

ORIGINAL ARTICLE

Prevalence of confirmed immediate type drug hypersensitivity reactions among school children

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To cite this article: Erkoçoğlu M, Kaya A, Civelek E, Özcan C, Çakır B, Akan A, Toyran M, Ginis T, Kocabas CN. Prevalence of confirmed immediate type drug hypersensitivity reactions among school children. *Pediatr Allergy Immunol* 2013; **00**.

Keywords

children; diagnostic work-up; drug allergy; drug allergy survey; drug hypersensitivity; epidemiology; immediate hypersensitivity

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Financial support: There are no sources of funding to declare.

Accepted for publication 3 January 2013

DOI:10.1111/pai.12047

Abstract

Background: Despite drug-related hypersensitivity reactions are an important health problem, epidemiologic data on drug allergy and hypersensitivity are limited, and studies including diagnostic work-up are scarce. The aim of this study was to determine the actual frequency of immediate type drug hypersensitivity using diagnostic tests in school children with parent-reported drug allergies.

Methods: This study involved three phases. The first phase is a survey of children with a mean age of 12.9 yrs attending grades 6–8 of primary schools with a questionnaire asking drug-related symptoms within 2 h of ingestion. The total population of sixth to eighth grade school children was 210,000, and a sample size of 9096 was deemed to be representative of Ankara [(p) = 1.0%, α < 0.05, β = 0.8, (d) = 0.2.] During the second phase, a detailed clinical history was obtained by phone from the parents of children who had positive parent-reported drug allergy. The final stage of the study consisted of a detailed diagnostic work-up of children with a clinical history consistent with immediate type drug hypersensitivity reaction.

Results: Overall, 11,233 questionnaires were distributed, 10,096 of which were retrieved after completion by parents. The rate of parent-reported immediate type drug hypersensitivity was 7.87% (792 children). However, phone survey revealed a clinical history suggestive of drug allergy in only 117 children (1.16%). After further diagnostic work-up, the true frequency of immediate type drug hypersensitivity was 0.11%.

Conclusion: Our results suggest that a positive clinical history is not enough to make a diagnosis of drug allergy, which highlights the significance of undertaking further diagnostic evaluation.

Drug allergies are acute and potentially life-threatening reactions that constitute one-third of all drug-related adverse reactions (1). Patients may often report various adverse drug reactions their children experienced as a drug allergy. The World Health Organization requires identification of the underlying immunologic mechanisms responsible for the reaction as a prerequisite in diagnosing 'drug allergy' (2). In current practice, on the other hand, the diagnosis of a drug allergy is often based on patient/caregiver declarations rather than standard diagnostic tests.

Despite the high relevance of drug-related hypersensitivity reactions in public health, epidemiologic data on drug allergy and hypersensitivity are limited (3–5). The prevalence of self-reported drug allergy among outpatient populations range

from 2.8% through 11.8% (6–10) but numerous studies have shown that a diagnosis of drug allergy based on history alone is unreliable (3, 11–13). Recent studies have revealed that only 4.4–6.9% of patients with a suspected drug allergy had a real immunologic hypersensitivity (3, 11). Although there are some studies reporting the prevalence of confirmed drug allergy in the hospital setting (3, 4) to our knowledge, there is not any population-based epidemiologic study on the frequency of proven immediate type drug allergy.

The aim of this study was to determine the actual frequency of immediate type drug hypersensitivity reactions (iDHR) among school children in Ankara. Drug allergy was screened by a questionnaire in a representative group of school children from grade 6 to 8, and phone survey was performed for further

evaluation of the history of the reaction. The diagnosis was confirmed by skin tests and provocation tests applied to children with suspected drug allergy according to the results of surveys.

Methods

The study design

This study was composed of three phases, as summarized in Fig. 1. The first phase was established as cross-sectional survey of children attending grades 6–8 of primary schools in Ankara, the capital of Turkey, during the 2010–2011 academic years. Phase 1 involved completion of a standardized questionnaire by parents of a representative group of students. In Phase 2, the parents of children reported to have drug allergy were contacted by phone to confirm whether their medical history is suggesting iDHR. In the last phase, children of consenting parents underwent further diagnostic testing.

The study population

According to data from the Ministry of Education, the estimated total population of children in grades 6 through 8 in the Ankara proper area was 210,000 children, attending 735 schools. In a previous study from Turkey, the reported

prevalence of parent-reported drug allergies was 2.8%, with a frequency of 1, 2% (7). A sample size of 9096 was considered to be representative of Ankara [(p) = 1.0%, α < 0.05, β = 0.8 and (d) = 0.2.] and with an anticipated participation of 70%; the minimum sample size to include in the first phase was calculated as 11,500 students. A one-step cluster sampling design was used and, of 735 registered schools in Ankara, 34 schools were randomly selected to participate in the study, and all students attending grades 6, 7, and 8 were invited for the study.

Data collection tool

During the first phase, a standard questionnaire was distributed to the selected group of children to be completed by their parents/main caregivers. After demographic data and contact details, parents were asked whether 'any drug reaction characterized by swelling of lips, tongue, eye or face, itching on the skin, skin rash, urticaria, angioedema, rhinitis, conjunctivitis, cough, shortness of breath, syncope or loss of consciousness; which occurred within 2 h after consumption of any drug' were present. Parents were asked to identify the responsible drug. In case of a positive response to any of the above-mentioned symptoms, the child was accepted as having 'parent-reported iDHR'. The presence of physician-diagnosed allergic diseases of the children, and their first degree relatives were also asked.

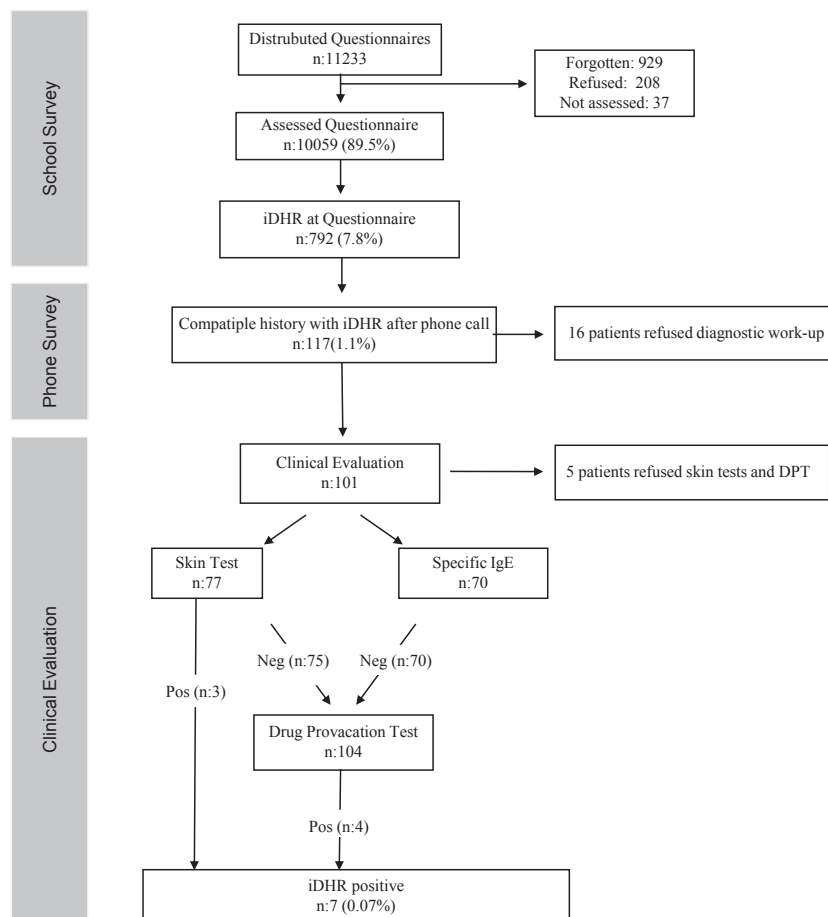


Figure 1 Study flow chart.

Phone survey

During the second phase, a pediatric allergist contacted the parents of children who had parent-reported iDHR, and a detailed clinical history was obtained by using an ENDA questionnaire by phone, and clinical histories of reactions that are compatible with iDHR and occurred within 1 h after use of drugs were accepted as compatible history with iDHR (14). Of the 9304 participants whose responses to the questionnaire were not suggestive of iDHR, 200 were chosen randomly and were contacted by phone for further questioning to investigate the false negativity of parental reporting.

Clinical evaluation

The final stage of the study consisted of a detailed diagnostic work-up of children with a clinical history consistent with iDHR.

Specific IgE

Allergen-specific IgE assays were performed in all participants with a history of drug allergy associated with beta-lactam antibiotics. For the penicillin group, serum levels of specific IgE against benzyl penicilloyl V, penicilloyl G, amoxycilloyl, and ampicilloyl were determined, whereas for the cephalosporin group, further testing for specific IgE titers against cefaclor was done, using Phadia CAP diagnostic system (ImmunoCAP 100E, Phadia, Uppsala, Sweden). Patients who had an elevated specific IgE level of >0.35 kIU/ml were considered as having drug allergy.

Skin test

Patients were subjected to prick and intradermal skin testing with beta-lactams (those with negative specific IgEs) macrolides and sulfonamide. Beta-lactams tested included benzylpenicilloyl poly-L-lysine (PPL), minor determinant (sodium benzylpenilloate) (MDM) (Diater Laboratorios S.A., Madrid, Spain), amoxicillin (20 mg/ml), ampicillin (20 mg/ml), penicillin G (10,000 IU/ml), and cephalosporin (cefaclor and culprit drug) (2 mg/ml) (15). Co-trimoxazole (0.8 mg/ml) and clarithromycin (0.5 mg/ml) were also used. Isotonic saline and histamine HCl (Stallergenes, SA Antony, France) were used as negative and positive controls, respectively.

Drug provocation test

Drug provocation testing was reserved to participants for whom other investigations were inconclusive and if the provocation test was not contraindicated. ENDA guidelines for skin and drug provocation tests were carefully respected (16, 17). A provocation test involved administering the suspected drug at divided doses every 30 min, until a cumulative dose close to the age-/weight-adjusted daily dose of the drug is achieved. The test is discontinued in the event of any adverse drug reaction.

Ethical issues

The survey was approved by the institutional ethics committee. Forms of consent were sent homes with the questionnaires, to be

filled and signed by the parents/caregivers. Written consent was also obtained prior to *in vivo* testing of participants invited to the pediatrics outpatient clinic for further diagnostic work-up.

Statistical analysis

Statistical analyses were performed using the SPSS-15 statistical software package (SPSS, Inc., Chicago, IL) for Windows. Frequency Tables were created for each question/response on the questionnaire, and standard descriptive statistics were conducted. The number of positive and negative answers was provided as valid percentages of the whole, including missing values (empty responses). The chi-square test was used to evaluate the significance between distributions of immediate type drug hypersensitivity cases across the groups. A *p*-value of ≤ 0.05 was considered indicative of statistical significance.

Results

Overall, 11,233 questionnaires were distributed, 10,096 of which were retrieved. A total of 1137 questionnaires were not returned (929 of the children claimed to have forgotten to present the questionnaires to their parents, whereas in 208 cases, parents/caregivers did not wish to participate in the study). After exclusion of 37 questionnaires due to incomplete responses on critical questions regarding drug allergy, final analysis was performed on a total of 10,059 questionnaires, that is, completion rate was 89.5%.

Questionnaire

The mean age of the participating children was 12.9 ± 0.9 yrs, 50.3% of which were girls. The rate of parent-reported drug allergy was 7.87% (792 children). Children with a positive history had a mean age of 12.9 ± 0.9 yrs, which was not significantly different from children without history of drug allergy ($p = 0.873$). The general characteristics of children with parent-reported immediate type drug allergy have been summarized in Table 1.

The frequency of physician-diagnosed allergic disorders of both children and their first degree relatives (asthma, allergic rhinitis, food allergy, drug allergy, and eczema) was significantly higher in the parent-reported iDHR group ($p < 0.001$ and $p < 0.001$, respectively) (Table 1).

Antibiotics were suggested as the cause of parent-reported reactions in 57.7% of the children, followed by NSAIDs in 12.5% of the participants. Dermatologic symptoms were the most frequently reported drug reactions (64%) (Table 2).

Phone Survey

Further detailed questioning by phone survey revealed that a clinical history suggestive of immediate type reaction was present in only 117 children (1.16%), 63 of which were girls (53.8%), with an overall mean age of 12.8 ± 0.9 yrs.

A phone survey on 200 randomly chosen participants from among the children who did not have parent-reported reactions, confirmed that none of them had any symptoms

Table 1 General characteristics of children with and without a parental reported iDHR and a compatible history with iDHR

	Total	Parental-reported iDHR			Compatible clinical history with iDHR		
	N: 10059	Positive n: 792	Negative n: 9267	p	Positive n: 117	Negative n: 9942	p
Age (mean $\pm$ s.d.)	12.9 $\pm$ 0.9	12.9 $\pm$ 0.9	12.9 $\pm$ 0.9	0.873	12.8 $\pm$ 0.9	12.9 $\pm$ 0.9	0.041
Female, n (%)	5062 (50.3)	429 (54.2)	4633 (50.0)	0.076	63 (53.8)	4999 (50.3)	0.742
Allergic disease n(%)							
Asthma	1238 (12.3)	194 (24.5)	1044 (11.3)	<0.001	27 (23.1)	1211 (12.2)	0.001
Allergic rhinitis	1626 (16.2)	249 (31.5)	1377 (14.9)	<0.001	42 (35.9)	1583 (15.9)	<0.001
Eczema	350 (3.5)	45 (5.7)	305 (3.3)	<0.001	8 (6.8)	342 (3.4)	0.048
Food allergy	356 (3.5)	108 (13.7)	248 (2.7)	<0.001	19 (16.2)	337 (3.4)	<0.001
Drug allergy	275 (2.7)	275 (2.7)	—	NA	77 (65.8)	198 (2.0)	<0.001
Familial allergic disease, n (%)*							
Asthma	2093 (20.8)	284 (35.9)	1809 (19.5)	<0.001	38 (32.4)	2055 (20.7)	0.002
Allergic Rhinitis	2729 (27.1)	342 (43.2)	2387 (25.8)	<0.001	50 (42.7)	2679 (26.9)	<0.001
Eczema	1120 (11.1)	140 (17.7)	980 (10.6)	<0.001	19 (16.2)	1101 (11.1)	0.084
Food allergy	860 (8.5)	156 (19.7)	704 (7.6)	<0.001	21 (17.9)	839 (8.4)	<0.001
Drug allergy	1114 (11.1)	205 (25.9)	909 (9.8)	<0.001	32 (27.3)	1082 (10.9)	<0.001

iDHR, immediate type drug hypersensitivity reaction; s.d., standard deviation.

*: Physician-diagnosed allergic disease in parents and/or sibling.

consistent with drug allergy, suggesting that the false negativity was comparably null (if any).

A personal and family history of another allergic condition was encountered more frequently in students with a positive clinical history suggestive of iDHR (Table 1). In this group, the most commonly responsible drugs were antibiotics (72.8%) and NSAIDs (34.2%), whereas skin findings were the most frequently reported hypersensitivity reaction (90.7%) (Table 2).

Results of evaluation for drug allergy in the outpatient clinic

Of the 117 patients with a clinical history of iDHR according to the phone survey, parents of 101 (86.3%) children accepted further diagnostic work-up. None of the children who accepted the invitation had been previously tested for drug allergies. Only 7 patients (0.07%) were diagnosed with iDHR following a thorough clinical evaluation.

Of the 101 patients, 70 had a history of iDHR to a beta-lactam antibiotic, 5 to a non-beta-lactam antibiotic, 32 to a NSAID and 3 to miscellaneous medications (iron supplements, multivitamins, pseudoephedrine). Eleven cases gave a history of a reaction due to more than one drug. The mean time elapsed from a drug reaction was 72.5 ± 38.3 months, with 27 cases experiencing a reaction within the year preceding the survey. Specific IgE measurements and skin tests were performed in 70 participants with an allergy to beta-lactam antibiotics. Specific IgE titers of all patients were undetectable. The parents of 5 of the children with negative specific IgE for penicillins did not consent to further testing. Three of the patients from the beta-lactam group with reported allergy tested positive with a skin prick/intradermal test (Table 3).

Overall, a total of 104 provocation tests were performed on 93 participants, 62 of which were with a beta-lactam antibiotic [amoxicillin/clavulanate(32), ampicillin/sulbactam(9), penicillin

V(7), amoxicillin(2), cefixime(3), cefdinir(2), cefaclor(2) and cefuroxime(5), and an additional five with a non-beta-lactam antibiotic co-trimoxazole (4) and clarithromycin (1)]. For the 32 patients with a reported allergy to NSAIDs, a total of 34 provocation tests were performed (16 with paracetamol, 10 with ibuprofen, 6 with aspirin, one with ketoprofen and metamizole each). Provocation tests were performed once, each with ferrous glycine sulfate (FGS), a multivitamin, and pseudoephedrine. In all, 11 participants were subjected to provocation tests with two different drugs. Results of the provocation tests have been summarized in Table 3. Two patients had positive provocation test with ibuprofen, 1 patient with aspirin, and 1 patient with an iron supplement, and all patients were reacted within 30 min after ingestion (Table 4).

When we compared the personal and family history of physician-diagnosed allergic diseases, there was no significant difference between the confirmed iDHR group and the rest of the total group ($p > 0.05$ for all parameters).

Of the 16 cases for whom parental consent was not given for further evaluation, 7 patients had reported reactions to beta-lactams, 2 siblings to co-trimoxazole, 4 to aspirin, and one each to FGS, paracetamol, metamizole sodium, and MAG-3. Four of these children had previous testing in an allergy clinic: two patients with a confirmed aspirin allergy, 1 with a penicillin allergy following a positive skin test, and 1 with a history of angioedema following an oral provocation test with metamizole. The parents of the remaining children did not provide consent: they were either scared of risk associated with the proposed diagnostic tests or stated a preference to use alternative drugs.

We have verified the diagnosis of 7 patients with skin tests and provocation (0.07%), and 4 of the children whose parents did not consent for diagnostic work-up had a previous diagnosis confirmed in other allergy clinics. A total of 11

Table 2 Type of drug and clinical manifestations in children with parental reported iDHR and compatible clinical history with iDHR

	Parental-reported iDHR (n: 792)	Compatible clinical history with iDHR (n: 117)
Physician-diagnosed drug allergy n(%)	275 (34.8)	77 (65.3)
Suspected drug n(%)		
Antibiotic	457 (57.7)	84 (71.8)
Beta-lactams	297 (37.5)	77 (65.8)
Other antibiotics	32 (4.0)	7 (5.9)
Not specified	132 (16.7)	–
NSAID	206 (26.0)	40 (33.9)
Other	63 (7.9)	5 (4.2)
Undefined	160 (20.2)	–
Reported symptoms n(%)		
Cutaneous		
Urticaria/angioedema	386 (48.7)	106 (90.6)
Maculopapular rash	121 (15.3)	–
Digestive	309 (39.0)	14 (10.7)
Respiratory	279 (35.2)	7 (5.4)
Ocular	166 (21.0)	4 (3.1)
Cardiovascular	92 (11.6)	2 (1.5)

NSAID, non-steroidal anti-inflammatory drug.

children had confirmed iDHR among 10,059 subjects included in the study, a prevalence of 0.11%.

Discussion

Data in the literature on the frequency of confirmed drug allergy are limited. A diagnosis was confirmed by further testing in very few of these studies, all of which were conducted among subjects from a hospital setting. To our knowledge, this is the first study attempting to establish the frequency of drug allergies in general child population utilizing objective diagnostic methods. The rate of parent-reported immediate type drug allergy in our patient population was 7.87% comparable to the observed rates of self-reported drug allergies (3, 4, 6–11) while only 1.16% of participants were found to actually have a compatible clinical history, following a detailed phone survey. After further diagnostic work-up, the true frequency of immediate type drug hypersensitivity reaction was 0.11%.

Parents tend to over-report drug allergies in their children (5). Nevertheless, a suspicion of a drug allergy is enough to sway physicians to prescribe an alternative drug to avert the risk of a severe allergic reaction such as anaphylaxis (18), and in many instances the alternative drug is more expensive and less effective, with more potential adverse effects (4, 19). This is of greater importance when the high rate of infections in the childhood period is taken into consideration. In accordance with our results, it is reported in the literature that even with a careful and detailed clinical history, up to 90% of patients may be wrongly diagnosed with drug allergy (4, 20). Therefore, patients with suspicion of a drug allergy should always be subjected to further diagnostic evaluation for confirmation (3, 11–13).

Table 3 Results of the *in vitro* and *in vivo* diagnostic procedures

	Specific IgE positive /performed	Skin Test positive /performed	Drug provocation test positive/ performed
Beta-lactams	0/70	3/70	0/62
Non-beta-lactam antibiotics	–	0/5	0/5
NSAID	–	–	3/34
Other drugs	–	–	1/3

The discrepancy between the frequency of self/parental reported iDHR and the actual frequency may be due to several reasons. In our study, as with previous studies, the most commonly reported clinical manifestations related to drug reactions were dermatologic symptoms (3, 4, 6–8), and many childhood infections may present with urticarial skin lesions which may mimic those of a drug allergy. Such lesions are often misreported as a drug-related reaction by parents and physicians alike (21). Additionally, previous studies have reported a positive association with drug allergy and family history for allergic conditions (9, 10), and the presence of a family member with an allergic disorder may be a cause of bias toward over-reporting of allergic reactions. In our study, in parallel to previous studies, patients with a reported drug allergy had a personal or family history of physician-diagnosed allergic conditions more frequently than in patients without any reaction. But when we compared confirmed iDHR group with the rest of study population, there was no significant difference according to the presence personal or familial allergic diseases. Although the number of children with confirmed iDHR is very low, these findings suggest that presence of familial allergic disease or personal history of physician-diagnosed allergic diseases do not increase the rate of confirmed iDHR, but it may increase the awareness of allergic diseases and their clinical manifestations which may lead them to report more frequently a drug allergy.

In our study, the frequency of parental reported iDHR was %7.8 which was much higher than the previously reported result from our country (7). This may be related to several reasons. It has been reported that the frequency of drug allergy increases with age (22) and the ages of children was between 6–9 yrs old in Orhan et al. study which much younger than our age group. In our questionnaire, we asked the presence of drug reaction instead of presence of drug allergy whereas they firstly ask 'In your opinion, does your child have drug allergy' and if the answer was 'yes', parents were then asked to indicate which symptoms occurred following drug intake. So, in that study, some parents may not have considered the reactions to be allergic and that might cause a decrease in parental reported drug allergy.

In adherence with international guidelines for evaluation of immediate type hypersensitivity reactions, we included a detailed allergic history and then performed specific IgE levels (for beta-lactam antibiotics) and skin testing (15). Although skin testing is the basic diagnostic tool, in patients with a

Table 4 Patients with confirmed immediate drug hypersensitivity: details on reactions and drugs involved

Patient	Gender	Suspected drug/s	Previous reaction	Time Elapsed after reaction (months)	slgE	Skin test results	DPT results	Delay between DPT and reaction (min)
1	Female	Paracetamol FGS	Urticaria	24	ND	Negative	Paracetamol negative FGS positive (urticaria)	30
2	Female	Procaine penicillin	Urticaria	60	Neg	Positive Prick Test Major determinant		
3	Male	Amox/clav	Urticaria	72	Neg	Positive ID Test Major determinant		
4	Male	Aspirin	Cough, wheezing, dyspnea	60	ND	ND	Aspirin positive (wheezing, cough)	30
5	Male	Ibuprofen	Urticaria, angioedema	12	ND	ND	Ibuprofen positive (Angioedema)	35
6	Female	Amp/sulb	Urticaria, angioedema	7	Neg	Positive Prick Test Ampicillin		
7	Male	Ibuprofen	Urticaria, angioedema	12	ND	ND	Ibuprofen positive (Angioedema)	45

Amox/clav, amoxicillin klavunat; Amp/sulb, ampicillin sulbactam; DPT, drug provocation test; FGS, ferrous glycine sulfate; ND, not done; slgE, specific immunoglobulin E.

history of severe reactions, *in vitro* tests may be the recommended choice, and the main advantage of the specific IgE antibodies compared to skin testing is that the former pose no direct risk to the patient. However, the reported specificity of specific IgE measurement for a diagnosis of a penicillin allergy is 90%, with a corresponding sensitivity of 50% (23), whereas a skin prick test has been shown to have a sensitivity of 70% (24, 25). So, we decided to do *in vitro* tests in first step followed by skin testing and drug provocation tests. Accordingly, none of the 70 patients in our study with parent-reported allergy were positive for specific IgE. Only three patients had a positive skin prick test, while one patient with a negative result tested positive following drug provocation. Based on these results, it is recommended that patients with a negative skin prick test and undetectable titers of specific IgE should be subjected to a drug provocation test as a gold standard, barring any contraindication (17, 26, 27).

The most frequently implicated group of drugs in clinical practice is the beta-lactams. In this group, the period between testing and development of a reaction is of importance, and sensitization has been shown to decrease with time (28–30). However, some studies have shown this effect to be less prominent in children (5, 31). In our study, 75.8% of cases who had a history of beta-lactam allergy had had their reaction before more than 1 yr. In the penicillin group, 1 patient with a positive skin test had developed reactions in <1 yr following exposure, whereas in two cases with positive skin prick tests, reaction was reported to occur before more than 5 yrs. In this study, it is possible that we have missed some of the patients who had a real immediate type reaction once but have lost their sensitivity in time. Although this may be one of the limitations

of our study to give a lifetime prevalence of drug allergy, still we can give a prevalence of current hypersensitivity.

One of the main limitations of this study may be over- or under-reporting due to recollection bias or withholding of information by parents. Studies reporting both lower and higher rates of self-reported drug allergies may be encountered in the literature (7, 9, 10). It is common knowledge that the actual frequency of drug allergies is much lower than the frequency of self-reported drug allergy, a fact that has been reiterated by our study. Secondly, we asked the reactions that occurred within 2 h after intake of drugs in order not to miss any immediate type drug reactions during the school survey. Because we thought that some of the parents might not mark the signs that occurred around 1 h. This might have the possibility to increase the rate of parental reported iDHR. But during the phone survey, we only accepted the drug reactions that occurred within 1 h after taking the drug.

Our study is one of a handful of studies in which further diagnostic methods were used to confirm a diagnosis of drug allergies, and to our knowledge, the only one conducted among a group representative of children between 12 and 15 yrs old. The sample size in our study was determined assuming an immediate type drug reaction rate of 1%, and even more patients were sampled. Moreover, only reactions which occurred within the first 2 h were taken into consideration as possible immediate drug allergy to avoid a missed diagnosis. To distinguish false positivity following the questionnaire, the parents of 200 participants who were negative for parent-reported drug allergy were contacted by phone, and detailed questioning did not reveal the presence of symptoms consistent with a drug allergy.

In conclusion, a true drug hypersensitivity reaction was established in a very small number of participants with parent-reported immediate drug allergy with a prevalence of 0.11%. At the end, 9.4% of the investigated reactions were confirmed as being iDHR, and it is also in the normal range of % confirmation of drug hypersensitivity suspicions (3, 11, 12, 32). Our results suggest that a positive clinical history is not enough to make a diagnosis of drug allergy, and a complete and careful

diagnostic work-up is essential to make an accurate diagnosis in children with a suspicion of drug allergy.

Acknowledgements

The authors have nothing to declare regarding competing interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Primary school survey for drug allergy.

PRIMARY SCHOOL SURVEY FOR DRUG ALLERGY

Name-Surname:		Phone (home):
Sex:	☐ Female ☐ Male	Mobile phone (Mother):
Birthday (day/month/year):		Mobile phone (Father):
School name:		Classroom:

Example of how to mark questionnaire YES NO

☐ ☒

Question 1: Has your child (who brings you the questionnaire) ever had any of the complaints listed below within 2 hours after use of (by orally or by injection) any medications? If yes, please check/mark all the complaints that had occurred. If you answered NO please skip to question 3.

☐ YES ☐ NO

	YES	NO
a. Skin rash, itching, urticaria	☐	☐
b. Swelling at lips, eye or other parts of the body	☐	☐
c. Cough - shortness of breath - wheezing	☐	☐
d. Nausea-vomiting-diarrea – abdominal pain	☐	☐
e. Chest pain-palpitation - syncope-loss of consciousness	☐	☐
f. Sneezing, itching, blockage or watery discharge of the nose	☐	☐
g. Redness, itching or watery of eyes	☐	☐

Question 2: If yes, Please mark below the type of drug that caused the complaints.

☐ Antipyretic/analgesics	☐ Antibiotics	☐ Vitamins	☐ Other
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If you can remember, please write the name of drug/s:.....

Question 3: Has your child (who brings you the questionnaire) ever been diagnosed with asthma or allergic asthma or allergic bronchitis by a physician?

☐ YES

☐ NO

Question 4: Has your child (who brings you the questionnaire) ever been diagnosed with allergic rhinitis or hay fever by a physician?

☐ YES

☐ NO

Question 5: Has your child (who brings you the questionnaire) ever been diagnosed with food allergy by a physician?

☐ YES

☐ NO

Question 6: Has your child (who brings you the questionnaire) ever been diagnosed with drug allergy by a physician?

☐ YES

☐ NO

Question 7: Has your child (who brings you the questionnaire) ever been diagnosed with eczema or atopic dermatitis or atopic eczema by a physician?

☐ YES

☐ NO

Question 8: Has you or your partner/spouse ever been diagnosed with asthma or allergic asthma or allergic bronchitis by a physician?

☐ YES

☐ NO

Question 9: Has you or your partner/spouse ever been diagnosed with allergic rhinitis or hay fever by a physician?

☐ YES

☐ NO

Question 10: Has you or your partner/spouse ever been diagnosed with food allergy by a physician?

☐ YES

☐ NO

Question 11: Has you or your partner/spouse ever been diagnosed with drug allergy by a physician?

☐ YES

☐ NO

Question 12: Has you or your partner/spouse ever been diagnosed with eczema or atopic dermatitis or atopic eczema by a physician?

☐ YES

☐ NO

Question 13: Has your child's sibling/s ever been diagnosed with asthma or allergic asthma or allergic bronchitis by a physician?

☐ YES

☐ NO

☐ He/she has no sibling

Question 14: Has your child's sibling/s ever been diagnosed with allergic rhinitis or hay fever by a physician?

☐ YES

☐ NO

☐ He/she has no sibling

Question 15: Has your child's sibling/s ever been diagnosed with food allergy by a physician?

☐ YES

☐ NO

☐ He/she has no sibling

Question 16: Has your child's sibling/s ever been diagnosed with drug allergy by a physician?

☐ YES

☐ NO

☐ He/she has no sibling

Question 17: Has your child's sibling/s ever been diagnosed with eczema or atopic dermatitis or atopic eczema by a physician?

☐ YES

☐ NO

☐ He/she has no sibling