Characteristics of Drug Hypersensitivity Reactions in Children: A Retrospective Analysis in an Allergy Outpatient Clinic

Çocuklardaki İlaç Aşırı Duyarlılık Reaksiyonlarının Özellikleri: Alerji Polikliniğinde Retrospektif Analiz

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ABSTRACT

Objective: Confirmation of drug hypersensitivity reactions (DHRs) is crucial—as various nonallergic reactions, such as viral infections, in children can mimic such reactions. This study aimed to evaluate the characteristics of children with suspected DHRs applying to an allergy outpatient clinic.

Material and Methods: This study involved children who visited our hospital's pediatric allergy outpatient clinic between April 1 and December 31, 2023, with suspected DHRs . The data of patients analyzed retrospectively. Patient demographics, reaction characteristics, culprit drugs, diagnostic procedures (including skin and/or provocation tests), and final diagnoses were recorded.

Results: The study included 163 reactions of 140 patients with 176 suspected drugs. The median age was 7.7 years (interquartile range [IQR]; 5.1–12 years), with an equal gender distribution. Notably, 27.1% of the patients presented with concurrent atopic diseases. The median age at the onset of reaction was 72 months (IQR; 34.5–108 months), with 16% of reactions occurring within hospital settings and the remainder at home. Oral administration accounted for 84.7% of the reactions, with antibiotics being the most common culprit drug group (75.5%). Immediate reactions constituted 41.1% (n = 67) of reactions, while delayed reactions accounted for 58.9% (n = 96). Skin symptoms were predominant (97.5%). DHRs were excluded in 75.5% (n = 123) of reactions but confirmed by diagnostic drug allergy tests in 4.9% (n = 8).

Conclusion: A through evaluation of suspected DHRs in children is essential. Despite high suspicion rates, confirmation via diagnostic tests was low, emphasizing the need for referral to specialized clinics and appropriate diagnostics for accurate management.

Key Words: Antibiotic allergy, Drug allergy, Drug hypersensitivity reactions

ÖZ

Amaç: Çocuklardaki viral enfeksiyonlar gibi alerjik olmayan çeşitli reaksiyonlar ilaç hipersensitivite reaksiyonları (İHR)'yi taklit edebildiğinden, ilaca aşırı duyarlılık reaksiyonlarının (İADR) doğrulanması çok önemlidir. Bu çalışma, alerji polikliniğine İADR şüphesi ile başvuran çocukların özelliklerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Çalışmaya 1 Nisan 2023-31 Aralık 2023 tarihleri arasında hastanemiz çocuk alerji kliniği'ne İADR şüphesi ile başvuran çocuk hastalar dahil edildi. Hasta verileri retrospektif olarak analiz edildi. Hastanın demografik verileri, reaksiyon özellikleri, şüpheli ilaçlar, uygulanan tanısal testler (deri ve/veya provokasyon testleri) ve reaksiyonların nihai tanıları kaydedildi.

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Bulgular: Çalışmaya 140 hastanın 176 süpheli ilaç ile olan 163 reaksiyonu dahil edildi. Ortanca yaşları 7.7 yaş (Çeyrekler Arası Aralık [ÇAA]; 5.1-12) ve cinsiyet dağılımı eşitti. Hastaların %27.1'inde eşlik eden diğer atopik hastalık mevcuttu. Reaksiyon ortaya çıkış yaş ortancası 72 ay (ÇAA; 34.5-108 ay)'dı. Reaksiyonların %16'sı hastanede, %84'ü hastane dışında gelişirken; ilaçların % 84.7'si oral yolla alınmıştı. En sık sorumlu ajanlar antibiyotiklerdi (%75.5).Reaksiyonların %41.1'i (n=67) erken, %58.9'u (n= 96) ise geç tip reaksiyondu. En sık cilt semptomu (%97.5) görüldü. Reaksiyonların %75.5'inde (n=123) İHR ekarte edildi; %4.9'unda (n=8) ilaç alerjisi tanısal testler ile doğrulandı.

Sonuç: Çocuklarda şüpheli İADR'nin ayrıntılı bir şekilde değerlendirilmesi önemlidir. Yüksek şüphe oranlarına rağmen tanı testleri ile doğrulama oranı düşüktü; bu da doğru yönetim için uzman kliniklere yönlendirmenin ve doğrulanmış tanıların gerekliliğini vurgulamaktadır.

Anahtar Sözcükler: Antibiyotik alerjisi, İlaç alerjisi, İlaç aşırı duyarlılık reaksiyonları

INTRODUCTION

Adverse drug reactions (ADRs) are unpredictable and dose-independent reactions caused by drugs (1). ADRs are divided into two main groups: allergic (IgE and non-IgE) and nonallergic. Allergic reactions include reactions that occur strictly through immunological pathogenesis, with prevalence varying by age and country (1). The prevalence of pediatric drug hypersensitivity reactions (DHRs) in the literature is approximately 10%, and a small proportion of these reactions have been found to be associated with confirmed drug allergies (2). According to recent studies, DHRs can be confirmed in only 4.4%–6.9% of patients with suspected drug allergies (3–5). The most common culprit drugs for drug allergies in the pediatric population are beta-lactam antibiotics, followed by nonsteroidal anti-inflammatory drugs (NSAIDs) and non-beta-lactam antibiotics (3,5).

DHRs can occur in a wide clinical spectrum from a mild rash to severe anaphylaxis or life-threatening drug reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (6). However, not every clinical finding is related to DHRs; some nonallergic reactions, such as viral infections, can mimic DHRs (7-9). Therefore, for admissions due to DHRs, it is crucial to exclude other possible causes and confirm such reactions. For DHR diagnosis, a detailed history, physical examination, and appropriate allergological tests (skin tests, specific IgE measurement, and/or drug provocation tests [DPTs]) are necessary (6,7).

Incorrect labeling of a child with a DHR may lead to less-effective, more harmful, and more expensive alternative drug treatments. Conversely, DHR underdiagnosis may cause the same or a more severe reaction when the same drug is taken (10). Hence, identifying and confirming DHRs is important for improving public health, clinical practices, and socioeconomic load. To confirm DHRs, patients with suspected DHRs should be referred to pediatric allergy clinics, and diagnostic allergological drug tests should be performed. This study aimed to retrospectively analyze the evaluation of children with suspected DHRs in an allergy outpatient clinic and contribute valuable insights to the literature.

MATERIALS and METHODS

Study Population

A total of 140 children (<18 years old) who admitted to Ankara Training and Research Hospital Pediatric Immunology and Allergic Diseases Clinic with suspicion of DHRs between April 1and December 31, 2023, were included in the study, retrospectively.

Sociodemographic characteristics of the patients, accompanying allergic disease/atopy status, family history of allergic disease and drug allergy, characteristics of the suspected allergic reaction, symptoms occurring at the time of the reaction, and information about the suspected drug (drug use duration and last dose at the time of the reaction, as well as route of administration) were recorded retrospectively in the data record form.

The diagnostic tests performed (skin and/or provocation tests), the final diagnoses of the reactions and the recommendations given to the patients were retrieved from the electronic records and also recorded in the data record form.

The study was approved by the Ankara Training and Research Hospital Ethics Committee (decision number: E-24-40).

Classification of reactions

Reactions were classified mainly based on the time of onset. Reactions occurring within 1 hour after drug intake were considered immediate reactions, and reactions occurring >1 hour later were considered delayed reactions (11). Reactions that occur with NSAIDs are exceptionally classified as immediate reactions, even if they occur within the first 6 hours, depending on the reaction character (7). Anaphylaxis and its severity were defined according to the European Academy of Allergy and Clinical Immunology (EAACI) anaphylaxis criteria (10).

Identification of the culprit drugs

Suspected drugs were defined as those taken in less than 1 hour before reaction onset for patients with immediate reaction findings (1–6 hours for NSAID reactions), after 1 hour, and within the last ≥1 day for patients with maculopapular exanthema.

Diagnostic Work-up

Diagnostic tests were performed based on national and international guidelines (2,4). Diagnostic tests were performed 4–6 weeks after nonsevere drug reactions. For patients with

chronic diseases, testing was performed within the first year after they became clinically stable and eligible for diagnostic testing. Diagnostic tests were not performed on patients who developed anaphylaxis, those who do not need to take the responsible drug in the near future, and those for whom consent could not be obtained. Patients with immediate reactions other than anaphylaxis were tested using skin prick and intradermal testing with the suspected drug(s). Provocation tests were performed only if these tests were negative. Direct provocation tests were applied to patients with delayed reactions.

Skin Tests

Skin tests were performed as skin prick and intradermal tests using the doses recommended in the national guide and EAACI guidelines (12,13). Antihistamines and other medications that may affect the results of skin tests were discontinued at least 1 week before testing (7,12,13).

Drug provocation tests

National and EAACI-ENDA guidelines were used to determine indications, contraindications, and application of DPT (12,14). If any reaction (urticaria, angioedema, respiratory symptoms, vomiting, or hypotension) occurred during the DPT, the test was immediately terminated, managed appropriately, and considered positive, confirming DHR diagnosis.

Final recommendations given to patients

We advised patients whose diagnostic drug test results were negative or who used the suspicious drugs later without any reaction that they could reuse such drugs. For patients with positive diagnostic drug test results, we advised they could no longer use the implicated drugs. We advised patients whose tests had not been completed or who had not been tested that they should not use the suspect drugs until their diagnostic tests are completed.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences version 22.0 (IBM Corp., Armonk, NY). Categorical values were presented as frequency and percentages. Continuous numerical values were not normally distributed and were presented as the median and interquartile range (IQR;25th–75th percentiles). A p-value <0.050 was considered significant.

RESULTS

Characteristics of patients

This study comprised 163 reactions to 176 drugs from 140 patients, with 50% being male. The median age was 7.7 years (IQR: 5.1–12 years). Table I shows the characteristics of the patients.

Characteristics of reactions

Of the 140 patients, 121 experienced a single reaction, while 15 patients reacted to different drugs at different times, resulting in a total of 163 distinct reactions. Of these 163 reactions, 152 involved a single suspected drug, 9 involved 2 different types of culprit drugs, and 2 involved 3 different suspected drugs. Therefore, this study identified a total of 176 suspected drugs.

The median age at the reaction was 72 months (IQR; 34.5–108 months). Eighty-four percent (n = 137) of the reactions

Table I:Demografic characteristics of patients (n:140)

Age (Month)-median (IQR*)	7.7 (5.1-12)
Gender (male)†	70 (50)
Other Atopic Diseases†	38 (27.1)
Asthma	19 (13.6)
Allergic Rhinitis	22 (15.7)
Atopic Dermatitis	1 (0.7)
Previous DHR history†	13 (9.3)
DHR history of family†	3 (2.1)
Atopic Diseases of family†	13 (9.3)

***IQR:** Inter Quartile Range, **†:** n(%), **DHR:** Drug Hypersensitivity Reaction*

Table II: Characteristics of reactions, n:163

Age at reaction (month)*	72 (34.5-108)
Type of reactions†	
Delayed type	96 (58.9)
Immediate type	67 (41.1)
Anaphylaxis	18 (11)
Symptoms during reactions†	
Dermatologic	159 (97.5)
Respiratory	14 (8.6)
Gastro-intestinal	6
Neurological	6
Cardio vascular	1
Time interval between reaction and admission, month*	5 (0.5-24)
Places which reaction occured†	
Home	137 (84)
Hospital	26 (16)
Administration Routes of Drugs†	
Oral	138 (84.7)
Intravenous	16 (9.8)
Intramuscular	6 (3.7)
Subcutaneous	3 (1.8)
Dosage of drugs at the reactions*	1 (1-6)
Types of culprit drugs (Total number of drug used in 163 reactions = 176)†	
ANTİBİOTİCS	
Betalactam	123 (69.8)
Penicillin	109 (61.9)
Aminopenicillin	8 (4.5) (
Amoxicillin clavulanic acid	83 (47.1)
Ampicillin	79 (44.8)
Sulbactam ampicillin	2 (1.1)

Table II: Characteristics of reactions, n:163	
Cephalosporins	2 (1.1)
Ceftriaxone	16 (9)
Cefixime	6 (3.4)
Cefuroxime axetil	5 (2.8)
Cefazolin	2 (1.1)
Cefdinir	2 (1.1)
Meropenem	1 (0.6)
Trimethoprim Sulfamethoxazole	1 (0.6)
Non-Betalactam	14 (7.9)
Macrolides	9 (5.1)
Clarithromycin	7 (3.9)
Azithromycin	2 (1.1)
Other	5 (2.8)
Vancomycin	1 (0.6)
Gentamycin	1 (0.6)
Amikacin	1 (0.6)
Ciprofloxacin	1 (0.6)
Unknown	1 (0.6)
NSAID	36 (20.4)
Paracetamol	15 (8.5)
Ibuprofen	17 (9.6)
Other	4 (2.3)
Dexketoprofen	2 (1.1)
Metamizole	1 (0.6)
Diclofenac sodium	1 (0.6)
Others	17 (9.6)
Local Anesthetics	5 (2.8)
General Anesthetics	1 (0.6)
Myorelaxan	1 (0.6)
Vitamin D	2 (1.1)
Iron Supplements	3 (1.7)
PPI	2 (1.1)
Prednisolone	1 (0.6)
Antipsychotics	1 (0.6)
Methylphenidate	1 (0.6)

***:** *Median (IQR),* **†:** *n(%),* ***IQR:** Inter Quartile Range,* ***NSAID:** Non-steroid anti-inflammatory drug,* ***PPI:** Proton Pump Inhibitor, Selective serotonin reuptake inhibitors*

occurred at home, and 16% (n = 26) occurred at the hospital. While 84.7% of the drugs were given via the oral route, 9.8% were given intravenously. The most common symptom was dermatological symptoms (96.9%). While 41.1% (n = 67) of the reactions were immediate, 58.9% (n = 96) were delayed. Anaphylaxis was detected in 18 (11%) of those with early reactions. Reaction characteristics are given in Table II.

Culprit drugs

The most common suspected drug group was antibiotics (n = 118, 72.4%), followed by NSAIDs (n = 31, 23%). Figure 1 presents the distribution of drugs.

Diagnostic work-up

During the diagnostic process, 116 DPTs (113 of which were via the oral route) and 70 skin tests were performed. Consequently, DHRs were confirmed in 8 (5.7%) patients (5 with intradermal tests and 3 with DPTs), while drug reactions were excluded in 123 patients (Table IV). Diagnostic testing is ongoing for

Table III: Characteristic of the patient with confirmed drug allergy						
Patient	**Age***	**Gender**	**Culprit drug**	**İnitial reaction symptoms**	**İnitial reaction type**	**Diagnostic tests**	**Alternative drug**
1	5.5	M	Methylprednisolone	Acute Cyanosis (in a minutes)	Immediate	Prick: negative, intradermal: positive	Deltacortil (prick negative, intradermal negative, OPT negative)
2	8	M	Lidocaine	Angioedema	Immediate	Prick: negative, intradermal: positive	Prilocain (prick negative, intradermal negative, subcutan provocation test negative)
3	7.5	M	Articaine	Angioedema	Immediate	Prick: negative, intradermal: positive	Prilocain (prick negative, intradermal negative, subcutan provocation test negative)
4	6	M	Ibuprofen	Angioedema	Immediate (15 minutes)	OPT: positive (at 2,5 hour, angioedema at right eye)	Paracetamol (since he has already used paracetamol without experincing any reaction, testing was not conducted)
5	6.5	F	Paracetamol	Urticaria+angioedema	Immediate	Prick: negative, intradermal: positive	Ibuprofen opt pozitif Diagnostic tests are continue
6	10	M	Paracetamol	Angioedema (recurrent history)	Delayed (at 24 hour)	OPT: positive (at 2 hour angioedema + urticaria)	Ibuprofen OPT negative
7	2.5	M	CAM	MPE	Delayed (4 hour)	OPT: positive (urticaria at 2. Dosage of OPT)	Macrolid (since he has already used macrolides without experincing any reaction, testing was not conducted)
8	11	F	Ceftriaxone	Urticaria, itching of throat, dyspnea (anaphylaxis)	Immediate	Prick: negative, intradermal: positive	Penicilin V/G, amoksisilin sIgE negative CAM OPT negatif

***:** *Age at reaction,* ***CAM:** Amoxicillin clavulanic acid,* ***F:** Female,* ***M:** Male,* ***OPT:** Oral provocation test,* ***MPE:** maculopapular exanthema*

TableIV: Allergological test and their results n (% of 163 reactions)	
Allergological tests*	
Skin tests	70 (42.9)
Prick	36 (22)
Intradermal	34 (20.8)
Specific IgE	3 (1.8)
Provocation tests	116 (71.1)
Oral	113 (69.3)
Subcutaneous	3 (1.8)
Last status of DHR based on allergological tests*	
Confirmed (tests were positive)	8 (4.9)
Excluded (tests were negative)	123 (75.5)
Tests were ongoing	32 (19.6)
Patients with determinated Alternative drugs*	21 (12.9)
Advices for patients*	
Can use again, tests were completed	116 (70.6)
Can use again, allergological tests were unnecessary (because had been given same drug without any reaction)	7 (4.3)
Can't use again, because tests were positive	8 (4.9)
Shouldn't be used again until tests would be completed	32 (19.6)

:** *n(%),* ***DHR: *Drug Hypersensitivity Reaction*

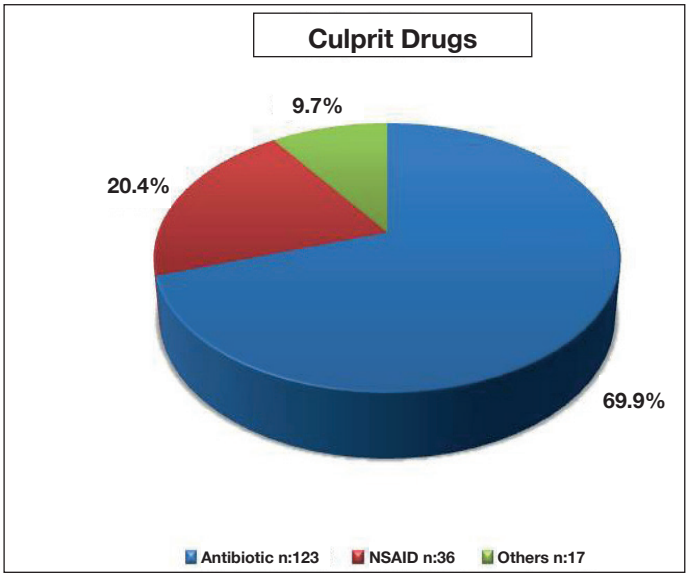

Figure 1: Distribution of culprit drugs.

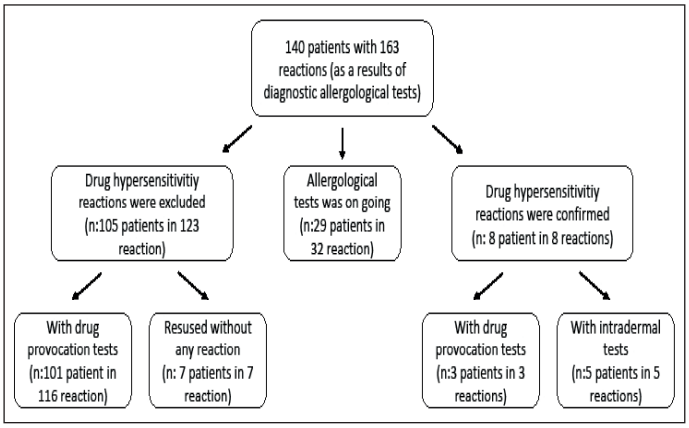

Figure 2: Last status of drug hypersensitivity reactions based on the allergological tests.

32 patients, and alternative treatment was determined for 21 patients with DPTs. The diagnostic approach is summarized in Figure 2, and the allergological work-up is depicted in Table III.

DISCUSSION

This study evaluated the diagnostic approach applied to children suspected with DHRs in the pediatric allergy outpatient clinic, and a DHR diagnosis was confirmed in only 4.9% of the reactions based on the results of diagnostic drug allergy tests.

The true prevalence of DHRs in children is not clearly known because the results of several studies in the literature were not confirmed by drug allergy tests, implying some of these results may include drug side effects (15). While approximately 10% of parents report that their children have DHRs, DHRs can be confirmed in only a very small number of them with drug allergy tests (2). In Capanoglu et al.'s (15) study , while 7% of parents stated that their children had DHRs, only 1.47% of them were suspected of having DHRs based on allergologists' evaluations, and drug allergy could be confirmed in 0.05% of them with the drug allergy tests. In another study, while the frequency of drug allergy was found to be 7.8% according to family declaration in secondary school students with an average age of 12.9 years, it was reported that this rate decreased to 1.16% after detailed anamnesis, and the frequency of drug allergy confirmed after diagnostic drug allergy tests was found to be 0.11% (5).

Milosevic et al. (16) reported that DHRs could be confirmed in 4.4% of patients presenting with suspicion of DHRs. Similarly, in our study, drug allergy could be confirmed in 4.9% of the reactions with drug allergy tests. The most important reason why the rates of confirmed DHRs in our study and Milosevic et al.'s (16) study are higher than those of other previous studies is because while the study population in both studies consisted of patients referred by another physician with suspicion of DHRs for applying to the allergy clinic, other studies adopted more of a population screening design. Moreover, the increase in the frequency of drug allergies over the years may be a secondary reason.

The low frequency of confirmed DHRs in studies conducted in patients presenting with suspected DHRs emphasizes the importance of diagnostic drug tests (15,16). Because many untested children with suspected DHRs may be incorrectly identified with drug allergy labels, which may lead to the unnecessary use of broad-spectrum, less-effective, and/or more expensive medications. This may increase the risk of antibiotic resistance and economic burden at both the individual and population levels (17,18) .

DHRs are most commonly reported with antibiotics and NSAIDs (15,19). In our study, antibiotics and NSAIDs were the most frequently reported suspicious drugs by families. In addition to the frequent use of these drugs in this age group (children), the fact that antibiotics can be used especially for viral infections

may be an important reason for the relevant situation. While viral infections themselves can often cause various rashes, less commonly, they can increase the allergenicity of some drugs through various immunological pathways (9). Therefore, it is recommended that drug allergy tests be performed to rule out these conditions. In Dibek Mısırlıoglu et al.'s (8) study, it was reported that rash developed in 16.6% of children who received antibiotics during Epstein-Barr virus infection, but when patients with rashes were evaluated with allergy tests, drug allergy was confirmed in only 3 (15%) patients. Therefore, drug testing in children is important to prevent over- or underdiagnosis because rashes caused by viral infections can lead to DHR overdiagnosis in children. On the other hand, real DHRs attributed to viral infections and not tested lead to DHR underdiagnosis.

Although the most common symptom in pediatric patients presenting with DHRs is dermatological findings, isolated other system findings or anaphylaxis can be seen. Milosevic et al. (16) reported that 96.2% of patients with suspected DHRs had skin findings, but and also extracutaneous findings had a statistically significant relationship with a positive allergy test. there weren't any skin findings in only 4 (2.4%) reactions, while and 18 (11%) reactions were anaphylaxis. It should be noted that DHRs may develop without skin findings so as to prevent more serious reactions and even mortality.

Based on drug allergy tests, patients are told that they can or cannot reuse the responsible drugs. Such patients should be informed about alternative drugs they can use when needed. Therefore, diagnostic testing may be sometimes required to determine alternative medications (15). In our study, alternative drugs were determined for 21 patients through DPTs. DHR drug identity were issued to the patients with confirmed DHRs.

CONCLUSION

The diagnostic approach for patients presenting to the pediatric allergy clinic with suspicion of DHRs indicates that DHR diagnosis is confirmed at a low rate based on drug allergy tests. Hence, referring pediatric patients with suspected DHRs to allergy clinics and performing diagnostic allergological examinations are crucial for preventing over-and underdiagnosis of DHRs in children. In addition, it is important to perform diagnostic tests to determine alternative drugs for cases diagnosed with confirmed DHRs

REFERENCES

1. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF,et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J AllergyClin Immunol 2004;113:832-6.
2. Gomes ER, Brockow K, Kuyucu S, Saretta F, Mori F, Blanca-Lopez N, et al; ENDA/EAACI DrugAllergy Interest Group. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. Allergy 2016;71:149-61.
3. Gomes ER, Fonseca J, Araujo L, Demoly P. Drug allergy claims in children: from self-reporting to confirmed diagnosis. Clin Exp Allergy 2008;38:191-8.
4. Seitz CS, Bröcker EB, Trautmann A. Diagnosis of drug hypersensitivity in children and adolescents: discrepancy between physician-based assessment and results of testing. Pediatr Allergy Immunol 2011; 22:405-10.
5. Erkoçoğlu M, Kaya A, Civelek E, Ozcan C, Cakır B, Akan A, et al. Prevalence of confirmed immediate type drug hypersensitivity reactions among school children. Pediatr Allergy Immunol 2013 ;24:160-7.
6. Waheed A, Hill T, Dhawan N. Drug Allergy. Prim Care 2016;43:393-400.
7. Demoly P, Adkinson NF, Brockow K,Castells M, Chiriac AM, Greenberger PA, etal. International Consensus on drug allergy. Allergy 2014;69:420-37.
8. Dibek Misirlioglu E, Guvenir H, Ozkaya Parlakay A, Toyran M, Tezer H, Catak AI, et al. Incidence of Antibiotic-Related Rash in Children with Epstein-Barr Virus Infection and Evaluation of the Frequency of Confirmed Antibiotic Hypersensitivity. Int Arch Allergy Immunol 2018;176:33-8.
9. Mori F, Liccioli G, Tomei L, Barni S, Giovannini M, Sarti L, et al. How to manage drug-virus interplay underlying skin eruptions in children. World Allergy Organ J 2024;17:100877.
10. Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. EAACI Task Force on Anaphylaxis in Children. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy 2007; 62:857-71.
11. Dykewicz MS, Lam JK. Drug hypersensitivity reactions. Med Clin N 2020;104:109-28.
12. Çelik G, Dursun BA. Approach to Drug Hypersensitivity Reactions: National Guidelines Update 2019. Turkish National Society of Allergy and Clinical Immunology Ankara 2019.
13. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al.Skin test concentrations for systemically administered drugs–an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2013; 68: 702-12.
14. Aberer W, Bircher A, Romano A,Blanca M, Campi P, Fernandez J, et al. European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity reactions:general consideration. Allergy 2003;58:854-63.
15. Capanoglu M, Erkocoglu M, Kaya A, Dibek Misirlioglu E, Ginis T, Toyran M, et al. Confirmation of drug allergy in a general pediatrics outpatient clinic. Ann Allergy Asthma Immunol 2022;129:784-89.
16. Milosevic K, Malinic M, Plavec D, Lekovic Z, Lekovic A, Cobeljic M, et al. Diagnosing Single and Multiple Drug Hypersensitivity in Children: A Tertiary Care Center Retrospective Study. Children (Basel) 2022;9:1954.
17. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunoll 2005; 5:309-16.
18. Shiohara T, Kano Y. A complex interaction between Drug allergy and viral infection. Clin Rev Allerg Immunol 2007;33:124-33.
19. Bergmann M, Caubet JC. Specific Aspects of Drug Hypersensitivity in Children. Curr Pharm Des 2016;22:6832-51