network for Drug Allergy (ENDA) (9,10). Initially, skin prick tests (SPT) were applied to the palmar side of the patient's forearm. In cases of negative SPT with the responsible drug, IDT was administered at diluted doses according to the test protocol of the predetermined drug. A positive test result was defined as swelling greater than 3 mm compared with the negative control 20 min after the test. The late reading of IDT was done 72-96 hours later.

Test drug patch

Patients with a history of late-type reactions, including penicillin G, penicillin V, ampicillin, amoxicillin trihydrate, potassium clavulate, cefixime, cefuroxime, and cefotaxime, underwent the drug patch test, and patients were evaluated after 48 and 96 hours.

Drug Provocation Test

All patients underwent DPT under hospital observation with the offending drug to confirm the diagnosis, except those with a history of drug-confirmed anaphylaxis or severe cutaneous reactions and those without family consent.

Each drug's recommended treatment dose was started at 1/100 or 1/10 and continued until the daily treatment dose was reached. When the treatment dose was reached or a positive reaction was observed, the test was terminated. Patients who could use the last dose of the drug without problems were kept under observation for at least 2 h. Patients without any symptoms were advised to use the drug at home for another 5 days in case of late reaction.

The test was considered negative when no reaction occurred.

Statistical analysis

The data encoded after the coding of the data" ifadesi fazladan bir tekrar içeriyor ve kafa karıştırıcı. Daha sade ve net bir ifade için: "The data obtained from the research were entered into SPSS (Statistical Package for Social Sciences) (Version 22 for Windows, SPSS Inc, Chicago, IL, USA) and analyzed. The suitability of all measured variables for normal distribution was assessed using the Kolmogorov-Smirnov Test. Continuous variables were expressed as medians (with minimum and maximum values) because they did not follow a normal distribution, whereas categorical data were expressed as numbers and percentages. The non-parametric test "Mann–Whitney U Test was used to compare continuous data across groups. Categorical data were compared using Pearson's chi-square test or Fisher's exact test. Univariate and multivariate binary logistic regression analyses were performed to identify risk factors for allergy type and drug provocation test results. Based on literature reviews of the variables included in the analysis, variables with a p-value < 0.20 were included in the statistical comparisons between groups.

It was considered appropriate to include variables with a p-value <0.20 in the statistical between-group comparisons conducted for the study, given the literature reviews of the variables to be modeled in this analysis. Highly correlated variables found in the multivariate analysis were included in the model. In all statistical comparisons, a significance level of $p < 0.05$ was considered.

RESULTS

The average age of the 141 patients included in the study was 127.6 ± 46.1 months, with a median age of 126 months (range: 12-254 months Of the patients, 77 (54.6%) were male and 64 (45.4%) were female. Age distribution analysis revealed that 35.5% of the patients were in the 73-120 months range, and 39.7% were in the 121-180 months range (Table 1). Among the patients, 45.5% had additional allergic diseases, and 12.8% had a family history of allergies.

İmmediate-type reactions were observed in 53.2% of patients, whereas non-immediate-type reactions were observed in 46.8%. IDT results were positive in 33 (23.4%) patients, whereas 8 (7.4%) of the 108 patients who underwent DPT tested positive. Table 2 presents the distribution of clinical and laboratory data of patients.

A single drug was responsible for allergic reactions in 120 patients (85.1%), whereas more than one drug was responsible in 21 (14.9%). In the evaluation, the drugs responsible for the allergy were penicillin in 127 (90.1%) patients, cephalosporin

Table 1. Demographic characteristics of the patients

Parameters		Total (n=141) n (%)*	Male (n=77) n(%)*	Female (n=64) n (%)*	p
Age (month)	Median (min-max)	126 (12-254)	120 (12-228)	131 (27-24)	0.23**
Age group (month)	12-72	16 (11.3)	9 (11.7)	7 (10.9)	0.60***
	73-120	50 (35.5)	30 (39.0)	20 (31.3)	
	121-180	56 (39.7)	30 (39.0)	26 (40.6)	
	≥181	19 (13.5)	8 (10.4)	11 (17.2)	

* Percentage of columns ** Mann–Whitney U test *** Pearson's ki-square test

Table 2. Clinical and laboratory data

Categorical Variables		n (%)*
Additional allergic disease	No	77 (54.6)
	Yes	64(45.4)
Family history of drug allergies	No	123 (87.2)
	Yes	18 (12.8)
Accompanying chronic disease	No	112 (79.4)
	Yes	29 (20.6)
The type of Reaction	Early	75 (53.2)
	Late	66 (46.8)
Reaction Form***	Urticaria	76 (46.1)
	Maculopapular rash	51 (36.2)
	Anaphylaxis	9 (6.4)
	Angioedema	5 (3.5)
	Bronchospasm	3 (2.1)
	Other ****	7 (5.0)
Drug skin test	Negative	108 (76.6)
	Positive	33(23.4)
Drug provocation test (n=108)	Negative	100 (92.6)
	Positive	8 (7.4)
Drug patch test (n=11)	Negative	9 (81.8)
	Positive	2 (18.2)
Responsible drug-specific IgE (n=114)	Negative	112 (98.2)
	Positive	2 (1.8)
Continuous Variables		Median (min-max)
Eosinophil (%)		2.4 (0-137)
Serum total IgE kU/L		83 (0.2-199.6)

** Percentage of column ** Additional allergic disease: Asthma, rhinitis, atopic dermatitis, atopic dermatitis, food allergy, chronic urticaria *** Some patients have more than one form of reaction **** Other: Serum Sickness-Like Condition*

in 35 (24.8%) patients, and penicillin + cephalosporin in 21 (14.9%) patients. Among the 127 patients with penicillin allergy, 17 (13.4%) were allergic to amoxicillin, 38 (29.9%) were allergic to ampicillin, and 72 (56.7%) were allergic to penicillin V. Among the 35 cephalosporin-allergic patients, 1st-generation cephalosporins were responsible for the allergy in 2 patients (5.7%), 2nd-generation cephalosporins in 14 patients (40.0%), and 3rd-generation cephalosporins in 22 patients (62.9%).

The age and median of patients with non-immediate reactions compared to the types of reactions were statistically smaller than the immediate type of the applicant (respectively p=0.001 and p= 0.002). According to the time of reaction, there were no significant differences between the groups in terms of additional allergic disease, family history of drug allergy, and presence of concomitant chronic diseases (p>0.05). The positivity of the DPT test was again higher in the non-immediate reaction group. However, there was no significant difference in the statistical level of the distributions between the groups (p=0.66). A comparison of some sociodemographic, clinical, and laboratory data according to the reaction time of the patients is shown in Table 3.

Table 3. Comparison of sociodemographic, clinical, and laboratory data according to response time

Parameters n (%)*		Early Reaction (n=75) n (%)*	Late Reaction (n=66) n (%)*	P[a]
Gender	Female	35 (46.7)	29 (43.9)	0.74
	Male	40 (53.3)	37 (56.1)	
Age group (month)	12-72	5 (6.7)	11 (16.7)	**0.002**
	73-120	19 (25.3)	31 (47.0)	
	121-180	38(50.7)	18 (27.3)	
	≥181	13 (17.3)	6 (9.1)	
Additional allergic disease	No	43 (57.3)	34 (51.5)	0.48
	Yes	32 (42.7)	32 (48.5)	
Family history of drug allergies	No	63 (84.0)	60 (90.9)	0.22
	Yes	12 (16.0)	6 (9.1)	
Accompanying chronic disease	No	60 (80.0)	52 (78.8)	0.85
	Yes	15 (20.0)	14 (21.2)	
Oral use of the medication	No	26 (34.7)	18 (27.3)	0.34
	Yes	49 (65.3)	48 (72.7)	
IM/IV drug use	No	43 (57.3)	46 (69.7)	0.12
	Yes	32 (42.7)	20 (30.3)	
Drug Skin Test	Negative	63 (84.0)	45 (68.2)	**0.027**
	Positive	12 (16.0)	21 (31.8)	
Drug provocation test (n=108)	Negative	58 (93.5)	42 (91.3)	0.66
	Positive	4 (6.5)	4 (8.7)	
Responsible drug-specific IgE (n=114)	Negative	56 (98.2)	56 (98.2)	1.00
	Positive	1 (1.8)	1 (1.8)	
Eosinophil (%), median (min-max)		2.45 (0.0-37.0)	2.1 (0.0-17.7)	0.95[c]
Total Ig E (IU/mL), median (min-max)		92.2 (0.2-155.2)	67.5 (0.8-199.6)	0.61[c]

* Sütun yüzdesi, [a]Pearson ki-kare test, [b] Fisher Exact test, [c]MannWhitney U test Other: Serum Sickness-Like Condition, IM: İntramuskuler, IV: İntravenöz

In the study, 108 (76.6%) patients underwent DPT, and 8 (7.4%) tested positive (Table 4). Among those who had a positive drug challenge test, 62.5% were male, 62.5% had additional allergic diseases, their ages ranged from 61 to 120 months, and their IDT results were negative. The frequency of oral drug use among patients with DPT was 75%. However, there were no statistically significant differences between the groups in terms of sociodemographic, clinical, and laboratory data (p > 0.05) (Table 5).

Table 4. Characteristics of patients with positive drug provocation test results

	Reaction type	Responsible Drug	IDT result	Reaction during drug provocation test
Case 1	Immediate	Penicillin+ Sefalosporin	Negative	Urticaria
Case 2	Immediate	Penicillin+ Sefalosporin	Negative	Urticaria
Case 3	Non-immediate	Penicillin+ Sefalosporin	Negative	Maculopapular rash
Case 4	Non-immediate	Penicillin	Negative	Maculopapular rash
Case 5	Non-immediate	Penicillin	Negative	Maculopapular rash
Case 6	Non-immediate	Penicillin	Negative	Maculopapular rash
Case 7	Immediate	Penicillin	Negative	Urticaria
Case 8	Immediate	Penicillin	Negative	Urticaria

Univariate binary logistic regression analyses performed to determine risk factors for DPT positivity, age, total serum IgE level, and the presence of additional allergic diseases were found to have no effect (p > 0.05). However, multiple drug use increased DPT positivity by 5.4-fold compared with single drug use (95% CI = 1.12-26.0; p = 0.036). Similarly, 3rd-generation cephalosporin use increased DPT positivity by 6.9-fold (95% CI = 1.38-34.2; p = 0.018). In the multivariate model, these factors did not have a combined effect on DPT positivity (p > 0.05 for all variables).

DISCUSSION

Beta-lactam antibiotics are widely used globally, and they are the most common cause of allergic reactions to medications (1). Maculopapular rashes and acute urticaria resulting from viral infections in children are often misinterpreted as allergic reactions to antibiotics administered during the same period. Relying solely on patient history for diagnosing BLA allergies can lead to unnecessary use of broad-spectrum antibiotics, which contributes to antibiotic resistance and economic costs (8).

After the diagnostic tests, more than 95% of the patients were safe to use this drug group (9). In the literature, the hypersensitivity rate due to BLA is reported to be between

Table 5. Comparison of sociodemographic, clinical, and laboratory data according to the results of the drug provocation test

Parameters		Drug Provocation Test (%)*		p[a]
		Negative (n=100)	Positive (n=8)	
Gender	Female	44 (44.0)	3 (37.5)	0.72
	Male	56 (56.0)	5 (62.5)	
Age group (month)	12-72	12 (12.0)	0 (0.0)	0.46 [b]
	73-120	38 (38.0)	2 (25.0)	
	121-180	38 (38.0)	4 (50.0)	
	≥181	12 (12.0)	2 (25.0)	
Additional allergic disease	No	58 (58.0)	2 (25.0)	0.13
	Yes	42 (42.0)	6 (75.0)	
Family history of drug allergies	No	87 (87.0)	7 (87.5)	1.00
	Yes	13 (13.0)	1 (12.5)	
Accompanying chronic disease	No	84 (84.0)	6 (75.0)	0.61
	Yes	16 (16.0)	2 (25.0)	
Oral use of the medication	No	28 (28.0)	2 (25.0)	1.00
	Yes	72 (72.0)	6 (75.0)	
IM/IV drug use	No	67 (67.0)	6 (75.0)	1.00
	Yes	33 (33.0)	2 (25.0)	
Reaction type	Urticaria	55 (55.0)	4 (50.0)	1.00
	Angioedema	4 (4.0)	0 (0.0)	1.00
	Maculopapular rash	37 (37.0)	3 (37.5)	1.00
	Other**	2 (2.0)	1 (12.5)	0.20
Intradermal test	Negative	98 (98.0)	8 (100.0)	1.00
	Positive	2 (2.0)	0 (0.0)	
Responsible drug-specific IgE (n=87)	Negative	80 (98.8)	6 (100.0)	1.00
	Positive	1 (1.2)	0 (0.0)	
		Median (min-max)		
Age (month)		121 (27-228)	13 (108-24)	0.10
Eosinophil (%)		2.6 (2.4-37.0)	1.2 (0.1-15.7)	0.34
Total Ig E (IU/mL)		115.0 (0.2-199.6)	14.3 (4.5-45.1)	0.17

* Percentage of column ** Other: Serum disease-like condition [a] Fisher Exact test , [b] Pearson ki-square test, [c] MannWhitney U test

6% and 16%, with a range of 1%–10% in children (10,11). In our study, 141 patients suspected of having BLA allergies underwent DPT, and only 5.6% tested positive. Among the IDT-positive patients who experienced anaphylaxis or who lacked family consent, 26.9% of them had a This result indicates that the actual frequency of drug allergies was lower, which is consistent with the findings of other studies. The risk factors

associated with drug allergies were also evaluated in our study. Multiple drug use increased the risk by 5.4 times compared with single drug use (95% CI = 1.12-26.0; p = 0.036), and 3rd-generation cephalosporin use increased the risk by 6.9 times (95% CI = 1.38-34.2; p = 0.018).

The risk factors associated with drug allergies were also evaluated in our study. Multiple drug use increased the risk by 5.4 times compared with single drug use (95% CI = 1.12-26.0; p = 0.036), and the use of 3rd-generation cephalosporins increased the risk by 6.9 times (95% CI = 1.38-34.2; p = 0.018).

Many patients who have been evaluated for suspected drug hypersensitivity may experience confusion because of multiple drug use at the same time. The frequency of allergy to more than one drug was assessed in a study by Orhan et al. (16), which reported a frequency of 2.4%. In a study conducted by Özhan et al. in Turkiye, 48.6% of patients with suspected drug allergy had a history of using multiple drugs simultaneously (17). A study by Dilber et al. conducted in our country found that 17.8% of patients had multiple drug allergies (18).

One factor that increased the risk in our study was the use of 3rd-generation cephalosporins, which are often administered intravenously (IV). It has been observed that the method of drug administration may also carry a potential risk for drug allergies. A study conducted by Akkelle found that drug allergies were higher in patients receiving parenterally administered drugs, although this difference was not statistically significant (19). In another study, 60% of the patients were given oral medication and 40% received parenteral medication because of DPT (8). In our study, 68.8% of patients used oral medications, whereas 36.9% used parenteral medications. Although more studies are needed to establish the exact risk of drug allergy, parenteral drug administration is believed to increase the risk.

Age is another risk factor for drug allergies, with children generally having a lower risk than adults. In our country, the average age is between 5.5 and 7.5 years (20, 14, 12). In other studies in the literature, the average age was 7–10 years (21-22). Although different results have been observed in various studies, it appears that the frequency of drug allergies increases with age. In our study, the average age of patients with BLA allergy was 80 months, and 52.5% of these patients presented at ages between 61 and 120 months; however, age was not identified as a risk factor in the regression analysis. It has been that the age-advancement hypothesis is supported by the occurrence of drug reactions if a patient is re-exposed to the same medication after being previously informed.

One known risk factor for drug allergy is a personal or family history of drug allergies, as demonstrated in numerous studies (21-24). In our study, 12.7% of participants had a family history of drug allergies, whereas only one of the eight patients with a positive DPT had a family history of drug allergies. This result may be attributed to the small number of patients. Zambonino et al. also reported that age, sex, history of drug allergies, or atopy were not identified as risk factors (25).

Drug reactions can range from mild to severe anaphylaxis and can affect multiple systems in the body (26). Physicians have reported that some children treated with BLA may experience urticaria and maculopapular rash (27). Of the 141 patients included in our study, 54% had urticaria, and 35% experienced maculopapular eruptions, consistent with the literature (17-28, 14).

Some laboratory parameters, such as elevated eosinophil counts and total IgE levels, are accepted as supporting findings for the diagnosis of drug allergies; however, this association has not been consistently demonstrated in recent years (23,29). In this study, eosinophil counts and total IgE levels were statistically compared between immediate and non-instantially reacting patient groups. The eosinophil and total IgE levels were higher in the immediate reaction group; however, there was no significant difference between the groups (p = 0.95 and p = 0.61).

There are also some limitations to our study. Data on suspected drug allergies were retrospectively collected from hospital records and parental reports. Although patients and parents can provide their medical history, they may not capture all the findings related to drug allergies.

In conclusion, beta-lactam antibiotics are widely used globally and are the most common cause of drug-induced allergic reactions (2). These reactions are often confused with rashes caused by viral infections in children, leading to unnecessary antibiotic use; therefore, diagnoses should be confirmed through diagnostic tests (3). As demonstrated in our study, the unnecessary use of multiple and parenteral medications should be avoided.

Ethics Committee Approval: This study was approved by the ethics committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (23.01.2023 25).

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- D.Ö., Ş.D.; Data Acquisition- Ş.D., D.Ö.; Data Analysis/Interpretation- D.Ö., Ş.D.; Drafting Manuscript- D.Ö., Ş.D.; Critical Revision of Manuscript- D.Ö., Ş.D.; Final Approval and Accountability- D.Ö., Ş.D.

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