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RESEARCH ARTICLE

Diagnostic evaluation and risk factors for drug allergies in children: from clinical history to skin and challenge tests

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Abstract *Background* Parent or self-reported drug allergy claims frequently overestimate the real incidence of hypersensitivity reactions. A detailed and algorithmic diagnostic evaluation of drug reactions may allow a proper diagnosis. *Objective* The aim of this study was to determine the confirmation rates and risk factors for confirmed allergic drug reactions in children. *Setting* Mersin University Hospital in Turkey. *Method* The study consisted of children between ages of 8 months and 18 years with the history of suspected drug allergy as reported by the clinician or the patients. Parents were interviewed by a clinician to complete questionnaires that included questions about demographic data and characteristics of index drug reaction. Immediate reactions (IRs) were assessed with immediate-reading skin prick (SPT) and intradermal tests (IDT). Nonimmediate reactions (NIRs) were assessed with SPT, both early and delayed reading of IDT and patch tests. In case of negative skin tests, drug provocation tests were performed. The possible risk factors for confirmed drug allergy in univariate analysis ($p < 0.1$) were entered into the multivariate logistic regression analysis to determine independent predictors. *Main outcome measure* (1) Confirmation rates of drug allergy (2) Risk factors related to confirmed drug allergy in children. *Results* We evaluated a total of 180 suspected drug allergy reactions in 97 children, mainly to antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and anticonvulsants. Among all suspected allergic drug reactions, 97 (53.9 %) were immediate type and 83 (46.1 %) were non-immediate type. The average time interval between the reaction and allergologic work-up was 5 months. Drug allergy confirmation rates were 30.1 % for beta-lactams, 27.2 % for non-beta-lactams, 21.1 % for NSAIDs and 30 % for anticonvulsants. Eight of 54 confirmed NIRs showed positivity on immediate skin tests. Regulatory T cells, TGF-β and IL-10 levels were not different between groups with and without confirmed drug allergy. A strong family and personal history of drug allergy were found to be significantly related to the confirmed allergic drug reactions. *Conclusion* Parent or self-reported drug allergy should be evaluated with a standardized diagnostic work-up before strict prohibitions are made. In addition, family and personal histories of drug allergy were significant risk factors related to allergic drug reactions in children.

Keywords Allergies · Challenge tests · Drug hypersensitivity · IL-10 · Regulatory T cells · Skin tests · TGF-beta

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Impact of findings on practice

- A clinician should be aware that a parent or self-reported history of drug allergy is not enough to make a diagnosis of drug allergy and an algorithmic diagnostic work-up is essential.

- Many allergists approach drug allergy diagnostic testing in a manner which may miss a considerable number of patients with real drug allergy because of vague history.
- IgE-mediated reactions may appear hours later, therefore that it may be problematic to use an arbitrary cut-off as '1 h' only to discriminate between IRs and NIRs.
- Family and personal histories of drug allergy are confirmed as significant risk factors for the development of allergic drug reactions.

Introduction

Adverse drug reactions, some of which are allergic, are frequently encountered in daily clinical practice. The prevalence of self-reported allergic drug reactions among outpatient populations ranges from 2.8 to 11.8 % [1–3]. Previous population based studies have confirmed that nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics are responsible for the majority of reactions [3, 4]. Proposed risk factors for adverse drug reactions are ages over 45 or between 1 and 4 and female gender [5]. Among other conditions, atopy was reported as a risk factor for both NSAIDs and antibiotic allergies [6, 7]. Kurt et al. [8] found that female gender, asthma, allergic rhinitis and eczema diagnoses were associated with drug hypersensitivity reactions. Prior studies have revealed that 5.5–58.3 % of suspected drug reactions were confirmed with skin or challenge tests in children [9, 10]. In a previous study, 1170 children with a clinical history of allergy to penicillins and/or cephalosporins were tested for immediate hypersensitivity to betalactams, 58.3 % cases overall were found to be skin or challenge test positive [10]. Gomes et al. [11] evaluated 60 patients with reported drug allergy and only 3 children were diagnosed as drug allergy, based on positive responses in skin (n = 1) and oral provocation (n = 2) tests.

A complete allergy work-up should include a detailed clinical history of the patient's reaction, associated risk factors and reaction interval. Immediate reactions (IRs) usually appear within 1 h of drug intake and are mediated by specific IgE antibodies, whereas non-immediate reactions (NIRs) occur more than 1 h after drug intake and are usually T cell mediated [12]. While IgE mediated allergic reactions should be assessed by immediate-reading skin tests, T-cell-mediated reactions should be evaluated by patch tests and delayed reading intradermal tests (IDTs) [12, 13]. The sensitivity of skin tests is not 100 % and drug provocation tests (DPTs) are considered to be the gold standard to establish or exclude drug hypersensitivity [14].

Regulatory T (Treg) cells play a central role in the maintenance of immune homeostasis. Drug hypersensitivity reactions may occur due to immune system dysregulation and reduced function or number of Treg cells [15]. To analyse the immune profiles in cases of confirmed drug allergy, serum levels of cytokines and Treg cells were evaluated in our study.

Despite recent developments in the area of allergy, research data on the frequency and related factors of confirmed allergic drug reactions in children remain sparse.

Aim of the study

The purpose of this study was to determine the confirmation rates of clinician or parent reported drug hypersensitivity reactions in children with a standardized diagnostic protocol based on European Network for drug Allergy (ENDA) guideline and to search for risk factors related to confirmed drug allergy.

Ethical approval

The Mersin University Hospital ethics committee approved this study. Prior to this study, parents of all the children received information about the possible risks of skin and challenge tests, and written informed consent was obtained.

Method

Study design

The present study comprised 2 phases. Phase 1 involved completion of a standardized questionnaire about drug allergy. In phase 2, children of consenting parents underwent further diagnostic testing.

Study population

All patients between the ages of 8 months and 18 years referred to the Pediatric Allergy Clinic of Mersin University with a suspicion of drug-induced hypersensitivity reaction were prospectively evaluated from May 2009 to March 2011. Of the 123 children with suspected drug allergy asked to participate in the study, 97 subjects accepted the diagnostic work-up. The response rate was 78.6 %.

Data collection

A comprehensive European Network of Drug Allergy (ENDA) questionnaire was applied to the children with the

history of drug allergy suspicion by the clinician or patient perspective [16]. This questionnaire included questions about demographic data, characteristics of index drug reaction, suspicious drugs, involvement of organ symptoms (including cutaneous, nasal, ocular, bronchial, gastrointestinal, laryngeal and cardiovascular), contributing factors (viral infection, fever and exercise), reaction interval, previous and subsequent administration of the culprit drug, management procedures, family and personal histories of drug allergy and atopy. Parents were interviewed by a clinician to complete the questionnaire. In some cases, it was completed by a clinician using information supplied by the referring physician. The responses were recorded in detail. Any patient whose parents provided a vague or inconclusive report and whose reaction was not observed by health care staff was considered to have a weak history. A strong history was defined as a reaction observed by a health care specialist (paediatrician, allergy specialist or dermatologist) and/or recorded in the patient's medical records.

Diagnostic evaluation

Skin tests

According to ENDA recommendations, IRs usually appear within 1 h of drug intake, whereas NIRs occur more than 1 h after drug intake [17, 18]. The 1-h cut-off is defined as the time from administering the drug to the reaction. In the IRs skin prick tests (SPTs), early and late readings of IDT were performed [17]. For beta-lactam (BL) allergy, SPTs and IDTs were carried out using major (penicilloyl-polylysine, $5 \times 10_{M}^{-5}$) and minor (MDM, $2x10_{M}^{-2}$) determinant mixtures (Diater, Madrid, Spain), benzyl-penicillin (BP), amoxicillin and the suspected BL. For the drugs, prick and IDTs were applied according to maximum non-irritant concentrations [17, 19]. IRs are documented by measuring the mean diameter of the wheal (and erythema) of the test preparations and the negative control 20 min later. The mean diameter was recorded by measuring the largest and smallest diameters at right angles to one another. Both diameters were recorded, summed and divided by 2. A positive SPT was defined as a wheal at least 3 mm larger than the negative control with surrounding erythema. When SPTs were negative, 0.02 mL of the reagent solution was injected intradermally on volar forearm skin, and the reaction was observed 20 min later. Results were considered positive when the maximum diameter of the wheal produced by the injection increased by 3 mm or more accompanied by erythema. Late readings of IDTs were performed after 48 and 72 h, and an infiltrated erythema with a diameter larger than 5 mm was considered a positive reaction. Positive controls for SPTs and IDTs were performed with histamine at 10 and 1 mg/mL respectively, and normal saline was used as a negative control [17, 20].

In patients with histories of NIR, SPTs, early and late reading IDTs were performed in addition to patch tests, because it may be problematic to use an arbitrary cut-off as '1 h' only and IgE-mediated reactions may appear hours later [12, 13]. For patch tests; the commercially available test drugs were prepared at concentrations of 5, 10 and 30 % in petrolatum, in accordance with the reported maximum non-irritant concentrations [21]. Initial tests were applied at much lower concentrations in severe allergic reactions, such as Stevens–Johnson syndrome (SJS) characterised by extensive detachment of epidermis and erosions of mucous membranes and Drug reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome characterised by skin rash, fever, lymph node enlargement and internal organ involvement. [17, 21]. Finn-chambers were used for application and were filled with 20–30 μL of the drug suspension. Patch tests were removed after 48 h and evaluated at 15 min, also 48, 72 and 96 h after removal. Reactions from + to +++ were regarded as positive [21].

Drug provocation test

In all children, except those with severe reactions, oral DPTs were performed when skin and patch tests were negative. In those who had experienced IRs, an initial dose of 1/10.000–1/100 of the therapeutic dose was administered depending on the severity of the reaction. During the DPT, 4–5 escalating doses of the culprit drug were administered at intervals of 30–60 min up to the full therapeutic dose. The children were kept under strict medical observation for up to 2 h after completing the test [14]. In those with NIRs, a starting dose of 1/1000–1/100 of the therapeutic dose and then 2–3 escalating doses of the culprit drug were administered, up to the full therapeutic dose, with intervals chosen acording to interval of the index reaction [12, 14].

Any patient with a history including a single NSAID was tested first with an SPT and IDT. If negative, they were then challenged with the culprit NSAID. Any subject with a history of hypersensitivity reactions to more than one NSAID was directly challenged with the culprit drugs [14, 18].

Assessment of atopy and immune profile

Atopy was assessed by questionnaire, serum total IgE, peripheral eosinophil counts, food and inhalant specific IgE levels and SPTs with inhalant allergens.

A blood specimen was obtained from any patient showing a positive drug skin test or DPT to evaluate their

immune profile. Treg (CD4 + CD25 + FoxP3), CD4+, CD8+ cells and cytokine (IL-10, TGF-beta) levels were analysed, and the results were compared with the healthy control group. Children in the healthy control group were matched for age and sex and had no histories of drug allergy, atopy or chronic disease.

Statistical analysis

Statistical analyses were performed using the SPSS 11.5.1 statistical software for Windows. The Shapiro–Wilk test was performed to test the suitability of the numerical data's normal distribution. Comparisons for continuous variables were made by the Mann–Whitney test, and comparisons between categorical variables were made by the Chi square test. The possible risk factors for confirmed drug allergy identified with univariate analysis ($p < 0.1$) and those thought to be clinically important were included in the multivariate logistic regression analysis to determine the independent predictors. The adjusted odds ratio (aOR) and its 95 % confidence interval (CI) were calculated. A p value of <0.05 was considered to be significant.

Results

Study population

We evaluated 180 suspected drug allergy reactions in 97 children who were admitted to the Pediatric Allergy Clinic of Mersin University between May 2009 and March 2011. Questionnaires were completed and diagnostic work-ups were accepted by the parents of the 97 child subjects, resulting in a response rate of 78.6 %.

Questionnaire

The mean age of the subjects was 6.9 (± 4.25 years; SD) and 46 (47.4 %) were female. Among all suspected allergic drug reactions, 97 (53.8 %) were immediate (interval ≤1 h) and 83 (46.1 %) were non-immediate-type (interval >1 h) reactions. The median time interval between the index reaction and allergologic work-up was 5 months (min 1 and max 14 months). Strong histories were found in 37 (38.1 %) of the children. Among all subjects, 22 (22.6 %) had family histories of drug allergy, 26 (26.8 %) had physician-diagnosed allergic disorders (asthma, allergic rhinitis, atopic dermatitis, food allergy) and 58 (59.7 %) had concomitant viral infections during the index reaction. Among the reported drug reactions, dermatologic symptoms were most common (96.9 %), followed by respiratory (6.2 %), cardiovascular (6.2 %) and gastrointestinal (3.2 %) manifestations. Of all the children, 46 (47.4 %) reported urticaria, 21 (21.6 %) urticaria with angioedema, 17 (17.5 %) maculopapular rash, 8 (8.2 %) anaphylaxis, 1 (1 %) SJS and 1 (1 %) DRESS syndrome.

Results of diagnostic tests

The mean number of suspected drugs per child was 1.81 ± 1.1 (min 1 and max 6 drugs). The culprit drugs were mainly antibiotics (55 %), of which 89.4 % were BLs, NSAIDs (32 %) and anticonvulsants (7.3 %). Amoxicillin-clavulanic acid was the most frequently implicated BL, followed by third-generation cephalosporins and ampicillin-sulbactam. Clarithromycin was the most frequently implicated non-BL. Ibuprofen was the most frequently suspected NSAID, followed by acetaminophen and metamizol. In the anticonvulsant group, lamotrigine was most commonly reported.

Of the 180 suspected drug allergy reactions, drug allergy was confirmed in 49 (27.2 %). Among the suspected antibiotic hypersensitivity reactions (n = 104, 93 BL and 11 non-BL), 31 (28 BL and 3 non-BL) (29.8 %) were confirmed with diagnostic tests. NSAID hypersensitivity was diagnosed in 12 (21.0 %) of the 57 suspected reactions. In the antiepileptic group, 3 (30 %) of the 10 suspected reactions were confirmed with diagnostic tests.

When the time interval between the clinical reaction and allergic work-up was analysed, there was no significant difference in the confirmation rate of drug allergy depending on whether the time interval was longer or shorter than 6 months ($p > 0.05$).

Of the 49 confirmed reactions, 27 (55.1 %) were diagnosed by skin tests and 22 (44.8 %) by DPT. Of the 97 immediate drug allergy reactions evaluated, 32 were confirmed; 18 (56.2 %) were diagnosed by skin tests and 14 (43.7 %) by provocation tests. Of the 83 NIRs evaluated, 17 were confirmed; 9 (52.9 %) were diagnosed by skin tests and 8 (47 %) by provocation tests.

Among the suspected immediate-type antibiotic reactions, 14 (25.4 %) were confirmed by skin tests and 5 (14.2 %) by provocation tests. Among the suspected non-immediate-type antibiotic reactions, 7 (14.8 %) were confirmed by skin tests and 5 (15.6 %) by provocation tests (Table 1). In our study, 8 of 54 confirmed NIRs showed positivity on SPT and/or early reading IDTs, although they were defined as NIR according to reaction interval.

Fifty-seven NSAID reactions were evaluated. Among the immediate-type, 3 (20 %) were confirmed by SPT/early reading IDT and 8 (22.2 %) by DPT. Among the non-immediate-type suspected antibiotic reactions, none were diagnosed by skin tests and only 1 (5.8 %) was confirmed by DPT (Table 2). The confirmation rate was highest for metamizol reactions.

Table 1 Distribution of reaction confirmation rates according to antibiotic group and type of diagnostic procedures

Reaction type	Immediate reactions			Non-immediate reactions					Total reactions
	SPT/early reading IDT	DPT	Confirmed drug allergy	Patch test	SPT/early reading IDT	IDT late reading	DPT	Confirmed drug allergy	Confirmed total drug allergy
Penicillins	8/26	3/16	11/26	0/15	5/22	0/11	3/13	8/24	19/50
	(30.7)	(18.7)	(42.3)	(0)	(22.7)	(0)	(23)	(33.3)	(38)
Cephalosporin	3/19	2/13	5/19	0/14	2/18	0/9	2/13	4/24	9/38
	(15.7)	(15.3)	(26.3)	(0)	(11.1)	(0)	(15.3)	(16.6)	(23.6)
All Beta-lactams	11/49	5/32	16/49	0/30	7/42	0/22	5/27	12/49	28/93
	(22.4)	(15.6)	(32.6)	(0)	(16.6)	(0)	(18.5)	(24.4)	(30.1)
Macrolides	3/6	0/3	3/6	0/3	0/5	0/2	0/5	0/5	3/11
	(50)	(0)	(50)	(0)	(0)	(0)	(0)	(0)	(27.2)
Other antibiotics	0/4	0/3	0/4	0/1	0/2	0/2	0/1	0/1	0/5
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Total	14/55	5/35	19/55	0/33	7/47	0/24	5/32	12/54	31/104
	(25.4)	(14.2)	(34.5)	(0)	(14.8)	(0)	(15.6)	(22.2)	(29.8)

* Results are given as the number of test positive reactions/number of performed tests (%)

SPT skin prick test, *DPT* drug provocation test, *IDT* intradermal test

Table 2 Distribution of reaction confirmation rates according to NSAIDs and type of diagnostic procedures

Reaction type	Immediate reactions			Non-immediate reactions				Total reactions
	SPT/early reading IDT	DPT	Confirmed drug allergy	Patch test	SPT/early and late reading IDT	DPT	Confirmed drug allergy	Confirmed total drug allergy
İbuprofen	0/6	5/19	5/19	0/8	0/8	1/8	1/8	6/27
	(0)	(26.3)	(26.3)	(0)	(0)	(12.5)	(12.5)	(22.2)
Acetaminophen	1/3	2/12	3/12	0/6	0/6	0/6	0/6	3/18
	(33.3)	(16.6)	(25)	(0)	(0)	(0)	(0)	(16.6)
Metamizol	2/6	1/3	3/6	0/2	0/2	0/2	0/2	3/8
	(33.3)	(33.3)	(50)	(0)	(0)	(0)	(0)	(37.5)
Aspirin	0/1	0/1	0/2	–	–	–	–	0/2
	(0)	(0)	(0)					(0)
Diclofenac	0/1	0/1	0/1	–	–	–	–	0/1
	(0)	(0)	(0)					(0)
Salisilazo sulfapyridine	–	–	–	0/1	0/1	0/1	0/1	0/1
				(0)	(0)	(0)	(0)	(0)
Total	3/15	8/36	11/40	0/17	0/17	1/17	1/17	12/57
	(20)	(22.2)	(27.5)	(0)	(0)	(5.8)	(5.8)	(21.0)

* Results are given as the number of test positive reactions/number of performed tests (%)

SPT skin prick test, *DPT* drug provocation test, *IDT*: intradermal test

Among the confirmed (n = 12) NSAID hypersensitivity reactions, 50 % (n = 6) of the patients showed cross-reactive-type NSAID hypersensitivity. For multiple analgesic allergy, the most frequently confirmed drugs were acetaminophen with ibuprofen.

Of the 19 other drug reactions evaluated, 6 were confirmed. Among the IRs, the SPT/IDT and DPT positivity rates were both 1 (33.3 %). Among the NIRs, the patch test positivity rate was 1 (6.6 %), SPT/IDT was 1 (33.3 %) and DPT was 2 (15.3 %) (Table 3).

Assessment of immune profile

In 18 cases with positive diagnostic tests (skin tests or DPT), the Treg (CD4 + CD25 + FOXP3+) and cytokine (TGF-beta and IL-10) levels were analysed the same day

Table 3 Distribution of reaction confirmation rates according to other drug groups and type of diagnostic procedures

	Immediate reactions		Non-immediate reactions			Total reactions
	SPT/IDT early reading	DPT	Patch test	SPT/early and late reading IDT	DPT	Confirmed drug allergy
Anticonvulsants	–	–	1/10 (10)	–	2/8 (25)	3/10 (30)
General/local anesthetics	1/2 (50)	0/1 (0)	–	–	–	1/2 (50)
H1 receptor antagonists	–	1/1 (100)	0/1 (0)	–	0/2 (0)	1/2 (50)
Steroid/chemotherapeutics	0/1 (0)	0/1 (0)	0/2 (0)	1/2 (50)	0/1 (0)	1/3 (33.3)
Mucolytics	–	–	0/2 (0)	0/1 (0)	0/2 (0)	0/2 (0)
Total	1/3 (33.3)	1/3 (33.3)	1/15 (6.6)	1/3 (33.3)	2/13 (15.3)	6/19 (31.5)

* Results are given as the number of test positive reactions/number of performed tests (%)

SPT skin prick test, *DPT* drug provocation test, *IDT* intradermal test

and concomitantly with the test results. The results were then compared with those of 18 children in the healthy control group. There was no significant difference between groups in serum levels of Treg cells ($p = 0.501$; mean percentage of Treg cells for patients with positive diagnostic tests was 1.96 % and for the control group was 2.31 %) and cytokines ($p = 0.796$ for IL-10 level and $p = 0.628$ for TGF-beta).

Comparison of the groups

When we compared the possible risk factors of the subgroups with (n = 49) and without (n = 131) confirmed drug allergy, we found that strong personal and family histories of drug allergy were significantly higher in the confirmed drug-allergy group (Table 4). On the other hand, 26.6 % of the patients with vague histories of drug allergy were confirmed by diagnostic tests. There was no significant difference between the groups with and without confirmed drug allergy in terms of atopy, presence of viral infection during index reaction, serum total IgE and eosinophilia.

Risk factors related to confirmed drug allergy

The groups were well matched in terms of age, sex, personal and/or family atopy. Multivariate logistic regression analysis of the possible risk factors related to confirmed drug allergy revealed that the children with family histories of drug allergy were 4.4 times more likely to have a confirmed drug allergy than those without family histories ($p = 0.010$, CI 1.43–13.62). In addition, the patients with strong personal histories of index drug reaction were 3.5 times more likely to have a confirmed drug allergy than those with weak histories ($p = 0.015$, CI 1.27–9.60). However, the other possible risk factors included in the model, such as age, sex, personal and/or family atopy, had no significant association with confirmed drug allergy.

Discussion

The present study reports the prevalence of confirmed allergic drug reactions and related risk factors in a paediatric population. We evaluated 180 reactions among 97 children, and 49 (27.2 %) of the suspected reactions were confirmed as drug allergy. Seitz et al. [22] evaluated 43 children and adolescents with histories of drug hypersensitivity reactions and excluded the diagnosis in 40 patients. A previous study evaluated 783 patients with symptoms suggestive of BL hypersensitivity, and only 62 cases (7.92 %) were confirmed as allergic [23].

One of the most frequently implicated groups of drugs for drug allergy are BLs because they are among the most prescribed drugs worldwide [24, 25]. In our study, 28 (30.1 %) of the suspected BL reactions were diagnosed as allergic, similar to a study by Pichichero, which obtained a confirmation rate of 23.5 %. However, our results conflict with those of Ponvert and Zambonino, who reported positive test results in 7.4 and 7.92 % of children, respectively [23, 24, 26].

Amoxicillin-clavulanic acid was the most frequently implicated BL in our study, followed by third-generation cephalosporins and ampicillin-sulbactam. In Ponvert's

Table 4 The comparison of possible risk factors for drug hypersensitivity in the groups with confirmed drug allergy and without drug allergy (a total of 97 patients)

	Patients with no drug allergy n = 63 (%)	Patients with confirmed drug allergy n = 34 (%)	*p* value
Female gender	33 (52.3)	13 (38.2)	0.183
Personal atopy	48 (76.1)	24 (72.7)	0.547
Positive family history of atopy	11 (17.4)	14 (41.1)	0.116
Positive family history of drug allergy	9 (14.2)	13 (38.2)	**0.007**
Strong history of index drug reaction	19 (30.1)	18 (52.9)	**0.028**
Viral infection during index drug reaction	35 (55.5)	23 (67.6)	0.147
Serum total IgE (IU/mL) (mean ± SD)	168 ± 229.80	279.67 ± 446.56	0.426
Serum eosinophilia %	3.15 ± 2.49	3.67 ± 3.13	0.617

The bold values are the ones which are statistically significant

study, amoxicillin alone or with clavulanic acid was the most frequently involved BL (64.9 %), followed by third-generation cephalosporins (21.5 %) [25]. Macrolides were the most common non-BL antibiotic in our study, and 27.2 % of the suspected macrolide hypersensitivity reactions were confirmed with diagnostic tests. Studies of patients with suspected macrolide allergy have shown confirmation rates of only 7.5–13.7 %, mainly by DPT [27, 28].

In the present study, NSAID hypersensitivity was diagnosed in 12 (21.1 %) of the 57 reported reactions, 50 % of which were the cross-reactive type. A previous study evaluated 63 children with histories of NSAID hypersensitivity, confirming 68.2 % as allergic [29]. Yilmaz et al. [30] investigated NSAID hypersensitivity in 58 children, confirming single-drug-induced and cross-reactive NSAID allergy in 5 of 36 (14 %) and 8 of 18 (44 %), respectively.

In our study, the average elapsed time between clinical reaction and allergic evaluation was 5 months. No significant difference was detected in the drug allergy confirmation rate depending on whether this time interval was longer or shorter than 6 months. This is of greater importance, as IgE related sensitization to BLs has been shown to decrease with time [31].

In our study, 8 patients in the NIR group according to case histories had positive SPTs and/or early leading IDTs. This finding is consistent with the study of Hjortlund et al. [32] who reported that 6 patients categorized as NIR based on histories, reacted immediately during challenge testing. Hence, the case history is not generally sufficient to discriminate between IRs and NIRs [33].

In this present work, 26.6 % of patients with vague histories of drug allergy were confirmed by drug-allergy diagnostic tests. Because of vague histories, many allergists approach drug-allergy diagnostic testing in such a way that they miss a considerable number of patients with real drug allergy. Stember et al. [34] reported that 6.7 % of patients with vague penicillin allergy histories had positive skin tests. Therefore, these patients should also undergo an algorithmic diagnostic procedure to exclude drug allergy.

Of the 49 confirmed reactions in our study, 27 (55.1 %) were diagnosed by skin tests and 22 (44.8 %) by DPT. However, the diagnosis of NSAID hypersensitivity was largely based on DPTs. In patients with multiple NSAID allergy, DPTs are also of great importance in establishing or excluding drug allergy and for suggesting safe analgesic drugs.

The results of the patch tests were mostly negative in our patients with histories of delayed skin reaction. Of the 78 patch tests performed for NIRs, the patch test was positive in only 1 case (1.2 %) with suspected lamotrigine allergy. In a previous study, 72 patients with presumed drug eruptions were assessed. Of these patients, 43 % showed positive skin patch tests. They concluded that the results of skin tests varied with the drug tested and clinical type of cutaneous adverse drug reactions [35].

A dysregulation of the immune system caused by impaired function or number of Treg cells, which can restrict immunopathology, may play a role in drug allergy [36]. In our study, there was no significant difference between groups with confirmed drug allergy and healthy controls in terms of Treg cells and cytokine levels. Qiao et al. [37] found significantly lower levels of IL-10 in patients with penicillin positive specific IgE compared with control subjects and patients with negative specific IgE.

Potential risk factors for drug hypersensitivity reaction have been defined in various reports [38, 39]. A recent study demonstrated that younger children seem to be at increased risk for adverse drug reactions [38]. The majority of drug reactions reported in children were attributable to infectious diseases or interactions between drugs and infectious agents [40]. We found no significant difference between the confirmation rates of groups with and without concomitant viral infection during the index reaction. In children with atopic disease, asthma and chronic urticaria, atopy was a significant risk factor for reactions with NSAIDs [41]. Yilmaz et al. [30] determined that family

history of NSAID hypersensitivity was the only significant predictor of DPTs. Our results were consistent with previous report showing that age, sex and atopy were not risk factors for drug allergy in children [24]. Strong personal and family histories of drug allergy were significantly related to drug allergy.

Strength and weaknesses

One of the limitations of our study was the relatively small number of subjects analysed. In terms of the variables which were not significant, the sample size may have been too small to detect a real difference. Second, the serum samples were obtained during the positive test response but not during the index reaction. Thus, our results may not reflect the actual levels of Treg and cytokines at the time of the original reaction.

Our study has several strengths. First, the patients were evaluated by a detailed questionnaire and a diagnostic protocol. Second, IgE-mediated reactions may appear hours later, so that we did not only use an arbitrary cut-off as "1 h" to discriminate between IRs and NIRs. Third, most of the diagnostic tests were performed within 6 months of the index reaction; therefore it is unlikely that any sensitization had been lost with time. Finally, considering the rarity of studies about drug hypersensitivity in children, the data in this study have provided important additive results about the frequency and risk factors of drug allergy in a tertiary care clinic in Turkey.

Conclusion

In conclusion, parent or self-reported allergic drug reactions should be evaluated with a standardized diagnostic work-up before mislabeling and prohibitions are made. In addition, family and personal histories of drug allergy are confirmed as significant risk factors for the development of allergic drug reactions. Studies focusing on the analysis of full-diagnostic work-up and risk factors related to suspected drug allergy in larger prospective series should be encouraged.

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