

## Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

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## ORIGINAL ARTICLE





# Immediate local anesthetic reactions and diagnostic test results in pediatric patients

Ahmet Selmanoglua, Hakan Güvenirb, Ilknur Kulhas Celika, Betul Karaatmacaa, Müge Toyran<sup>c</sup>, Ersoy Civelek<sup>c</sup>, Emine Dibek Misirlioglu<sup>c\*</sup>

<sup>a</sup>Ankara City Hospital, Division of Pediatric Allergy and Immunology, Ankara, Turkey

bHealth Sciences University, Kocaeli Derince Training and Research Hospital, Department of Pediatric Allergy and Immunology, Kocaeli, Turkev

<sup>c</sup>Health Sciences University, Ankara City Hospital, Department of Pediatric Allergy and Immunology, Ankara, Turkey

Received 22 October 2020; Accepted 23 November 2020 Available online 1 May 2021

## **KEYWORDS**

local anesthetics; hypersensitivity; children; immediate reaction; skin test; subcutaneous challenge

#### Abstract

Background/objectives: Adverse reactions to local anesthetics are relatively common, but proven IgE-mediated allergy is extremely rare. We aimed to determine the frequency of local anesthetic allergy in pediatric patients.

Patients and methods: The medical records of 73 patients who presented to our clinic with a history of suspected allergic reaction to local anesthetics and underwent diagnostic testing between 2012 and 2020 were retrospectively analyzed. Diagnoses were based on case histories, skin tests, and subcutaneous challenge tests.

Results: A total of 75 test series were carried out on the 73 patients (43 boys; median [IQR] age 9.25 [7.26-14.25] years, range 3-17.8 years). The most commonly tested drugs were lidocaine (n = 38; 50.6%) and prilocaine (n = 15; 20%). Local anesthetic allergy was confirmed in one (1.3%) of the 73 patients by positive subcutaneous challenge test with mepivacaine.

Conclusion: There are limited data in the current literature regarding local anesthetic allergies and diagnosis test results in pediatric patients. Proven local anesthetic allergy is less common than expected by society and physicians, and therefore diagnostic tests are needed for patients with no contra-indications such as severe or life-threatening reactions.

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\*Corresponding author: Emine Dibek Misirlioglu, Health Sciences University, Ankara City Hospital, Department of Pediatric Allergy and Immunology, Ankara, Turkey. Email address: edibekm@yahoo.com

## Introduction

Hypersensitivity reactions may develop in local anesthesia procedures. Local anesthetics (LAs) are commonly used for various medical procedures. Adverse reactions including hypersensitivity increased with widespread LA use. However, LA allergy is extremely rare, and less than 1% of reactions to LA occur by an allergic mechanism. LAs generally contain additional drugs and substances such as epinephrine and methyl parabens. Epinephrine can lead to systemic symptoms such as palpitations, tachycardia, tremulousness, headaches, and other symptoms that can be confused with a hypersensitivity reaction. Some allergic skin symptoms may occur due to additives and preservatives such as methyl parabens and sulfites. This spectrum of non-IgE mediated reactions to LAs can cause confusion and suspicion of an IgE-mediated reaction. Therefore, allergic reactions to LAs are overestimated.

LAs are classified in to two groups: benzoic acid esters (e.g., benzocaine, procaine, and butacaine), which cross-react with each other, and amides (e.g., lidocaine, bupivacaine, and prilocaine), which do not cross-react with each other or agents from the benzoic acid esters group. The ester group may cause a higher rate of allergic reactions than the amide group.<sup>2</sup>

Studies evaluating LA allergies and diagnostic test results in children are limited in the literature. The present study aimed to determine the prevalence of proven LA allergy among children referred for suspected hypersensitivity and to describe the main characteristics of reactions and to evaluate patients' test results of hypersensitivity reactions to LA.

## Materials and methods

This retrospective chart review included patients who presented to the allergy department with a history of symptoms associated with LA use and were referred to our clinic for suspected LA hypersensitivity between January 2012 and March 2020. The study was approved by the Ankara City Hospital Ethics Committee.

When patients are referred to our clinic for drug allergy, a detailed history, physical examination findings, and diagnostic test results are recorded in a standardized form that is included in their file. These records were reviewed and the patients' demographic characteristics, any history of LA allergy and hypersensitivity reactions to drugs other than LAs, medical procedure(s) requiring anesthesia, name of suspect drug, reaction type, time from LA reaction to allergy work-up, and any concomitant allergic diseases.

## Allergy work-up

Diagnostic tests with LA were performed at least 4 weeks after the hypersensitivity reaction. Antihistamines and antihistamine-containing medicines were stopped at least 1 week prior to skin tests. Testing was not performed if the patient had an acute infectious disease, fever, or inflammatory reaction unless the skin test was urgently needed.

Preparations that did not contain vasoconstrictors were used for diagnostic testing because these components can mask a local wheal and flare reaction.<sup>3</sup>

As a rule, the suspect drug was tested when known; for cases in which the culprit drug was unknown, patients were tested with either lidocaine or an LA that the physician requested for an upcoming procedure. If there was not available lidocain preparate without vasoconstrictor, we performed the test with the LA without including vasoconstricor, that planned to be used. All patients underwent skin prick test (SPT) and intradermal test (IDT), followed by a subcutaneous provocation test (SCT) with the tested LA agents. 5.6

For the SPT, all LAs were initially tested on the volar forearm skin using the prick method with undiluted, LA solution without epinephrine, with 10 mg/mL histamine as the positive control and 0.9% NaCl as the negative control. The skin test sites were examined after 15 min. A wheal  $\geq$  3 mm is considered positive. When a skin test yielded a positive result, the patient was considered to be hypersensitive to the tested drug, and the procedure was interrupted. Patients with a negative SPT underwent IDT.

The IDT was performed by injecting 0.02-0.05 mL of LA solution intradermally to raise a small bleb. The LAs were tested at gradually increasing concentrations (1/100, 1/10) with 0.9% NaCl as a negative control. If a more diluted concentration caused a wheal become 3 mm or greater in diameter accompanied by erythema at 20 min, the test was considered positive and more concentrated dilutions were not tested.<sup>7</sup>

Subcutaneous challenges are considered the gold standard for confirming of true IgE-mediated LA allergy. 8,9 Patients with negative results in both SPT and IDT underwent SCT with increasing doses of LA (0.1 mL and 1 mL) administered subcutaneously to the lateral surface of the patients' arms. Local findings around the injection site, general symptoms, and vital signs were observed for up to 1 h. SCT was considered positive on the development of objective allergy symptoms (skin symptoms and/or respiratory, circulatory symptoms) within 2 h of provocation. 5

#### **Statistics**

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc. Chicago, IL, USA). Numbers and percentages were reported for discrete variables. Continuous variables were expressed as mean and standard deviation for data with a normal distribution and as median and interquartile range (IQR, 25th-75th percentile values) for non-normally distributed data. Chi-square (x²) test was used to compare nonparametric data; Mann-Whitney U test was used for comparisons among non-normally distributed continuous variables and independent samples t-test for normally distributed continuous variables. A P value of less than 0.05 was considered statistically significant.

## Results

The records of 73 patients with a history of LA reaction were evaluated in this study. Of these, 43 patients (58.9%)

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were male and 30 (41.1%) were female. Two patients were tested with two different LAs. Additional allergic diseases were present in 29 (39.7%) of the patients. Asthma was the most common concomitant allergic disease (n = 15, 20.6%). One patient had known food allergy and one patient had nonsteroidal anti-inflammatory drug (NSAID) allergy. In all cases, only LA was used at the time of the reaction and we included patients who only had a reaction history with LA. In addition, only one LA drug was administered to the patients during testing. There were no patients who reported the use of any co-administered drug such as NSAIDs or antibiotics at the time of the reaction, and other anesthetics such as drugs used for induction were not related because patients had only local anesthesia.

The most common medical procedures requiring LA were dental interventions (72.6%) and circumcision (16.4%; Table 1). The median (IQR) age at reaction was 9.25 (7.26-14.25) years (min-max: 3-17.8 years). Median (IQR) time to reaction was 30 (15-45) min (min-max: 2-180 min). Median (IQR) time from LA reaction to allergy work-up was 6 (2.5-14) months (min-max: 1.5-46 months).

Tests were performed with the suspect drug in 65 of the patients and alternative drugs in eight patients. We prefer using the suspect drug if it is available in a formulation that does not contain adrenaline. However, an adrenaline-free formulation of the suspect drug was not available for five patients and another three patients did not know the name of the LA used. Therefore, an alternative drug that could be used for the following operations was used for diagnostic tests. Five of the LAs were in the ester group and 70 were in the amide group. Lidocaine was the most commonly tested drug (n = 38; 50.6%), followed by prilocaine (n = 15; 20%). The most common manifestation was urticaria (n = 31; 36.8%), followed by erythema (n = 22; 26.1%) and angioedema (n = 16; 19%; Table 1).

Of the eight patients tested with an alternative LA, five (62.5%) were boys. The alternative LA used for testing was mepivacaine in five patients, lidocaine in two patients, and prilocaine in one patient. The suspect drug was articaine in three patients, lidocaine in two patients, and the name of the drug could not be determined from the medical records of three patients. The median (IQR) age at reaction was 9.46 (7.6-14.2) years (min-max: 3-15 years). The most common manifestation was urticaria, and the median (IQR) reaction time was 27.5 (6.25-60) min (min-max: 5-180 min). Median (IQR) time from LA reaction to allergy work-up was 9 (7.6-14.2) months (min-max = 1-132 months; Table 2).

None of the patients in our study had positive SPT or IDT results, and just one of our patients had a positive SCT with mepivacaine. Because the LA to which this patient had a reaction could not be determined with their file, the patient's drug testing was performed with mepivacaine. SPT and IDT results were negative, and SCT with 0.1 mL mepivacaine elicited no reaction. However, 15 min after administration of 1 mL mepivacaine, the patient developed symptoms such as numbness in his right leg, tremor in the mouth and body, weakness, tachycardia, hyperemia in the neck, and hives on his chest. His blood pressure was measured as 120/80 mmHg. Adrenaline (0.3 mg/dose intramuscular) was administered, followed by methylprednisolone (1 mg/kg/dose) and antihistaminic (1 mg/kg/dose). The patient's symptoms regressed and he was observed

**Table 1** Clinical characteristics of pediatric patients who underwent testing for suspected local anesthetic allergy.

Study population, n Female/Male, n (%) Reason for local anesthetic use  Circumcision 12 (16.4%) Suture 5 (6.8%) Tooth filling 1 (1.4%) Hypospadias 1 (1.4%) Hypospadias 1 (1.4%) Asthma 15 (20.6%) Food allergy 1 (1.4%) NSAID allergy 1 (1.4%) Mastocytosis 1 (1.4%) Age at reaction (years) Median (IQR) 9.25 (7.26-14.25) Min-max (3-17.8) Reaction time (minutes) Median (IQR) 30 (15-45) Min-max (2-180)  Time from reaction to testing (months) Local anesthetic test performed  Median (IQR) 6 (2.5-14) Min-max (1-132) Local anesthetic test performed  Reaction type  Urticaria 31 (36.8%) Erythema 22 (26.1%) Angioedema 16 (19%) Itching 9 (10.7%) Shortness of breath 2 (2.38%) Vomit 1 (1.19%) Unconsciousness 1 (1.19%) Eye flushing 1 (1.19%) Eye flushing 1 (1.19%)		<u> </u>
Reason for local anesthetic use  Circumcision 12 (16.4%) Suture 5 (6.8%) Tooth filling 1 (1.4%) Hypospadias 1 (1.4%) Asthma 15 (20.6%) Hay fever 12 (16.5%) Food allergy 1 (1.4%) NSAID allergy 1 (1.4%) Mastocytosis 1 (1.4%) Age at reaction (years)  Reaction time (minutes) Median (IQR) 9.25 (7.26-14.25) Min-max (3-17.8)  Reaction time (minutes) Median (IQR) 30 (15-45) Min-max (2-180)  Time from reaction to testing (months) Local anesthetic test performed  Median (IQR) 6 (2.5-14) Min-max (1-132) Lidocaine 38 (50.6%) Prilocaine 15 (20%) Articaine 8 (10.6%) Mepivacaine 9 (11.9%) Procaine 5 (6.6%)  Reaction type  Urticaria 31 (36.8%) Erythema 22 (26.1%) Angioedema 16 (19%) Itching 9 (10.7%) Shortness of breath 2 (2.38%) Vomit 1 (1.19%) Unconsciousness 1 (1.19%) Maculopapular rash 1 (1.19%)	Study population, n	73
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Vomit 1 (1.19%) Unconsciousness 1 (1.19%) Maculopapular rash 1 (1.19%)		Itching 9 (10.7%)
Unconsciousness 1 (1.19%) Maculopapular rash 1 (1.19%)		Shortness of breath 2 (2.38%)
Maculopapular rash 1 (1.19%)		Vomit 1 (1.19%)
		Unconsciousness 1 (1.19%)
Eye flushing 1 (1.19%)		Maculopapular rash 1 (1.19%)
		Eye flushing 1 (1.19%)

in the emergency department. No additional symptoms occurred and the patient was discharged. After 3 months, he was tested with lidocaine and all results were negative. Therefore, the use of lidocaine was recommended for this patient in the future.

For all of the other patients who exhibited no reaction to the suspect drug, we advised the use of the tested drug in the future.

#### Discussion

Although adverse reactions to LA are frequently reported by patients, most of these reactions are not proven LA allergy. We evaluated the test results of 73 patients who had a history of reaction to LA. The suspect drug was tested in 65 of the patients and alternative drugs were tested in eight patients; LA allergy was confirmed in only one (1.36%) of the 73 patients.

LA allergy is extremely rare, accounting for reactions less than 1% of.¹ Nonallergic reactions to LAs are far more common than proven allergic reactions. Nonallergic symptoms can be caused by vasovagal reactions or anxiety-related symptoms. The clinical manifestations of

1.5

1.5

46

2

1.5

14

3

4

5

6

7

8

9

7

8

3

15

14

F

M

F

Articaine

Unknown

Unknown

Articaine

Prilocaine

Mepivacaine

Mepivacaine

Lidocaine

Mepivacaine

Mepivacaine

		•	ients who und ients' test resi		ing with an alterna egative.	tive drug due	e to suspected	allergic reactio	n to local
Patient number	Age at reaction (years)	Sex	Test drug	Suspect drug	Reason for using alternative drug	Reaction time (min)	Clinical manifestation	Concomitant allergic diseases	Time from reaction to testing (months)
1	14	F	Lidocaine	Unknown	Unknown drug name	45	Urticaria	none	1.5
2	9	M	Mepivacaine	Articaine	Vasoconstrictor	5	Shortness of	asthma	1.5

free agent

Unknown drug

free agent

Unknown drug

Vasoconstrictor

name

agent

agent

agent

name

Lidocaine Vasoconstrictor

Lidocaine Vasoconstrictor

Vasoconstrictor free

nonallergic reactions may mimic allergic reactions, and symptoms such as dyspnea, hypotension, and syncope can be seen in both allergic and nonallergic reactions. All of the patients in our study experienced the suspicious reactions before presenting to our clinic for allergy evaluation. For this reason, we do not have objective data about the initial reaction. Some of the patients may have had vasovagal reactions, but we do not have enough data to confirm this. However, we did not detect any vasovagal symptoms during the diagnostic tests we performed.

In our study, all patients' presenting symptoms were compatible with immediate hypersensitivity reactions, including urticaria, angioedema, erythema, itching, shortness of breath, vomiting, unconsciousness, and eye redness. Symptoms generally occurred within 1 h, but one patient had a reaction time of 180 min and the manifesting symptom was urticaria. The ENDA/EAACI Drug Allergy Interest Group recommends diagnostic skin tests if IgErelated symptoms develop within 1 to 6 h.7

There are several other studies in the literature on this topic, though none have included exclusively pediatric patients (Table 3). Berkun et al. evaluated adverse reactions to LA experienced by 236 both pediatric and adult patients were divided into five groups according to presenting symptoms. In the immediate hypersensitivity group, 51 patients (21.6%) reported symptoms of urticaria, angioedema, dyspnea, wheezing, loss of consciousness, or hypotension shortly after LA injection. In their cohort, 188 (79.7%) of the 236 patients were female and the mean age at evaluation was  $40.6 \pm 19.8$  years (min-max: 4-83 years), but there is no extra information about the pediatric patients.10

A study by Harboe et al. included 135 patients with a mean age of 36 years (min-max: 2-76 years) at the time of reaction and a female:male ratio of 4:1. They also did not provide detailed information about the pediatric patients in their study. They reported that the most common presenting symptoms were loss of consciousness (31%), feeling ill (23%), feeling faint (20%), and generalized unspecified rash (15%), while other manifestations commonly associated with IgE-mediated allergy were less frequently reported, such as documented hypotension (13%), itching (11%), generalized urticaria (10%), tachycardia (7%), and bronchospasm (1.5%). There were two adult cases of proven LA allergy in their series.11

none

none

none

none

hay fever

food allergy

breath

breath

Vomiting

Eye redness,

Shortness of

Angioedema

Angioedema

Urticaria

Urticaria

60

10

10

60

5

180

Batinac et al. evaluated a total of 311 patients suspected of having LA allergy (age range 8-88 years, median age 50 years) but provided no information on the number of pediatric cases. As in the study by Harboe et al., their series showed a strong female predominance (78% females, 22% males). They classified symptoms as general and local, with the most common generalized symptoms being weakness (17.3%), hypertension/hypotension (10.4%), itching (10.2%), dyspnea/bronchospasm (10.2%), and rash (9.2%). Local symptoms included erythema of the face and neck 17 (38.6%) and edema of the face and cheeks (36.4%).<sup>12</sup>

Kvisselgaard et al. evaluated 162 patients (89 females, 73 males; mean age 49 years, min-max: 2-85 years, nine pediatric and 153 adult patients) according to LA diagnostic test results and reported that all patients had negative SCT results to the suspect LA. The patient's reactions most commonly involved the skin (85%), followed by the circulation (62%), airway (37%), and breathing (18%).13

Trautmann et al. evaluated adverse reactions to LA in 402 patients (316 females, 86 male) with a median age of 50 years (max-min: 3-86 years) in an allergy clinic over a period of 20 years. They reported that the most frequent manifestations were palpitations/tachycardia (44.0%), chest tightness/dyspnea (40.5%), and central nervous

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Table 3 Sur	Summary of previous studies of local anesthetic	ocal anesthetic allergy.				
Authors	Patient number, Sex, Mean age, Pediatric cases	Presenting symptoms	Proven LA allergy	LA tested, alternative or suspect	Time from LA reaction to allergy work-up	Time from LA exposure to reaction
Berkun et al. <sup>11</sup>	n = 236, F/M: 188/48, 40.6 ± 19.8 years (range, 4-83 years)	<ol> <li>Immediate hypersensitivity group (n = 51, 21.6%) with urticaria, angioedema, dyspnea, wheezing, loss of consciousness, or hypotension shortly after LA injection</li> <li>Local swelling at the injection site (n = 27, 11.4%)</li> <li>Nonspecific symptoms such as weakness, dizziness, and nausea (n = 64, 27.1%)</li> <li>Delayed reactions such as rash, cough, or dyspnea that appeared hours after injection (n = 36, 15.3%)</li> </ol>	0 patients	All with alternative	No information	No information
Harboe et al. <sup>10</sup>	n = 135, F/M ratio 4:1, 36 years (range, 2-76 years)	J. Fatterits with instory of atopy (if = 30, 24.0%)  Loss of consciousness (31%), feeling ill (23%), feeling faint (20%), and generalized unspecified rash (15%)  Other manifestations of IgE-mediated allergy: documented hypotension (13%), itching (11%), generalized urticaria (10%), tachycardia (7%), and hypothesisem (15%)	2 adult patients (1.5%)	Alternative (n = 9), Suspect (n = 109)	Median 21 months, (range, 1 month-44 years)	<30 min in 69%, 30 min-48 h in 20%, not recorded in 11% of cases
Batınac et al.¹²	n = 331, F/M: 258/73, 50 years (range, 8-88 years )	Generalized symptoms: Weakness (n = 85, 17.3%), hypertension/hypotension (n = 51, 10.4%), itching (n = 50, 10.2%), dyspnea/bronchospasm (n = 50, 10.2%), rash (n = 45, 9.2%)  Local symptoms: Erythema of face and neck (n = 17, 38.6%), edema of face and cheeks (n = 16, 36.4%)	3 adult patients (0.91%)	110 patients' drug name was unknown	<ul><li>6 months in</li><li>134 patients</li><li>(40.5%),</li><li>1 year in 202</li><li>patients (61%)</li></ul>	<30 min (n = 156, 47%) 30-60 min (n = 76, 23%)
Kvisselgaard et al. <sup>5</sup>	n = 162, F/M. 89/73, 49 years (range, 2-85 years)	Symptoms involving the skin (n = 137, 85%), circulation (n = 100, 62%), breathing (n = 29, 18%), and airway (n = 60, 37%).	0 patients	Bupivacaine (n = 82, 51%), Lidocaine (n = 80, 49%)	No information	<30 min in all patients
Trautmann et al.¹	n = 402, F/M: 316/86 50 years (range, 3-86 years)	Cardiovascular symptoms (palpitations, tachycardia) (n = 177),  Lower respiratory symptoms (chest tightness, dyspnea) (n = 163),  Neurologic symptoms (dizziness, visual disturbance, hearing impairment) (n = 158)	2 patients (0.5%)	Articaine (n = 314), Mepivacaine (n = 251)	Less than 1 year (49.8%) to more than 10 years (13.7%)	<1 min (n = 54) 1-5 min (n = 213) 6-15 min (n = 64) 16-30 min (n = 71)
Yılmaz et al.¹5	n = 228, F/M: 187/41 44.22 ± 1.28 years (range, 16-74 years)	Most common reason for referral for testing with LA was a history of DHR to drugs other than LAs (n = 128, 56.1%), history of LA allergy (n = 64, 28.1%), asthma (n = 49, 21.5%)	10 patients (4%) No positive pediatric patients	Alternative (n = 39, 60.9%), Suspect (n = 25)	No information	No information
Cetinkaya et al.¹6	157 atopic asthmatic children, 11.2 years (range, 8-15 years)	All patients had bronchial asthma alone and/or asthma with allergic rhinitis	0 patients	No history with LA		

system symptoms of dizziness, visual disturbance, and hearing impairment (39.3%).

The differences in symptoms observed in these studies are likely attributable to the fact that most were not true drug allergy reactions. We observed that presenting symptoms in children were often objective findings (urticaria, rash, angioedema, and vomiting), while in adults they were subjective findings (weakness, feeling faint, and feeling sick). One patient in our study had a history of symptoms consistent with anaphylaxis, including shortness of breath and eye redness. Information about the suspect drug was not available in the patient's records, so diagnostic tests were performed with mepivacaine and yielded negative results. Harboe et al. also performed diagnostic tests in seven patients with presenting symptoms compatible with anaphylaxis, three of whom were administered an alternative LA, and all of the patients had negative SCT results.<sup>11</sup>

Skin tests with LA are used as a primary diagnostic test for evaluating local anesthetic allergy. In their review of 178 patients who underwent 227 skin tests, McClimon et al. reported the negative predictive value of skin tests for LA allergy to be 97%. In our study, we evaluated the test results of 73 patients. There were no positive skin test results, but one patient had positive SCT (1.36%).

Yılmaz et al. reported that 39 (60.9%) of the 64 patients in their study did not know the name of the suspect LA, and their tests were performed with an alternative LA (usually lidocaine).<sup>15</sup> Of the 118 patients who underwent SCT in the study by Harboe et al., the culprit LA was unknown in 19 patients (16%) and SCT was performed with an alternative LA in nine patients (8%).<sup>11</sup> We tested alternative agents in eight patients, none of whom displayed positive results.

LA allergy is rare in the literature and our findings also reflect this view. Bhole et al. investigated suspected cases of LA allergy in the English literature between 1952 and 2011 and reported the prevalence of proven IgE-mediated allergy as 0.97%.8 This is similar to the rates of proven LA allergy reported by Harboe et al. (1.5%, 2/135, both adults)11 and Batinac et al. (0.91%, 3/331 patients, all adults).<sup>12</sup> Trautman et al. determined that two patients (0.5%) had proven allergy and positive intradermal skin tests to LAs, but age information was not provided for positive cases.1 Kvisselgaard et al. reported no positive skin or challenge tests results in their 162-patient series including nine pediatric patients (median age 15, max-min: 2-17 years).<sup>13</sup> Yilmaz et al. reported positive test results in 4.4% (10/228) patients aged 16 to 74 years. They performed diagnostic tests on three groups of patients, drug allergy, suspected LA allergy, and asthma, referred to the allergy clinic. In their study series, seven patients who had negative results in skin tests demonstrated positive SCT, but there were no positive pediatric cases.15 Although data on the number of children are limited in many of these studies, those that provide details of the positive cases indicate no confirmed LA allergy among the pediatric patients.

All of these studies included both child and adult patients. In our study focusing on pediatric patients, the prevalence of LA allergy was similar to that reported in the adult studies at 1.36% (1/73) and the median (IQR) age at time of reaction was 9.25 (7.26-14.25) years.

Cetinkaya investigated 157 atopic asthmatic children aged 8-15 years (mean 11.2 years). They performed tests

with lidocaine in all patients and found no positive results. <sup>16</sup> That study was the first in the literature that included only children, but the sample consisted of patients with asthma and atopy, not those with a history of reactions to LA. Cetinkaya aimed to investigate the relationship between asthma and LA allergy, but did not detect one. In our study, we determined that the most common concomitant allergic disease was asthma (20.6%), followed by allergic rhinitis (16.5%). The only patient with proven LA allergy in our study had no comorbid allergic diseases, so we also did not observe a relationship between LA allergy and allergic diseases.

In the study by Yılmaz et al., multiple drug allergy was present in 77 patients overall (35.3%) and six of the 10 positive patients (60%).<sup>15</sup> In our study, only one patient had a history of NSAID drug allergy and the patients' LA allergy test results were negative. However, NSAID hypersensitivity reactions and multiple drug allergies are less common in children than in adults.<sup>17</sup>

LAs are used to provide patient comfort in many medical interventions. We investigated which medical procedures are most frequently associated with suspected LA allergies. In predominantly adult samples, anesthesia was most often required in dental interventions, followed by minor surgical or orthopedic interventions. <sup>1,10,12</sup> Likewise, in our study, we found that most common indications for LA were dental procedures (72.6%) and circumcision (16.4%). <sup>1</sup> We believe that the differences in LA indications are due to the difference in average patient age between studies, because orthopedic and minor surgical interventions are carried out less frequently in children than in adults. Additionally, circumcision is a frequent medical procedure in some religions.

Generally, the time to allergy clinic referral after the initial reaction is prolonged, resulting in a delay in diagnostic testing. In our study, the median (IQR) interval between LA reaction and allergy work-up was 6 (2.5-14) months. Harboe et al. reported a median interval of 21 months (min-max: 1 month-44 years), while Trautmann et al. found the time ranged from less than 1 year (49.8%) to more than 10 years (13.7%).<sup>1,11</sup> Batinac et al. found median time was 6 months in 134 patients (40.5%), while it was within a year in 202 patients (61%).<sup>12</sup>

We also investigated the interval between LA exposure and the emergence of the associated clinical reaction and determined a median (IQR) interval of 30 (15-45) min. Harboe et al. reported that this interval was 30 min in 69% of patients, between 30 min and 48 h in 20% of the patients, and was not recorded in 11% of the cases, 11 while Batinac et al. found that the time interval was 30 min in 156 patients (47%). 12 Trautmann et al. reported that all of the patients in their study developed reactions within 30 min of LA administration and that more than half of the patients presented symptoms in the first 5 min. 1

Patients with suspected LA allergy should be referred to allergy clinics to determine whether these reactions are true LA allergy or not and to identify a safe LA for future procedures. However diagnostic procedures should be performed carefully especially for patients who had life-threatening reactions including anaphylaxis. The risk-benefit ratio of procedures should be discussed in detail with the patient and/or care givers of children 5.5

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## Conclusion

The current literature data provide limited information regarding local anesthetic allergies and diagnosis test results in pediatric patients. Proven LA allergy is less common than expected by society and physicians, and therefore diagnostic tests are required if not contra-indicated. LA is required for children undergoing dental interventions, circumcision procedures, and painful procedures such as suturing, so our goal is to identify a safe LA for our patients. Our findings demonstrate that true LA allergies are rare, as stated in the literature. Diagnostic tests with challenge have a high negative predictive value, and are highly reliable for determining safe drugs. Most previous studies with LAs included mixed samples of adults and children, but the proportion of children is small and the data are limited. To our knowledge, our study is the first in the literature to report the results of diagnostic tests performed in children with a history of reaction to LAs.

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