

Large local reactions from stinging insects: from epidemiology to management

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Purpose of review

Large local reactions (LLRs) caused by insect stings have attracted the interest of clinicians for decades, especially because of their possible role as risk factor for subsequent more severe reaction. Nonetheless, the literature on epidemiological and clinical aspects of LLR is fragmentary. Therefore, we aimed at reviewing the data available so far on the argument and the clinical implications.

Recent findings

Our knowledge on the epidemiology and risk factors of LLR relies on studies performed many years ago. All those studies and our personal observation agree on the fact that LLRs are followed by a systemic reaction in not a negligible proportion of patients (10–15%). More recent studies have underlined the possible role of specific immunotherapy, including sublingual, in the treatment and prevention of LLRs.

Summary

LLRs should deserve a detailed diagnostic work-up, just as for systemic reactions. The prescription of autoinjectable adrenaline would seem advisable. Specific research on the predictive role of LLR for systemic reactions is needed, as well as studies assessing the benefits of treating all patients with LLR with immunotherapy.

Keywords

Hymenoptera venom allergy, large local reaction, systemic reaction

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Introduction

Within Hymenoptera, the families of Apidae (bees), Vespidae (yellow jacket, wasp, hornet) and Formicidae (ants) are those most relevant to human pathology. Within Apidae, the most important genera are *Apis* and *Bombus*, whereas within Vespidae, the most important are *Vespa*, *Vespula*, *Dolichovespula* and *Polistes* [1]. Finally, among Formicidae, the genus *Solenopsis* (fire ants), mainly present in the southern United States and South America has some relevance [2,3]. In the recent years, the rate of systemic reactions caused by other Formicidae has been reported to be increasing in Asia, Australia and Europe [4,5]. Hymenoptera stings can cause reactions with either toxic or allergic mechanisms and those reactions may largely vary in severity, from local to systemic anaphylaxis. Among the Hymenoptera-induced reactions, the so-called large local reactions (LLRs) have been classified as a special aspect for decades, mainly in relation to their possible predictive value for subsequent systemic reactions. The definition of LLR is essentially clinical and empiric. A LLR is defined as a reaction of oedema, erythema and pruritus, with a diameter greater than 10 cm and which peaks at 24–48 h, and then subsides (Figs 1 and 2). Despite the general interest, the literature systematically addressing

the problems related to LLR is overall poor and fragmentary. In the present article, we will review our current knowledge on LLRs induced by insect stings, also taking into account our personal database, which includes about 3500 patients. The review is necessarily limited to Hymenoptera stings, as standardized diagnostic approaches are available only for these insects.

Epidemiological, clinical and diagnostic aspects

Hymenoptera stings can provoke both irritative/toxic and allergic reactions. Toxic reactions, due to the irritant components of the venom, are essentially dose-dependent and may be generalized or local [6]. Among the components of venoms, phospholipase, hyaluronidase, melittin, mast cell degranulating peptide and mastoparan-C are able to produce direct damage of the skin, muscles, blood cells and central nervous system cells. The blood cell and muscular cell damage can sometimes induce a tubular necrosis with acute renal failure [7]. On the other hand, allergic reactions require the presence of specific IgE to one or more components of the venom. These reactions are usually rapid in onset (within minutes and less than 1 h) after the sting and also rapidly decline, especially if adequate treatment is given.

Figure 1 Example of large local reactions involving arm



Allergic reactions can be local or systemic. The latter have a large spectrum of severity, which is graded according to Mueller [8] and may result in full-blown anaphylaxis. On the contrary, as mentioned before, a LLR is operatively defined as oedema and erythema at the site of sting, with a diameter greater than 10cm and peaking in intensity at 24–48 h. [9,10]. Also LLRs can in principle be evoked only by a toxic mechanism, but it is generally believed that an IgE-mediated or even cell-mediated pathogenesis occurs in the majority of cases [11,12].

The prevalence of LLR in the general population is variable across the studies and it has been reported to range from 2.4 [13] to 10% [14], with a maximum of 26.4% [15]. These percentages are far greater in individuals heavily exposed to stings, as happens in beekeepers,

Figure 2 Example of large local reactions involving face

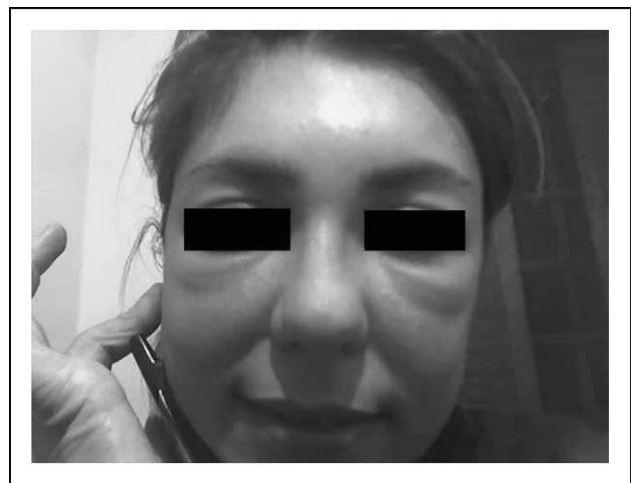


Table 1 Percentages of patients with IgE level greater than 250 in four severity groups and large local reactions

	Number of patients	Percentage of patients with IgE >250 kU/l
LLR	578	23.8
Muller grade I	230	23.0
Muller grade II	305	25.2
Muller grade III	667	24.4
Muller grade IV	766	17.4*

LLR, large local reaction.
* $P < 0.5$.

where the prevalence has been reported to be as high as 38% [16]. The large variability in the reported prevalence is probably the result of a nonuniform definition of LLR across studies of the different methodology of surveys and of the considered populations [17].

It has been suggested that LLR could be ‘protective’ for the subsequent development of systemic reactions [15], although adequate prospective studies are needed to confirm this hypothesis. On the other hand, it is well known that a short time interval between two stings increases the risk for a systemic reaction after a further sting [18], whereas the risk decreases as the interval elapsed between two stings increases [16]. Numerous and frequent stings (>200/year) seem to be able to induce a tolerance or hyposensitization, as shown in beekeepers [19]. Concerning the presence of atopy, there is no evidence of an increased prevalence of LLRs (and systemic reactions) in atopic individuals. A recent study [20] has shown that individuals with a total IgE level greater than 250 kU/l develop less severe reactions than those with lower total IgE. In our database with more than 3500 patients with Hymenoptera allergy, the percentage of patients with total IgE greater than 250 kU/l is lower in grade IV reactions than in grade I–III and LLRs, as shown in Table 1.

Also, we observed (Table 2) that the mean age of patients with systemic reactions is significantly greater than that of patients with LLR, and that the time between the last sting and the diagnosis is shorter in patients with systemic reactions. This latter observation can be explained by the fact that LLRs tend to be considered trivial, whereas

Table 2 Characteristics of patients with systemic reactions and large local reactions

	LLR (n = 808)	SR (n = 2223)	P
Sex M/F	461/347	1878/793	NS
Atopy	178 (22%)	355 (13.2%)	NS
Serum tryptase	4.5 ± 2.5	6.6 ± 3.5	NS
Mean age	34.16 ± 15	42.1 ± 18	0.05
Time between last sting and diagnosis (months)	15.5 ± 3	12.7 ± 3.8	0.05
Monosensitized	276 (34.2%)	680 (25.5%)	0.05

F, female; LLR, large local reaction; M, male; NS, not significant; SR, systemic reaction.

patients experiencing a systemic reaction immediately seek medical advice. Finally, the percentage of monosensitized patients is higher in the LLR group and this could be explained by the fact that multiple positivities make the patients more prone to develop systemic reactions.

It is estimated that the risk of developing a systemic reaction after a LLR is relatively low, ranging from 5 to 15% [21–24] and this observation is consistent in adults and children. On the other hand, some authors reported in a limited case series that LLRs are not at all at risk for subsequent systemic reactions [25]. Therefore, it could be argued that patients presenting with a LLR would not need a diagnostic work-up involving cutaneous and biological tests. On the other hand, it is true that the majority of patients with LLR have positive diagnostic tests [26], although the degree of skin positivity does not correlate with the severity of reaction, and patients with LLR do not have necessarily a lower skin reactivity or lower specific IgE levels. Limited data are available on the natural history of LLRs induced by fire ants [3,27,28] and these data suggest a benign outcome.

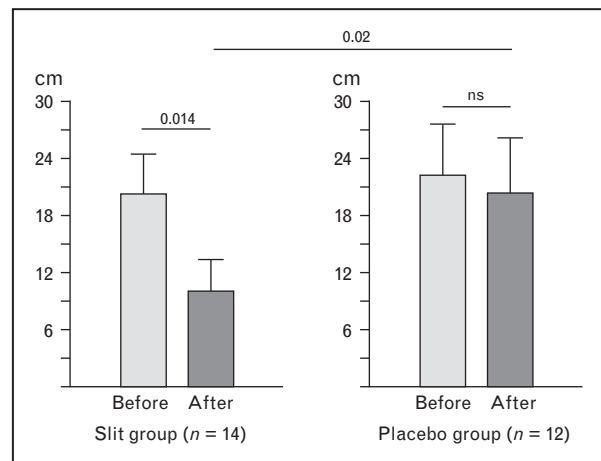
Prevention and treatment

The treatment of LLR is essentially symptomatic and relies on the use of systemic antihistamines and topical corticosteroids [10,29]. Immediate application of ice at the site of the reaction is helpful in relieving symptoms and reducing the extension of the LLR. When oedema is spreading, systemic corticosteroids (e.g. prednisone 50 mg) should be added for a few days. Systemic steroids are recommended when the LLR involves the limbs with functional impairment, or the face and the lips.

Unfortunately, there is no way to reliably predict whether a patient with a previous LLR will subsequently develop a systemic reaction or will maintain a LLR, and even in the absence of a clinically relevant reaction, the risk for a systemic reaction at subsequent stings cannot be ruled out [30]. Based on this, the opinions about the management of LLRs are sometimes conflicting, especially concerning the prescription of autoinjectable adrenaline, also because it is perceived as burdensome and unsuitable treatment by most venom allergic patients [31]. Other authors recommend that patients carry the adrenaline with them [30]. This latter position seems to be more prudent and reasonable, also due to the relative safety of autoinjectable adrenaline. In our database, more than 30% of the patients with a systemic reaction had a previous LLR in their clinical history; thus, we agree on the usefulness of carrying out a diagnostic procedure in LLRs, as well as, on the prescription of adrenaline.

Specific venom immunotherapy (VIT) is highly effective in Hymenoptera allergy. It confers an almost complete

Figure 3 Peak diameter of large local reaction (median, SEM) at honeybee sting challenge in sublingual immunotherapy and placebo patients before and after 6 months



Reproduced from [37**].

protection against subsequent stings [29,30,32] and also improves the quality of life [33]. Despite this, VIT is currently not recommended in patients with LLR, based on the assumed low risk of future systemic reactions. In highly exposed patients, who would require multiple treatments with systemic steroids, VIT could be prescribed to reduce the use of steroids.

Looking at the literature, there are few studies of VIT to specifically treat LLR. In two early studies, injection VIT was shown capable of reducing or preventing LLRs caused by fire ant [34] or honeybee [35] stings. The results of a more recent placebo controlled trial of VIT [36] were even more favourable. In fact, after 6–10 weeks of treatment, the size of LLRs was reduced by 47% in treated patients in comparison with 18% in controls, and the reduction reached 70% after 2–4 years of VIT. Also, the duration of LLRs was reduced by 52% in those receiving VIT and by 20% in controls. Another recent randomized double-blind placebo controlled study [37**] assessed the effect of sublingual immunotherapy (525 µg honeybee venom) on the LLRs induced by sting challenge. After 6 months of treatment, the diameter of LLRs was reduced by more than 50% in 60% of the treated patients, with no change in the placebo group (Fig. 3). Of note, in this study, one placebo patient (10%) developed a systemic reaction at the second challenge.

Conclusion

LLRs are classified as a ‘special’ kind of reaction but, despite this, the literature is fragmentary and there are few systematic studies. Although it is clear that the risk of developing systemic reactions after a LLR is overall low,

it seems reasonable to recommend that patients with LLRs undergo the standard diagnostic procedure to demonstrate the presence of an IgE-mediated mechanism. In this case, it is advisable that patients are instructed to carry autoinjectable adrenaline and to use it if systemic symptoms appear. Based on practical considerations, specific immunotherapy may be prescribed to patients who are at high risk of repeated stings, in order to avoid the repeated use of systemic corticosteroids. Finally, trials specifically assessing the extent of the effect of VIT in LLRs are needed to better define the management attitude [11,38].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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