

ORIGINAL ARTICLE

Differential diagnosis of late-type reactions to injected local anaesthetics: Inflammation at the injection site is the only indicator of allergic hypersensitivity

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Background: Anaphylaxis-like reactions developing within a few minutes are the most frequent complications of subcutaneous or submucosal injections of local anaesthetics (LAs), and topically applied LAs are potential contact allergens. In addition, injected LAs have been reported to induce delayed reactions, including local inflammation at the injection site, and various general symptoms.

Objectives: To assess the frequency and symptoms of late-type hypersensitivity occurring several hours after LA injections.

Methods: We retrospectively evaluated clinical data and test results from all patients referred to our allergy clinic in a period of 20 years for diagnostic work-up of LA-associated late-type reactions.

Results: Of 202 patients reporting symptoms with onset at least 1 hour after LA injection, 40 had cutaneous inflammation confined to the injection site, and 162 reported various systemic symptoms. LA hypersensitivity could be excluded in all patients with systemic complaints by means of skin testing and subsequent subcutaneous provocation. In 8 of the 40 patients (20%) with local inflammatory reactions, late-type allergic LA hypersensitivity was confirmed.

Conclusions: Late-type LA allergy commonly causes inflammatory skin reactions confined to the injection site. Conversely, LAs are highly unlikely to trigger delayed systemic symptoms such as urticarial or exanthematous skin eruptions.

KEYWORDS

challenge testing, drug adverse reaction, drug allergy, drug hypersensitivity, exanthem, local reaction, provocation testing, urticaria

1 | INTRODUCTION

Local anaesthetics (LAs) are among the most commonly administered drugs worldwide. Immediate-type, presumably IgE-mediated LA allergy is an exceedingly rare cause of anaphylaxis-like incidents during or after LA injections.^{1–4} In contrast, allergic contact dermatitis caused by topical LA application is relatively common. Besides the ester-LA benzocaine, cinchocaine is frequently identified as a contact allergen.^{5,6} In addition to these well-defined LA-associated clinical

reactions, injected LAs have been reported to cause different late-type reactions within hours or even days after LA injection.

Cellulitis-like erythema and swelling or eczematous dermatitis confined to the injection site have been reported to develop within hours after subcutaneous/submucosal LA injections and to persist for several days.^{2,7–9} These types of local tissue inflammation are presumably caused by T cell-mediated allergic LA hypersensitivity.^{1,10,11} Reliable experimental data on antigenic LA determinants are lacking, and hypotheses regarding cross-reactivity patterns are based on clinical observations in patients with allergic contact dermatitis induced by topically applied LAs. Cross-reactivity between the ester-LAs

Abbreviations: α -Gal, galactose- α -1,3-galactose; ACE, angiotensin-converting enzyme; LA, local anaesthetic; NSAID, non-steroidal anti-inflammatory drug.

benzocaine, procaine, and tetracaine, for example, has been attributed to *p*-aminobenzoic acid being their common metabolite.^{1,5,6} Cinchocaine, which is a quinoline derivative, does not seem to cross-react with the other, above-mentioned ester-LAs.¹² Allergic contact hypersensitivity to amide-LAs is apparently less frequent.^{5,12,13} No antigenic components of amide-LAs have been identified to date, and cross-reactions do not seem to follow a consistent pattern.¹² In addition to injection-associated local side-effects and contact dermatitis, LA injections have been reported to cause a variety of delayed systemic reactions, ranging from generalized skin eruptions to a broad spectrum of subjective complaints.^{14,15}

We retrospectively evaluated data from a large and homogeneous group of consecutive patients who presented for allergy work-up of LA-associated late-type reactions over a period of 20 years. Our aim was to determine the prevalence of true late-type LA allergy within the broad spectrum of local and systemic reactions.

2 | METHODS

We retrospectively evaluated 202 cases referred to our allergy clinic from January 1997 until December 2017 for diagnostic work-up of local and systemic late-type reactions attributed to LA injections by patients and/or treating physicians. Only patients who reported reactions to injected LAs were evaluated; patients in whom LAs were applied topically were excluded. A late-type reaction was defined as a reaction occurring >1 hour after LA injection, either as local inflammation at the injection site or as a systemic reaction. The institutional review board of the University Hospital Würzburg consented to the retrospective review and publication of anonymized clinical data.

The data considered included age and sex, treating physician, indication for LA application, and the time between LA injection and the onset of symptoms. In patients with a history of >1 LA-associated reaction, the most recent episode was included. Clinical complaints were assigned to 2 main patterns: (a) local effects confined to the site of LA injection, that is, erythema, swelling, and eczematous dermatitis; and (b) systemic symptoms (eg, generalized cutaneous eruptions, exacerbation of asthma, loss of consciousness, and subjective complaints). Additional information was retrieved from treating physicians, caregivers or medical records when necessary. We additionally recorded whether the clinical reaction had prompted an emergency call, and the time interval between the clinical reaction and presentation for allergy work-up.

Preservative-free, single-dose vials were used for intradermal skin testing and provocation; in selected cases, we additionally tested preservative-containing multidose preparations. A standard panel of 3 LAs consisting of 2 amides (articaine and mepivacaine) and the ester procaine was tested in most patients. Additional LAs were included according to the patient's history. Intradermal LA skin testing was performed according to international guidelines, and invariably included readings at 15 minutes, 24 hours, and 48 hours; additional late readings at 72 and 96 hours were performed in selected cases.¹⁶ Dilutions of 1:10 of the original LA preparations in physiological saline solution were used for intradermal testing, yielding, for example, 1 mg/mL articaine, 1 mg/mL mepivacaine, and 1 mg/mL procaine. Immediate

wheel-and-flare reactions at the 15-min reading were considered to be irritant if they subsided on further dilution to 1:100, as described previously.⁴ Clearly defined erythematous and infiltrated plaques at 24 and 48 hours were assessed as positive late-type skin test reactions.

Provocation testing was performed in all patients to definitely exclude LA allergy. Subcutaneous injections of undiluted LA (eg, 10 mg/mL articaine or 10 mg/mL mepivacaine) were administered every 30 min at incremental volumes of 0.1, 0.2, 0.5, 1.0 and 2.0 mL into the outside of the upper arm, yielding a cumulative dose of 3.8 mL (eg, 38 mg of articaine or 38 mg of mepivacaine). This step-wise increase in doses may be considered unnecessary for the assessment of late-type reactions. The use of multistep protocols including several injections, however, allows for prolonged monitoring and/or intermittent placebo injections in patients with a high likelihood of having anxiety-related subjective symptoms.⁴ Only 1 LA was given per day. Outpatients were observed for at least 1 hour after the last injection, and were advised to present for objective examination if any symptoms developed subsequently.

The final diagnosis was based on an overall assessment including history, clinical complaints and symptoms, and the results of intradermal testing and subcutaneous provocation. Differential diagnoses, including spontaneous urticaria, psychosomatic reactions, non-allergic or allergic drug hypersensitivity, allergic contact dermatitis, latex allergy, food allergy, neurocardiogenic syncope, viral exanthem, and atopic dermatitis, were based on published consensus criteria.^{17–27}

3 | RESULTS

The medical records of 202 patients with a history of local or systemic late-type reactions occurring at least 1 hour after LA injections were evaluated. LAs were most commonly injected by dentists (106), orthopaedists (54), general practitioners (17), surgeons (11), and dermatologists (8). Accordingly, the main indications for LA injection were dental interventions (106), back pain (46), skin surgery (19), joint pain (18), and peripheral nerve blockade (13). Table 1 shows baseline clinical data including the patients' age and sex, incriminated LA, time interval to onset of symptoms, and clinical signs. One hundred and seventy-eight patients (88.1%) underwent medical treatment of the LA-associated reaction, which was most commonly provided by general practitioners (58 cases), dermatologists (53 cases), or the physicians who injected the LA (36 cases); emergency medical services were called in 31 cases (15.3%). The time intervals between the LA-associated reaction and presentation for allergy-work up are shown in Table 2; it was <1 year in most patients (66.8%).

3.1 | Test results

An overview of the results of intradermal testing is shown in Table 2. No cases of immediate-type sensitization were identified at the 15-minute reading. Of the 8 patients with late-type LA allergy, 6 showed clearly positive skin test results at the late readings at 24 and 48 hours (Table 3). Skin testing showed either isolated sensitization to procaine or prilocaine, or different patterns of cross-reactivity between amide-LAs (Table 3).

TABLE 1 Patient characteristics

Number of patients	202
Males/females (n)	51/151
Age (years), median (range)	52 (5-89)
Incriminated LA (n)	
Articaine	97
Mepivacaine	28
Lidocaine	25
Prilocaine	19
Bupivacaine	12
Procaine	11
Not specified	10
Hours from LA administration to first symptoms (n)	
1 to 2	44
>2 to 6	65
>6 to 12	39
>12 to 24	43
>24	11
Clinical signs (n)	
Local injection-site reactions	
Erythema	9
Erythema and swelling	27
Eczematous dermatitis	4
Systemic reactions	
Urticaria, angioedema	75
Exanthem	17
Eczematous dermatitis	12
Purpura	1
Flushing	11
Asthma exacerbation	3
Cyanosis and fever	1
Subjective complaints	30
Syncope	12
Duration of symptoms (n)	
<24 hours	90
1 to 4 day	76
≥1 week	25
Not specified	11

Abbreviation: LA, local anaesthetic.

Subcutaneous provocation tests with skin test-negative LAs were performed in all 202 patients. More than 1 LA was given in 121 cases, resulting in a total of 354 provocation procedures. LA allergy was definitely excluded in 194 patients by a negative result of subcutaneous provocation with the incriminated LA. In 2 of the 8 patients with late-type LA allergy, allergic hypersensitivity could only be diagnosed by positive subcutaneous provocation (Table 3). These 2 patients developed a cellulitis-like, deep tissue inflammation with redness and swelling at the injection sites on the upper arms, which began several hours after LA injection and persisted for 2 to 3 days (patient no. 6 reacted to articaine, and patient no. 7 reacted to procaine). In all cases with definite LA allergy, including the 2 patients with false-negative skin test reactions to the culprit substance, an alternative tolerated LA could be identified by a negative subcutaneous provocation

TABLE 2 Results of skin testing and subcutaneous local anaesthetic (LA) provocation, and final diagnosis

Number of patients	202
Years between LA-induced reaction and allergy work-up (n)	
<1	135
1 to 5	39
>5 to 10	7
>10	21
Late reading of intradermal LA skin tests (n)	Negative Positive
Articaine	192 2
Mepivacaine	188 1
Procaine	180 3
Lidocaine	71 1
Prilocaine	41 2
Bupivacaine	37 0
Subcutaneous LA provocation (n)	Negative Positive
Articaine	140 1
Mepivacaine	102 0
Lidocaine	46 0
Prilocaine	27 1
Bupivacaine	19 0
Procaine	17 1
Final diagnosis (n)	
Late-type LA allergy	8
Spontaneous urticaria with or without angioedema	50
Hyperventilation, panic attack	30
LA-independent, non-allergic drug hypersensitivity	
NSAID-exacerbated/NSAID-induced urticaria	17
NSAID-exacerbated respiratory disease	3
ACE inhibitor-induced angioedema	7
LA-independent, allergic hypersensitivity	
Allergic contact dermatitis	5
Drug allergy	3
Fixed drug eruption	4
IgE-mediated latex allergy	3
α-Gal-mediated meat allergy	1
Wound infection or postoperative swelling	25
Vasovagal (neurocardiogenic) syncope	12
Viral exanthem	11
Atopic dermatitis	11
Steroid side-effects	11
Cutaneous small-vessel vasculitis	1
Methaemoglobinaemia	1

Abbreviations: ACE, angiotensin-converting enzyme; NSAID, non-steroidal anti-inflammatory drug; galactose-α-1,3-galactose.

result. The results of repeated subcutaneous provocation with prilocaine following a positive skin test result in patient no. 5 have been described in detail in a previous case report.²⁸ Twenty-nine patients (14.4%) complained of subjective symptoms after the first LA injections during subcutaneous provocation, for example, shortness of breath, paraesthesia, palpitations, and dizziness. These complaints were not documented in detail, so their frequency cannot be specified. However, all symptoms were invariably mild and improved after the patients had been reassured. The provocation procedure was

TABLE 3 Clinical data of the 8 patients with confirmed late-type local anaesthetic (LA) allergy

Patient	Indication/ procedure	Incriminated LA	Latency time period	Local symptoms at the injection site	Time interval between LA-induced local reaction and allergy work-up	Positive intradermal LA skin tests	Subcutaneous LA provocation	
							Negative	Positive
1, 44 y, F	Skin surgery	Procaine	12 h	Eczematous dermatitis	4 mo	Procaine: 24 h and 48 h	Articaine, prilocaine	No ^a
2, 69 y, M	Joint pain	Procaine	5 h	Redness and swelling	2 mo	Procaine: 24 h and 48 h	Mepivacaine, bupivacaine	No ^a
3, 52 y, F	Skin surgery	Procaine	10 h	Redness and swelling	>10 y	Procaine: 24 h and 48 h	Articaine, mepivacaine	No ^a
4, 55 y, F	Dental intervention	Articaine	24 h	Redness and swelling	4 y	Articaine, lidocaine, mepivacaine: 24 h and 48 h	Procaine, prilocaine	No ^a
5, 42 y, F	Skin surgery	Prilocaine	4-5 d	Eczematous dermatitis	2 mo	Prilocaine: 24 h, 48 h, 72 h, and 96 h	Articaine	Prilocaine
6, 55 y, F	Dental intervention	Articaine	4 h	Redness and swelling	>10 y	No	Prilocaine, mepivacaine	Articaine
7, 46 y, F	Nerve block	Procaine	10 h	Redness and swelling	3 y	No	Articaine	Procaine
8, 72 y, F	Nerve block	Prilocaine	12 h	Eczematous dermatitis	3 mo	Prilocaine, articaine: 24 h, 48 h, 72 h, and 96 h	Mepivacaine	No ^a

Abbreviations: F, female; M, male; h, hours; d, days; mo, months; y, years.

^a Provocation tests with skin test-positive LAs were not performed.

continued in all 29 cases and the results were considered to be negative, because subsequent injections were tolerated without further symptoms.

3.2 | Definitive diagnosis

The final diagnoses are shown in Table 2. The most probable differential diagnosis was chosen according to history and other available information. However, definite proof of the final diagnosis was not possible in most cases. Approximately one-quarter (24.8%) of our patients most likely suffered from a coincidental episode of spontaneous urticaria. Twenty-seven reactions (13.4%) were classified as non-allergic hypersensitivity to other drugs taken in temporal relationship with the LA injection: 17 as non-steroidal anti-inflammatory drug (NSAID)-induced or NSAID-exacerbated urticaria with or without angioedema (4 acetylsalicylic acid, 4 ibuprofen, 4 diclofenac, 3 metamizole, 1 piroxicam, and 1 phenylbutazone), 3 as NSAID-exacerbated respiratory disease (2 ibuprofen and 1 diclofenac), and 7 as angiotensin-converting enzyme (ACE) inhibitor-induced angioedema. In 16 patients (7.9%), the symptoms initially attributed to LA injections were probably caused by concurrent allergic reactions to other drugs, contact allergens or foods, as follows: 5 cases of allergic contact dermatitis caused by either nickel, formaldehyde, tosylamide/formaldehyde resin, sodium metabisulfite, or triamcinolone acetonide; 3 cases of late-type allergic drug hypersensitivity causing maculopapular exanthem (1 iomeprol, 1 sulfamethoxazole, and 1 tetrazepam); 4 cases of fixed drug eruption (2 metamizole, 1 piroxicam, and 1 phenylbutazone); 3 cases of IgE-mediated latex allergy; and 1 case of meat allergy to galactose- α -1,3-galactose (α -Gal). Panic attacks or hyperventilation were retrospectively diagnosed in 30 patients (14.9%). In 25 patients (12.4%), wound infection or postoperative swelling were apparently responsible for local reactions at the injection site. In 11 cases (5.4%),

viral exanthem, atopic dermatitis and steroid-induced flushing were retrospectively diagnosed. In 1 case, a recurrent but self-limited course of cutaneous small-vessel vasculitis was initially attributed to LA injections. After the vasculitis lesions had cleared, provocation testing with the suspected LA was tolerated without any symptoms. One case of prilocaine-induced methaemoglobinaemia was previously published as a case report.²⁹

3.3 | Localized allergy cases

The reported time between LA injections and the onset of symptoms varied from 4 hours to up to 4 days (Table 3). The LA-induced local reactions were described as resembling either allergic contact dermatitis (3 cases), or cellulitis-like, deep tissue inflammation (5 cases). Late-type LA allergy was detected by intradermal skin testing in 6 cases, whereas subcutaneous provocation was required to confirm the diagnosis in 2 patients with false-negative skin test results. Procaine allergy with tolerance of all amide-LAs tested was found in 4 patients. Different patterns of monosensitization and/or cross-reactivity between amide-LAs were observed in the remaining 4 cases.

4 | DISCUSSION

Anaphylaxis-like reactions within a few minutes after LA injection are by far the most common adverse events reported.¹⁻⁴ Both patients and treating physicians, however, occasionally also associate LA injections with local or even systemic symptoms developing with a delay of several hours. In the present study, we were able to confirm late-type LA allergy in 8 (4.0%) of 202 patients with suspected LA-induced delayed reactions. All patients with confirmed LA allergy belonged to a subgroup of 40 cases with a history of LA-induced

local reactions, that is, delayed inflammation confined to the injection site (Figure 1). In our patients, 20.0% of these local reactions were caused by late-type LA allergy, whereas the remaining 80% were mainly attributed to wound-infection and/or postoperative swelling. In all 162 cases with a history of delayed systemic symptoms (eg, urticaria, exanthem, eczematous dermatitis, or subjective complaints), diagnostic subcutaneous provocation with the suspected LA was tolerated (Figure 1). We were able to identify several differential diagnoses that were likely to have caused the reported symptoms coinciding with LA injections.

In intradermal skin testing, irritant (false-positive) wheal-and-flare responses are commonly observed at the reading after 15 minutes if undiluted LA preparations are used. Dilutions of 1:100 of the original pharmacological preparations are generally recommended for routine intradermal testing, to minimize irritant test reactions while maintaining a sensitivity of almost 100% with regard to the detection of

IgE-mediated LA allergy.^{1,4} Our present data, however, suggest that higher concentrations might be required for the detection of LA-induced late-type hypersensitivity, because false-negative intradermal test results occurred even at dilutions of 1:10 in 2 of 8 patients. In these 2 cases, LA allergy could be confirmed only by subcutaneous provocation. The opposite risk of false-positive intradermal test reactions in late readings, that is, after 24, 48 and 72 hours, seems to be negligible in view of our series including 194 unequivocally skin test-negative patients who subsequently tolerated the incriminated LA. We did not perform patch testing with LAs, although this is generally recommended for the assessment of late-type LA reactions, especially in cases with suspected contact hypersensitivity.^{1,2} Additional patch testing might have yielded positive results in our 2 patients with false-negative intradermal testing.

The extent and clinical manifestations of LA-induced, allergic local reactions seem to depend on the depth of LA injection, meaning that

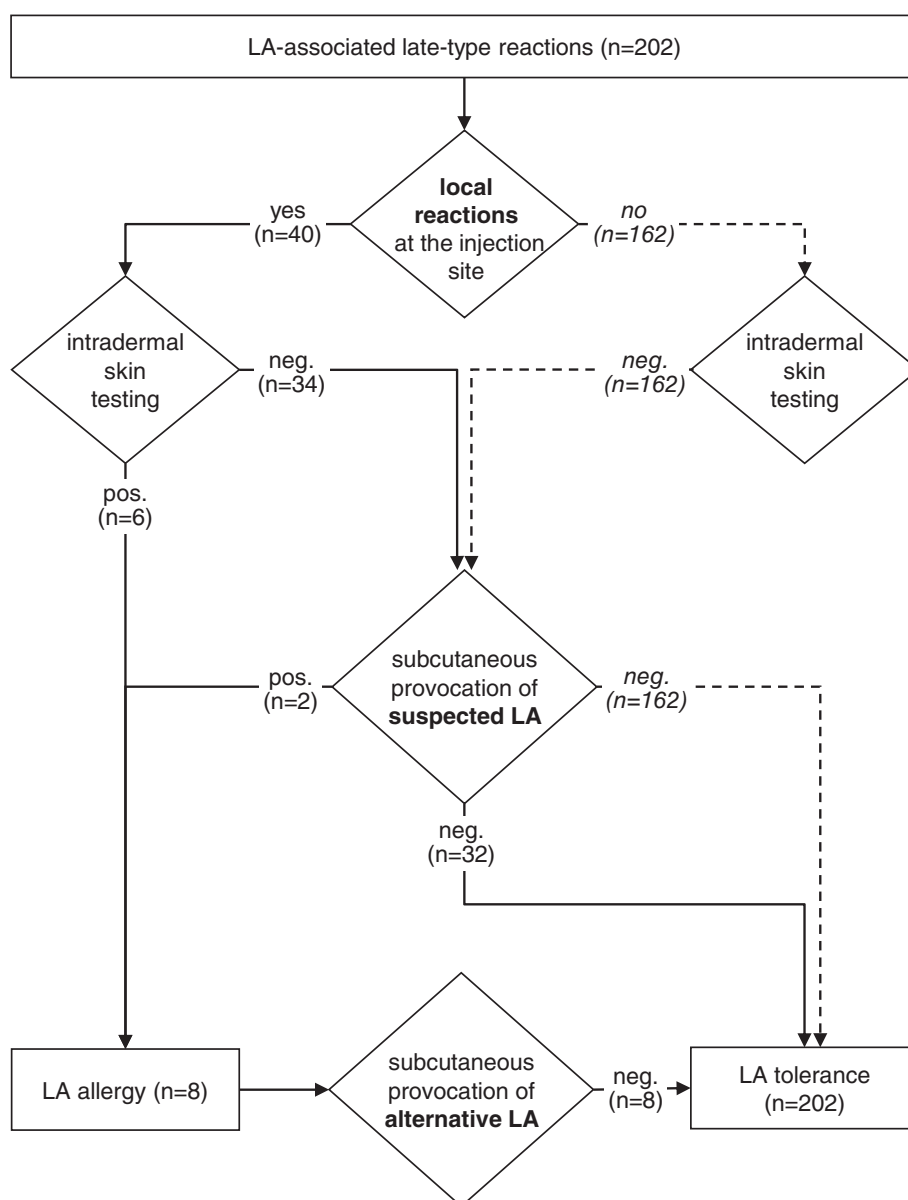


FIGURE 1 Results of allergy work-up in patients with or without local anaesthetic (LA)-associated late-type local reactions. neg., negative; pos., positive

superficial LA injections might cause symptoms other than those caused by deep subcutaneous injections. Our present data include relatively superficial eczematous reactions resembling allergic contact dermatitis, and deep, cellulitis-like tissue inflammation. These observations are in accordance with case reports covering the same range from superficial eczematous to deep cellulitis-like reactions.^{7,8,30–35} The term “deep impact contact allergy” has been proposed to refer to the latter.⁸ In a previous case report, we reported that LAs may be clinically tolerated despite sensitization if they are deliberately injected into the deep subcutaneous tissue.²⁸ We conclude that diagnostic LA injections during standard subcutaneous provocation testing should be administered in the upper subcutaneous tissue to optimize sensitivity.

The most frequent and thus most important differential diagnosis of LA-associated late-type reactions observed in 50 cases of our patients was a coinciding episode of urticaria. In approximately half of these cases, there was a history of concurrent infection, including purulent dental root inflammation or respiratory tract infection, as a potential trigger.¹⁷ A spontaneous episode of urticaria was suspected in the remaining cases, because skin tests and provocation with LA and alternative triggers, including foods and/or other drugs, gave negative results. NSAIDs are commonly administered in the context of orthopaedic or dental procedures. It is thus not surprising that NSAIDs, as strong cyclooxygenase-1 inhibitors, were identified as the triggers of urticaria or asthma exacerbation by oral provocation in 20 patients.¹⁹ In 7 cases, ACE inhibitors were found to be the most likely triggers of LA-associated episodes of angioedema, which did not recur once the ACE inhibitor was discontinued or replaced.²⁶ It is tempting to speculate that prolonged local pressure or vibration during dental treatments may trigger episodes of ACE inhibitor-induced angioedema.

Panic attacks or hyperventilation were retrospectively considered to be the most likely differential diagnoses in 30 patients (14.9%). This is significantly below the proportion of 55.7% observed in our recently published case series assessing immediate-type LA-associated anaphylaxis-like reactions.⁴ Together with neurocardiogenic syncope, panic reactions and hyperventilation were still the most frequent causes of emergency medical calls, which were prompted by 31 patients.

Further differential diagnoses of late-type LA hypersensitivity can be discussed only briefly, and we refer to the literature cited. In 1 case, late-type triamcinolone acetonide hypersensitivity was diagnosed following a combined injection with lidocaine because of joint pain.³⁶ Sodium metabisulfite, which is a common additive in epinephrine-containing LA preparations, is a rare but important elicitor of allergic contact dermatitis.³⁷ Nickel, formaldehyde and tosylamide/formaldehyde resin are found in alloys, cosmetics, and nail polish, and may occasionally cause contact dermatitis coinciding with LA injections.^{20,38,39} IgE-mediated latex allergy is an infrequent differential diagnosis of late-type reactions to LA. One case of delayed urticaria could be traced back to α -Gal-mediated meat allergy, and an episode of cyanosis and fever beginning 60 minutes after LA injection was finally diagnosed as prilocaine-induced methaemoglobinaemia.^{27,29}

5 | CONCLUSIONS

1. Cutaneous symptoms and systemic complaints occurring between 1 hour and several days after LA injections are occasionally perceived as allergic reactions by patients or treating physicians, but late-type LA allergy is only rarely confirmed.
2. Inflammatory reactions confined to the injection site represent the most common if not the only clinical manifestation of late-type LA allergy.
3. Systemic symptoms, including generalized urticaria, eczematous dermatitis, and exanthem, as well as a broad spectrum of non-cutaneous systemic complaints are not suggestive of late-type LA allergy. Common differential diagnoses include spontaneous urticaria and non-allergic or allergic hypersensitivity to other, concurrently administered, drugs, but also panic attacks or hyperventilation.
4. Intradermal tests with 1:10 or 1:100 dilutions of LA have limited sensitivity in the diagnosis of late-type LA hypersensitivity, which might be improved by additional patch testing.
5. LA injections for subcutaneous provocation should be administered in the superficial rather than in the deep subcutaneous tissue, in order to prevent false-negative results.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

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